Clinicopathologic Characterization of Nasopharyngeal Carcinoma Seen in the Radiotherapy and Oncology Department, Ahmadu Bello University Teaching Hospital, Zaria, Nigeria: 2006-2010

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ABSTRACT

Aims and Objective: To evaluate the clinical and pathological characteristics of nasopharyngeal carcinoma (NPC) patients seen in the Radiotherapy and Oncology department, Ahmadu Bello University Teaching Hospital, Nigeria. **Materials and Methods:** Between January 2006 and December 2010, 45 patients with histologically confirmed NPC were seen and evaluated irrespective of age, co-morbidity and performance status. Patients' folders were reviewed retrospectively with a structured pro forma. Data were analyzed using Epi Info software and results presented in simple tables. **Results:** A total of 45 patients had NPC accounting for 2%. The mean age was 42 years (range 15-75 years). The sex ratio was M:F = 2.2:1. 21 of the patients were from North-West geopolitical zone. Hausa-Fulani was the predominant ethnic group in 23 patients. At presentation, 41 had neck mass followed by nasal blockage in 34, cranial nerve deficits in 27 and epistaxis in 25 (55.6%) patients. The commonest cranial nerves affected were vestibulocochlear 17, followed by glossopharyngeal 14. Only 14 patients presented within 12 months of onset of symptoms with a range of 3-60 months. The commonest histologic type seen was WHO-2 (Non-keratinizing Squamous Cell Carcinoma) in 28 patients. Locally advanced disease (IVA and IVB) seen in 25 patients and metastatic disease (IVC) seen in 13 patients. The site of metastases was the bones seen in 6 patients followed by lungs in 5 patients. Only 2 patients were positive for HIV antibodies. 38 patients were treated with chemotherapy and 18 received radiation therapy. **Conclusion:** Nasopharyngeal cancer is commoner in males. Neck mass with nasal and auditory symptoms were the commonest symptoms. More than half of the patients had cranial nerve deficits at presentation. WHO-2 is the commonest histology and locally advanced and metastatic disease is the commonest stage at presentation.

Key words: Clinicopathologic characterization; WHO classification; nasopharyngeal cancer

Introduction

Nasopharyngeal carcinoma (NPC) is common in southern China, Southeast Asia, the Arctic, the Middle East, and North Africa, where it is endemic.[1,2] This distinctive racial, ethnic, and geographical predisposition to NPC implies that both genetic susceptibility and environmental factors contribute to the development of the tumor.[2] NPC is an Epstein–Barr virus (EBV)-associated tumor, and this has been demonstrated by serologic studies and by the detection of the viral genome in tumor samples.[3-5] Diet (salt-cured fish and meat), tobacco, and alcohol are other probable risk factors in a minority of the cases.[6] NPC is relatively uncommon in Nigeria.

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Carcinoma of the nasopharynx frequently arises from the lateral wall, with predilection for the fossa of Rosenmuller and the roof of the nasopharynx. The tumor may involve the mucosa or grow predominantly in the submucosa, invading adjacent tissues including the nasal cavity, oropharynx, and base of skull. The lateral wall is formed by the pharyngeal fascia which offers relatively little resistance to tumor spread. Deep to the fascia is the

parapharyngeal space containing the lateral retropharyngeal lymph nodes (nodes of Rouvière), cranial nerves IX–XII, carotid artery, and internal jugular vein.[7] Direct extension or nodal involvement can lead to IX–XII cranial nerve palsies (retroparotidian syndrome).[8] The tumor can grow out of the parapharyngeal space superiorly into the middle cranial fossa, and anteriorly into the pterygopalatine fossa and inferior orbital fissure toward the orbit. This anatomy provides relatively little barrier to local invasion into the cavernous sinus, which contains cranial nerves III–VI and the internal carotid artery, and results in deficits of cranial nerves III-VI (retrosphenoidal syndrome).[8] The tumor may extend into the posterior or medial walls of the maxillary antrum and ethmoidal sinus. The symptoms and signs of NPC are related to tumor growth, locoregional infiltration, nodal enlargement, and distant metastasis.[7,8]

