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Nasopharyngeal Carcinoma: Profile, Challenges and 5-Year Outcome in a Nigerian Tertiary Hospital

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Abstract

BACKGROUND: Nasopharyngeal carcinoma is encountered regularly in otolaryngological practice in Nigeria. However, it is often misdiagnosed due to varied presenting symptoms, hence the need to describe the pattern of presentation and the challenges of treatment of the patients that presented to our centre with nasopharyngeal carcinoma. **METHODS:** The pathology and clinical records were retrieved for all histologically confirmed cases of nasopharyngeal carcinoma from the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) cancer registry. The epidemiological data, symptoms and stage at presentation, type of treatment, outcome and challenges encountered were obtained from the records. **RESULTS:** A total of 384 histologically confirmed head and neck malignancies were seen over the review period, and nasopharyngeal carcinoma constituted 32 (8.33%). There were 24(75.0%) male and 8(25.0%) female. The age ranged from 17 - 80 years with a mean of 54.5 + 12.2 years. All the patients presented with neck swelling, Nasal obstruction 14(43.75), Epistaxis 11(37.5%), Trismus 2(6.25%), and proptosis 2(6.25%). Twenty-four (75%) presented with stage four tumour. Treatment was primarily radiotherapy. Fifteen (46.88%) completed radiotherapy. Two (6.25%) patients had chemo-radiation and 15(46.88%) defaulted at different stages of treatment mainly due to financial constraints, others include beliefs and breakdown of radiotherapy machines. Prognosis was very poor with 1-year survival of 21.9% and five-year survival of 9.25%. **Conclusion:** Neck swelling, Epistaxis and nasal blockade are the most common presenting symptoms. Patients

present late leading to poor prognosis. Financing treatment out of pocket is a major reason for presenting late and defaulting during management.

Keywords: Nasopharyngeal; Neck swelling; Carcinoma; Nigerian.

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1. Introduction

Nasopharyngeal carcinoma (NPC) occurs worldwide with high incidence in the south east Asian countries such as china, the Pacific Island and Mediterranean countries [1, 2]. It is a unique tumor of the head and neck region as a result of its epidemiology, racial predisposition, distinctive immunogenetics as well as its association with Epstein Barr (EB) virus [3, 4].

There is a male preponderance in the incidence of NPC with M: F ratio of 2-3:1 and a bimodal age incidence has been described in endemic areas [5, 6]. The first peak age incidence is in the 2nd decade of life and this is commonly seen in an endemic area while the 2nd peak is in the 5^{th} decade of life [7].

The aetiological factors associated with NPC are exposure to Epstein Barr (EB) virus infection. This is based on the fact that the EB viral capsid antigen VCA, nuclear Antigen (EBNA) and early Antigen were demonstrated in the tumor cells and EB viral antibody had been demonstrated in affected patients [8-11]. A genetic factor has also been implicated based on the fact that it is commoner in the Chinese, and the Orientals in addition to the association with the HLA A, B, CD, DR, BW6 2 and 17, 5, 6. SIN 2 + HZ (California) (Singapore).

Other factors implicated in the aetiology of NPC are food and cooking habits, it is found to be commoner in people who consumed a lot of ungutted smoked fish, engage in religious activity with burning of incense, and the use of Joss stick [12-16]. Also implicated are exposure to industrial fumes in certain occupations and to heavy metal like Arsenic and several other factors [15, 16]. Tumors of the nasopharynx may masquerade their symptoms to regions other than the primary site thereby presenting in many different ways [17-19]. Diagnosis is also often difficult because of the non-specific nature of early clinical symptoms and the difficulty in visualizing the nasopharynx leading to late diagnosis and this is associated with a poor prognosis.

This article describes the incidence, pattern of presentation and the challenges of treatment of nasopharyngeal cancer in a tertiary health care facility in South-Western Nigeria.

2. Materials and Methods

This is a retrospective study of all histologically confirmed cases of nasopharyngeal carcinoma from the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) cancer registry over a fourteen year period (2008-2012) with patients' entry points of NPC being mainly from the Otolaryngological unit. The hospital records of the patients as well as the histopathology files of the hospital over the stated period were reviewed. The demographic details, two major presenting complaints and their duration or complaints elicited during history taking or principal clinical findings, stage of the disease at presentation, histological types based on WHO classification, treatment modalities and outcome after 5 years were recorded. All the patients had panendoscopy and biopsy with tissue specimens sent for histopathology. Staging of the disease was done using the TNM classification. The absolute survival rates using the percentage of patients that are alive after one and five years of diagnosis were calculated. The data were entered into a proforma and analyzed using descriptive statistics.

