Nasopharyngeal Carcinoma: A 15 Year Study with Respect to Clinicodemography and Survival Analysis

Shaqul Qamar Wani¹ · Talib Khan² · Saiful Yamin Wani³ · Liza Rafiq Mir³ ·
Mohammad Maqbool Lone¹ · Tariq Rasool Malik¹ · Arshad Manzoor Najmi¹ ·
Fir Afroz¹ · Mohammad Ashraf Teli¹ · Nazir Ahmad Khan¹

Received: 15 June 2016 / Accepted: 31 August 2016 / Published online: 19 September 2016
© Association of Otolaryngologists of India 2016

Abstract Nasopharyngeal carcinoma (NPC) is a rare malignancy in Kashmir with distinct pattern, hence we planned to study its clinicodemographic and survival profile. Kashmir has unique lifestyle and dietary habits which may be the source of carcinogenic compounds, most likely implicated in causation of NPC. A total of 148 patients of NPC registered from January 2000 to December 2014 were analyzed. The Mean $\pm$ SD age was 45.15 ± 17.092 years (range 11–85 years). The males were 72.3 % (N = 107) with male: female ratio of 2.61:1. Most of the patients were from rural area 81.90 % (N = 95) and non-smokers were 53.44 % (N = 62). Neck swelling was commonest presentation. WHO Type III NPC was commonest histopathological diagnosis 65.3 % (N = 92). Stage IV 36.1 % (N = 51) was commonest stage followed by stage III was 32 % (N = 46). Majority of the patients of NPC received CCRT

68.7 % (N = 78) followed by SCRT 13 % (N = 15) and Induction + CCRT 13 % (N = 15). The overall mean survival of NPC was 49.56 months. There was no significant correlation of age, gender, smoking, histopathology and treatment on the overall survival. However the stage was the only strong predictor of overall survival. Also the patients with intracranial extension had low survival which is turn depicts the advanced stage of disease. NPC survival is directly related to the stage of the disease irrespective of the treatment modality received. The negative EBV status in our patients implies that there are other risk factors involved in the causation of NPC for which further studies are needed to establish the etiological insult.

Keywords Nasopharyngeal carcinoma · Lifestyle · Dietary habits · Nitrosoamines · Smoking · Histopathology · Staging · Demographics · Neck swelling · Nasal obstruction

Affiliation where the Study was carried out: Department of Radiation Oncology and Regional Cancer Centre, Sher-I- Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, Jammu and Kashmir, India, PIN - 190011.

✉ Shaqul Qamar Wani
drsqamar1@gmail.com

Talib Khan
drtalibkhan@hotmail.com

¹ Department of Radiation Oncology and Regional Cancer Centre, Sher-I- Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, Jammu and Kashmir 190011, India

² Department of Anaesthesiology, Critical Care and Pain, Sher-I- Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, Jammu and Kashmir 190011, India

³ Directorate of Health Services Kashmir, Government of Jammu and Kashmir, Srinagar, Jammu and Kashmir 190001, India

Introduction

Nasopharyngeal carcinoma (NPC) arises from the epithelial cells lining the nasopharynx and usually originates in the lateral wall of the nasopharynx from the fossa of Rosenmuller [1].

Nasopharyngeal carcinoma (NPC) is a rare malignancy in most part of the world and it is one of the most confusing, commonly misdiagnosed, and poorly understood disease. NPC and has a remarkable racial and geographical distribution [1–6].

Nasopharyngeal carcinoma (NPC) occurs in high frequencies in China and South East Asia and is particularly high among the Southern Chinese [1–5, 7] besides it also occurs in Eskimos and other natives of the Arctic region,

and the mainly Arab populations of North Africa and Kuwait [3, 8]. NPC is uncommon in the Indian subcontinent except in the Northeastern part of the country [9]. The incidence of NPC is low in Indians (<1 per 100,000 per year) [10], with young age peak in second decade [11] both of which are comparable to UK [1].

