Nasopharyngeal cancer: an update on diagnosis and treatment

Nazofarinks kanseri: Tanı ve tedavide güncelleme

Bengu Cobanoglu[1], Selcuk Arslan[1]

[1]*Dept. of Otorhinolaryngology, Karadeniz Technical University, Faculty of Medicine, Trabzon, Turkey*

Abstract

Nasopharyngeal carcinoma (NPC) has distinct epidemiological and histological features among head and neck cancers. Clinical signs in patients with NPC change according to the tumor size and the status of lymph node metastases. Tumor can expand anteriorly to nasal cavity, pterygoid fossa or maxillary sinus, laterally to parapharyngeal space and infratemporal fossa, or posterosuperiorly to cranial base, clivus and intracranial structures. Radiotherapy is the primary treatment in NPC. In tertiary centers, intensity modulated radiotherapy (IMRT) is the preferred radiotherapy module. Concurrent chemoradiotherapy is the standard treatment of locally advanced NPC. Standard regimen includes radiation to 70 Gy to the gross tumor in daily fractions of 2 Gy and additional chemotherapy which includes 100 mg/m^2 of cisplatin every 3 weeks or 30-40 mg/m^2 once a week.

In this article, updated staging in American Joint Committe on Cancer (AJCC) 8th edition guidelines, diagnostic methods and treatment modalities in NPC are reviewed and presented in the light of current literature.

Key words: *nasopharynx, carcinoma, treatment*

Özet

Nazofarengeal karsinom (NPC), baş boyun kanserleri arasında belirgin epidemiyolojik ve histolojik özelliklere sahiptir. Hastalarda klinik bulgular, tümör boyutuna ve lenf nodu metastazlarının durumuna göre değişir. Tümör anteriordan burun boşluğuna, pterygoid fossa veya maksiller sinüse, lateral olarak parafarengeal boşluğa ve infratemporal fossaya ya da posterosuperiordan kraniyal baz, klivus ve intrakraniyal yapılara yayılabilir. Radyoterapi, primer tedavidir. İleri merkezlerde yoğunluk modülasyonlu radyoterapi (IMRT) tercih edilen radyoterapi modülüdür. Eş zamanlı kemoradyoterapi lokal ileri hastalığın standart tedavisidir. Standart rejim, 2 Gy günlük fraksiyonlarda brüt tümöre 70 Gy radyasyon ve üç haftada bir 100 mg/m^2 veya haftada bir 30-40 mg/m^2 cisplatin içeren kemoterapinin eklenmesidir.

Bu makalede, American Joint Committe on Cancer (AJCC) 8. baskı kılavuzlarındaki güncellenmiş evreleme, NPC'deki tanı yöntemleri ve tedavi yöntemleri literatür ışığında gözden geçirilmiş ve sunulmuştur.

Anahtar kelimeler: *nazofarenks, kanser, tedavi*

Corresponding author: Bengu Cobanoglu, Dept. of Otorhinolaryngology, Karadeniz Technical University, Faculty of Medicine, 61080, Trabzon, Turkey, Phone: +904623775884, E-mail: benguyc@yahoo.com
Received: 15 March 2019 ***Accepted:*** 25 March 2019
Conflicts of Interest: None
Funding: None

Introduction

Nasopharyngeal carcinoma (NPC) has distinct epidemiological and histological features among head and neck cancers. The prevalence changes regarding to ethnicity and geographical areas. The majority of nasopharyngeal carcinoma cases is diagnosed as non-keratinized indifferentiated type.[1]

Nasopharyngeal carcinoma can show direct invasion to the cranial base and parapharyngeal space in early stages and the lymphatic involvement is common due to rich lymphatic vasculature of nasopharynx. Along with the higher ratio of lymphatic spread, the probability of systemic spread is also higher in contrast to squamous carcinoma of other head and neck regions.[2]

The primary treatment modality is radiotherapy. In early stage disease the treatment has promising results. In locally advanced disease, there is high recurrence rate with radiotherapy alone. Therefore, numerous studies have focused on induction chemotherapy, concurrent chemoradiotherapy, adjuvant chemotherapy and different fractionation schemes to maintain locoregional control and to prevent distant metastases.[3] In this article, updated staging in American Joint Committe on Cancer (AJCC) 8th edition guidelines, diagnostic methods and treatment modalities in NPC are reviewed and presented in light of the literature.

