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## Research Article

### PRIMARY EXTRANODAL LYMPHOMAS IN THE HEAD AND NECK REGION- A RETROSPECTIVE STUDY FROM A TERTIARY CANCER CENTRE IN SOUTH INDIA

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#### ABSTRACT

Lymphomas are malignant neoplastic proliferations of the immune system, broadly classified as Hodgkin's lymphoma (HL) or NonHodgkin's lymphoma (NHL). NHL may present at extranodal sites with 18-28 % of Extra Nodal Lymphoma (ENL) developing in the head and neck region. However, there is paucity of data regarding the demography, treatment modalities and end results of primary ENL of Head and Neck in the Indian population. The present paper analyses sixteen cases of primary extranodal lymphomas of head and neck treated at a tertiary cancer centre in South India in a time period of 3 years.

The mean age of presentation in our study was 60.6 years with a male to female ratio of 1.28:1. 75% of cases presented with swelling in the head and neck region. Radiological evaluation done in 14 cases, of which, 4 were diagnosed as lymphoma. Maxilla was the most common site of occurrence which is in contrast with the literature where salivary glands is the commonest site. Histopathological diagnosis was NHL in all cases (100%). The predominant subtype was DLBCL (31%). Lymph node involvement was noted in 31% cases, ipsilateral alone in 25% and bilateral involvement in 6.2%. 32% cases each were diagnosed at Stage IEA and 2EA. Of 13 patients who received treatment, 76.9% cases received chemotherapy, 35.7% received radiation and 38.4% received both chemotherapy and radiation.

Of the 8 patients who have completed treatment, 6 had achieved complete response and 2, partial response to treatment. One patient succumbed to disease while 4 were lost to follow up.

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#### INTRODUCTION

Lymphomas are malignant neoplasms of immune system arising as a result of somatic mutations in lymphocyte progenitor cells. They constitute a clonally proliferated heterogeneous group known for their spectrum of behaviour. Lymphomas range from relatively indolent to highly aggressive disease. They are broadly classified as Hodgkin's lymphoma (HL) or NonHodgkin's lymphoma (NHL). HL rarely presents in an extranodal site alone. However about 25-30% of NHL are extranodal at presentation (Hanna E *et al*, 1997).

The incidence of NHL is on a rise globally with upto 35% increase in incidence in some countries (Chan JK, 2000; Gospodarowicz MK, 1995). However an improved survival rate is observed with an increase of 30-50.8% in 5 year survival rates (Shankland KR *et al*, 2012).

Lymphomas predominantly involve nodal or lymphatic sites. For the purposes of coding and staging (AJCC 7<sup>th</sup> edition, 2010) has considered lymph nodes, Waldeyer's ring, thymus, and spleen as nodal or lymphatic sites. Extranodal or extralymphatic sites include the bone marrow, the gastrointestinal tract, skin, bone, central nervous system, lung, gonads, ocular adnexae (conjunctiva, lacrimal glands, and orbital soft tissue), liver, kidneys, uterus, etc.

Primary extranodal NHL is defined as those with presentation in an extranodal site with or without regional lymph node involvement (A.D.G Kroll *et al*, 2003) 18-28 % Extra Nodal Lymphoma (ENL) is observed to develop in the head and neck region. (D'Amore F *et al*, 1991).

Approximately 16,000 patients are diagnosed with NHL annually in India and 11000 patients die due to the disease (Globocan, 2012). A multimodality treatment with multi-agent chemotherapy with or without radiotherapy is considered

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optimum. However, there is paucity of data regarding the demography, treatment modalities and end results of primary ENL of Head and Neck in the Indian population. The present paper analyses sixteen cases of primary extranodal lymphomas of head and neck treated at a tertiary cancer centre in South India in a time period of 3 years along with a review of previously published literature.

