

## Nasopharyngeal Carcinoma: A Clinicopathological Study

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**Abstract:** Nasopharyngeal carcinoma is commonly a squamous cell carcinoma arising from the epithelial lining of nasopharynx more frequently seen at the fossa of Rosenmüller.

It is a leading form of cancer in a few well-defined populations, including natives of Southern China, Southeast Asia, the Arctic, and the Middle East/ North Africa. Nasopharyngeal carcinoma is very common among the inhabitants of Nagaland and in some hill districts of Manipur. The TNM Classification of Malignant Tumours (TNM) is a globally recognised standard for classifying the extent of spread of cancer. This study is undertaken to assess the etio-pathology and clinical features of nasopharyngeal carcinoma and the factors associated with or which influence the treatment outcome. The study included 30 patients attending Department of Otorhinolaryngology, Regional Institute of Medical Science, Imphal, with Nasopharyngeal carcinoma between September 2016 to August 2018. It was found that males were more affected than females, the peak age group being in the fifth decade and Bimodal peak was seen in 7<sup>th</sup> decade with Nagas being the most common ethnic group affected. EBV DNA was detected in all the cases. Cervical lymphadenopathy was the most common presentation seen. Most common histopathological picture was non-keratinizing carcinoma- undifferentiated type.

**Keywords:** Nasopharyngeal carcinoma, TNM classification of malignant tumours, EBV DNA.

Date of Submission: 22-07-2019

Date of Acceptance: 07-08-2019

### I. Introduction

Nasopharyngeal carcinoma is commonly a squamous cell carcinoma arising from the epithelial lining of the nasopharynx. This neoplasm could arise from any site in the nasopharynx and is more frequently seen at the fossa of Rosenmüller.<sup>1</sup> Although nasopharyngeal carcinoma is rare in most population, it is a leading form of cancer in a few well-defined populations, including natives of Southern China, Southeast Asia, the Arctic, and the Middle East/ North Africa.<sup>2</sup> This tumour is uncommon in India with incidence of 0.9 per million.<sup>3</sup> Nasopharyngeal carcinoma is very common in this part of country among the inhabitants of Nagaland and in some hill districts of Manipur.<sup>4</sup> The nasopharyngeal carcinoma cells are basically squamous cell carcinoma in origin with minimal differentiation.<sup>5</sup> Undifferentiated carcinoma constitute the major histological type worldwide.<sup>6</sup> Only the non-keratinizing variant is associated with Epstein-barr virus (EBV) infection.<sup>7,8</sup> The most common mode of presentation of nasopharyngeal carcinoma is a painless unilateral metastatic cervical lymph node.<sup>9</sup> Thirty percent of patients presented with nasal symptoms including blood stained nasal discharge, nasal obstruction, post nasal drip or even frank epistaxis. Twenty percent patients present with aural symptoms including deafness, tinnitus and otalgia.<sup>10</sup> Middle ear effusion is present in more than 40% of patients at diagnosis.<sup>11</sup> Neurological involvement comprises of headache and cranial nerve symptoms. Headache occurs in 20% of patients.<sup>9</sup>

Endoscopic examination provides valuable information on mucosal involvement and tumour extent and allows guided biopsy. The endoscopic examination, however, cannot determine deep extension or skull base involvement of the tumour.<sup>12</sup> Computed tomography and magnetic resonance imaging studies have improved the accuracy of staging and have allowed radiotherapy planning and treatment.<sup>13</sup> The TNM Classification of Malignant Tumours (TNM) is a globally recognised standard for classifying the extent of spread of cancer. Nasopharyngeal carcinoma is an extremely radiosensitive tumour and the mainstay of treatment for primary local and regional disease is invariably radiotherapy, almost irrespective of the stage of the disease. For patients with advanced disease, the addition of chemotherapy appears to enhance the overall treatment results. Surgery, at present is only used to salvage local and regional failures.<sup>14</sup>

In this background, the present study is undertaken to assess the etio-pathology and clinical features of nasopharyngeal carcinoma and the factors associated with or which influence the treatment outcome.

