CXCL8, MMP1, MMP2, and FN1 Gene Expression and Tumor Extension in Nasopharyngeal Cancer Patients: A Cross-sectional Study

Rahmat Cahyanur,[1] Cosphiadi Irawan,[1] Lisnawati lisnawati,[2] Marlinda Adham,[3] Achmad Fauzi Kamal,[4] Ahmad Rusdan Handoyo Utomo,[5] Mardiah Suci Hardianti,[6] Muchtaruddin Mansyur,[7] Thariqah Salamah[8]*

[1]Hematology Medical Oncology Division, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia—Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
[2]Department of Anatomical Pathology, Faculty of Medicine Universitas Indonesia—Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
[3]Department of Ear, Nose, and Throat, Head and Neck Surgery, Faculty of Medicine Universitas Indonesia—Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
[4]Department of Orthopedics and Traumatology, Faculty of Medicine Universitas Indonesia—Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
[5]Graduate School of Biomedical Sciences, Yarsi University, Jakarta, Indonesia.
[6]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia.
[7]Department of Community Medicine, Faculty of Medicine Universitas Indonesia—Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.
[8]Department of Radiology, Faculty of Medicine Universitas Indonesia—Cipto Mangunkusumo General Hospital, Jakarta, Indonesia.

Corresponding Author:
Rahmat Cahyanur, MD. Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia—Cipto Mangunkusumo Hospital. Jl. Diponegoro No. 71, Jakarta, Indonesia. Email: rahmat.cahyanur01@ui.ac.id.

ABSTRACT

Background: *There are correlations between tumor staging, lymph node involvement, and patient survival in Nasopharyngeal cancer (NPC) which is one of the most common types of cancer in Indonesia. The inflammation process plays a role in tumor progression over the long term and this marked by increased proinflammatory cytokine and gene overexpression. This study aims to identify differentially expressed genes (DEGs) in NPC using T and N staging.* ***Methods:*** *This is a cross-sectional study of NPC patients in Cipto Mangunkusumo, Jakarta, between 2018 and 2022. DEGs were identified based on the amount of mRNA detected on paraffin blocks with a 1.5- to -1.5-fold change and an adjusted p-value of <0.05.* ***Results:*** *We included 48 subjects. The mean age of subjects was 47.75 (10.48) years, and most were male (77.1%). Non-keratinized squamous cell carcinoma was the most common histopathology type. Differences in the tumor size of the T4 and non-T4 in metastatic (33.3%) group when compared to the non-metastatic (37.5%) group were insignificant (p = 0.763). The proportion of N3 subjects in the metastatic vs non-metastatic group was different significantly (83.3% vs. 50%, p = 0.030). Gene expression analysis showed that C-X-C motif ligand 8 (CXCL8), matrix metalloproteinase-1 (MMP1), matrix metalloproteinase-1 (MMP2), and fibronectin-1 (FN1) genes of the T4 and non-T4 group to be different*

significantly. ***Conclusion:*** *There was significant finding in the N3 subjects of the metastatic and non-metastatic groups. The DEGs of CXCL8, MMP1, MMP2, and FN1 were statistically significant in the T4 when compared to the non-T4 group.*

Keywords**:** *nasopharyngeal cancer, C-X-C Ligand 8, matrix metalloproteinase-1, matrix metalloproteinase-2, fibronectin-1.*

INTRODUCTION

Nasopharyngeal cancer (NPC) is a type of head and neck cancer that develops in the mucosa epithelium of the nasopharynx (an area behind the nose and above the throat).[1] According to the data, the incidence rate of NPC is approximately 1.2 per 100,000 people. After the Republic of China, the disease is most prevalent in Southeast Asia.[2] In Indonesia, the mortality rate caused by NPC is the second highest among other countries in Asia after the Republic of China. NPC is Indonesia's most common type of cancer (28.4%).[3] A study conducted at Dr. Cipto Mangunkusumo National Referral Hospital discovered 878 cases of NPC between 2012 and 2015. The study also revealed that most patients who sought treatment were diagnosed with advanced stage (18.9%) or advanced local stage (30.1%) cancers.[3]

