Chapter

Diagnosis and Therapy of Nasopharyngeal Carcinoma

Tingting Huang, Zhe Zhang and Xiaoying Zhou

Abstract

Nasopharyngeal carcinoma (NPC) is a malignancy with unique biological and clinical characteristics. It has highly associated with Epstein–Barr virus (EBV) infection and is sensitive to radiotherapy. Due to the extreme relevance between EBV infection and incidence of NPC, testing antibodies against EBV has been applied to screening "high-risk" populations of NPC. The pathological diagnosis of nasopharyngeal biopsy is the gold standard for the diagnosis of NPC. Radiotherapy has been recognized as the first choice for NPC treatment. With the improvement of intensity-modulated radiation therapy (IMRT), the 5-year disease-specific survival rate in NPC patients at an early stage has reached 95%. However, the efficacy brought by radiotherapy has reached the bottleneck in advanced patients. Recently, the 5-year overall survival rate was increased around 60-80% in locoregionally advanced NPC patients by introducing concurrent chemoradiotherapy. In addition, molecular targeted therapy and immunotherapy have been introduced to many clinical trials. In this chapter, we mainly focus on the current early screening and diagnosis of NPC patients, and the development of therapeutic approaches.

Keywords: nasopharyngeal carcinoma, population-based screening, symptoms, diagnosis, treatment

1. Introduction

As a part of the pharynx, the nasopharynx lies behind and communicates with the nasal cavities. It is up to the cranial base, down to the soft palate plane, forward through the back of the nose to the nasal cavity, and pharynx tonsils in the backward. Behind the inferior turbinate, there is an opening of the eustachian tube, which leads through the nasopharynx to the tympanic cavity. A recess in the lateral of the pharyngeal wall extending posteriorly to the opening of the eustachian tubal torus, which is called Fossa of Rosenmüller, is the predilection site of nasopharyngeal carcinoma (NPC).

As one of the malignant head and neck cancer, NPC arises from epithelial cells within the nasopharyngeal mucosa, with a unique geographical and ethnic distribution.. Epstein–Barr virus (EBV) infection, carcinogen exposure, and genetic susceptibility contribute to the carcinogenesis of NPC. In the endemic area, more than 95% of NPC patients were EBV positive, therefore, testing antibodies against EBV or cell-free EBV DNA has been established for screening assays targeted "high-risk" populations of NPC. Nasopharyngeal endoscopy is recommended for EBV-seropositive individuals to find out NPC patients at an early stage. The common clinical symptoms of NPC were nasal congestion, bloody nose, hearing loss,

and headache, but not specific at early stages. At present, the pathological diagnosis of nasopharyngeal biopsy remains the golden standard for NPC. Most undifferentiated NPC is moderately sensitive to radiation therapy, leading it the first choice for NPC treatment. Taking advantage of accurate staging systems, modern radiotherapy techniques, and concurrent chemotherapy, the locoregional control and overall survival of NPC patients have substantially improved along with the decline of treatment-induced toxicity in the past two decades. However, residual/recurrent disease and metastatic disease are still crucial challenges in managing NPC.

1.1 Epidemiology

Globally, NPC is uncommon cancer with approximately 129,000 new cases reported in 2018 and accounting for 0.7% of all cancers [1]. The incidence of NPC is relatively concentrated, about 80% of NPC occurs in Asia, and China accounts for almost half of the total [2]. For instance, the incidence rate in North America and Europe is less than 1/100,000 person-years, but greater than 20/100,000 person-years in Southern China and Southeast Asia [3, 4]. Importantly, NPC incidence is higher in males than in females, with a ratio of 2-3 [5]. The age-specific incidence of NPC is different from other types of cancer as well. The bimodal distribution of age showed two peaks between 16 and 20 and 45-60 years [3]. Besides, family aggregation is a characteristic of NPC in the endemic area which is well documented [6, 7]. Even people migrate from Southern China to non-endemic areas, the incidence remains high, suggesting that genetic inheritance is one of the main factors for NPC pathogenesis. However, the reduced incidence has been observed in second-generation migrants [8]. In addition, according to recent epidemiology studies, the global incidence of NPC is also declining gradually [9–11]. These findings indicate that lifestyle alterations are highly correlated with the pathogenesis of NPC.