## II. Materials And Method

It included 30 patients attending Department of Otorhinolaryngology, Regional Institute of Medical Science, Imphal, with Nasopharyngeal carcinoma between September 2016 to August 2018. Inclusion criteria include all newly diagnosed, histologically and radiologically confirmed cases of nasopharyngeal carcinoma coming with any one of the symptoms of nasopharyngeal carcinoma. All previously treated or recurrent or residual cases of nasopharyngeal carcinoma are excluded from the study. Thorough clinical examination of the head and neck was done. Examination of the nose, 0° and 30° endoscopy for the nasopharynx, oral cavity, oropharynx, indirect laryngoscopic/ 70° endoscopic examination was also done. Special emphasis was given on history of consumption of smoked meat/fish, tobacco chewing, smoking and alcohol consumption. Pre-treatment serological test for EBV DNA was done using RT-PCR. Radiological examination including chest x-ray, contrast enhanced CT and/or MRI of the head and neck region was carried out. Fine-needle aspiration cytology (FNAC) from the neck node and biopsy from the nasopharyngeal mass for histopathological study was done to arrive at a diagnosis. Following diagnosis, proper staging was carried out with latest TNM classification and treatment was given accordingly like radiotherapy, chemo-radiotherapy, chemotherapy and/or salvage neck node dissection.

## III. Statistical Analysis:

Data entry was done using statistical package for social sciences (SPSS) version 25.0 (Armonk NY: IBM Corp). Descriptive and analytical statistic was done. Summarization and presentations of qualitative data were done using proportions and percentage and quantitative data with mean, median and standard deviation. Chi square test (statistical test of significance) was used to find out p value. All comparisons were two-sided and the P-values of < 0.05, < 0.01 and <.001 were treated as the cut off values for significance, highly significant and very highly significant respectively. Approval of the study from the Research and Ethics Board, Regional Institute of Medical Sciences (RIMS), Imphal was sought.

## IV. Results And Observation

The study was based on the primary data of 30 patients of both sexes.

### Age distribution

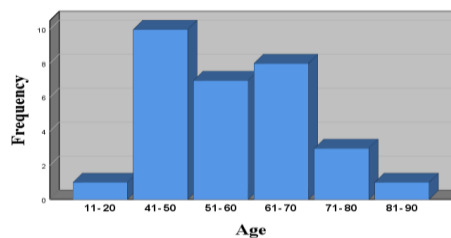


Figure 1: Bar diagram showing age distribution

Out of the 30 patients, 10(33.3%) cases belonged to the age group of 41-50 years followed by 8 (26.7%) cases in the age group of 61- 70 years.

### Sex distribution

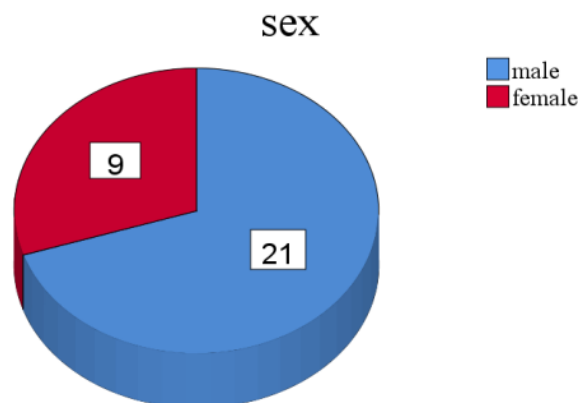


Figure 2: Pie chart showing gender distribution

**Ethnic distribution**

**Table 1:** Ethnic distribution of patients (n= 30):

Ethnicity	Frequency	Percentage (%)
Naga	16	53.3%
Meitei	4	13.3%
Kuki	7	23.3%
Meitei Pangal	2	6.7%
Mizo	1	3.3%
Total	30	100%

In this study, majority accounting to 16 patients (53.3%) belongs to Naga ethnic group.

**Distribution of patients with food habits**

**Table 2:** Distribution of patients with Food Habits (n= 30):

Food habits	Frequency	Percentage (%)
Smoked meat, dry/salted fish	14	46.7%
Smoked meat	2	6.7%
Dry/salted fish	7	23.3%
Normal non veg diet	6	20%
Normal veg diet	1	3.3%
Total	30	100%

**Distribution of patients with respect to addiction:** Twenty (66.6%) patients were smokers and 18 (60%) were alcoholics out of 30 patients. Six patients (20%) were pan chewer alone.