Tumor staging and lymph node involvement are key factors that are associated with patient survival. Wang et al.[4] showed that stage T4 NPC has a distant metastasis-free and disease-free overall survival probability. By comparison, Chen et al.[5] reported that N3 patients have higher metastatic rates and lower five-year survival rates. Nevertheless, patients with the same staging could have different disease progressions, therapeutic responses, and relapse rates. Metastatic progression is known to be determined by a tumor's biological and genetic characteristics.[6, 7]

Inflammation has been known to increase proliferation, cancer cell survival, and metastases.[8] This inflammation process can occur through several intrinsic factors caused by gene overexpression and mutation. Gene overexpression, followed by increasing inflammatory cytokines, stimulates the recruitment of pro-inflammatory cells. In addition, immune reactions increase in response to existing tumors. A high inflammatory state in the long term can cause further immunosuppression, providing an opportunity for tumor progression.[9] The purpose of this study is to assess differentially expressed genes (DEGs) among patients with NPC according to the T and N stages from the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual*, 8th edition.

METHODS

This is a cross-sectional study. The subjects were NPC patients at Cipto Mangunkusumo Hospital from 2018–2022. The inclusion criteria required subjects to be adults 18 years or older with complete medical records and radiological data. All radiological data were evaluated by a radiological expert. Radiological evaluation was performed using a CT scan, MRI, or bone scan. The *AJCC Cancer Staging Manual*, 8th edition was used.[10] Histopathology was evaluated by a head and neck pathologist.

Gene expression was measured using a customized NanoString® panel consisting of 60 inflammatory and metastasis genes (a list of genes is shown in the supplementary table). The expressions were measured by counting the amount of mRNA extracted from formalin-fixed paraffin-embedded tissue. The analysis was completed using the ROSALIND platform. A fold change of 1.5 to -1.5 was used to detect DEGs, with an adjusted p-value of < 0.05.

This research was granted ethical permission by the Faculty of Medicine Ethical Commission (number KET-1181/UN2.F1/ETIK/PPM.00.02/2022). The research was granted operational permission from the Cipto Mangunkusumo General Hospital in Jakarta.

RESULTS

Demographic Characteristics

This study identified 48 subjects who had NPC between January 2018 and December 2022. The mean age of the subjects was 47.75 (10.48) years. Most subjects were male (77.1%) and had a histopathology of non-keratinized squamous cell carcinoma (SCC). The subjects were divided into the following groups: those with metastases (n = 24) and those without metastases (n = 24). **Table 1** shows the clinical and radiological characteristics of patients with metastatic NPC-based metastasis status.

Comparisons of stage T4 and non-T4 tumor size in the metastatic (33.3%) and non-metastatic (37.5%) groups resulted insignificant value of p = 0.763. The proportion of subjects in the metastatic group with N3 staging showed significance when compared to the non-metastatic group (83.3% vs. 50%, p = 0.030). Most of the metastatic group (83.3%) had > 1 metastatic lesion that was primarily located in the bone (79.9%). Further tumor-extension-based evaluation among the T4 subjects can be found in **Table 2**. The majority of the subjects showed involvement in the parapharyngeal space.

Table 1. Characteristics of the Subjects.

Variables	Metastasis (n = 24)	Non-metastasis (n = 24)	p-value
Age, mean (years)	46.5 (9.19)	49.0 (11.69)	0.333
Gender			
Men, n (%)	17 (70.83)	20 (83.33)	
Women, n (%)	7 (29.17)	4 (16.67)	0.303
Histopathology			
Keratinized squamous cells, n (%)	0 (0)	1 (4.16)	
Non-keratinized squamous cells, n (%)	24 (100)	23 (95.83)	1.000*
Stage T			
T1, n (%)	0 (0)	0 (0)	
T2, n (%)	10 (41.6)	5 (20.83)	
T3, n (%)	6 (25)	10 (41.67)	
T4, n (%)	8 (33.3)	9 (37.5)	0.763
Stage N			
N0, n (%)	0 (0)	1 (4.165)	
N1, n (%)	1 (4.16)	1 (4.165)	
N2, n (%)	3 (12.5)	10 (41.67)	
N3, n (%)	20 (83.3)	12 (50)	0.030
Metastasis Count			
1 organ only, n (%)	4 (16.6)	N/A	
>1 organ, n (%)	20 (83.3)	N/A	
Site of Metastasis			
Liver, n (%)	6 (25)	N/A	
Lung, n (%)	7 (29.16)	N/A	
Bone, n (%)	19 (79.16)	N/A	
Brain, n (%)	2 (8.3)	N/A	

Table 2. Radiological Characteristics of T4 Subjects.