1.2 Etiology

So far, the etiology of NPC is not fully clear. It is widely accepted that genetic susceptibility, EBV infection, and exposure to harmful carcinogens such as intake of salted fish and preserved food, etc., are the main pathogenic factors for NPC. The single factor mentioned above can not induce the occurrence of NPC in animal models, therefore all these factors contribute together and their interaction might be more important and worth deeply understanding [12]. Recently, poor oral hygiene has been proposed as a risk factor for NPC [13]. The composition of the oral microbiome is shown to be different between NPC patients and their population-based controls [14]. Moreover, the anaerobic metabolites of *F. nucleatum*, *n*-butyrate acid is a strong lytic-cycle inducer of EBV [15]. More potential pathogenic factors are being discovered.

In the endemic area, almost all NPC patients are associated with EBV infection and are more sensitive to radiotherapy [16]. Besides, it is difficult to achieve effective treatment by surgery in NPC patients, because the anatomy of the nasopharynx is concealed and the peripheral nerves and blood vessels, and more than 80% of patients show lymph node metastasis at the time of diagnosis [17, 18]. Therefore, radiotherapy is the first choice in the treatment of NPC. At present, the local control rate of NPC patients under radiotherapy exceeds 90%, and the 5-year survival rate is close to 80% [19, 20]. It is noteworthy that early diagnosis is a key point. The earlier diagnosis of NPC patients, the greater improvement of survival [21]. To date, distant organ metastasis remains the largest obstacle and the main factor of failure. In this chapter, we mainly introduce the early population screening of NPC in the endemic area, as well as the approaches for NPC diagnosis and treatment.

2. Population screening of NPC

As literature reported, before the clinical onset of NPC, the serological EBV antibody level has already been sustained elevated within a window of 37 months, which serves as an efficient screening biomarker [22]. At present, serological detection of EBV, testing the titers of viral capsid antigen (VCA)-IgA, early antigen (EA)-IgA, and EBV nuclear antigen 1 (EBNA1)-IgA antibodies of EBV is widely used in the mass screening of NPC in an endemic region, which is helpful for early diagnosis [23–25]. No matter using the traditional immunofluorescent/Immunoenzymatic assays or enzyme-linked immunosorbent assays (ELISA) assay, once the elevated EBV-IgA were detected in screening participants, they were defined as "high-risk" objects of NPC. Next, an indirect mirror examination in the nasopharynx and/or lymphatic palpation should be carried out. If abnormal enlargement of the lymph node in the upper neck and elevate, rough nasopharyngeal surface were observed, the objects will be concluded as suspicious NPC patients. Further fiberoptic endoscopy and biopsy are necessary for diagnosis [25]. The benefit of screening was illustrated by finding early NPC cases.

Scientists are devoted to improving the methods of detecting EBV to enhance the effectiveness of screening. For instance, collecting nasopharyngeal swabs for additional nasopharyngeal EBV DNA load analysis could effectively reduce the "high risk" population who needed follow-up examination [26]. Recently, utilizing circulating cell-free EBV DNA has been proposed for early NPC screening, with sensitivity and specificity as 97.1% and 98.6%, respectively [27].

3. Symptoms and diagnosis of NPC

Due to the concealed anatomical location of NPC, most cases show no specific symptoms at all when the disease is initiated, until they present lymph node metastasis, typically in the neck. Thus, most of the patients missed the opportunity of diagnosis at the early stages.

3.1 Symptoms of NPC

NPC usually occurs in the lateral walls, it grows either within the nasopharynx or extends outward. Being a malignant tumor, NPC can infiltrate or invade surrounding structures, for instance, the base of the skull, the palates, nasal cavity, and the oropharynx. The most common presenting symptom is cervical lymph node enlargement, followed by nasal, aural, and neurological symptoms. Among them, the most noteworthy early symptoms of NPC are the first retracted snot with blood in the morning, which is often overlooked by patients. Enlargement of NPC within the nasopharynx may cause nasal obstruction-related symptoms, such as congestion, and bleeding. A blockage of the eustachian tube may lead to unilateral tinnitus, hearing loss, and catarrhal otitis media. The brain nerve invasion or skull base bone damage by NPC are often the causes of headaches [28].

