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CLINICAL AND HISTOPATHOLOGICAL STUDY OF KERATINIZING AND NON-KERATINIZING NASOPHARYNGEAL SQUAMOUS CELL CARCINOMA

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ABSTRACT

Background: nasopharyngeal carcinoma (NPC) is unique in its epidemiologic pattern. It is common in certain ethnic groups; Epstein Barr Virus infection has been proposed as a risk factor but per-sue it is not sufficient to cause malignancy. Other co factors like genetic and environmental susceptibility may contribute in the carcinogenesis of NPC. Aims: To study various presentations of NPC and its relation with disease severity and date of diagnosis. To analyze the correlation between risk factors and the disease entity. To assess the relative frequency of histopathological results. **Patients and Methods:** this is combined prospective and retrospective study of 25 patients with confirmed NPC between 2017 and 2020 conducted in Al Yarmouk Teaching Hospital, all patients included fulfill the questionnaire sheet with assistance of radiological and histopathological department, and we classify them according to WHO classification and AJCC staging system and investigate the finding with various parameters. **Results:** in current study we found that 18 (72%) of cases were male patients and 7 (28%) were female, the most common age presentation was in the 7th decade (9 patients) with second peak between 20-29 years old, the most frequent clinical presentation in general was neck mass in 20 (80%) of cases, 21 (84%) of patients diagnosed with NKSCC and the remaining 4 (16%) patients had KSCC, advanced disease presented in 18 (72%) of cases while only 7 (28%) were in early stages. **Conclusions:** the present study reveals a bimodal age distribution at (60 years and more) in 36% of patients, the next frequently affected age group was (20-29) year by 20% of patients, male is more common affected than female in a ratio of 2.5:1, most common histopathology was NKSCC, there is a significant relation between neurological symptoms and advanced stage of disease. Also a significant relation between initial otological presentation and long interval till proper diagnosis.

KEYWARDS: Nasopharyngeal carcinoma, risk factors, histopathology.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) often originates from the fossa of Rosenmuller and can be difficult to detect in early stages.[1,2,3] It spreads in various directions, including anteriorly to nasal structures (1, 4), posteriorly to retropharyngeal space.[4] superiorly to the sphenoid sinus and intracranial cavity (1, 4), inferiorly to the oral cavity (4), and laterally to the parapharyngeal space.[1,4] NPC metastasis may also involve the internal carotid artery due to its proximity to retropharyngeal lymph nodes.[1] NPC has a high incidence in southern China, particularly in Guangdong province, with varying rates across the country.[1,2] Intermediate to low rates are observed in Southeast Asia, North Canada, Greenland, North Africa, and the Middle East.[1,2] Males comprise three-quarters of NPC patients, and over 80% are diagnosed between 30 and 60 years old,[5] Age distribution differs between low-incidence and endemic areas, with bimodal peaks in low-incidence areas and a peak at 40-59 years in endemic areas.[2,6]

NPC development is associated with genetic factors, environmental factors, and Epstein-Barr Virus (EBV).[5] Genetic factors include family clusters, human leukocyte antigen associations, and chromosomal changes.[1,3,5] Environmental factors involve diet, nitrosamines, chemical fumes, wood dust, and smoking.[1,2,5,7] The exact role of EBV in NPC development is still unclear, but it may involve genetic susceptibility and environmental factors transforming the nasopharyngeal

epithelium.[1,5] NPC classification has evolved over time, with the 1978 WHO classification including three types.[3] It was revised in 1991, combining types II and III into non-keratinizing.[8] The 2005 WHO classification further divides NPC into non-keratinizing, keratinizing, and basaloid SCC.[9] Non-keratinizing tumors are associated with EBV, while keratinizing SCC has a link to smoking (10). Non-keratinizing carcinoma has higher local tumor control and distant metastasis rates and is characterized by lymphoepithelial histologic features.[1,3] Early NPC symptoms can be subtle and undetected, with the tumor's central location allowing it to spread in various directions.[1] Common presentations include nasal symptoms (50% of patients), otological symptoms (30-40%), neck symptoms (70% with enlarged painless neck lymph nodes), and neurological symptoms (headache in 20%)[1,3,5] Systemic metastasis symptoms are relatively uncommon, but can involve the vertebra, liver, and lung.[3]

