RESEARCH ARTICLE

Head and neck extra nodal NHL (HNENL) - Treatment Outcome and Pattern of failure - A Single Institution Experience

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Abstract

Background: Extra nodal lymphoma (ENL) constitutes about 33 % of all non-Hodgkin's lymphoma. 18-28% develops in the head and neck region. A multimodality treatment with multi-agent chemotherapy (CT) and radiotherapy (RT) is considered optimum. Materials and Methods: We retrieved the treatment charts of patients of HNENL treated in our institute from 2001-2012. The charts were reviewed and the demographic, treatment details and outcome of HNENL patients were retrieved using predesigned pro-forma. Results: We retrieved data of 75consecutive patients HNENL. Median age was 47years (Range: 8-76 years). Of the 75 patients 51 were male and 24 were female. 55patients were evaluable. The patient and tumor characteristics are summarized in Table 1. All patients were staged comprehensively with contrast enhanced computed tomography of head, neck, thorax, abdomen, pelvis and bone marrow aspiration and biopsy 66 patients received a combination multi-agent CT with CHOP being the commonest regimen. 42 patients received 4 or lesser number of cycles of chemotherapy whereas 24received more than 4 cycles chemotherapy. Post radiotherapy, 41 out of 42 patients had a complete response at 3 months. Only 21patients had a complete response after chemotherapy. All patients received radiation (mostly involved field radiation) as a part of the treatment. The median radiation dose was 45 Gray (Range: 36 Gray-50 Gray). The radiation was planned by 2D fluoro simulation based technique in 37cases and by 3 Dimensional conformal radiation therapy (3DCRT) in 36 cases. Two patients were planned by the intensity modulated radiation therapy (IMRT) technique. IMRT was planned for one thyroid and one nasal cavity primary. 5 patients experienced relapse after a median follow up of 19 months. The median survival was not reached. The estimated two and three year survival were 92.9% (95%CI- 68.6- 95.35) and 88% (95%CI- 60.82 - 92.66) respectively. Univariate analysis revealed higher stage and poorer baseline performance status to be significantly associated with worse progression free survival. 5 patients progressed (relapse or primary disease progression) after treatment. Of the 5 patients, two patients were primary orbital NHL, two patients had NHL nasal cavity and one was NHL thyroid. Conclusions: Combined modality treatment in HNENL confers excellent disease control with acceptable side effects.

Keywords: Head and neck - extra nodal - NHL - chemotherapy - radiotherapy - India

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Introduction

ENL constitute about 33 % of all non-Hodgkin's lymphoma (Gospodarowicz et al., 1995). 18-28 % ENL is observed to develop in the head and neck region (Amore et al., 1991). Approximately 16,000 patients are diagnosed with NHL annually in India and 11000 patients die due to the disease annually (Globocan, 2012). A multimodality treatment with multi-agent chemotherapy followed by radiotherapy is considered optimum. However, there is paucity of data regarding the demography, treatment modalities, side effects and end results of HNENL in the Indian population. Most treatment protocols are extrapolated from nodal NHL management. We intended to report our experience of treating HNENL and analyze demography, treatment and survival outcomes of patients with HNENL in Indian population.

Materials and Methods

Patients

We retrieved the treatment charts of patients of HNENL treated in our institute from 2001-2012. The charts were reviewed and the demographic, treatment details and outcome of HNENL patients were retrieved using predesigned pro-forma.

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Evaluation and staging

The patients were jointly evaluated by a multidisciplinary team (Head and Neck Clinic) comprising of a head and neck surgeon, radiation oncologist and a medical oncologist. The detailed evaluation included physical evaluation, laboratory investigations with complete blood count, Liver function test and renal function test, computed tomography (CT) and/or magnetic resonance imaging of the head and neck area, direct laryngoscopy or pan endoscopy (where clinically indicated) and X-ray/ CT of the thorax. Positron emission tomography (PET-CT) was done to rule out or confirm doubtful lymph nodes on CT that were inaccessible to tissue diagnosis. A biopsy and immuno-histochemistry was done to characterize the tumor. A MUGA scan or 2DECHO was done to assess left ventricular ejection fraction.