3. Results

The total number of Head and Neck malignancies seen over the review period was 384. The numbers of histologically diagnosed NPC were 32. Nasopharyngeal carcinoma accounted for 8.33 % of all head and neck malignancies in our hospital.

3.1. Age and Sex Distribution

There was a male preponderance with 24(75.0%) males and 8(25.0%) female. The Male: Female ratio is 3:1. The age of the patients ranged from 17 - 80 years with a mean age of 54.5 years ± 12.2 years. Peak incidence is in the 51-60 age group (Table I).

3.2. Presenting Symptoms

Table II shows the presenting complaints with painless neck swelling being the most common presentation and unilateral in 84.4% of patients, other symptoms include; epistaxis, nasal blockade, proptosis and trismus.

3.3. Staging of the Disease

Table III shows the clinical staging of the disease at presentation. Seventy five percent (24) of the patients present with a stage IV disease while only 6.25% had stage I disease.

3.4. Histology

Keratinizing Squamous Cell Carcinoma was seen in 19 (59.38%), undifferentiated in 8 (25.00%) and non keratinizing squamous cell carcinoma in 5(15.62%)

3.5. Treatment

All the patients were referred for Radiotherapy alone except two patients (6.25%) who was referred for chemoradiotherapy. however, only 15(46.88%) out of the 30 patients for radiotherapy alone completed it, the remaining 15(46.88%) could not complete the appropriate treatment modality due majorly to financial constraints. Two (6.25%) patients for concomitant chemotherapy and radiotherapy also completed treatment.

3.6. Challenges

The challenges experienced during the course of management ranged from late presentation, financial constraints, and lack of family support or support group to availability of few functioning radiotherapy centers at any particular time (Table IV).

3.7. Prognosis

Prognosis was found to be very poor, only seven patients survived for one year after the commencement of therapy. The overall one year survival was 21.9%. Five-year survival was 9.4% with no recurrence.

4. Discussion

Nasopharyngeal Carcinoma is a disease with a remarkable racial and geographical distribution. It is very rare in most parts of the World except in Southern China in the Eskimos of the Arctic region, South East Asia, The Arabs of Northern Africa and Kuwait [20]. In the present study Nasopharyngeal Carcinoma accounted for 8.3% of all head

and neck malignancies. This figure is quite high when compared with the reports from Europe and America that found NPC to account for less than 2% of all head and neck cancers.

There was a male preponderance with a male to female ratio of 3:1. Obafunwa et al and Fong et al also found a male preponderance with a male to female ratio of 2:1 and 2.5:1 respectively[21, 22]. The mean age of our patients was 54.5 years and peak age incidence was found to be in the 6th decade of life. The average age is similar with findings by Carla et al that found a mean age of 53 years and differs from the peak age incidence of 2nd and 4th -5th decade of life found by Kitcher and Chu et al respectively [6, 23, 24]. However the bimodal peak age incidence was not observed in this series.

The most common presentations include painless neck swelling, Epistaxis, and nasal blockade (Table III). These features are similar to what had been documented in the literature [6, 25]. Other presentations include some degree of hearing impairment usually associated with blockage of Eustachian tube, Tinnitus and cranial nerve palsies due to extension into the base of the skull. All our patients (32,100%) presented with painless neck swelling which is more than the documented 63-80% mostly because majority of them present late [26].

Late presentation is a common finding in these patients, the late presentation as seen in this work could be due to the fact that the tumor could masquerade their symptoms to other regions other than the primary site, inadequate diagnostic facilities, inadequate number of otolaryngologists and the endemic poverty in developing countries. Other attributed causes of late presentation include inefficiency of referral system, delay in diagnosis by primary care physicians and initial treatment by alternative medical practitioner [6, 27, 28].Keratinizing Squamous cell Carcinoma (WHO type I) was the most commonhistopathological variant observed in this work, this was seen in over fifty percent of the patients. Obafunwa in Northern part of Nigeria had 40% of his patients with WHO type I while WHO type III was more common in Ghana. While the most common type of nasopharyngeal carcinoma among US-born Chinese and Whites is WHO type I tumors, among Chinese who reside in Hong Kong, Taiwan, and Macao, WHO type III tumors predominate. WHO type I has been said to be common in endemic regions [6, 21, 29].