NPC prognosis is heavily influenced by factors such as stage at presentation, with two-thirds of patients classified as stage III or IV at diagnosis.[5,10] Other negative prognostic factors include increasing tumor volume.[10] elevated EBV DNA levels,[10] fixation of neck nodes, male gender, age over 40 years, and cranial nerve palsy.[10] Histopathological type also plays a role, as K-NPC has been suggested to be less responsive to radiotherapy and have a worse prognosis than NK-NPC.[1,10] The research goals include examining the correlation between the stage of nasopharyngeal cancer at diagnosis and prognosis, investigating the relationship between risk factors and the development of the illness, and assessing the frequency of histological findings that align with the WHO's criteria for nasopharyngeal cancer.

METHOD

This descriptive case series study combines prospective and retrospective data from patients diagnosed with nasopharyngeal cancer (NPC) between January 2017 and December 2020 at Al-Yarmouk-Teaching-Hospital. A total of 25 patients were included, with ages ranging from 17 to 76 years old. The study adhered to ethical considerations and obtained necessary permissions. Patients with incomplete data were excluded. Data analysis involved reassessing retrospective data through patient history, radiological imaging, and histopathological reports. Prospective data was collected through thorough patient history, physical examination, and radiological assessment. Endoscopic post-nasal space biopsy techniques were used for tissue collection, and the samples were sent for histopathological study. Brain CT scans, chest X-rays, and abdominal ultrasounds were used to evaluate distant metastasis. Data were entered into Microsoft Excel 2016 and refined and revised before being put into SPSS version 24. Tables and graphs showed descriptive statistics. Chi square test determined the significance of categorical variable associations. The significance threshold was 0.05.

RESULTS

This study included 25 patients, the information of 20 patients was taken from patient's records retrospectively, and the remaining 5 patients were interviewed by the researcher prospectively. The age of the patients was ranged from (17 – 76) years old and the standard deviation was 47.48 ± 16.5 yr. Nine (36%) patients aged 60 years and more forming the peak incidence of NPC, the next frequently affected age group was (20-29) year and forming 5 (20%) patients, 4 (16%) patients were between (50-59) year, also 4 (16%) patients were between (40-49) year, 2 (8%) of our patients aged within (30-39) year and only one patient was below 20-year-old as shown in figure 3.1.

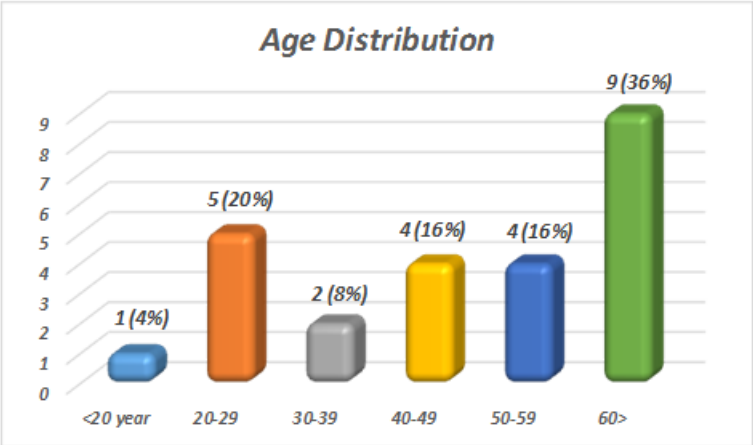

Figure 1: Age Distribution.

Eighteen (72%) of patients in this study were males, and 7 (28%) were females; Male to Female ratio is 2.5:1 as shown in figure 2.

