OUTCOME OF HEAD AND NECK CANCER PATIENTS MANAGED WITH CHEMORADIATION AT THE RADIOTHERAPY DEPARTMENT NATIONAL HOSPITAL ABUJA (A FIVE YEAR RETROSPECTIVE STUDY)

BY

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MAY, 2017

DECLARATION

I hereby declare that this case report study was written by me. It has not been written in any previous post-graduate research work in the faculty of Radiological Science to the best of my knowledge.

All quotations are indicated and sources of information specifically acknowledged by means of references.

fatima 27/1/2017

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CERTIFICATION

This is to certify that this patients were managed by Dr.Uba Fatima of the Department of Radiotherapy,National Hospital Abuja, under my supervision.

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DEDICATION

This book is dedicated to Almighty God for his grace, love and favour, my teachers, from whom I gained experience, and my family for their love and support.

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SUMMARY

OUTCOME OF HEAD AND NECK CANCER PATIENTS MANAGED WITH CHEMORADIATION AT THE RADIOTHERAPY DEPARTMENT NATIONAL HOSPITAL, ABUJA

Background of the Study

Head and neck cancers (HNC) are malignancies that occur in the head and neck regions of the body.[1] Chemoradiation is the combination of chemotherapy and radiotherapy given concurrently in the treatment of malignant cell. Addition of chemotherapy sensitize tumour cells to radiation therapy and increase locoregional control.

Research design: This was a retrospective cross sectional study.

Objectives: To determine the outcome of head and neck cancer patients managed with chemoradiation at the radiotherapy department NHA.

Methodology: Data extraction form was used to obtain Sociodemographic and clinical variables from treatment records and case notes of patients with head and neck cancer treated with chemoradiation are compared with patients who had single treatment from January, 2009 to December, 2013 at the radiotherapy department, National Hospital, Abuja. Outcomes of chemoradiation were analysed.

Results: A total of 384 cases with histologically diagnosed HNC seen during this five years period were analyzed. The mean age was 43.5 years, with a male to female ratio of 2;1, 248 males (64.6%) and 136 females (35.4%). Nasopharyngeal cancer (NPC) was the commonest type 102 (26.6%), Oral cavity 52(13.5%), Nose/paranasal

48(12.5%) and larynx 46(12.0%) cases respectively. Carcinomas made up greater than 80% of all the histologies with squamous cell carcinoma (SCC) at the fore-front, 214 (85.2%). The most frequently presented symptom was neck mass and cisplatin is the commonest chemotherapy used. Almost half of the patients 133 (42%) presented with stage IV disease, 92(29%) presented with stage III, 57(18%) presented with stage II, and 34(11%) presented with stage I disease . By the Second year of follow-up of patients that had chemoradiation , 124(39.2%) were disease free, 136 (43.3%) alive with the disease, 40 (12.6%) died of the disease, 16 (5.6%) were lost to follow-up,

The overall survival at 5 years of follow up was 24.6% for concurrent chemoradiation and 14.4% for radiotherapy alone. 7.9% were lost to follow-up probably on account of either complications of treatment, financial constraint, disease progression or unreported deaths.

Conclusion: large number of patients in our environment present with advanced stage disease and mostly aggressive which results in poor outcome. Addition of chemotherapy sensitizes tumour to radiation and increases locoregional control and there by improved treatment outcome. In this study, it was observed that, despite the late presentation, there was better outcome and improves curability compared with patients who received radiotherapy alone, this is similar to the reports in the literature review.

CHAPTER ONE

1.1 BACKGROUND OF THE STUDY

Head and neck cancers are malignancies that occur in the head and neck regions of the body.[2] Head and neck is the fifth most common cancer worldwide with an estimated annual global incidence of 533,100 cases. Approximately 44,660 people in the US and, 76,000 in Europe per year are diagnosed with head and neck cancer. Although the term "head and neck cancers" is usually assumed to mean squamous cell carcinomas. The majority of them (> 90%) are squamous cell carcinomas,[3] other histologic types (e.g. adenocarcinomas, Adenoid cystic carcinomas, Mucoepidermoid carcinomas, undifferentiated carcinomas. Head and neck cancer is divided into three clinical stages early, locoregionally advanced and metastatic or recurrent. More than 50% of newly diagnosed patient will relapse locally or at a distant site and patients with recurrent or metastases have a poor prognosis with median survival time of less than a year. Advanced locoregional disease has a poor prognosis. It is estimated that approximately 50-60% of patient have local disease recurrence within 2years and 20-30% 0f patient develop metastatic disease. These cancers tend to show similar response to the same combination of cytotoxic chemotherapeutic agents, e.g. cisplatin, docetaxel, carboplatin adriamycin, cyclophasphamide bleomycin, etoposide, 5FU and methotrexate.[4] Head and neck cancer are subdivided into many anatomical sub-sites which vary in many respects epidemiology, aetiology tumor biology, and clinical presentation, frequency of nodal spread and chances of contra-lateral node involvement. For head and neck tumors, as for all types of cancers, the chances of effecting a cure are greatly enhanced when the patient presents to the oncologist in the early, resectable stage of the disease. However, most

patients in Nigeria and, indeed, the less developed countries present at a late stage, often terminal stage of the disease. Ignorance, poverty, patient consulting traditional healers and spiritual faith healers tend to contribute to needless delay. At this stage, the only option of treatment left is usually of palliative, rather than curative intent.[5] Even for those who present to a Physician at a Primary or Secondary level of medical care, the period intervening between their presentation and referral for specialist oncology care is so long that the tumor inevitably becomes a metastatic one at presentation. This is because the Physicians at the peripheral hospitals take an unduly long time trying to arrive at a diagnosis of malignancy. Even after diagnosis, many are not willing to refer to the specialists immediately. Thus, an adequate knowledge of how these tumors present in the Nigerian context will help to increase clinical suspicion, which will aid early recognition of the disease and make for speedy referrals to specialist oncologists. Presenting features depend on the primary site of disease. One of the common presentations is unknown primary site. The early symptoms do not produce functional limitations or cosmetic problems because they are usually vague and non-specific so they are often ignored or not suspected. Most patient in our environment present at advanced stage of the disease.[6,7] In diagnosing head and neck cancers, it requires a good knowledge of disease pattern and high index of suspicions. Sites like larynx, pharynx and maxillary antrum are not readily visible or palpable requiring examination under anaesthesia. Endoscopic examination of mucosal surfaces, imaging technique, multiple biopsies of suspected primary sites and histological diagnosis are some of the requirements for proper diagnosis. The skill and materials for these are not readily available in first hospital of contact. Hence the need for screening programs, public education and

awareness regarding early detection of head and neck cancer, education and retraining of health care providers. This study is to review outcome of chemoradiation in HNC patient, aiming to highlight the magnitude and challenges encountered in the management of patient with head and neck cancer in National Hospital Abuja.

