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# Clinico-pathological Profile of Nasopharyngeal Carcinoma

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***Abstract:***
***Background:*** *Nasopharyngealcarcinoma(NPC) comprises 1-2% of all the malignant tumors of head and neck. In India, Nasopharyngeal carcinoma constitutes only 0.06% of all body cancers. But in the North-Eastern state of India,especially Manipur and Nagaland where an incidence of 1.15% has been reported. The aim of this study is to understand the aetiological factors and clinic-pathological presentation of Nasopharyngeal Carcinoma in the North-Eastern state of India.*
***Methods:*** *A prospective study was carried out in the Department of Otorhinolaryngology and Head & Neck Surgery, Regional Institute of Medical Sciences, Imphal between 2014 to 2018. Data was analyzed using SPSS version 21.*
***Results:*** *Data from 330 patients were analyzed. Out of the 330 cases, 176 cases from the age group between 31 – 50 years of age (51.51%). 253 cases(76.7%) gave a positive history of consuming salted dry smoked meat/fish. 221 cases (66.7%) lived in houses generally consisting of only one door and a window. 286 cases (86.6%) presented with a neck mass out of which bilateral cervical lymphadenopathy was seen in 121 cases (36.66%). VI cranial nerve is the most commonly involved cranial nerve in 45 cases(13.63%). 222 cases (67.27%) had WHO type III carcinoma. 223 cases (67.57%) had stage IV disease. There was complete response in 52.85% with chemoradiation and 34.4% with radiation alone, partial response in 41.7% with CTRT and 50% with RT alone.*
***Conclusion:*** *NPC is quite prevalent in North-Eastern state of Manipur and Nagaland. Clinicians should have a higher index of suspicion in diagnosing NPC to enable early diagnosis and prompt treatment of such malignant neoplasm.*
***Key Word:*** *Clinico- pathological, Nasopharynx, Carcinoma, North East.*

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## I. Introduction

Nasopharyngeal carcinoma is well known for its bewildering signs and symptoms and also because of its unique nature. The nasopharynx is a clinical blind spot situated in the middle of skull base and because of its anatomical seclusion diagnosis is relatively late despite the ongoing rapid advancement in the diagnostic field in medical sciences.

Malignant tumours of the nasopharynx have been described in the literature as one of the most intriguing cancers of the head and neck. The difficulty in the diagnosis of the disease has been reported as early as 1920 where as many as 8.7%cases were erroneously operated upon prior to the actual diagnosisbecause of its non-specificpresentation. The tumours have a long latent period with relatively very few primary symptoms which has led to its diagnosis and treatment.[1]

Malignant disease of nasopharynx constitutes 1-2% of all malignant diseases and 14% of all tumours of the pharynx (oropharynx=40% and laryngopharynx=46%).[2] Epidemiologically, nasopharyngeal carcinoma is commonest among the Chinese residing in Southern China in the Central Guangdong province and was once called the " Guangdong tumour".[3] In India, the disease is common in the North-Eastern states, especially in Manipur and Nagaland where an incidence of 1.15% has been reported against the all-India figure of 0.06% of all cancers.[4]

Nasopharyngeal carcinoma is of great interest because current studies suggest that genetic, ethnic and environmental factors could have arole in the cause of the disease.[5] This study was carried out prospectively to understand the aetiological factors and clinico-pathological presentation of nasopharyngeal carcinoma in the North-Eastern states of India which have a high predilection for these tumours as compared with rest of India.

## II. Materials And Methods

This prospective study was carried out in the department of Otolaryngology and Head & Neck surgery, Regional Institute of Medical Sciences, Imphal between 2014 and 2018. 330 cases diagnosed with nasopharyngeal carcinoma who attended the Out-patient depart economic status formed the study group. A

detailed history with regards to the onset of symptoms, duration and previous history of treatment was taken. A thorough ENT examination included anterior and posterior rhinoscopy as well as endoscopic examination of the nasopahrynx. Investigations included endoscopic nasopharyngoscopy, CT scans (Axial & coronal views) and MRI when there was suspicion of intra-cranial extension. The definitive diagnosis of NPC was made by endoscopic nasopharyngeal biopsy and histopathological examination in all the cases.

After the diagnosis was confirmed, patients were planned for chemo radiation or radiation alone in consultation with the Department of Radiotherapy. Data was analyzed using SPSS version 21.