In low-risk populations, a bimodal age distribution is observed. The first peak incidence occurs at 15–25 and the second peak at 50–59 years of age. In contrast, the incidence in high risk populations rises after 30 years of age, peaks at 40–60 years, and declines thereafter 59 years. The age distribution is similar in both genders. The incidence rates in male populations are commonly two to three fold that of female populations [2, 4, 11–13].

NPC has attracted world-wide attention because of complex interactions of genetic, viral, smoking, environmental, dietary, occupational factors, etc., which have been implicated in the causation of NPC [1–6, 9–13].

The clinical presentations of NPC may sometimes be insidious and nonspecific. They are usually related to the local, regional and distant spread or metastasis of the lesion. They may include cervical lymphadenopathy, nasal blockage, epistaxis, hyponasal speech and otologic and neuro-ophthalmic manifestations. The clinical morphology may be infiltrative, ulcerative or exophytic [6]. The WHO classifies NPC based on histology as Keratinizing squamous carcinoma as Type 1 and nonkeratinizing squamous carcinomas as Type 2 and Type 3 as undifferentiated, with highly variable cell types (clear cell, spindle cell, anaplastic) [1, 4, 10, 12, 14].

Kashmir valley is northern part of Indian subcontinent distinct from rest of India with respect to its geography, lifestyle and socio-culture aspects [15]. Though the incidence of NPC is low over all, but NPC follows the pattern distinct from rest of India and global trend which led us to study these cases.

Aim and Objectives

The case sheets of these patients were reviewed with regard to demographic profile, lifestyle aspects, clinical presentation, histopathology, stage of disease at presentation, and treatment received. To assess overall survival and its correlation with various variables.

Materials and Methods

After the approval from the institutional review board, this present study was conducted in tertiary referral and university teaching hospital in the Department of Radiation Oncology and Regional Cancer Centre, Sher-I-Kashmir

Institute of medical Sciences (SKIMS), Srinagar from the year 2000 to 2014. The study included the patients of NPC registered from January 2000 to December 2014. The case sheets of these patients were reviewed without any patient participation with regard to demography, clinical presentation, histopathological diagnosis, staging at presentation, treatment received and follow up time. The EBV status was done only in 16 patients. The survival analysis was done and correlated to various factors.

The addiction status was missing in two patients in their records. The histology was known in 141 patients, seven patients did not report with biopsy results. The staging was completed in 141 patients. The treatment was received by only 115 patients out of 148 registered patients of NPC. The survival analysis was done only in those who received the treatment and was also correlated to other factors.

Statistical Analysis

The data collected was analyzed using SPSS statistics software version 20 (SPSS Inc., Chicago, IL). Survival analysis was done using Kaplan–Meier method and comparison between two survival curves was done using log-rank test. The results were considered statistically significant if *P* value was <0.05.

Results

The study included 148 patients of nasopharyngeal malignancies, aged 11–85 years with Mean $\pm$ SD age of 45.15 ± 17.26 years. In relation to age distribution the commonest age group involved was 31–50 years 41.9 % (*N* = 62), followed by 51–70 years 31.8 % (*N* = 47), ≤ 30 years 23 % (*N* = 34), and ≥ 70 years 3.4 % (*N* = 5) respectively (Table 1).

The males were 72.3 % (*N* = 107) with male: female ratio of 2.61:1. Most of the patients were from rural area 81.90 % (*N* = 95). With regard to addiction, current smokers were 39.65 % (*N* = 46), ex-smokers 3.45 % (*N* = 4), snuff user 3.45 % (*N* = 4), and non-smokers were 53.44 % (*N* = 62). Addiction status was not known in 2 patients (Table 1). The antibody titers were negative for EBV in all the 16 patients tested for titers.

