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Review

Recent advances in early detection of nasopharyngeal carcinoma

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Abstract
Nasopharyngeal carcinoma (NPC) arises from the mucosal epithelium of the nasopharynx and is frequently located in the pharyngeal crypts. This is a highly aggressive malignant tumor that frequently leads to distant metastases in many cases and poses a significant public health challenge, particularly in certain geographic regions globally. This review discusses the epidemiology, risk factors, diagnosis, and treatment options for NPC, emphasizing the importance of early detection and comprehensive management strategies in improving patient outcomes. Moreover, the article explores the intricate mechanisms that cause NPC. Comprehending these fundamental principles can assist in creating specific prevention and therapy approaches for NPC. Recent advances in diagnostic methods, including imaging tests and molecular biomarkers, are emphasized to improve early diagnosis and individualized treatment strategies for individuals with NPC. The review also explores the most recent advancements in treating early-stage (stage I and II) NPC patients, highlighting the changing landscape of individualized therapy approaches for this particular set of patients.

Keywords Nasopharyngeal carcinoma · Early detection · Personalized treatment · Diagnostic techniques · Risk factors

1 Introduction

Nasopharyngeal carcinoma (NPC) is a cancer that develops from the squamous epithelial cells lining the lateral wall of the nasopharynx, exhibiting distinct epidemiology, pathology, clinical features, and treatment outcomes [1]. NPC is most prevalent in Southern China, South East Asia, Northern Africa, Greenland, and Alaska but has a very low occurrence in Western countries [2, 3]. It was so widespread in Guangdong Province in southern China during the early twentieth century that it was dubbed 'Guangdong cancer' [4]. Southeastern Asian communities have an incidence rate of over 15 per 100,000 person-years, while in the United States, the incidence rate is below 1 per 100,000 person-years [5]. Demographic studies show that men are two to three times more likely to acquire NPC than women, with the peak age of disease occurrence being 45 years old [6]. The WHO categorizes it as non-keratinizing and keratinizing kinds, as well as basaloid squamous cell carcinoma, based on the level of differentiation. Non-keratinizing tumors are classified as either undifferentiated or differentiated [5]. The keratinizing subtype is rare globally, representing fewer than 20% of cases, and is uncommon in locations where the disease is prevalent. The non-keratinizing subtype is the most common in endemic regions, accounting for over 95% of cases, and is strongly linked to Epstein-Barr virus (EBV) infection [7]. Precise pathological categorization is crucial for selecting suitable treatment strategies. Early disease detection necessitates a high clinical acumen, with diagnosis mostly dependent on histological analysis. The current treatment for early-stage NPC has excellent control, a good prognosis of up to 90%, and is effective in controlling the disease. The appearance of

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distant metastases is uncommon. [2] Risk factors for NPC may include EBV infection, alcohol consumption, exposure to dust and formaldehyde, hereditary factors, smoking, and the intake of salted fish or other preserved foods.

The primary method for evaluating the risk of patients with NPC is the utilization of the tumor-node-metastasis (TNM) system, which serves as a valuable tool for prognostic purposes. [8] Tumor heterogeneity leads to considerable variations in overall survival (OS) across NPC patients, even those with the same clinical stage. Using TNM staging as the only basis for treatment decisions is not ideal. Age, gender, comorbidities, EBV DNA levels, lactate dehydrogenase (LDH) levels, albumin (ALB) levels, hemoglobin (HGB) levels, and C-reactive protein (CRP) levels are essential parameters for the diagnosis of NPC [8, 9]. The advancement of technology in managing NPC, particularly the use of intensity-modulated radiation (IMRT), has greatly enhanced the local control of this type of cancer. The primary reason for therapy failure is distant metastases [10]. Due to the deep anatomical location of the nasopharynx, early local lesions are challenging to detect, often leading to the diagnosis of NPC in its middle or late stages [11, 12]. A poor prognosis and unfavorable result are linked to up to 80% of NPC patients are diagnosed at advanced stages (clinical stages III and IV) and 10% at distant metastases [1]. The advancement of health education and the introduction of early cancer screening techniques like narrow band imaging, plasma EBV DNA screening, and nasopharyngeal brushing samples detection have significantly enhanced the detection of early-stage NPC in high-risk populations, leading to a notable rise in the incidence of stage II NPC [6]. After treatment, the 5-year disease-specific survival rate (DSSR) of stage II NPC is 97.3% [12, 13]. The 3-year failure-free survival rate (FFSR) for newly diagnosed nonmetastatic NPC is more than 80% [14]. Early detection and timely treatment of NPC are important for preventing disease progression, improving patient prognosis, reducing mortality, and reducing the healthcare burden. This article provides a comprehensive overview of the pathology and risk factors of NPC, a complete summary of the latest advances in the field of early diagnosis of NPC, and an update of the latest treatments for early-stage NPC in order to improve the theoretical framework for the management of these patients.