Radiotherapy was the mainstay of management in our patients. Chemotherapy can also be combined with radiotherapy as in two patients (6.3%). However 15 (46.9%) did not complete radiotherapy majorly due to socioeconomic constraints. This has also been documented in treatment of other cancers in developing Countries [30]. To get placement for radiotherapy is also becoming difficult due to availability of the service in only few centres necessitating long queues, incessant break down of machines and consequent ineffective radiotherapy at the hospital they were referred to because of the large volume of patients using the same facility [30]. Delayed placement worsens the prognosis even when patients present relatively early, they do not get to commence radiotherapy immediately. Some Oncology centres however gives neoadjuvant chemotherapy while waiting for the radiotherapy.

The challenges encountered in our facility during management also include limited, unavailable or broken down diagnostic and treatment facilities, the inability of the patients to afford the cost of investigations and treatment due to high cost of services when available and poverty state of the patients [30-32]. All the patients treated were referred to another tertiary hospital for radiotherapy +/- Chemotherapy and majority subsequently defaulted or are haphazard in clinic appointments in our facility. They defaulted from our facility because of the distance they had to cover from their homes to attend both hospitals appointment and the fact that the available fund was being kept for chemoradiotherapy bills such that when they develop complications either from the disease or treatment, the patients may not present early leading to late treatment.

One-year survival was 7(21.9%) while 5 years survival was found to be 9.4%. This is low compared to Carla et al who had a five year actuarial survival rate of 65.1% although 58% of his cases were WHO Type III and it is known that WHO Types II and III also have a better prognosis than WHO type I tumours [3, 23, 33]. Early age of diagnosis, localized stage at presentation (versus distant), radiation therapy (versus none), undifferentiated non-keratinizing carcinoma (versus keratinizing squamous cell carcinoma) were associated with improved survival [34]. The 5-year survival rate is significantly better for non-keratinizing carcinoma than keratinizing squamous cell carcinoma of the nasopharynx (51% versus 6%) [34]. In addition, non keratinizing carcinomas are generally associated with EBV positivity and EBV positivity in turn has been shown to be associated with improved survival [35]. Recent studies have demonstrated that concurrent chemotherapy and radiotherapy are effective in the treatment of local and regionally advanced nasopharyngeal cancer [36, 37]. Similarly, neoadjuvant and adjuvant chemotherapy in local and regionally advanced disease has resulted in consistently high response rates [38, 39]. Nevertheless, distant metastases continue to impede improvement of survival rates for patients with nasopharyngeal cancer. The prognosis in this series is poor. Delay in diagnosis leading to late presentation as well as the cancer type, financial constraints, the long waiting period at the radiotherapy clinic could have been responsible for this poor outcome.

There is need to create awareness about this disease among clinicians so as to heighten their suspicion and to encourage early referral. The government also need to attend to these challenges urgently by implementing policies to equips the available cancer treating hospitals with state of art equipment, increase coverage of national health insurance scheme to cover non- government workers or makes cancer treatment free of charge so that many more patients will have access to diagnostic tests, treatment and therefore better prognosis and outcome [30].

5. Conclusion

Nasopharyngeal Carcinoma has an incidence of 8.3% of all head and neck malignancies at OAUTHC. Neck swelling, Epistaxis and nasal blockade are the most common presenting symptoms. Financing treatment out of pocket is a major reason for presenting late and defaulting during management thereby leading to poor prognosis.

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Age group	Male (%)	Female (%)	Total (%)
0-10	0 (0.00)	0 (0.00)	0(0.00)
11-20	1(3.13)	0 (0.00)	1 (3.13)
21-30	0 (0.00)	1(3.13)	1(3.13)
31-40	3(9.38)	2 (6.25)	5 (15.63)
41-50	6(18.75)	0 (0.00)	6 (18.75)
51-60	6(18.75)	4 (12.50)	10 (31.25)
61-70	5(15.63)	1 (3.13)	6 (18.75)
71-80	3(9.38)	0 (0.00)	3 (9.38)
Total	24(75.00)	8 (25.00)	32 (100.00)
Mean age: 54.5 +	12 2vears		

Table-I. Age and Sex Distribution of Patients with NPC.