## MATERIALS AND METHODS

This is a retrospective analysis of patients who presented in the outpatient department of head and neck division of our institute, with various symptoms, and on evaluation were diagnosed to have primary extra nodal lymphoma. The study included patients who were diagnosed between June 2013 and June 2016 (3years). The diagnosis of extra nodal lymphoma was established by histopathologic examination and immunohistochemical study of biopsy specimen. The case files of individual patients were retrieved from institutional cancer registry and information regarding age and gender of patients, habits, retrovirus status, presenting symptoms, site of involvement, radiological and cytological diagnosis, final diagnosis and nodal status were collected. Stage of disease, treatment modality and follow up status were also analysed.

## RESULTS

During the study period, 16 patients were diagnosed to have primary extra nodal lymphomas. All 16 cases wer sub types of NHL. Not a single case of HL was observed.

**Table 1** Lymphoma Type in Each Site

SITE	LYMPHOMA
Orbit	Follicular lymphoma
	Low grade B cell lymphoma
Scalp	Follicular lymphoma
	Low grade B cell lymphoma
Submandibular Gland	Follicular lymphoma
	Low grade B cell lymphoma
Maxilla (commonest site)	Extranodal NK/T cell lymphoma
	Plasmablastic lymphoma
	DLBCL
Nasal cavity	Extranodal NK/T cell lymphoma
	Follicular lymphoma
Parotid gland	DLBCL
Mandible	DLBCL
Thyroid	DLBCL
Lacrimal gland	DLBCL

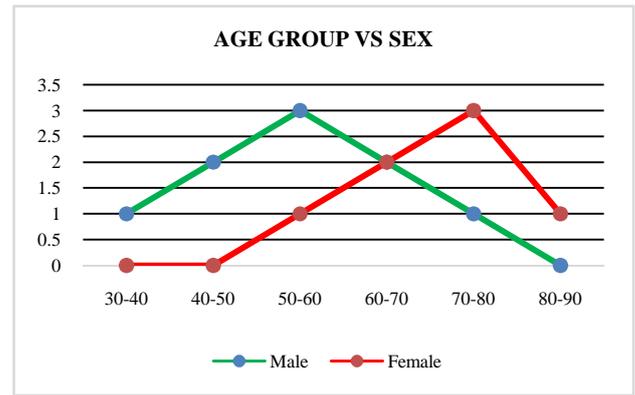
Our study included 9 males and 7 females, with a male: Female ratio of 1.28:1

The mean age of presentation was 60.6 years. 50% of cases belonged to age group of 61-80 years (n=8). There were 5 cases in age group of 41-60 yrs, 2 cases in 21-40 yr group and a single case in 81-100 yr age group. (Fig 1)

Of the 16 cases, 4 were smokers, 2 were pan chewers. Majority (62.5%) had no habits. 1 patient was HIV positive.

75% of cases (n=12) presented with swelling in the head and neck region with second common presenting symptom being nasal obstruction (12%). Nasal bleed and watering of eye was seen in 1 case each.

56% (n=9) of cases were clinically diagnosed as lymphoma while the rest were diagnosed as carcinoma.



**Figure 1**

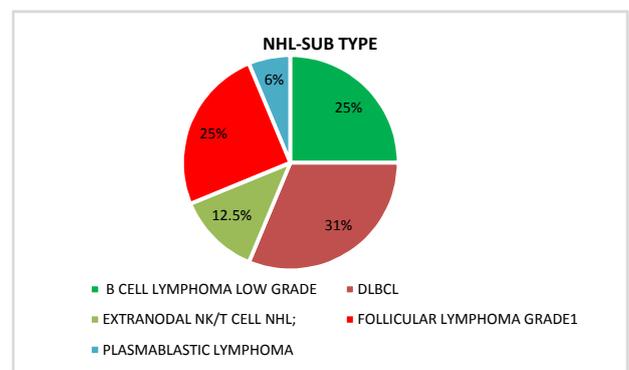
Radiological evaluation was done in 14 cases, of which, 4 were diagnosed as lymphomas, 6 as malignant lesions and 4 were inconclusive.

Maxilla is the most common site of occurrence (25%), followed by nasal cavity and paranasal sinus and orbit (19%), and 1 case (6%) each in scalp, lacrimal gland, mandible, thyroid, parotid and submandibular salivary gland.

