

RESEARCH COMMUNICATION

Nasopharyngeal Carcinoma- An Update of Treatment and Acute Radiation Induced Reactions from a Tertiary-Care Hospital in Pakistan

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Abstract

Introduction: Nasopharyngeal carcinoma (NPC) is a diverse entity with a multi-factorial etiology and a distinct racial and geographical distribution. It is curable if diagnosed and treated early. **Methods:** This descriptive study covered 30 patients who underwent radiotherapy (RT) for nasopharyngeal malignancies during February 2006 till November 2010 at the Department of Radiation Oncology, Aga Khan University Hospital (AKUH), Karachi. **Results:** Thirty cases of nasopharyngeal tumors were registered; a case of embryonal rhabdomyosarcoma and another of diffuse large B-cell lymphoma were not included in the final analyses. There were 20 (71.0%) males and 8 (29.0%) females, 2 and 5 being observed in adolescents. The mean age of the male and female patients was 43.7 [SD 20.1] and 30.3 years [SD 17.9], respectively. Nodal involvement was seen in 23 cases and cranial in 8. Almost two-thirds the patients presented with a stage IV disease and all but two received chemotherapy. Electrons or photons were used for 23 cases; low anterior neck field was used in 25 cases. The doses of radiotherapy delivered ranged between 2000cGy to 7400cGy, the lower ones being given for palliation only. Once spinal cord tolerance was reached, electron boost fields were used in order to treat the posterior neck. A nasogastric tube was required for feeding in 2 (10.0%) male and 2 (25.0%) female patients; gastrostomy was needed for 1 (5.0%) patient. Radiotherapy (RT) induced reactions were observed in 90% of the patients, but were mild in most cases. **Conclusions:** In the presence of clinician based expertise and technical constraints in Pakistan, nasopharyngeal tumors are still being treated optimally with the need of creating a better awareness in public for early detection.

Keywords: Nasopharyngeal carcinoma - radiotherapy - acute radiation reactions - Karachi - Pakistan

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Introduction

Nasopharyngeal carcinoma (NPC), ICD-10 (International Classification of Diseases 10th Revision) category C11 is a tumor arising from the surface epithelial cells of the nasopharynx. Pakistan is a moderate to high risk region for NPC, with an estimated 752 cases diagnosed annually (Ferlay et al., 2010). Globally, the estimation of new nasopharyngeal cancers (NPC) has been quoted as 84,000 cases diagnosed annually, with an age-standardized rate (ASR) of 1.2 per 100,000 for both sexes (Ferlay et al., 2010). South East Asia is a high risk region for NPC especially southern regions of China, where the malignancy is observed in middle-aged individuals. NPC is also endemic in African children (Richard et al., 2002). The risk factors for NPC apart from Chinese ancestry include Epstein-Barr virus (EBV) exposure, familial clustering, and heavy alcohol intake (Chien et al., 2001; Chen et al., 2009).

NPC is not amenable to surgery, due to its anatomical

position and close proximity to the spinal cord, brain stem and optic chiasma. Its presentation with cervical lymph node metastases is utilized for histological verification of cases; biopsy of involved lymph nodes often being the only possible surgical procedure. High-dose radiation therapy with chemotherapy is the primary treatment of NPC, both for the primary tumor site and the neck glands (Baujati et al., 2006). NPC is highly radiosensitive, nonetheless locally advanced NPC poses a clinical challenge to the radiation oncologists, as these tumors can invade locally into the orbit and intracranial fossae.

The objective of this study was to understand NPC in Karachi, in context to stage at presentation, treatment, and acute radiation-induced reactions in patients presenting to a tertiary care hospital.

Materials and Methods

This retrospective study was conducted at the Radiation Oncology Department of Aga Khan University

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Hospital (AKUH) Karachi. The department is equipped with 2 Linear Accelerators and 3 dimensional conformal planning systems. We reviewed cases that had been referred to our department during 1st February 2006 and 30th November 2010. All cases were discussed in the in-house multi-disciplinary expert panel tumor boards.