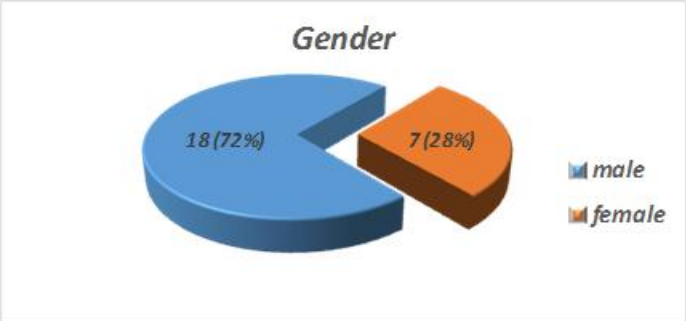

Figure 2: Gender Distribution.

Only one patient was suggested a family history of NPC, 21 (84%) patients had EBV +ve by immunohistochemical staining, and the remained 4 (16%) patients show EBV -ve, only 7 (28%) patients from total of 25 referred that they exposed to carcinogens, 17 (68%) patients were smoker (dividing to 9 current smokers, 8 x-smokers), while 8 (32%) patients never smoke as clarified in table 1 below.

Table 1: Risk Factors.

Possible Risk Factors			
Family history	Yes	1	4.0%
	No	24	96.0%
EBV	Positive	21	84.0%
	Negative	4	16.0%
Environmental (carcinogenic exposure)	Yes	7	28.0%
	No	18	72.0%
Smoking	Smoker	9	36.0%
	X smoker	8	32.0%
	Never	8	32.0%

Seven (28%) patients were exposed to carcinogens in the following orders: 2 patients exposed to bad dietary habit, 2 patients got chemical fume exposure, other carcinogens like gunpowder, industrial gases, and industrial dust exposure were found among one patient for each as clarified in the table 2 below.

Table 2 Carcinogenic risk factors.

Carcinogen type	**No. of patients**	**Percentage**
Bad dietary habit	2	28.6%
Gun powder	1	14.3%
Industrial gas	1	14.3%
Chemical fume	2	28.6%
Industrial dust	1	14.3%

Focusing on the most frequent clinical presentation in general, 20 (80%) patients had neck mass, 18 (72%) had hearing impairment, 15 (60%) had nasal obstruction, 11 (44%) had blood stained discharge, 9 (36%) had tinnitus, 9 (36%) had otalgia, 8 (32%) had headache, 7 (28%) had facial numbness, 6 (24%) had epistaxis and only 1 (4%) had proptosis as shown in figure 3 below.

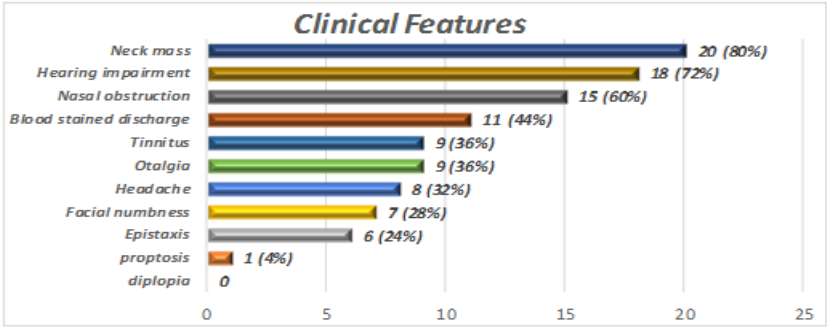

Figure 3 collective clinical manifestations.

Hearing impairment was the first complaint in 11 (44%) patients, neck mass in 8 (32%), nasal obstruction in 4 (16%), epistaxis in 2 (8%) as clarified in table 3 below.

Thirteen (52%) patients complained from the disease in less than 6 months' while 12 (48%) patients take equal or more than 6 months' interval as shown in figure 4.

Table 3: Chief complaints.

