ORIGINAL ARTICLE

MMP9 and ADNP Gene Expressions in Secondary Bone Metastasis of Locally Advanced Nasopharyngeal Cancer

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ABSTRACT

Background: *Nasopharyngeal cancer (NPC) is a malignancy of the nasopharyngeal mucosal epithelium. Primary and secondary metastases in nasopharyngeal cancer are generally prevalent in the bones. Gene expression plays a critical role in regulating fundamental cellular processes in cancer cells, including metastasis.* ***Methods:*** *A total of 29 patients with non-metastatic NPC were included in the study.* ***Results:*** *The mean age of the participants was 48.45±9.98 years old. Most participants were male (75.9%). More than half of the participants had T4 and N2, 52.7% and 51.0% respectively). Secondary metastasis was observed in 9 of the 29 participants within two years. Patients with secondary metastases had a higher proportion of T4 (7/9) and N2 (4/9) disease. Bone was the first site of secondary metastasis (6/9 patients). The median time to secondary bone metastasis was 14.0 (6.8-21.2) months. Based on the differential expression gene (DEG) analysis, the MMP9 gene was upregulated 12.50 (4.18–37.40), adjusted p <0.01, and the ADNP gene was downregulated 0.141 (0.04–0.43), adjusted p 0.04, among patients with secondary bone metastasis.* ***Conclusions:*** *Bones are the first site of metastasis, with a time to metastasis of 14.0 (6.8-21,2) months. MMP9 was upregulated, and ANDP was downregulated in patients with bone metastasis compared to those without metastasis.*

Keywords**:** *MMP9, ADNP, nasopharyngeal cancer, secondary bone metastasis.*

INTRODUCTION

Nasopharyngeal cancer (NPC) is a malignancy arising from the mucosal epithelium of the nasopharynx.[1] The global incidence of nasopharyngeal cancer is 1.2 per 100,000 people. In Indonesia, it is the most common head and neck cancer, accounting for 28.4% of cases.[2] Most cases in Indonesia are diagnosed at advanced or locally advanced stages (30.1% and 18.9%, respectively).[3] Metastases in nasopharyngeal cancer can affect the bone, liver, lung, or brain.[3,4] The mechanisms underlying metastasis remain a key research focus. Several factors contribute to metastasis, including cytokines and their receptors (IL-8, MMP-2, MMP-9, and IL-6), cell surface proteins (EGFR), and intracellular proteins (c-SRC and Annexin A1). Additionally, the interaction of cyclin D1 with CDK 4/6 and the PI3K/AKT signalling pathway has been implicated in metastatic progression.[5]

Bone is a common site for both primary (metastasis at the time of initial diagnosis) and secondary metastases (metastasis developed six months or more after the initial diagnosis) in nasopharyngeal cancer.[6,7] Secondary bone metastases typically develop within 7–18 months after diagnosis. Several genes associated with bone metastasis in nasopharyngeal cancer include CXCR4, RANK, RANKL, BMP2, Osteopontin, PTHrP, IL-8, and SRC.[8-12]

Gene expression plays a crucial role in regulating cancer cell processes. In malignancies, alterations in gene expression support cancer cell survival by modulating proliferation, apoptosis, differentiation, metabolism, migration, and invasion.[13] Various techniques can be used to analyse gene expression, including Northern blotting, qPCR, DNA microarrays, RNA-Seq, and nCounter.[14, 15] The NanoString nCounter™ system is a technology for nucleic acid analysis.[16]

Limited research has explored the relationship between gene expression and secondary metastasis in nasopharyngeal cancer. Such studies are essential to deepen the understanding of secondary metastasis risk factors. Identifying the genes involved in secondary metastasis may also facilitate the development of targeted interventions for high-risk patients. This study aimed to evaluate gene expression and its association with secondary metastasis in locally advanced nasopharyngeal cancer.