With regard to clinical symptomatology neck swelling was commonest presentation and was present in 68.9 % (*N* = 102) followed by Nasal obstruction (32.4 %), Headache (30.4 %), Epistaxis (27 %), Hearing impairment (14.9 %), Otalgia (10.8 %), Nasal twang (9.5 %), Tinnitus (8.8 %), Intracranial extension (8.1 %), Hoarseness of voice (6.1 %), Diplopia (6.1 %), Proptosis (6.1 %), Nasal discharge (5.4 %), facial pain (5.4 %), Impairment of vision (4.7 %), Cranial nerve involvement (4.7 %), Skull

Table 1 Demographics of NPC patients

		N	%
Age in years	≤30	34	23.0
	31–50	62	41.9
	51–70	47	31.8
	>70	5	3.4
	Total	148	100.0
	Minimum	11	
	Maximum	85	
	Mean ± SD	45.15 ± 17.26	
Gender	Male	107	72.3
	Female	41	27.7
	Total	148	100.0
Dwelling	Rural	120	81.1
	Urban	28	18.9
	Total	148	100.0
Addiction	Non smoker	76	51.4
	Current Smoker	63	42.6
	Exsmoker	4	2.7
	Snuff users And others	3	2.0
	Total	146	98.6
	Status unknown?	2	1.4
EBV analysis	Negative	16	100
	Positive	0	0
	Total	16	100
Cases registered	2000	8	0.76
	2001	13	1.28
	2002	6	0.53
	2003	18	1.51
	2004	6	0.46
	2005	11	0.91
	2006	14	1.0
	2007	4	0.19
	2008	12	0.48
	2009	7	0.23
	2010	11	0.35
	2011	7	0.22
	2012	14	0.42
	2013	7	0.20
	2014	10	0.25

base involvement (4.7 %), Decrease in eye movements (2.7 %) (Table 2).

WHO Type III NPC was commonest histopathological diagnosis 65.3 % (N = 92) followed by Type II 25.5 % (N = 36), Type I 4.3 % (N = 6) and others 4.9 % (N = 7) (Table 3).

With regard to stage at presentation, stage IV was 36.1 % (N = 51) followed by stage III 32 % (N = 46), stage II 29.73 % (N = 42) and stage I 1.4 % (N = 2) (Table 4).

Table 2 Clinical presentation of NPC Patients

Clinical features	N	%
Cx LAP	102	68.9
Nasal obstruction	48	32.4
Headache	45	30.4
Epistaxis	40	27.0
Hearing impiarment	22	14.9
Otalgia	16	10.8
Nasal Twang	14	9.5
Tinnitus	13	8.8
IC Ext	12	8.1
HOV	9	6.1
Diplopia	9	6.1
Proptosis	9	6.1
Nasal discharge	8	5.4
Facial pain	8	5.4
↓Vision	7	4.7
CN palsies	7	4.7
Skull base	7	4.7

Table 3 Histopathology Types of NPC

HPE type	N	%
WHO I	6	4.3
WHO II	36	25.5
WHO III	92	65.3
Others	7	4.9
Total	141	100.0

Majority patients of NPC received CCRT 68.7 % (N = 78) followed by SCRT 13 % (N = 15) and Induction + CCRT 13 % (N = 15). Palliative RT was received by 4.3 % (N = 5) patients, curative RT was received by two patients of stage I NPC (Table 5).

The overall mean and median survival of NPC was 49.56 and 38.23 months respectively (Fig. 1). There was no significant correlation of age (Fig. 2), gender (Fig. 3), smoking (Fig. 5), histopathology (Fig. 6) and treatment (Fig. 8) on the overall survival. However the stage was the only strong predictor of overall survival (Fig. 7). Also the patients with intracranial extension have also low survival which is turn depicts the advanced stage of disease (Fig. 4).

Discussion

Nasopharyngeal carcinoma (NPC) arises from the epithelial lining of the nasopharynx but frequently develops at the fossa of Rosenmuller around the ostium of the Eustachian

Table 4 Staging of NPC Patients

		N	%
T	1	29	20.6
	2	45	31.9
	3	26	18.4
	4	41	29.1
	Total	141	100.0
N	0.	27	19.1
	1.	62	44.0
	2.	40	28.4
	3.	1	0.7
	3a	1	0.7
	3A	7	5.0
	3B	3	2.1
	Total	141	100.0
M	0	135	95.7
	1	6	4.3
	Total	141	100.0
Stage	I	2	1.4
	II	43	30.5
	III	45	32.0
	IV	51	36.2
	IVA	37	26.2
	IVB	9	6.4
	IVC	5	3.5
	Total	141	100.0

Table 5 Treatment received by NPC patients

Treatment modality	N	%
CCRT	78	67.8
SCRT	15	13.0
Induction + CCRT	15	13.0
Palliative RT	5	4.3
RT Only	2	1.7
Total	115	100.0

tube medially in the lateral wall of the nasopharynx [1, 4, 12, 14, 16].