Chief Complaints	No. of patients	Percentage
Hearing impairment	11	44.0%
Neck mass	8	32.0%
Nasal obstruction	4	16.0%
Epistaxis	2	8.0%

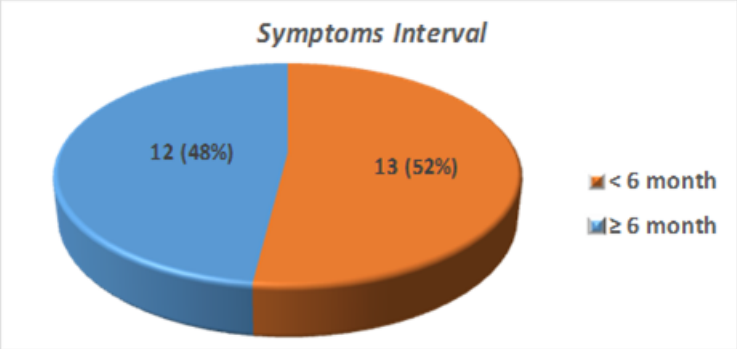

Figure 4 Duration of symptoms before diagnosis.

There is significant association between hearing impairment and longer duration until diagnosis, followed by nasal obstruction, while neck mass and epistaxis were found to be diagnosed among shorter duration of time (< 6 months) as clarified in table 4 below.

Table 4: Association between chief complaints and duration.

Duration / Chief complaint	< 6 months	≥ 6months
Hearing impairment	2	9
Neck mass	8	0
Nasal obstruction	1	3
Epistaxis	2	0
P value	0.001	

NK-SCC account for 21 (84%) patients, but K-SCC present only in 4 (16%) patients as shown in figure 5.

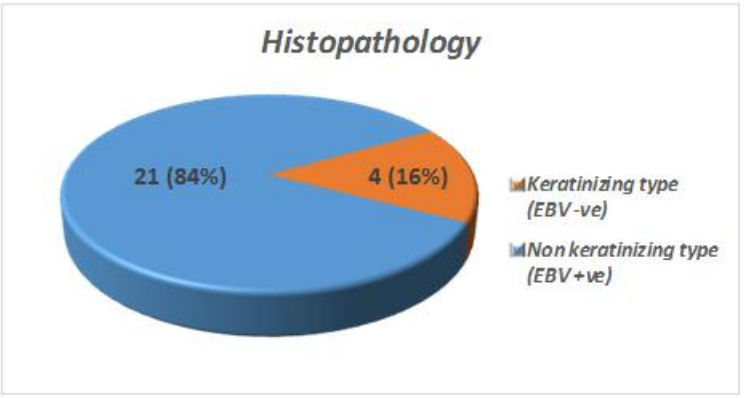

Figure 5: Histopathological Result.

Regarding the association between the age of the patients and histopathological finding, 15 patients of non-keratinizing type of histopathology aged above 30 years and 6 of them aged less than 30-year-old. On the other

hand, no case with keratinizing type encountered below 30 years. P value shows no significant association as clarified. We noticed that non-keratinizing SCC present among smoker (13 patients) and nonsmoker (8 patients). But keratinizing subtype present exclusively in smokers. P value = 0.134. Regarding relation between EBV and histopathological result we noticed that all cases with non-keratinizing type were found to be EBV positive, and 4 patients of keratinizing type were EBV negative. As in table 5.

Table 5: Association between Age and Histopathology, Association between Smoking and Histopathology, Association between EBV and Histopathology.

H.P / Age	NKSCC	KSCC	Total
<30 years	6 (24.0%)	0 (0.0%)	6 (24.0%)
=>30 years	15 (60.0%)	4 (16.0%)	19 (76.0%)
P value	0.220		
H.P / Smoking	NKSCC	KSCC	Total
Yes	13 (52.0%)	4 (16.0%)	17 (68.0%)
No	8 (32.0%)	0 (0.0%)	8 (32.0%)
P value	0.134		
H.P / EBV	NKSCC	KSCC	
Positive	21 (84.0%)	0 (0.0%)	
Negative	0 (0.0%)	4 (16.0%)	

Only seven (28%) patients diagnosed at the early stages of disease (stage I, II), while 18 (72%) patients catches in late stages (stage III, IV), as shown in figure 6.