Size of the lesion was assessed radiologically and in cases where radiological evaluation couldn't be done, size was assessed clinically. The smallest lesion measured 1.7x1.3cm and the largest measured 10x5x4cm.

FNAC was attempted in lesions in accessible areas and with a clinical suspicion of carcinoma (n=4) of which 2 cases were diagnosed as lymphoproliferative disorder, 1 as reactive lymphoid population and the 4th case yielded insufficient material for diagnosis.

Histopathological diagnosis was NHL in all cases (100%). IHC was done for confirmation and subtyping. Basic panel of CD3, CD20 and Ki67 was done in all cases, Bcl2 was done in all follicular lymphomas, CD10 in DLBCL. Antibodies like CD56 (NK/T cell lymphoma), EBV (plasmablastic lymphoma) was done from an outside centre as they were not available in our lab. The predominant subtype was DLBCL (31%). We had 4 cases each of Follicular lymphoma- grade 1 and low grade B cell lymphoma (which could not be further subtyped as tissue was scanty and the patient lost to follow up) 2 cases of Extranodal NK/ T cell nasal type lymphoma and 1 case of plasmablastic lymphoma (Fig.2)



**Figure 2**

Lymph node involvement was noted in 31% cases (n=5), ipsilateral alone in 4 cases (25%) and bilateral involvement in 1 case(6.2%). Lymphadenopathy was diagnosed during a period between 2 weeks to 5 months from initial diagnosis. Cervical lymphnodes-Level I-III were the usually involved group.

32% cases (n=6) each were diagnosed at Stage IEA and 2EA. Treatment was initiated as per NCCN guidelines. For limited stage disease (stage I and II) 3 cycles chemotherapy followed by IFRT (Involved Field Radiation Therapy) was given if high grade, IFRT alone if low grade and without B symptoms. For advanced stage disease, (stage III and IV) 6 cycles chemotherapy was given depending upon factors like histology, grade, stage, presence or absence of B symptoms, cytopenias, organ dysfunctions of 13 patients who received treatment, 76.9% (n=10) cases received chemotherapy, 35.7% (n=6) received radiation and 38.4% (n=5) received both chemotherapy and radiation.

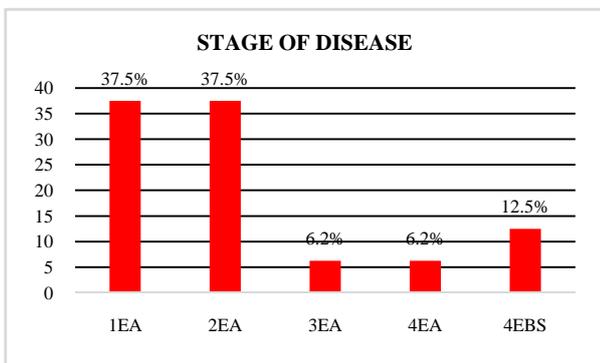


Figure 3

Of the 8 patients who have completed treatment,6 cases had achieved complete response and 2, partial response to treatment.

Follow up period varied from 2 weeks to 30 months.

At present 1 case is under treatment, 8 are under follow up, 2 cases showed progressive disease and are on best supportive care. (Fig 4)

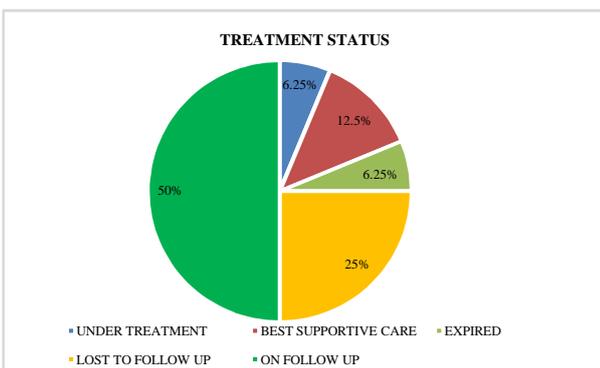


Figure 4

One patient succumbed to disease while 4 were lost to follow up.