1.2 AIMS AND OBJECTIVES

Broad Objectives

The aim of the study is to determine the outcome of chemoradiation in patients that had treatment in the radiotherapy department National Hospital, Abuja.

Specific Objectives

i. The outcome of chemoradiation in head and neck cancer patients in National Hospital Abuja will be known.

ii. To determine the most common symptoms and signs of head and neck cancers in patients presenting at National Hospital Abuja.

iii. To determine the most common histological types

iv. The findings will enhance early recognition, as well as timely referral of head and neck malignancies for specialist care.

CHAPTER TWO

LITERATURE REVIEW

Epidemiology

Head and neck cancers occur worldwide. Approximately 40,000 patients are newly diagnosed annually with squamous cell carcinoma of the head and neck in the United States. Worldwide, approximately 600,000 patients are afflicted. Nearly 60% of this population presents with locally advanced, but non metastatic disease. Locoregional failure constitutes the predominant recurrence pattern, and most fatalities result from uncontrolled local and/or regional disease. They account for estimated 5% of all malignant disease in united State of America. In Scotland it is the 6th most common malignancy in men and 13th most common in women.[8] The age adjusted incidence is higher among black men, and stage for stage, survival among African Americans is lower than in white. Each year in UK there are 8000 cases of head and neck cancer leading to a total of 2500 deaths per annum. Nearly 90 percent arise in the over 50s, the incidence increasing with age, and there is a strong male predominance with a male to female ratio of 2:1 for oral cancer and 5:1 for laryngeal cancer. Incidence rates vary greatly from region to region within each country, and the incidence and mortality rates are increasing. Worldwide, the highest incidence in India and Sri Lanka where in some areas they are the most common cancers, constitutes up to 40 percent of the total. Other pockets of high incidence include South America and the Bas-Rhin region of France (oral cancer), and Newfoundland (lip**).** Chemoradiation has been the favored approach to tumors with adverse prognostic features. Adenipekun, et al,[9] in a study of outcome of chemoradiation in the management of a Nigeria child with maxillary neuroblastoma a long time

disease–free survival following chemo radiation was achieved in an African child with neuroblastoma of the maxillary antrum. The patient has been clinically free of disease for 12 years of follow up of treatment. Most patients in our environments are offered chemo radiation because of late presentation. A study by Babagana et al.[10] In advance laryngeal cancer (T3-T4) post operative chemoradiation achieved loco-regional control. The head and neck intergroup study reported by Al-Sarraf et al[11] used a combination of concurrent chemo radiation followed by adjuvant chemotherapy achieved significant difference in 5years overall survival. A meta- analysis comparing combined chemo radiation vs radiation therapy alone in locally advanced nasopharyngeal cancer include patients from six randomized studies (1,528) the addition of chemotherapy to radition therapy increased disease –free/progression free survival by 37% at 2 years, 40% at 3 years and 34% at 4years after treatment.[12] Overexpression of the epidermal growth factor receptor (EGFR-1) is associated with an adverse outcome in squamous HNC.[13] An open label, phase III trial tested the impact of weekly injections of cetuximab (C225), a chimeric monoclonal antibody to EGFR, added to a course of radiotherapy alone.[14] Oral cavity primary tumors were ineligible for enrollment. Two-year local regional increased from 48% with RT to 56% with RT/cetuximab. Three-year survival was similarly increased from 44% with RT alone to 57% with the addition of cetuximab.

This trial provides an important proof of principle that adding a biologically targeted agent to a physically targeted modality improves therapeutic outcome. One third of the patients enrolled had stage III disease, however, and thus had less advanced disease with more favorable prognoses than a significant proportion of patients undergoing CRT.

Recently Browman et al[15] reported a meta-analysis including 18 trials with 3,192 patients, in which concurrent chemoradiation therapy was compare to radiation therapy alone. The chemoradiation therapy arm gain superior than radiation alone. Single fraction, two fractions a day irradiation, single agents, combination chemotherapy, and especially cisplatin-5FU provided statistically significant results. A German multicenter trial further supports the notion that concurrent therapy is superior to maximally intensive single-modality irradiation. Three hundred and eighty-four patients, 93% of whom had either stage 3 or 4 oropharyngeal or hypopharyngeal primaries, were enrolled. As in the Duke University trial, the total dose of RT delivered in the concurrent arm of this study was lower than that in the radiation-alone control arm. Radiation-only patients received an accelerated course of 77.6 Gy in 6 weeks (14 Gy at 2 Gy once daily followed by 63.6 Gy at 1.4 Gy twice daily), and combined modality patients received 70.6 Gy during 6 weeks (30 Gy at 2 Gy per day followed by 40.6 Gy at 1.4 Gy twice daily). Chemotherapy consisted of mitomycin C (10 mg/m^2) on days 5 and 35 and 5-FU given as a single bolus of 350 mg/m^2 and a 5-day continuous infusion of 600 mg/m^2/day. Two-year survival was significantly better in the combined modality arm (54% vs. 45%), as was locoregional control (61% vs. 45%). Acute and chronic toxicity were equivalent in the two treatment populations.

