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Review article

Epstein-Barr Virus and Nasopharyngeal Carcinoma: A Review on Virology, Oncogenic Mechanisms, and Clinical Implications

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Abstract: Epstein-Barr virus (EBV) is a ubiquitous human gammaherpesvirus with the unique ability to establish lifelong latency and drive oncogenic transformation in several malignancies, including nasopharyngeal carcinoma (NPC). This review summarizes the essential virology of EBV, highlighting its structural components, infection mechanisms, and latent gene expression programs that facilitate immune evasion and cellular transformation. A strong epidemiological and molecular correlation exists between EBV infection and the development of NPC, particularly in endemic regions. EBV exhibits a tropism for epithelial cells lining the nasopharynx, where it invades through receptor-mediated entry and establishes latent infection. Key viral oncogenes such as latent membrane protein 1 (LMP1), LMP2, and EBNA1 activate multiple oncogenic pathways including NF-κB, JAK/STAT, PI3K/AKT, and MAPK, promoting proliferation, resistance to apoptosis, and genomic instability. Additional biomarkers such as circulating EBV DNA and serological antibodies offer diagnostic and prognostic value. The review also outlines the current staging system for NPC, which guides clinical management and treatment decisions. Understanding the interplay between EBV virology, host immune responses, and molecular drivers provides critical insights into NPC pathogenesis and highlights potential targets for early detection, prevention, and therapeutic intervention.

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Introduction

Cancer stands as a leading cause of substantial global mortality. It is estimated that cancers linked to Epstein-Barr viruses (EBV) contribute to around 1.5% of total cancer cases globally, leading to 1.8% of deaths attributed to cancer (Ahmed et al., 2023). EBV is linked to various human cancers, encompassing both epithelial and lymphoid cancers, including nasopharyngeal carcinoma (NPC) (Teow et al., 2017). NPC is an important cancer, with a high incidence rate in southern China but a low rate in Jordan. NPC originates in the nasopharynx's epithelial cells. Typically, the tumor point is observed at the fossa of Rosen Müller within the confines of the nasopharynx. From this point, the tumor extends into nearby anatomical spaces or organs (Chua et al., 2016). Hence, NPC is classified as a kind of head and neck cancer. Though the incidence of NPC is thought to be low globally, it is associated with a poor prognosis that translates into a lower survival rate (da Costa et al., 2015).

EBV is a very common viral infection that causes a latent infection in 95% of the world's population. Most of these infections are benign. However, EBV has been implicated as a potential causative agent for various human cancers, including NPC, especially the poorly differentiated NPC that is particularly prevalent

in the Southern Chinese population. In NPC, cells are found to be infected with EBV (Dunmire et al., 2018). Latent EBV infection is characterized by the expression of many latent EBV genes. Somatic mutations in lesions that are precancerous and EBV infections are thought to interact robustly to influence the development of NPC (Rostgaard et al., 2019). Given the strong association between latent EBV infection and the development of NPC, detecting EBV-deoxyribonucleic acid (EBV DNA) and other EBV genes that play a role in oncogenicity can be a very useful diagnostic and prognostic tool (Ahmed et al., 2022).

Basic Virology of Epstein-Bar Virus (EBV)

EBV is one of the major human herpes viruses. Human herpesvirus 4 (HHV-4) is another name for EBV. Other pathogenic human herpes viruses include human herpes simplex viruses (HSVs) 1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV), and human herpes viruses (HHVs) 6, 7, and 8 (Jassim et al., 2021). The double stranded, linear DNA genome of EBV virions is protected by a protein capsid, just like that of other herpesviruses. The envelope itself is studded with glycoproteins essential for cell tropism, host range, and receptor binding, and a protein tegument lies between the envelope and the capsid. The diameter of mature virions usually ranges from 120 to 180 nm. The approximately 100 genes that make up the EBV genome have had their precise structure fully unraveled (Ahmed et al., 2022).

