# Collaborative breakthroughs in precision diagnosis and treatment of nasopharyngeal cancer: Biomarker-driven screening and endoscopic minimally invasive surgery reshape the new paradigm of early intervention (Review)

E JIN*, WANG LIN* and XIANDONG ZENG

Department of Gastroenterology, The Fourth People's Hospital of Shenyang City, The First Affiliated Hospital of Shenyang University, Shenyang, Liaoning 110000, P.R. China

Received June 10, 2025; Accepted December 8, 2025

DOI: 10.3892/or.2026.9058

**Abstract.** The management of nasopharyngeal carcinoma (NPC), a malignancy with pronounced geographic prevalence in Southeast Asia, is undergoing a paradigm shift toward precision medicine driven by innovations in early detection and minimally invasive therapy. Breakthroughs in Epstein-Barr virus (EBV)-based screening, such as CRISPR-associated protein 12a (Cas12a) amplification-free assays, P85 antibody profiling and T-cell receptor sequencing, now achieve 97.9% sensitivity and 99.3% specificity, enabling ultra-early risk prediction 6-12 months before clinical diagnosis. These advances synergise with multimodal imaging techniques such as narrow-band imaging and I-scan virtual chromoendoscopy, which detect sub-5 mm lesions with 90% sensitivity, revolutionizing screening protocols. Therapeutically, endoscopic nasopharyngectomy (ENPG) exemplifies precision oncology, achieving ≥90% negative resection margins and a 92.1% 5-year survival rate in early-stage NPC while preserving key functions (such as swallowing and hearing) and reducing radiotherapy-related morbidity. Yet, it should be regarded as an indication-bounded option for carefully selected T1-T2 disease in experienced centers and does not constitute a universal substitute for radiotherapy. Persistent challenges, including tumor heterogeneity, limited access to advanced technologies in resource-constrained regions and restrictive ENPG eligibility, underscore the need for artificial intelligence-driven multi-omics risk models, portable diagnostic tools and multi-national trials to validate long-term outcomes. By integrating surgical-immune synergy (such as neoadjuvant programmed cell death protein 1 inhibitors) and equitable implementation strategies, NPC care is transitioning from empirical approaches to a precision framework targeting >80% early diagnosis and >90% functional preservation, offering a roadmap to mitigate the global burden of this regionally concentrated cancer.

## Contents



## 1. Introduction

*Epidemiology and unmet clinical needs.* Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor of the nasopharynx with an uneven global distribution. East and Southeast Asia account for ~80% of cases, with the highest incidence concentrated in southern China, particularly Guangdong, Guangxi and Fujian (1), making NPC both regionally clustered and globally consequential. The disease primarily affects individuals aged 40-70 years and shows a pronounced sex disparity, with men affected 2- to 3-fold more often than women (1). Despite advances in cross-sectional imaging and conformal radiotherapy, early detection remains elusive and long-term quality of life is still shaped by late toxicities, such as xerostomia, dysphagia and otologic injury.

Clinical presentation in the early stages is frequently silent or non-specific and includes blood-tinged sputum, unilateral nasal obstruction or painless cervical lymphadenopathy, so that 70-80% of patients are diagnosed at advanced

*Correspondence to:* Dr Xiandong Zeng, Department of Gastroenterology, The Fourth People's Hospital of Shenyang City, The First Affiliated Hospital of Shenyang University, 20 Huanghe South Street, Huanggu, Shenyang, Liaoning 110000, P.R. China
E-mail: xiandongzeng@yeah.net

*Contributed equally

*Key words:* nasopharyngeal cancer, Epstein-Barr virus, endoscopic nasopharyngectomy, multiomics integration, minimally invasive surgery

stages (III/IV) (2) This late-stage predominance at diagnosis largely explains the pronounced survival gradient across stages and highlights the clinical value of shifting detection toward earlier disease: The 5-year survival rate is >90% when NPC is detected early, but falls to >40% in late-stage disease. Distant metastasis and local recurrence remain the principal modes of treatment failure (3). Collectively, these realities define three persistent unmet needs: i) Scalable, non-invasive screening deployable at the population level; ii) risk-stratified care pathways that minimise overtreatment without compromising oncologic safety; and iii) implementation models that preserve quality and outcomes in resource-limited settings (4). Addressing these gaps will require earlier, more reliable detection and exact therapies capable of improving durable survival while mitigating treatment-related morbidity.

*Current diagnostic bottlenecks and emerging precision solutions*. Legacy serology and conventional imaging lack the resolution to capture preclinical or very-early NPC across diverse populations (5). Epstein-Barr virus (EBV)-centric assays have advanced non-invasive detection but remain vulnerable to EBV-negative disease and cross-platform variability; T-cell receptor (TCR) repertoire profiling and radiomics/radiogenomics add discrimination yet require standardized pipelines and prospective external validation (6). In practice, the present review advocates a molecular-imaging co-screening approach that pairs liquid-biopsy signals with advanced endoscopy to address historical blind spots in very-early disease (4).

*The emergence of molecular and surgical precision paradigms*. Converging advances now support a dual-front precision strategy for NPC. On the molecular/imaging side, CRISPR-enabled assays, antibody-augmented platforms and integrated multi-omics/radiomics enable non-invasive, risk-stratified co-screening suitable for population deployment (2). On the interventional side, endoscopic nasopharyngectomy (ENPG) has re-emerged as an organ-preserving option restricted to carefully selected T1-T2 disease in experienced centers; it does not constitute a universal substitute for radiotherapy. Bringing these strands together, a pragmatic tri-axis framework was adopted: Molecular detection, precision surgery (indication-bounded ENPG) and immune modulation, coordinated through analytics spanning screening, diagnosis/triage, treatment and surveillance (long-term endpoints and PROs have been synthesised in Table SI) (4).

Looking ahead, the field will hinge on harmonising precision detection with targeted intervention to shift care upstream. Artificial intelligence-assisted models that fuse multi-omics [including circulating tumor DNA (ctDNA)], immune-repertoire signatures and radiomic biomarkers can refine dynamic risk stratification and flag pre-clinical disease. In parallel, rational sequencing, for example, protocol-guided programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) strategies alongside indication-bounded ENPG, may sustain oncologic control while preserving function in selected patients. Progress will depend on multi-center prospective programs with harmonized endpoints [5/10-year OS; late ≥G3 toxicities and PROs such as M.D. Anderson dysphagia inventory (MDADI)/quality of life questionnaire-head and neck module (QLQ-H&N35)], and on equitable implementation via portable diagnostics and tele-enabled expertise in endemic regions where the burden is greatest.

## 2. Early screening for NPC: Current status and recent advances

*EBV and its associated biomarkers*. The EBV, a central oncogenic driver of NPC, establishes its pathogenicity through persistent latent infection and immune evasion (1,2), making EBV-specific biomarkers important for early detection. Current serological screening strategies targeting EBV antigens, such as viral capsid antigen IgA (VCA-IgA) and early antigen IgA, exhibit limited diagnostic utility, with single-antibody assays achieving only a sensitivity of ~25% (6). Dual-antibody approaches (such as VCA-IgA with EBNA1-IgA) have been shown to improve sensitivity to ~75%, yet their clinical translation is hampered by persistently low positive predictive values (<20%) and high false-positive rates, underscoring the need for complementary biomarkers (7,8).

Legacy serology and conventional imaging lack the granularity to consistently detect preclinical or very-early NPC across heterogeneous populations. EBV-centric assays, including plasma EBV DNA and methylome (cfDNA), exhibit advanced non-invasive detection but remain vulnerable to EBV-negative disease, pre-analytical variability and cross-platform threshold drift (9-11). TCR repertoire profiling and radiomics/radiogenomics add discriminatory power, yet require standardised pipelines and rigorous prospective external validation (7,12). The net effect is a patchwork evidence base marked by heterogeneous cut-offs and inconsistent reporting windows, which impedes guideline adoption and real-world scale-up (13,14).

Recent advances in NPC screening have revolutionized EBV biomarker detection through multi-dimensional technological innovations. Next-generation sequencing (NGS)-enabled composite models now decode both quantitative and fragmentomic profiles of plasma EBV DNA via real-time PCR, achieving unprecedented precision (15). A landmark study by Lam *et al* (15) demonstrated that algorithmic optimization of NGS data elevates screening specificity from 98.6 to 99.3% and boosts positive predictive value by 78% (from 11.0 to 19.6%), markedly enhancing early-stage detection. Parallel breakthroughs in nucleic acid testing include the CRISPR-Cas12a-based non-amplification digital detection system developed at Sun Yat-sen University Cancer Center, Guangzhou, China (15,16). By targeting EBV genomic repetitive sequences, this platform outperforms conventional quantitative PCR (qPCR), achieving superior sensitivity (98.5 vs. 95.2%) and specificity (99.1 vs. 97.8%), while reducing assay time by 60% and enabling real-time monitoring of tumor load dynamics. These innovations not only address historical limitations in EBV-driven screening but are also aligned with global efforts to reduce mortality due to NPC in endemic regions, where >80% of the cases occur (17).

Serological testing for NPC has undergone transformative innovation, addressing long-standing gaps in early detection. The VCA-IgA/EBNA1-IgA dual-antibody ELISA platform increases screening sensitivity threefold (from 25 to 75%) while maintaining 98.5% specificity, earning endorsement

as the National Health Commission's preferred protocol for high-incidence regions (15). Complementing this, the P85 antibody (P85-Ab) assay, co-developed by Xiamen University (Xiamen, China) and Wantai Biotech marks a paradigm shift in serological screening. As a standalone test, it achieves 97.9% sensitivity and 98.3% specificity, surpassing conventional biomarkers. When integrated with dual-antibody screening (18), P85-Ab elevated the positive predictive value from 10 to 44.6%, quadrupling diagnostic efficiency while reducing per-test costs by 30% in pilot implementations (19). Approved for clinical use in late 2024, this combinatorial strategy redefines cost-effective mass screening, particularly in endemic areas where NPC accounts for >80% of global cases (6). By harmonizing high-throughput serology with precision biomarkers, these advances align with World Health Organization targets to reduce NPC-caused mortality through early interception, exemplifying how translational innovation can bridge diagnostic accuracy and scalability in resource-variable settings (20).

