CLINICAL CHARACTERISTICS OF PATIENTS WITH STAGE III – IVA UNDIFFERENTIATED NASOPHARYNGEAL CARCINOMA

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ABSTRACT

Objective: To describe the clinical characteristics of patients with stage III–IVa undifferentiated nasopharyngeal carcinoma (NPC). Marterials and methods: A cross-sectional descriptive study was conducted on 84 undifferentiated type NPC patients. Results: Patient age ranged from 7 to 72 years, with a mean of 46.92 years; the 30–60 age group predominated, and the male-to-female ratio was approximately 2:1. The most common signs were cervical lymphadenopathy (38.1%), headache (32.1%), and tinnitus (27.4%), with onset mostly within three months (57.1%). The primary tumor was most frequently located at the posterior-superior wall of the nasopharynx (39.3%), with the exophytic type being the most common (52.4%). Bilateral cervical lymph nodes were observed in 64.3%, and 90.5% showed loss of the nodal hilum structure on imaging. Tumors frequently invaded the nasopharyngeal soft tissue (34.5%), skull base (28.6%), and cranial nerves/intracranial structures (21.4%). T3–T4 stages accounted for 64.2%, N2 stage for 47.6%, and TNM stages were evenly distributed between stage III (46.4%) and stage IVa (53.6%). Significant differences were found in age distribution, symptoms, tumor location, tumor morphology, and T–N stage ($p < 0.05$). cf EBV DNA concentration at stage IVA media was 3964.0copy/mL which was higher than at stage III ones with 2003.0 copy/mL. Most of patients in both groups were in the level > 4000 copy/ mL. Conclusions: Stage III–IVa undifferentiated NPC

commonly occurs in men aged 30–60 years, characterized by bilateral cervical lymphadenopathy, exophytic primary lesions at the posterior-superior wall of the nasopharynx, extensive local invasion, and advanced nodal metastases, concentration of cf EBV DNA were mostly over 4000 copy/mL.

Keywords: nasopharyngeal carcinoma, undifferentiated type, advanced stage

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the most common malignant diseases among head and neck cancers in both the world and Vietnam [1], [2], [3]. The undifferentiated carcinoma type is the highest and closely related with Epstein Barr virus (EBV) infection, acouted for 90% cases in the Southeast Asia and China [1], [4]. Base on anatomy site and borrowed manifestations of others therefore most of NPC patients were diagnosed in advanced stage III-IV [1], [5], [6]. In Vietnam, there were about 70% patients who were diagnosed in advanced stage and over 90% cases were undifferentiated carcinoma type [5], [6], [7]. Therefore, we conducted this study with the objective: *"To describe the clinical and paraclinical characteristics of patients with stage III-IVa undifferentiated nasopharyngeal carcinoma".*

1. MARTERIALS AND METHODS

1.1 Marterials

The study was on 84 patients with undifferentiated NPC at stage III–IVA, treated at Vietnam National Cancer Hospital, Tan Trieu Campus, from August 2021 to December 2021.

* *Inclusion Criterias:* patients with undifferentiated NPC (WHO 4th subtype III); stage III - IVa (UICC/AJCC 8th); Patients was mesuared the cf EBV DNA concentration before treatment; Patients consented to participate in the study.

* *Exclusion Criterias:* Not complete medical records.

1.2. Method

* *Methodology* : A cross-sectional descriptive study

* *Sample selection:* Whole population sampling.

* *Indicators and variables in the study:* Age, sex, sign symptomes, tumor features (site, characteristic and invase level), stage (UICC/AJCC 8th), cf EBV DNA concentrations.

* *Steps to conduct research:*

- Admission and selection of patients for study
- Assessment stage of diseases
- Summary and analyse

* **Quantification of plasma EBV DNA:** Plasma cf EBV DNA was measured using real-time quantitative polymerase chain reaction (PCR), following the previous published protocol [9]. All blood tests were performed at the Department of Genomics and Cytogenetics, Institute of Biomedicine and Pharmacy, Vietnam Military Medical University, Hanoi, Vietnam.

* Data analysed*:* Statistical analyses were performed using IBM SPSS version 22.0. The Chi-square test or Fisher's exact test was applied to assess differences in the distribution of categorical variables. The independent-samples t-test was used to evaluate differences in mean values.