Two subtypes of EBV are distinguished from one another by differences at the EBV level. While type 1 and type 2 are equally dispersed throughout Africa, type 1 is more common in the Western Hemisphere and Southeast Asia. These subtypes are distinguished by unique restriction endonuclease digestion patterns that demonstrate varying capacity for cellular transformation as well as the potential to start the lytic cycle on their own (Jha et al., 2016). There are three different stages of differentiation for this kind of cancer, depending on the histological characteristics. Keratinization squamous cell carcinoma (KSCC) is the first type; nonkeratinizing carcinoma (NKC) is Type II; and undifferentiated carcinoma (UDC), also known as lymphoepithelioma and containing lymphoplasmacytic infiltrate, is Type III, according to the World Health Organization (WHO) (Ayadi et al., 2007) .EBV Infection and Oncogenesis EBV is a lymphocryptoviral that can infect a host during both the lytic and latent phases of infection. The EBV genome replicates just once every cell cycle while the infection is latent. However, during the lytic phase, several viral genomes are produced and bundled into infectious particles for transmission. Although latent infection is the most common kind of infection in epithelial malignancies, lytic infection is the usual course of EBV infection in normal epithelium (Young et al., 2016).

Consequently, one of the key stages in the development of EBV-related epithelial malignancies may be the emergence of latent EBV infection. EBV most likely survives in epithelial cells because of somatic mutations and changes in cell signaling in premalignant epithelial cells that aid in the change from the normally default lytic infection to latent infection. When premalignant epithelial cells become infected and develop into cancerous cells, several latent EBV genes that are expressed in these cells later drive the cells' malignant transformation. Moreover, according to certain theories, the lytic EBV genes that are typically present in a very small proportion of NPC cells produce chemicals that evade the immune system, hence facilitating the in vivo growth of EBV-infected NPC (Shen et al., 2015).

Summary of EBV's Function as a Cancer-Causing Virus in Humans

Initially, it was believed that EBV was the first virus to induce a tumor in a human (Kanakry and Ambinder, 2015). Since, EBV has been associated with various malignancies. For example, 30%–40% of cases of classical Hodgkin’s lymphoma, 10% of cases of gastric carcinoma (also known as EBV-associated gastric cancer, or EBVaGC), and 100% of cases of non-keratinizing nasopharyngeal carcinomas (NKNPCs), the most prevalent histological subtype of NPC in endemic areas, have been reported to have EBV infection worldwide(Linke-Serinsöz et al., 2017). EBV infection is also found in leiomyosarcomas, T-, and natural killer (NK)-cell lymphomas, and it causes lymphoproliferative disorders following transplantation (Young et al., 2016). A minor proportion of breast cancer, gastric carcinoma (GC), and cervical cancer could contribute to EBV infection.

Strong Correlation Between NPC and EBV Infection

The human tumor form most closely associated with EBV infection is the undifferentiated histological type of

NPC, which is prevalent in Southeast Asia and southern China (Teow et al., 2017). NPCs are divided into two categories by the WHO: (a) KSCC is the first type, and (b) NKC is Type II. In endemic regions like Hong Kong and the Southern Chinese provinces, NPC is primarily NKC and strongly linked to EBV infection. Except for salivary gland tumors, almost all UNNPCs and almost all NPC cells are infected with EBV; other types of head and neck cancer are infected with the virus (Young et al., 2016).

The original connection between EBV infection and NPC was discovered when patients had substantial titers of serum antibodies against EBV antigens, such as viral capsid antigen (VCA) and early antigen diffuse (EAd/BMRF1). Through in situ hybridization (ISH), the EBV genome's presence in NPC cells was subsequently confirmed (Tsao et al., 2017) .