METHODS

This analytical, retrospective study evaluated the association between gene expression levels and secondary metastasis within two years after diagnosis in non-metastatic NPC. The study used paraffin blocks from the Department of Anatomical Pathology and medical records of patients with nasopharyngeal cancer at Cipto Mangunkusumo General Hospital from to 2018-2022. Nucleic acids were extracted from paraffin blocks at the Department of Anatomical Pathology. Gene expression was evaluated using NanoString technology at the Genetica Science Laboratories. This study used total sampling, with the inclusion criterion being age > 18 years, with histopathological examination results indicating nasopharyngeal cancer. The exclusion criteria were incomplete medical records, the presence of more than one primary cancer, and unavailable paraffin blocks for histopathological examination. The time to metastasis was defined as the time from diagnosis to the first confirmed metastasis.

Data were processed using SPSS 23 software. Gene expression analysis was performed using the nSolver® 4.0 application.[16] Differentially expressed gene (DEG) analysis was conducted to compare the gene expression between groups. The reference genes used in this study were *HPRT1*, *YARS*, *EIF3S7*, *PDCD1*, *PDCD1LG2*, *TIGIT*, and *TRAT1*.[17] This study used a customised panel consisting of 80 target genes, along with nine negative and six positive control genes (Supplemental 1, Table 1). The results are presented in tables and volcano plots, with statistical significance defined by an adjusted p (p-adj) value < 0.05, based on the Benjamini-Hochberg method.

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (KET-1181/UN2.F1/ETIK/PPM.00.02/2022, version 2).

RESULTS

A total of 29 patients with non-metastatic NPC were included in the study. Table 1 provides an overview of the demographic and clinical characteristics of the participants. The mean age of the participants was 48.45±9.98 years old. Most of the participants were male (75.9%). More than half of the participants had T4 and N2, 52.7% and 51.0% respectively). The most common histopathological type observed in this study was non-keratinising squamous cell carcinoma (93.1%). Most patients received chemoradiation (37.9%) or neoadjuvant chemotherapy, followed by chemoradiation (37.9%).

Secondary Metastasis Pattern

Secondary metastases were found in 9 out of 29 patients within two years of diagnosis. Patients with secondary metastases had a higher proportion of T4 (77.8 vs. 40.0) compared with patients without secondary metastasis. Organ distribution of secondary metastases is shown in **Table 2**. In the present study, bone was the site of secondary metastasis. We found that 66.7% patients had secondary metastasis involving the bone.

Table 1. Clinical and Demographic Characteristics of the Participants

Subject Characteristics	Results (n = 29)
Age, average (years)	48.45±9.98
Sex	
Male, n (%)	22 (75.9)
Female, n (%)	7 (24.1)
Histopathology	
Keratinising carcinoma, n (%)	2 (6.9)
Non-keratinising squamous cell carcinoma, n (%)	27 (93.1)
Basaloid squamous cell carcinoma, n (%)	0 (0.0)
T stage	
T1, n (%)	0 (0.0)
T2, n (%)	5 (17.2)
T3, n (%)	9 (31.0)
T4, n (%)	15 (52.7)
N stage	
N0, n (%)	3 (10.3)
N1, n (%)	2 (6.9)
N2, n (%)	15 (51.7)
N3, n (%)	9 (31.0)
First-line treatment	
Chemoradiation, n (%)	11 (37.9)
Neoadjuvant Chemo + Chemoradiation, n (%)	11 (37.9)
Chemoradiation + Adjuvant Chemo, n (%)	5 (17.2)
Incomplete	2 (6.9)

Table 2. Secondary Metastasis Pattern

Subject characteristics	Secondary Metastasis	
	Yes (n=9)	No (n=20)
T stage*		
T2, n	0 (0)	5 (20.0)
T3, n	2 (22.2)	7 (35.0)
T4, n	7 (77.8)	8 (40.0)
N stage		
N0, n	0 (0)	3 (15,0)
N1, n	2 (22.2)	0 (0)
N2, n	4 (44.4)	11 (55.5)
N3, n	3 (33.3)	6 (30.0)
First-line therapy		
Chemoradiation	3 (33.3)	8 (40.0)
Neoadjuvant Chemo + Chemoradiation	4 (44.4)	7 (35.5)
Chemoradiation + Adjuvant Chemo	2 (22.2)	3 (15.0)
Secondary metastasis site		
Bone, n	6 (66.7)	
Liver, n	3 (33.3)	
Lung, n	4 (44.4)	

*. No cases T1 and T2

Based on the sequence of metastases, bone involvement was the first site of secondary metastasis. The median time to secondary bone metastasis was 14.0 (6.8-21.2) months.