3.2 Diagnosis

The detection of NPC is based on clinical symptoms and physical examination, but a definitive diagnosis requires a biopsy of the lesion. The first choice of the diagnosis of the primary NPC is biopsy under the nasopharynx endoscope [28]. Cervical lymph node biopsy by fine-needle aspiration should only be used when the

pathological finding in primary tumor biopsy is negative but remains highly suspicious of NPC. Combining with EBV encoded small RNAs (EBERs) *in situ* hybridization examination could help clinical doctors promptly identify the primary lesions [29]. To further assess the tumor size and location, a series of radiologic tests, including computed tomography (CT) scans and magnetic resonance imaging (MRI) of the head and neck are required. This provides additional but necessary information for evaluating the stage of NPC.

Currently, the staging system of NPC is the eighth edition of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) TNM Classification, based on the tumor-node-metastasis (TNM) criteria (**Table 1**) [30]. This system is an important guideline for the treatment, as well as the basis for evaluating the treatment outcomes of patients. With the development of imaging techniques and treatment approaches for NPC patients, the TNM classification systems will be significantly refined again. Notably, monitoring plasma EBV DNA and circulating tumor cells (CTC) can further improve the prediction of prognosis [31, 32].

Primary tumor (T)	
T_X	Primary tumor cannot be assessed.
T_0	No tumor was identified, but EBV positive cervical node(s) involvement.
T_1	Nasopharynx, oropharynx, or nasal cavity without parapharyngeal extension.
T_2	Parapharyngeal extension, adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles.
T_3	Bony structures (skull base, cervical vertebra) and/or paranasal sinuses
T_4	Intracranial extension, cranial nerve, hypopharynx, orbit, extensive soft tissue involvement (beyond the lateral surface of the lateral pterygoid muscle), parotid gland.
Lymph nodes (N)	
N_X	Regional lymph nodes cannot be assessed.
N_0	No regional lymph node metastasis.
N_1	Unilateral cervical, unilateral or bilateral retropharyngeal lymph nodes, above the caudal border of cricoid cartilage;≤6 cm.
N_2	Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the caudal border of the cricoid cartilage.
N_3	>6 cm and/or below the caudal border of the cricoid cartilage (regardless of laterality).
Distant metastasis (M)	
M_0	No distant metastasis.
M_1	Distant metastasis.
Group staging	
I	T1N0M0
II	T1N0M0; T2N0-1 M0
III	T1-2N2M0; T3N0-2 M0
IV	IVA: T4 or N3M0; IVB: Any T Any N M1

Table 1.
The UICC/AJCC staging system for nasopharyngeal carcinoma (8th edition).

3.3 Pathological classification

Histologically, NPC cells are regarded to be squamous in origin, but with a high background of lymphoid cells. According to the world health organization (WHO), NPC was categorized into three types: nonkeratinizing carcinoma, keratinizing squamous cell carcinoma, and basaloid squamous cell carcinoma [33]. In the endemic areas, over 95% of the cases belong to the nonkeratinizing type, while less than 5% belong to the keratinizing squamous cell carcinoma type, and basaloid squamous cell carcinoma type is extremely rare. On the contrary, in nonendemic western countries like the United States, keratinizing squamous cell carcinoma accounts for more than 25% of NPC cases [34, 35].

4. Treatment of NPC

NPC is relatively sensitive to ionizing radiation, and radiation therapy (RT) is the mainstay modality of curative-intent treatment for patients with the non-disseminated disease. The 5-year disease-specific survival rate in stage I NPC is now expected to be around 95% with IMRT alone [36]. By introducing concurrent chemoradiotherapy to patients with locoregionally advanced diseases, the 5-year overall survival rate was around 60-80% recently [37]. Researchers are making exploratory effects on molecular-targeted medicine and immunotherapy in the treatment of NPC. Several encouraging results from clinical trials will be discussed below.

4.1 Radiation therapy

The ideal modality of RT should fully cover the complex-shaped gross tumor with high doses needed for eradication while providing maximum sparing for adjacent organs. Photon-based radiotherapy techniques have evolved from conventional two-dimensional (2D) radiotherapy to 3D conformal radiotherapy and intensity-modulated radiation therapy (IMRT). Charged particle therapy is gaining more and more attention in the treatment of NPC, especially the locoregionally advanced disease.

IMRT technique allows for the conform radiation dose to deliver precisely to a gross tumor and minimize the dose to adjacent normal tissues by controlling the intensity of the radiation beam. There is compelling evidence from numerous randomized controlled trials (RCTs) reporting a superiority of IMRT over conventional techniques. Over 90% 5-year locoregional control rate and 80% of overall survival rate were achieved, along with significant protection of the saliva gland and reduction of other radiation-induced complications [38–44]. Compared with 2D or 3D radiotherapy, IMRT was significantly associated with better 5-year locoregional control and overall survival [45].