A pre-coded questionnaire was developed for this study, which included simple demographic details viz. age, gender and ethnicity; information regarding the malignancy i.e. tumor morphology, staging, nodal and intracranial involvement; information regarding the treatment i.e. total tumor doses delivered to the patients and complications. Complications were categorized into radiation therapy (RT) symptoms related to skin, salivary gland, mucosa, pharynx, esophagus and larynx (Table 2). The cancers were staged using the UICC/AJCC TNM system.

As a standard practice, all cases were treated with acceptable tolerance doses to the organs at risk, namely spinal cord, brainstem and optic chiasma. ‘Dose Volume Histograms’ were thoroughly studied and plans approved with ‘Quality Assurance’ (QA) specifications set up by International Commission on Radiation Units and Measurements (ICRU). The data were retrieved from the medical records of AKUH with a total of 27 patients receiving RT after chemotherapy, with 3 without a preceding chemo because of palliation. Data entry and analysis was done on SPSS (version 17.0).

Results

Thirty cases of nasopharyngeal tumors were registered, including primary, recurrent and metastatic disease. Two cases could not be categorized as NPC; one was a case of embryonal rhabdomyosarcoma in a male patient aged 13 years and the other a case of diffuse large B-cell lymphoma in a female patient aged 61 years. These 2 cases were not included in the analyses for NPC.

There were 20 (71%) males and 8 (29%) females, the male: female ratio being 2.5. Two (10.0%) male and 5

Table 1. Distribution of Cases by Ethnicity and Gender

Ethnicity	Male	Female
	# (%)	# (%)
Sindhi	4 (20.0)	3 (37.5)
Punjabi	4 (20.8)	-
Pushtuns	4 (2.0)	-
Baluch	-	1 (12.5)
Mohajir (Urdu speaking)	8 (40.1)	1 (12.5)
Mohajir (Gujrati speaking)	-	3 (37.5)

Table 2. Distribution of Nasopharyngeal Cancers according to UICC/AJCC TNM Staging

Stage	Stage Grouping	Male n (%)	Female n (%)
Stage 0	Tis, N0, M0	-	-
Stage I	T1, N0, M0	-	-
Stage II	T2,N0,M0 or T1/T2,N1,M0	5 (25.0)	-
Stage III	T3,N0-N2,M0 or T1/T2,N2, M0	1 (5.0)	2 (25.0)
Stage IVA	T4,N0-N2, M0	9 (45.0)	3
Stage IVB	Any T,N3,M0	3 (15.0)	2 (25.0)
Stage IVC	Any T, any N, M1	2 (10.0)	1

T, primary; N, regional lymph nodes; M, metastasis; is-in situ

(62.5%) female cases were observed in adolescents i.e. those below 20 years of age. The mean age of the male patients was 43.7 years (95%CI 34.3, 53.1; SD±20.1; range 70 (15-85) years). Females presented earlier, with a mean age of 30.3 years (95%CI 15.3, 45.2; SD±17.9; range 44 (11-55) years). The highest number of cases amongst males was observed in Urdu speaking mohajirs,

Table 3. Radiotherapy Induced Reactions

Skin Reactions		Male n (%)	Female n (%)
Group 0	No change above base-line	2 (10.0)	1 (10.0)
Group 1	Follicular, faint/dull erythema, epilation, dry desquamation, decreased sweating	13 (65.0)	3 (37.5)
Group 2	Tender or bright erythema, patchy moist desquamation with moderate edema	4 (20.0)	2 (25.0)
Group 3	Confluent, moist desquamation other than skin folds with pitting edema	1 (5.0)	2 (25.0)
Salivary gland reactions			
Group 0	No change above base-line	2 (10.0)	1 (12.5)
Group 1	Mild mouth dryness, slightly thickened saliva, altered taste such as metallic taste	13 (65.0)	4 (50.0)
Grade 2	Moderate to complete dryness, thick, sticky saliva and markedly altered taste	5 (25.0)	3 (37.5)
Mucosal reactions			
Group 0	No change above base-line	2 (10.0)	1 (5.0)
Group 1	Mild pain not requiring analgesics	7 (35.0)	2 (10.0)
Group 2	Patchy mucositis with inflammatory sero-sanguinous discharge with moderate pain requiring analgesics	6 (30.0)	2 (10.0)
Group 3	Confluent fibrinous mucositis with severe pain requiring narcotics	4 (20.0)	3 (15.0)
Group 4	Ulceration, hemorrhage or necrosis	1 (5.0)	-
Pharyngeal & Esophageal reactions			
Group 0	No change above base-line	2 (10.0)	1 (12.5)
Group 1	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	12 (60.0)	4 (50.0)
Group 2	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	6 (30.0)	3 (37.5)
Laryngeal reactions			
Group 0	No change above base-line	2 (10.0)	1 (12.5)
Group 1	Mild or intermittent hoarseness/ cough, not requiring antitussive; mucosal erythema	17 (85.0)	6 (75.0)
Group 2	Persistent hoarseness, able to vocalize; referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic or cough requiring antitussive	1 (5.0)	-
Group 3	Whispered speech throat pain or referred ear pain requiring narcotic/cough requiring antitussive	-	1 (12.5)