EBV Invasion into The Cells That Line the Nasal Cavity

EBV is a human tumor virus that is widely distributed and causes productive and latency-associated viral replication. It is a lifetime infection that dwells in the oral epithelium and B lymphocytes. As evidenced by a restricted viral gene expression profile that facilitates viral evasion of immune surveillance and long-term persistence, B cells promote the latent phase of the viral lifecycle Reactivation of latently infected EBV-positive B cells into a productive lifespan is known as viral reactivation (Damania et al., 2022). Early EBV infection often starts in the tonsillar area. EBV primarily targets host cells, such as B lymphocytes and epithelial cells (Young et al., 2016) . It is interesting to remember that during its infection cycle, the virus moves between epithelial cells and B cells, which aids in its persistence and spread in people (Tao et al., 2020).

EBV attacks oral epithelial cells and is spread by saliva. Within the top, differentiated layers of the epithelium, epithelial cells facilitate the productive reproduction of viruses. EBV uses a variety of latency programs in B cells to help in B cell differentiation and maturation as well as to promote B cell proliferation and survival. Memory B cells are long-lived cells that serve as a continuous reservoir for latent EBV infection. EBV reactivation is triggered when memory B-cells differentiate into plasma cells. This results in the production of fresh progeny virions that infect the epithelium, are excreted in saliva, or re-infect other naïve B-cells (Ward et al., 2022).

The binding of EBV to B cells is facilitated by the interaction between the viral gp350 protein and CD21 on B cells. Following this, EBV gp42 engages with B-cell human leukocyte antigens II (HLA-II) molecules, leading to the union of the virus with the host cell membrane. In epithelial cells lacking CD21, the interaction between the EBV BMRF-2 protein and β1 integrin takes place, triggering fusion. Subsequently, the EBV gH/gL envelope protein interacts with αvβ6/8 integrin's, initiating the fusion process in these cells. The virus undergoes endocytosis into vesicles, and the fusion with the vesicle membrane releases the nucleocapsid into the cytoplasm. Once the viral nucleocapsid dissolves, the genome is transported to the nucleus, where DNA polymerases play a role in facilitating replication. During the lytic phase of the viral life cycle, viral DNA polymerase propels linear viral replication (Zhu et al., 2020). have conducted a comprehensive assessment of both lytic and latent replications. It is thought that human pharyngeal epithelial cells serve as reservoirs for lytic EBV infection, a process in which infectious virus particles are released into saliva to propagate the infection and amplified EBV genomes. There is general agreement that normal pharyngeal epithelium expresses CD21 either minimally or not at all (Su et al., 2023).

On the other hand, tonsillar and adenoid epithelia micro dissected histological sections have revealed CD21 mRNA transcripts, according to real time polymerase chain reaction (RT-PCR). Interestingly, dysplastic pharyngeal epithelia have higher levels of CD21 transcript expression (Liu et al., 2021). EBV infection in pharyngeal epithelial cells is thought to typically involve lytic replication. Patients with weakened immune systems may develop hairy leukoplakia, a form of epithelial hyperplasia, on the lateral surfaces of their tongues. EBV lytic replication has been found in this situation (Liu et al., 2021).

EBV infection of resting B lymphocytes causes them to proliferate into lymphoblastic cells, which ultimately renders them immortal. The progression of EBV- infected B cells will eventually stop in healthy people with functioning immune systems, with EBV causing a lifelong infection in the circulatory memory B-cell compartment. In contrast, primary epithelial cells infected with EBV do not proliferate or become immortal (Sinha et al., 2022). The host's immunological response to the lytic viral antigen expressed during EBV infection in dysplastic nasopharyngeal epithelium at an early stage of NPC development may be reflected in the early antibody response. There are wide variations in the effectiveness of EBV infection in B cells and

epithelial cells. High efficiency EBV infection of B cells can be accomplished by directly incubating the cells with supernatant obtained from virus-producing B cells that have been stimulated to experience lytic infection. On the other hand, for EBV to infect epithelial cells, producer B cells must come into contact with one another for the virus to spread (Al-Anazi et al., 2023). A co-culture procedure has produced a highly efficient EBV infection (20–50%) of native or immortalized nasopharyngeal epithelial cells (Tsang et al., 2019).

