



NASOPHARYNGEAL CARCINOMA: METASTASES AND CLINICAL CONSIDERATIONS

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ABSTRACT

Nasopharyngeal carcinoma (NPC) is a challenging cancer due to its tendency for local recurrence and distant metastasis, with bone metastasis being the most common site of metastases. This review explores the etiological role of Epstein-Barr virus (EBV) infection in NPC tumorigenesis and discusses the clinical implications of NPC metastasis, including the most common patterns and the "seed and soil" theory. Risk factors associated with NPC are also addressed, including the consumption of salted fish, instant noodles, tobacco smoking, and exposure to carcinogenic substances such as wood dust, insecticides, and grilled food. Men and older individuals are at higher risk of developing distant metastases. Understanding the distant metastasis patterns in NPC is crucial for prognosis and treatment. Bone is the most common site of metastasis, and histological type and N3 stage are predictors of poor prognosis. Dual-site metastasis is more common than single-site metastasis, with identified trends in combined organ metastases. Further research is needed to better understand NPC metastasis and improve treatment outcomes.

Keywords: Nasopharyngeal carcinoma, Metastasis, Risk factors

Introduction

Nasopharyngeal carcinoma (NPC) is a type of cancer that affects the nasopharynx, which is a prevalent condition. The fossa of Rosenmuller is the most frequently affected area by this cancer, especially in Southeast Asia, with an annual incidence of 6.2 cases per 100,000 people, representing 0.7% of all cancers globally. Although intensity-modulated radiotherapy and chemotherapy have helped to reduce the mortality rate associated with NPC, the treatment is still faced with significant challenges due to the high occurrence of regional recurrence and distant spread. Although advancements in treatments have been made, the five-year survival rate for patients with nasopharyngeal carcinoma (NPC) is currently at 45%, it drops significantly to 22.3% for patients who develop distant metastases, which happens in approximately 12-13% of cases. Bone metastasis is the most common type of metastasis observed in NPC patients is distant metastasis, which occurs in around 64-67% of cases. Patients who have regional metastases in specific lymph nodes are at a higher risk of developing distant metastases than others. Unfortunately, the median life expectancy for patients with distant metastasis at diagnosis is only about 10-36 months^{1,2}

The nasopharynx is made up of two types of epithelium - squamous and ciliated columnar - which have transitional zones between them. Additionally, the nasopharynx contains submucosal lymphoid tissue, primarily located in the adenoid, which is located in the upper back part of the nasopharynx, specifically in the area that faces upwards and backwards, there is a common location for NPC tumors to form. Adenoid hypertrophy is common in children, while atrophy is more frequently observed in adults. Although the precise contribution of Epstein-Barr virus (EBV) infection to NPC pathogenesis is still unknown, it has been extensively studied for its connection to NPC progression. Biomarkers associated with EBV have been used in clinical practice to help predict the likelihood of developing or recurring NPC. Early detection of NPC is challenging, even in regions with high incidence rates. However, screening individuals at high risk can help improve early detection rates. In regions with high endemicity, the majority of NPC cases are detected at later stages, with roughly 10% of patients presenting with metastases at the time of identification.³

NPC often metastasizes to the bone, lungs, liver, distant

lymph nodes, and occasionally, the brain. Nonetheless, the occurrence of brain metastasis in NPC from endemic areas is low, and its underlying mechanism is unclear. As per the "seed and soil" theory, the communication between brain microenvironment and NPC cells has been proposed, may be essential in limiting the establishment and/or growth of NPC cells in the brain tissue. Several gene products and signaling pathways, as well as interactions between the malignant microenvironment and cancer cells, are involved in regulating cancer cell metastasis. This review aims to provide a comprehensive understanding of NPC metastasis from multiple perspectives and identify potential avenues for future research on NPC.²⁻⁴

Risk Factor

Men have a greater likelihood of developing distant metastases, primarily because of their increased contact with cancer-causing agents such as cigarette, wood particles, smoke and alcohol. Higher levels of androgen in men may also contribute to the development of tumors. VEGF-2578 expression is higher in men, which is associated with larger tumors and more advanced cancer stages. On the other hand, estrogen has been found to inhibit cancer cell growth.⁷