2 Pathology and risk factors

Risk factors for NPC may include EBV infection, dietary habits, lifestyle choices, smoking, exposure to environmental and occupational risks, genetic susceptibility (particularly chromosomal regions and genes), family history of NPC, and ethnicity (Fig. 1) [15]. The National Comprehensive Cancer Network (NCCN) Oncology clinical practice recommendations identify several cancer susceptibility genes, including BRCA1, BRCA2, and TP53, and advocate assessing cancer risk in patients with a family history of NPC [16]. Genome-wide association studies (GWASs) are mostly undertaken in sporadic cases of NPC. Most of the common SNPs associated with NPC identified by GWASs are located in non-coding regions of susceptibility loci, such as the human leukocyte antigen (HLA) locus and non-HLA loci including 3q26 (MECOM), 5p15.33 (CLPTM1L/TERT), 9p21.3 (CDKN2A/CDKN2B), 13q12 (TNFRSF19), and 16p13 (CIITA). A recent study discovered two more susceptibility loci for NPC development, located at 9q22.33 and 17q12 [17, 18]. Research has indicated that the deletion of chromosome 3p and 9p regions is an initial occurrence in the progression from normal nasopharyngeal epithelium to a transformed state [19]. GWAS found a consensus in the HLA locus on 6p21.3 [20]. Both HLA class I and class II alleles, such as HLA-A2, -A11, -B13, -B46, -B58, -C03, -C04, -C07, -DRB1*03, -DRB1*09, and -DRB1*12, were linked to NPC in a case–control study [21]. Patients with NPC with MHC Class I abnormalities are known to have a poor survival prognosis [22]. Polymorphisms in CYP2E1, mutation of p53 codon 72 Arg > Pro, CYP2A6, and the absence of GSTM1 and/or GSTT1 were linked to a 2- to fivefold higher likelihood of developing NPC [24, 25]. Research indicates that the hOGG1 rs1052133 polymorphism may be involved in the development of NPC, particularly in females over 40 years old and individuals with no history of smoking [26]. Furthermore, abnormal methylation of tumor suppressor genes (TSG) such as cadherin 4 (CDH4), cyclin-dependent kinase inhibitor 2A (CDKN2A/p16), and RAS association domain family protein 1A (RASSF1A) occurs early in NPC development [27].

Salt-preserved food contains nitrosamines, bacterial mutagens, direct genotoxins, and chemicals that reactivate EBV. The CYP2E1 polymorphism found in preserved foods induces NPC by activating pre-carcinogens like nitrosamines [28]. When compared to no consumption or very little consumption, the relative risk linked to NPC consumption in studies of Chinese people was typically between 1.4 and 3.2 for weekly consumption and between 1.8 and 7.5 for daily consumption [24]. One risk factor is smoking. Tobacco contains active carcinogenic byproducts called nitrosamines, which can damage DNA and induce persistent inflammation of the nasopharyngeal mucosa [29]. Regarding alcohol intake, opinions differ. Furthermore, a number of papers point to increased risks associated with wood dust, working in poorly ventilated spaces, formaldehyde inhalation from the printing sector, and exposure to cotton dust and combustion in the textile industry [23]. In general, men are more likely than women to get NPC, and women also have a lower death rate

Fig. 1 Risk factors for NPC

from the disease. This could be associated with biological differences between the sexes in terms of lifestyle, behavioral factors, delayed diagnosis, and sex hormones [30].

As a group I carcinogen for NPC, the human gammaherpesvirus EBV has been categorized by the International Agency for Research on Cancer [31]. Local non-keratinized NPC is thought to be primarily caused by EBV infection [2]. Acquired during infancy, it replicates briefly in nasopharyngeal epithelial cells before actively replicating in B lymphocytes after acute infection and remaining latent in memory B cells for the duration of life. In nasopharyngeal cancer cells, EBV genomic fragments and latent proteins linked to immune recognition evasion, such as EBNA1, LMP1, and LMP2, were found [32]. It has been revealed that LMP1 links the C-Jun N-terminal kinase (JNK) and NF-κB signaling pathways, as well as signaling cascades, to play a significant role in the pathogenesis of NPC [18]. Numerous loss-of-function mutations were found in NFKBIA, CYLD, and TNFAIP3, three NF-κB signaling negative regulators that have a major effect on NF-κB activity and NPC cell proliferation [19]. Additionally, BNRF1 V1222I and BALF2 I613V, two high-risk NPC mutations, are present in EBV-peptides [20]. An in-depth study of molecular abnormalities and genomic positioning in individual or subgroups of NPC patients to identify reliable biomarkers for developing precisely targeted therapies that may lead to improved treatment results, enhanced quality of life, and more cost-effective healthcare.