Radiation therapy

Patients were immobilized in a thermoplastic immobilization device in supine position with arms by the side of the patient. Conventional radiation technique included, lateral opposed or oblique wedge pair fields. Conformal radiation technique (three dimensional conformal radiation therapy, 3D-CRT and Intensity modulated radiotherapy, IMRT), involved planning CT scan (with intravenous contrast) with 3 mm slice thickness on Philips large bore CT scanner. Treatment was delivered with 6 Megavoltage photons on CL 2300 CD (Varian Medical System, Palo Alto, California, United States). The gross tumor volume (GTV) was defined as the tumor evident on the planning CT scan. The CTV was formed by isotropic expansion of 1-1.5 cm in cases of primary disease of orbit, parotid, thyroid. However, in cases with involvement of waldeyers ring the entire nodal chain was irradiated. The CTV volume was restricted with respect to natural barrier such as bone. CTV was expanded by isotropic 3-5 mm expansion for generating planning target volume (PTV). The dose prescription ranged from 36-45 Gray at 1.8-2 Gray per fraction. During the radiotherapy planning high priority was given to achieve a conformal dose distribution covering the PTV followed by maximal sparing of the eye and optic apparatus.

Chemotherapy

Combined modality approach was the key for treatment of such cases. CHOP or RCHOP based chemotherapy was prescribed for high and intermediate grade disease. In cases of low grade NHL a CVP or COP regimen was prescribed. Chemotherapy was administered for maximum of six cycles.

Assessment of toxicity and follow up

Acute toxicities were assessed as per acute radiation morbidity scoring of Radiation therapy oncology group (RTOG). All patients were assessed weekly during radiation therapy and patients receiving concurrent chemotherapy also had weekly complete blood counts. After the completion of treatment, patients were evaluated at 1 month and then every 3 months for first two years and 6 monthly in subsequent years. Clinical examination was performed at each follow up and imaging (CT/MRI) was done every 4-6 months or earlier in case of clinical suspicion of progression.

Clinical outcome end-points and statistics

DFS (disease free survival) for the primary treatment was defined from the start of first treatment to the diagnosis of recurrence. Patients not having any event at the time of last follow up were censored. For survival analysis Kaplan Meier method was used and log rank test was used for evaluation of prognostic variables on survival. The following prognostic variables were planned for analysis: 1) Age <50 *vs* ≥ 50 years, 2) Histology (DLBCL *vs* Others), 3) Treatment modality (CHOP *vs* COP; CHOP *vs* RCHOP). Cox-regression model was used for multi-variate analysis and p value of < 0.05 was taken significant for all statistical analysis.

Results

Patient characteristics

We retrieved data of 75 consecutive patients HNENL treated during the period of 2001-2012. Median age of the patient cohort was 47 years (Range: 8-76 years). Of the 75 patients 51 were male and 24 were female with a male: female ratio of approximately 2:1 (2.2:1). However, only 55 patients were found evaluable. The patient and tumor characteristics have been tabulated in Table 1.

Symptoms

A palpable mass 33 (44%) was noted to be the commonest symptom followed by proptosis in 18 (24%) patients. 8 patients had nasal blockade and epistaxis, 5 had visual disturbances and 2 patients had dysphagia as initial presentation. Proptosis and visual symptoms were found in patients with orbital primary only. The median symptom duration was 4.5 months (Range: 1-60 months).

Treatment

All patients were staged comprehensively with CECT of head, neck, thorax, abdomen, pelvis and bone marrow aspiration and biopsy. The Costwald modification of Ann Arbor staging was used. A combined modality approach was followed to treat most cases and some patients received only radiation. 66 patients received a combination multi-agent chemotherapy with CHOP being the commonest regimen. 42 patients received 4 or lesser number of cycles of chemotherapy whereas 24 received more than 4 cycles chemotherapy. All patients received radiation (mostly involved field radiations) as a part of the treatment. The median radiation dose was 45 Gray (Range: 36 Gray-50 Gray). The radiation was planned by 2D fluorosimulation based technique in 37cases and a 3DCRT was used in 36 cases. Two patients one each of primary thyroid and nasal cavity were planned by the IMRT technique.

Response assessment

Response assessment was done by clinical examination and CECT scans. Post completion of chemotherapy, 21patients had a complete response, 30 patients had a partial response, 4 patients had stable disease and 1 patient

had progressive disease. Response to chemotherapy was not documented in 19 patients. Post RT, 41 of 42 patients in whom early response to radiation (< 3 months) was documented had a complete response. In addition 3 patients with stable disease after chemotherapy achieved remission post radiation.

Survival analysis

5 of 44 patients relapsed after a median follow up of 19 months. The median survival was not reached (Figure 1). The estimated two and three year survival were 92.9% (95%CI-68.6- 95.35) and 88 % (95%CI-60.82-92.66). Univariate analysis revealed higher stage and poorer baseline performance status to be significantly associated with worse progression free survival. The results of univariate analysis for the remaining prognostic variables have been tabulated in Table 2.