Epidemiology

Nasopharynx is a cuboidal shaped room under the cranial base and posterior to nasal cavity. It is 2.5 cm in height and 3 cm in width and its depth varies between 2.5 to 3 cm in the superior part and 4 to 4.5 cm in the inferior part. The total volume is 14 to 15 cm^3.[4] Nasopharyngeal carcinoma originates from nasopharyngeal epithelium and is rare in comparison to other head and neck carcinomas. Its geographical distribution is different than other head and neck carcinomas. Nasopharyngeal cancer has a worldwide prevalence of around 2% among head and neck carcinomas and 0.2% of all cancer types.[5] Seventy-one per cent of nasopharyngeal carcinoma cases are seen in Eastern Asia and Africa.[5] The annual incidence is reported to be 8-12 / 100.000 in Mediterranean countries, including our country.[5,6] The prevalence of NPC is 2 to 3 times more in men than women and it is most frequent in 5th and 6th decades.[6] Based on the World Health Organization (WHO) criteria, nasopharyngeal carcinoma is divided into three pathological groups according to the grade of differentiation. Well-differentiated and keratinized tumors are defined as Type I while differentiated non-keratinized and indifferentiated tumors are classified as Type II and Type III, respectively. In endemic areas, 95% of cases are of non-keratinized and Ebstein-Barr (EBV) related histopathology whereas in other countries Type I NPC is more prevalent.[7,8] EBV infection is the most studied factor implicated in the etiology. By using in-situ hybridization techniques, EBV has been detected in tumor cells but not in normal nasopharyngeal epithelium. This finding shows the necessity of EBV activation in the pathogenesis of NPC.[9] Human papilloma virus (HPV) is another virus implicated in the etiology of non-endemic forms but data is limited regarding the relationship of HPV with NPC for non-endemic forms being relatively rare. Yet, small scaled studies demonstrated that HPV could be the causal factor in keratinized and non-keratinized NPC in white race.[10] When HPV or EBV-related NPC cases are reviewed, lower survival and local control rates are found in HPV-related NPC whereas failure in treatment of distant metastases is seen more in EBV-related cancer.[11] In addition, the worst prognosis is seen in patients with EBV and HPV negative NPC.[10]

In endemic areas of NPC, genetic factors have also been searched. A possible locus has been detected in HLA gene codes (HLA-A, HLA-B, HLA-C, HLA-DQ, HLA-DR) of 6p21 chromosome.[12,13] Research on dietary factors that could play a role in the etiology NPC revealed that N-nitrosamine in salted fish products had carcinogenic effect and package food, herbal teas, slowly cooked soup and alcohol could be considered as risk factors.[14]

Clinical manifestations and patient evaluation

Clinical signs in patients with NPC change according to the tumor size and the status of lymph node metastases. Tumor can expand anteriorly to nasal cavity, pterygoid fossa or maxillary sinus, laterally to parapharyngeal

space and infratemporal fossa, or posterosuperiorly to cranial base, clivus and intracranial structures.