3 Current nasopharyngeal carcinoma screening, diagnosis and limitation

Although there are no specific clinical signs of NPC, there are risk factors such as headaches, facial numbness, neck lumps, nasal congestion, epistaxis, and otitis media that should raise suspicions about the disease. NPC has a poor prognosis due to the late start of lesions, inadequate knowledge of molecular causes, a lack of appropriate early detection indicators, and a poor response to current therapy [33]. In 2020, Zhongshan People's Hospital survey figures show that the 5-year overall survival rate for stage IV patients is 67.2%, whereas the overall survival rate for stage I patients is 100% [15]. Early detection of NPC is crucial. We outline the latest advancements in the early detection of NPC to enhance its diagnostic accuracy, reduce patients' suffering, and enhance their quality of life.

Nasopharyngeal endoscopy, along with histological analysis of suspicious lesions, remains the most reliable way for diagnosing NPC. Clinical symptoms and family history can also offer valuable insights [14]. Tumor lining in the submucosa or tiny early tumors might cause false negatives in endoscopic examinations. Imaging assessment is advised to ascertain the cancer stage prior to diagnosis, utilizing techniques including multislice computed tomography (CT), magnetic

resonance imaging (MRI), and Positron emission tomography-computed tomography (PET–CT) [2]. Three prospective investigations by King AD and Liu Z teams found that MRI is more sensitive than endoscopy in detecting almost all tumors, including those not visible during endoscopy. Furthermore, the significant negative predictive value demonstrated by MRI is useful for ruling out NPC [34–36]. PET-CT is more accurate in detecting tiny lymph node metastases, while ultrasound-guided FNAC(fine needle aspiration cytology) is indicated for examining suspected cervical lymph node metastases [37]. PET/MR Dual-modality imaging is more precise in assessing the primary tumor and lymph node staging of NPC compared to MRI and PET/CT. It is anticipated to become the single-step method for staging NPC [38]. These methods are mostly utilized to diagnose patients suspected of having NPC and are not ideal for early detection or large-scale screening of the disease. The use of plasma anti-EBV antibody, EBV-DNA detection, nasopharyngeal exocytology, and cell-free DNA (cfDNA) methylation for early screening of NPC is gaining increasing interest (Fig. 2).

3.1 Serological screening and EBV-DNA detection

Currently, there are three primary targets for detecting anti-EBV antibodies in clinical settings: anti-EBV capsid antigen (VCA IgA), anti-EBV nuclear antigen (EBNA-1 IgA), and early antigen EA-IgA. Enzyme-linked immunosorbent test (ELISA) replaced the conventional immunoenzyme-labeling approach [15]. Two ELISA tests utilizing VCA-IgA and EBNA1-IgA were employed for NPC screening, resulting in a sensitivity of 91.45% and a specificity of 93.45%. The combination of VCA-IgA and EBNA1-IgA showed a more effective screening outcome than either marker alone [39]. A prospective mass-screening study conducted by Liu et al. from May 2008 to February 2009 in Sihui City, China, confirmed that the accuracy of VCA-IgA combined with EBNA1-IgA was the highest, with a sensitivity of 95.3% and a specificity of 94.1% [40]. Due to the heterogeneity of NPC, the primary techniques for early screening of NPC involve detecting various antigens and screening with multiple markers. Plasma EBV-DNA detection offers higher sensitivity and specificity compared to IgA serologic testing for detecting EBV. Chan et al. conducted prospective research to assess the viability of using EBV DNA for early NPC screening. EBV DNA was detected in 1112 individuals, with 309 showing consistently positive results, and 34 of them were diagnosed with NPC. Negative predictive value (NPV) was 99.995% [41]. Lam et al. later incorporated sequencing-based DNA analysis, resulting in an increase in the positive predictive value (PPV) of plasma EBV DNA from 11.0 to 19.6% [42]. A recent study compared the diagnostic accuracy of EBV antibodies and DNA load. The EBV antibody had a sensitivity of 88.4% and a specificity of 94.9%, while the EBV DNA load had a sensitivity of 93.2% and a specificity of 98.1% (Table 1). The sensitivity and specificity of EBV-DNA copy number varied across different studies, with results that were not comparable among laboratories due to variations in DNA extraction reagents and protocols, differences in the selection of amplification fragments, variations in polymerase chain reaction (PCR) reagents and instruments, and discrepancies in standards and standard curves. Laboratories can collaborate to establish a standardized protocol for plasma EBV DNA testing and harmonize the quantitative testing methodologies for EBV-DNA. This would help minimize the discrepancies in test results across different laboratories. Standardized PCR tests are required to target single-copy