**Distribution of patients with symptoms**

**Table 3:** Distribution of patients with symptoms (n= 30):

Symptoms	Frequency	Percentage (%)
Neck swelling	27	90%
Sticky sensation of throat	7	23.3%
Epistaxis	5	16.6%
Nasal discharge	11	36.6%
Nasal obstruction	9	30%
Tinnitus	9	30%
Fullness of ears	15	50%
Hearing loss	13	43.3%
Otalgia	2	6.6%
Facial pain	9	30%
Headache	11	36.6%
Dysphagia	3	10%
Nasal regurgitation	5	16.6%
Diplopia	4	13.3%
Ptosis	2	6.6%
Trismus	2	6.6%
Throat pain	2	6.6%
Oral swelling	1	3.3%

Out of 30 patients, 9(30%) patients had neurological involvement.

Out of 9 patients with cranial nerve involvement, most common cranial nerve involved was trigeminal nerve 7(77.7%) followed by abducens 4(44.4%). Glossopharyngeal and vagus were involved in 3(30%) patients each. Two (22.2%) patients had oculomotor involvement.

**Classification of cases according to histological type of primary lesion:**

**Table 4:** Distribution of patients according to histological type of primary lesion (n= 30):

Histopathological appearance	Frequency	Percentage (%)
Keratinizing Squamous cell carcinoma (SCC)	2	6.7%
Non keratinizing differentiated	9	30%
Non keratinizing undifferentiated	19	63.3%
Total	30	100%

Out of 30 patients, 19(63.3%) patients were histologically diagnosed with Non Keratinizing undifferentiated, 9(30%) were Non keratinizing differentiated and 2(6.7%) were Keratinizing squamous cell carcinoma.

**Classification of cases according to fine needle aspiration cytology (FNAC) findings of neck nodes**

Out of 30 cases, 27(90%) patients were presented with neck nodes and FNAC showed features of metastatic undifferentiated carcinoma.

**Classification of cases according to CT scan findings:**

**Table 5:** Distribution of patients according to specific CT scan findings of primary lesion (n= 18):

CT Scan finding	Frequency	Percentage (%)
Skull base erosion	10	33.3%
Foramen lacerum	1	3.3%
Foramen ovale	1	3.3%
Parapharyngeal space involvement	3	10%
Intracranial extension	3	10%
Total no patients	18	100%

In the present study, Computed Tomography (CT) was done in all 30 cases. 10(33.3%) patients had skull base erosion and 3(10%) patient had intracranial extension on CT scan. 3(10%) patient had parapharyngeal space/ infratemporal fossa involvement. One patient (3.3%) each showed extension of growth causing widening of foramen lacerum and foramen ovale.

Out of 30 patients, all patients' blood sample detected Epstein barr virus (EBV) DNA using Real Time Polymerase chain reaction (RT-PCR).

**Distribution of cases according to stage of disease:** In the present study out of 30 patients, 17(56.6%) patients presented with stage IV of nasopharyngeal carcinoma 9(30%) patients with stage III and 4(13.3%) patients with stage II.

**Distribution of cases according to treatment modality:**

**Table 6:** Distribution of Patients according to treatment modality (n= 30):

Treatment	Frequency	Percentage (%)
Surgery	0	0%
Radiotherapy alone	0	0%
Concurrent chemo-radiotherapy (CCRT)	6	20%
Neo-adjuvant chemotherapy (NACT) followed by CCRT	24	80%
CCRT with adjuvant chemotherapy	0	0%
Total	30	100%

Out of 30 patients, 24(80%) patients were treated with NACT followed by CCRT and 6(20%) patients with CCRT alone. No patients were given radiotherapy alone.

All 30 patients received Radiotherapy. Seventy (70) Gy was given in divided dose for 35 days as external beam radiotherapy using Cobalt-60.

In this study out of 24 patients treated with NACT with CCRT, 10 patients(41.6%) chemotherapeutic combination for NACT was Paclitaxel + Carboplatin, followed by Cisplatin + 5FU in 7 (29.1%) patients, Cisplatin + Paclitaxel in 4 (16.6%) patients, Doclitaxel+ Carboplatin in 2 (8.3%) patient and Carboplatin + 5FU in 1(4.1%) patient.

