

## Characteristics of Nasopharyngeal Cancer in Jos, Nigeria.

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### Abstract

**Background:** Nasopharyngeal cancer (NPC) has been reported by scholars as the most lethal and emotionally traumatic malignancy globally, with the outlook even poorer in African Natives from late presentation. We therefore sought to study the characteristics of NPCs in our environment.

**Method:** We retrospectively evaluated all histo-pathologically confirmed cases of NPC managed between May 1, 2009-April 30, 2017 from retrieved case files using the ICD-10 version 10 standard codes at the Jos University Teaching Hospital.

**Results:** Thirty cases, accounting for 0.2% of new Ear, Nose and Throat(ENT) outpatients were analysed. This represents the commonest Head & Neck Cancer and the 3rd general body squamous cancer with 9.3%. Age range was 18years-69years with a bimodal distribution at the 3<sup>rd</sup> and 7<sup>th</sup> decades of life. Alcohol consumption/Cigarette smoking was recorded in 73.3% with a maximum pack years of 31.5years. Predominant feature was neck masses in 66.7% where 65.0% had

nodes>6cm, 76.7% had T4 tumours and 56.7% anaemia while 76.7% presented late. The WHO type III predominated with 60.0%. Definitive therapy was administered in 16.7% with a dismal follow-up visit as 70.0% never returned. Mortality was difficult to ascertain as all were referred.

**Conclusion:** NPC remains infrequent in Africa with WHO type III the predominant form. It is associated with late presentation, advanced disease, inadequate cancer care infrastructure and poor access to chemo-radiation. Early detection strategy using EBV biomarkers is a priority to prevent the misery associated with NPC.

**Key Words;** Nasopharyngeal cancer, Characteristics, advanced disease, late presentation

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### Introduction

Nasopharyngeal carcinoma (NPC) is a highly invasive tumour which is universally associated with Epstein-Barr virus (EBV). NPC conveys a grave outcome as 75% present with advanced disease with a 2-year survival of 20%-30% and 0% in those without and with distant metastasis, respectively.<sup>1,2</sup> The Regaud type of NPC (WHO type I) is associated with HPV 11,16 and occur sporadically while the Schmincke type(WHO types II &III) is associated with EBV.<sup>3</sup> Recently, a proposed classification divided NPC into two namely; squamous cell carcinomas (SCCs) and undifferentiated carcinomas of the nasopharyngeal type (UCNTs) that has been shown to have a prognostic value. UCNTs have a higher local tumour control rate with therapy, and a high incidence of distant metastasis.<sup>4,6</sup>

NPC originates at the fossa of Rosenmuller with an

unbalanced geographical distribution as in endemic regions like southern China/ South East Asia, WHO type III is the predominant form.<sup>7,8</sup> EBV-associated NPC has an increased tendency to metastasize to regional lymph nodes and distant sites.<sup>9,10</sup> The highly metastatic capability of NPC has been linked to the EBV latent membrane protein 1 (LMP1). LMP1 promotes metastasis through induction of Matrix metalloproteinase-9, vascular endothelial growth factor, fibroblast growth factor-2 and Mucin-1(MUC-1).<sup>11</sup> LMP1 has been shown to downregulate apoptosis, cell-cell adhesion and upregulate cell motility. This property plays an essential role in tumour metastasis by opposing cell adhesions.<sup>12,13</sup> Approximately 10% of patients present with metastatic NPC at initial diagnosis, 50-60% develop distant metastasis subsequently and an additional 10% develop metastatic failure after therapy: metastatic NPC is incurable.<sup>2,8,14</sup> Radical surgical resection is extremely difficult due to its deep-seated nature making chemo-radiation the only viable treatment options.<sup>15,16</sup>

EBV-encoded small RNAs (EBER)-hallmark of EBV infection, have been shown to trigger inflammation in NPC. This connection between inflammation and cancer has led to emerging interest in the prognostic value of inflammatory factors. Studies have revealed that the pre-treatment Neutrophil-lymphocyte ratio(NLR), Lymphocyte-Monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) in NPC may predict the disease-

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specific survival (DSS), distant metastasis free survival (DMFS) and the overall survival (OS). NLR has been found to correlate with TNM staging.<sup>12,13</sup> Therefore, vaccine development where the EBV surface glycoprotein-gp 350/220 had been targeted by WHO and screening for early detection using biomarkers are future targets.<sup>15-17</sup>

We therefore sought to evaluate the characteristics of NPC in our hospital.