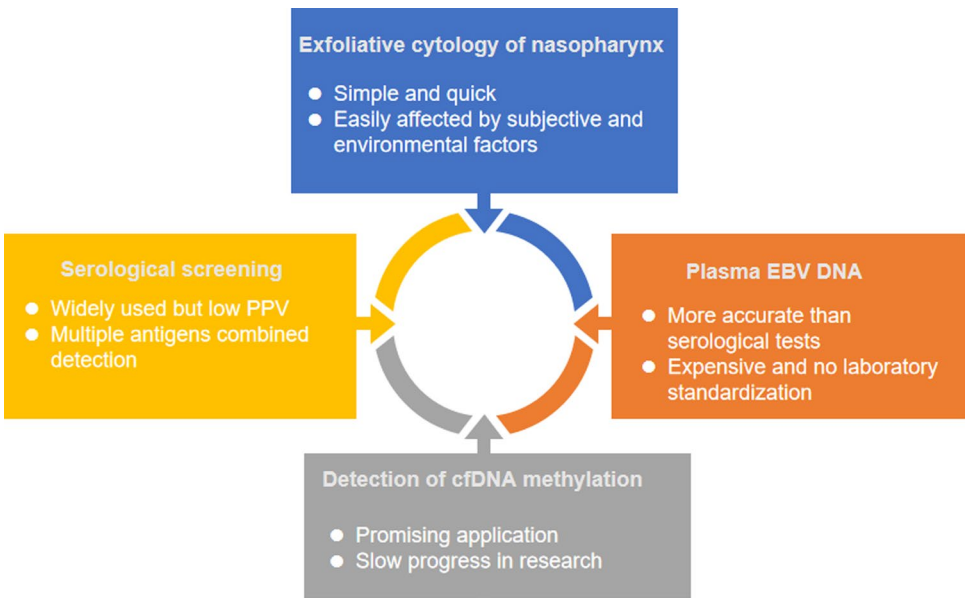

Fig. 2 Current clinical early screening methods of NPC

Table 1 Sensitivity, specificity, and PPV of the studies

Study	Sample size	Marker	Sensitivity (%)	Specificity (%)	PPV	NPV (%)	References
Rao et al	10254[a]	VCA-IgA and EBNA1-IgA	91.45	93.45	–	99.79	[39]
Liu et al	528[b]	VCA-IgA and EBNA1-IgA	95.3	94.1	–	97.24	[40]
Chan et al	20,174	EBV DNA	97.1	98.6	11%	99.995	[41]
Lou et al	5064[c]	EBV antibody	88.4	94.9	–	94.61	[43]
		EBV DNA load	93.2	98.1	–	96.94	

[a]234 NPC patients + 10,020 healthy individuals

[b]191 NPC patients + 337 controls

[c]2522 individuals were measured by EBV antibodies with enzyme-linked immunosorbent assay (EBV antibody score), 802 cases + 1720 controls; 2542 individuals were measured by EBV DNA load with real-time PCR, 797 cases + 1745 controls

EBV genes like EBNA-1 and multicopy EBV genes like BamHI-W. The BamHI-W fragment that targets EBV DNA has greater sensitivity compared to other EBV targets. Furthermore, EBV-DNA positivity varies over time in healthy people, whereas plasma EBV-DNA remains present in patients with NPC. Consequently, conducting repeat tests on patients who initially test positive for EBV-DNA can assist in distinguishing true positives from false positives. On the contrary, the two ELISA kits utilized for producing EBV antibody scores are commercially accessible, readily standardized, and can be more simply utilized in the laboratory [15, 27, 43]. Both assays must be thoroughly evaluated for early screening of persons in high-risk areas. In areas where NPC is common, it is advisable to employ plasma EBV DNA together with endoscopy and MRI to diagnose early asymptomatic NPC [44].

3.2 Cell-free plasma EBV DNA and DNA methylation

Recently, circulating cell-free DNA (cfDNA) liquid biopsy methods have become increasingly popular. Liquid biopsy involves analyzing tumor DNA from cell-free DNA fragments released into the bloodstream during apoptosis, necrosis, and active secretion. Examining DNA methylation in cell-free DNA enables the noninvasive and real-time evaluation of disease progression in patients with both early-stage and late-stage cancer [15]. The primary epigenetic occurrence is hypermethylation of the polychromosomal 3p TSG. Abnormal DNA hypermethylation in NPC results in the inactivation of TSG located on chromosomes, such as ADAM, BLU, DLEC1, GNAT1, LARS2, LTF, MLH1, RASSF1A, RAR-β, TIG1, VLH1, PTPRG, and ITGA9, contributing significantly to the development of this type of cancer [45]. In 2013, Tian et al. studied the hypermethylation of five tumor suppressor genes (RASSF1, CDKN2A, DLEC1, DAPK1, and UCHL1) and discovered that they were methylated in 17.5, 22.5, 25.0, 51.4, and 64.9% of the patients, respectively. DNA hypermethylation of TSG in serum is suggested as a reliable technique for diagnosing NPC [46]. Yang et al. evaluated the methylation status of four tumor suppressor genes (RASSF1A, WIF1, DAPK1, and RARβ2) in comparison to an EBV DNA marker. The former exhibited greater sensitivity and specificity compared to the EBV DNA marker in cell-free plasma from NPC patients in early Stages (I and II). Moreover, the amalgamation of both can enhance the sensitivity of early detection of NPC [47]. Xu et al. investigated the methylation rates of RERG, ZNF671, ITGA4, and SHISA3 in NPC using real-time PCR (qAMP) and found that the methylation rates were significantly elevated in NPC. The RERG locus in circulating cell-free DNA was the most effective in detecting NPC, with an accuracy of 73.7%, a sensitivity of 80%, and a specificity of 100% (Table 2) [48]. Currently, a new technology for detecting cfDNA methylation using next-generation sequencing has been developed and has demonstrated its benefits in clinical applications for early cancer detection [15]. In the future, it is anticipated that more sophisticated analytical methods will become widespread, and extensive clinical investigations will be conducted.