Mean age: 54.5 ± 12.2 years

Table-2. The two prominent presenting complaints in patients with NPC.

Symptoms	Male	Female	Number (%)
Neck swelling	24	8	32 (100.00)
Epistaxis	9	2	12 (37.50)
Nasal blockade /Nasal mass	9	5	14 (43.75)
Trismus	2	0	2 (6.25)
Facial swelling	2	0	2 (6.25)
Proptosis	2	0	2 (6.25)
Post nasal dripping	0	1	1 (3.13)
others	9	3	12 (37.50)

Table-3. Staging of the disease at presentation

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Clinical staging	Male	Female	Number (%)
Stage IV	17	7	24 (75.00)
Stage III	0	0	0 (0.00)
Stage II	6	0	6 (18.75)
Stage I	1	1	2 (6.25)
Total	24	8	32 (100)

Table-4. Challenges experienced during management of Patients with NPC

1	Late Presentation to specialists
2	Lack of family support/Support group
3	Out of pocket payment/Poverty
4	Different radio-oncology Centres with different protocols of treatment
5	Few functional machine at any point in time/incessant breakdown of
	machines for long periods
6	Long waiting time (queue)
7	Influence of spiritual undertones/Personal Beliefs concerning diseases
	and treatment.
8	Distance covered to Oncology Centres

References

- [1] Shotelersuk, K., Khorprasert, C., Sakdikul, S., Pornthanakasem, W., Voravud, N., and Mutirangura, A., 2000. "Epstein-Barr virus DNA in serum/plasma as a tumor marker for nasopharyngeal cancer." *Clinical Cancer Research*, vol. vol. 6, , pp. 1046-1051.
- [2] Warnakulasuriya, K. A. A. S., Johnson, N. W., Linklater, K. M., and Bell, J., 1999. "Cancer of mouth, pharynx and nasopharynx in Asian and Chinese immigrants resident in Thames regions." *Oral Oncology*, vol. 35, pp. 471-475.
- [3] Marks, J. E., Phillips, J. L., and Menck, H. R., 1998. "The National cancer data base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma." *Cancer*, vol. 83, pp. 582-588.
- [4] Wilke, J., Swoboda, R., and Sauerbrei, A., 1987. "The role of epstein-barr virus in the etiology of nasopharyngeal cancer." *Otolaryngologiapolska= The Polish Otolaryngology*, vol. 42, pp. 151-157.
- [5] Nwawolo, C. C., Ajekigbe, A. T., Oyeneyin, J. O., Nwankwo, K. C., and Okeowo, P. A., 2001. "Pattern of head and neck cancers among Nigerians in Lagos." *West African Journal of Medicine*, vol. 20, pp. 111-116.
- [6] Kitcher, E. D., Yarney, J., Gyasi, R. K., and Cheyuo, C., 2004. "Nasopharyngeal cancer: A review of cases at the korle-bu teaching hospital." *Ghana Medical Journal*, vol. 38, pp. 104-108.