The current landscape of EBV-related biomarker detection is characterized by three key developments. First, NGS and CRISPR-based technologies are enhancing diagnostic precision through multi-indicator nucleic acid testing strategies. Secondly, the identification of novel biomarkers, such as P85-Ab, has opened new avenues for early screening. In combination, these advances provide key technical support for establishing a tiered prevention and control framework encompassing initial screening, refined screening and definitive diagnosis. Of note, the advent of high positive predictive value assays contributes to reducing the risk of overdiagnosis in clinical settings. Despite these promising developments, challenges remain. The high costs associated with NGS and CRISPR limit their accessibility at the primary care level, while the long-term stability and clinical utility of emerging biomarkers such as P85-Ab require validation in large-scale cohorts. Future research directions include the development of portable, low-cost diagnostic platforms, the integration of multi-omics data to construct dynamic early warning systems and the application of artificial intelligence to optimize screening algorithms. These innovations aim to enable standardized, accurate and widely accessible early detection of NPC.

*Plasma free DNA cfDNA and ctDNA*. Recent advances in circulating biomarkers and protein-based assays have transformed the non-invasive diagnosis and prognostic stratification of NPC. cfDNA, comprising short DNA fragments shed into the bloodstream, includes a tumor-derived fraction, ctDNA, that harbors somatic alterations such as TP53 and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA) mutations (21,22). Leveraging ultra-sensitive platforms such as digital PCR and NGS, trace levels of ctDNA can now be reliably detected, enabling earlier diagnosis and real-time monitoring of tumor burden in patients with NPC. Complementing these molecular assays, the immunohistochemical analysis of the p53 tumor suppressor protein provides key prognostic insights: Loss-of-function TP53 mutations often result in aberrant p53 accumulation and elevated p53 expression within NPC tissues has been consistently associated with worse overall and disease-free survival (23). Together, ctDNA profiling and p53 immunostaining offer a powerful, minimally invasive toolkit for guiding individualized treatment decisions, facilitating both the early detection of NPC and the tailoring of therapeutic intensity based on tumor biology (Fig. 1).

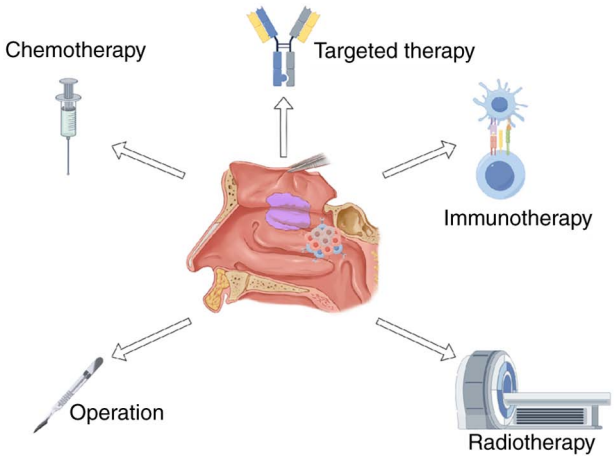


Figure 1. The mainstream treatment methods of nasopharyngeal carcinoma are radiotherapy, chemotherapy, surgery, targeted therapy and immunotherapy (by Figdraw.com).

## 3. Biomarker detection

*Progress in microRNA (miRNAs) research of related biomarkers*. miRNAs, a class of ~22-nucleotide non-coding RNAs, modulate gene expression post-transcriptionally by binding to the 3' untranslated regions of target messenger RNAs, thereby playing key roles in oncogenesis. In NPC, a distinct and consistent pattern of miRNA dysregulation has been widely observed, underscoring their potential as diagnostic and prognostic biomarkers (24-26). This aberrant miRNA expression landscape not only reflects underlying tumor biology but also offers a promising avenue for non-invasive molecular diagnostics. However, the clinical translation of miRNA-based biomarkers in NPC remains contingent on the development of robust, standardized detection platforms and optimized analytical strategies that ensure sensitivity, specificity and reproducibility across diverse patient populations.

Early studies on miRNAs focused on identifying miRNAs specific to NPC. Zhang *et al* (27) found that miR-93 was markedly upregulated in NPC tissues and Zhou *et al* (28) further confirmed its serum levels were positively associated with tumour stage. However, the sensitivity and specificity of miR-93 alone for diagnosis are insufficient, suggesting the limited clinical value of a single miRNA. Zhou *et al* (28), Duan *et al* (29), and Zhang *et al* (30) demonstrated that the combined detection of miR-17-5p and miR-20a can increase the sensitivity of early NPC to 80% and the specificity to 87%, notably outperforming traditional serum antibodies (such as VCA-IgA). Of note, the specificity of miR-17-5p in distinguishing patients with early-stage NPC from healthy individuals is relatively low (73%), indicating the need to combine other markers to improve accuracy.

The inherent limitations of single-miRNA diagnostic approaches have catalyzed the development of multi-analyte

biomarker integration strategies, with recent advancements demonstrating marked improvements in clinical detection accuracy. Of note, Zhu *et al* (31) pioneered a serum triplex miRNA panel (miR-140-3p, miR-192-5p and miR-223-3p) achieving 93.2% sensitivity and 93.5% specificity through the synergistic regulation of Wnt/β-catenin signaling and epithelial-mesenchymal transition (EMT) pathways. This paradigm shift toward biomarker combination was further validated by Jiang *et al* (32), who reported that incorporating circulating EBV microRNA BART2-5p (miR-BART2-5p) into screening/triage markedly improved diagnostic performance (AUC ~0.96-0.97 in validation cohorts)., outperforming conventional plasma EBV DNA assays (50% detection rate), while maintaining 94.2% sensitivity. Considerably advancing the field, Li *et al* (24,25) and Allaya *et al* (22) established a multi-omics diagnostic framework combining miR-10b with EBV Latent Membrane Protein 1 (LMP1). EBV-related transcripts (for example, LMP1) and host regulators such as TWIST1 have been associated with NPC pathobiology, supporting their potential as components of multi-marker panels (24). These collective findings underscore the potential of cross-modal biomarker integration in overcoming biological heterogeneity and pathway redundancy limitations inherent to single-marker approaches, establishing a new standard for precision diagnostics in complex disease states.

Although miRNA biomarkers hold considerable promise for the clinical management of NPC, their translation into routine practice is hindered by three principal challenges. First, tumor heterogeneity poses a notable obstacle: Molecular subtypes of NPC, such as variations in EBV latency patterns and the degree of stromal infiltration, result in marked differences in miRNA expression profiles. For instance, miR-93 is consistently upregulated in EBV type III latency tumors, yet exhibits variable expression in type I, limiting its utility as a broadly applicable biomarker (33). Secondly, the lack of technical standardization undermines reproducibility and comparability across studies. While qPCR and microarray platforms are widely used for miRNA detection, there remains no consensus on key methodological parameters, including sample preprocessing protocols (such as exosome isolation) and reference gene selection (such as U6 small nuclear RNA vs. cel-miR-39). Finally, the clinical utility of miRNAs has been predominantly explored in the context of diagnosis, whereas their potential roles in prognosis and therapy remain underdeveloped. Of note, miR-205 has been implicated in radiotherapy resistance, highlighting the need to further investigate miRNAs as prognostic indicators and therapeutic targets (34). Addressing these challenges will be essential for harnessing the full clinical potential of miRNA-based tools in NPC.

*Genetic markers*. Recent large-scale genomic sequencing efforts have substantially advanced understanding of the molecular landscape of NPC, revealing recurrent alterations in tumor suppressor genes and oncogenic drivers with marked clinical implications. Among these, TP53 mutations, one of the most common genetic events across different types of human cancer, display distinct patterns in NPC, being predominantly enriched in EBV-negative subtypes and recurrent tumors. These mutations, which include missense variants, point mutations and splice site alterations, result in the functional inactivation of the p53 protein, thereby impairing key pathways involved in DNA damage response, cell cycle regulation and apoptosis. The consequence is enhanced tumor resistance to radiotherapy and chemotherapy, often associated with poor clinical outcomes (35-38).

In parallel, the dysregulation of the PI3K/AKT signaling pathway carries out a complementary oncogenic role. Activating mutations in PIK3CA, notably E545K and H1047R, directly enhance AKT phosphorylation, promoting cell proliferation and survival (39). Meanwhile, the tumor-suppressive function of PTEN, a key negative regulator of this pathway, is frequently compromised by inactivating mutations or copy number loss, resulting in a sustained activation of the PI3K/AKT/mechanistic target of rapamycin axis. These molecular aberrations are further amplified by the dysregulation of EGFR signaling (39,40). In EBV-positive NPCs, EGFR amplification or overexpression concurrently activates multiple downstream pathways, including MAPK, PI3K/AKT, and Janus kinase/signal transducer and activator of transcription signaling pathway, which collectively contribute to radioresistance and the acquisition of cancer stem cell-like properties. This mechanistic convergence provides a compelling rationale for the clinical evaluation of EGFR-targeted therapies, such as erlotinib, in selected subsets of patients with NPC (41-43). Given the clinical relevance of EGFR, the use of targeted therapies, including anti-EGFR monoclonal antibodies such as cetuximab (44,45), are increasing. Detecting EGFR expression levels allows for the selection of more appropriate treatment strategies and facilitates the prediction of patient response and overall prognosis.

The dysregulation of cell cycle checkpoints in NPC exemplifies a paradigm shift in understanding tumorigenic mechanisms. The amplification of cyclin D1 (CCND1) drives the aberrant $G_1$/S transition through the enhanced assembly of cyclin D1-Cyclin-dependent kinase 4 and 6 (CDK4/6) complexes, while the concomitant epigenetic silencing of cyclin-dependent kinase inhibitor 2A (CDKN2A) via promoter hypermethylation induces the functional inactivation of cyclin-dependent kinase inhibitor 2A, isoform p16, thereby relieving its restraint on CDK4/6 kinase activity. This dual disruption of cell cycle surveillance constitutes a hallmark of NPC pathogenesis, providing a robust biological rationale for the clinical evaluation of CDK4/6 inhibitors that have shown a therapeutic promise in other head and neck malignancies (46-49). Paralleling these proliferation anomalies, the tumor microenvironment (TME) exhibits constitutive NF-κB activation, a pathognomonic feature mediated by convergent genetic lesions including nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α truncating mutations impairing IκBα function and heterozygous deletions affecting TNF receptor-associated factor 3/cylindromatosis-mediated negative regulation. These molecular defects sustain NF-κB transcriptional activity, resulting in the paracrine secretion of immunosuppressive cytokines (such as IL-6 and TNF-α) that create a pro-tumorigenic niche while conferring radioresistance through EMT programming (50-52).