The prevalence of HNC is on the increase due to better diagnostic tools.[16] However, Adisa et al[17] at UCH, reported an annual frequency of 62 cases per year in 1,192 patients' biopsy report over 19 year period from oral pathology and pathology department; remain the same with a fifteen years study of Adeyemi et al.[18] Majority of

patients affected are adults and lower socioeconomic status. Published literature in Nigeria show that ages of patients with head and neck cancers range from 9 months to over 80 years[17,19] Reports from Jos and Maiduguri in Northern Nigeria show peak incidence of head and neck cancers to be in the 3rd and 4th decades,[20 ,21] while reports from Lagos and Ibadan show a peak incidence in the 6th decade with a male: female ratio of 1.8:1[17,18.]In a study by Nwawolo et al[18] on pattern of head and neck cancer among Nigerians in lagos, the yearly incidence of 38 cases with male preponderance was noted in patients seen in LUTH 45% of patients with head and neck cancers were in their fourth and fifth decades of life. Studies done within Nigeria, however, show variance with this result. The two most common histological types of head and neck cancers in Ibadan are squamous cell carcinoma (47.8%), followed by lymphomas (19.3%).[17,20] Researchers in Lagos, Jos and Port-Harcourt all show that sarcomas are the second most common Histological type in Nigeria.[18,22] Concomitant chemoradiation using radiosensitizers has significantly improved the response rates of radiotherapy alone. Adelstein et al[23] using cisplatin in a dose of 100mg/m2 every 3 weeks, as a single agent along with radiotherapy showed complete response rate of 42% and an estimated 3 year overall survival of 37%. Al Sarraf[24] using similar dosage schedule reported a better response rate of 89.2% and an overall survival of 76%. Several studies have reported various dosing schedules of paclitaxel in the treatment of head and neck squamous cell carcinoma. Hoffmann et al[25] administered escalating weekly doses of paclitaxel concomitant with standard radiotherapy total doses of 60-70Gy to 18 patients with unresectable head and neck cancer. The dose limiting toxicity in this study was mucositis with a maximum tolerated paclitaxel dose of 30mg/m^2/wk. Of the seven patients who had undergone prior surgery.

Four (57%) had a complete response. Of the eleven treated primarily with paclitaxel and radiation four (36%) had complete response. A study of oral squamous cell carcinoma by Morita et al[26], suggested that COX-2 overexpression may cause lymphangiogenesis of tumour and lymph node metastasis. Inactivation of COX-2 by administration of COX-2 inhibitor may suppress this lymphangiogenesis and lymph node metastasis. In a retrospective study of a ten year experience of maxillary antral carcinomas among Asian population, Sanjiv Sharma et al[27] showed that 98.24% of carcinoma of maxillary antrum presented with T3, T4 lesion, with a three year disease free survival of 39.58% with radiation therapy alone and 51.91% with combined modality treatment. Dulguerov[28] and colleagues reported a 5-year survival rate of 45%. Others have reported a survival rate as high as 70% with a local reccurence rate of 30%. The Christie Hospital in Great Britain evaluated radiotherapy (RT) and 100 mg/m^2 of single-agent methotrexate (MTX) given at the commencement of and after 2 weeks of a 3-week course of treatment.[29] Most of the 313 patients in this protocol received 50 to 55 Gy in 15 or 16 fractions. Mucositis was significantly greater in the patients receiving MTX, but there was no difference in long-term toxicity. The addition of MTX increased local control from 50% to 70% and survival from 37% to 47%. The greatest benefit was seen in patients with oropharyngeal primaries who constituted one third of the study population. Local control with RT/MTX was 78% versus 38% with RT alone in this patient subset. Survival was 25% with RT alone and 50% with RT/MTX.

5-FU has been used in conjunction with RT more frequently than any other chemotherapeutic agent. Lo et al.[30] originally reported a significant improvement in local control and survival with the addition of 5-FU to RT in squamous carcinoma of the oral

cavity. The chemotherapy was given via bolus injection. It is now generally accepted that continuous infusion is a superior mode of 5-FU administration in concurrent RT and chemotherapy regimens.

Browman et al.[31] compared RT and continuous infusion 5-FU against RT alone in a controlled randomized trial sponsored by the National Cancer Institute of Canada. All 175 patients received 66 Gy in 2 Gy fractions. 5-FU was given in a dose of 1,200 mg/m^2/day for the first 3 days of the first and third weeks of irradiation. Confluent mucositis was more frequent in the 5-FU arm, than in the radiotherapy arm.

Head and neck cancer is the 6th most common malignancy in the USA.[32] The most common sites in United States are the oral cavity, pharynx, larynx, and hypopharynx. Nasal cavity, paranasal sinus, salivary gland cancers, and various sarcomas, lymphomas, and melanoma are less common. In Nigeria nasopharyngeal cancer is the commonest,[5,18,20,33] while larynx the 3th commonly affected site.,[18,20,21,34] Amusa et al[35] and Otoh et al[5] reported differently that malignancy of the oral cavity was the commonest in Ile-Ife (south west) and Maiduguri (North central) Nigeria. A review on common sites of oro-facial malignancy from Lagos noted mandible, Maxilla, palate, tongue, cheek, lip and floor of the mouth as the commonly affected sites.[36]

Tumour of the oropharynx, hypopharynx and skin were also seen but in low prevalence in some reports.[5,18,20,33] Recent studies from Ibadan (South west) reported oral cavity and oropharynx as the most commonly affected sites, (31.1%) followed by NPC, (16.4%) nose and paranasal sinuses(15%) cancer of the ear was few.[5,18,33]