The mean age at presentation among the studied subjects was 45.15 ± 17.26 years. The commonest age involvement in other Indian states is 15–19 and 65–69 having two peaks [17], this is similar to low incidence areas [12]. The maximum incidence in 4th and 5th decade is also seen in the study of Boljesíková et al. [13] India has low over all incidence of NPC which is comparable to UK with annual incidence of 0.9 per million population [1, 12].

Males were predominantly affected with male to female ratio (M:F) of 2.61:1. The male predominance is also seen in the other studies [1, 2, 10, 12, 13, 16–22].

In our study 81.1 % (N = 120) patients were from rural areas. The reason being that more than 70 % of population in our part of Indian subcontinent is rural [23].

Though the number of nonsmokers were more as compared to smokers, the reason might be the presence of other factors which may be involved in causation of NPC.

Nasopharyngeal carcinoma (NPC) has a unique and complex etiology that is not completely understood. Although rare, but well-established risk factors for NPC include elevated antibody titers against the Epstein-Barr virus, consumption of salt-preserved fish, a family history of NPC, and certain human leukocyte antigen class I genotypes. Consumption of other preserved foods, tobacco smoking, and a history of chronic respiratory tract conditions may be associated with elevated NPC risk [1–3, 12, 16].

In spite of the high incidence of cancer of the oral cavity and other parts of pharynx, NPC is uncommon in the Indian subcontinent except in the Northeastern part of the country [9].

The significant difference in geographical, ethnicity and dietary habits within our country could predispose people of Northeastern India for high incidence of NPC. One study from this region reveals an association of this cancer with consumption of smoked meat and herbal nasal medicine [24]. Another study on smoked meat of this region has shown the presence of volatile nitrosamine which is already known as strong carcinogen [25, 26].

Historically, the Indian population is a conglomeration of multiple cultures and races. The evolutionary history of India entails migrations from central Asia and South China, resulting in a rich tapestry of sociocultural, linguistic, and biological diversity [9]. But Kashmir has a non-migrant pure ethnic population who have special social, personal, and dietary habits. The Kashmir valley is far northern part of Indian subcontinent with the trends of malignant disorders distinct from the rest of the India [27]. In Kashmir valley upper GI malignancies are more prevalent than other malignancies as compared to rest of India [23, 27, 28]. We studied NPC as it being rare in Kashmir.

Various risk factors have been associated to its causation like genetic, viral and environmental factors. Our study showed negative results for EBV antibodies signaling either genetic or environmental risk factors for causation of NPC. Environmental factors, Life style and Dietary habits of Kashmir valley has been found to be distinct than rest of the India and world too, may play a role in the causation of NPC but needs further studies to establish the likely factor.

The most important specific food habit in Kashmir is the frequent consumption of hot salt tea with added sodium bicarbonate [27, 28], which is a source of various volatile nitroso compounds [29]. Another specific dietary habit which is very particular to Kashmiri population sun dried

raw food stuffs [30], and contain significant amounts of N-nitroso compounds [31]. In addition, other Kashmiri food items contributing substantial amount of N-nitroso compounds include salt tea, dried fish, vegetables especially *Brassica oleracea* (*haak*), red chillies, and spice cake (*wur*) [31–33].

Another type of diet among Kashmiri population is the use of smoked fish (*Pherr*) which is made by partially burning the fish wrapped in the dried grass. Other type of fish consumed is small fishes dried in sunlight called *Hokhegaad*.

With regard to lifestyle, people of Kashmir live during cold winter for quite good time in hammams, isolated and ill ventilated stone rooms which is warmed over fire. The families live together in rooms which are kept warm by burning the fire wood in iron jacket called *Bukharis*, which is also the source of smoke.