Of note, the immunogenetic predisposition of NPC reveals an evolutionary arms race between viral persistence and host

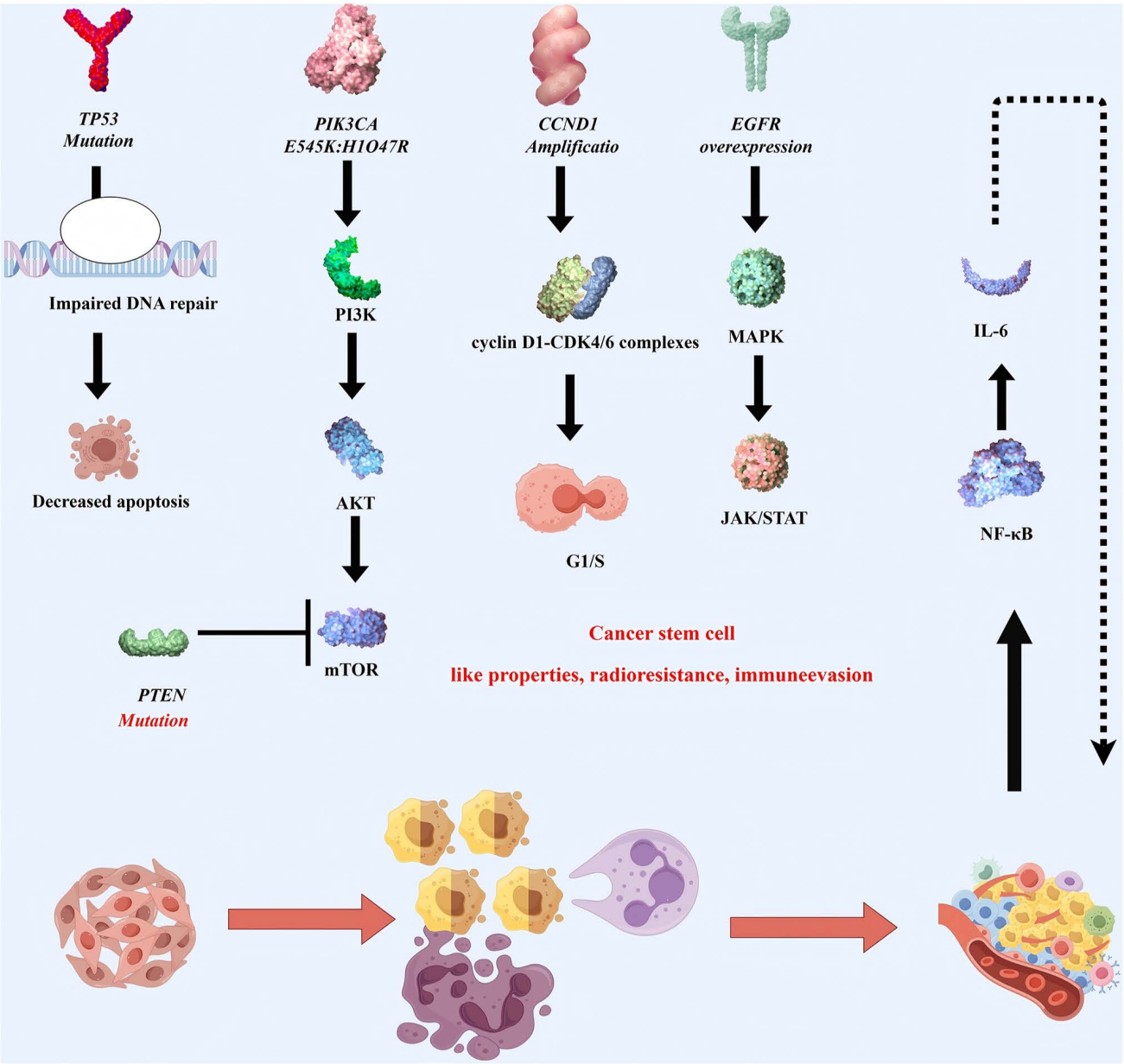


Figure 2. Molecular interaction mechanism diagram of associated genes (by Figdraw.com).

immunity: Genome-wide association studies implicate human leukocyte antigen A/B (HLA-A/B) class I allele variants in defective EBV antigen presentation, compromising cytotoxic T-cell surveillance and enabling viral oncogene-mediated transformation (53-55). The synergistic interplay between these cell-intrinsic (CCND1/CDKN2A axis) and cell-extrinsic (NF-κB-inflammatory loop) drivers, superimposed upon (HLA)-restricted immune evasion mechanisms, defines the landscape of the molecular heterogeneity of NPC. Such integrative molecular cartography not only elucidates the biological basis of the distinct clinical behavior of NPC but also informs precision therapeutics, exemplified by the combinatorial targeting of PI3K/AKT and EGFR axes that converge on dysregulated growth factor signaling. This multi-layered mechanistic dissection positions NPC as a paradigm for viro-immunogenetic tumor models requiring context-specific therapeutic interventions (Fig. 2).

*Epigenetic markers*. The epigenetic and transcriptional dysregulation of key genetic elements has emerged as a key mechanism in the pathogenesis of NPC. One notable example is Septin 9 (SEPT9_v2), a tumor suppressor gene whose promoter hypermethylation leads to transcriptional silencing and is closely associated with NPC progression. Functional studies have demonstrated that SEPT9_v2 suppresses tumor cell proliferation, migration and invasion by inhibiting the Wnt/β-catenin signaling cascade through the miR-92b-3p/frizzled class receptor 10 axis (55,56). Conversely, the kinesin family member kinesin family member 23 (KIF23), an established oncogene, is notably overexpressed in NPC tissues and promotes tumor aggressiveness through the activation of the same Wnt/β-catenin pathway. Of note, KIF23 expression is transcriptionally regulated by the androgen receptor, providing a mechanistic association with the observed sex-specific differences in NPC

incidence and outcomes. Collectively, these findings underscore the dual role of the Wnt/β-catenin pathway as both a downstream effector and an integrative hub for epigenetic and hormonal regulation in NPC, positioning SEPT9_v2 and KIF23 as promising biomarkers for prognostic evaluation and as candidate targets for therapeutic intervention.

Emerging evidence highlights the key role of non-coding RNA signatures and epigenetic alterations in shaping the molecular landscape and clinical trajectory of NPC. Specific miRNA expression profiles, particularly hsa-miR-142-3p, hsa-miR-29c and hsa-miR-30e, have shown robust associations with overall survival and when integrated with clinical parameters, substantially improve the accuracy of prognostic models. In addition to their intracellular regulatory functions, miRNAs packaged into exosomes, such as miR-34a-5p, exert paracrine effects that modulate the TME and intercellular signaling networks (57,58).

Epigenetic dysregulation, especially DNA methylation, is another hallmark of NPC. The promoter hypermethylation of protocadherin 17 (PCDH17) leads to its complete silencing across NPC cell lines and the functional restoration of PCDH17 inhibits angiogenesis and suppresses vascular endothelial growth factor secretion (59). In addition, differentially methylated regions in genes such as calcitonin-related polypeptide α, ALX homeobox 4 and homeobox D9 are detectable in cfDNA, laying the foundation for non-invasive liquid biopsy-based diagnostics (60,61). Of particular note, the methylation status of SEPT9_v2 and protocadherin 17 not only holds diagnostic potential but may also serve as predictive biomarkers for treatment responsiveness, underscoring the multifaceted utility of epigenetic markers in early detection, prognosis stratification and therapy optimization.

*Metabolomics markers*. Metabolic reprogramming represents a hallmark of NPC, contributing to tumor progression, invasion and metastasis. One notable feature of NPC is the abnormal accumulation of metabolites, such as lactic acid and glutamine, within the TME, reflecting a shift in energy metabolism and biosynthetic demands (62). By integrating single-cell Raman spectroscopy with mass spectrometry, recent studies (63-65) have revealed markedly elevated levels of unsaturated fatty acids in highly metastatic NPC cell lines (such as 5-8F and CNE2), implicating dysregulated lipid metabolism as a driver of metastatic potential. Complementary NMR-based metabolomics analyses have identified specific lipoprotein subfractions, very low-density lipoprotein and low-density lipoprotein, as closely associated with NPC onset. A metabolite-derived risk score incorporating these lipoproteins demonstrated strong discriminative power in multicentre cohorts (AUC=0.841), supporting their potential as early diagnostic and stratification biomarkers (66).

Furthermore, disturbances in amino acid metabolism, particularly elevated levels of 4-aminobutyric acid, have been shown to facilitate tumor invasion through the activation of the ubiquitin-proteasome pathway, specifically through ubiquitin-conjugating enzyme E2C (67). These findings not only enhance understanding of the metabolic underpinnings of NPC but also provide a framework for the development of targeted metabolic interventions. The integration of multi-omics platforms with artificial intelligence-aided analysis is expected to further refine metabolic phenotyping and identify actionable vulnerabilities in NPC (Fig. 3).

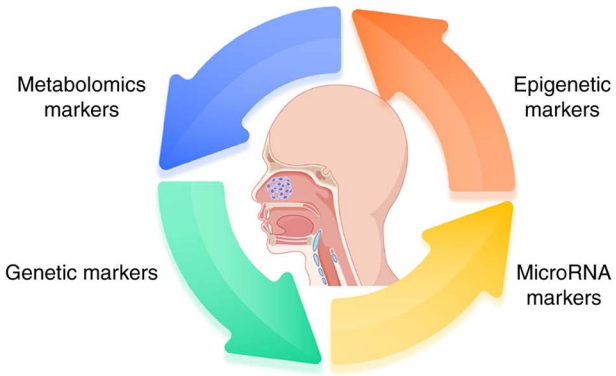


Figure 3. Biological markers of nasopharyngeal carcinoma.

## 4. Application and cutting-edge progress of immunotherapy in NPC

In NPC, an EBV-associated malignancy with pronounced immune infiltration and viral antigenicity, immune checkpoint blockade has emerged as a transformative modality. The PD-1/PD-L1 axis plays a central role in immune evasion by impairing cytotoxic T-cell activation within the TME. High PD-L1 expression, driven in part by EBV-related inflammation and epigenetic regulation (such as acetylation-mediated nuclear translocation), suppresses anti-tumor immunity, enabling tumor persistence (68-70). PD-1/PD-L1 inhibitors restore T-cell function and have demonstrated meaningful clinical efficacy in recurrent/metastatic NPC (R/M NPC).