Concomitant chemo-radiation employed in the management of patient, has been reported to achieve a higher complete response over induction chemotherapy followed by radiotherapy[37]. In a study by Elumelu and Adenipekun et al[38] report of a patient with advanced nasophryngeal carcinoma,who had chemo-radiation with cisplatin based chemotherapy and total midplane dose of 60Gy. Six year post treatment, patient is disease free. Adding concurrent chemotherapy to radiotherapy (chemoradiation) is now recognized to improve outcome in advanced head and neck cancer patients compared with once-daily radiotherapy alone and has become a standard approach for non-metastatic disease. Furthermore, the addition of chemotherapy to radiotherapy following surgery for resectable head and neck cancer with high-risk features shows improved locoregional control and disease-free survival.[39,40] However, in both the definitive and post-operative head and neck setting, the enhanced survival outcome is accompanied by an increase in overall treatment toxicity profiles.[38,41] At the 2004 annual meeting of the American Society of Clinical Oncology, preliminary findings were presented from the first large-scale trial to investigate the efficacy of adding cetuximab to radiotherapy for locoregionally advanced head and neck cancer patients. This international multicentre phase III study showed that the addition of cetuximab to high-dose radiotherapy significantly improved locoregional disease control and survival compared with radiotherapy alone in patients with locoregionally advanced SCCHN.[42] In this study, 424 patients were stratified by Karnofsky performance index (90–100% vs 60–80%), regional node involvement (no vs. yes), tumour stage (T1-3 vs T4) and radiation fractionation (concomitant boost vs. once-daily vs. twice-daily) and then randomized to treatment with radiation alone or in combination with cetuximab. Following completion of trial

treatment, patients were followed up with radiographic imaging every 4 months for 2 years and then every 6 months for up to 5 years.

The median age of patiens was 57 years and, as expected with head and neck cancers, 80% were male. Over two-thirds (69%) of patients had a KPS of 90–100%. The majority of patients presented with oropharyngeal tumours (60%), 25% had laryngeal tumours and 15% had hypopharyngeal tumours. The treatment arms were well-balanced with regard to patient and treatment characteristics. Patients were followed up for a median of 38 months.

The use of cetuximab prolonged overall survival, almost doubling the median survival from 28 months to 54 months. The two- and three-year survival rates of patients were 55% and 44% for those receiving radiotherapy alone, and 62% and 57% for those receiving radiotherapy and cetuximab. chemoradiotherapy is the ‘standard of care’ for advanced head and neck cancer patients not receiving definitive surgery.

Aetiology

Smoking and alcohol use have a very close association with head and neck cancers. Chewing tobacco and tobacco-like substances also increase the risk of oral cavity cancers. In many parts of Asia and some parts of Africa chewing betel with or without tobacco and slaked lime is associated with premalignant lesions and oral squamous cancers.[43,44] Genetic tendency is another important risk factor. A previous history of head or neck cancers as well as a history of cancer in first-degree family members is also a risk factor. Head and neck cancers can be seen simultaneously or metachronously in multiple locations in the same person. Exposure to radiation, as well as to sun (ultraviolent

radiation), is closely related to the risk of head and neck cancer. Exposure to radiation can occur in various ways, such as through previous radiotherapy in the head and neck region, or radioactive contamination from nuclear reactor accidents (e.g. Chernobyl) or nuclear weapons (e.g., Hiroshima and Nagasaki). Nutritional disorders and vitamin deficiencies are other risk factors. Bad nutritional habits and iron deficiency anemia particularly in women may cause these types of cancers.

Poor oral hygiene, use of inappropriate prostheses, chronic infections, gastroesophageal reflux, and particular viral infections (EBV, HPV) are additional risk factors. In a report from Maiduguri, tobacco smoking, tobacco chewing and chewing of kola nuts were associated with carcinoma of the oral cavity. However, from Enugu, Lagos and Ile-Ife, most patients with laryngeal cancer were found to be non-smokers.[7,34]. In contrast, in women of Andrah Pradesh in India, cancer of the hard palate is endemic due to the local custom of "reverse chutta smoking". This involves holding the lit end of a slowly burning cheroot in the mouth. For pipe and cigar smokers, the incidence of lip and oral cavity cancers is much higher due to concentrated carcinogens and chronic thermo-mechanical irritation. Chewing tobacco and oral snuff increases the risk of oral carcinoma. The main carcinogens in tobacco are the tobacco-specific nitrosamines, tar and benzopyrenes. Second malignancies can be prevented by treatment with cis-retinoic acid,[17] suggesting a protective effect of vitamin A and its derivatives. There is increasing evidence that viruses play a role in the pathogenesis of head and neck cancer. The link of Ebstein-Barr Virus (EBV) infection and nasopharyngeal carcinoma (NPC) has long been recognized. Epstein-bar virus (EBV) had been detected in virtually all non keratinizing and undifferenciated nasopharyngeal cancer but in squamous nasopharyngeal cancers is less

consistent. Ebstein-Barr Virus and Human Papilloma Virus (HPV) are also risk factors in certain head and neck cancers especially in younger age group.[45] Also, the association of Human Papilloma Virus (HPV) and oral cancer has been suggested and may be a major contributing factor in patients without carcinogen exposure.[1,46] Herpes simplex viruses are seen more in oropharyngeal cancers. It causes inactivation of p53 via elaboration of E6 and E7 oncogens.[47,48] Another risk factor associated with head and neck cancers is occupational exposure to wood dust, textile fibres, nickel and cadmium. These have been associated mainly with adenocarcinomas of the paranasal sinuses.

Pathology

Most head and neck tumours (90-95%) arise from the surface epithelium and are therefore squamous cell carcinoma or of its variants including lymphoepitheliomas, spindle cell carcinoma, verrucous carcinoma and it could be undifferentiated cancer. The remaining are made up of mucoepidermoid cancer, adenocystic cancer, adenocarcinoma lymphoma and a wide variety of other malignant neoplasm.[49, 50] Lymphoepithelioma is a carcinoma with lymphoid stroma and it occurs in areas with lymphoid aggregates in submucosa-like nasopharyngeal cancer, tonsil and base of tongue.[51] Spindle cell is found in 2-5% upper aerodigestive tract malignancies and it is considered as a high grade malignancy.[50] Verrucous carcinoma is a low grade squamous cell carcinoma that often has discrete margin and a roughened surface found mostly in the oral cavity especially gingival and oral mucosa. It usually has indolent growth pattern and often associated with chronic use of snuff or chewing of tobacco and betel.[5,52]

Lymphomas occurring in the upper aerodigestive tract almost always show a diffuse non-Hodgkin's lymphoma histological pattern[48] and it rarely involves mucosa site.