EBV Infection's Role in the Development of NPC

EBV DNA is steadily detected in patients with almost all NPC, regardless of the region's incidence rates. Various techniques, including PCR, ISH, and immunohistochemistry staining (IHS), confirm the presence of EBV in all NPC samples. It has been determined that a latent EBV infection is a precursor to cancer development (Tsao et al., 2017). An early stage of the development of NPC is the formation of a stable EBV infection in the pre-invasive nasopharyngeal epithelium. It is possible that both latent and lytic genes contribute to the development of NPC in the pre-invasive nasopharyngeal epithelium. The information about how EBV infection may have a role in the development of NPC is covered in detail in below, and multiple routes could be used by an EBV infection to cause the pathogenesis of NPC. Tumor suppressor gene inactivation and the promotion of a hypermethylation phenotype in the host are caused by EBV infection. EBV-induced hypermethylation may be the direct result of viral genes, like Latent Membrane Protein 1 (LMP-1), activating DNA methyl transferases (DNMTs), or it may be a host defense mechanism (Tsao et al., 2017).

NPC formation may be influenced by both latent and lytic EBV genes. To help virally infected cells evade the immune system, the lytic EBV genes may cause genomic instability and promote the release of cytokines that dampen the immune system. In NPC cells, the expression of latent genes also promotes carcinogenesis and the development of stemness (Tsao et al., 2017). NPC Incidence and Risk Factor NPC is a rare head and neck tumor originating from nasopharynx epithelial cells, with an incidence below 1 per 100,000 people per year in North America and Western countries. It is the third most common cancer among men in South China, with 15 to 50 cases per 100,000 people per year (Simon et al., 2022).

Even though NPC is rare in Arab countries, exposure to a wider range of risk factors is increasing the disease's occurrence. In Saudi Arabia, a number of the risk factors linked to NPC have become more apparent. The population of Saudi Arabia is frequently exposed to risk factors, which include higher antibody titers against the EBV, consumption of preserved foods, tobacco smoking combined with alcohol consumption, family history of NPC, specific human leukocyte antigen class I genotypes, history of chronic respiratory tract conditions, exposure to various inhalants, herbal medicines, and occupational exposures (Alotaibi et al., 2019). Of all newly registered NPC patients worldwide, 85.2% are from Asia (Banko et al., 2016). Males are more inclined than females to be affected by NPC in Jordan, where it affects both adults and children with an incidence rate of one per 100,000 people. The NPC incidence in 2018 was 45 cases, or 0.6% of the total, of which 28 cases (0.8%) were male and 17 cases (0.5%) were female, according to the Jordanian Ministry of Health (Ahmed et al., 2022).

LMP-1 and other molecular markers

LMP-1 is an EBV-encoded oncoprotein and a pivotal player in cellular transformation and cancer development (Smatti et al., 2018). LMP1 is a latent gene product encoded by EBV. Due to its ability to cause several phenotypic alterations in both B cells and epithelial cells, as well as its traditional oncogenic capabilities in mouse fibroblast transformation, it is believed to be an important oncoprotein. The fact that 78% of NPC samples express LMP-1 highlights the role that this protein plays in NPC carcinogenesis (Lao and Le, 2019). The presence of LMP-1 is correlated with an increased likelihood of metastasis in NPC. LMP-1 identification in primary NPC can help as an instant indicator of latent metastasis. Although 90% of NPC cases are related to EBV, the expression percent of LMP-1 described using available methods is between 50% and 80% (Lao et al., 2021).

Furthermore, a point mutation at nucleotide position G169425T in the LMP-1 gene has also been detected. This mutation causes the deletion of XhoI, a restriction site found in the cytoplasmic N-terminal tail. As a result, samples from patients with NPC frequently include the XhoI polymorphism, whereas samples from healthy people do not (da Costa et al., 2015).