### Method

We retrospectively studied all case files of histopathologically confirmed cases of NPC managed at Jos University Teaching Hospital (JUTH), Plateau State, Nigeria over an 8-year period (May 1, 2009-April 30, 2017) using the ICD-10 version 10 standard codes for retrieval and JUTH Cancer registry. Data were generated from biodata, Life-style, BMI, Clinical features, TNM staging, Investigation results [FBC, Serum Biochemistry, Chest X-Rays/Abdominal Ultrasonography, Fine needle aspiration cytology (FNAC), CT-Scan, Histopathologic Reports], WHO classification, Diagnosis, treatment, outcome and follow-up. Results were presented in figures and tables. Ethical Clearance was obtained from JUTH's Institutional Health Research Ethical Committee (IHREC).

### Results

Thirty cases, representing 0.2% of total new ENT outpatients (15,923) were analysed. This represents the commonest Head and Neck cancer (HNC) with 27.0% and the 3<sup>rd</sup> general body squamous cancer with 9.3% after Cervix and Skin. The Male: Female ratio was 1.7:1 with an age range of 18 years-69 years and a mean of 52 years  $\pm$  19 years. There was a bimodal age distribution with peaks in the 3<sup>rd</sup> and 7<sup>th</sup> decades of life (Fig 1). Sinonasal malignancies were the 2<sup>nd</sup> predominant HNC with 24.3% then Metastatic neck disease- the 3<sup>rd</sup> with 20.7%.

Self-referral occurred in 12(40.0%), 6 (20.0%) referred from Secondary Health Centres and 5

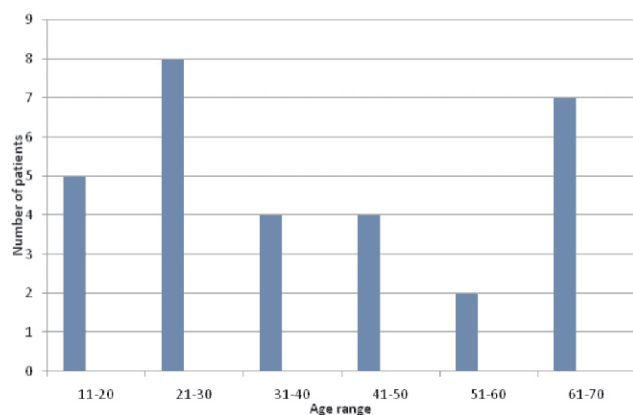


Fig 1: Age distribution (Years) of NPC

Table 1: Source of referral and Clinical presentation of NPC

Characteristic	Frequency	Percentage (%)
Source of referral		
Self	12	40.0
Secondary Health Centre	6	20.0
General Surgeons	5	16.3
General Practitioners	4	13.3
Ophthalmologists	2	06.7
NGO	1	03.3
Clinical Presentation		
Neck masses	20	66.7
Nasal blockage/epistaxis	15	50.0
Aural fullness /Hearing loss/Otorrhoea	13	43.3
Weight loss	11	36.7
Proptosis /diplopia	9	30.0
Palatal fistula	3	10.0

NGO: Non governmental organization

patients(18.7%) referred by the General Surgeons (Table 1). On life-style; 22 (73.3%) engaged in both alcohol consumption and cigarette smoking with pack years range of 2.3years to 31.5years, and a mean of 14.7 years  $\pm$  8.4 years. Cigarette smoking alone was present in 10 (33.3%) while alcohol consumption alone was present in 8 (26.7%), mainly males, for an average duration of 8.1 years  $\pm$  11.1 years. The mean age at smoking/alcohol consumption was 42.1years  $\pm$  20.2 years.