Epidermoid carcinomas usually begin as surface lesions but sometimes arise from ducts of minor salivary glands. This occurs in floor of mouth, base of tongue and nasopharynx. In Nigeria, most common histology was squamous cell carcinoma.[5,17,18,20,53] It is about 66.7% of all epithelial tumours study from Ibadan. Lymphomas were the second most frequent cell type seen in many centre.,[5,20,32,51] Nwawolo et al,[18] Okoye et al[33] and Lilly-Tariah[54] found sarcomas to be the second most occurring histological type. The two most common head and neck cancers in Ibadan were squamous cell carcinoma which account for 47.8% of all cases followed by lymphomas which accounted for 19.3% cases.[55] Ajayi et al[56] from Lagos reported epithelial malignant tumours (69%) mostly squamous cell carcinoma as most common orofacial malignant tumors followed by sarcomas (18%) and lymphomas (13%). Spread of disease in head and neck tumors depends on the local anatomy which is peculiar to each anatomic site. It may spread along muscle or fascia planes. It may attach to the periosteum but bone or cartilage invasion is usually a late event. Entrance of tumour into parapharyngeal space allows superior or inferior spread from the base of skull to the root of the neck. Perineural spread is an important pathway, especially in squamous cell carcinoma and this predicts a poorer rate of local control when managed with surgery.[57]

Lymphatic Spread

Most patients present with spread to the cervical lymph nodes. Some patients may present with squamous cell carcinoma in a cervical Lymph Node and the primary site of origin remained undetermined in approximately 60% of patients.[58, 59] A primary site might appear later but some may never show a primary site.[60]

Evaluation of a Patient with Head and Neck Cancer

Symptoms Includes Persistent complaints of loose teeth, ill-fitting dentures, otalgia, a sore throat or hoarseness. A firm neck mass in an elderly smoker/drinker must be considered a metastatic squamous cell cancer until proven otherwise.[2] About 90% of patients with head and neck squamous cell cancer will have an identifiable primary tumor somewhere in the upper aerodigestive tract mucosa. Thus, cancer in the neck generally represents a metastatic spread from a primary tumor. Other common symptoms are nasal discharge, epistaxis, nasal obstruction, tinnitus, hearing loss, recurrent ear discharge, headache, diplopia, squint, facial numbness, slurring of speech, weight loss and difficulty in swallowing or limited mouth opening[2,61] A "hot potato" voice suggests a lesion in the tongue base, oropharynx or hypopharynx.[1]

Examination of the Head and Neck

The entire accessible mucosa of the upper aerodigestive tract must be examined. Multiple primary tumors may develop simultaneously or metachronously. The mouth is examined thoroughly. This includes examination of the gums, the inner aspect of the cheeks, the tongue, the hard and soft palates, the tonsils. At the end of the oral cavity inspection, the tongue (especially the base) and the floor of the mouth should be palpated with a gloved finger. Since this will make the patient gag momentarily, it is preferably saved for last. Trismus suggests a deeply infiltrative process in the oropharynx involving the pterygoid muscles. Examination of all other relevant systems (e.g. respiratory system, gastro-intestinal system and central nervous system) should also be done.

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Investigations and Work-Up

Examination of head and neck carcinoma should include a flexible fiber optic panendoscopy and, when the instrumentation and experience exist, an indirect video endoscopic examination. Additional pretreatment evaluation includes a scan of the head and neck, a chest radiograph at the time of initial visit, CT Scan from skull base to the clavicle with contrast (which is the scan of choice for head and neck sites) and an MRI Scan. An ultrasound scan , as well as a PET-CT study and bone scan may be done. Routine blood work should include a complete blood count, electrolytes, liver function tests, Alkaline phosphates', total protein, albumin, blood urea and creatinine. Baseline hormonal profile may also be done.[2]

Staging

Following extensive clinical and radiological evaluation, the cancer is assigned a stage. The American Joint Committee of Cancer (AJCC)[62] recommends the Tumor, Node, Metastases (TNM) system of classification. The T, or primary stage, is defined for each anatomy of the specific sites. Generally, T_1, T_2 and T_3 represent increasing tumour size, whereas T4 is defined by invasion of surrounding structures (skin, nerve, blood vessels cartilage, bone). The Node or N stage is identical for most head and neck sites and is outlined in appendix:

NASOPHARYNGEAL CANCER

The nasopharynx is the upper part of the pharynx. The commonest malignancy of the nasopharynx is nasopharyngeal carcinoma, first described as a separate clinical entity by Regaud and Schmincke in 1921. Nasopharyngeal cancer is a malignant neoplasm originating from the mucosal epithelium of the nasopharynx, most commonly the lateral

walls. 82% of these cancers arise from the fossa of Rossenmuller, 12% from the midline and 6% has normal nasopharyngeal mucosa. Nasopharyngeal carcinoma is an uncommon cancer in most parts of the world.[63] The age-adjusted incidence rate (100,000 people per year) among men ranges from 0.6 in the United States and Japan to 5.4 in Algeria, 5.8 in the Philippines, 11.0 in Singapore, 17.2 among Eskimos, Indians, and Aleuts in Alaska to 17.8 and 26.9 in Hong Kong and Guangdong province in Southern China, respectively.