1.3. Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of 103 Military Hospital of Vietnam Military Medical University (Number 1811/CNChT-HĐĐĐ date 23rd July, 2021). The study data were approved for use and publication by Military Hospital 103. The authors declare that they have no conflicts of interest related to this research

2. RESULTS

Table 1. Age and sex

Age group \ Sex	Male		Female		Total		p
	n	%	n	%	n	%	
< 30	6	10.9	7	24.2	13	15.5	*<0.0001*
30-45	18	32.7	11	37.9	29	34.5	
46-60	20	36.4	10	34.5	30	35.7	***<0.001***
>60	11	20.0	1	3.4	12	14.3	
Total	55	100	29	100	84	100	
Mean ± SD	45.98 ± 15.62		48.10 ± 13.02		46.92 ± 14.46		*0.416**
Min – Max	7-72		24-71		7-72		

Fisher exact test và * Independent T sample test

The age of onset ranged from 7 to 72 years, with a mean age of 46.92 years. The most common age groups were 30–45 years and 46–60 years. Males were affected more frequently than females, with a male-to-female ratio of 55:29 (≈2:1). Among males, the most frequent age group was 46–60 years (36.4%), whereas in females it was 30–45 years (35.7%). A statistically significant difference was observed among the age groups ($p < 0.05$); however, there was no statistically significant difference in the mean age between sexes ($p > 0.05$)

Table 2. Signs

	N	%	p
Chief complain			
Headache	27	32.1	
Neck lymph nodes	32	38.1	*<0.0001*
Epixtasis	7	8.3	
Hemoptysis	28	33.3	
Nasal optruction	30	35.7	***<0.001***
Nasal discharge	18	21.4	
Tinnitus	23	27.4	
Otorrhea	1	1.2	
Otalgia	2	2.4	
Pharyngodynia	2	1.2	
Snoring	1	1.2	
Globus sensation	3	3.6	
Blurred vision	1	1.2	
Facial numbness	1	1.2	
Diplopia	1	1.2	
Proptosis	1	1.2	
Duration of symptoms			
≤3 months	48	57.1	*<0.0001*
>3-6 months	20	23.8	
>6-12 months	13	15.5	
> 12 months	3	3.6	
Min - Max	0.25-24.00		
Mean ± SD	4.60 ± 4.46		

Chi-Square test

The most common presenting symptoms were cervical lymphadenopathy (38.1%), headache (32.1%), and tinnitus (27.4%). The least frequent symptoms were blurred

vision, facial numbness, diplopia, and proptosis, each accounting for 1.2%. The duration of symptoms was less than 3 months in 57.1% of patients, while only 3.6% had symptoms for more than 12 months. The duration of symptoms ranged from 0.25 to 24 months, with a mean of 4.60 months. Both the presenting symptoms and the duration of symptoms showed statistically significant differences.

Table 3. Tumor and lymph node

	n	%	p
Primary tumor sites			
Indeterminate	0	0	*<0.001*
Posterior-superior wall	33	39.3	
Rosenmüller's fossa	22	26.2	
Torus tubarius of Etachian tube	2	2.4	
Diffuse spread	27	32.1	
Total	84	100	
Tumor characteristics on endoscopy			
Unspecified	1	1.2	*<0.001*
Exophytic	44	52.4	
Infiltrative	3	3.6	
Ulcerative	0	0	
Necrotic/hemorrhagic	0	0	
Submucosal	0	0	
Mixed	30	35.7	
Angiogenesis	6	7.1	
Total	84	100	
Lymph node involvement			
No nodal involvement	2	2.4	*<0.001*
Unilateral	28	33.3	
Bilateral	54	64.3	
Nodal characteristics			
Preserved architecture	5	6.0	*<0.001*
Loss of architecture	76	90.5	
Lymph node aspiration			
Not performed	50	59.5	*<0.001*
Negative	9	10.7	
Metastasis	25	29.8	
Lymph node size: 20.11 ± 12.20 mm (range 0–44 mm)			
Tumor size: 34.06 ± 14.93 mm (range 0–75 mm)			
Tumor invasion			
Confined to the nasopharynx	3	3.6	*<0.001*
Invasion into nasopharyngeal soft tissues	29	34.5	
Skull base/vertebral invasion	24	28.6	
Paranasal sinus invasion	1	1.2	

	n	%	p
Orbital invasion	0	0	
Cranial nerve or intracranial extension	18	21.4	
Parotid gland, hypopharynx, or parapharyngeal space invasion	1	1.2	
Invasion of more than one site	8	9.5	