- [7] Haugen, M., Bray, F., Grotmol, T., Tretli, S., Aalen, O. O., and Moger, T. A., 2009. "Frailty modeling of bimodal age-incidence curves of nasopharyngeal carcinoma in low-risk populations." *Biostatistics*, vol. 10, pp. 501-514.
- [8] Pavelka, R., Popow-Kraupp, T., and Radaszkiewicz, T., 1985. "Immunoglobulin A serum antibodies against the capsid antigen of Epstein-Barr virus in the differential diagnosis and follow-up of nasopharyngeal cancer." *Wiener klinische Wochenschrift*, vol. 97, pp. 588-595.
- [9] Tang, Z. H., 1982. "Detection of iga serum antibodies to eb virus vca in patients having survived nasopharyngeal cancer for over 15 years (author's transl)." *Zhonghuayixuezazhi*, vol. 62, pp. 167-169.
- [10] Chang, K. P., Hsu, C. L., Chang, Y. L., Tsang, N. M., Chen, C. K., Lee, T. J., Tsao, K. C., Huang, C. G., Chang, Y. S., *et al.*, 2008. "Complementary serum test of antibodies to Epstein-Barr virus nuclear antigen-1 and early antigen: a possible alternative for primary screening of nasopharyngeal carcinoma." *Oral Oncology*, vol. 44, pp. 784-792.
- [11] Tang, J. W., Rohwäder, E., Chu, I. M., Tsang, R. K., Steinhagen, K., Yeung, A. C., To, K. F., and Chan, P. K., 2007. "Evaluation of epstein-barr virus antigen-based immunoassays for serological diagnosis of nasopharyngeal carcinoma." *Journal of Clinical Virology*, vol. 40, pp. 284-288.
- [12] Guo, X., Johnson, R. C., Deng, H., Liao, J., Guan, L., Nelson, G. W., Tang, M., Zheng, Y., De, T. G., et al., 2009. "Evaluation of nonviral risk factors for nasopharyngeal carcinoma in a high-risk population of Southern China." *International Journal of Cancer*, vol. 124, pp. 2942-2947.
- [13] Farrow, D. C., Vaughan, T. L., Berwick, M., Lynch, C. F., Swanson, G. M., and Lyon, J. L., 1998. "Diet and nasopharyngeal cancer in a low-risk population." *International Journal of Cancer*, vol. 78, pp. 675-679.
- [14] Ning, J. P., Yu, M. C., Wang, Q. S., and Henderson, B. E., 1990. "Consumption of salted fish and other risk factors for nasopharyngeal carcinoma (npc) in tianjin, a low-risk region for npc in the people's republic of China." *Journal of the National Cancer Institute*, vol. 82, pp. 291-296.
- [15] Yan, L., Xi, Z., and Drettner, B., 1989. "Epidemiological studies of nasopharyngeal cancer in the Guangzhou area, China preliminary report." *Acta Oto-laryngologica*, vol. 107, pp. 424-427.
- [16] Parkin, D. M., Whelan, S. L., Ferlay, J., Raymond, L., and Young, J., 1997. Cancer incidence in five continents vol. VII. Lyon, IARC: France, International Agency for Research on Cancer Scientific Publication No.143. pp. 334-337.
- [17] Ingegnoli, F., Sciascera, A., D'ingianna, E., and Fantini, F., 2008. "Systemic sclerosis, capillary leak syndrome and nasopharyngeal carcinoma: an unusual association or paraneoplastic manifestations?" *Rheumatology*, vol. 48, pp. 201-202.
- [18] Wang, M. C., Tsai, T. L., Liu, C. Y., Shu, C. H., and Lin, C. Z., 2003. "Nasopharyngeal lymphoid hyperplasia of an hiv car rier, mimicking nasopharyngeal cancer." *Journal of Chinese Medical Association*, vol. 66, pp. 189-191.
- [19] Lal, P., Gupta, S. D., and Thakar, A., 2009. "Sjogren's syndrome masquerading as nasopharyngeal carcinoma." *American Journal of Otolaryngology*, vol. 30, pp. 209-211.
- [20] Hubert, A., 1982. "Dietary behavior, way of life, and nasopharyngeal cancer." *Bulletin Du Cancer*, vol. 69, pp. 476-482.
- [21] Obafunwa, J. O. and Bhatia, P. L., 1991. "Nasopharyngeal carcinoma in Plateau State, Nigeria: a pathological study." *European Journal of Surgical Oncology*, vol. 17, pp. 335-337.
- [22] Fong, K. W., Chua, E. J., Chua, E. T., Khoo-Tan, H. S., Lee, K. M., Lee, K. S., Sethi, V. K., Tan, B. C., Tan, T. W., *et al.*, 1996. "Patient profile and survival in 270 computer tomography-staged patients with nasopharyngeal cancer treated at the Singapore general Hospital." *Annals of the Academy of Medicine, Singapore*, vol. 25, pp. 341-346.
- [23] Carla, d. E. A., Pedro, M., Pedro, H., and Miguel, M. O., 2009. "Nasopharyngeal carcinoma: our experience." *European Archives of Oto-Rhino-Laryngology*, vol. 266, pp. 833-838.
- [24] Chu, A. M., Cuthler, S. J., and Young, J. L., 1974. "Third national cancer surgery; incidence date." *Nath Can Inst. Mongram*, vol. 41, p. 1454.
- [25] Lee, A. W., Foo, W., Law, S. C., Poon, Y. F., Sze, W. M. O. S. K., Tung, S. Y., and Lau, W. H., 1997. "Nasopharyngeal carcinoma-presenting symptoms and duration before diagnosis." *Hong Kong Medical Journal*, vol. 3, pp. 355-361.
- [26] Sham, J. S., Poon, Y. F., Wei, W. I., and Choy, D., 1990. "Nasopharyngeal carcinoma in young patients." *Cancer*, vol. 65, pp. 2606-2610.
- [27] Lee, S. C., Tang, I. P., Avatar, S. P., Ahmad, N., Selva, K. S., Tay, K. K., Vikneswaran, T., and Tan, T. Y., 2011. "Head and neck cancer: Possible causes for delay in diagnosis and treatment." *Medical Journal of Malaysia*, vol. 66, pp. 101-104.
- [28] Sing, T. and Subramaniam, S., 2006. "Factors of late presentation and diagnosis of nasopharyngeal carcinoma in Sarawak Malaysia." *Internet Journal of Head and Neck Surgery*, vol. 1, pp. 1-18.
- [29] Sun, L. M., Epplein, M., Li, C. I., Vaughan, T. L., and Weiss, N. S., 2005. "Trends in the incidence rates of nasopharyngeal carcinoma among Chinese Americans living in Los Angeles county and the San Francisco metropolitan area, 1992–2002." *American Journal of Epidemiology*, vol. 162, pp. 1174-1178.
- [30] Eziyi, J. A. E., Amusa, Y. B., Fatusi, O., and Otoghile, B., 2014. "Challenges of surgical management of maxillary tumours in a developing country." *Journal of Medicine and Medical Sciences*, vol. 5, pp. 162-168.