Despite the rapid improvement in radiotherapy techniques, successful RT of NPC relies on precise delineation and accurate dose delivery to the gross tumor volume (GTV), clinical target volume (CTV), and critical organs at risk (OARs) [46]. Advanced imaging techniques, such as MRI, CT, 18F-fluorodeoxyglucose (18F-FDG)-positron emission tomography (PET)/CT, and fusion of images from different techniques with the planning CT images of radiotherapy, together with endoscopy and clinical examination are most commonly used for facilitating primary GTV delineation. The international guidelines and consensus have recently been propounded for the delineation of CTV and OARs, allowing improved consistency and providing helpful references in NPC radiation management [41, 47–49].

Besides, the application of automation, deep learning, and artificial intelligence has been investigated currently [50–52]. It will be an integral piece of RT to improve accuracy, consistency, and cost-efficiency while reducing labor-intensive costs soon.

4.2 Chemotherapy in non-metastatic NPC

While stage I NPC is treated by IMRT alone with little doubt, locoregionally advanced disease (stage II to stage IVB) requires the combination of chemotherapy with comprehensive consideration [53, 54] (**Table 2**). The modalities of chemotherapy include concurrent chemoradiotherapy (CRT), adjuvant chemotherapy, and induction chemotherapy, while the regimens vary between studies/centers.

For stage II NPC, the National Comprehensive Cancer Network (NCCN) guideline suggests RT plus concurrent chemotherapy ± sequential chemotherapy, whereas the EHNS-ESMO-ESTRO clinical practice guideline proposes concurrent chemoradiotherapy (**Table 2**). The controversy between the two guidelines may partly reflect the contentious evidence from numerous clinical trials based on different RT techniques [2, 55–57]. In the IMRT era, many recently retrospective studies and meta-analyses demonstrated that RT alone might be sufficient for patients with stage II disease to achieve desirable long-term outcomes and avoid increased toxicity [58–61].

There is a consensus among guidelines that concurrent chemoradiotherapy ± sequential chemotherapy may be mainstay treatment in stage III to IVB diseases with a remarkable survival benefit [2, 48]. Recently, a study based on 7,940 patients from 27 trials suggests that patients treated with induction-concurrent CRT (IMRT) gained the highest overall survival, progress-free survival, and distant metastasis-free survival [62]. To date, induction-concurrent CRT is becoming more and more important in treating locoregionally advanced NPC and adopted by many treatment centers. Several ongoing trials (NCT01536223, NCT01872962, NCT02512315, NCT 03306121, and NCT03503136) comparing induction-concurrent CRT and concurrent CRT with detailed combinations of different regimens, such as taxane, cisplatin, and 5-fluorouracil are anticipated, which results would provide further evidence for clinical practice.

Stage (8th Ed[a])	**NCCN (v2.2020[b])**	**EHNS-ESMO-ESTRO (2012[c])**
Stage I	Radiotherapy (RT) alone	RT alone
Stage II	RT plus Chemotherapy (C): Concurrent C + Adjuvant C (2A[d])	RT + C: Concurrent (I, B[e])
Stage III	or Induction C + Concurrent C (2A)	RT + C: Concurrent ± Adjuvant (I, A)
Stage IVA-B	or Concurrent C (2B)	RT + C: Concurrent ± Adjuvant (I, A) or Induction C + Concurrent C (II, B)
Stage IVC	C alone or RT + C	

[a] *Stage: American Joint Committee on Cancer (AJCC) – TNM Staging System for the Nasopharyngeal Carcinoma (8th ed. 2017).*
[b] *National Comprehensive Cancer Network (NCCN) Guidelines Version 2.2020.*
[c] *EHNS-ESMO-ESTRO Clinical Practice Guidelines (2012).*
[d] *NCCN Categories (1-3) of Evidence and consensus.*
[e] *Level of evidence (I-V) used in the EHNS-ESMO-ESTRO Clinical Practice Guidelines.*

Table 2.
Treatment strategies for different stages.