Because NPC is relatively uncommon in this environment, misdiagnosis along with patient neglect commonly contributes to an advanced stage at presentation and resultant poor survival. Many patients present with cervical nodal metastasis as the first sign of disease, and a thorough examination must be performed to identify the primary site, and NPC should be included in the differentials. Lee *et al*. showed further that there was a significant association between the duration of symptoms before diagnosis and the presenting stage, which in turn affected survival.[9,10] Increased awareness by both the public and the primary care physicians is necessary to minimize delay in diagnosis. Radiography is a necessary component of the evaluation. It is now standard practice to order a computed tomography (CT) scan of the head and neck for any patient with suspected NPC. Not only does this examination help to evaluate the location and size of the primary tumor, but also any possible metastasis.[11] Survival decreases as cervical lymph node involvement progresses from the upper to middle and lower nodes. Bilateral cervical lymph node involvement, histology type, tumor stage, and the presence of keratin are adverse prognostic features for local control and overall survival.[9,10]

The classification of the World Health Organization (WHO) divides nasopharyngeal carcinoma into three types, namely, WHO-1, keratinizing squamous cell carcinoma; WHO-2, nonkeratinizing squamous carcinoma; and WHO-3, undifferentiated carcinoma and lymphoepithelioma.[1,12] WHO-2 and WHO-3 are closely associated with EBV infection; high levels of EBV antibodies are found in these subtypes and correlate with stage and response to treatment.[3] Other malignancies occurring in the nasopharynx include lymphoma, plasmacytomas, melanomas, and in the pediatric population, juvenile angiofibromas and rhabdomyosarcomas.[12]

Because the nasopharynx is immediately adjacent to the base of the skull, surgical resection with an acceptable tumor-free margin is often impossible. Radiation therapy has been the choice of treatment for early carcinoma of the nasopharynx.[13] Rarely, surgery has been performed for the treatment of neck node metastasis and salvage treatment for recurrent NPC. Neoadjuvant or adjuvant chemotherapy and radiotherapy have been used in more extensive tumors. Recent reports suggest improved tumor control and disease-free survival when chemotherapy is combined with irradiation.[14]

One of the major limitations in this study was the poor and deficient cancer registry in the hospital which made it difficult to ascertain the total number of NPCs seen in the hospital. Secondly, despite its effectiveness, radiotherapy remains underused in this environment in the management of nasopharyngeal cancer due to nonreferral. Thirdly, the number of patients in this study does not cover all the patients with NPC in this hospital and its environs because patients are managed by other specialists within and outside the hospital without referral to the radiotherapy and oncology department. Currently, there is little published data on NPC, absence of a multidisciplinary tumor board, and no established guidelines and protocols for managing NPC, contrary to what is available in developed countries. The aim of this study is to evaluate the clinicopathological characteristics of NPC seen in the radiation therapy department of Ahmadu Bello University Teaching Hospital (ABUTH).

Materials and Methods

Between January 2006 and December 2010, a total of 45 new patients with NPC were seen and evaluated. Only patients with histologic confirmation of NPC were included in the study irrespective of age, comorbidity, and performance status. Patients' folders were reviewed retrospectively with a structured pro forma. Information retrieved from patients' folders included age, histology type according to the WHO, sex, ethnicity, symptoms and signs at presentation, duration of symptoms, HIV status, stage of disease, sites of metastases, types of treatment received, and follow-up status. Histology results from outside ABUTH were reviewed by the hospital pathologist for harmonization so as to fit into the WHO classification. All positive cases with histologic reports of biopsies obtained from the nasopharynx or cervical lymph nodes were included. Tumors evident in the nasopharynx were identified either clinically or radiologically. Metastatic sites were confirmed using relevant investigation (CT scan, chest X-rays, ultrasound of abdomen, bone scan, skeletal X-rays). No metastatic site was biopsied for histologic confirmation. Clinical staging was based on findings at examination under anesthesia (EUA) and biopsy, general examination, and results of investigations at presentation using Tumor, node, metastasis (TNM) classification of Union for International Cancer Control (UICC) 1997. Exclusion criteria included all cases diagnosed as lymphoma, sarcoma, or any other histologic type outside the WHO classification for NPC. Two patients with non-Hodgkin's lymphoma and Kaposi sarcoma of nasopharynx were excluded. Tumors arising from

neighboring sites like posterior nasal space, nostrils, sinuses, and extending to the nasopharynx were also excluded. Data were analyzed using Epi Info software 3.4.1, 2007 edition, and results presented in the form of simple tables.