Therefore, symptoms can vary according to affected anatomical structures. Patients can refer with an array of symptoms such as epistaxis, nasal obstruction, hearing loss or cranial nerve paralysis.[15] CNIII, CNV, CNVI and CNXII are the most affected cranial nerves. Nearly 75% of patients have cervical lymph node metastasis at the time of diagnosis. Retropharyngeal and Level 2 lymph nodes are the typical regions of lymph node metastasis.[16] Skip metastases to other lymph node regions is extremely rare. In an American study involving 378 patients, the presenting symptoms were cervical mass in 41%, hearing loss and otorrhea in 27%, epistaxis and unilateral nasal obstruction in 21% and cranial nerve deficits in 8% of patients.[15] A detailed otorhinolaryngological examination is necessary for all patients with a suspicion of NPC. Possible cervical lymph node metastasis must be searched and endoscopic examination of nasopharynx must be done to deliniate the expansion of the tumor and to biopsy at the same time. Computed tomography (CT) or magnetic resonance imaging (MRI) is useful as imaging modalities. Magnetic resonance imaging is superior in the evaluation of soft tissues in comparison to CT and can be used in staging of NPC. American Journal of Cancer Committee (AJCC), revised head and neck cancer staging in 2017.[17] Table 1 demonstrates staging of NPC.

Diagnosis and management of nasopharyngeal carcinoma

When planning the management of nasopharyngeal carcinoma, optimum imaging plays a big role. As we know, MRI provides better resolution than CT in terms of soft tissues such as pharapharyngeal spaces, cervical nodes and intracranial extension of the disease. PET-CT (18F-flourodeoxyglucose positron emission tomography) could be used for follow-up and detecting recurrence or metastasis, after treatment. In terms of detecting distant metastasis, studies show that 18F-FDG-PET has a sensitivity of 70-80% and accuracy of 90%.[18,19]

Radiotherapy is the primary treatment in NPC. In tertiary centers intensity modulated radiotherapy (IMRT) is the preffered radiotherapy module. Intensity modulated radiotherapy provides us to deliver the maximum dose to tumor and minimizes dose to adjacent normal tissues. Modifying the dose or fraction size is still uncertain in NPC. Radiation therapy can be used as primary single mode therapy in early stages of NPC. Xiao et al. reported 5 year survival rates as T1 N0 96.6%, T2N0 91.3%, T1N1 95.8%.[20] Concurrent chemoradiotherapy is the standart treatment of locally advanced NPC.

Table 1. Staging of nasopharyngeal carcinoma

T Staging	Cervical N staging
T1: Same as AJCC 7th Ed. Tumor confined to nasopharynx	N1: Unilateral lymph node metastasis ≤ 6 cm in supracricoid region and/or unilateral or bilateral retropharyngeal lymph node metastases
T2: Tumor extended to parapharyngeal space and/or medial pterygoid, lateral pterygoid, and /or prevertebral muscles	N2: Bilateral lymph node metastasis ≤ 6 cm in supracricoid region
T3: Tumor invaded the cranial base, cervical vertebrae, pterygoid structures and/or bony structures as paranasal sinuses	N3: Lymph node metastasis > 6 cm and/or metastatic lymph node below cricoid region
T4: Intracranial extension and/or cranial nerve deficit, hypopharynx, orbita or parotid gland invasion	

Standard regimen includes radiation to 70 Gy to the gross tumor in daily fractions of 2 Gy and addition of chemotherapy which includes 100 mg/m^2 of cisplatin every 3 weeks or 30-40 mg/m^2 once a week.[21,22] Common acute radiotherapy related effects include xerostomia, mucositis, dysphagia, dermatitis. Chemoradiotherapy releated effects are associated with haematological findings. Assessment of tumor response includes detailed examination, nasal endoscopy, endoscopic biopsy if needed and MRI findings. Positron emission tomography is superior in detecting post-radiotherapy changes and residual tumors. EBV-DNA is a prognostic marker for recurrences in NPC. Detection of EBV-DNA after treatment suggests tumor recurrence and poor prognosis.[23,24] After the treatment, if recurrence occurs the patient can be treated with either surgery or radiotherapy. Despite therapy, 10% of neck masses may persist. In these cases surgical neck dissection is the preferred management. In terms of managing distant metastasis radiotherapy, cisplatin and fluorouracil is the standart treatment. If the tumor is platinium-resistant disease, then the second-line treatment must include docetaxel, capecitabine and gemcitabine.[25,26] Reirradiation is the optimal choice for treatment of recurrent NPC with high doses of radiation with IMRT.