The LMP-1 protein exhibits a structured composition, encompassing distinctive segments, including a brief cytoplasmic N-terminus, six hydrophobic transmembrane domains, and an extensive cytoplasmic C-terminus. Crucial regions facilitating cellular interactions include carboxy-terminal activating region 1,2 (CTAR1 and CTAR2), with a variable 11-amino-acid-repeat structure situated between them. Specific sequences within this repeat region play a crucial role in enabling the interaction with Janus kinase 3 (JAK3). Endeavors have been undertaken to scrutinize LMP-1 genes in malignancies where it is expressed, such as NPC, Hodgkin's disease (HD), and lymphoproliferative diseases, with comparative analyses against genes from healthy carriers. Initially, a 30- bp deletion in the LMP-1 gene was associated with certain EBV strains from NPC patients, which exhibited increased transforming ability and the potential to induce tumors. However, subsequent research found this deletion occurs not only in HD cases but also in healthy individuals outside NPC-endemic areas (Ahmed et al., 2022).

Recent findings show that LMP-1 genes isolated from Russian and German patients with NPC-like tumors in the parotid gland lack the 30-bp deletion but contain LMP-1 variants typical for their respective geographic regions. Given that the 30-bp deletion is present in both NPCs and healthy carriers, this calls into question the notion that it merely serves as a risk factor for the development of NPCs (Moyano et al., 2024). A study conducted in Tunisia scrutinized a genetic variation in the LMP1 gene, specifically a 30-base pair (BP) deletion (del- LMP1), within NPC patients. Notably, this del-LMP1 variant was prevalent in a significant percentage of NPC cases and was also identified in non-tumor samples. Furthermore, the study delves into a larger 69-bp deletion variant detected in certain NPC patients, drawing comparisons to its prevalence in other cancer types. The passage also touches upon the high incidence of NPC in North Africa, particularly in Tunisia, and introduces the examination of a genetic marker in the BamHI fragment N leftward reading frame 1 (BNLF1) gene within NPC biopsies and control specimens (Moyano et al., 2024).

The C-terminus of LMP-1, which has been identified as a mutational hotspot, is thought to be essential for oncogenesis. In a molecular analysis conducted on 21 cases of HD characterized by EBV positivity, in each instance, the viral DNA of the LMP gene was examined for polymorphisms such as deletions, insertions, and mutations using PCR amplification using certain primers. Using nested primer PCR and internal oligonucleotide hybridization, the magnified targets' selectivity was confirmed (Ahmed et al., 2022). All cases showed uniformity in the 5' LMP gene region, which codes for the transmembrane, short additional cytoplasmic domains, and amino terminus. On the other hand, minor DNA sequence insertions or deletions within the coding area of the intracytoplasmic LMP domain were present in about 20% of instances. In one instance, DNA sequencing was used to precisely locate a 30-base-pair loss. Notably, the 3' untranslated LMP region showed a notably high prevalence of DNA polymorphism (30% of instances). In contrast, when the LMP gene was examined under seven benign circumstances, no DNA polymorphism was found (Al-Hasnawy et al., 2016).

These variations, particularly in the LMP-1 gene, have been observed in different viral isolates, including those from Chinese nasopharyngeal carcinoma and various EBV- associated tumors (Khalifa et al., 2025). Researchers have identified a minimum of four primary categories of viral isolates, labeled Groups A through D, based on these variations. Some of the notable sequence changes in the LMP-1 gene involve the damage of an XhoI restriction site and a C-terminal 30-base pair deletion. These genetic alterations are thought to be associated with increased tumorigenicity and may vary among different geographic populations. However, it is important to note that these variations alone cannot serve as definitive markers for oncogenic EBV strains related to specific forms of EBV-associated tumors (Khalifa et al., 2025).