NPC is more common among older people due to mutations or exposure to carcinogens, and distant metastases are often seen in those aged 40-50. However, the incidence of distant metastases is not significantly different between older and younger patients.¹

The most frequently cited risk factors for NPC include consuming instant noodles (83.3%), preserved fish (85.7%), and having a past medical record of smoking (81.0%). In areas where NPC is prevalent, cured fish and processed foods, when combined with genetic vulnerability, are known to increase the risk of NPC. Preserved foods that have been salted or fumigated contain N-nitrosamines, a carcinogenic substance that forms when nitrates and sunlight interact. Genetic factors such as human leukocyte antigen (HLA) genotype and cytochrome P450 genetic alteration, including HLAA1, AW19, BW46, and B17, can also influence the risk. Tobacco use is a significant hazard for NPC, and a 2017 meta-analysis discovered that the probability of NPC rises with the quantity of tobacco products

consumed. Drinking more than seven alcoholic drinks per week is also an independent risk factor for NPC. Wood dust and insecticide exposure are less commonly reported risk factors. Grilled food, heterocyclic amines, and polycyclic aromatic hydrocarbons have been associated with cellular injury and genetic mutations resulting in cancer development. Mosquito coils, which contain formaldehyde and acetaldehyde, have been identified as significant risk factors for NPC in Indonesia and Malaysia.^{8,9}

Distant Metastasis Patterns in NPC

According to research, it is crucial to comprehend the distributions of distant metastasis in NPC because patients with distant metastases usually have worse clinical outcomes than those without metastases. The bone is the most commonly affected site of spread among NPC, whereas the brain has the lowest incidence. Additionally, the tissue type of NPC is a standalone prognostic risk factor, and the N3 stage has been identified as a significant predictor of poor prognosis in patients, which is consistent with findings from previous research. Moreover, patients with stage N3 disease are more likely to have distant metastases in any of the five organs studied, possibly due to extranodal extension.¹¹

While there is little research on combined metastases in NPC, previous studies suggest that dual-site metastasis is more common than single-site metastasis, perhaps due to changes in the cancer microenvironment after spread to one organ. Certain trends in combined organ metastases have also been identified. Bone spread is more likely to be associated with liver or brain spread, whereas lung spread is more commonly observed in patients with liver or distant lymph node spread.²

Cellular and Animal Models

The Mechanisms of Pre-Metastatic Niche Formation in Nasopharyngeal Carcinoma

The Role of High Endothelial Venules (HEVs) in Nasopharyngeal Carcinoma (NPC) Metastasis

The human body possesses a network of blood vessels called high endothelial venules (HEVs), which aid the movement HEVs are responsible for the migration of lymphocytes from blood vessels to lymphatic tissue, but not including the spleen. These vessels are composed of glycoproteins, specifically the peripheral lymph node addressin (PNAd), which interact with lymphocyte L-selectin receptors to help immune function. However, recent research has indicated that primary tumors can modify the role of The sentinel lymph node contains HEVs, shifting their function from immune response to oxygen supply. Upon The infiltration of cancer cells that have metastasized, these modified HEVs are exploited, and they become a Component of the tumor's blood vessels.. This leads to restructuring that could cause the loss of PNAd expression, making it easier for tumor cells to enter the bloodstream, resulting in distant metastasis.