Besides people use Fire pot (*Kangris*) to keep themselves warm during cold winter which is also the likely source of inhaled carcinogens.

The ingestion of salted fish and other kinds of preserved foods constitutes the most important cause of NPC [8].

The clinical presentations of NPC may sometimes be insidious and nonspecific [1, 6]. They are usually related to the local, regional and distant spread or metastasis of the lesion. They may include cervical lymphadenopathy, nasal blockage, epistaxis, hyponasal speech and otologic and

neuro-ophthalmic manifestations. The clinical morphology may be infiltrative, ulcerative or exophytic [6]. The clinical manifestations in our study were in accordance with studies of Brennan [1], Sharma et al. [34] Farooq et al. [35], Al-Rajhi et al. [36], Clifford et al. [37].

Al-Rajhi et al. [36] observed that the majority of patients had advanced disease (stage III and IV) at the time of evaluation (79.2 %), while Li et al. [38] observed diseases at stages I/II accounted for 25.2 %, while those with stage III/IV accounted for 74.8 % [37]. Similarly in our study, majority of patients presented with stage III and IV 68.2 %. Amaro et al. [39] showed 54 % patient in Stage IV, Downing et al. [40] showed 92 % presented in stage III, Tiong et al. [41] showed 85 % of the patient presented in advanced stage (stage III and IV), Skinner et al. [42] showed 70 % of patients presented in Stage III disease and Ibrahim et al. [43] also showed the advanced stage 86 % presentation of the patients in stage III and IV.

Sun et al. [44] showed WHO type II was commonest histopathology followed by WHO type I. WHO type III was the common HPE variant observed by Ibrahim et al. [43], Sharma et al. [34] similar results were seen in our study.

Almost all NPC are treated with radiation therapy due to anatomical constraints for complete surgical resection [12, 45]. The current recommendation is to treat patients with stage I disease with definitive RT, and those with

Fig. 1 Overall Survival of NPC patients

Fig. 2 Overall Survival analysis in relation to Age distribution

Fig. 3 Overall Survival analysis in relation to Gender

Fig. 4 Overall Survival analysis in relation to intracranial tumour extension (IC Ext)

Fig. 5 Overall Survival analysis in relation to Addiction

Fig. 6 Overall Survival analysis in relation to histopathologic types

Fig. 7 Overall Survival analysis in relation to Stage of the NPC

Fig. 8 Overall Survival analysis in relation to Treatment Modality received

stage II or more disease with concurrent chemoradiotherapy (CCRT) [46]. Majority of our patients received CCRT 68.7 % (N = 78) due to the advanced presentation of disease.

The mean overall survival (OS) of NPC was 49.56 months. There was no significant correlation of age, gender, smoking, histopathology and treatment on the overall survival. However the stage was the only strong predictor of overall survival in our study. Also the patients with intracranial extension had low overall survival which in turn depicts the advanced stage of disease. The prognostic role of age and gender on the survival of NPC was seen in the study of Xiao et al. [22] where in younger men were more likely to have distant metastases and exhibited inferior overall survival and disease progression-free survival rates.

However there are other studies which showed better survival in younger patients [47].

Also female NPC patients had favorable treatment outcomes, with 5-year survival rates exceeding 80 %. The favorable prognosis of female NPC patients was not only attributed to early diagnosis and treatment but might also be attributed to some intrinsic factors of female patients which may play an important role in the prognosis of NPC [48].

Gender significantly affected the survival of nasopharyngeal carcinoma, with a definite female advantage across

all end points, independent of other prognostic factors [49]. Males had better survival as compared to females in our study but was not statistically significant.

Shen et al. [50], Ouyang et al. [51] analysed that smoking status is of poor prognostic value for survival in NPC patients. Our study does not show any correlation of smoking on survival.

The survival correlates well with the histological variant of NPC with better survival for radioresponsive nonkeratinising and undifferentiated variant [52]. However our study did not show the histological correlation with overall survival in NPC patients (Fig. 6).