EBV is classified into type 1 or type 2 primarily through the assessment of variations within the Epstein-Barr nuclear antigen 2 (EBNA2) gene. This gene plays a crucial role in the transformation of B lymphocytes by EBV (Banko et al., 2016). Although the geographical distribution of these genotypes has been well documented, this specific association with diseases is not yet clearly understood. Epstein- Barr nuclear antigen 1 (EBNA1), the singular EBV gene that manifests expression in every infected cell, is thought to play a crucial role in EBV related tumors. It has been associated with inhibiting apoptosis and preventing the display of EBNA1 on major histocompatibility complex (MHC) class I molecules. EBNA1 sequence changeability is classified into subtypes and subvariants. The association between EBNA1 sequence variability and tumor status is debated, but the geographic distribution of EBNA1 subtypes is well established (Banko et al., 2016).

A crucial factor in deterministic EBV types lies in the sequence disparities within the (EBNA) 2 gene, distinguishing between A and B types. The A-type is predominantly associated with NPC, whereas the B-type

is correlated with B or T lymphomas. Further categorization through restriction fragment length polymorphism (RFLP) analysis reveals C and D types, along with prototype F and f variants. Regions with high incidence rates in southern Asia frequently exhibit the EBV C type and f variants (Lao et al., 2017).In both endemic and non-endemic NPC cases, the detection of plasma EBV-DNA has become a useful prognostic marker that is essential for treatment planning and patient monitoring. The in-house multiple-repeat fragment-focused BamHI-W test is the widely used technique for measuring EBV-DNA in endemic locations and clinical trials. Regulatory bodies in Europe advise using CE-labeled diagnostic tests that are especially made for in vitro diagnostic applications (Taverna et al., 2022).

A lot of CE-assays that target single-copy genes are particularly recommended. The predictive relevance of EBV-DNA measurement makes it recommended by NPC guidelines to be included in pre- and post-treatment evaluations (Taverna et al., 2022). Nevertheless, there is not sufficient data to provide a formal comparison of these techniques, and technical variations raise questions about the measurement of EBV-DNA (Taverna et al., 2022). The BamHI-W test, which measures variable repeats in the EBV-DNA region, holds the potential for increased sensitivity but introduces the possibility of bias in the quantification among subjects (Taverna et al., 2022).

Staging of NPC

The most accurate predictive tool for patient stratification for therapy and outcome evaluation is still the current TNM classification for NPC, developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (Kattan et al., 2016). The tumor, node, and metastasis (TNM) staging of nasopharyngeal malignant tumors is referred to as nasopharyngeal cancer staging. Although nasopharyngeal carcinomas make up the great majority of relevant tumors, smaller salivary gland tumors and other nasopharyngeal epithelial malignancies are also included. The TNM means (T: primary tumor, N: regional lymph node, M: distant metastasis) (Liao et al., 2022). Primary tumor (T) TX: It is not possible to evaluate the main tumor. T0: EBV- positive nodal involvement but absence of evidence of a primary tumor. Tis: in situ carcinoma. T1: The tumor is limited to the nasopharynx, or it spreads to the nasal cavity or oropharynx without affecting the Para pharynx. T2: The tumor affects neighboring soft tissue, such as the lateral, medial, or prevertebral muscles, or it extends to the Para pharynx. T3: The tumor invades the paranasal sinuses, pterygoid structures, cervical vertebra, and/or bone structures near the base of the skull. T4: any one or more of the following tumor invasions: Within the skull are the parotid gland, orbit, hypopharynx, and cranial nerves (Liu et al., 2015).

Regional lymph node (N) classification: NX indicates nodes not assessed; N0 indicates no regional nodal metastasis; N1 represents metastasis above the caudal border of cricoid cartilage involving unilateral cervical lymph node(s) and/or unilateral or bilateral retropharyngeal lymph node(s) with a greatest dimension of ≤6 cm; N2 represents bilateral cervical lymph node metastasis ≤6 cm, above caudal border of cricoid cartilage; N3 represents unilateral or bilateral cervical lymph node metastasis >6 cm and/or lymph node metastasis extending below the caudal border of cricoid cartilage. Note that in TNM, all nodal sizes are expressed as "greatest dimension," not as short axis diameter (Mousa, 2016).