3.3 Exfoliation cytology and nasopharyngeal swabs

To decrease the incorrect positive diagnosis of serological detection of NPC and lessen the need for frequent monitoring, using nasopharyngeal (NP) brushing to detect EBV DNA load or the methylation status of EBV DNA C promoter as a secondary screening test for individuals at high EBV serologic risk has garnered significant interest [49, 50]. In 2015, Chen and his team carried out a prospective, population-based cohort analysis. Specimens were collected from 905 participants who had serum immunoglobulin A (IgA) antibodies against viral capsid antigen (VCA) titers ≥ 1:5, and these specimens were subsequently used for quantitative PCR testing. EBV DNA tested positive in 89% (802 out

Table 2 Hypermethylation of markers

Study	Sample size	Marker	Sensitivity	Specificity (%)	NPV (%)	References
Tian et al	81[a]	RASSF1	17.5%	95.1	54.2	[46]
		CDKN2A	22.5%	97.6	56.3	
		DLEC1	25.0%	92.7	55.9	
		DAPK1	51.4%	90.2	68.5	
		UCHL1	64.9	80.5	71.7	
Yang et al	87[b]	RASSF1A, WIF1, DAPK1, and RARβ	64.6%	96	–	[47]
		EBV DNA	51.2%	88	–	
Xu et al	108[c]	RERG	60.0%	100.0	–	[48]
		ZNF671	64.7%	80.0	–	
		ITGA4	75.0%	60.0	–	
		SHISA3	74.1%	90.0	–	

[a]40 NPC patients + 41 healthy subjects

[b]23 of stage I, 64 of stage II

[c]79NPC patients + 29 healthy subjects

of 905) of the subjects. Eight patients with recently diagnosed NPC showed a notable rise in EBV levels, with 87.5% (7/8) having early-stage NPC. Measuring EBV viral load in the nasopharynx of high-risk individuals could decrease the need for frequent monitoring and could be incorporated into a screening protocol for NPC in high-risk groups [51]. One thousand one hundred eleven subjects who tested positive for VCA/EBNA-1 IgA were assessed, and nasopharyngeal swabs were taken to measure EBNA1 gene EBV DNA load. The reflex test for Nasopharyngeal swab EBV DNA is anticipated to identify high-risk people based on serology, leading to around a 40% decrease in referrals compared to using serologic screening alone while maintaining a similar level of sensitivity [52].

EBV was found in the nasopharyngeal epithelium as a latent type II infection marked by hypermethylation of the C promoter (Cp), which serves as a reliable signal for detecting NPC with sensitivity and specificity above 90% [50]. Zhang et al. conducted a study to assess the possibility of identifying methylation markers (RASSF1A and DAPK) of tumor cells in nasopharyngeal swabs using MMSP (multiplex methylation specific-PCR) for diagnosing NPC. The study found that the sensitivity of identifying methylation markers in nasopharyngeal swabs for diagnosing NPC was 98%. The specificity was 100%, matching that of the biopsy [53]. A meta-analysis was conducted to assess the significance of RASSF1A methylation. The total frequency of RASSF1A methylation in the case group was 59.68%, while in the control group was 2.65%. This meta-analysis is the first to offer scientific proof that RASSF1A methylation can serve as a diagnostic, prognostic, and early screening biomarker for NPC [54]. A recent study discovered that methylation of H4C6, RASSF1A, and SEPT9 genes is more prevalent in NPC. The combination of SEPT9 and H4C6 shows the most effective diagnostic outcome (Table 3) [55]. The conclusions from individual investigations must be validated with bigger cohorts. Nasopharyngeal swab/ brushing could serve as a screening technique for NPC because of its simplicity and convenience.

Several studies have demonstrated that aberrant alterations in circulating miRNAs expression can differentiate NPC from healthy cells [56]. The BamHI-A rightward transcripts (BART), a group of miRNAs encoded by EBV, are strongly associated with the development of NPC. Jiang et al. suggested that detecting miRNA BART2-5p could enhance the PPV of extensive serologic screening. It has a sensitivity of 90.9% and a specificity of 54.5% in differentiating preclinical NPC cases from serologically high-risk controls with elevated EBV VCA IgA and EBNA-1 IgA levels [57]. A study measured the copy counts of miR-BART2-5p, miR-BART17-5p, miR-BART18-5p, and BamHI-W DNA before and after therapy. The study results indicated that the circulating BamHI-W DNA copy number was a more effective biomarker than the three tested BART-miRNAs for the first diagnosis of NPC. Identifying miR-BART17-5p posttreatment can provide a possible indicator for unfavorable prognosis [58]. Future research is anticipated to utilize circulating miRNAs expression studies for early NPC screening, enhancing PPV in conjunction with serological screening and EBV-DNA detection.