Multiple early-phase trials have established the monotherapeutic activity of PD-1 blockade in pretreated R/M NPC. The KEYNOTE-028 study reported an objective response rate (ORR) of 25.9% and median overall survival (OS) of 16.5 months with pembrolizumab (71), while the NCI-9742 trial showed similar outcomes for nivolumab (ORR, 20.5%; OS 17.1, months) (72). Camrelizumab also achieved an ORR of 28.2% in the CAPTAIN trial (73). However, despite encouraging activity, monotherapy responses were limited by modest durability and heterogeneous patient benefit, prompting combination strategies.

The paradigm shifted with the emergence of immune-chemotherapy combinations. In the landmark JUPITER-02 trial, toripalimab plus gemcitabine-cisplatin prolonged progression-free survival (PFS) to 11.7 vs. 8.0 months with chemotherapy alone, reducing the risk of mortality by 40% (73). Similar benefits were observed in NCT03707509 with camrelizumab, further confirming the synergy between chemotherapy-induced immunogenic cell death and PD-1 blockade (74). Of note, PD-L1 positivity and EBV DNA clearance were predictive of superior responses (75), underscoring the importance of biomarker-driven treatment selection.

Yet, immune resistance remains a key challenge. Mechanisms include loss of PD-L1 expression, T-cell exhaustion, immune desertification and neoantigen depletion (75-78). Tumor-intrinsic alterations, such as NF-κB pathway activation and cytokine-driven immunosuppression, further impair

durable response (79). To overcome these barriers, neoadjuvant immunotherapy (such as PD-1 inhibitors preceding ENPG), immune-antiangiogenic combinations and AI-assisted immune landscape modeling are being investigated.

In conclusion, PD-1/PD-L1 inhibitors have redefined the therapeutic landscape of NPC, particularly in the metastatic setting and are increasingly being integrated into frontline regimens. Future directions focus on optimizing combinatorial immunotherapy, identifying predictive biomarkers and tailoring interventions based on EBV load, TME and host immune features. These efforts aim to achieve durable functional remission in a historically therapy-resistant malignancy (Fig. 4).

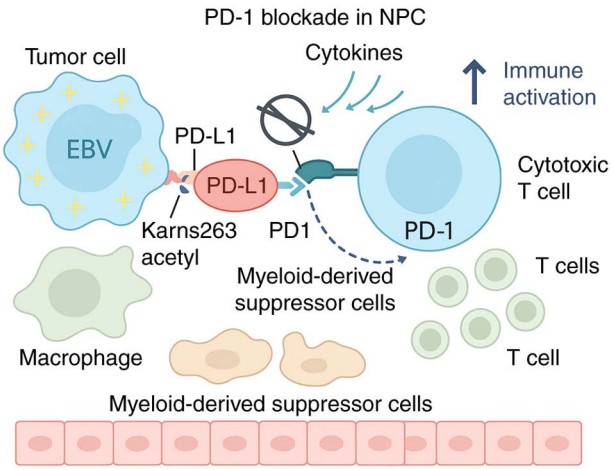


Figure 4. The therapeutic mechanism of PD-1 and the immune environment of NPC. NPC, nasopharyngeal carcinoma. PD-1, programmed cell death protein 1.

## 5. Examination and treatment of NPC

In the early screening system for NPC, endoscopic technology has progressed from traditional white light observation to advanced image enhancement stages. Optical enhancement platforms, represented by narrow band imaging (NBI) and I-scan virtual chromoendoscopy, have markedly transformed the mucosal lesion identification system (80-82). NBI enhances microvascular patterns using narrow-band blue-green light, excelling in detecting microinvasive lesions with diameters >5 mm, achieving a sensitivity of 92.3% and specificity of 93.1%, far surpassing white light endoscopy. I-scan, through digital image post-processing, enhances vascular morphology and glandular structure details, identifying potential vascular abnormalities in white-light negative regions with a detection rate of 23%, thus making it a powerful secondary screening tool for high-risk populations. However, challenges in clinical application remain, such as high false-positive rates, operator dependence and high equipment costs (83). Future breakthroughs will likely focus on building a multimodal fusion intelligent screening system, integrating signals such as EBV DNA load, TCR subtype typing and AI image recognition, to establish a new 'visual + molecular diagnosis' paradigm for grassroots applications.

Radiotherapy has long been regarded as the first-line treatment for early-stage NPC. However, the long-term survival benefit of re-irradiation is limited (5-year OS <45%), with a high incidence of complications (such as NP necrosis and temporal lobe damage), leading to the return of surgery as the core treatment approach. Traditional open surgical methods, such as those involving the hard palate or maxillary bone, achieve high local control rates (10-year OS ≤73.8%) (84-87). However, their high margin positivity rates (≤29%), postoperative functional impairment (such as swallowing and facial issues) and aesthetic damage limit their applicability. The rise of endoscopic technology (such as ENPG) marks a key turning point in NPC surgical treatment paradigms. By offering high-definition magnification views, ENPG allows for precise exposure of the skull base structures while preserving key anatomy (such as the eustachian tube and internal carotid artery), achieving a postoperative 5-year OS improvement to 48-52%, while markedly reducing the incidence of ≥3-grade toxicity events (88,89). More importantly, the anatomical classification system developed based on the endoscopic platform, such as the four-segment internal carotid artery classification for the parapharyngeal segment and four-level recurring NPC surgical classification, provides key support for enhancing surgical safety and expanding indications.

Building on the demonstrated efficacy of ENPG in treating recurrent NPC, clinical studies have progressively extended its application to patients with early-stage NPC (90-92). Several prospective studies indicate that for patients at T1-T2 stage, the combination of ENPG with chemotherapy or low-dose radiotherapy achieves survival outcomes comparable with those of standard radiotherapy [3-year OS of 100% and disease-free survival (DFS) of 95.8-100%]. Of note, ENPG also enhances quality of life metrics, particularly in preserving salivary gland function, reducing dry mouth and improving speech function. More importantly, ENPG successfully meets the dual objectives of precise lesion resection and functional preservation by shortening the irradiation path, circumventing the need for repeated radiation and minimizing the trauma to the adhesion zones (Table I).

Although ENPG is currently used as part of a multimodal treatment regimen, emerging evidence is gradually confirming its potential as a standalone therapy for stage INPC. A 10-year retrospective study from the Cancer Center of Sun Yat-sen University revealed that patients with stage T1N0M0 NPC who underwent ENPG alone achieved a 100% three-year PFS, markedly surpassing intensity-modulated radiotherapy (IMRT) in terms of cost-effectiveness and quality of life (93,94). This finding suggested that minimally invasive surgery could challenge the established standards of radiotherapy for specific NPC subtypes. However, this approach remains in its infancy and current evidence is constrained by small sample sizes and limited follow-up durations. Future research should prioritize multicenter randomized controlled trials that incorporate molecular characteristics, such as EBV DNA load, PD-L1 expression and TME features. This would enable the development of a more refined treatment model, emphasizing surgery complemented by immunoradiotherapy. The focus should be on targeting low-risk molecular subgroups, with the aim of expanding the role of ENPG as a curative therapy. Accordingly, ENPG is not recommended beyond T1-T2 indications and should not be generalized outside centers with the requisite skull-base expertise; radiotherapy remains the reproducible standard elsewhere.

Table I. Summary of key advances in early detection technologies for NPC, focusing on innovations in diagnostic platforms and their clinical applicability. The table provides an overview of sensitivity, specificity, advantages and limitations of each method discussed in the manuscript.

| Detection method | Key technology | Sensitivity (%) | Specificity (%) | Advantages | Limitations |
|---|---|---|---|---|---|
| CRISPR-Cas12a (Amplification-free) | CRISPR-based non-amplification digital detection | 98.5 | 99.1 | High sensitivity and specificity; rapid and cost-effective | Requires advanced technology and trained personnel |
| P85 antibody profiling | Antibody detection (P85) | 97.9 | 98.3 | High positive predictive value; cost-efficient for mass screening | Limited validation across different populations |
| T-Cell receptor sequencing | TCR sequencing of EBV-related clonal expansions | 98.6 | - | Ultra-early prediction of NPC risk (6-12 months prior to clinical diagnosis) | Not widely accessible; requires high-throughput sequencing platforms |
| Narrow-band imaging | Optical enhancement with blue-green light | 92.3 | 93.1 | Can detect micro-invasive lesions <5 mm; superior to white light endoscopy | High false-positive rate; operator-dependent |
| I-Scan virtual chromoendoscopy | Image enhancement for detailed mucosal patterns | 87.5 (Stage II) | - | Enhances vascular morphology and glandular structure detail | Limited to higher-end equipment; operator-dependent |

NPC, nasopharyngeal carcinoma.

Looking ahead, three key strategies are poised to establish ENPG as a primary treatment modality: i) Preoperative neoadjuvant therapy, such as PD-1 inhibitors combined with gemcitabine-platinum regimens, can markedly reduce tumor volume and broaden surgical indications; ii) intraoperative integration of AI-assisted navigation, enhanced vascular imaging and robotic manipulation will lower technical barriers and iii) the incorporation of multidisciplinary collaboration (involving ENT, radiotherapy, oncology and immunology) alongside the dynamic monitoring of EBV load will enable the development of an individualized treatment decision-making system, ultimately targeting 'functional cure' rather than mere 'lesion elimination' (Table II).

## 6. Long-term outcomes and functional assessment

Across available comparative studies, endoscopic nasopharyngectomy has been explored as an organ-preserving option in highly selected early-stage disease, with oncologic outcomes that appear broadly comparable to radiotherapy in some cohorts, while potentially offering advantages in selected functional domains; however, the evidence remains limited by small sample size, centre expertise, and heterogeneity in endpoints and follow-up (90,93,94). Beyond oncologic parity, convergent patient-reported data indicate functional advantages, with higher MDADI scores for swallowing-related quality of life and lower European Organisation for Research and Treatment of Cancer QLQ-H and N35 symptom burdens in xerostomia-linked domains (such as dry mouth and sticky saliva), consistent with the organ-preserving intent of ENPG (1,3,95). Accordingly, radiotherapy remains the reproducible standard, whereas ENPG should be reserved for carefully selected T1-T2 patients in experienced centres, ideally within registries or prospective trials (90,93).To provide a transparent evidence map for clinicians and health systems, 5-/10-year survival and functional readouts were synthesized and summarized in Supplementary Table SI, annotated by assessment windows (baseline, 12-24 months, and last follow-up) and highlighting the heterogeneity of instruments that currently limits cross-study pooling (93,96-100).