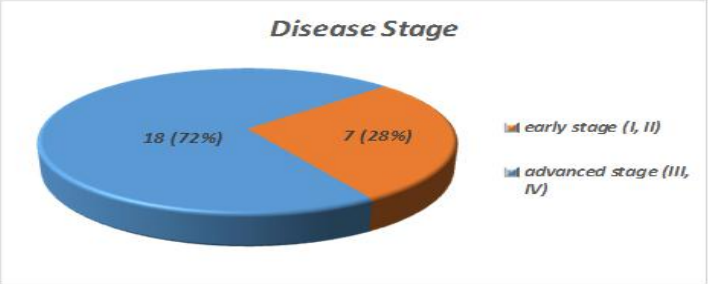

Figure 6 Disease stage.

According to TNM classification 3 (12%) patients presented at T1, 7 (28%) patients presented at T2, 10 (40%) patients presented at T3, and 5 (20%) patients presented at T4, regarding nodal metastasis one patient presented with N0, 12 (48%) patients presented with N1, 9 (36%) of them presented with N2, and 3 (12%) patients presented with N3, no any patient present with distant metastasis, as clarified in table 6.

Table 6: Distribution of patients according TNM classification, distribution of patients according to their AJCC staging system.

TNM classification	TNM series	No. of patients	Percentage
T	1	3	12.0%
	2	7	28.0%
	3	10	40.0%
	4	5	20.0%
N	0	1	4.0%
	1	12	48.0%
	2	9	36.0%
	3	3	12.0%
M	1	0	0.0%

Stage groups	TNM subtype	No. of patients	Total
Stage I	T1N0M0	1	1 (4.0%)
Stage II	T1N1M0	2	6 (24.0%)
	T2N0M0	0	
	T2N1M0	4	
Stage III	T1N2M0	0	12 (48.0%)
	T2N2M0	3	
	T3N0M0	0	
	T3N1M0	6	
	T3N2M0	3	
Stage IVa	T4N0M0	0	3 (12.0%)
	T4N1M0	0	
	T4N2M0	3	
Stage IVb	T1 N3M0	0	3 (12.0%)
	T2N3M0	0	
	T3N3M0	1	
	T4N3M0	2	
Stage IVc	Any T Any N M1	0	0 (0.0%)

According to AJCC, 7 (28%) of patients presented at stage II or below, 12 (48%) at stage III, and 6 (24%) at stage IV in the form of 3 at stage IVa, and 3 at stage IVb, as shown in figure 7.

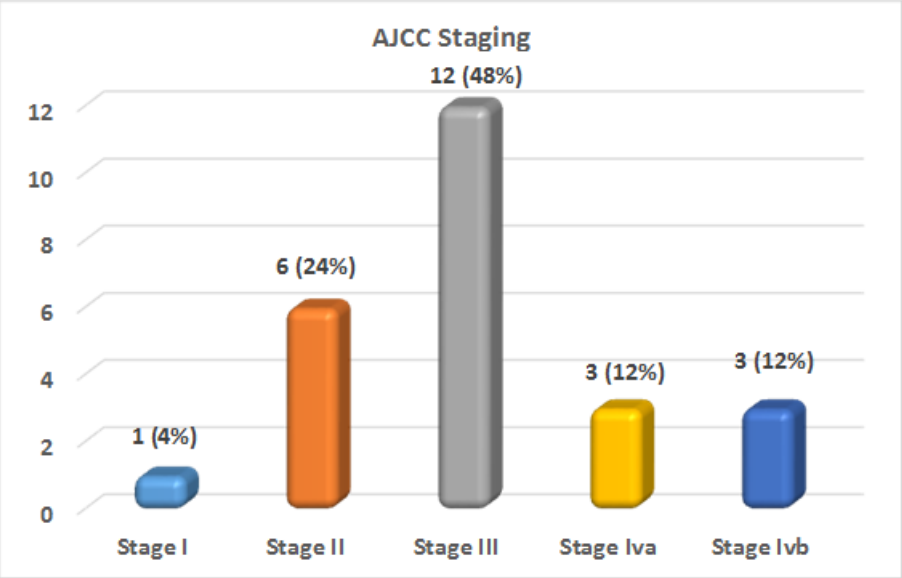

Figure 7: AJCC Staging System.