When we evaluate the outcome and long term survey, Xie et al had a study with 62 patients with NPC. They showed that patients with a lower maximum standardized uptake value (SUV max) (<8) of tumor had a higher overall survival than the patients with higher SUV max.[27]

Promising treatment options

Immunotherapy: Nasopharyngeal cancer is an EBV-associated malignancy therefore immune T cell-related viral antigens and dendritic cell based vaccines are now in trials of phase 2 and parallel trials in UK as well as in US.[28,29]

Moleculer-targeted therapy: In platinium refractory carcinomas, inhibition of vascular endothelial and epithelial growth factors (EGFR and VEGF) has shown promising results.[30,31] The only concern about VEGF inhibitors is the increased risk of bleeding, so this must be kept in mind while designing trials.

Conclusion

Nasopharyngeal cancer is uncommon among head and neck carcinomas. Radiotherapy is the single modality treatment that has 10-year survival rates such as 34-43%. In the treatment of advanced or recurrent disease, concurrent chemoradiation is gold standard. Novel techniques about EBV-DNA or EBV-associated antigens for intensive treatment may play a role in the near future.

References

1. Wee JT, Ha TC, Loong SL, Qian CN. Is nasopharyngeal cancer really a "Cantonese cancer"? Chin J Cancer 2010;29:517-26.
2. Yu MC. Nasopharyngeal carcinoma: epidemiology and dietary factors. IARC Sci Publ 1991;105:39-47.
3. Henderson BE, Louie E, SooHoo Jing J, Buell P, Gardner MB. Risk factors associated with nasopharyngeal carcinoma. N Engl J Med 1976;295:1101-6.
4. Hyare H, Wisco JJ, Alusi G, et al. The anatomy of nasopharyngeal carcinoma spread through the pharyngobasilar fascia to the trigeminal mandibular nerve on 1.5 T MRI. Surg Radiol Anat 2010;32:937-44.
5. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:359-86.
6. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 2005;365:2041-55.
7. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ WHO Classification of Head and Neck Tumours, WHO Classification of Tumours, 4th Edition, Volume 9, pp:357-68.
8. Chan AS, To KF, Lo KW, et al. High frequency of chromosome 3p deletion in histologically normal nasopharyngeal epithelia from southern Chinese. Cancer Res 2000;60:5365-70.
9. Tsang CM, Deng W, Yip YL, et al. Epstein-Barr virus infection and persistence in nasopharyngeal epithelial cells. Chin J Cancer 2014;33:549-55.
10. Lin Z, Khong B, Kwok S, et al. Human papillomavirus 16 detected in nasopharyngeal carcinomas in white Americans but not in endemic Southern Chinese patients. Head Neck 2014;36:709-14.
11. Stenmark MH, McHugh JB, Schipper M, et al. Nonendemic HPV-positive nasopharyngeal carcinoma: association with poor prognosis. Int J Radiat Oncol Biol Phys 2014;88:580-8.