4.3 Disease surveillance, management of residual/recurrent disease

Close follow-up for NPC patients is essential in terms of disease surveillance. Despite relatively desirable treatment outcomes among solid cancers, unfortunately, about 10-20% of NPC patients will suffer from residual disease or develop recurrent disease after primary treatment, T4 disease among them is reported with up to 45% local recurrence rate [43, 63–67]. Early detection is critical given that extent of relapse determines the chance of salvage, and patients with T1-T2 recurrent disease are more likely to achieve long-term benefit [68, 69]. Initial assessment of residual disease is usually conducted at 12 weeks after the completion of RT or CRT [70, 71]. A detailed history and physical examination, nasopharyngoscopy (with/without biopsy), and radiation imaging (CT/MRI/18F-FDG-PET-CT) are highly recommended in a comprehensive response assessment. Recently, the post-treatment plasma EBV DNA is considered for monitoring for NPC in the context of locoregional failure, distant metastasis, and survival [72].

Emerging evidence suggests that aggressive salvage modalities might increase the chances of better prognosis among patients with recurrent NPC [68, 73, 74]. Neck dissection is widely recommended for isolated regional failure. Re-irradiation is considered for a tumor that recurs more than one year after the completion of primary RT. In contrast, salvage surgery is esteemed if the one recurs within one year and is resectable.

4.4 Management of metastatic disease

Patients with metastatic NPC have various clinical characteristics and outcomes. Around 10% of newly diagnosed NPC patients present with synchronous distance metastases. Unfortunately, up to 15%-30% of the non-metastatic NPC patients will experience distant failure after primarily curative treatment [2, 48]. Compelling evidence suggests these patients may achieve a median overall survival of 10-15 months by receiving palliative chemotherapy. The overall survival can be improved among those who are indicated for locoregional RT and local treatment of metastatic lesions [63, 75–81]. Thus, a personalized treatment strategy is necessary for metastatic NPC. Researchers and clinicians have made a hard effort to build up predictive models for prognosis to stratify risk groups and provide treatment strategies accurately [82–87].

Recommending by NCCN guideline, the first-line regimens of systemic therapy for NPC patients with recurrent, or unresectable, or metastatic disease are cisplatin plus gemcitabine. Other recommended regimens include the combination of cisplatin/5-fluorouracil, cisplatin or carboplatin/docetaxel or paclitaxel, carboplatin/cetuximab, gemcitabine/carboplatin, as well as the single-use of them. A recent view suggests that neither VEGFR nor EGFR targeting therapies are recommended as high priority for recurrent and/or metastatic NPC, with unimpressive response rates around 10% or less [67, 88–93]. Reported toxicities of anti-VEGF therapy and anti-EGFR therapy can be severe and life-threatening, which should not be neglected.

Remarkably, several single-arm trials evaluating immunotherapy targeted the programmed death 1/programmed death-ligand 1 (PD1/PD-L1) pathway in recurrent/metastatic NPC patients have shown promising outcomes [94–96]. In principle, NPC tumors are featured by high PD-L1 expression and abundant infiltration of non-malignant lymphocytes, suggesting the feasibility of immune checkpoint blockade therapies in NPC patients [97–100]. Some ongoing phase 3 trials investigating anti-PD-1 therapies among treatment naïve locoregionally advanced disease, recurrent, or metastatic disease, will improve clinical practice [2]. Likewise, a phase

1 trial of a recombinant vaccinia virus (MVA-EL), which encodes an EBNA1/LMP2 fusion protein designed to boost T-cell immunity to these antigens, has shown clinical efficacy in heavily pretreated NPCs [101]. Evidence from phage 2/3 RCTs on immunotherapies targeting EBV and/or PD1/PD-L1 is awaited to manage locoregional, recurrent, and metastatic NPC in the near future.

5. Conclusion

Early diagnosis and early therapy is the most effective method to improve the curative effect of NPC. It is necessary to strengthen the population-based screening of NPC in the endemic region and optimize the screening methods to elevate efficiency. Improving the treatment approach is critical as well. With the great progress in staging systems, radiotherapy techniques, and concurrent chemotherapy, the locoregional control and overall survival of NPC patients have improved substantially. Meanwhile, molecular targeted therapy and immunotherapy have gained much interest and are now being introduced to many clinical trials. Although encouraging outcomes are achieved, treatment-related toxicities, residual/recurrent disease, and metastatic disease are still crucial challenges in managing NPC, worthy of further attention and effort.

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Conflict of interest

The authors declare no conflict of interest.

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