Neck masses predominated with 20(66.7%) where 13(65.0%) had N3 disease (Node>6cm) while the rest had N2 disease. Rhinologic and otologic symptoms occurred in 15(50.0%) and 13(43.3%) patients respectively. Of these patients, 23(76.7%) had T4 tumours while 7(23.3%) were T3. On haemogram, 17(56.7%) had anaemia. Severe weight loss was present in 11(36.7%). Neuro-ophthalmic features were present in 9(30.0%) while 10.0% of the patients had malignant palatal fistulas. (Table 1). Only 2 patients (6.7%) had HIV and 23 patients (76.7%) presented within 6-18months of onset of symptoms.

Diagnosis was both from clinical assessment, FNAC (metastatic neck disease confirmation) and histopathology with further classification into: WHO type II-40.0%, WHO type III-60.0%.

Chemo-radiation was administered on 5(16.7%) of which 4(13.3%) had radiotherapy alone with Cobalt-60 external beam therapy while one had combined Chemo-radiation using 5-FU, Cis-Platinum and radiotherapy. By implication, 25(83.3%) neither received radiotherapy and/or chemotherapy. Follow-up visits were poor as 21(70.0%) never returned, 4(13.3%) visited for 2 months while one patient for 6months and 4(13.3%) requested

for discharge on diagnosis.

Mortality was not ascertained as all were referred for definitive care elsewhere estimated at 239km away with no information on survival status.

### Discussion

Rarity of NPC in African natives had been reported<sup>18,19</sup> and similarly observed in this study accounting for 0.2% below the global prevalence of 0.7%.<sup>2</sup> However, the past four decades witnessed a slight rising incidence in Africa.<sup>3,20,21</sup> Our series confirmed this as NPC constituted the predominant HNC and the 3<sup>rd</sup> general body squamous cancer. In Africa, the previous rarity may have been from underdeveloped diagnostic technology with dearth of expertise as corroborated by da Lilly-Tariah et al<sup>22</sup>. This may explain the frequent self-referrals probably from poor outcome. The male gender was afflicted twice as common as widely reported and are said to be heavily involved in cigarette smoking and alcohol consumption as seen in this study; which have been found to confer a fifteen times increase in cancer risk and may explain the poor outcome in them.<sup>22-24</sup> An estimated 100 million tobacco-associated deaths occurred in the 20<sup>th</sup> century with 70% from the high income countries.<sup>22</sup> However, this trend is expected to reverse with the low income countries projected to lead the estimated 1 billion tobacco-associated deaths in the 21<sup>st</sup> century from unhealthy life-style which starts in early life.<sup>22</sup>

We recorded a bimodal age distribution with peaks at the 3<sup>rd</sup> and the 7<sup>th</sup> decades of life contrary to the 2<sup>nd</sup> and 4<sup>th</sup> decades of life reported by several scholars.<sup>3-7</sup> Research on this unique phenomenon in NPC has shown three established etiologic risks: genetics, EBV and the environment have been implicated.<sup>25,26</sup> Studies from South East Asia/North Africa reported the involvement of the under-fives where the interplay between genetic/familial factors and EBV tend to play a major role, however, we recorded the 2<sup>nd</sup> decade as the youngest age group.<sup>25,26</sup> In regions where the disease is sporadic, HPV 11,16 and unhealthy life-style become prominent features from the cumulative effects of carcinogenesis risks, speculated to be responsible for the second peak, typically higher than the 1<sup>st</sup>, according to the bimodal age-distribution frailty model theory<sup>2,24</sup> though reversed in this series. Cancers in Africa tend to involve the young and are aggressive.<sup>19,22</sup> Cachexia and anemia which occurred in 36.7% and 56.7% of patients respectively in this series have been described as unfavourable prognostic factors that affect the overall survival(OS) of victims.<sup>15,21,27</sup> Furthermore, the prevalent poor health-seeking behavior and economic restrictions in Africa have late presentation as a consequence seen in over 75% of patients in this study which may explain the presence of palatal fistulas in 10.0%.<sup>19,22</sup>