12. Maxwell JH, Kumar B, Feng FY, et al. HPV-positive/p16-positive/EBV-negative nasopharyngeal carcinoma in white North Americans. Head Neck 2010;32:562-7.
13. Chan YH, Lo CM, Lau HY, Lam TH. Vertically transmitted nasopharyngeal infection of the human papillomavirus: does it play an aetiological role in nasopharyngeal cancer? Oral Oncol 2014;50:326-9.
14. Dogan S, Hedberg ML, Ferris RL, et al. Human papillomavirus and Epstein-Barr virus in nasopharyngeal carcinoma in a low-incidence population. Head Neck 2014;36:511-6.
15. Sanguineti G, Geara FB, Garden AS, et al. Carcinoma of the nasopharynx treated by radiotherapy alone: determinants of local and regional control. Int J Radiat Oncol Biol Phys 1997;37:985-96.
16. Kamran SC, Riaz N, Lee N. Nasopharyngeal carcinoma. Surg Oncol Clin N Am 2015;24:547-61.
17. Lydiatt WM, Patel SG, O'Sullivan B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:122-37.
18. Chua ML, Ong SC, Wee JT, et al. Comparison of 4 modalities for distant metastasis staging in endemic nasopharyngeal carcinoma. Head Neck 2009;31:346-5.
19. Chang MC, Chen JH, Liang JA, et al. Accuracy of whole-body FDG-PET and FDG-PET/CT in M staging of nasopharyngeal carcinoma: a systematic review and meta-analysis. Eur J Radiol 2013;82:366-73.
20. Xiao WW, Han F, Lu TX, et al. Treatment outcomes after radiotherapy alone for patients with early-stage nasopharyngealcarcinoma. Int J Radiat Oncol Biol Phys 2009;74:1070-6.
21. Chen QY, Wen YF, Guo L, et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. J Natl Cancer Inst 2011;103:1761-70.
22. Tao CJ, Lin L, Zhou GQ, et al. Comparison of long-term survival and toxicity of cisplatin delivered weekly versus every three weeks concurrently with intensity-modulated radiotherapy in nasopharyngeal carcinoma. PLoS One 2014;9:e110765.
23. Le QT, Jones CD, Yau TK, et al. A comparison study of different PCR assays in measuring circulating plasma epstein-barr virus DNAlevels in patients with nasopharyngeal carcinoma. Clin Cancer Res 2005;11:5700-7.
24. Lin JC, Wang WY, Liang WM, et al. Long-term prognostic effects of plasma epstein-barr virus DNA by minor groove binder-probe real-time quantitative PCR on nasopharyngeal carcinoma patients receiving concurrent chemoradiotherapy. Int J Radiat Oncol Biol Phys 2007;68:1342-8.
25. Zhang AM, Fan Y, Wang XX, et al. Increased treatment-related mortality with additional cisplatin-based chemotherapy in patients with nasopharyngeal carcinoma treated with standard radiotherapy. Radiother Oncol 2012;104:279-85.
26. Kong L, Zhang Y, Hu C, Guo Y, Lu JJ. Effects of induction docetaxel, platinum, and fluorouracil chemotherapy in patients with stage III or IVA/B nasopharyngeal cancer treated with concurrent chemoradiation therapy: Final results of 2 parallel phase 2 clinical trials. Cancer 2017;123:2258-67.
27. Xie P, Yue JB, Zhao HX, et al. Prognostic value of 18F-FDG PET-CT metabolic index for nasopharyngeal carcinoma. J Cancer Res Clin Oncol 2010;136:883-9.
28. Hui EP, Taylor GS, Jia H, et al. Phase I trial of recombinant modified vaccinia ankara encoding Epstein-Barr viral tumor antigens in nasopharyngeal carcinoma patients. Cancer Res 2013;73:1676-88.
29- Taylor GS, Jia H, Harrington K, et al. A recombinant modified vaccinia ankara vaccine encoding Epstein-Barr Virus (EBV) target antigens: a phase I trial in UK patients with EBV-positive cancer. Clin Cancer Res 2014;20:5009-22.
30. Lim WT, Ng QS, Ivy P, et al. A Phase II study of pazopanib in Asian patients with recurrent/metastatic nasopharyngeal carcinoma. Clin Cancer Res 2011;17:5481-9.
31. Hui EP, Ma BBY, Loong HHF, et al. Efficacy, Safety, and Pharmacokinetics of Axitinib in Nasopharyngeal Carcinoma: A Preclinical and Phase II Correlative Study. Clin Cancer Res 2018;24:1030-7.