Table 4. Distribution of Cases by Stage of Nasopharyngeal Carcinoma at Presentation and Radiation Phases

Stage	2	3	4a	4b	4c	Total
Phase 1	-	-	-	-	2	2
Phase 1+2	1	-	1	1	-	3
Phase 1+2+3	2	3	6	4	-	15
Phase 1+2+3+4	2	-	5	-	-	7
Total	5	3	12	5	2	27

i.e. those of Indian descent, whereas in females an equally high number of cases were observed in the Sindhi and Gujrati speaking ethnicities (Table 1).

Our review included one patient who presented with nasal discharge and epistaxis because of local invasion, one with decreased hearing and tinnitus caused by the postero-lateral extension of the tumor into the paranasopharyngeal space, leading to the Eustachian tube dysfunction. There were two patients with unilateral proptosis because of orbital extension of the tumor, and one with 3rd, 6th, 7th and 9th cranial nerve palsies because of involvement of the base of skull.

Nodal involvement was seen in 16 (80.0%) male and 7 (87.5%) female patients. Cranial involvement was seen in 6 (30.0%) male and 2 (25.0%) female patients at the time of diagnosis. Almost all patients presented at an advanced stage (Table 2). Eighteen (90.0%) male and all female patients received chemotherapy. Electrons or photons were used for 16 (80%) male and 7 (87.5%) female patients.

Nasogastric tube was required for feeding in 2 (10.0%) male and 2 (25.0%) female patients; gastrostomy was needed for 1 (5.0%) male patient. Seventeen (85.0%) male and 6 (75.0%) female patients did not require intervention for feeding. Radiotherapy (RT) induced skin, salivary gland, mucosal, pharyngeal, esophageal and laryngeal reactions were observed in 90% of the patients (Table 3).

Patients were treated with variable doses in different phases, from phase I to IV. Phase I patients with palliative treatment and a 12 year old child with embryonal rhabdomyosarcoma who was treated as per international pediatric protocol. The doses delivered ranged between 2000cGy to 7400cGy, the lower ones being given for palliation only. Once the spinal cord tolerance was reached, electron boost fields were used in order to treat the posterior neck (Table 4).

Discussion

Pakistan is considered a moderate to high risk region for nasopharyngeal cancers in both genders. The reported rates of NPC from Karachi are ASRs 1.3 per 100,000 in men and 0.9 per 100,000 in women (Bhurgri et al., 2000). NPC shows a distinct racial and geographical distribution, being rare in most parts of the world. Globocan 2008 grades the ASRs per 100,000 of NPC into 5 categories, which in women are <0.0, <0.2, <0.3, <0.6 and <4.5. In men these ASRs per 100,000 are <0.2, <0.5, <0.8, <1.4 and <11.5 (Ferlay et al., 2010).

During the last several decades, the highest incidences were reported from Southern China (native and foreign-born Chinese), South East Asia (Thailand, Philippine, Viet

Nam), North Africa (Algeria and Morocco) and the Arctic Region (Canada and Alaska). The highest incidence was observed in Hong Kong (Parkin DM et al., 2001). It is gradually diminishing.