DEGs Among Organ-specific Secondary Metastasis

DEG analysis was performed by comparing the gene expression levels between participants with and without organ metastases (**Table 2**). A comparison of the expression levels of the top 40 genes that differed between the two groups is shown in the volcano plot (**Figure 1**). Based on the DEG analysis, the MMP9 gene was upregulated 12.50 (4.18–37.40), adjusted p <0.01, and the ADNP gene was downregulated 0.141 (0.04–0.43), adjusted p 0.04 among participants with secondary bone metastasis (**Figure 1B**).

DISCUSSION

Subject Characteristics

In this study, most of the subjects were male (75.9%) with a mean age of 48.45 ± 9.98 years. Previous studies in Indonesia have also reported a higher prevalence of NPC in men. Adham et al.[4] found that NPC was 2.4 times more frequent in men than in women. Similarly, Hayati et al.[3] (2017) reported that men accounted for 73.8% of the cases, with a median age at diagnosis of 46 years.

Most subjects in this study were diagnosed with large tumours (T4, 52.7%) and had lymph node involvement (N2, 51.0%), reflecting the predominance of locally advanced NPC cases in Indonesia. Histopathological analysis showed that non-keratinising nasopharyngeal cancer

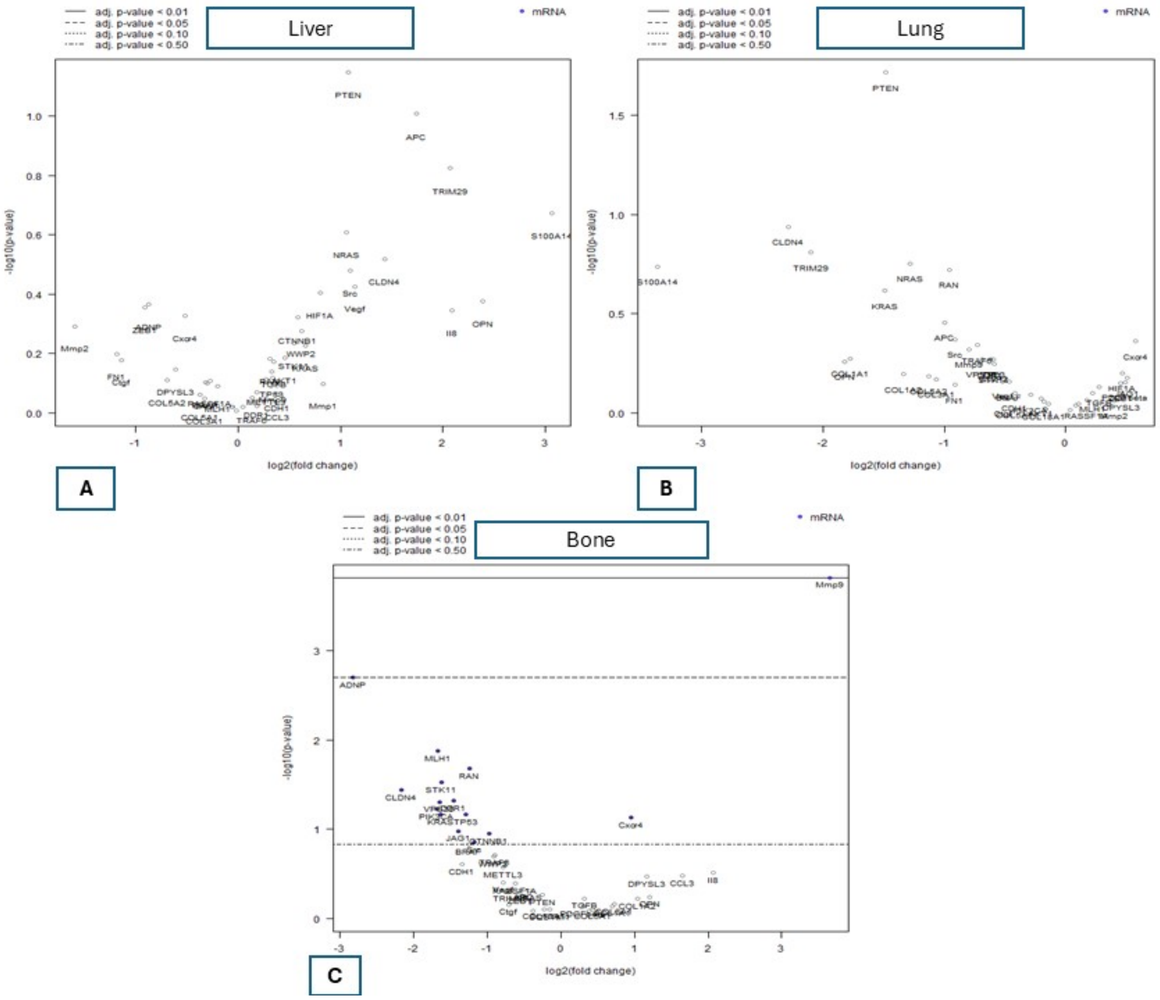

Figure 1. Volcano plot of DEG analysis among participants with secondary metastasis compared to non-metastasis: A. Liver, B. Lung, C. Bone. MMP9 was upregulated, and ANDP was downregulated in subjects with secondary bone metastasis

was the most common subtype, consistent with findings from the Asian region.[3, 4]

Secondary Metastasis Profile

Among the 29 subjects, 9 experienced secondary metastases within two years after diagnosis. These cases were generally characterised by large tumours (T4) and lymph node involvement (N2 and N3). The literature indicates that approximately 85% of NPC cases present with lymph node involvement at diagnosis due to the high lymphatic flow in the nasopharyngeal mucosa. [18,19] Metastatic spread in NPC is often associated with advanced T stage, lymph node involvement, and N3 classification.[20] One factor contributing to lymphatic metastasis is the presence of high endothelial venules (HEVs) in the nasopharyngeal mucosa. HEVs facilitate lymphocyte migration from blood vessels to lymph nodes for antigen recognition. However, in NPC, cancer cells reportedly alter HEV function and repurpose it as an oxygen source. This transformation is marked by modifications in PNAd expression on the endothelium.[21]