## 7. Conclusion

In recent years, notable advances have been made in the early screening and treatment strategies for NPC, culminating in the development of a new paradigm of 'precise screening-minimally invasive intervention-functional preservation' (9). In the realm of screening, continuous innovations in detection technologies for EBV-related markers have substantially improved diagnostic performance (18,101). The introduction

Table II. A comparative analysis of ENPG and traditional radiotherapy in treating early-stage NPC. This table highlights key clinical outcomes, functional preservation and the challenges associated with each treatment modality.

| Parameter | ENPG | Traditional radiotherapy |
|---|---|---|
| 5-Year survival rate | 92.1% | ~90% |
| Negative resection margins | ≥90% | N/A |
| Functional preservation | Swallowing, hearing and cervical mobility preserved | Notable loss in swallowing, hearing and neck mobility |
| Radiotherapy-related morbidity | Reduced incidence of mucosal necrosis, fibrosis and other side effects | High incidence of mucosal necrosis, neck fibrosis and functional impairments |
| Eligibility | Early-stage (I/II) and recurrent NPC; precision-based patient selection | Broader eligibility, including advanced stages |
| Technical requirements | High precision surgery; AI-assisted navigation; specialized equipment | High-dose radiotherapy; established protocols |
| Patient recovery | Faster recovery; fewer long-term side effects | Slower recovery; long-term functional impairments |
| Cost and accessibility | Expensive; limited access in low-resource regions | Widely available; lower initial treatment cost |

ENPG, endoscopic nasopharyngectomy; NPC, nasopharyngeal carcinoma.

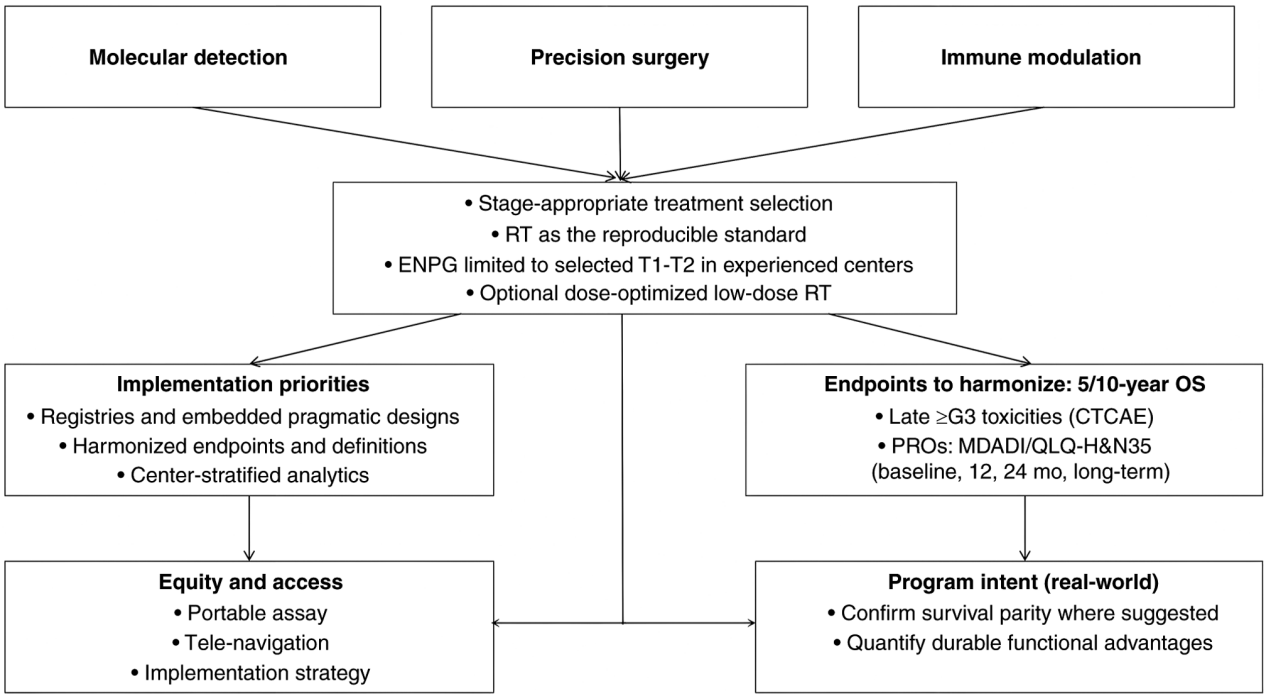


Figure 5. Practice-facing outlook for NPC precision care. NPC, nasopharyngeal carcinoma. RT, radiotherapy; ENPG, endoscopic nasopharyngectomy; OS, overall survival; CTCAE, Common Terminology Criteria for Adverse Events; PROs, patient-reported outcomes; MDADI, MD Anderson Dysphagia Inventory; QLQ-H&N35, EORTC Quality of Life Questionnaire-Head and Neck 35; mo, months; T1-T2, tumor stage T1-T2; G3, grade 3.

of CRISPR/Cas12a-based non-amplification detection and the novel P85-Ab has enhanced the sensitivity and specificity of NPC screening to 97.9 and 98.3%, respectively (18,102). Furthermore, the integration of mRNA multi-marker combined detection (such as the miR-140-3p triad model) with imaging techniques, such as NBI and I-scan, marks a notable shift from a 'single indicator' approach to a more robust 'molecular-imaging' collaborative model (30,82).

In the treatment domain, ENPG has raised the 5-year survival rate for patients with early-stage NPC to 92.1% through precise resection and functional preservation. In addition, quality-of-life metrics, such as swallowing and hearing functions, are markedly superior when compared with those achieved with traditional radiotherapy, signifying a shift in treatment goals from 'survival first' to a balanced emphasis on both 'survival and quality of life' (90,93). However, several

key challenges persist, tumor heterogeneity results in limited universality of markers (such as fluctuations in miR-93 expression) (103); the low penetration of NBI/I-scan technologies at the grassroots level and the lack of operational standards hinder their widespread use, and the indications of ENPG remain confined to early-stage NPC, with long-term efficacy requiring further large-scale validation (104). EBV-based detection anchors current non-invasive screening, yet gaps persist in EBV-negative disease and cross-population generalizability; ENPG remains indication-bounded (selected T1-T2; experienced centers), with radiotherapy as the reproducible standard elsewhere (105,106).

Future research should prioritize multi-omics integration to build AI-driven risk stratification models combining EBV-related signals with immune and metabolic features. Surgery-immunotherapy synergy also warrants exploration, including neoadjuvant PD-1 blockade with ENPG in trial settings and adjuvant strategies guided by dynamic EBV monitoring. Meanwhile, standardization and access should be improved through portable assays and consensus endoscopic grading systems. Multidisciplinary collaboration across ENT/head-and-neck surgery, oncology and radiotherapy is essential to implement stage-appropriate precision care. Finally, multicenter prospective studies with harmonized endpoints and standardized PROs are required to validate long-term efficacy and functional benefit.

The diagnosis and treatment of NPC are rapidly evolving from empirical approaches to precision medicine. By fostering interdisciplinary collaboration and embracing technological innovation, the goal of achieving an 'early diagnosis rate of >80% and functional preservation rate >90%' is within reach. Ultimately, these advancements will help overcome the persistent challenges in the prevention and control of NPC.

Going forward, the present review will adopt an indication-bounded pathway anchored by three coordinated axes. Molecular detection (EBV DNA/methylome cfDNA, TCR and selected multi-omics) will be deployed as co-screening with predefined cut-offs and external controls (107,108). Treatment selection remains stage-appropriate: Radiotherapy as the reproducible standard, and ENPG reserved for carefully selected T1-T2 in experienced centers (with optional dose-optimized low-dose RT). Immune modulation (PD-1/PD-L1) is integrated for high-risk biology and in trial settings. Implementation will prioritize registries and embedded pragmatic designs with harmonized endpoints, 5/10-year OS, late ≥G3 toxicities and standardized PROs (MDADI/QLQ-H&N35 at baseline, 12 months, 24 months and long-term), and will explicitly address equity and access (such as, portable assays, tele-navigation and center-stratified analytics) (109,110). This program is intended to confirm survival parity where suggested and to quantify any durable functional advantages under real-world constraints (Fig. 5).

*Limitations*. Several constraints temper inference from the present synthesis. i) Biology and case-mix: EBV-centric algorithms underperform in EBV-negative NPC and may vary across ethnicities and prevalence settings; current evidence lacks adequately powered, externally validated cohorts for these subgroups. ii) Assay and pipeline heterogeneity: Platforms (qPCR/ddPCR/NGS/CRISPR), thresholds and pre-analytics (plasma handling, batching) differ across studies, introducing spectrum and incorporation biases that limit cross-study pooling. iii) Functional outcomes and toxicity: PROs (MDADI, QLQ-H&N35) are inconsistently timed and analyzed (directionality, responder thresholds) and acute vs. late (≥G3) toxicities are not uniformly separated. iv) Surgical generalizability: ENPG results largely reflect stringent selection (T1-T2) and center experience/learning curves; requirements for navigation, imaging and rescuability restrict applicability in low-resource settings. v) Long-term endpoints: 10-year OS/DFS and durable functional stability remain sparse and heterogeneous, with non-randomized designs susceptible to residual confounding (adjuvant and salvage policies). vi) Implementation and equity: Few studies report cost-effectiveness, access or workforce implications, impeding translation at scale.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

**Availability of data and materials**

Not applicable.

**Authors' contributions**

EJ contributed to the study design, literature search and selection and analysis of the literature/information. WL and XZ were involved in the writing process, including manuscript drafting, editing and reviewing, as well as the creation of figures and tables. All authors have read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Tang LL, Chen YP, Chen CB, Chen MY, Chen NY, Chen XZ, Du XJ, Fang WF, Feng M, Gao J, *et al*: The Chinese society of clinical oncology (CSCO) clinical guidelines for the diagnosis and treatment of nasopharyngeal carcinoma. Cancer Commun (Lond) 41: 1195-1227, 2021.
2. Bossi P, Chan AT, Licitra L, Trama A, Orlandi E, Hui EP, Halámková J, Mattheis S, Baujat B, Hardillo J, *et al*: Nasopharyngeal carcinoma: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 32: 452-465, 2021.