Distant metastases (M): The TNM categories MX and pM0 are no longer applicable. The following classifications can be applied to patients who have been diagnosed with cancer before receiving treatment (clinical classification (c)) or to patients for whom surgery is the first and only definitive therapy (pathological classification (p)): pM1: distant metastasis, verified by microscopy; cM0: no evidence of metastases; and pM1: distant metastasis (Ok et al., 2015).

Stage groupings: Stage 0: Tis, N0, M0, Stage I: T1, N0, M0, Stage II: [T0, T1], N1, M0, T2, [N0, N1], M0, Stage III: [T0, T1, T2], N2, M0, T3, [N0, N1, N2], M0, Stage IVA: T4, [N0, N1, N2], M0, [Any T], N3, M0, Stage IVB: [Any T], [Any N], M1 (Soehartono et al., 2024).

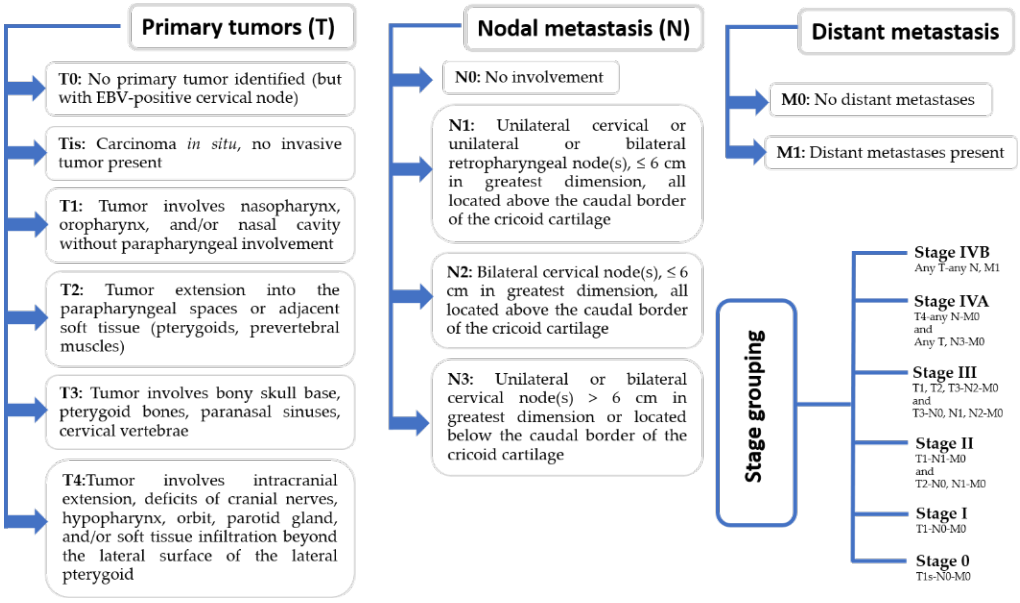

Figure 1. The TNM staging for NPC. The figure is adopted from (Ahmed et al., 2022).

Conclusion

EBV plays a central and well-established role in the initiation and progression of NPC through its ability to infect nasopharyngeal epithelial cells and activate oncogenic latent gene expression. Strong epidemiological evidence supports its association with NPC, particularly in regions with high disease incidence. Viral proteins such as LMP1 and other molecular markers contribute to signaling dysregulation, enhanced proliferation, and tumor progression. Advances in molecular diagnostics, including EBV DNA quantification, have improved early detection and risk stratification. Continued research on EBV-driven mechanisms may facilitate the development of targeted therapies and preventive strategies, ultimately reducing the global burden of NPC.

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