In this study, bone was the most frequent site of secondary metastasis and the first location affected in patients with multi-organ metastatic lesions. Previous studies have also indicated that bone is the primary metastatic site in NPC.[22, 23] The median time to secondary bone metastasis was 14.0 months (range: 6.8–21.2 months). Earlier studies report that secondary bone metastases occur in approximately 50% of cases within 9 months, 80% within 2 years, and nearly 90% within 3 years of NPC diagnosis.[24, 25]

Gene Expression

DEG analysis revealed a significant upregulation of MMP9 and downregulation of ADNP in the secondary bone metastasis group compared to the non-metastatic group. The results of this study indicate that the progression and metastasis of nasopharyngeal cancer are multistep processes involving various genes. Research on nasopharyngeal cancer in Indonesia has identified that the genes CXCL8, MMP1, MMP2, and FN1 are associated with larger tumor sizes.[26] Meanwhile, studies related to primary metastasis report that the genes CXCR4 and CXCL8 play a role in the occurrence of bone metastasis.[27] This study, however, demonstrates that MMP9 and ADNP are genes that play a role in secondary metastasis. Secondary metastasis has been reported to have different characteristics compared to primary metastasis. Additional genetic and epigenetic alterations occurred during tumorigenesis.[28]

MMP9

The MMP family is a group of endopeptidases capable of degrading the extracellular matrix (ECM), particularly type IV collagen. MMPs contribute to malignancy by facilitating tumour cell extravasation during metastasis. Their primary substrates are extracellular proteins, particularly those found in the basement membrane. MMP9 plays a significant role in bone metastasis, particularly in prostate cancer, due to its impact on ECM degradation, bone cell interactions, and direct effects on tumour cells.[29] MMP-9 is secreted as an inactive proenzyme (pro-MMP9, 92 kDa) and requires activation by proteases such as cathepsin K (CTSK), which is secreted by osteoclasts. Under acidic conditions, such as in bone tissue, CTSK activates pro-MMP9 into its functional form, contributing to bone matrix degradation and bone catabolism.[30]