## III. Results

**Incidence:**

Nasopharyngeal carcinoma has been reported in all age groups with a predilection for younger age groups. Out of the 330 cases, there were 83 cases each for the age groups between 31-50 years of age (25.15% each), 21.82% in the 61-70 years age group and 20.30% in the 61-70 years age group. The youngest patient was a 13 year old girl who is still attending the department 7 years after chemoradiation. The male: female ratio was 2.8:1(table 1)

**Table 1** Showing the age groups in 330 cases of NPC

| Sl.no | Age(years) | % | No. of patients |
|---|---|---|---|
| 1 | 11-20 | 0.61 | 2 |
| 2 | 21-30 | 1.82 | 6 |
| 3 | 31-40 | 25.15 | 83 |
| 4 | 41-50 | 25.15 | 83 |
| 5 | 51-60 | 21.82 | 72 |
| 6 | 61-70 | 20.30 | 67 |
| 7 | 71-80 | 4.85 | 16 |
| 8 | 80 above | 0.3 | 1 |

**Genetics:**

Genetic links regarding nasopharyngeal carcinoma have been stipulated because many authors have reported the disease between siblings and other blood relations. In our study, we found one case of NPC between twin brothers who had simultaneously been treated one after the other.

**Environmental factors:**

In our study 221 cases (66.7%) lived in houses generally consisting of only one door and a window necessitating very poor or rather minimal ventilation. The striking feature of the North east states of Manipur and Nagaland is their dietary habits. Most of the people of the region season the salted fish/meat over the fireplace to be consumed by all the members of the family during lean season. Out of the 330 cases, more than 76.7%(253 cases) gave a positive history of consuming salted dry smoked meat/fish.

**Clinical presentation:**

The most common clinical presentation of this study was cervical lymphadenopathy. 286 patients(86.6%) presented with aneck mass out of which bilateral cervical lymphadenopathy was seen in 121 out of 330 cases(36.66%). Unilateral cervical lymphadenopathy was seen on the left neck in 100 cases (30.3%) and 65% (19.69%) on the right neck. The second commonest presentation was blood stained nasal discharge or frank nasal bleeding which was present in 145 cases (43.93%). Nasal obstruction, presence of nasal mass was seen in 86(26.36%) and conductive hearing loss was seen in 82 cases (24.84%). Table 2

**Table 2** Clinical presentation in 330 cases of NPC

| Sl.no | Symptoms | No. of patients | % |
|---|---|---|---|
| 1 | Cervical lymphadenopathy | | |
| | Unilateral (left) | 100 | 30.3 |
| | Unilateral (right) | 65 | 19.6 |
| | Bilateral | 121 | 36.6 |
| 2 | Blood stained nasal discharge/epistaxis | 145 | 43.93 |
| 3 | Nasal obstruction | 86 | 26.36 |
| 4 | Conductive hearing loss | 82 | 24.84 |
| 5 | Cranial nerve paralysis | 60 | 18.18 |
| 6 | Altered sensation of face | 33 | 10 |
| 7 | Proptosis | 3 | 0.1 |
| 8 | Distant metastasis | 8 | 2.42 |

**Cranial nerve paralysis:**

Cranial nerve paralysis was present in 60 cases (18.18%). Of all the cranial nerves affected in these 330 cases, the commonest cranial nerve paralysis was of the VI nerve where as many as 45 cases (13.63%) were affected. The other cranial nerves affected are V nerve (7.27%), IX nerve (4.54%), III nerve (2.72%), II nerve (2.12%), X nerve (1.81%), IV nerve (1.21%), XII (1.21%) and XI nerve (0.30%). Cranial nerve paralysis was followed by altered sensation of the face of the face in 33 cases (10%) and 3 cases (0.1%) of proptosis. In our study there were 8 cases (2.42%) of distant metastasis- 2 cases each to the lungand intracranium and one case each to the lumbar spine, cervical spine, cavernous sinus and liver. (Table 3)

**Table 3**Cranial nerve involvement in 330 cases of NPC

| Sl.no | Cranial nerve | % | No. of patients |
|---|---|---|---|
| 1 | VI | 13.63 | 45 |
| 2 | V | 7.27 | 24 |
| 3 | IX | 4.54 | 15 |
| 4 | III | 2.72 | 9 |
| 5 | II | 2.42 | 8 |
| 6 | VII | 2.12 | 7 |
| 7 | X | 1.81 | 6 |
| 8 | IV | 1.21 | 4 |
| 9 | XII | 1.21 | 4 |
| 10 | XI | 0.30 | 1 |