## DISCUSSION

Head-Neck Extra Nodal Lymphoma (HNENL) are a distinct subset of lymphomas as they often remain localized to the primary site and shares <20% of all extra nodal NHL and <5%

of all head and neck cancer (Al Diab AR *et al*, 2011). Approximately 5% of all malignant neoplasms of the head and neck area are lymphomas. (Vega F *et al*, 2005)

These tumors are mostly diagnosed in 6th decade of life (Nathu RM *et al*, 1999; Nimmagadda RB *et al*, 2013)with most patients being older than 50 years. The mean age of presentation in the present study is 63 years which is in concordance with the previous studies. (Shankland KR, 2012)

Usually HNENL occur more often in men, with approximately 55-77% male preponderance (Triantafillidou K *et al*, 2012; Etemad-Moghadam S *et al*, 2010) though our sample size is small, the observation is similar.

In a recently published study about extranodal lymphomas of the head and neck region, (Shankland KR, 2012) the most common site were the salivary glands with 41%. Manifestations in the mandible and the maxilla together accounted for another 41%, and the remaining non-Hodgkin lymphomas appeared at the paranasal sinus, and the orbit.

In this present study of 16 cases, the most common site were the maxilla with 25% , followed by nasal cavity and paranasal sinus and orbit (19%), and 1 case (6%) each in scalp, lacrimal gland, mandible, thyroid, parotid and submandibular salivary gland.

According to E Zucca *et al*, 1999 lowgrade Bcell lymphoma of MALT type is the most common type of lymphoma of salivary glands and orbit. DLBCL dominates among primary thyroid lymphomas and lymphomas of adult bones. Lowgrade Bcell lymphoma of MALT type predominates in lacrimal gland. (Natasha Townsend *et al*, 2012)

Previous studies mention that the symptoms of NHL are nonspecific (Epstein JB *et al*, 2001) the most common symptom being a non-pathognomonic swelling.75% of cases in our study presented as swelling in head and neck region, in concordance with the previous studies.

The most common histology seen in literature is DLBCL followed by Marginal Zone Lymphomas (MZL) (Wotherspoon AC *et al*, 1993; Mertsoylu H, 2014). In The current study DLBCL was the most common histological subtype, followed by follicular lymphoma. NK/ Tcell nasal type extranodal lymphoma, a rare type T cell NHL constituted 12% of cases. MZL constitutes two third cases of orbital NHL in western literature. But among orbital lymphomas, DLBCL was the commonest histology in the present series.

Nearly 15% of patients with acquired immunodeficiency syndrome (AIDS) present with lymphoma, and the B-cell NHL has become a Centers for Disease Control and Prevention (CDC) criterion for presumptive HIV diagnosis.(Finn DG,1995;MMWR, 1991)

In our study a single case was retropositive and had a histological diagnosis of plasmablastic lymphoma, one of the commonest lymphomas associated with HIV infection.

The treatment of HNENL might be based on what we know from the therapy of lymphomas of nodal origin as nodal type histologies are predominant. (E Zucca *et al*, 1999). However, indications for local radiotherapy might be more stringent for these lymphomas than for nodal lymphomas. (E Zucca *et al*,

1999). In our study 62.5% (n=10) cases received chemotherapy and 37.5% (n=6) received radiation and 31.2% (n=5) received both chemotherapy and radiation.

Mean follow up period was 16.5 months with 10 cases still visiting the centre.

## CONCLUSION

Literature search shows that our data regarding extranodal lymphomas of head and neck region especially in Asian and Indian population are limited.

This study is a humble attempt to understand the scenario in North Malabar Area of South India. The limitations of the study include its small sample size and the fact that it is a retrospective study- there is always a question of correct documentation.

The diagnosis of lymphoma in head and neck region is a frequent challenge to the pathologists, due to their morphological mimics, and varied clinical presentations. Therefore, the possibility of pENL should be kept in mind even though it arises in an extranodal site. Further studies throwing light on the genetic profile of lymphomas and treatment outcome are required to understand the biological variations of this group of diseases.

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