Association between Clinical Features and Stage of the disease: No significant association between stage of the disease and clinical features except for the neurological symptoms, details are clarified in the following tables: Regarding early stages (I, II) only one patient of total 7 was experienced neurological symptoms, by comparison with late stages (III, IV) we had 10 (stage III ʻ4ʼ, stage IV ʻ6ʼ) of total 18 patients presented with neurological symptoms, p value 0.021. Regarding early stages (I, II) all patients experienced otological symptoms, by comparison with late stages (III, IV) we had 13 (stage III ʻ8ʼ, stage IV ʻ5ʼ) of total 18 patients presented with otological symptoms, p value 0.101, Regarding early stages (I, II) 6 patients (stage I ʻ1ʼ, stage II ʻ5ʼ) of total 7 were experienced nasal symptoms, by comparison with late stages (III, IV) we had 13 (stage III ʻ10ʼ, stage IV ʻ3ʼ) of total 18 patients presented with nasal symptoms, p value 0.127, Regarding early stages (I, II) four patients (stage II ʻ4ʼ) of total 7 was experienced neck swelling, by comparison with late stages (III, IV) we had 16 (stage III ʻ10ʼ, stage IV ʻ6ʼ) of total 18 patients presented with neck swelling, p value 0.078. **as shown in table 7.**

Table 7: Association between stages of the disease and neurological symptoms. Association between stage of the disease and ontological symptoms, Association between stage of the disease and nasal symptoms, Association between stage of the disease and neck swelling.

Stage	No. of patients	Neurological Symptoms	
		Yes (11)	No (14)
I	1	0	1
II	6	1	5
III	12	4	8
Iva	3	3	0
IVb	3	3	0
Total	25	11	14
P value	0.021		

Stage	No. of patients	Otological Symptoms	
		Yes (20)	No (5)
I	1	1	0
II	6	6	0
III	12	8	4
Iva	3	3	0
IVb	3	2	1
Total	25	20	5
P value	0.101		

Stage	No. of patients	Nasal Symptoms	
		Yes (19)	No (6)
I	1	1	0
II	6	5	1
III	12	10	2
Iva	3	1	2
IVb	3	2	1
Total	25	19	6
P value	0.127		

Stage	No. of patients	Neck Swelling	
		Yes (20)	No (5)
I	1	0	1
II	6	4	2
III	12	10	2
Iva	3	3	0
IVb	3	3	0
Total	25	20	5
P value	0.078		

DISCUSSION

This study focused on the clinical and histopathological patterns of NPC patients in a non-endemic region, with 25 of the initially recruited 32 patients being included due to data quality and accessibility issues.

1. Age distribution in this study showed bimodal peaks, aligning with findings from Nigeria and North Tunisia, but differing from the single peak observed in China.[11-13]
2. Males were predominantly affected, with a male-to-female ratio similar to studies from Jeddah, Iran, and Indonesia.[14-16]
3. Occupational carcinogenic exposure and poor dietary habits were weakly associated with NPC risk in this study, indicating the need for larger sample sizes.[17]
4. Most patients presented with multiple symptoms, with neck mass and hearing impairment being the most common. A significant correlation was found between initial hearing impairment complaints and delayed diagnosis, likely due to misdiagnoses and treatment for other conditions.[14,18,19]
5. Histopathological classification revealed non-keratinizing SCC as the more common subtype, consistent with a Nigerian study and a meta-analysis on NPC subtype and smoking.[11,20]
6. Advanced stage (III, IV) presentation occurred in 72% of cases, similar to a Malaysian study. A significant relationship was found between

neurological manifestations and advanced stage presentation, as also observed in an Indonesian study.[16,21]

CONCLUSION

1. The age distribution exhibits dual peaks, with the majority of cases occurring in the 3rd and 7th decades of life.
2. Males are more frequently affected by NPC than females, at a ratio of 2.5:1.
3. The most prevalent histopathological subtype is NKSCC, which is linked to EBV exposure.
4. A significant connection exists between initial otological symptoms and prolonged intervals before an accurate diagnosis is made.
5. A notable association is present between neurological manifestations and advanced stages of the disease.

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