HEVs are present in the nasopharynx is considered a lymphoid organ due to its role in the immune system, and NPC cells are often observed near these HEVs. Nonetheless, further investigation is necessary to ascertain the exact function of HEVs in NPC metastasis.³

The Role of MDSCs in NPC Metastasis

In lung cancer, the pre-metastatic environment involves the

In order to study metastasis in nasopharyngeal carcinoma (NPC), it is important to create both cellular and animal models. Murine models are typically classified as either spontaneous or experimental, with the former involving the development of a primary tumor and subsequent metastasis, and the latter involving the direct injection of cancer cells into the blood vessels to generate metastases in remote organs. In NPC research, the most commonly utilized experimental metastasis model is by injecting cancer cells into the tail vein to induce lung lesions. However, the spontaneous metastasis model is preferred since it mimics the complete process of metastasis. Unfortunately, a dependable mouse model for NPC that mimics the primary tumor's location is currently unavailable, and researchers frequently utilize an alternative model that involves an injection in the footpad before popliteal lymph node spread in nude mice. Another commonly employed spontaneous metastasis model involves injecting NPC cells into the spleen, which leads to liver metastasis.¹²

Pathological Classifications

The pathological classification system for nasopharyngeal carcinoma (NPC) by World Health Organization (WHO) divides NPCs into three categories. However, this system lacks the ability to predict patient outcomes after treatment, especially with regards to post-treatment metastasis. In a multicenter study, a new pathological classification system for NPC was proposed based on morphologic features, which includes four types of NPC. Patients with sarcomatoid carcinoma, one of the four types, have a relatively poorer overall survival rate and their metastatic potential cannot be overlooked. Further investigation is necessary to determine the metastatic potential of sarcomatoid NPC and to identify patients at a higher risk of developing distant metastasis. These patients can then be selected for anti-metastasis treatments.^{13,14}

contribution of non-cancerous cells, including myeloid-derived suppressor cells (MDSCs), monocytes, and regulatory T cells. These cells play a vital function in cancer treatment, targeting MDSCs in the pre-metastatic niche A promising approach has emerged in cancer treatment, involving the pre-metastatic niche in lung cancer, where non-cancerous cells such as MDSCs, monocytes, and regulatory T cells are crucial. This approach has also been studied in the case of NPC, MDSCs are considered an essential component of the pre-metastatic niche. Research indicates One study found that MDSCs may enhance the spread of NPC by increasing the levels of COX-2 in cancer cells, which then activates the beta-catenin/TCF4 signaling pathway. However, further studies are necessary to better comprehend the interaction and communication between different cell types involved in the development of pre-metastatic niches in NPC.

EMT and NPC Metastasis: Marker Expression and Significance

The process of EMT refers to the process in which epithelial cells undergo a transformation into cells that resemble mesenchymal cells and is often considered the initial stage of cancer metastasis. However, some studies suggest that EMT may not be necessary for metastasis. EMT is identified by the The upregulation of mesenchymal markers and the downregulation of epithelial markers signify the occurrence of epithelial-to-mesenchymal transition, such as E-cadherin, N-cadherin, CD44v6, Twist, Snail, and Cyclin D1, which are frequently used in cancer research. A study conducted on a large group of patients with nasopharyngeal carcinoma (NPC) revealed that, the

expression levels of these markers were found to be associated with patient prognosis. In patients with nasopharyngeal carcinoma (NPC), the presence of high levels of E-cadherin was linked to a favorable prognosis. On the other hand, increased levels of N-cadherin, CD44v6, Twist, Snail, and Cyclin D1 have been linked to a poor prognosis.¹⁵

Our findings and previous research suggest that EMT is connected to the capacity of NPC cells to metastasize. In animal models, inhibiting NPC metastasis can be achieved by suppressing EMT via CLCA2 and NOTCH2. However, it's unclear if triggering the mesenchymal-to-epithelial transition or reversing EMT is effective in inhibiting NPC metastasis. Additionally, certain cytokines that promote NPC metastasis may not induce traditional EM, indicating that NPC cell metastasis may or may not depend on EMT.¹⁶