**Diagnosis:**

The nasopharynx is a blind spot in a relatively big and inert space at the skull base and hence carcinomas in this region can remain silent for a very long time. The basis of diagnosis of NPC is ahigh index of suspicion by the examining physician, a complete history and a thorough physical examination of the head andneck by direct and indirect nasopharyngoscopy. Evaluation of the cases with nasopharyngograms showed positive indications of malignancy like obliteration of the fossa of Rosenmuller, roof and posterior wall in 74% of the cases. Contrast enhanced high resolution computed tomography of the nasopharynx provided the highest accuracy in 96% cases.

With regard to the site of the primary lesion, 58.3% of the lesion were seen in the fossa Rosenmuller at the lateral nasopharyngeal wall. 16.7% of the lesionswere present in the roof of the nasopahrynx and 6.3% were seen in the posterior wall. In most of the patients (18.8%), the disease was multicentric. In the 330 cases studied, the gross histopathology showed exophytic lesions in 47.4%, ulcerative lesions in 26.3% and 26.3% infiltrative lesions.

The pathology of nasopharyngeal carcinoma has been categorized by WHO in to three types, namely Type I- keratinizing squamous cell carcinoma, Type II-non keratinizing squamous cell carcinomaand type III-undifferentiated carcinoma. In our study, 44 cases (13.3%) had Type I, 64 cases (19.39%) had Type II and 222 cases (67.27%) had type III carcinomas. (Table 4)

**Table 4** shows the type of carcinoma (WHO classification)

| Types of carcinoma(WHO Classification) | No. of patients | % |
|---|---|---|
| Type I (Keratinizing SCC) | 44 | 13.33 |
| Type II (Non keratinizing SCC) | 64 | 19.39 |
| Type III (Undifferentiated Ca) | 222 | 67.27 |

**Staging:**

With regard to the clinical staging at the time of diagnosis, most of the patients attended the hospital at a late stage. Almost67.57%(223/330) cases that attended our institute had stage IV disease, 20% (66/330) cases had stage III and 10%(33/330) had stage II disease. There were only 8 patients(2.42%) who were detected with the disease at stage I. (Table 5)

**Table 5** showing the stages of NPC in 330 cases

| Staging of NPC | % | No. of patients |
|---|---|---|
| Stage I | 2.42 | 8 |
| Stage II | 10 | 33 |
| Stage III | 20 | 66 |
| Stage IV | 67.57 | 223 |

**Treatment:**

Radiotherapy remains the mainstay treatment for carcinoma of nasopharynx. Evaluation of treatment response to chemotherapy alone and combined chemoradiation was done. The patients were treated with

telecobalt-60 radiation till a tumour dose of 7000centigray (cGy) was achieved. In another group,radiosensitiser drugs like Cisplatin (30mg/ body meter square) at weekly intervals was given before radiotherapy. The response was recorded using Millers WHO criteria, i.e. "Complete response" when there is complete regression of the tumour more than 4 weeks, "Partial response"- 50% or more reduction in the product of the two largest perpendicular diameters of all measurable lesions, and "No response"- no change after completion of treatment. In our series, there was complete response in 52.85% with chemoradiation and 34.4% with radiation alone, partial response in41.7% with CTRT and 50% with RT alone. No response was seen in 5.6% cases of CTRT and15.6% with RT alone. (Table 6)

**Table 6** shows treatment of 330 cases with Chemoradiation/Radiation alone.

| Treatment | Chemoradiation | Radiation |
|---|---|---|
| Complete response (CR) | 34.4% | 52.8% |
| Partial response (PR) | 41.7% | 50% |
| No response (NR) | 15.6% | 5.6% |

## IV. Discussion

Head and neck neoplasia is a major form of cancer in India accounting for 23% of all cancers in male and 6% in females.[6] Nasopharyngeal carcinoma is quite rare in India, its incidence being 0.71% of all cancers in Mumbai and 0.6% in Assam.[7] In Manipur, head and neck cancers constitute atleast 36.4% of whole body cancer cases and nasopharyngeal carcinoma was found to be the third most common cancer of the whole body(12.8%) and the commonest of all head and neck cancers(23.3%).[8,9] In our series of 330 patients, 198(60%) patients were from Manipur and 125(37.8%) were from Nagaland. It is interesting to note that 83.3% of the patients were Mongoloids indicating the disease preference to the Mongoloids. In Manipur, the incidence was highest among the Tanghkul tribe(a Naga sub-tribe ) and maximum number of patients were from Ukhrul district where 60% of the population is Tangkhuls. The Indian Council of Medical Research Bulletin released in September 2003 stated that "the Mongoloid population particularly Nagas have a high risk of the disease as the incidence was as high as 4.3/100000 population per year".