NPC risk diminishes in successive generations, and migration from a high to low incidence zone does not affect the disease risk (Chan et al., 2005). This was also evident from the studies which looked into the incidence of NPC in Chinese immigrants to Asia and North America (Buell, 1974; Dickson and Flores, 1985). This observation suggests a heterogeneous pathogenesis for NPC, a probable interplay of genetic susceptibility, Epstein-Barr virus (EBV) infection and environmental factors (dietary and non-dietary) (Chan et al., 2005). Other environmental risk factors are cigarette smoking, occupational exposure to smoke and chemicals and radiation (Ning et al., 1990; Yu et al., 1990; Armstrong et al., 2000; Chen and Hsu, 2000; Yuan et al., 2000; Hildesheim et al., 2001).

The mean age at diagnosis was 43.7 and 30.3 years in males and females. NPC was observed in adolescents of both genders. Females presented a decade earlier, though globally the age distribution is similar in males and females (Parkin et al., 2002). We thus have a relatively younger age group of NPC, especially in females, as compared with the high risk populations of South-East Asia, where NPC incidence rises after the age of 30 years and peaks at 40-60 years (Parkin et al., 2001, Parkin et al., 2002). The risk factors in Pakistan may thus be interplay of genetic and viral factors of undetermined nature or previously known risk factors effecting individuals at an earlier age. Considering the younger age of females involved, the indoor cooking methods need to be further studied.

NPC accounts for approximately 1% of all childhood malignancies. Whereas almost all adult nasopharyngeal malignancies are carcinomas, only 35-50% are carcinomas in children. In the pediatric population, additional nasopharyngeal malignancies include rhabdomyosarcoma or lymphomas. Of the two childhood cases seen by us, both observed in females, one was a histologically proven NPC, but the other was an embryonal rhabdomyosarcoma.

Nodal involvement was seen in 16 (80.0%) male and 7 (87.5%) female patients. Cranial involvement was seen in 6 (30.0%) male and 2 (25.0%) female patients at the time of diagnosis. This is a global characteristic of NPC, considered notorious for its loco-regional infiltration and early lymphatic spread (Sham et al., 1990).

Two-thirds of our cases presented with a stage IV disease (Table 2). Even in the best of health-care centres, diagnosing NPC at an early stage is usually difficult because of obscure symptomatology. Therefore, testing the Epstein Bar virus DNA in high risk groups has now become a major screening tool for early diagnosis, along with a combination of a thorough clinical exam, a biopsy and specific imaging which would definitely be confirmatory in studying the extent of disease.

Management of NPC depends upon the stage at diagnosis. The extent of the primary tumor can be seen precisely with cross-sectional imaging. Even though, positron emission tomography (PET) scanning is not yet widely available to us, but its role in detection of distant metastasis has been established (Nakamoto et al., 2003).

PET is more sensitive than computerized tomography (CT) and Magnetic resonance imaging (MRI) at detecting residual and recurrent tumors in the nasopharynx though each of the other diagnostic modalities have specific sensitivities. MRI is the imaging of choice with loco-regional disease, whilst CT depicts cortical bone erosion (Chong and Fan, 1996; Ng et al., 1997; Yen et al., 2003).

Pakistan is still in the infancy of technological development, MRI inspite of its limitations in evaluation of bone details, where CT still outweighs MRI in tumors involving base of skull (Olmí et al., 1995) is preferably being used, rather than computed tomography (CT) for a better resolution and distinction of the tumor from surrounding soft tissue (particularly intracranial extension) and metastasis to the retropharyngeal cervical lymph nodes (Dillon et al., 1984), and bone marrow infiltration (Cheng et al., 1998).

Radiotherapy with or without chemotherapy is the mainstay of treatment, depending upon the extent and stage of disease, however intensity modulated radiotherapy (IMRT) with or without chemotherapy have improved the disease control by precision in targeting the tumor volumes and minimizing long term side effects (Wei and Kwong, 2010) by sparing adjacent normal tissues.

Dependent upon the location and stage of presentation, patients with nasopharyngeal tumors may present in particular with nasal, otologic and ocular symptoms, or neck masses with or without general symptoms of malignancy in certain advanced cases. Even though, headaches, facial pain and numbness have also been reported, but all these are usually sequelae to cranial nerve involvement and localized tissue compressions because of tumor extension.

In conclusions, in the presence of clinician based expertise and technical constraints in Pakistan, nasopharyngeal tumors are still being treated optimally with the need of creating a better awareness in public for early disease detection, and that among researchers to study the overall survival.

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