Results

A total of 2,212 new patients were seen at the radiotherapy and oncology department during the study period of whom 45 patients had NPC accounting for 2% of the patients. The mean age was 42 years, with a median age of 40 years (range: 15-75 years). Twenty-nine (64.5%) patients were at least 30 years old at presentation. Table 1 shows patients' characteristics. The male-to-female ratio was 2.2:1, with males dominating. Twenty-one (46.7%) of the patients were from the North-West geopolitical zone where the institution is located and another 15 (33.3%) patients from the North-East and North-Central zones. Only nine (20%) patients were from the southern part of the country. Hausa-Fulani was the predominant ethnic group seen, accounting for 23 patients (51.1%), followed by the Ibo and Yoruba ethnic groups with five (11.1%) and four (8.9%) patients, respectively. Other minority ethnic groups were seen in 13 (29%) patients. At presentation, 41 patients (91.1%) had a neck mass, followed by nasal blockage in 34 (75.6%), cranial nerve deficits in 27 (60%), and epistaxis in 25 (55.6%) patients. Headache and deafness were seen in 23 (51.1%) patients each. The commonest cranial nerves affected were vestibulocochlear: 17 (37.8%), followed by glossopharyngeal: 14 (31.1%), vagus: 10 (22.2%), and hypoglossal: 8 (17.8%). Tables 2 and 3 show the symptoms and signs at presentation. Only 14 (31.1%) patients presented within 12 months of onset of symptoms; the remaining presented after 12 months with a mean of 18 months, median duration of 12 months, and range of 3-60 months. The commonest histologic type seen was WHO-2 (nonkeratinizing squamous cell carcinoma) in 28 (62.2%) patients, followed by WHO-3 (undifferentiated and lymphoepithelioma) in 11 (24.4%) and WHO-1 (keratinizing squamous cell carcinoma) in six (13.3%) patients. All the three patients aged 20 years and below had WHO-3 histologic type. Early-stage disease (stages I, IIA, IIB, III) was seen in seven (15.6%) patients, locally advanced disease (IVA and IVB) in 25 (55.6%), and metastatic disease (IVC) was seen in 13 (28.9%) patients. The site of metastasis was the bones seen in six (13.3%) patients, followed by lungs in five (11.1%) patients. Multiple sites of metastases (bone and liver) were seen in one patient only. Only two (4.4%) patients were positive for HIV antibodies; 38 (84.4%) were negative and the status was unknown for five (11.1%) patients. Thirty-eight (75.6%) patients were treated with chemotherapy and 18 (40%) received radiation therapy. Definitive treatment with chemotherapy or radiation therapy was not possible for three (6.7%) patients. At the time of data analysis, 15 (33.3%) patients were alive, 25 (55.6%) were lost to follow-up, and five (11.1%) were confirmed dead.

Table 1: Shows the patients characteristics

Characteristics	Number of patients (%)
Total patients	45
Age group	
10 – 20	3 (6.7)
21 – 30	13 (28.9)
31 – 40	7 (15.6)
41 – 50	7 (15.6)
51 – 60	9 (20.0)
61 – 70	5 (11.1)
> 70	1 (2.2)
Gender	
Male	31 (68.9)
Female	14 (31.1)
Ethnic group	
Hausa-Fulani	23 (51.1)
Ibo	5 (11.1)
Yoruba	4 (8.9)
Others	13 (29)
Histology	
WHO-1	6 (13.3)
WHO-2	28 (62.2)
WHO-3	11 (24.4)
Cervical lymphadenopathy	
Positive	41 (91.1)
Negative	4 (8.9)
Cranial nerve	
Deficit	24 (53.3)
Intact	21 (46.7)
HIV Status	
Negative	38 (84.4)
Positive	2 (4.4)
Unknown	5 (11.1)
Stage	
I, IIA, IIB, III	7 (15.6)
IVA	14 (31.1)
IVB	11 (24.4)
IVC	13 (28.9)
Site of metastasis	
Bones	6 (13.3)
Lungs	5 (11.1)
Liver	2 (4.4)
Brain	1 (2.2)
Treatment received	
Chemotherapy	34 (75.6)
Radiotherapy	18 (40)
Palliative	3 (6.7)
Follow up status	
Alive	15 (33.3)
Lost	25 (55.6)
Confirmed dead	5 (11.1)