In Nigeria nasopharyngeal cancer is the commonest of the head and neck cancer.[5,18,20,32] A bimodal age distribution is observed in low-risk populations. The first peak incidence arises between 15 – 25 years of age. With the second peak at 50 to 59 years of age.[62] In high-risk populations, the peak incidence occurs in the fourth and fifth decades of life. Both genders have a similar age distribution; however, the male-to-female incidence ratio is 2:1 to 3:1. This distinct racial and geographic distribution of nasopharyngeal carcinoma suggests a multifactorial cause. Current epidemiologic and experimental data identify at least three important etiologic factors: (i) genetic, (ii) environmental, and (iii) viral. World Health Organization (WHO) classified nasopharyngeal cancer into 3 histological subtypes: Type 1 represents well differentiated keratinized squamous cell cancer; Type 2 is moderately differentiated non-keratinized carcinoma; Type3 is the undifferentiated type which typically contains a lot of inflammatory cells like lymphocytes – hence the name lymphoepithelioma. However, more than one histological type exists in 26% of cases. Whereas Type1 (which has been associated with smoking) is the commonest type among US- born Chinese and whites, WHO Type3 (which is strongly associated with Ebstein-Barr virus infection and inflammatory cells) is the most common among Chinese who reside in Hong Kong, Taiwan and Macao. It commonly invades adjacent structures

like the posterior nasal cavity, Eustachian tubes, soft palate, skull base, cavernous sinus, cranial nerves and paranasal sinuses. Due to vulnerability to invasion of these structures, nasopharyngeal cancer commonly presents with nasal obstruction, anosmia, epistaxis, nasal quality of voice, serous otitis, hearing loss, pseudo- gradenigo syndrome, cranial nerve palsies (especially V and VI). 60 – 72% of patients present with cervical nodal metastasis.[45]

Because of the deep-seated location of the nasopharynx and the anatomic proximity to critical structures, radical surgical resection is very difficult. The role of surgery is therefore limited to biopsy for histological confirmation of malignancy and salvage of persistent or recurrent disease. Megavoltage radiotherapy is thus the mainstay of treatment. Concurrent chemotherapy has been shown to have significant survival benefit.

Radiotherapy

Prior to radiotherapy, all patients should have dental evaluation and dietician consultation. They should be advised to abstain from smoking and drinking alcohol. The patient is set in a supine position with head extended and a customized thermoplastic mask covering the head to shoulder region is made to help in immobilizing the patient. Computerized planning for Intensity-Modulated Radiotherapy (IMRT) is recommended. Fusion of diagnostic Magnetic Resonance Imaging (MRI) with planning CT is useful for accurate delineation of the target tumor and critical structures. A mouth-bite minimizes dose to the oral cavity for patients treated by conventional two-dimensional technique. The target volume encompasses the primary tumor and potential routes of spread, and the entire lymphatic drainage of the neck. The patient is treated initially with a bilateral, large facio-cervical field which covers the target volume in continuity-including the spinal

cord, to a dose not exceeding 40Gy given in four weeks with 2Gy daily fractionation. The volume is then divided into an area covering the primary tumor-which is treated with 2 small opposing lateral fields, and the rest of the neck (sparing the spinal cord). However, low cervical nodes may have to be treated with direct anterior field because of the position of the shoulders, using half beam blocking at the junction with the lateral fields, with central shielding to protect the spinal cord and larynx. If the posterior deep cervical nodes have not regressed sufficiently or the depth dose is inadequate, a small electron boost is given to residual disease. Thus the total dose to the tumor is 66Gy in 33 fractions over 6 and half weeks. Development in Computerized 3D Planning is a very important technical advance for treatment of nasopharyngeal cancer (as well as all head and neck cancers) with proven better tumor dose coverage while reducing normal tissue dose in comparison with conventional 2D techniques. IMRT techniques offer a further improvement in conformity of dose distribution, because it has the clear advantage of sculpting the high-dose volume with dose gradients around the targets. Doses up to 70Gy may be delivered to the tumor volume with minimal toxicity.

Chemotherapy

As a result of the notorious predilection of nasopharyngeal cancer for haematogenous dissemination and the need for further improvement of local control, systemic chemotherapy is usually needed for patients with advanced locoregional disease. Methotrexate, Bleomycin, 5-Flourourcil, Cisplatin, Carboplatin and Adriamycin have been studied extensively as individual agents for not only nasopharyngeal tumours, but all head and neck carcinomas, More recently, Ifosfamide, Taxanes and Vinorelbine have been shown to have some activity. Multiple attempts have been made to improve single-

agent response rates with combination chemotherapy. A number of studies using Methotrexate, Bleomycin, 5-Flourouacil, Cisplatin, Carboplatin and Taxanes in a variety of schedules have been reported.

Concurrent Chemotherapy and Radiotherapy

Bleomycin, 5-Flourouacil, Methotrexate and Cisplatin have been administered synchronously with radiation therapy in attempts to demonstrate synergistic effect. Most uncontrolled studies suggested improved tumour responses and some gain in survival for patients with unresectable disease. However, enhance mucositis has been a common limitation of combined treatment

Surgery

Apart from biopsy for histological diagnosis, surgical salvage has a place in the management of patients who develop local or nodal persistent/recurrent disease without distant metastasis. Radical neck dissection may be done for patient with nodal failure following radiotherapy. For selected patients with persistent/recurrent disease localized in the nasopharynx, surgical salvage by nasopharyngectomy is an option.

Brachytherapy

For patients with persistent/recurrent tumor extending beyond the lymph node confines and involving nearby structures, addition of after – loading brachytherapy to the tumor bed following radical dissection might be useful.