RT toxicity

36 patients developed of radiation toxicity. Grade I and II dermatitis and mucositis was seen in all cases, but one. All toxicities were managed conservatively without any treatment interruption and hospitalization.The details

Table 1. Patient Characteristics and Treatment Details

Patient Characteristics & treatment details	(N=75)	(%)
StageI	55	73
II	9	12
III	3	4
IV	2	2.7
Not mentioned	6	8
Histology		
DLBCL	36	47
NHL (NOS)	20	26
MZL	5	7
NK-T Cell	3	4
Diffuse T cell NHL	2	3
Small cell NHL	5	7
Follicular	1	1.5
Burkitt	1	1.5
Diffuse HNL	2	3
Grade		
Low	6	8
Intermediate	8	11
High	31	41
Not mentioned	30	40
Size of the lesion		
<5 cm	47	63
>5 cm	17	23
Not mentioned	11	14
CT regimen		
CHOP	40	53
COP	17	23
RCHOP	5	7
CEOP	2	2
Others	4	5
No CT	7	9
CT response		
CR	21	28
PR	30	40
SD	4	5
PD	1	1
Unknown	19	26

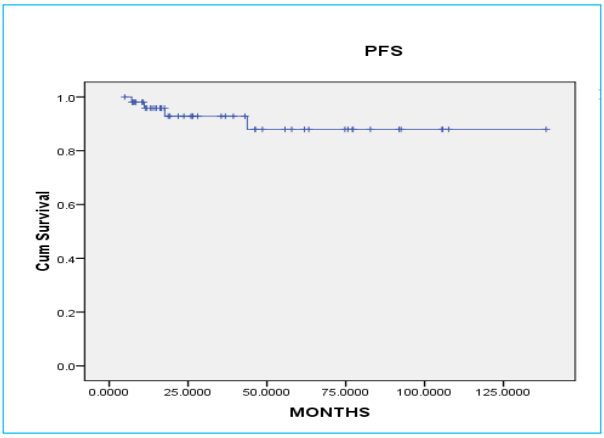

Figure 1. Cumulative PFS

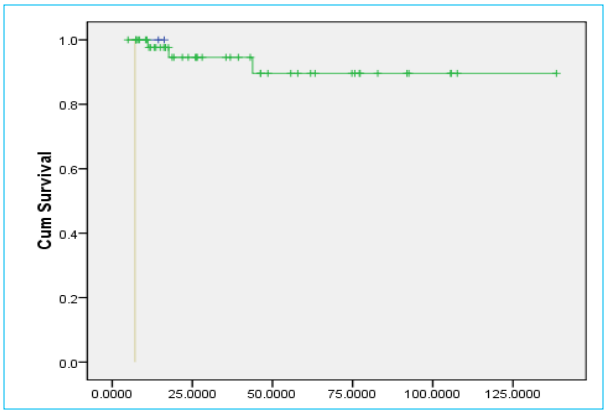

Figure 2. Cumulative PFS in Different Performance Status at Presentation

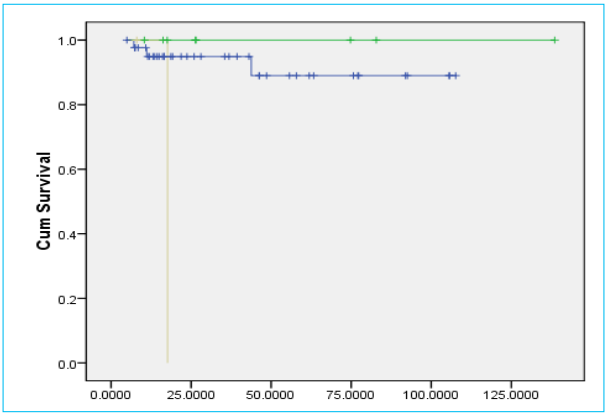

Figure 3. Cumulative PFS in Different Stages

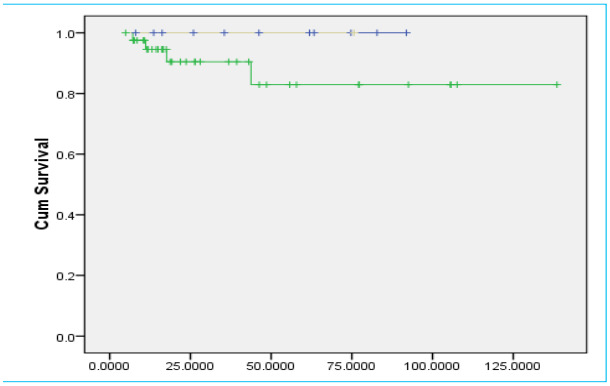

Figure 4. Cumulative PFS According to Age Groups

of radiation toxicities are tabulated in Table 3.