EBV and NPC Metastasis

EBV is a dormant virus that is present in more than 90% of the adult population globally and has been linked to NPC and lymphoid malignancies. In endemic areas, almost all NPC cases are related to EBV infection. EBV genes are expressed in genetic material of NPC cells is derived from both protein-coding and non-protein-coding genes, including BARTs and BHRF1 miRNA clusters. These genes are involved in multiple processes related to NPC progression, such as EMT, metastasis, and resistance to treatment. The gHgL and gB glycoproteins are crucial for the fusion of EBV with all cell types, including nasopharyngeal epithelial cells. protein gB has been observed to bind with neuropilin 1, which triggers EGFR signaling and facilitates the entry of the virus into cells via two processes: macropinocytosis and endocytosis dependent on lipid raft. Recent studies have suggested that reducing the amount of FBXO2, a protein that attaches to the N-glycosylation sites present on gB, increases the location of gB on the exterior of the epithelial cells of the nasopharynx boosts the merging of membranes and the entry of the virus.^{17,18}

To summarize, EBV plays a substantial part in the formation and advancement of nasopharyngeal carcinoma (NPC) due to its involvement in multiple signaling pathways. NPC metastasis is largely dependent on epithelial-mesenchymal transition (EMT), which is regulated by EBV. An approach to prevent the metastasis of nasopharyngeal carcinoma involves inducing a mesenchymal-to-epithelial transition or reversing the process of EMT has not been definitively shown to inhibit NPC metastasis, suppressing EMT via CLCA2 and NOTCH2 has yielded promising results in animal models. The EBV genome encodes both protein-coding and non-protein-coding genes, and its gHgL and gB glycoproteins are essential for membrane fusion with all cell types. EBER1 and EBER2, two small EBV-encoded RNAs overexpressed in NPC cells, induce the secretion of pro-inflammatory cytokines and participate in generating a neoplastic microenvironment that is pro-tumorigenic and promotes the growth of nasopharyngeal carcinoma (NPC).¹⁹

Additionally, the incorporation of the EBV genetic material into the human genome can occur and downregulate genes such as TNFAIP3, PARK2, and CDK15 that inhibit motility or metastasis. LMP1, which is encoded by EBV, has a significant role in NPC development by regulating various signaling pathways. LMP1 activates cell migration, angiogenesis, necroptosis, stemness, and metastasis. It also activates NF- κ B signaling and downregulates miR-203, which may lead to EMT and potentially promote metastasis. LMP1 induces Twist, a transcriptional factor that promotes the process of EMT is closely associated with metastasis and is considered a key factor in this process.³

LMP2A, an EBV-encoded membrane protein expressed in

most NPC cases, plays a crucial role in controlling various signaling pathways, such as PI3-K/Akt, JNK/SAPK, ERK-MAPK, and Wnt/beta-catenin, which control cellular proliferation, differentiation, and apoptosis. Moreover, LMP2A suppresses the interaction between ITGbeta4 and SYK, thereby facilitating NPC cell movement and infiltration. Moreover, a number of microRNAs encoded by EBV, including miR-BART6-3p, miR-BART7-3p, miR-BART8-3p, miR-BART9, miR-BART13, and miR-18-5p, are involved in this process, have been identified as promoters of NPC cell invasion and metastasis. In summary, EBV infection plays a critical role in enhancing NPC cellular motility and promoting metastasis by affecting several genes and proteins that are critical for tumor suppression and cell migration inhibition through multiple signaling pathways.^{20,21}