The extent of local invasion, regional lymphatic spread, and distant metastasis, as reflected by the TNM staging, is the most important prognostic factor. In general, advanced T-category is associated with worse local control and overall survival; advanced N-category predicts increased risk of distant metastasis and worse survival. Presence of distant metastasis (M1) upon presentation usually indicates poor prognosis, and treatment has conventionally been palliative in nature [12]. Clinical staging was shown to be the independent prognostic factor in overall survival analysis in NPC [53, 54]. Also in our study, the only significant indicator in terms of overall survival was disease stage at presentation.

Compliance with Ethical Standards

Conflict of interest None.

Ethical Standards The study is exempted from the institutional ethical approval at our institute due to retrospective nature of study and non participation of patients.

References

- Brennan B (2006) Nasopharyngeal carcinoma. *Orphanet J Rare Dis* 1:23
- Kumar S (2003) Epidemiological and etiological factors associated with nasopharyngeal carcinoma. *ICMR Bull* 33(9):1–9
- Chang ET, Adami HO (2006) The enigmatic epidemiology of nasopharyngeal carcinoma. *Cancer Epidemiol Biomark Prev* 15:1765–1777
- <http://www.cancer.org/acs/groups/cid/documents/webcontent/003124-pdf.pdf>. Accessed 24 July 2012
- Chan SH (1990) Aetiology of nasopharyngeal carcinoma. *Ann Acad Med Singap* 19:201–207
- Wani SQ, Khan T, Wani SY, Najmi AM, Malik TR, Lone MM et al (2015) Nasopharyngeal carcinoma with atypical ophthalmic presentation – a rare case report. *World J Surg Med Radiat Oncol* 4:36–40
- Fedder M, Gonzalez MF (1985) Nasopharyngeal carcinoma—brief review. *Am J Med* 79:365
- Yu MC (1991) Nasopharyngeal carcinoma: epidemiology and dietary factors. *IARC Sci Publ* 105:39–47
- Kataki AC, Simons MJ, Das AK, Sharma K, Mehra NK (2011) Nasopharyngeal carcinoma in the northeastern states of India. *Chin J Cancer* 30:106–113
- Shanmugaratnam K (1980) Nasopharyngeal carcinoma: epidemiology, histopathology and aetiology. *Ann Acad Med Singap* 9:289–295
- Balakrishnan U (1975) An additional younger-age peak for cancer of the nasopharynx. *Int J Cancer* 15:651–657
- Lee AWM, Perez CA, Law SCK, Chua DTT, Wei WI, Chong V. Nasopharynx. Chapter 38; pp 820–857. In: Perez and Brady's principles and practice of radiation oncology. 5th ed. 2008 Publisher Lippincott Williams & Wilkins, Philadelphia, 19106 USA
- Boljesiková E, Durkovský J, Michalíková B (1982) Our experience with the treatment of nasopharyngeal tumors. *Neoplasma* 29:351–357
- Chou Josephine, Lin Yu-Ching, Kim Jae, You Liang, Zhidong Xu, He Biao, Jablons David M (2008) Nasopharyngeal carcinoma-review of the molecular mechanisms of tumorigenesis. *Head Neck* 30:946–963
- http://en.wikipedia.org/wiki/Jammu_and_Kashmir. Accessed 24 July 2012
- Wei WI. In Bailey BJ, Johnson JT, Newlands SD (2006) Head & Neck surgery- otolaryngology, 4th edition, 2006; vol 2 Publisher Lippincott Williams & Wilkins, Philadelphia, 19106 USA
- Bray F, Haugen M, Moger TA, Tretli S, Aalen OO, Grotmol T (2008) Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiological implications. *Cancer Epidemiol Biomark Prev* 17:2356–2365
- Lathi A, Syed MMA, Kalakoti P, Qutub D, Kishve SP (2011) Clinico-pathological profile of sinonasal masses: a study from a tertiary care hospital of India. *Acta Otorhinolaryngol Ital* 31:372–377