Pattern of failure and salvage

5 patients progressed after treatment. Of the 5 patients, two patients had distant failure, two patients had primary site failure and one had nodal failure Table 4.

Discussion

Table 2. Impact of Prognostic Variables and the Survival at 6, 12, 24 and 36 Months

Variable	n	Event	Survived months				P value
			6	12	24	36	
Age							
≤50	22	2	100%	95%	86%	87%	0.59
>50	22	3	100%	95%	89%	76%	
Age							
≤ 40	8	2	100%	87%	58%	58%	0.13
>40	36	3	100%	97%	93%	87%	
Gender							
Male	30	4	100%	93%	84%	76%	0.4
Female	14	1	100%	100%	91%	91%	
Sub-site							
Orbit	25	3	100%	100%	85%	75%	0.86
Others	19	2	100%	89%	89%	89%	
Subsite							
PNS+Nasal	6	1	100%	83%	83%	83%	0.89
Pharynx	5	0	100%	100%	100%	100%	
Orbit	25	3	100%	100%	85%	75%	
Others	8	1	100%	85%	85%	85%	
HPE							
DLBCL	18	2	100%	94%	94%	82%	0.91
Non- DBLCL	26	3	100%	96%	82%	82%	
LESION SIZE							
≤5 cm	35	5	100%	94%	83%	76%	0.19
>5 cm	9	0	100%	100%	100%	100%	
Stage							
I	25	4	100%	94%	85%	85%	
II-IV	19	1	100%	75%	75%	75%	0.98
No of CT cycles							
≤ 4	31	2	100%	96%	91%	90%	0.6281
>4	11	2	100%	91%	90%	75%	
CT response							
CR	16	0	100%	100%	100%	100%	0.0001
PR	31	3	100%	100%	87%	79%	
SD	4	1	100%	75%	75%	0%	
PD	1	1	100%	0%	0%	0%	

HNENL are a distinct subset of NHL 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 et al., 2011; Savita et al., 2012). These tumors are mostly diagnosed in 6th decade of life; Nathu et al., 1991 (Nimmagadda et al., 2013). From the present analysis it appears to be one decade earlier in the Indian population. This could be just a chance phenomenon due to a small sample number but may also be related to poorer nutritional status leading to a generally weaker immune system in the Indian population thus leading to a higher NHL risk (Chihara et al., 2015).

HNENL are mostly diagnosed in stage I andII (Zucca et al., 1999). The most common histology seen is DLBCL followed by MZL (Wotherspoon et al.1993; Diab et al, 2011; Mertsoylu et al. 2014). The current study observed majority in early stage and DLBCL (40%) was the most common histology. MZL constituted less than 10 % of cases (n=5). MZL constitutes two third cases of orbital NHL. But among orbital lymphomas, DLBCL in contrast to western literature was the commonest histology in the present series. The reason could be the presence of less number of domesticated birds and decreased incidence of Chlamydia psittaci infections in India as these infections are a known risk factor for MZL (Moslehi et al., 2006).

Combined modality (CMT) approach has long been considered the cornerstone of therapy for HNENL. A study by Aviles et al on NHL of Waldeyer ring showed that the 5 year overall survival was 90 % *vs* 50 % in the Combined modality therapy versus radiotherapy alone respectively (Aviles et al., 1996).

In the SWOG 8736 study, 401 patients with limited stage aggressive lymphoma (75 percent DLBCL) were randomly assigned to treatment with either eight cycles of CHOP chemotherapy or three cycles of CHOP plus involved field RT (40 to 55 Gy). At a median follow-up of 4.4 years, combination therapy with three cycles of CHOP plus involved field RT resulted in higher rates of five-year progression-free (77 versus 64 percent) and overall (82 versus 72 percent) survival. The study concluded three cycles of CHOP followed by IFRT is better than eight cycles of CHOP alone (Miller et al., 1998). It was seen in SWOG 8736 study that patients having a response to induction chemotherapy (PR or CR) had better outcomes in terms of OS (Miller et al.1998). However, in our study