PARANASAL SINUSES AND NASAL CAVITY

Cancers of paranasal sinuses are relatively uncommon. Fewer than 4,500 cases are diagnosed each year in the United States, an incidence of 0.75 per 100,000. Cancers of the maxillary sinus are twice as common as those of the nasal cavity: Cancers of the ethmoid, frontal, and sphenoid sinuses are extremely rare.[64] They generally develop after the age of 40 years. Except for esthesioneuroblastoma which has a unique bimodal age distribution and occurs twice as often in men than in women. These tumors are most common in Japan and South Africa. The etiologic factors vary by tumor type and location. Adenocarcinoma of the nasal cavity and ethmoid sinus have been reported to occur more frequently in carpenters and saw-mill workers who are exposed to wood dust,[63, 65, 66] Synthetic wood, binding agents, and glues may also be involved as co-carcinogens. Squamous cells carcinomas of the nasal cavity has been seen more often in nickel workers. Maxillary sinus carcinomas have been associated with radio-active thorium-containing contrast material (thorotrast) used for radiographic visualization of the maxillary sinuses in the past. Occupational exposure in the production of chromium, mustard gas, isopropyl alcohol, and radium also may increase the risk of sinonasal carcinoma. Cigarette smoking is reported to increase the risk of nasal cancer, with a doubling of risk among heavy or long-term smokers and a reduction in risk after long-term cessation. After adjustment for smoking, a significant dose-response relationship has also been noted between alcohol consumption and risk of nasal cancer.[67] The symptoms include nasal obstruction, epistaxis, diplopia, epiphora, a lump in the face or about the eye, “sinus pain” ill-fitting dentures or loosing of maxillary teeth. Sinus cancer is mostly

squamous carcinomas, but others may also be found e.g adenocarcinomas, sarcoma, esthesioneuroblastoma and lymphomas.

Nasal cavity and Paranasal sinuses

Treatment of nasal cavity and paranasal sinus tumors involves interplay of surgery, radiotherapy and chemotherapy. The extent of each modality depends on the stage of the disease. For nasal vestibule tumors, primary radiotherapy may be preferable for better cosmetic outcome, although surgery can yield a high control rate with excellent cosmetic result in selected small superficial tumors. Radiation can be delivered by external-beam irradiation, brachytherapy or both. For nasal cavity and ethmoid sinuses, radiotherapy and surgery are equally effective for early lesions. Thus, the choice of therapy depends on size, locations and anticipated cosmetic outcome. Traditionally, however, ethmoid sinus carcinomas have been managed with surgery and postoperative radiotherapy. Selected cases may be managed with radiation alone or with radiotherapy and concurrent chemotherapy to avoid structural or functional deficits. For maxillary sinus tumors, surgery alone can yield a high control rate for patients with T1 or T2 tumors of the infrastructure. For patients with more advanced lesions, the combination of surgery and postoperative radiotherapy is the treatment of choice.[68] Radical maxillectomy with or without orbital exenteration may be necessary. Chemotherapy may be used in the neoadjuvant setting (to reduce tumor volume), or as concomitant chemotherapy. In general, concomitant chemotherapy is more effective than neoadjuvant chemotherapy with respect to local control. Chemotherapy may also be used for palliative care.

Cytotoxic agents of proven effectiveness for these tumors include Cisplatin, Bleomycin, Etoposide, Methotrexate and Taxanes – commonly used in various combinations. Since most cancers are advanced at the time of diagnosis, a combination of surgery and radiation is necessary to optimize local control. However, even with combination therapy, local control is rarely accomplished. The sequence of combination treatment appears to have little impact on the overall result.[67]

Oral Cavity

The oral cavity is composed of the lip, anterior 2/3 of the tongue (oral tongue), floor of the mouth, buccal mucosa, gingiva, hard palate and retro molar trigone. A study from lagos Nigeria, showed peak age of incidence of oral cancer was in the fifth decade of life[55] As elsewhere in the head and neck, squamous cell cancer is the most common type of malignancy except in the hard palate, where most tumors originate from the minor salivary glands and are adenocarcinoma.

Oropharynx

The oropharynx is continuous with oral cavity anteriorly, the larynx and hypopharynx posterior-inferiorly, and superiorly with the nasopharynx. Oropharynx include the tonsil, base of tongue, soft palate and the portion of the pharyngeal wall the nasopharynx and the pharyngoepiglottic fold. Normal function of the oropharynx is critical for speech and swallowing. Most cancers of the base of tongue and tonsil are squamous cell carcinomas, which are typically poorly differentiated for base of the tongue. However, for the soft palate, salivary gland tumors and lymphomas also occur. Patients with cancer of the oropharynx commonly present with cervical Lymphadenopathy, with the jugulodigastric lymph nodes being most commonly involved. Radiation therapy or surgery is equivalent

treatment for patients with early-stage disease. But due to common involvement of cervical lymph nodes bilaterally, radiation therapy is usually recommended for early-stage patients. More advance tumors (T_3 and T_4) are managed by radiation therapy alone, or by surgery with post-operative radiation. Advanced tumors often require a "Composite resection" (or jaw-neck resection/disscetion).

For tumors of the tonsilla fossa and/or soft palate, T1 lesions less than 1 cm can be treated with surgical resection or irradiation to the primary lesion to a dose of 66 Gy in 33 fractions. The majority of T2 tumors of these regions are treated by irradiation – the ipsilateral neck inclusive, be it electively or because of N+ disease. For T3 and T4 tumors, surgery of the primary is often advocated and may involve removal of the primary tumor, partial removal of the mandible in combination with an Ipsilateral neck dissection. Because of high incidence of a recurrence with surgery alone, surgery is followed by postoperative radiotherapy. Tumors of the base of tongue, in every stage can be treated by external-beam radiotherapy, interstitial radiotherapy or surgery; whereas more advanced lesions are treated by surgery plus Postoperative radiotherapy. Also, external-beam radiotherapy followed by a boost of interstitial radiotherapy or intraoral cone and/or Concomitant chemotherapy for more advance lesions, is frequently used. With regards to tumors of the lateral and posterior pharyngeal walls, these tumors generally do not do so well with either radiotherapy or surgery as opposed to previously mentioned oropharyngeal tumors.

Hypopharynx

The hypopharynx consists of the pyriform sinus, the posterior pharyngeal wall and the postcricoid space. The lymphatic of the hypopharynx are abundant, and roughly 75% of patients present with lymph node mestastasis.

Pyriform sinus carcinoma account for the larger majority of hypopharyngeal cancer. Cancers of the posterior pharyngeal wall account for 15% of hypopharyngeal tumors

For early lesions of the pyriform sinus (T_1 and selected T_2), management may be successful with partial laryngopharyngectomy or radiation therapy. For more advance lesions (T_3 and T_4), total largngectomy or laryngopharyngectomy with postoperative radiation therapy is the common treatment of choice. This treatment however, requires flap reconstruction. Radiation portals include the primary disease as well as regional lymph nodes. For advanced pyriform sinus cancers, combination surgery and radiation therapy is reported to give better local control compare with radiation therapy or surgery alone.