- Tse KP, Su WH, Yang ML, Cheng HY, Tsang NM, Chang KP, Hao SP, Shugart YY, Chang YS (2011) A gender- specific association of CNV at 6p21.3 with NPC susceptibility. *Hum Mol Genet* 1–8. doi:10.1093/hmg/ddr191
- Herity B, Moriarty M, Bourke GJ, Daly L (1981) Case-control study of head and neck cancer in The Republic Of Ireland. *Br J Cancer* 43:177–182
- Tse LA, Yu ITS, Mang OWK, Wong SL (2006) Short communication. Incidence rate trends of histological subtypes of nasopharyngeal carcinoma in Hong Kong. *Br J Cancer* 95:1269–1273
- Xiao GL, Cao YB, Qiu XB, Wang WH, Wang YF (2013) Influence of gender and age on the survival of patients with nasopharyngeal carcinoma. *BMC Cancer* 13:226
- Wani SQ, Khan T, Wani SY, Koka AH, Arshad S, Rafiq L, Maqbool LM, Afroz F (2012) Clinicoepidemiological analysis of female breast cancer patients in Kashmir. *J Cancer Res Ther* 8:389–393
- Chelleng PK, Narain K, Das HK, Chetia M, Mahanta J (2000) Risk factors for cancer nasopharynx: a case-control study from Nagaland, India. *Natl Med J India* 13:6–8
- Sarkar S, Nagabhushan M, Soman CS, Tricker AR, Bhide SV (1989) Mutagenicity and carcinogenicity of smoked meat from Nagaland, a region of India prone to a high incidence of nasopharyngeal cancer. *Carcinogenesis* 10:733–736
- Kumar S, Zinyu R, Chetia M, Dutta LP (1992) Genotoxic effect of smoked-dried meat extract in swiss albinos mice using sperm head shape abnormality test. *Cancer Lett* 64:51–53
- Ayub SG, Ayub T, Khan SN, Rasool S, Hussain M, Wani KA et al (2011) Epidemiological distribution and incidence of different cancers in Kashmir Valley-2002–2006. *Asian Pac J Cancer Prev* 12:1867–1872
- Dhar GM, Shah GN, Naheed B (1993) Epidemiological trend in the distribution of cancer in Kashmir Valley. *J Epidemiol Commun Health* 47:290–292
- Siddiqi M, Tricker AR, Preussmann R (1988) Formation of N-nitroso compounds under simulated gastric conditions from Kashmir food stuffs. *Cancer Lett* 39:259–265
- Siddiqi M, Preussmann R (1989) Oesophageal cancer in Kashmir—an assessment. *J Cancer Res Clin Oncol* 115:111–117
- Tricker AR, Siddiqi M, Preussmann R (1988) Occurrence of volatile N-nitrosoamines in dried chillies. *Cancer Lett* 38:271–273
- Siddiqi M, Tricker AR, Preussmann R (1988) The occurrence of preformed N-nitroso compounds in food samples from a high risk area of oesophageal cancer in Kashmir. *India. Cancer Lett.* 39:37–43
- Siddiqi M, Tricker AR, Kumar R, et al. (1990) Dietary Sources of N-nitrosamines in a high risk area for oesophageal cancer, Kashmir, India. In: O'Neill IK, Chen JS, Lu SH, Bartsch H, eds. Relevance to human cancer of N-nitroso compounds, tobacco smoke and Mycotoxins. IARC Publication no 105, Lyon, IARC, p. 235–7
- Sharma TD, Singh TT, Laishram RS, Sharma LDC, Sunita AK, Imchen LT (2011) Nasopharyngeal carcinoma—a clinico-pathological study in a regional cancer centre of Northeastern India. *Asian Pacific J Cancer Prev* 12:1583–1587
- Farooq MU, Shaikh SM, Jawaid MA, Ahmed A (2009) clinical presentation of the nasopharyngeal carcinoma at civil hospital Karachi. *Otolaryngology* 15:98–100
- Al-Rajhi N, El-Sebaie M, Khafaga Y, AlZahrani A, Mohamed G, Al-Amro A (2009) Nasopharyngeal carcinoma in Saudi Arabia: clinical presentation and diagnostic delay. *Eastern Mediterranean Health J* 15:1302–1307
- Clifford P, Beecher JL (1964) Nasopharyngeal cancer in Kenya clinical and environmental aspects. *Br J Cancer* 18:25–43
- Li JX, Lu TX, Huang Y, Han F, Chen CY, Xiao WW (2010) Clinical features of 337 patients with recurrent nasopharyngeal carcinoma. *Chin J Cancer* 29:82–86