Upregulated MMP9 in NPC has been linked to the expression of Zta, an Epstein-Barr virus (EBV) lytic protein. Zta, also known as BZLF1, is a transcription factor that facilitates the switch from EBV latency to the lytic cycle. By binding to promoter regions, Zta regulates viral lytic genes and host cellular genes.[31] In vitro studies show that Zta expression in keratinocyte cell lines enhances cell motility and invasiveness in collagen gels, mediated by increased expression of MMP3 and MMP9.[31]

ADNP

The Activity-Dependent Neuroprotector Homeobox (ADNP) gene, located on chromosome 20q12, encodes a protein involved in neuroprotection and cell cycle regulation. ADNP regulates key cell cycle genes, including CDC25A, which mediates the G1/S and G2/M checkpoints, CCNE, which regulates the G1/S transition, and CCNB, which is required for G2/M progression.[32] Early research on ADNP primarily focused on its role in neurological disorders, such as autism and speech impairments.[32] The gene is crucial for neuronal differentiation via activation of the Wnt/β-catenin pathway.[32] However, its role in cancer remains incompletely understood.[33] Blaj et al.[34] reported that ADNP expression negatively regulates the Wnt pathway in colorectal cancer, where Wnt signalling is critical for tumour invasion and progression. Additionally, ADNP has been identified as a tumour suppressor in triple-negative breast cancer.[35] Conversely, studies in hepatocellular carcinoma[36], bladder cancer[37], and other malignancies suggest that ADNP expression may promote proliferation, invasion, and tumour progression. This indicates that the function of ADNP is context-dependent and varies with cancer type and biological environment. This study showed that ADNP expression was downregulated in the bone metastasis group.

Comparison with Previous Studies

The results of this study indicate that the progression and metastasis of nasopharyngeal cancer are a multistep process involving various genes. Research on nasopharyngeal cancer in Indonesia has identified that the genes CXCL8, MMP1, MMP2, and FN1 are associated with larger tumor sizes. Meanwhile, studies related to primary metastasis report that the genes CXCR4 and CXCL8 play a role in the occurrence of bone metastasis. This study, however, demonstrates that MMP9 and ADNP are genes that play a role in secondary metastasis.

Strength and Limitation

This study is the first to simultaneously evaluate multiple gene expression levels by measuring mRNA in patients with NPC, with a specific focus on secondary bone metastases. A limitation of this study is that it did not assess the role of the tumour microenvironment in secondary metastasis.

CONCLUSION

Bone is the primary site of secondary metastasis in nasopharyngeal cancer. The median time to bone metastasis was 14.0 (6.8-21.2) months. Among participants with secondary bone metastases, MMP9 was upregulated, whereas ADNP was downregulated compared to the non-metastatic group.

ACKNOWLEDGMENTS

The authors extend their gratitude to Joshua Kurnia Tandi, MD; Idzhar Arrizal, MD; Clareta Vero Patricia Widya, MD; Alfonsus Pramudita, MD; Harits Adi Putra, MD; Endang Farihatul Izza, MD; Pinky Nur Alfaini, MD; Tasyaa Fillahihasanah, MD; and Annisa Tsana Madadika, MD, for their assistance with data collection. Special thanks are also given to Mrs. Supriyati and Mrs. Indriana Karmila from the Department of Anatomical Pathology for providing paraffin-embedded samples.

FUNDING

This work was supported by the Penelitian Dasar Unggulan Perguruan Tinggi (PDUPT) Grant 2021–2022 (NKB-130/UN2.RST/HKP.05.00/2021) and funded by the Ministry of Research and Technology of the Republic of Indonesia, National Research and Innovation Agency.

CONFLICT OF INTERESTS

The authors declare no competing interests.

Data availability statement.

Data will be shared upon reasonable request in accordance with the data-sharing policy.

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