3. Chen YP, Ismaila N, Chua ML, Colevas AD, Haddad R, Huang SH, Wee JT, Whitley AC, Yi JL, Yom SS, *et al*: Chemotherapy in combination with radiotherapy for definitive-intent treatment of stage II-IVA nasopharyngeal carcinoma: CSCO and ASCO guideline. J Clin Oncol 39: 840-859, 2021.
4. Lam WJ, King AD, Miller JA, Liu Z, Yu KJ, Chua ML, Ma BB, Chen MY, Pinsky BA, Lou PJ, *et al*: Recommendations for Epstein-Barr virus-based screening for nasopharyngeal cancer in high-and intermediate-risk regions. J Natl Cancer Inst 115: 355-364, 2023.
5. Cao SM, Liu Z, Jia WH, Huang QH, Liu Q, Guo X, Huang TB, Ye W and Hong MH: Fluctuations of epstein-barr virus serological antibodies and risk for nasopharyngeal carcinoma: A prospective screening study with a 20-year follow-up. PLoS One 6: e19100, 2011.
6. Liu Y, Huang Q, Liu W, Liu Q, Jia W, Chang E, Chen F, Liu Z, Guo X, Mo H, *et al*: Establishment of VCA and EBNA1 IgA-based combination by enzyme-linked immunosorbent assay as preferred screening method for nasopharyngeal carcinoma: A two-stage design with a preliminary performance study and a mass screening in southern China. Int J Cancer 131: 406-416, 2012.
7. Li Y, Wang K, Yin SK, Zheng HL and Min DL: Expression of Epstein-Barr virus antibodies EA-IgG, Rta-IgG, and VCA-IgA in nasopharyngeal carcinoma and their use in a combined diagnostic assay. Genet Mol Res: Mar 18, 2016 (Epub ahead of print).
8. Ai P, Wang T, Zhang H, Wang Y, Song C, Zhang L, Li Z and Hu H: Determination of antibodies directed at EBV proteins expressed in both latent and lytic cycles in nasopharyngeal carcinoma. Oral Oncol 49: 326-331, 2013.
9. Jiang W, Zheng B and Wei H: Recent advances in early detection of nasopharyngeal carcinoma. Discov Oncol 15: 365, 2024.
10. Lo KW, To KF and Huang DP: Focus on nasopharyngeal carcinoma. Cancer Cell 5: 423-428, 2004.
11. Wong KC, Hui EP, Lo KW, Lam WKJ, Johnson D, Li L, Tao Q, Chan KCA, To KF, King AD, *et al*: Nasopharyngeal carcinoma: An evolving paradigm. Nat Rev Clin Oncol 18: 679-695, 2021.
12. Zhang S, Zhou Y, Liu Z, Wang Y, Zhou X, Chen H, Zhang X, Chen Y, Feng Q, Ye X, *et al*: Immunosequencing identifies signatures of T cell responses for early detection of nasopharyngeal carcinoma. Cancer Cell 43: 1423-1441, 2025.
13. Ni XG and Wang GQ: The role of narrow band imaging in head and neck cancers. Curr Oncol Rep 18: 10, 2016.
14. Chan JL, Lin L, Feiler M, Wolf AI, Cardona DM and Gellad ZF: Comparative effectiveness of i-SCAN™ and high-definition white light characterizing small colonic polyps. World J Gastroenterol 18: 5905-5911, 2012.
15. Lam WKJ, Jiang P, Chan KCA, Cheng SH, Zhang H, Peng W, Tse OYO, Tong YK, Gai W, Zee BCY, *et al*: Sequencing-based counting and size profiling of plasma Epstein-Barr virus DNA enhance population screening of nasopharyngeal carcinoma. Proc Natl Acad Sci USA 115: E5115-E5124, 2018.
16. Wu X, Tay JK, Goh CK, Chan C, Lee YH, Springs SL, Wang Y, Loh KS, Lu TK, and Yu H: Digital CRISPR-based method for the rapid detection and absolute quantification of nucleic acids. Biomaterials 274: 120876, 2021.
17. Jiang C, Zheng X, Lin L, Li X, Li X, Liao Y, Jia W and Shu B: CRISPR Cas12a-mediated amplification-free digital DNA assay improves the diagnosis and surveillance of Nasopharyngeal carcinoma. Biosens Bioelectron 237: 115546, 2023.
18. Li T, Li F, Guo X, Hong C, Yu X, Wu B, Lian S, Song L, Tang J, Wen S, *et al*: Anti-Epstein-Barr virus BNLF2b for mass screening for nasopharyngeal cancer. N Engl J Med 389: 808-819, 2023.
19. Pan YX, Huang Q, Xing S and Zhu QY: A novel serum protein biomarker for the late-stage diagnosis of nasopharyngeal carcinoma. BMC Cancer 25: 585, 2025.
20. Ji MF, He YQ, Tang MZ, Xue WQ, Yu X, Diao H, Yang DW, Mai ZM, Cheong IH and Zhao ZY: Epstein Barr virus antibody and cancer risk in two prospective cohorts in Southern China. Nat Commun 16: 5940, 2025.
21. Xu Y, Zhao W, Mo Y, Ma N, Midorikawa K, Kobayashi H, Hiraku Y, Oikawa S, Zhang Z and Huang G: Combination of RERG and ZNF671 methylation rates in circulating cell-free DNA: A novel biomarker for screening of nasopharyngeal carcinoma. Cancer Sci 111: 2536-2545, 2020.
22. Hsu CL, Chang YS and Li HP: Molecular diagnosis of nasopharyngeal carcinoma: Past and future. Biomed J 48: 100748, 2025.
23. Islam KA, Chow LKY, Kam NW, Wang Y, Chiang CL, Choi HCW, Xia YF, Lee AWM, Ng WT and Dai W: Prognostic biomarkers for survival in nasopharyngeal carcinoma: A systematic review of the literature. Cancers 14: 2022, 2122.
24. Li G, Wu Z, Peng Y, Liu X, Lu J, Wang L, Pan Q, He ML and Li XP: MicroRNA-10b induced by Epstein-Barr virus-encoded latent membrane protein-1 promotes the metastasis of human nasopharyngeal carcinoma cells. Cancer Lett 299: 29-36, 2010.
25. Allaya N, Khabir A, Sallemi-Boudawara T, Sellami N, Daoud J, Ghorbel A, Frikha M, Gargouri A, Mokdad-Gargouri R and Ayadi W: Over-expression of miR-10b in NPC patients: Correlation with LMP1 and Twist1. Tumor Biol 36: 3807-3814, 2015.
26. Chen Y, Lin T, Tang L, He L and He Y: MiRNA signatures in nasopharyngeal carcinoma: Molecular mechanisms and therapeutic perspectives. Am J Cancer Res 13: 5805-5824, 2023.
27. Zhang Y and Xu Z: miR-93 enhances cell proliferation by directly targeting CDKN1A in nasopharyngeal carcinoma. Oncol Lett 15: 1723-1727, 2018.
28. Zhou W, Chang A, Zhao H, Ye H, Li D and Zhuo X: Identification of a novel microRNA profile including miR-106b, miR-17, miR-20b, miR-18a and miR-93 in the metastasis of nasopharyngeal carcinoma. Cancer Biomark 27: 533-539, 2020.
29. Duan B, Shi S, Yue H, You B, Shan Y, Zhu Z, Bao L and You Y: Exosomal miR-17-5p promotes angiogenesis in nasopharyngeal carcinoma via targeting BAMBI. J Cancer 10: 6681-6692, 2019.
30. Zhang H, Zou X, Wu L, Zhang S, Wang T, Liu P, Zhu W and Zhu J: Identification of a 7-microRNA signature in plasma as promising biomarker for nasopharyngeal carcinoma detection. Cancer Med 9: 1230-1241, 2020.
31. Zou X, Zhu D, Zhang H, Zhang S, Zhou X, He X, Zhu J and Zhu W: MicroRNA expression profiling analysis in serum for nasopharyngeal carcinoma diagnosis. Gene 727: 144243, 2020.
32. Jiang C, Chen J, Xie S, Zhang L, Xiang Y, Lung M, Kam NW, Kwong DL, Cao S and Guan XY: Evaluation of circulating EBV microRNA BART2-5p in facilitating early detection and screening of nasopharyngeal carcinoma. Int J Cancer 143: 3209-3217, 2018.
33. Lyu X, Fang W, Cai L, Zheng H, Ye Y, Zhang L, Li J, Peng H, Cho WC, Wang E, *et al*: TGFβR2 is a major target of miR-93 in nasopharyngeal carcinoma aggressiveness. Mol Cancer 13: 51, 2014.
34. Yang W, Tan S, Yang L, Chen X, Yang R, Oyang L, Lin J, Xia L, Wu N, Han Y, *et al*: Exosomal miR-205-5p enhances angiogenesis and nasopharyngeal carcinoma metastasis by targeting desmocollin-2. Mol Ther Oncolytics 24: 612-623, 2022.
35. Hsia B, Sure A, Dongre R, Jo N, Kuzniar J, Bitar G, Alshaka SA, Kim JD, Valencia-Sanchez BA, Brandel MG, *et al*: Molecular profiling of nasopharyngeal carcinoma using the AACR project GENIE repository. Cancers (Basel) 17: 1544, 2025.
36. Wan X, Liu Y, Peng Y, Wang J, Yan SM, Zhang L, Wu W, Zhao L, Chen X, Ren K, *et al*: Primary and orthotopic murine models of nasopharyngeal carcinoma reveal molecular mechanisms underlying its malignant progression. Adv Sci (Weinh) 11: e2403161, 2024.
37. Chen W, Yang KB, Zhang YZ, Lin ZS, Chen JW, Qi SF, Wu CF, Feng GK, Yang DJ, Chen M, *et al*: Synthetic lethality of combined ULK1 defection and p53 restoration induce pyroptosis by directly upregulating GSDME transcription and cleavage activation through ROS/NLRP3 signaling. J Exp Clin Cancer Res 43: 248, 2024.
38. Agaoglu FY, Dizdar Y, Dogan O, Alatli C, Ayan I, Savci N, Tas S, Dalay N and Altun M: P53 overexpression in nasopharyngeal carcinoma. In Vivo 18: 555-560, 2004.
39. Li YY, Chung GT, Lui VW, To KF, Ma BB, Chow C, Woo JKS, Yip KY, Seo J, Hui EP, *et al*: Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations. Nat Commun 8: 14121, 2017.
40. Papa A and Pandolfi PP: The PTEN-PI3K axis in cancer. Biomolecules 9: 153, 2019.
41. Zhang S, Hong HI, Mak VCY, Zhou Y, Lu Y, Zhuang G and Cheung LWT: Vertical inhibition of p110α/AKT and N-cadherin enhances treatment efficacy in PIK3CA-aberrated ovarian cancer cells. Mol Oncol 19: 1132-1154, 2025.
42. Shamsuri AS and Sim EU: In silico prediction of the action of bromelain on PI3K/Akt signalling pathway to arrest nasopharyngeal cancer oncogenesis by targeting phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha protein. BMC Res Notes 17: 346, 2024.
43. Zhou Z, Li P, Zhang X, Xu J, Xu J, Yu S, Wang D, Dong W, Cao X, Yan H, *et al*: Mutational landscape of nasopharyngeal carcinoma based on targeted next-generation sequencing: Implications for predicting clinical outcomes. Mol Med 28: 55, 2022.