Chi-Square test

The most common primary site of lesion was the posterior-superior wall (39.3%), followed by diffuse involvement (32.1%), while the least common site was the torus tubarius (2.4%). In terms of morphology, exophytic type accounted for 52.4%, mixed type 35.7%, and infiltrative type 3.6%. Bilateral cervical lymphadenopathy was observed in 64.3% of patients, while unilateral cervical lymphadenopathy was found in 33.3%. Loss of nodal hilum structure was seen in 90.5%, and 29.8% had positive results on cervical lymph node aspiration. Tumor invasion into soft tissues and muscles of the nasopharyngeal region was most common (34.5%), followed by skull base and vertebral invasion (28.6%), and cranial nerve or intracranial extension (21.4%)

Table 4. Stage (N=84)

Stage	N	%	**p**
Tumor			
T0	0	0	***<0.0001**
T1	10	11.9	
T2	20	23.9	
T3	27	32.1	
T4	27	32.1	
Node			
N0	4	4.8	***<0.0001**
N1	18	21.4	
N2	40	47.6	
N3	22	26.2	
TNM			
III	39	46.4	*0.513*
IVA	45	53.6	

Chi-Square and *Fisher exact test

T3 and T4 tumors accounted for 32.1%, while T1 was the lowest at 11.9%. Regarding nodal status, N2 was the most frequent (47.6%), followed by N3 (26.2%), whereas N0 was the least common at 4.8%. The differences

among T and N stages were statistically significant. According to the TNM staging system, the distribution was relatively balanced between stage III (46.4%) and stage IVA (53.6%).

Table 5. Plasma cf DNA EBV concentration

cf DNA EBV concentration	III		IVa		p
	N	%	n	%	
0	2	5.1	2	4.4	*0.728*
1-<300	4	10.3	4	8.9	
300 - <500	2	5.1	3	6.7	
500-<1500	7	17.9	6	13.3	
1500 - 4000	12	30.8	9	20.0	
>4000	12	30.8	21	46.7	
Total	39	100	45	100	
Media	2003.0		3964.0		*0.160**
Q1-Q3	621.0-9482.0		840.0-13471.5		
Min – Max	0-31691.0		0-718553.0		

Fisher exact test and * Mann-Whitney Test

The median pre-treatment plasma cf EBV DNA level in stage IVA was 3,964.0 copies/ml, higher than that in stage III (2,003.0 copies/ml). In the subgroup analysis, the highest proportion was observed in the >4,000 copies/ml group, accounting for 12/39 patients (30.8%) in stage III and 21/45 patients (46.7%) in stage IVA. However, no statistically significant differences were found in plasma cf EBV DNA levels between TNM stages or among the subgroups ($p > 0.05$).

3. DISCUSSION

In our study, undifferentiated NPC (stage III–IVa) was observed in patients aged 7–72 years, with a mean age of 46.92 years, most commonly in the 30–60 age group. These findings are consistent with both national and international studies, indicating that the disease frequently occurs in individuals of working age, particularly in males, with an incidence nearly twice that of females [1], [5], [6]. This may be related to occupational factors, lifestyle habits, tobacco smoking, alcohol consumption, and exposure to environmental risk factors, as

well as the association with EBV infection and sex-related differences in immune response [2], [3], [4].

The most common clinical symptom was cervical lymphadenopathy (38.1%), followed by headache (32.1%) and tinnitus (27.4%), reflecting the tendency of the disease to metastasize early to the cervical lymph nodes due to the rich lymphatic network. Ocular and neurological symptoms were rare, suggesting that most patients at this stage had not yet developed deep invasion into the skull base or cranial nerves, or that these symptoms may have been overlooked. The duration of symptoms was mainly less than 3 months (57.1%), indicating both a lack of awareness among patients and the possibility of missed diagnoses at the primary healthcare level. In the study by Hoang Đao Chinh, the most common symptoms were cervical lymphadenopathy (74%), nasal symptoms (70%), ear symptoms (58%), and headache (39%) [5]. According to Pham Lan Son, cervical lymphadenopathy accounted for 33.8%, followed by epistaxis and nasal obstruction, both at 22.1% [6]. International studies have similarly reported cervical lymphadenopathy as the most common presenting feature, followed by sinonasal and middle ear symptoms, cranial nerve palsy, and headache [1], [3].