Out of 30 patients, 18(60%) patients were treated with cisplatin as chemotherapeutic agent in CCRT and rest of the patients 12(40%) with carboplatin.

## V. Discussion

It is a cross sectional study, conducted from September 2016 to August 2018. All the patients coming with histopathologically proven nasopharyngeal carcinoma were included in the study. Total 30 patients who attended ENT outpatient department were admitted and evaluated. The findings of present study are elaborated, compared and discussed with the finding of other authors under the following headings.

**Age and sex variation:** The ages ranged from 20 to 83 with the peak age group in the fifth decade. This finding agrees with the studies in Hong Kong and Taiwan, which also reported peak age group at fifth decade.<sup>18,22</sup> Some studies reported a peak age at fifth decade and bimodal peak was seen in most of them.<sup>16,17,19</sup> Bimodal peak was seen in this study too.

This study composed of males and females with a male: female ratio of 2.3:1.

Chi square test was performed to know the incidence of different histopathological types to sex of patient and was found statistically insignificant (p-value = 0.718)

**Demographic profile:** In the present study, comprising of 30 nasopharyngeal carcinoma patients, majority of the patients were Nagas 16(53.3%), followed by Kuki- 7(23.3%), Meitei- 4 (13.3), Meitei Pangal (local Manipuri Muslim)- 2(6.7%) and Mizo- 1(3.3%). This is comparable to a study in North East India where among 58 patients, Naga constituted majority of case 41 out of 58 patients (70.7%).<sup>4</sup> This shows that there are some significant geographical variations within country with respect to the distribution of nasopharyngeal carcinoma reflecting ethnic susceptibility for the disease.

In this study 20(66.6%) patients were smokers and 18 (60%) patients were alcoholics out of 30. In a study in Singapore, the effect of cigarette smoking, shown to be significant in several retrospective studies, could be explained in part by epidemiological phenomena such as sex difference on incidence, male being three times more commonly affected.<sup>16</sup> Some studies found smoking to be associated risk factor for nasopharyngeal carcinoma.<sup>23,24</sup> A study conducted in India observed significantly high relative risk among the smokers, particularly for the well differentiated nasopharyngeal carcinoma.<sup>25</sup> Smoking was the main risk factor for squamous cell nasopharyngeal carcinoma, while its association with undifferentiated or non-keratinizing nasopharyngeal carcinoma has not been demonstrated.<sup>26</sup> However most of our cases were undifferentiated carcinoma and this may explain why smoking was not particularly found associated with the disease in our study.

All the patients were non vegetarian except one. Out of 30 patients 23 had the habit of taking smoked meat and/or dry salted fish. A study conducted in Assam found that 82.75% of the patients were in the habit of taking smoked meat and fish.<sup>4</sup> A case control study on nasopharyngeal carcinoma in Nagaland strengthens the hypothesis which indicated that consumption of smoke dried meat and use of herbal nasal medicine were the significant risk factors for the nasopharyngeal carcinoma.

**Modes of clinical presentation:** In the present study most common presenting feature was painless cervical lymphadenopathy, which occurred in 27(90%) patients. 27 of the patients in this study had palpable cervical lymph nodes at presentation of which 5(16.6%) had bilateral cervical lymphadenopathy. This finding is similar to a Jamaican study on 35 patients of nasopharyngeal carcinoma found 86% of the patients had cervical lymphadenopathy on presentation.<sup>19</sup> A retrospective study on 966 patients in Taiwan, where 729 (75.5%) of patients presented with neck mass.<sup>18</sup> In a study in north eastern Nigeria, the commonest symptoms at presentation was cervical lymphadenopathy present in 72.5% of patients.<sup>27</sup> However a study in Hong Kong reported a lower percentage of 55%.<sup>28</sup> The high incidence of cervical lymphadenopathy reemphasizes the tendency of early metastasis to cervical lymph nodes in nasopharyngeal carcinoma. The typical glandular metastasis develop posterior to the angle of the jaw, over the mastoid process beneath the sternocleidomastoid, where they later extend distally. Upper jugular nodes are most frequently involved followed by mid jugular nodes. The cervical glands being frequently the only sign of a nasopharyngeal carcinoma through half or whole years they are often mistakenly diagnosed as lymphomas, tuberculosis or other infectious origin and treated otherwise.