44. Zhu Q, Duan XB, Hu H, You R, Xia TL, Yu T, Xiang T and Chen MY: EBV-induced upregulation of CD55 reduces the efficacy of cetuximab treatment in nasopharyngeal carcinoma. J Transl Med 22: 1111, 2024.
45. Piao Y, Yang Y, Wu S and Han L: Toripalimab plus cetuximab combined with radiotherapy in a locally advanced platinum-based chemotherapy-insensitive nasopharyngeal carcinoma patient: A case report. Front Oncol 14: 1383250, 2024.
46. Fang Y, Lv X, Li G, Wang P, Zhang L, Wang R, Jia L and Liang S: Schisandrin B targets CDK4/6 to suppress proliferation and enhance radiosensitivity in nasopharyngeal carcinoma by inducing cell cycle arrest. Sci Rep 15: 8452, 2025.
47. Li HP, Huang CY, Lui KW, Chao YK, Yeh CN, Lee LY, Huang Y, Lin TL, Kuo YC, Huang MY, *et al*: Nasopharyngeal carcinoma patient-derived xenograft mouse models reveal potential drugs targeting cell cycle, mTOR, and autophagy pathways. Transl Oncol 38: 101785, 2023.
48. Li HP, Huang CY, Lui KW, Chao YK, Yeh CN, Lee LY, Huang Y, Lin TL, Kuo YC, Huang MY, *et al*: Combination of epithelial growth factor receptor blockers and CDK4/6 inhibitor for nasopharyngeal carcinoma treatment. Cancers (Basel) 13: 2954, 2021.
49. Liao LJ, Hsu WL, Chen CJ and Chiu YL: Feature reviews of the molecular mechanisms of nasopharyngeal carcinoma. Biomedicines 11: 1528, 2023.
50. Tao W, Jiang C, Velu P, Lv C and Niu Y: Rosmanol suppresses nasopharyngeal carcinoma cell proliferation and enhances apoptosis, the regulation of MAPK/NF-κB signaling pathway. Biotechnol Appl Biochem 72: e2750, 2025.
51. Liang Y, Xiong XY, Lin GW, Bai X, Li F, Ko JM, Zhou YH, Xu AY, Liu SQ, He S, *et al*: Integrative transcriptome-wide association study with expression quantitative trait loci colocalization identifies a causal VAMP8 variant for nasopharyngeal carcinoma susceptibility. Adv Sci (Weinh) 12: e2412580, 2025.
52. Wang Y, Chen Y, Liu Y, Zhao J, Wang G, Chen H, Tang Y, Ouyang D, Xie S, You J, *et al*: Tumor vascular endothelial cells promote immune escape by upregulating PD-L1 expression via crosstalk between NF-κB and STAT3 signaling pathways in nasopharyngeal carcinoma. Cell Death Dis 16: 129, 2025.
53. Wang R, Hu Y, Yindom LM, Huang L, Wu R, Wang D, Chang C, Rostron T, Dong T and Wang X: Association analysis between HLA-A, -B, -C, -DRB1, and -DQB1 with nasopharyngeal carcinoma among a Han population in Northwestern China. Hum Immunol 75: 197-202, 2014.
54. Barber LD, Percival L, Valiante NM, Chen L, Lee C, Gumperz JE, Phillips JH, Lanier LL, Bigge JC, Parekh RB and Parham P: The inter-locus recombinant HLA-B*4601 has high selectivity in peptide binding and functions characteristic of HLA-C. J Exp Med 184: 735-740, 1996.
55. Su WH, Chiu CC and Shugart YY: Heterogeneity revealed through meta-analysis might link geographical differences with nasopharyngeal carcinoma incidence in Han Chinese populations. BMC Cancer 15: 598, 2015.
56. Xu H, Liu J, Zhang Y, Zhou Y, Zhang L, Kang J, Ning C, He Z and Song S: KIF23, under regulation by androgen receptor, contributes to nasopharyngeal carcinoma deterioration by activating the Wnt/β-catenin signaling pathway. Funct Integr Genomics 23: 116, 2023.
57. Ji Y, Wang M, Li X and Cui F: The long noncoding RNA NEAT1 targets miR-34a-5p and drives nasopharyngeal carcinoma progression via Wnt/β-catenin signaling. Yonsei Med J 60: 336-345, 2019.
58. Song P, Ye LF, Zhang C, Peng T and Zhou XH: Long non-coding RNA XIST exerts oncogenic functions in human nasopharyngeal carcinoma by targeting miR-34a-5p. Gene 592: 8-14, 2016.
59. Yang S, Dai Z, Li W, Wang R and Huang D: Aberrant promoter methylation reduced the expression of protocadherin 17 in nasopharyngeal cancer. Biochem Cell Biol 97: 364-368, 2019.
60. Loyo M, Brait M, Kim MS, Ostrow KL, Jie CC, Chuang AY, Califano JA, Liégeois NJ, Begum S, Westra WH, *et al*: A survey of methylated candidate tumor suppressor genes in nasopharyngeal carcinoma. Int J Cancer 128: 1393-1403, 2011.
61. Li T, Patel KB, Yu X, Yao S, Wang L, Chung CH and Wang X: Unveiling targeted cell-free DNA methylation regions through paired methylome analysis of tumor and normal tissues. bioRxiv 29: 10.1101/2023.06.27.546654, 2023.
62. Xu J, Chen D, Wu W, Ji X, Dou X, Gao X, Li J, Zhang X, Huang WE and Xiong D: A metabolic map and artificial intelligence-aided identification of nasopharyngeal carcinoma via a single-cell Raman platform. Br J Cancer 130: 1635-1646, 2024.
63. Yi L, Dong N, Shi S, Deng B, Yun Y, Yi Z and Zhang Y: Metabolomic identification of novel biomarkers of nasopharyngeal carcinoma. RSC Advances 4: 59094-59101, 2014.
64. Liao Z, Zhao L, Zhong F, Zhou Y, Lu T, Liu L, Gong X, Li J and Rao J: Serum and urine metabolomics analyses reveal metabolic pathways and biomarkers in relation to nasopharyngeal carcinoma. Rapid Commun Mass Spectrom 37: e9469, 2023.
65. Zhou J, Deng Y, Huang Y, Wang Z, Zhan Z, Cao X, Cai Z, Deng Y, Zhang L, Huang H, *et al*: An individualized prognostic model in patients with locoregionally advanced nasopharyngeal carcinoma based on serum metabolomic profiling. Life (Basel) 13: 1167, 2023.
66. Zhou Z, Tang T, Li N, Zheng Q, Xiao T, Tian Y, Sun J, Zhang L, Wang X, Wang Y, *et al*: VLDL and LDL subfractions enhance the risk stratification of individuals who underwent epstein-barr virus-based screening for nasopharyngeal carcinoma: A multicenter cohort study. Adv Sci (Weinh) 11: e2308765, 2024.
67. Liu H, Wang J, Wang L, Tang W, Hou X, Zhu YZ and Chen X: Multi-omics exploration of the mechanism of curcumol to reduce invasion and metastasis of nasopharyngeal carcinoma by inhibiting NCL/EBNA1-mediated UBE2C upregulation. Biomolecules 14: 1142, 2024.
68. Nie RC, Zhao CB, Xia XW, Luo YS, Wu T, Zhou ZW, Yuan SQ, Wang Y and Li YF: The efficacy and safety of PD-1/PD-L1 inhibitors in combination with conventional therapies for advanced solid tumors: A meta-analysis. Biomed Res Int 2020: 5059079, 2020.
69. Zhou S, Zhu J, Xu J, Gu B, Zhao Q, Luo C, Gao Z, Chin YE and Cheng X: Anti-tumour potential of PD-L1/PD-1 post-translational modifications. Immunology 167: 471-481, 2022.
70. Lu MM and Yang Y: Exosomal PD-L1 in cancer and other fields: Recent advances and perspectives. Front Immunol 15: 1395332, 2024.
71. Hsu C, Lee SH, Ejadi S, Even C, Cohen RB, Le Tourneau C, Mehnert JM, Algazi A, van Brummelen EMJ, Saraf S, *et al*: Safety and antitumor activity of pembrolizumab in patients with programmed death-ligand 1-positive nasopharyngeal carcinoma: Results of the KEYNOTE-028 study. J Clin Oncol 35: 4050-4056, 2017.
72. Ma BBY, Lim WT, Goh BC, Hui EP, Lo KW, Pettinger A, Foster NR, Riess JW, Agulnik M, Chang AYC, *et al*: Antitumor activity of nivolumab in recurrent and metastatic nasopharyngeal carcinoma: An international, multicenter study of the mayo clinic phase 2 consortium (NCI-9742). J Clin Oncol 36: 1412-1418, 2018.
73. Yang Y, Zhou T, Chen X, Li J, Pan J, He X, Lin L, Shi YR, Feng W, Xiong J, *et al*: Efficacy, safety, and biomarker analysis of camrelizumab in previously treated recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN study). J Immunother Cancer 9: e003790, 2021.
74. Yang Y, Qu S, Li J, Hu C, Xu M, Li W, Zhou T, Shen L, Wu H, Lang J, *et al*: Camrelizumab versus placebo in combination with gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (CAPTAIN-1st): A multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol 22: 1162-1174, 2021.
75. Shi Y, Han G, Zhou J, Shi X, Jia W, Cheng Y, Jin Y, Hua X, Wen T, Wu J, *et al*: Toripalimab plus bevacizumab versus sorafenib as first-line treatment for advanced hepatocellular carcinoma (HEPATORCH): A randomised, open-label, phase 3 trial. Lancet Gastroenterol Hepatol 10: 658-670, 2025.
76. Xue J, Ma T and Zhang X: TRA2: The dominant power of alternative splicing in tumors. Heliyon 9: e15516, 2023.
77. Xiao M, Xue J and Jin E: SPOCK: Master regulator of malignant tumors (Review). Mol Med Rep 30: 231, 2024.
78. Briante R, Zhai Q, Mohanty S, Zhang P, O'Connor A, Misker H, Wang W, Tan C, Abuhay M, Morgan J, *et al*: Successful targeting of multidrug-resistant tumors with bispecific antibodies. Mabs 17: 2492238, 2025.
79. Li D, Wang J, Li X, Wang Z, Yu Q, Koh SB, Wu R, Ye L, Guo Y, Okoli U, *et al*: Interactions between radiotherapy resistance mechanisms and the tumor microenvironment. Crit Rev Oncol Hematol 210: 104705, 2025.
80. Kumazawa Y, Ikenoyama Y, Takamatsu M, Kido K, Namikawa K, Tokai Y, Yoshimizu S, Horiuchi Y, Ishiyama A, Yoshio T, *et al*: ]Differences in clinical characteristics between missed and detected laryngopharyngeal cancers. J Gastroenterol Hepatol 40: 2037-2045, 2025.