Radiological Characteristics	Metastatic Proportion (n = 8)	Non-Metastatic Proportion (n = 9)
Intracranial extension, n	4/8	6/9
Cranial nerve involvement, n	0/8	1/9
Hypopharynx involvement, n	2/8	0/9
Orbital involvement, n	0/8	2/9
Parotid gland involvement, n	1/8	0/9
Soft tissue adjacent (over the lateral surface and pterygoid lateral muscle), n	0 (0)	5/9
Parapharyngeal space involvement, n	8/8	9/9
Masticator space involvement, n	5/8	59

Gene Expression Compared to Tumor Staging and Lymph Node Involvement

We analyzed 60 gene expressions. The analysis revealed evidence of DEGs in the T4 stage group when compared to the non-T4 stage group. The investigator found four genes with different expressions: C-X-C Ligand 8 (CXCL8), matrix metalloproteinase-1 (MMP1), matrix metalloproteinase-2 (MMP2), and fibronectin-1 (FN1). A gene heatmap is presented in Figure 1. In addition, descriptions of every fold change and adjusted p-value for each gene are provided in **Table 3**.

DEGs analysis was not performed in subjects with lymph node involvement since most of those subjects were in stage N3. This group comprised 83.3% of the metastatic subjects.

DISCUSSION

Demographic and Clinical Characteristics

The mean age of the evaluated patients was 47.75 years and NPC is the most common occur in men. This aligns with a previous report in Indonesia that NPC is dominant in men.[11] Adham et al.[12] reported that men were 2.4 times