WHO – World health organization

Discussion

The study shows that NPC accounted for 2% of the total

Table 2: Patients' symptoms and signs at presentation

Symptoms	Number of patients (%)
Neck mass	41 (91.1)
Nasal blockage	34 (75.6)
Cranial nerve deficits	27 (60)
Epistaxis	25 (55.6)
Headache	23 (51.1)
Tinnitus	23 (51.1)
Nasal discharge	22 (48.9)
Deafness & partial deafness	21 (46.7)
Hoarseness of voice	19 (42.2)
Difficulty in breathing	17 (37.8)
Weight loss	12 (26.7)
Pain in neck mass	11 (24.4)
Loss of taste	10 (22.2)
Pallor	10 (22.2)
Cough	9 (20)
Trismus	9 (20)
Difficulty in swallowing	9 (20)
Double vision	7 (15.6)
Halitosis	7 (15.6)
Tooth ache	6 (13.3)
Proptosis	6 (13.3)
Bone pain	5 (11.1)
Deviation of tongue	4 (8.9)
Blindness	4 (8.9)
Loss of smell sensation	4 (8.9)
Ear discharge	3 (6.7)
Sore throat	3 (6.7)
Ulceration of neck mass	1 (2.2)

Table 3: Cranial nerves involved at presentation

Cranial nerve deficits*	Number of patients (%)
Olfactory	7 (15.6)
Optic	8 (17.8)
Oculomotor	4 (8.9)
Trochlear	2 (4.4)
Trigeminal	5 (11.1)
Abducens	4 (8.9)
Facial	7 (15.6)
Vestibulocochlear	17 (37.8)
Glossopharyngeal	14 (31.1)
Vagus	10 (22.2)
Spinal accessory	1 (2.2)
Hypoglossal	8 (17.8)

*Multiple cranial nerves deficits were seen in 23 out of 27 patients

patients seen during the study period. This is low when compared with the population in endemic areas like southern China and the Chinese population in the United States where it accounts for 5% of all new cancers seen annually.[7,8] Despite their relatively low numbers in clinical practice, research and management of head and neck cancers continue to receive significant emphasis owing to the rich anatomic and functional complexity of this body site, which is critical to issues of self-esteem, communication, and social integration.[12] Table 1 shows the characteristics of patients with NPC.

The age range was 15-75 years with a mean age of 42 years. There were two peak modal ages at 21-30 years and 51-60 years, and these are consistent with the literature.[2,12] The median age (40 years) of cases in this study was similar to that reported from South China and the Middle East but it is 5-10 years lower than that reported from the United States.[4] In this study, 67% (30) patients were below 50 years at presentation which is similar to more than 60% of the patients diagnosed before the age of 50 years in Southeast Asia.[10]

The predominance of males in the study with a male-to-female ratio of 2.2:1 is similar to the sex ratio seen in nonendemic countries with NPC and in publications from other centers in Nigeria.[15-17] The male-to-female ratio was slightly lower than that reported from the Middle East, the Southeast Asian region, and Western series with male-to-female ratios of 2.7:1, 3.0:1, and 2.5:1, respectively.[18-20]

The institution is located in the North-West geopolitical zone and the predominant ethnic group is the Hausa-Fulani people. Therefore, it is not surprising that more than half of the patients are Hausa-Fulani. The result does not imply that NPC is rare in other ethnic groups. Publications from other health institutions within the country showed that NPC is seen in all geopolitical zones and the pattern of presentation is not different.[15-17]

It is a pathetic situation to have a duration of 3-60 months for the patients to present at the hospital after the onset of symptoms. The mean was 18 months compared to less than two months in the developed and endemic countries.[20] The late presentation in the study environment is often related to the use of herbal and traditional medications, ignorance, wrong beliefs, poverty, and low index of suspicion. In some instances, it is due to delayed referral from general practitioners, delay in diagnosis, or patient's delay due to repeated courses of antibiotics for otitis media or sore throat.