Cervical nodal metastasis, a feature of late disease was the predominant symptom as widely reported.<sup>19,20,23</sup> The EBV Oncogene, LMP-1 has been implicated in the high incidence of distant metastasis even in N0 disease in 17% while over 73% in N3 disease that accounts for NPCs DMFS and loco-regional relapse free survival (LRRFS)-a major source of mortality.<sup>28-30</sup> The single most important prognostic factor in cancer is nodal involvement. Presence of a single positive node carries a 60% risk of recurrence, 2-4 positive nodes up to 75% risk while more than 4 positive node has a 90% risk.<sup>31</sup> Researchers further investigated the prognostic value of parotid region nodes now classified as Level VIII which were found to correlate N3 disease.<sup>32</sup> In this study, N3 prevalence was 65.0%, however, distant metastasis was difficult to confirm because of the prohibitive cost of CT scan in our environment. The cheapest and frequently used diagnostic tool in our region for metastasis assessment is the ultrasonography and plain radiographs which are often less sensitive or specific.<sup>33</sup> The initial early nasal or ear presentations, which accounted for 83.3% in a study in North Western Nigeria<sup>23</sup> are often non-specific which may account for the late presentation.<sup>2,18</sup> In the endemic regions, a unilateral otitis media/epistaxis in an adult are diagnostic criteria.<sup>18,23</sup> Prevalence of T4 disease of 76.7% in our series may have a tremendous impact on the outcome. In a recent report on the prognostic value of total tumor volume (TTV)-primary tumor volume and volume of nodes involved: a TTV of >28cm<sup>3</sup> confer a bad prognosis.<sup>34</sup> Inadequate chemo-radiation doses from poor objective assessment can lead to resistance/relapse while over dose is a source of severe toxicity with its lethal consequences.<sup>2</sup>

The WHO type II(the non-keratinizing SCC) and WHO type III(the Undifferentiated carcinoma) were the predominant forms in this series similarly reported<sup>2,35</sup> This has a bearing on outcome as they are highly chemo-radiosensitive yet poor LRRFS and DMFS due to high rate of distant metastasis. However, the WHO type I (the keratinizing SCC) is less invasive but poorly responsive to chemo-radiation and a high propensity for poor LRRFS.

Access to care in this study was poor as 83.3% had no form of chemo-radiation. However, the 16.7% that had either chemotherapy or radiotherapy (RT) or both-13.3% underwent RT alone while one had chemo-radiation at a facility estimated at 239km. According to the National Comprehensive Cancer Network guideline (NCCN);RT is recommended for stage I whereas chemo-radiation for stages II-IV without distant metastasis.<sup>36</sup> Platinum-based chemotherapy is recommended for metastatic disease.<sup>29</sup> Introduction of intensity modulated radiotherapy (IMRT) and neo-adjuvant, concurrent and adjuvant chemo-radiation has made stages I/II disease

curable while the OS, DMFS, Cancer-specific free(CSF) and LRRFS have improved with stage III and IV.<sup>29,37</sup> RT has been reported to promote cell cycle arrest and cellular apoptosis through the Ataxia Telangiectasia mutated (ATM) and Smad pathways.<sup>38</sup> Unfortunately, an estimated 5% of the total chemotherapeutic agents in cancer care reach Africa which are often costly that may account for the poor access in this series. Furthermore, the cost for oversea cancer treatment globally is at an estimated \$100b annually while no African country yet to establish a modern cancer care infrastructure.<sup>22,27</sup> With the invasive nature of NPC, the stage at presentation, the plethora of unfavourable factors and poor access to chemo-radiation in this series, we may speculate that the 70.0% that defaulted follow-up might never made it to one year.<sup>16</sup> The poor follow-up is a limitation that would require a prospective study which may permit outcome pronouncement.

### Conclusion

NPC remains uncommon in Africa with WHO type III the predominant form. It is associated with late presentation, advanced disease, inadequate cancer care infrastructure and poor access to chemo-radiation. Early detection strategy using EBV biomarkers is a priority to prevent the misery associated with NPC.

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