In the present study, nasopharyngeal carcinoma has been reported most frequently between 31-50 years although there was an age variation of 13-80 years which is consistent with the findings of many authors.[8,10]The youngest patient was a 13 year old girl who is still attending the department 7 years after chemoradiation although Grotts (1949) reported the disease in apatient as young as 2 years old.[11] The male: female ratio in this study was 2.8:1 which is almost in agreement with authors with similar reports of a M:F ratio of 2.3:1, 3:1 and2.4:1 respectively.[3,10,12]

There was only one case of nasopharyngeal carcinoma between a set of twin brothers from Nagaland who were simultaneously treated one after the other. This was also reported in two brothers by Stinson (1940).[13] Using DNA sequencing immune-histochemical staining, Chen et al (1995)[14] found that P53 gene mutation was of common occurrence in NPC and suggested that the change was essential inthe multi-step process of pathogenesis of NPC. It may therefore be cited that NPC may be linked to the genes; however, genetics alone may not explain many things. Changes in lifestyle and food habits, environmental exposure to smoke andpoor ventilation may be the other causative factors for the pathogenesis of the disease.

The present study, indicates that 221/330 cases(66.7%) lived in poorly ventilated places. In Ukhrul district of Manipur and Tuengsang district of Nagaland, the climate is very cold and windy and most of the houses are constructed with only a single door and window necessitating minimal ventilation. Moreover the whole house is warmed up by burning the easily available pinewood trees which have been proved to be carcinogenic (as pine generates lot of soot). A few reports have attributed that suspected irritating inhalants and smoke producedby burning wood in poorly ventilated native Kenyan huts as a possible factor in the carcinogenesis of NPC.[15,16] As regards to the dietary habits, 253/330 cases (76.7%) gave a positive history of consuming salted dry smoked meat/ fish. Geser et al (1978)[17] opined that salted fish given to babies at weaning was responsible for NPC in his study on the Cantonese NPC patients. Another study by Yu et al(1989)[18] at Guangzhou city, China also associated Nasopharyngeal carcinoma with consumption of fermented fish sauce, salted shrimp paste and salted fish.

The most common clinical presentation of this study was cervical lymphadenopathy. 286 patients(86.6%) presented with aneck mass out of which bilateral cervical lymphadenopathy was seen in 121 out of 330 cases(36.66%). Unilateral cervical lymphadenopathy was seen on the left neck in 100 cases (30.3%) and 63 cases (19.69%) on the right neck. Only 3 cases presented with a fungating mass in the neck. The high incidence of lymph node matastasis is due to the presence of extensive submucosal lymphatic plexus in the nasopharynx plus therelatively weak barriers to spread in to the parapharyngeal space.[3] The second commonest presentation was blood stained nasal discharge or frank nasal bleeding which was present in 145 cases (43.93%). Nasal obstruction and presence of nasal mass was seen in 86(26.36%) and conductive hearing loss was seen in 82 cases (24.84%).

Cranial nerve paralysis was present in 60 cases (18.18%). Of all the cranial nerves affected in these 330 cases, the commonest cranial nerve paralysis was of the VI nerve where as many as 45 cases (13.63%) were affected. The other cranial nerves affected are V nerve (7.27%), IX nerve (4.54%), III nerve (2.72%),II nerve (2.12%), X nerve (1.81%), IV nerve (1.21%), XII (1.21%) and XI nerve (0.30%). Cranial nerve paralysis was followed by altered sensation of the face of the face in 33 cases (10%) and 3 cases (0.1%) of proptosis. In our study there were 8 cases (2.42%) of distant metastasis- 2 cases each to the lung and intracranium and one case each to the lumbar spine, cervical spine, cavernous sinus and liver.These findings were similar to other studies.[4,19]