81. He R, Jie P, Hou W, Long Y, Zhou G, Wu S, Liu W, Lei W, Wen W and Wen Y: Real-time artificial intelligence-assisted detection and segmentation of nasopharyngeal carcinoma using multimodal endoscopic data: A multi-center, prospective study. EClinicalMedicine 81: 103120, 2025.
82. Si YF, Deng ZX, Weng JJ, Si JY, Lan GP, Zhang BJ, Yang Y, Huang B, Han X, Qin Y, *et al*: A study on the value of narrow-band imaging (NBI) for the general investigation of a high-risk population of nasopharyngeal carcinoma (NPC). World J Surg Oncol 16: 126, 2018.
83. Filauro M, Vallin A, Fragale M, Sampieri C, Guastini L, Mora F and Peretti G: Office-based procedures in laryngology. Acta Otorhinolaryngol Ital 41: 243-247, 2021.
84. Wu KP, Li QQ, Luo XQ, Wang XX, Lai YZ, Tian D, Yang HC, Wei XL, Wang LY, Li QM, *et al*: Chemoimmunotherapy as induction treatment in concurrent chemoradiotherapy for patients with nasopharyngeal carcinoma stage IVa. Ann Med 57: 2453091, 2025.
85. Lan K, Liu S, Li S, Sun X, Xie S, Jia G, Sun R and Mai H: Comparing outcomes and toxicities among patients with nasopharyngeal carcinoma treated with daytime versus evening radiotherapy: A retrospective analysis with propensity score matching. Int J Cancer 157: 345-354, 2025.
86. Liang YJ, Luo MJ, Wen DX, Wang P, Tang LQ, Mai HQ and Liu LT: Optimal induction chemotherapy courses in nasopharyngeal carcinoma in the IMRT era: A recursive partitioning risk stratification analysis based on EBV DNA and AJCC staging. Oral Oncol 167: 107404, 2025.
87. Lin SJ, Guo QJ, Liu Q, Ng WT, Ahn YC, AlHussain H, Chan AW, Chow J, Chua M, Corry J, *et al*: International consensus guideline on delineation of the clinical target volumes (CTV) at different dose levels for nasopharyngeal carcinoma (2024 Version). Int J Radiat Oncol Biol Phys 123: 415-421, 2025.
88. Qiu QH, Li N, Zhang QH, Chen Z, Huang Y, Jiang Y and Yang XT: Clinical efficacy of endoscopic nasopharyngectomy for initially diagnosed advanced nasopharyngeal carcinoma. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 52: 365-371, 2017 (In Chinese).
89. Emanuelli E, Albu S, Cazzador D, Pedruzzi B, Babighian G and Martini A: Endoscopic surgery for recurrent undifferentiated nasopharyngeal carcinoma. J Craniofac Surg 25: 1003-1008, 2014.
90. Liu YP, Wen YH, Tang J, Wei Y, You R, Zhu XL, Li J, Chen L, Ling L, Zhang N, *et al*: Endoscopic surgery compared with intensity-modulated radiotherapy in resectable locally recurrent nasopharyngeal carcinoma: A multicentre, open-label, randomised, controlled, phase 3 trial. Lancet Oncol 22: 381-390, 2021.
91. You R, Liu YP, Xie YL, Lin C, Duan CY, Chen DP, Pan Y, Qi B, Zou X, Guo L, *et al*: Hyperfractionation compared with standard fractionation in intensity-modulated radiotherapy for patients with locally advanced recurrent nasopharyngeal carcinoma: A multicentre, randomised, open-label, phase 3 trial. Lancet 401: 917-927, 2023.
92. Weng J, Gao J, Li M, Wei J, Zhang S, Lan G, Li B, Qin D, Huang B, Zhu Z, *et al*: Effect of endoscopic surgery combined with chemotherapy and radiotherapy on prognosis of early nasopharyngeal carcinoma patients in high incidence area. Lin Chuang Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 38: 472-476, 2024.
93. Liu YP, Lv X, Zou X, Hua YJ, You R, Yang Q, Xia L, Guo SY, Hu W, Zhang MX, *et al*: Minimally invasive surgery alone compared with intensity-modulated radiotherapy for primary stage I nasopharyngeal carcinoma. Cancer Commun (Lond) 39: 75, 2019.
94. Liu J, Zeng Z, Wang D and Qin G: Minimally invasive surgery for early-stage nasopharyngeal carcinoma. J Craniofac Surg 33: e834-e837, 2022.
95. Chen YP, Wang YQ, Li WF, Chen L, Xu C, Lu TX, Lin AH, Yao JJ, Li YC, Sun Y, *et al*: Critical evaluation of the quality and recommendations of clinical practice guidelines for nasopharyngeal carcinoma. J Natl Compr Canc Netw 15: 336-344, 2017.
96. Zhang B, Li Y, Weng J, Huang B, Ban M, Lan G, Lu Y, Luo J, Qu S and Si Y: Efficacy and safety of endoscopic nasopharyngectomy combined with low-dose radiotherapy for primary T1-2 nasopharyngeal carcinoma. Technol Cancer Res Trea: Apr 26, 2021 (Epub ahead of print).
97. Weng JJ, Wei JZ, Li M, Zhang SJ, Wei YZ, Wang HW, Qin DX, Lu JL, Jiang H, and Qu SH: Effects of surgery combined with chemoradiotherapy on short- and long-term outcomes of early-stage nasopharyngeal carcinoma. Cancer Manag Res 12: 7813-7826, 2020.
98. Su SF, Han F, Zhao C, Chen CY, Xiao WW, Li JX and Lu TX: Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone. Int J Radiat Oncol Biol Phys 82: 327-333, 2012.
99. Wu LR, Liu YT, Jiang N, Fan YX, Wen J, Huang SF, Guo WJ, Bian XH, Wang FJ, Li F, *et al*: Ten-year survival outcomes for patients with nasopharyngeal carcinoma receiving intensity-modulated radiotherapy: An analysis of 614 patients from a single center. Oral Oncol 69: 26-32, 2017.
100. Niu X, Xue F, Liu P, Hu C and He X: Long-term outcomes of nasopharyngeal carcinoma patients with T1-2 stage in intensity-modulated radiotherapy era. Int J Med Sci 19: 267-273, 2022.
101. Chan KA, Woo JK, King A, Zee BC, Lam WJ, Chan SL, Chu SW, Mak C, Tse IO, Leung SY, *et al*: Analysis of plasma Epstein-Barr virus DNA to screen for nasopharyngeal cancer. N Engl J Med 377: 513-522, 2017.
102. Zheng XH, Li XZ, Tang CL, Zhang YM, Zhou T, Yang XJ, Liao Y, He YQ, Wang TM, Xue WQ and Jia WH: Detection of Epstein-Barr virus DNA methylation as tumor markers of nasopharyngeal carcinoma patients in saliva, oropharyngeal swab, oral swab, and mouthwash. MedComm (2020) 5: e673, 2024.
103. Sun J, Yong J and Zhang H: microRNA-93, upregulated in serum of nasopharyngeal carcinoma patients, promotes tumor cell proliferation by targeting PDCD4. Exp Ther Med 19: 2579-2587, 2020.
104. Siak PY, Khoo ASB, Leong CO, Hoh BP and Cheah SC: Current status and future perspectives about molecular biomarkers of nasopharyngeal carcinoma. Cancers 13: 3490, 2021.
105. He Q, Zhou Y, Zhou J, Zhao D, Li L, Li X, Huang Y, Wang Q, Zou H, Zhang K, *et al*: Clinical relevance of plasma EBV DNA as a biomarker for nasopharyngeal carcinoma in non-endemic areas: A multicenter study in southwestern China. Clin Chim Acta 541: 117244, 2023.
106. Lee VHF, Adham M, Kridis WB, Bossi P, Chen MY, Chitapanarux I, Gregoire V, Hao SP, Ho C, Ho GF, *et al*: International recommendations for plasma Epstein-Barr virus DNA measurement in nasopharyngeal carcinoma in resource-constrained settings: Lessons from the COVID-19 pandemic. Lancet Oncol 23: e544-e551, 2022.
107. Lam WKJ and Lo YMD: Plasma epstein-barr virus DNA analysis for personalised management of nasopharyngeal carcinoma-current opportunities and challenges. Ann Nasopharynx Cancer 6: 1-8, 2022.
108. Economopoulou P, Lianidou E and Psyrri A: Epstein-Barr virus DNA detection by targeted sequencing in post-treatment plasma samples and prognosis of locally advanced nasopharyngeal cancer: Implications for clinical research. Ann Oncol 33: 747-749, 2022.
109. Chen AY, Frankowski R, Bishop-Leone J, Hebert T, Leyk S, Lewin J and Goepfert H: The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: The MD Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg 127: 870-876, 2001.
110. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF, Biorklund A, de Leeuw JRJ, Fayers PM, Jannert M, *et al*: Quality of life in head and neck cancer patients: Validation of the European Organization for research and treatment of cancer quality of life questionnaire-H&N35. J Clin Oncol 17: 1008-1008, 1999.