Table 3 EBV DNA load or methylation status of EBV DNA C promoter detected by nasopharyngeal brushing

Study	Sample size	Marker	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	References
Chen et al	905[a]	EBVDNA load	87.5	98.9	41.2	99.9	[51]
Liu et al	1111[b]	EBV DNA load	72.4	97.6	97.6	97.6	[52]
Zhang et al	69[C]	EBNA1/LMP1/RASSF1A/ DAPK/ β-ACTIN	98	100	–	95.2	[53]
Lao et al	1688[d]	RASSF1A	46.73	100	–	–	[54]
Qian et al	93[e]	RASSF1A	79.3	85.9	71.9	90.2	[55]
		H4C6	79.3	90.6	79.3	90.6	
		SEPT9	65.5	82.8	63.3	84.1	

[a]905 VCA/IgA antibody titers ≥ 1:5, 802 subjects showed positive EBV DNA in nasopharyngeal swab

[b]1111with positive VCA/EBNA1-IgA antibodies detected by nasopharynx swab; 20 NPC cases detected from 317 high-risk individuals and 4 NPC cases from 794 medium-risk individuals

[c]49 NPC patients and 20 noncancerous controls

[d]1165 NPC samples, and 523 from non-cancerous samples

[e]29 NPC cases and 64 healthy subjects

4 Treatment for stage I or stage II disease

Local disease, categorized as early stage I disease, includes patients with a tumor confined to the nasopharynx, or adjacent oropharynx, nasal cavity, without parapharyngeal involvement (T1), and no lymph node (N0) or distant metastases (M0). Stage II (T1/T2, N1 or T2 N0), sometimes referred to as intermediate illness, is not classified as an advanced situation [33]. Advancements in early diagnosis have led to an increasing number of people being diagnosed with stage I or II.

4.1 The role of radiation therapy (RT) and intensity-modulated radiation therapy (IMRT)

RT has been the primary treatment since the 1950s due to its radiosensitive nature and deep-seated anatomic placement [59]. Radiotherapy techniques have evolved, with IMRT demonstrating better results than 2DRT (two-dimensional radiotherapy) and 3DRT (three-dimensional radiotherapy). With the development of the RT technique, a local control of > 90% was achieved in stage I/II NPC patients, the 5-year OS of non-metastatic NPC population has increased to approximately 80%. 2,450 individuals with NPC were included in the trial, with 157 of them receiving treatment with IMRT. The OS and locoregional control (LRC) rates for stage I/II NPC patients treated with IMRT were 100, 98, 96, 94, and 94% for OS and 100, 98, 96, 96, and 96% for LRC at 1, 2, 3, 4, and 5 years, respectively [60, 61]. Chen et al.'s study found that IMRT showed a better therapeutic ratio than 2DRT in patients with NPC after a 10-year follow-up, leading to significant improvements in LFFS (local failure-free survival), FFS(failure-free survival), and OS. The occurrence of severe temporal lobe necrosis, cranial neuropathy, eye damage, ear damage, neck soft tissue damage, trismus, and dry mouth was notably reduced in the IMRT group compared to the 2DRT group [62]. IMRT alone is the recommended treatment for stage I NPC and offers the best local recurrence-free survival(LRFS). Lee et al. assessed nine patients with stage I illness who had treatment with IMRT exclusively. None of these patients experienced locoregional failure throughout a median follow-up period of 2.6 years [63]. Treatment for stage II NPC involves radiotherapy with or without concurrent chemotherapy, depending on the risk of disease recurrence.

Despite advancements in radiation therapy techniques, patients may still face both immediate and delayed side effects. Significant modifications in radiation therapy for NPC now allow for the option of avoiding treatment to both sides of the neck, instead offering selective radiation to specific areas in the node-negative neck, such as retropharyngeal lymph nodes and levels II, III, and VA [64]. The most recent meta-analysis found that upper-neck irradiation showed comparable OS, distant metastasis-free survival (DMFS), and relapse-free survival (RFS) to whole-neck irradiation. There were no differences in acute and late toxicity between upper-neck irradiation and whole-neck irradiation [65]. Pretreatment EBV-DNA levels are identified as prognostic markers affecting the 5-year survival rate in early-stage