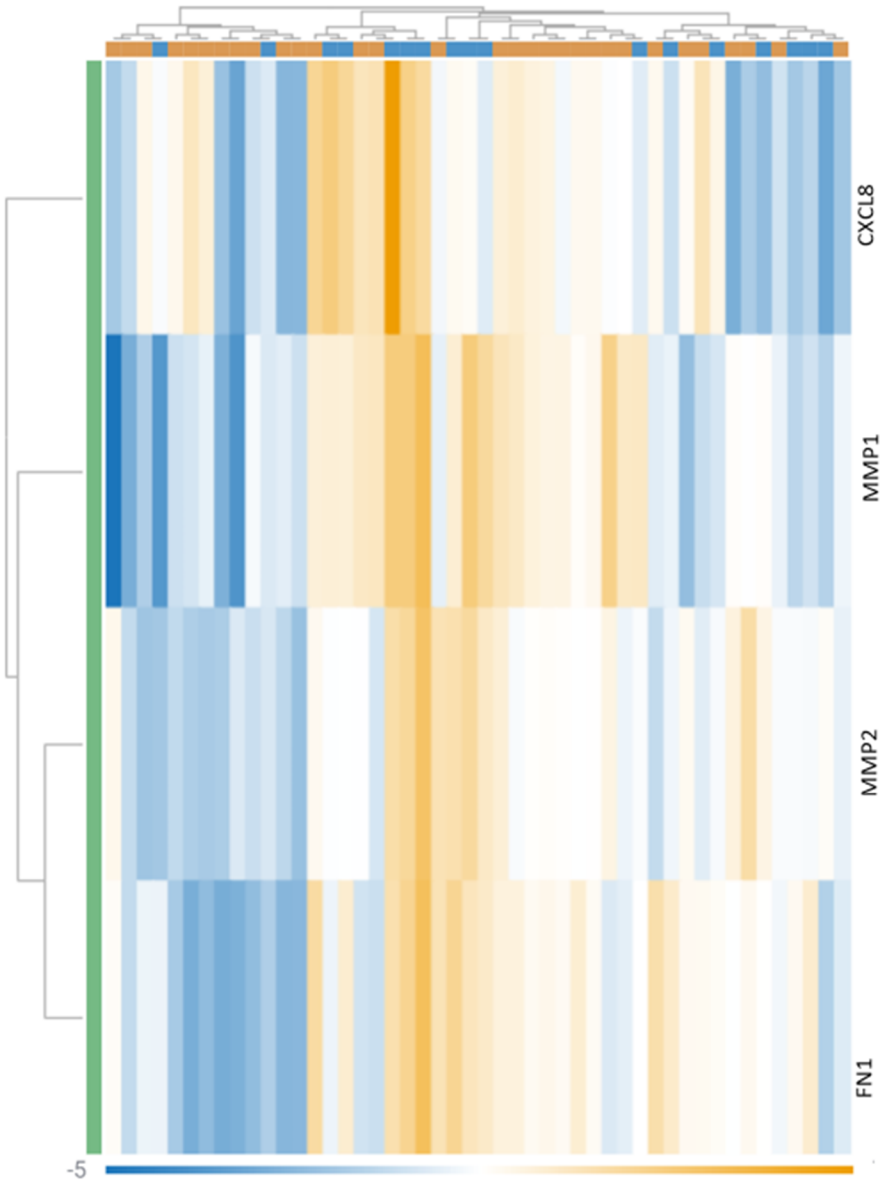

Figure 1. DEGs between the T4 Stage Group and the non-T4 Stage Group (irrespective of metastatic status)

Table 3. Log2 Fold Change and Adjusted p-value of Each Gene

Gene	Log2 Fold Change	p-value (adjusted)
CXCL8	2.09	0.03
MMP2	1.57	0.03
MMP1	1.70	0.03
FN1	1.47	0.03

more likely to have NPC than women. Similarly, Hayati et al.[3] found that the disease was more common in men (73.8%) than in women, with a median age of 46 years. The present study found that the proportion of N3 subjects was larger in the metastatic group and showed statistical significance. This is in line with Chen et al.'s[5] research, which determined that N3 subjects have a higher risk of distant metastases and a poor five-year survival rate. This present study also found most subjects (79.16%) were revealed to have bone metastases, followed by metastases of the lung and liver. According to the existing literature, bone is the most common organ metastases associated with NPC.[13, 14]

Differentially Expressed Genes

After calculating the metastatic and non-metastatic groups, CXCL8, MMP1, MMP2, and FN1 gene expression showed significance in the T4 stage subjects when compared to non-T4 stage subjects. According to the *AJCC* Cancer Staging Manual, 8th edition, T4 staging is defined as the growth of tumor cells into the intracranial region, affecting the cranial nerves, the hypopharynx, the orbit, the parotid gland, and/or more wide-ranging soft tissue (over the lateral surface and pterygoid lateral muscles).[10] Most of the subjects in this study had parapharyngeal space involvement. Based on a previous study, parapharyngeal extension was found in 72–83% of NPC cases at diagnosis. The involvement of the parapharyngeal space affects local tumor failure, regional tumor failure, and distant metastases.[15, 16]

C-X-C Ligand 8

CXCL8 was overexpressed in subjects with T4 staging. CXCL8 is a chemokine ligand that plays a vital role in cancer development, and CXCR1 and CXCR2 are its main receptors. CXCL8 is undetectable under normal conditions.[17, 18] Increases in CXCL8 concentrations are detected in cancerous conditions. Secretion of CXCL8 by cancer cells results in the increased proliferation and migration of cancer cells.[17, 18]

Previous studies have shown that CXCL8 can lead to tumor progression via the activation of the CXCL8 and CXCR1/CXCR2 signaling pathways in an autocrine or paracrine mechanism. CXCL8/CXCR1 and/or CXCL8/CXCR2 stimulation in cancer cells induces phosphatidylinositol-3-kinase (PI3K) expression by activating an intracellular cascade that leads to the phosphorylation of its substrate Akt (PI3K/AKT). This process is followed by protein phosphorylation, which causes cell differentiation, proliferation, and cellular response. Another pathway involves mitogen-activated protein kinase (MAPK) cascades, wherein CXCL8 can be activated through the RAF/MAP/ERK pathway. This process induces the activation of small GTPase and Ras from the Ras-GTP complex, which activates MEK1/MEK2 and catalyzes ERK1/ERK2 activation. The result is a transducing Ras/Raf/MEK cascade that leads to migration, proliferation, survival, differentiation, and chromatin remodeling. In cancer, MAPK signaling is dysregulated, which in turn causes resistance to apoptosis and increases cell proliferation. CXCL8 expression is also indirectly affected by the activation of the JNK/NF-κB pathway that leads to potent cancer enhancers.[19] In general, higher expression of CXCL8 is found in more advanced stages of cancer, including metastases.[17, 18] In head and neck cancers, the CXCL8-CXCR12 axis plays a key role in the development of SCC.[17]