39. d'EspineyAmaro C, Montalvão P, Henriques P, Magalhães M, Olias J (2009) Nasopharyngeal carcinoma: our experience. *Eur Arch Otorhinolaryngol* 266:833–838
40. Downing NL, Wolden S, Wong P, Petrik DW, Hara W, Le QT (2009) Comparison of treatment results between adult and juvenile nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 25
41. Tiong TS, Selva KS (2005) Clinical presentation of nasopharyngeal carcinoma in Sarawak Malaysia. *Med J Malaysia* 60:624–628
42. Skinner DW, Van Hasselt CA, Tsao SY (1991) Nasopharyngeal carcinoma: modes of presentation. *Ann OtolRhinolLaryngol* 100:544–551
43. Ibrahim HK, Shouman T, Taher AN, Nasr AM, Atef H (2015) A retrospective study of clinicoepidemiological aspects of nasopharyngeal cancer at NCI-Cairo (2000–2010). *J Cancer Ther* 6:971–980
44. Sun Li-Min, Christopher IL, Haung EY, Vaughan TL (2007) Survival differences by race in nasopharyngeal carcinoma. *Am J Epidemiol* 165:271–278
45. Mendenhall WM, Werning JW, Pfister DG. Cancer of the Head and Neck. In: DeVita VT, Lawrence TS, Rosenberg SA, Editors. DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology, 8th Ed. Vol 1, Chapter 36; Philadelphia:Wolters Kluwer/Lippincott Williams & Wilkins. 2008
46. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Cancer of the Nasopharynx Version 2.2014. 05/30/2014; National Comprehensive Cancer Network
47. Sze HC, Ng WT, Chan OS, Shum TCY, Chan LLK, Lee AWM (2012) Radical Radiotherapy for Nasopharyngeal Carcinoma in Elderly Patients: the Importance of Co-Morbidity Assessment. *Oral Oncol* 48:162–167
48. Lu X, Wang FL, Guo X, Wang L, Zhang HB, Xia WX, Li SW, Li NW, Qian CN, Xiang YQ (2013) Favorable prognosis of female patients with nasopharyngeal carcinoma. *Chin J Cancer* 32(5):283–288
49. OuYang PY, Zhang LN, Lan XW, Xie C, Zhang WW, Wang QX, Su Z, Tang J, Xie FY (2015) The significant survival advantage of female sex in nasopharyngeal carcinoma: a propensity-matched analysis. *Br J Cancer* 112(9):1554–1561
50. Shen GP, Xu FH, He F, Ruan HL, Cui C, Chen LZ, Zeng YX, Jia WH (2012) Pretreatment Lifestyle Behaviors as Survival Predictors for Patients with Nasopharyngeal Carcinoma. *PLoS ONE* 7(5):e36515
51. OuYang PY, Su Z, Mao YP, Liang XX, Liu Q, Deng W, Xie FY (2013) Prognostic impact of cigarette smoking on the survival of patients with established nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 22(12):2285–2294
52. Marks JE, Phillips JL, Menck HR (1998) The national cancer data base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. *Cancer* 83:582–588
53. Hu D, Cao KJ, Xie GF, Huang PY, Wang CT, Zhang YY (2008) Correlation of imaging-based staging to prognosis of nasopharyngeal carcinoma. *Chinese Journal of Cancer* 27(7):60–64
54. Lombardi F, Gasparini M, Gianni C, De Marie M, Molinari R, Pilotti S (1982) Nasopharyngeal carcinoma in childhood. *Med PediatrOncol* 10(3):243–250