Table 2 shows the symptoms and signs at presentation. Neck mass was the predominant symptom followed by nasal symptoms (nasal blockage, discharge, epistaxis), followed by aural symptoms (tinnitus, deafness). Ocular symptoms which are very common in Asian and western countries was less common in this study.[19,20] This difference may be an indication of the site of onset of the nasopharyngeal cancer in the nasopharynx and the pattern of spread and infiltration. In advanced lesions, cranial nerve abnormalities may be present. Similarly, the frequency of cranial nerve involvement and the pattern of cranial nerve deficit are different from the pattern seen in the literature. Sixty percent of the patients presented with cranial nerve deficiency diagnosed clinically

compared to a lower frequency of 3-26% at presentation in the endemic areas.[13,20] This implies that the frequency of cranial nerve deficits in the study environment is likely to be higher if diagnostic instruments like CT scan and magnetic resonance imaging (MRI) are done in all patients. Although in the literature, the cranial nerves commonly affected are cranial nerves III, IV, V, and VI,[13] in this study, the pattern was different where the predominant cranial nerve deficits were in VIII, IX, X, and XII [Table 3]. The pattern of cranial nerves seen may also support the origin of nasopharyngeal cancer in the nasopharynx and the spread through the foramen in the base of the skull.[21]

The pattern of histologic findings in the study is not different from the histologic pattern in endemic countries especially of that in China where EBV has been implicated.[3] Even though EBV was never tested for in the study population, the patients may have been exposed to EBV. This may also support the pattern of presentation in which most patients presented with locally advanced and metastatic disease. Distant metastasis is uncommon with WHO-1, where the main problem is poor locoregional control and high incidence of recurrence/relapse.[22] The types of histology in this study were predominantly WHO-2 and WHO-3 which is similar to reports from other endemic areas, for example, the Chinese born in Hong Kong and Taiwan most often present with undifferentiated carcinoma, whereas non-Chinese Americans most often present with keratinizing squamous carcinoma.[12,23] High-risk populations have a larger proportion of WHO-3 type. However, WHO-2 and WHO-3 were not common in nonendemic areas.[12] The implication of the result from this study suggests the pattern to be similar to endemic areas even though the number of patients is small. There may be a high prevalence of EBV in this environment.

NPC has a high metastatic potential for regional nodes and distant sites. Occult nodal metastasis is present in more than 60% of the patients with nonpalpable cervical lymph nodes at presentation.[13] WHO-1 has the greatest propensity for uncontrolled local tumor growth and the lowest propensity for distant metastatic spread (60% clinically positive nodes) compared with WHO-2 and WHO-3 cancers (80 to 90% clinically positive nodes).[7,8] Even though WHO-1 cancer is associated with a lower incidence of distant metastases than WHO-2 and WHO-3, its prognosis is worse because of a higher incidence of deaths from uncontrolled primary tumors and nodal metastases.[22,24] More than 90% of the patients studied presented with enlarged cervical lymphadenopathy, which is similar to the pattern in the literature. Similarly, late presentation in the environment contributed to bulky disease and extensive nodal involvement at presentation. Late presentation was a common denominator in the study environment as shown from previous studies.[25]