The use of existing antitumor therapies has led to decreased levels of CXCL8. A reduced level of CXCL8 has been shown to be associated with higher patient survival in cancer patients receiving anti-PD1.[20, 21] Researchers have previously noted that CXCL8 increases the expression of PD-1 in macrophages, limiting the action of anti-PD1 therapy.[22, 23] This suggests that CXCL8 can be used as a prognostic biomarker in cancer therapy.[20, 21, 24]

Matrix Metalloproteinase

MMP1 and MMP2 had higher expression among subjects with T4 stage. Matrix

metalloproteinases (MMPs) are endopeptidases that cause proteolytic and degradation processes in the extracellular matrix (ECM). MMPs play a regulatory role in tumor progression and cancer biology by degrading the ECM through migration, differentiation, and tumor growth. MMP1 overexpression causes proliferation, migration, invasion, and metastasis in various types of cancer, such as esophageal SCC, breast cancer, colorectal cancer, and lung cancer.[25] A study by Zhang et al.[25] revealed that MMP1 mRNA expression showed upregulation in head and neck SCC patients when compared to their normal counterparts. This gene overexpression correlated with pathological grading ($p = 0.0006$), advanced tumor size ($p = 0.0097$), and cervical node metastasis ($p = 0.0280$).[25]

One study revealed that MMP2, a subfamily of the MMPs, had a high expression in non-differentiated NPC.[26] This gene plays a role in the degradation of collagen IV, collagen V, and gelatin in the basal membrane and in the ECM in cancer. Overexpression of the gene can lead to tumor invasion, metastasis, and the proliferation and apoptosis of cancer cells.[27] MMP2 overexpression has also been associated with higher tumor grades (OR = 2.09, $p = 0.001$), higher histological grades, and metastases.[27] Other studies have revealed that MMP2 upregulation can promote the motility, proliferation, and metastases of cancers.[28] MMP2 and matrix metalloproteinase-9 (MMP9) play a role in neoangiogenesis and bone metastases.[29] MMP2 promotes bone metastases through collagen degradation, ECM degradation, angiogenesis, cytokine activation, immune regulation, and the formation of pre-metastatic lesions in the bone. By comparison, MMP9 can process the ECM and lead to bone remodeling, reabsorption, vascular endothelial growth factor (VEGF) formation, and angiogenesis.[30]

Fibronectin-1

FN1 is an ECM glycoprotein belonging to the fibronectin family, which plays a role in cell adhesion and migration processes in physiological and pathological mechanisms, such as cell differentiation.[31, 32] The function of and correlation between FN1 expression and cancer levels has been explored in several cancer types. In addition to its role in cell differentiation, FN1 has been found to contribute to tumor architecture and metastases.[32, 33] This mechanism results from the invasion of cancer cells to a deeper layer, which is stimulated by the high expression of FN1.[31]

In gastric cancer, the upregulation of FN1 and several other genes have been associated with poor prognoses.[34, 35] The migration and invasion of cancer cells are also known to have been enhanced by FN1 in several cancers, such as colon cancer and papillary thyroid cancer.[35] In head and neck SCC, FN1 expression is found to be abundant in stromal and invasive regions, suggesting its role in metastases and thus reducing survival.[36] Xinchen Liu et al.'s [36] analysis illustrated a significant relationship between FN1 overexpression and higher staging in head and neck SCC.

CONCLUSION

The proportion of subjects with N3 staging in the metastatic group was significantly higher than the number of patients with N3 staging in the non-metastatic group. CXCL8, MMP1, MMP2, and FN1 gene expression were significantly different between T4 group and non-T4 group.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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