Table 4. Summary of recurrence patterns and outcomes of salvage treatment

Primary	Local Failure	Nodal Failure	Distant Failure	Salvage Treatment	Status At Last Follow Up
Orbit	Yes	No	No	Chemotherapy	No Evidence Of Disease
Orbit	No	Cervical And Axillary	No	Chemotherapy	No Evidence Of Disease
Nasal Cavity	Yes	No	No	Chemotherapy	No Evidence Of Disease
Nasal Cavity	No	No	Yes	Palliative Radiation	Lost To Follow Up
Thyroid	No	No	Yes	No Treatment	Lost To Follow Up

Table 3. Acute and late toxicity in the present cohort

	Dermatitis	Mucositis	Conjunctivitis	Dysphagia	Xerostomia	Lacrimal	Others
Acute	Grade III=1	Grade II=13	Grade II=8	Grade II=1	Nil	Nil	
Late	Nil	Nil	Dry eye=3	Grade I=1	Grade III=1 Grade II=2	Epiphora=5	Cataract=1 Decreased hearing=1

no statistically significant correlation between response to chemotherapy and PFS has been found Table 2. The reason could be a small sample size and inherent bias of retrospective nature of analysis or may be related to a different biology of HNENL in comparison to nodal NHL. These tumours are generally localized and disseminate slowly. Slower growing tumours can be expected to respond slowly to cytotoxic therapy including chemotherapy thus nullifying the statistical correlation between early response to chemotherapy and PFS.

The addition of rituximab is expected to improve outcomes further in NHL. In a study by Coiffier et al, the addition of rituximab improved overall survival and event free survival in DLBCL patients (Coiffier et al., 2002). Dose dense regimens of RCHOP have not shown much benefit. In a study by Richard Delarue et al, a comparison between 3 weekly RCHOP and 2 weekly RCHOP was done. No improvement in efficacy was seen between the two regimens (Delarue et al., 2013). In our study no statistically significant correlation was found between PFS and chemotherapy regimens. This could be because of small sample size and short median follow up.

PET-CT has become a predictor of treatment outcomes in NHL patients. In a meta-analysis by Zhu et al, PET-CT after completion of chemotherapy was found to be a predictor of overall survival in NHL patients (Zhu et al., 2013). The importance of radiation dose was studied in a phase III trial that included 640 sites of aggressive non-Hodgkin lymphoma (82 percent DLBCL) that randomly assigned radiation at lower doses (30 Gy in 15 fractions) or higher doses (40 to 45 Gy in 20 to 23 fractions) in patients who had a complete response to chemotherapy. At a median follow-up of 5.6 years, lower dose radiation resulted in similar rates of in-field progression; progression-free survival and overall survival (Lowry et al., 2011). In the current study all patients received IFRT to a dose of 45 Gray in 25 fractions over 5 weeks. This was because all patients could not be evaluated by PET scans due to logistic and cost issues.

This dose can lead to acute side effects like dermatitis, mucositis, xerostomia and conjunctivitis and many late effects like xerostomia and dry eyes affecting quality of life. The most common side effect seen was acute conjunctivitis (22 %) and only three patients had late dry eyes. Only two patients developed grade 3 toxicity. Thus our analysis indicates that a CMT of induction chemotherapy followed by IFRT provides excellent control rates with acceptable toxicity in ENHL of head and neck among the north Indian population.

In this analysis it was also seen that 20% of patients presented in OPD after more than 12 months of onset of symptoms and 45% presented 6 months after onset of symptoms. These are pointers toward the lack of awareness in the Indian population regarding signs, symptoms and treatment available for cancers. It may also point towards the lack of resources and infrastructure to detect and treat such cancers early in India. It may also point towards a different biology of HNENL making it slower growing and making outcomes favorable.

This is a retrospective analysis with its inherent bias making it difficult to interpret the statistical results. Further prospective studies are needed to define optimum radiotherapy dose, number of cycles of induction chemotherapy, the role of conformal RT and the efficacy of rituximab in control of disease in HNENL of head and neck in a resource limited country like India. A re-look into the molecular perturbations in HNENL is warranted as these tumours seem to have better outcomes even in presence of aggressive histology like DLBCL.

In conclusion, there are no randomized control studies to define the treatment in HNENL specifically. There is a paucity of data of the clinical characteristics, survival, response to chemotherapy, radiation therapy and toxicity profile of treating HNENL in Indian population. Our analysis indicates that induction chemotherapy followed IFRT is effective with acceptable toxicity.

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