The tumor sites in our study were consistent with the classical description of the undifferentiated type [1], [6], [7]. The proportion of bilateral cervical lymph nodes was high (64.3%), and most nodes showed loss of the hilum structure on imaging (90.5%), indicating extensive nodal metastasis. The tumor and nodal sizes in our study were consistent with previous reports, reflecting the late stage of disease, with primary tumors often >3 cm and nodes >2 cm. According to Pham Lan Son, the most common sites of involvement were the right wall, left wall, and vault of the nasopharynx [6]. Pham Huy Tan reported that the Rosenmüller fossa and the posterior-superior wall accounted for 72.3% of cases [1]. Macroscopically, our results were

similar to those reported by Tran Thi Kim Phuong, with the exophytic type accounting for the highest proportion (74.2%), followed by the ulcerative type (21%) and the infiltrative type (4.8%) [8]. Do Tram Anh also observed that the exophytic type was predominant, followed by the ulcerative and infiltrative types [9].

Paraclinical investigations using ultrasound, computed tomography, or magnetic resonance imaging are employed to evaluate the primary tumor and regional lymph node metastases. Our findings were consistent with those of other authors such as Do Tram Anh, Pham Huy Tan, and Pham Lam Son [6], [7], [9]. Imaging modalities allow more accurate assessment of nodal status, reduce unnecessary interventions, and facilitate rapid diagnosis [5], [6]. The extent of tumor invasion in our study showed a high rate of involvement of the nasopharyngeal soft tissues (34.5%) and the skull base (28.6%). This explains the predominance of advanced stages T3–T4 (64.2%). Regarding nodal metastasis, N2 accounted for the highest proportion (47.6%), followed by N3 (26.2%), reflecting the extensive lymphatic drainage of the nasopharynx. Hoang Dao Chinh reported that common sites of tumor invasion included the skull base (64.9%), parapharyngeal space (63.2%), skull base foramina (42.1%), and paranasal sinuses (38.6%) [5]. According to Do Tram Anh, the most frequent anterior extension was invasion of the posterior nasal cavity (56.5%) [9]. Pham Huy Tan reported that most patients presented with T4 (31.1%) and T2 (30.3%) disease [7], while Wang W. Y. (2016) found that over 50% of patients were in T3 or T4 stages [2]. Pham Huy Tan (2017) also showed that the majority of patients presented with N1 (41.2%) and N0 (25.2%) disease [7]. Recent studies in endemic regions further confirm that the majority of NPC patients are diagnosed at stage III–IV [1], [2], [10]. According to Pham Huy Tan (2018), the median pre-treatment plasma cf EBV DNA level in stage III and IV

patients was 4.2×10^4 copies/ml [7]. Similarly, Pham Lam Son (2023) reported comparable results to our study, with a mean pre-treatment level of 9,995 copies/ml, and 100% of patients achieving EBV DNA negativity after treatment [6]. Our results before and immediately after treatment were also consistent with other Vietnamese studies, such as Do Tram Anh (2020) [9]. International studies have further established that pre-treatment plasma cf EBV DNA levels ≥ 4,000 copies/ml are considered a "high-risk" threshold for recurrence and metastasis after treatment [2], [4], [10]. These patients require close monitoring and evaluation during and after treatment [2], [4].

The limitations of this study include its cross-sectional descriptive design and the relatively small sample size from a single center; therefore, the results may not fully reflect the overall epidemiological and clinical characteristics nationwide. Nevertheless, this study provides an important source of data, offering practical evidence for planning screening, diagnosis, and treatment of the disease at advanced stages.

CONCLUSION

Undifferentiated nasopharyngeal carcinoma (stage III–IVa) were most commonly seen in patients aged 30–60 years, with a mean age of 46.92 years, and occured about twice as frequently in males as in females. The most common clinical manifestations included cervical lymphadenopathy, headache, and tinnitus, with symptoms usually appearing within three months before diagnosis. The most frequent tumor site were the posterior-superior wall of the nasopharynx, with the exophytic type being predominant. Cervical lymph nodes were often bilateral, typically showing loss of the hilum structure on imaging. The primary tumor tended to invade adjacent soft tissues and the skull base, with some cases extending to cranial nerves and the intracranial region. Tumor staging was predominantly T3–

T4, nodal staging is mainly N2, and overall TNM stages were relatively evenly distributed between stage III and IVa. The median pre-treatment plasma EBV DNA concentrationn in stage IVA was 3,964.0 copies/ml, higher than that in stage III (2,003.0 copies/ml). In the subgroup analysis, the highest proportion was observed in the >4,000 copies/mL group.

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