IMRT. A cut-off point of < 4000 copies/mL corresponds to a 91% survival rate, whereas > 4000 copies/mL corresponds to a 64% survival rate [66]. Primers and probes that target the BamHI-W region of the EBV genome demonstrated predictive significance in measuring EBV DNA burdens in plasma or serum before and after treatment. In regions where a disease is common, the suggested threshold for therapy initiation ranges from 1500 to 4000 copies/ml. Pre-treatment EBV DNA's prognostic significance has been documented in non-endemic areas using PCR amplification of the EBNA-1 protein gene [44]. Post-treatment EBV-DNA levels are important for predicting distant metastases and categorizing patients for additional treatment or monitoring. Zhou et al. gathered data on the remaining plasma EBV DNA levels of 300 patients after 3 months of IMRT. Analysis revealed that EBV DNA levels over 688 IU/ml were independently linked to poorer DMFS and progression-free survival [67]. Chen et al. examined 1984 individuals with nonmetastatic NPC who received IMRT. Blood samples were initially taken within 3 months and then at intervals of 3 to 12 months for cfEBV DNA analysis. Among 767 patients with detectable cfEBV DNA, the recurrence rate was 63.8%, substantially higher than in patients without detectable cfEBV DNA. Plasma cfEBV DNA was detected in individuals with NPC, indicating an early indication of tumor recurrence, particularly in cases of extrapulmonary metastases [68]. Radiotherapy is still the preferred treatment method. Future research is expected to continue improving efforts to reduce negative reactions, fine-tune patient care measures, and improve overall prognosis.

4.2 The role of endoscopic nasopharyngectomy (ENPG)

Recent advancements in anatomy knowledge and surgical skills have led to the increasing utilization of endoscopic surgery in the treatment of NPC, either as a supplementary or primary surgical approach. It can prevent the significant trauma of open surgery, lessen patient discomfort, speed up patient recovery post-surgery, and mitigate the adverse effects of radiation therapy. The National Comprehensive Cancer Network recommendations suggest that salvage surgery is the preferred treatment for all cases of locally recurrent nasopharyngeal carcinoma (rNPC) if feasible [69]. Recently, researchers have investigated the use of endoscopic surgery for treating early-stage NPC, and its short-term effectiveness shows promise. The surgical evolution of NPC has progressed through three stages: external nasal approach surgical adjuvant treatment, minimally invasive surgical adjuvant treatment, and minimally invasive surgical radical treatment [70]. Liu et al. gathered 339 individuals with stage I NPC between 2007 and 2017. They administered ENPG to 10 patients who declined radiation, while the other 329 patients underwent IMRT. After a median follow-up of 59 months, the results indicated that all 10 patients who received ENPG had a 100% 5-year OS, 100% LRFS, 100% regional recurrence-free survival rate(RRFS), and 100% DMFS. These rates were comparable to those of the IMRT group, which were 99.1%, 97.7%, 99.0%, and 97.4%, respectively. The ENPG group exhibited reduced medical costs and enhanced quality of life scores in areas such as discomfort, swallowing, dry mouth, and thick saliva compared to the IMRT group [71]. Zhang and colleagues investigated the viability and safety of ENPG coupled with low-dose radiation (LDRT) for treating T1-2 NPC. 37 patients received ENPG + LDRT treatment, and 132 patients received IMRT treatment. There were no statistically significant variances in 5-year OS, DMFS, LRFS, and RRFS between the ENPG group and IMRT group (97.3% versus 97.7%, 97.3% versus 90.2%, 100% versus 95.5%, 100% versus 97.0%, all $P > 0.05$). Moreover, patients in the ENPG group experienced higher quality of life and a reduced incidence of late radiotherapy-related complications [12]. Weng et al. documented the immediate and prolonged prognostic impacts of ENPG when coupled with chemoradiotherapy for early-stage NPC. There were 58 patients who had ENPG combined with chemoradiotherapy and 98 patients who received conventional chemoradiotherapy, and they were matched. The study findings indicated that the surgery group had greater 5-year OS, disease-free survival (DFS), and RFS compared to the nonsurgery group (98.3% versus 91.7%, 98.3% versus 81.4%, 100% versus 90.1%). No cancer remnants were found in the surgical group after the completion of therapy [72].

The study suggests that endoscopic nasopharyngectomy is a viable option for treating early-stage NPC. Thorough case selection, exceptional operator abilities, maximizing negative margins, and precise postoperative follow-up care are all essential. While the short-term effectiveness is promising, the long-term effectiveness requires more observation. Multicenter and large-sample clinical investigations are necessary to confirm the reliability of the effectiveness.

4.3 The role of concurrent chemoradiotherapy (CCRT)

The CSCO guidelines in 2023 recommend radiotherapy as level 1A evidence for treatment of T2N0 with EBV DNA < 4000 copies/mL and small tumor size. CCRT as level 2A evidence; recommend CCRT as level 2A evidence for treatment of N1 in stage II. Radiotherapy as 1A if no lymph node ≥ 3 cm, IV/VB lymph node metastasis, extracapsular lymph node invasion,

EBV DNA ≥ 4000 copies/mL. Consider induction or adjuvant chemotherapy if high-risk features (bulky tumor volume, high serum EBV DNA copy number).