Nasal symptoms were present in 14(46.6%) patients. Nasal symptoms included nasal discharge in 11(36.6%) patients, sticky sensation at the back of nose in 7(23.3%) of the patients, epistaxis in 5(16.6%) patients. This finding also agrees with study a study in Tel Aviv reported nasal symptomatology in 44% patients.<sup>15</sup> A Jamaican study reported nasal symptoms in 77% of patients with epistaxis in 60% patients, nasal obstruction in 14%, post nasal discharge in 14% and nasal mass in 6% of the patients.<sup>19</sup> As the tumour almost always arises from the lateral wall of nasopharynx, nasal obstruction is initially unilateral. As the tumour enlarges there will be bilateral nasal obstruction. Most of them had blood stained nasal discharge rather than frank epistaxis.

Aural symptoms were present in 18(60%) patients aural symptoms consisted of tinnitus seen in 9(30%), fullness of the ears 15(50%) and hearing loss in 13(43.3%) of the patients, and otalgia in 2(6.6%) of the patients. Study in Taiwan reported a higher occurrence of aural symptoms, present in 68.9% of patients which is consistent with our finding.<sup>18</sup>

In this study neurological symptoms were present in 9(30%) of the patients. Neurological complications associated with nasopharynx range from 30 to 70% in large series.<sup>15</sup> A study in Taiwan of 966 cases, reported neurological manifestation in 22.2%.<sup>18</sup> Neurophthalmic manifestations were commonly found among patients diagnosed as nasopharyngeal carcinoma at Illorin, Nigeria where 60% of patients had neuroophthalmic manifestations.<sup>30</sup>

In the present study most commonly involved nerves were as follows, trigeminal in 7(77.7%) patients, followed by abducens nerve in 4(44.4%) patients. Thus the present finding is in agreement with most of the studies that found trigeminal nerve to be the most common nerve involved.<sup>29,31,32,33</sup>

**FNAC of neck nodes:** FNAC of neck node(s) of all cases presenting with cervical lymphadenopathy (27 cases) was done and all had features of metastatic undifferentiated carcinoma.

**Histopathology:** The cases were classified according to the World Health Organization (WHO) classification in 2005. Most common was Non-keratinizing carcinoma undifferentiated comprising of 19 patients (63.3%), followed by non keratinizing carcinoma- differentiated comprising 9 patients (30%), and least common was keratinizing squamous cell carcinoma comprising of only 2 patients (6.7%). Basaloid squamous cell carcinoma was not seen in this study. In our study, 94% of the cases were non-keratinizing carcinoma. This is in accordance with the literature that in endemic areas, grade 2 or non-keratinizing tumours constitute more than 90% of all cases.<sup>34</sup> A Jamaican study found non-keratinizing carcinoma in 95% of the cases.<sup>19</sup>

**Serology for EBV DNA:** Using real time PCR, qualitative assessment of EBV DNA was performed in blood plasma sample. All 30 patients blood sample was detected positive for EBV DNA. In a study by Lo *et al.* applied real-time PCR analysis for more sensitive detection of circulating, cell-free EBV DNA. EBV DNA was detected in 96% (55 of 57) of patients with NPC.<sup>35</sup> In addition to the much improved sensitivity over conventional PCR for detecting NPC, real-time PCR was also capable for quantifying EBV DNA in patient plasma. Thus, Lo *et al.* showed that the concentration of plasma EBV DNA was 8-fold higher in patients with advanced NPC (stages III/IV) compared with patients with early disease (stages I/II). Subsequent analyses showed that the sensitivity for detecting NPC was related to the clinical stage of the disease.<sup>36,37</sup> Leung *et al.* demonstrated that the sensitivity for detecting early and advanced NPC was 90% and 98%, respectively; for the same cohort of patients, the sensitivities of VCA-IgA serology were 72% and 85%, respectively.<sup>36</sup> The superior diagnostic accuracy of plasma EBV DNA over VCA-IgA serology was independently confirmed by other research groups.<sup>38,39</sup> Because of the remarkable sensitivity and specificity of plasma EBV DNA for NPC, this marker has rapidly been adopted for research and clinical management of patients with NPC.<sup>40,41,42</sup>