Factors promoting metastasis in NPC

Cytokines

Various cytokines contribute to the metastasis of nasopharyngeal carcinoma (NPC) through autocrine and paracrine pathways. For example, According to our study, The Kazal-type serine proteinase inhibitor 6 (SPINK6) has been discovered as a suppressor of several kallikrein-related peptidases (KLKs), such as KLK5, KLK7, and KLK14. Nevertheless, our results imply that SPINK6 also acts as a ligand for the epidermal growth factor receptor (EGFR) in cells of nasopharyngeal carcinoma (NPC), promoting metastasis by inducing EGFR dimerization and activating AKT signaling, irrespective of its ability to inhibit serine protease activity, SPINK6, a Kazal-type serine proteinase inhibitor, functions as an EGFR ligand in NPC cells. Conversely, serglycin, a proteoglycan, facilitates NPC metastasis by binding to CD44 receptor and activating MAPK/b-catenin signaling, while also maintaining NPC cell self-renewal in an autocrine fashion. Interleukin 8 (IL8), secreted by cancer cells and other cells, also contributes to NPC metastasis by activating AKT signaling through CXCR1 and CXCR2 receptors and suppressing. An interesting finding of the study was that the expression of E-cadherin in NPC cells could be suppressed by the promotion of E-cadherin promoter DNA methylation, while the involvement of Wnt family member 5A (WNT5A) was also observed. In addition, Wnt family member 5A (WNT5A) promotes epithelial-to-mesenchymal transition (EMT) in NPC cells. The induction of EMT in NPC cells by WNT5A leads to the accumulation of stem-like cells expressing CD24/CD44+ and stimulates NPC metastasis through the activation of PKC signaling. Moreover, CCL2 acts as a promoter of NPC metastasis by activating the ERK1/2-MMP2/9 signaling pathway via its receptor, CCR2. Additionally, serglycin, a proteoglycan, enhances NPC metastasis by activating MAPK/b-catenin signaling through binding to CD44 receptor and inhibiting E-cadherin expression by increasing the methylation of its promoter in NPC cells. Finally, TNFAIP2, IL-6, and IL-17A are among other cytokines that have the potential to enhance the mobility of nasopharyngeal carcinoma cells and induce metastasis.³

The Role of Cell Surface Proteins in Promoting Metastasis

The ErbB family of receptor tyrosine kinases, comprising of EGFR, among others, is involved in the topic under discussion, is known to be dysregulated in several human cancers. Recent research has shown that EGFR can be activated through the binding of its natural ligand, EGF exacerbates NPC metastasis through downstream molecules such as PKM2. In addition, EGFR activation can be promoted not only by its native ligand EGF but also by other ligands such as SPINK6, which can enhance NPC metastasis. Additionally, uPAR is a membrane-bound protein that also contributes to NPC metastasis that can be activated by its ligand uPA via the binding of vitronectin, which

facilitates NPC cell migration and invasion. Additionally, Ezrin is involved in the regulation of several signaling pathways, including the PI3K/AKT and MAPK/ERK pathways, and has been identified as a metastatic promoter in breast cancer. Ezrin, belonging to the Ezrin-Radixin-Moesin protein family, has been shown to facilitate metastasis in breast cancer by connecting the plasma membrane and actin cytoskeleton. However, in NPC, suppression of Ezrin expression inhibits cellular migration and invasion. Circular RNA circARHGAP12 can increase the mRNA stability of Ezrin. While Glypican 6 is known to promote NPC cellular motility as a potential cell surface co-receptor for growth factors, its function in enhancing metastasis is still uncertain. TSPAN8, another transmembrane protein, has also been documented to activate Akt/MAPK signaling to promote NPC cellular motility.¹⁴

Intracellular proteins that Promote Metastasis in NPC

ErbB receptor tyrosine kinase family, which includes EGFR, a protein that is often deregulated in human cancers. Recent research has shown that stimulation of NPC metastasis can occur through EGFR activation by EGF ligand leads to the activation of downstream molecule PKM2. Additionally, in addition to EGF, SPINK6 is also capable of binding to EGFR and facilitating NPC metastasis. Another protein, uPAR, is a glycosylphosphatidylinositol-anchored membrane protein that is activated by its ligand uPA via the binding of vitronectin. Ezrin, which belongs to the protein family called Ezrin-Radixin-Moesin, has been shown to promote metastasis in breast cancer. However, in NPC, suppressing Ezrin expression can hinder cellular migration and invasion. Moreover, circular RNA circARHGAP12 can enhance its mRNA stability, is known to facilitate the spread of cancer in breast tissue, while suppressing Ezrin expression in NPC inhibits cellular migration and invasion. FLJ10540 CIP4 activates N-WASP and EGFR signaling, up-regulating MMP2, while the activation of ERBB3/EGFR-ERK signaling by LACTB promotes NPC metastasis. Meanwhile, SNAIL, a transcriptional repressor, promotes NPC metastasis partly by down-regulating TEL2 and consequently reducing E-cadherin expression.³