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- [31] Fatusi, O., Akinpelu, O., and Amusa, Y., 2006. "Challenges of managing nasopharyngeal carcinoma in a developing country." *Journal of the National Medical Association*, vol. 98, pp. 758-764.
- [32] Adeyi, A. and Olugbenga, S., 2011. "The challenges of managing malignant head and neck tumors in a tropical tertiary health center in Nigeria." *Pan African Medical Journal*, vol. 10, p. 31.
- [33] Burt, R. D., Vaughan, T. L., and McKnight, B., 1992. "Descriptive epidemiology and survival analysis of nasopharyngeal carcinoma in the United States." *International Journal of Cancer*, vol. 52, pp. 549-556.
- [34] Reddy, S. P., Raslan, W. F., Gooneratne, S., Kathuria, S., and Marks, J. E., 1995. "Prognostic significance of keratinization in nasopharyngeal carcinoma." *American Journal of Otolaryngology*, vol. 16, pp. 103-108.
- [35] Shi, W., Pataki, I., MacMillan, C., Payne, D., O'Sullivan, M. B., Bernard, J., Warde, P., and Liu, F. F., 2002. "Molecular Pathology Parameters in Human Nasopharyngeal Carcinoma." *Cancer*, vol. 94, pp. 1997-2006.
- [36] Sanguineti, G., Geara, F. B., Garden, A. S., Tucker, S. L., Ang, K. K., Morrison, W. H., and Peters, L. J., 1997. "Carcinoma of the nasopharynx treated by radiotherapy alone:determinants of local and regional control." *International Journal of Radiation Oncology* Biology* Physics*, vol. 37, pp. 985-996.
- [37] Cheng, S. H., Jian, J. J. M., Tsai, S. Y., Chan, K. Y., Yen, L. K., Chu, N. M., Tan, T. D., Tsou, M. H., and Huang, A. T., 1998. "Prognostic features and treatment outcome in loco-regionally advanced nasopharyngeal carcinoma following concurrent chemotherapy and radiotherapy." *International Journal of Radiation Oncology* Biology* Physics*, vol. 41, pp. 755-762.
- [38] Chan, A. T., Teo, P. M., and Johnson, P. J., 1998. "Controversies in the management of loco-regionally advanced nasopharyngeal carcinoma." *Current Opinion in Oncology*, vol. 10, pp. 219-225.
- [39] Chan, A. T., Teo, P. M., Leung, T. W., and Johnson, P. J., 1998. "The role of chemotherapy in the management of nasopharyngeal carcinoma." *Cancer*, vol. 82, pp. 1003-1012.