In the management of Stage I disease, RT alone is the preferred treatment approach, while patients with Stage II NPC may benefit from CCRT involving cisplatin at a dosage of 30 mg/m^2 per week in the context of 2D-RT. Notably, when IMRT was utilized, there was no significant difference in survival outcomes between CCRT and RT alone [44]. In 2011, Chen et al. published a randomized research demonstrating notable enhancements in 5-year OS and progression-free survival (PFS) in support of CCRT compared to RT alone for stage II NPC. CCRT decreased distant failure without significantly enhancing LRC compared to RT alone. Subsequently, an updated analysis was conducted to assess the ten-year survival outcomes and toxicity profiles of CCRT versus RT during the 2DRT era. The findings revealed that CCRT could enhance the OS of patients in Stage II without increasing late toxicities compared to standard RT. However, the survival advantages associated with CCRT were primarily observed in the T2N1 population [73, 74]. In a separate investigation, the addition of CCCT to 2DRT significantly improved OS, PFS, and LRFS in cases with T1N1/T2N1, although no significant difference was noted in patients with T2N0 [75]. An analysis of 11 comparative studies involving 2138 patients with stage II NPC determined that CCRT was more effective than 2DRT alone, showing significant improvement in LRFS. Additionally, IMRT alone was found to be superior to CRT, resulting in similar survival rates and fewer severe acute side effects [76, 77]. During the IMRT period, low-risk NPC patients treated with IMRT alone achieved 3-year FFSR comparable to those receiving CCRT [78]. Liu et al. found that CCRT provided a survival benefit over IMRT for high-risk patients (5-year: 89.9% vs. 72.1%; 10-year: 72.5% vs. 34.2%, p = 0.011), but not for low-risk patients [79].

Patients with detectable pretreatment plasma EBV DNA were more likely to undergo induction chemotherapy (IC) compared to those with undetectable levels. A Propensity Score Matching (PSM) analysis demonstrated that IC followed by RT significantly enhanced the 5-year OS and DMFS in patients with stage II NPC compared to CCRT [80]. In two Phase III trials, it was observed that the inclusion of IC led to a significant improvement in the 5-year OS and DMFS for patients with T1-T2N0-N1 NPC [81]. Nevertheless, certain studies present contrasting results and viewpoints. Lai et al. discovered that incorporating IC into CCRT or IMRT alone resulted in reduced PFS and DMFS. They concluded that IC should not be advised for stage II NPC patients [82]. He and colleagues conducted a study that showed that IC-RT and CCRT have comparable survival results and treatment-related toxicities in terms of OS, PFS, DMFS, and LRFS for patients with NPC [83]. Adjuvant chemotherapy(AC) following CCRT is a subject of debate because of its variable effectiveness. Only a minority of individuals see benefits with AC following CCRT due to its negative effects. The retrospective cohort analysis found that adding AC to CCRT did not enhance survival outcomes but was linked to increased occurrences of acute treatment-related toxicities compared to CCRT alone in stage II NPC patients [84]. All these findings must be validated through larger-scale, prospective, multicenter randomized controlled trials.

In addition to assessing cervical lymph nodes, it is essential to consider prognostic factors,including TNM stage, plasma EBV DNA levels, gender, age, and smoking status [85]. This comprehensive evaluation can facilitate risk stratification of the diverse group of patients with stage II NPC and enable personalized chemotherapy tailored to high-risk subgroups**.** The main objective, regardless of the chemotherapy regimen used, is to enhance survival rates while reducing the incidence of adverse events. Undoubtedly, risk categorization improves decision-making and treatment planning.

5 Conclusions and future directions

The growing spread of health information and improvements in diagnostic tools have resulted in a significant increase in the detection of early-stage nasopharyngeal carcinoma (NPC) cases. Individuals diagnosed with NPC at early stages have much better prognosis and treatment outcomes compared to those detected at advanced or late stages. This review thoroughly analyzes the genetic predisposition to NPC, exploring the complex interaction between environmental influences and individual actions. Furthermore, the review explores the utilization of recent molecular markers driven by genetic alterations for mass screening, showcasing the potential for enhanced early detection rates. While current clinical examination methods for suspected NPC patients are characterized by refinement, the strategic screening of high-risk populations undoubtedly facilitates the timely identification and intervention for a greater number of stage I and II NPC cases. Additionally, the review elucidates tailored treatment strategies specifically designed for stage I and II NPC patients. Despite the extensive research efforts devoted to the diagnosis and management of nasopharyngeal carcinoma (NPC), this paper is dedicated to a comprehensive investigation of the etiology, diagnosis, and treatment strategies specifically tailored for early-stage NPC. The primary objective is to significantly enhance the overall early detection rates of NPC and optimize treatment outcomes, thereby alleviating patient morbidity and improving long-term prognosis.

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