Early-stage disease (I, IIA, IIB, and III) was seen only in seven (15.6%) patients. Head and neck cancers are expected to present early due to associated disfiguring, symptoms associated with speech and swallowing, and location, but patients usually delay their presentation due to the treatment of recurrent otitis media, sore throat, and tuberculosis which are the common differential diagnoses.[7,8] The belief that cancer is caused by evil spirits and cannot be treated with orthodox treatments was a confounding factor in the study environment. Most patients usually present in the hospital after failure of herbal, traditional, and spiritual treatments. At this point, the disease has often progressed significantly with distant metastasis. A total of 84.5% of the patients presented with locally advanced and metastatic disease at the time of presentation. This is a different pattern from that seen in endemic areas with low metastatic stage at presentation due to the high index of suspicion and regular screening for NPC among the population.[20] The late pattern is not different from the studies in other parts of Nigeria and Africa.[15-18] The site of metastasis in nasopharyngeal cancer seen in the study environment is similar to that in the literature and in endemic environments, with bone metastasis being the commonest, closely followed by lung and liver metastases.[7,23] The unusual finding in this study was the high frequency of distant metastases at presentation. In China and other endemic areas, distant metastases are commonly seen later in the course of the disease or as part of the relapse after successful initial treatment and predominantly involving bones, lungs, and liver.[9] In this study, there is high incidence of distant metastasis and cervical lymph node involvement.

Only two patients were positive for HIV antibodies. Among HIV patients with head and neck cancers, there is a high incidence of conjunctival and oral cavity cancers but not nasopharyngeal cancers.[26] Other causes of immunosuppression predispose individuals to an increased risk of some head and neck squamous cell carcinomas especially carcinomas of the lip in renal and cardiothoracic transplant recipients.[27] HIV-related malignancies generally are more aggressive, having a shorter duration of symptoms, advanced stage at presentation, and poor response to conventional treatments with decreased patient survival and metastasis to unusual sites.[28]

Due to the stage of disease at presentation, 75.6% of the patients received neoadjuvant or induction chemotherapy prior to the use of radiotherapy. The chemotherapy was used to downstage the disease in those with locally advanced disease.[29] Concomitant chemoradiation was not used due to long waiting time on the radiation therapy machine. Chemotherapy followed by radiotherapy in sequence was the mode of treatment. The choice of chemotherapy was cisplatin and fluorouracil (5-FU) for those with financial constraints and poor performance status, and BPF (BPF: Bleomycin, cisplatin, and 5-FU) for those who could afford it and had a good performance status. A total of six cycles of chemotherapy was given followed by radiation therapy. Bleomycin was stopped after four cycles or doses were

modified to avoid pulmonary toxicity. The performance status was very poor in three patients and only palliation was done. Recently, a significant impact on long-term survival has been reported for NPC. Neoadjuvant, adjuvant chemotherapy, and concomitant (usually cisplatin) chemoradiation have all been reported to improve local control and overall survival rates. The relative chemosensitivity of NPC and high rate of distant metastases makes neoadjuvant treatment theoretically attractive, but there is no proof so far of benefit from clinical trials in early stages.[29,30]

Radiotherapy was given to 18 patients mostly after completion of chemotherapy. The volume irradiated included the nasopharynx, adjacent parapharyngeal tissues with a 1 to 2 cm margin, and all of the cervical and supraclavicular lymphatics. Standard fields include the posterior ethmoid cells, posterior one-third of the maxillary antrum, and the nasal cavity, but not the orbit (unless warranted). Radiation has been part of the standard treatment, with good results and is often combined with chemotherapy in advanced disease (stage IIb, III, and IV).[31] Surgery is usually not recommended because of anatomic considerations and the pattern of spread of the cancer via the retropharyngeal lymphatics. The role of surgery is confined to neck dissections for persistent or recurrent lymphadenopathy, or rarely, to salvage recurrent nasopharyngeal disease.[12]

Follow-up is a major challenge in the study environment. Most patients with slight improvement in symptoms abandon hospital treatment and follow-up; 55.6% of the patients were lost to follow-up and only 33.3% are alive and attending follow-up. Five patients were confirmed dead.

Conclusion

Nasopharyngeal cancer was commoner in males. Neck mass with nasal and auditory symptoms were the commonest symptoms. More than half of the patients had cranial nerve deficits at presentation and cranial nerves VIII, IX, X and XII were the commonest. WHO-2 was the commonest histology type seen and locally advanced and metastatic disease was the commonest stage at presentation. There is a need for further studies to characterize NPC with respect to the presence of EBV in patients with NPC. Loss to follow-up was a problem in the study environment.

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