**Radiography:** In the present study, computed tomography (CT) was done for all 30 cases and Magnetic Resonance Imaging (MRI) was done for 10 (33.3%) patients to study the tumour extent. Ten patients (33.3%) had skull base erosion and 3 patients (10%) had intracranial extension on computed tomography scan (CT). This is comparable to a study in Hong Kong which observed erosion of the base of the skull in 31.3% of patients but reported a lower percentage of intracranial extension of 12.2%.<sup>20</sup> Two patients showed extension of tumour causing widening of foramina- foramen lacerum- 1 (3.33%) and foramen ovale-1(3.33%).

In Singapore, it was found in a study that the most common route of intracranial spread is through the foramen ovate (12/35 patients, 34%), followed by skull base destruction (6/35 patients, 17%), foramen lacerum (6/35 patients, 17%), sphenoid sinus (6/35 patients, 17%), and combined foramen ovale and foramen lacerum (5/35 patients, 14%).<sup>21</sup>

In the present study, staging was done by TNM staging system according to the latest 8<sup>th</sup> edition of the International Union Against Cancer/ American Joint Committee on Cancer (UICC/AJCC) Cancer staging manual published in 2016. In the present study, 17 patients presented with stage IV of nasopharyngeal carcinoma, 9 patients with stage III and 4 patients with stage II.

**Treatment:** All the patients after diagnosis were referred to Radiotherapy department for treatment and further management. Out of 30 patients, 24 patients were treated with NACT followed by CCRT and 6 patients with CCRT alone. No patients were given radiotherapy alone.

## VI. Conclusion

In this study of 30 patients of histologically confirmed cases of nasopharyngeal carcinoma, males were seen to be more affected than females. The peak age group was seen in the fifth decade. Bimodal peak was seen in 7<sup>th</sup> decade. Nagas were the most common ethnic group affected by nasopharyngeal carcinoma. Cervical lymphadenopathy was the most common presentation seen in 90% of the cases and was the first symptom noticed in 73.3% of patients. Neurological symptoms were present in 30% of the cases. Facial pain or trigeminal neuralgia was the most common neurological symptom. Trigeminal nerve was the most commonly involved nerve. The most common histopathological picture was non-keratinizing carcinoma- undifferentiated type. FNAC from all neck nodes showed undifferentiated metastatic carcinoma. All 30 cases detected EBV DNA (qualitative assessment) by Real Time PCR (RT-PCR), but pre-treatment and post treatment viral load (quantitative assessment of EBV DNA) will be useful to know the response to treatment and for prognostication, which was not done in our study due to unavailability of test. Qualitative detection of EBV DNA may be useful in screening of nasopharyngeal carcinoma in endemic population; further studies should be carried out to know the specificity and sensitivity of test. Zero degree rigid endoscope for nasopharynx examination in any of the suspected case of nasopharyngeal carcinoma should be used routinely in detection of any growth in lateral wall of nasopharynx as the exophytic growth is most common and will not expose to harmful radiation like in Computed Tomography (CT) scan. Computed Tomography was done in all cases and MRI in 10 cases. 10 patients had skull base erosion and 3 had intracranial extension. CT and/ or MRI is necessary for staging of disease, to know the extent of disease and for proper planning of treatment. In this study, 24 cases out of 30 treated with NACT and CCRT, and rest with CCRT alone. NACT with CCRT is adapting more in clinical practice due to its better control in loco-regional spread and distant metastasis. All the 30 cases, radiotherapy was delivered by Cobalt-60. Intensity modulated radiotherapy (IMRT) would have been a better mode of delivery of radiation to reduce the side effects and to protect vital organs in and around nasopharynx, which was lacking in our institute. In our study most of the cases were presented in stage III and stage IV, we would like to suggest a community level screening programs in at risk population for early detection and treatment as nasopharyngeal carcinoma is extremely radiosensitive tumour.

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Yumnam Anupama Devi,. "Nasopharyngeal Carcinoma: A Clinicopathological Study." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 8, 2019, pp 27-34.