Non-coding RNAs

Non-coding RNAs have been identified as significant contributors to the promotion of NPC metastasis. The lncRNA AFAP1-AS1 activates Rho/Rac signaling by competing with endogenous RNA miR-423-5p. Similarly, FAM225A serves as a competing endogenous RNA (ceRNA) by absorbing miR-590-3p/miR-1275 and upregulating ITGB3 to promote NPC metastasis. Non-coding RNAs have been identified as important regulators of NPC metastasis. One example is lncRNA AFAP1-AS1, which promotes metastasis by activating Rho/Rac signaling through competition with endogenous RNA miR-423-5p. Another is FAM225A, which serves as a competitive endogenous RNA (ceRNA) by sequestering miR-590-3p/miR-1275. LINC01503 stimulates metastasis by activating the transcription of Fos-like 1 (FOSL1) via recruitment of splicing factor proline- and glutamine-rich (SFPQ). MicroRNA-494-3p targets Sox7 and enhances NPC cellular motility and proliferation. Further research is required to identify additional non-coding RNAs that regulate NPC metastasis.¹⁶

NPC Metastatic Inhibitors

In recent years, the discovery of NPC metastatic inhibitors has become increasingly important due to the complexity of NPC metastasis and the various mechanisms through which inhibitors work. These mechanisms include transcriptional regulation, membrane receptor regulation, and central pathway regulation,

among others.

One effective approach for inhibiting NPC metastasis is through transcriptional regulation. TEL2, a member of the E26-transformation specific transcription factors, suppresses the expression of SERPINE1, which is linked to the inhibition of NPC metastasis. Similarly, ZNF582 regulates the process of transcribing and expressing nectin-3 and NRXN3 adhesion molecules to inhibit NPC metastasis.¹⁷

Membrane receptor regulation is another mechanism that can inhibit NPC metastasis. Activation TLR3 activation has been documented to reduce the expression of CXCR4, a chemokine receptor and therefore inhibit NPC metastasis.¹⁸

Central pathway regulation is a third mechanism that inhibits NPC metastasis. SHROOM2 can inhibit NPC metastasis through both both RhoA-ROCK signaling-dependent and -independent mechanisms of metastasis. CHL1 impedes NPC metastasis by blocking the PI3K/AKT signaling pathway via the disruption of the interaction between integrin b1 and merlin. Finally, NID2 inhibits metastasis-related pathways, such as EGFR/Akt and integrin/FAK/PLC α pathways can be suppressed.¹⁹

In addition to the previously mentioned mechanisms, non-coding RNAs have also been found that NKILA, which is a type of non-coding RNA, has a noteworthy function in suppressing NPC metastasis, suppresses NF- κ B signaling, thereby inhibiting NPC metastasis. Similarly, miR-99a targets HOXA1 to inhibit NPC metastasis. There are several proteins and non-coding RNAs that have the potential to hinder NPC metastasis by suppressing NPC cell migration and invasion. These include but are not limited to TNFAIP3, BPIFB1, MYH10, miR-30e-5p, miRNA-101, and miR-451.³

In conclusion, the discovery of these NPC metastatic inhibitors, acting through different mechanisms, highlights the complexity of NPC metastasis and underscores the need for continued research to better understand and combat the disease.

Conclusion

NPC is a type of cancer that presents a significant challenge due to its high probability of recurrence in the same area and spread to distant sites. Bone is the most frequent site of metastases. The onset of NPC is associated with the infection of Epstein-Barr virus (EBV), and various risk factors, such as the consumption of salted fish, instant noodles, tobacco smoking, and exposure to carcinogenic substances, are associated with NPC. Men and older individuals are at higher risk of developing distant metastases. Understanding the distant metastasis patterns in NPC is crucial for prognosis and treatment, with histological type and N3 stage being predictors of poor prognosis. Further research is needed to better understand NPC metastasis and improve treatment outcomes.

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