The nasopharynx is a blind spot in a relatively big and inert space at the skull base and hence carcinomas in this region can remain silent for a very long time. The basis of diagnosis of NPC is a high index of suspicion by the examining physician, a complete history and a thorough physical examination of the head and neck by direct and indirect nasopharyngoscopy. Evaluation of the cases with nasopharyngoscopy showed positive indications of malignancy like obliteration of the fossa of Rosenmuller, roof and posterior wall with a success rate of almost 80%.[20] Contrast enhanced high resolution computed tomography of the nasopharynx provided the highest accuracy in 90% cases and studies have cited that the most striking feature was obliteration of the para-nasopharyngeal space in 84.4% either unilateral or bilaterally as well as abnormal soft tissue mass in the nasopharynx in 97% of patients.[21]

With regard to the site of the primary lesion, 58.3% of the lesion were seen in the fossa of Rosenmuller at the lateral nasopharyngeal wall. 16.7% of the lesions were present in the roof of the nasopahrynx and 6.3% were seen in the posterior wall. In most of the patients (18.8%), the disease was multicentric. In the 330 cases studied, the gross histopathology showed exophytic lesions in 47.4%, ulcerative lesions in 26.3% and 26.3% infiltrative lesions with similar findings noted by other authors.[3,4]

Biopsy is mandatory for the confirmation of the disease. It is desirable that multiple deep specimens be taken from different sites to come to a diagnosis. Endoscopic nasopharyngeal biopsy was carried out in almost all cases. In our study, 44 cases (13.3%) had Type I, 64 cases (19.39%) had Type II and 222 cases (67.27%) had type III carcinomas. When the growth was small and extended submucosally, CT guided fine needle aspiration biopsy(FNAB), though expensive gives an early, rapid, safe and nonsurgical method of diagnosis. In this study CT guided FNAB provided positive results in 3 cases which were otherwise reported negative by conventional biopsy. In most studies, the commonest histopathological was WHO type III(Undifferentiated Carcinoma).[3]

In the present study, 67.57%(223/330) cases that attended our institute had stage IV disease, 20% (66/330) cases had stage III and 10%(33/330) had stage II disease. There were only 8 patients(2.42%) who were detected with the disease at stage I. the detection of NPC at an early stage remains a challenge till date as the nasopharynx is a clinically blind spot and similar studies reported that stage I tumours accounted for less than 10% of all cases of NPC.[3]

Evaluation of treatment response to chemotherapy alone and combined chemoradiation was done. The patients were treated with telecobalt-60 radiationtill a tumour dose of 7000centigray (cGy) was achieved. In another group, radiosensitiser drugs like Cisplatin (30mg/ body meter square) at weekly intervals was given before radiotherapy. The response was recorded using Millers WHO criteria, ie. "Complete response" when there iscomplete regression of the tumour more than 4 weeks, "Partial response"- 50% ormore reduction in theproduct of the two largest perpendicular diameters of all measurable lesions, and "Noresponse"- no change aftercompletion of treatment. In our series, there was complete response in 52.85% with chemoradiation and 34.4% with radiation alone, partial response in 41.7% with CTRT and 50% with RT alone. No response was seen in 5.6% cases of CTRT and15.6% with RT alone. Thus in the present study, patients receiving concurrent chemoradiation had a better overall treatment response compared to radiotherapy alone in all WHO histological types. Undifferentiated carcinoma was found to be the most radiosensitive among the three histological types. Chang et al(2004) found that the use of neoadjuvant chemotherapy followed by concurrent chemoradiation had encouraging results and that concurrent Cisplatin radiation with or without adjuvant chemotherapy should be considered as standard practice for locoregionally advanced Nasopharyngeal carcinoma.[22]

## V. Conclusion

Nasopharyngeal carcinoma is very common in Manipur amongst all head and neck cancers. 60% of the cases were from Manipur, 37.7% from Nagaland and 2.3% from other states. The disease was more predominant in males than females with M:F ratio 2.8:1 and commoner age group 31-50 years. Poor ventilated living quarters, irritating fumes with habitual eating of salted smoked fish/meat may be attributed to the cause of disease. The commonest clinical presentation is cervical lymphadenopathy (86.66%) and the fossa of Rosenmuller is the most common site of origin (58.3%). CT scans of nasopharynx is the most preferred imaging technique. Histologically Undifferentiated was the commonest(67.6%). The most preferred treatment in most cases was chemoradiation.

It may be concluded that nasopharyngeal carcinoma is quite prevalent in North eastern states of Manipur and Nagaland and a protocol for its early detection and treatment is required to reduce the mortality of patients prone to suffer from this disease.

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