Larynx

The larynx is divided into the supraglottis, glottis, and subglottis. The supraglottis consist of the epiglottis, false vocal cords, laryngeal ventricles, aryepiglottic folds, and the arytenoids. The glottis includes the true vocal cords and the anterior commissure. The subglottic is located below the vocal cords. Most supraglottic cancers are squamous cell carcinomas, although adenocarcinoma, small cell and adenoid cystic carcinoma are rarely seen. Supraglottic tumors have a high incidence of clinical lymph node involvement.

For vocal cord cancer, cordectomy may be performing for small lesions of the middle third of the cord. Vertical partial laryngectomy allows removal of limited cord lesions with preservation of voice. For T_1 and selected T_2& T_3 lesions, supracriciod partial laryngectomy may be used, and entails removal of both true and false cords as well as the entire thyroid cartilage. Total laryngectomy with or without neck dissection is the operation of choice for advanced lesions and as a salvage procedure for radiation therapy failure in lesions that are not suited for conservation surgery. Irradiation for T_1 or T_2 vocal cord cancer is delivered by small portals covering only the primary lesions, with the cervical lymph node chain not electively treated. The field size ranged from 4x4cm to 5x5cm (plus an additional 1cm of "flash" anteriorly) and is occasionally 6x6cm for large T_2 lesions. A commonly used dose-fractionation schedule is 66Gy for T1 lesions and 70 Gy for T_2 cancers given in 2-Gy fractions. Irradiation of T3 and T4 lesion requires larger portal, which include the jugulodigastric and middle jugular lymph nodes. The jugular lymph nodes are included in a separate low –neck portal. The initially large portal is treated up to 40Gy in 20 fractions; then reduced portals (covering only the primary lesion) are treated up to 66-70 Gy. Patients with supraglottic laryngeal carcinoma may be considered to be in an early/favorable group suitable for radiation therapy or conservation laryngectomy. Treatment of the primary lesions for the early group is by external-beam irradiation or supraglottic laryngectomy, with or without adjuvant irradiation. Although a subset of patients with unfavourable disease may be surgical option. Selected lesions, especially exophytic type, may be treated by radiotherapy with concomitant chemotherapy with total laryngectomy reserved for radiation failure.

Salivary Gland

Seventy percent of all salivary tumors arise in the parotid gland, 8 percent in the submandibular gland, and 22 percent in the minor salivary glands.[69] The proportion of malignant tumors increase from parotid (25%) to submandibular (43%) to minor salivary glands (65%).[68,70] There is a preponderance of benign tumors in women; malignant tumors exhibit an equal sex distribution.[71] Patient with benign tumors are younger (mean age, 46years) compared with those with malignant tumors (mean age, 54 years), with a trend to an older age for submandibular and minor salivary gland locations.[69] From 2% to 3% of salivary neoplasms occur in children, in whom half of the tumors are malignant.[68] The majority of cancer are located in the parotid gland, with mucoepidermoid cancers predominating. The tumors in children are mostly less advanced, and a 95% 5-year survival is reached.[68] In contrast to cancers in mucosal sites, squamous carcinomas are rare in salivary glands. Usual histologic types are adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma and acinic cell carcinoma. Signs and symptoms vary with site, but the commonest feature is an asymptomatic lump. Symptoms of parotid cancer include pain and facial nerve paralysis. The general management of salivary gland malignancies in most patients includes surgical excision followed by radiation therapy for unfavorable prognostic factors. Postoperative radiotherapy to enhance local control is recommended for T3-4 tumors, close or incomplete resection, bone involvement, perineural invasion, high-grade cancer, and recurrent cancer.[72,73,74] To date, adjuvant chemotherapy has not been considered efficacious. For advanced, inoperable, and recurrent salivary gland cancers, primary neutron therapy may lead to superior local control rates, compared with primary photon therapy, without evidence of improved

survival rates.[75] The use of conventional radiation therapy along with hyperthermia has been reported to have similar efficacy in this patient population.

Surgical technique depends on location and extent of primary disease and regional adenopathy. Preservation of the facial nerve, at least partially, followed by postoperative radiotherapy is the preferable treatment unless the facial nerve is involved by tumor. Aggressive surgery does not improve disease-free survival. A decrease in extended surgery, resulting in a decrease of sacrifice of the facial nerve, has been shown in the course of years. Cable facial nerve grafting with the greater auricular nerve graft decreases the incidence of facial palsy postoperatively, especially if branches and not the main trunk are involved.[76] Adjuvant postoperative radiotherapy has no negative effect on facial nerve function.[73]

The prognosis of salivary gland cancers is closely related to histologic differentiation, with low-grade tumors having a much better prognosis.

Management Head and Neck Cancer

Treatment of head and neck cancers depend on the initial localization of tumor on patients, co-morbidity and/or potential side effect of treatment. Surgical resection, Radiotherapy, Chemoradiation Radiobiotherapy with anti-epidermal growth factor receptor (EGFR) like cetuximab and other anti EGFR is the therapeutic methods in locally advanced cases.

Surgery

This includes resection of tumor and/or its local/regional extension. Preservation of functions such as swallowing, voice or vision and cosmesis must be considered in any management plan. Tumor extension to bone i.e mandible and maxilla usually requires resection and reconstruction to minimize long term morbidity. Metastases to cervical lymph nodes are best treated surgically. In inoperable condition adjuvant radiotherapy and/or chemotherapy may facilitate the need for surgery.

Radiotherapy

Radiotherapy can control many cancers of head and neck with better consequent function and cosmesis than surgery. It is given in fractions: there are no anatomical barriers to radiotherapy, although there are specific tissue tolerance limitations. It can be used as primary treatment or adjuvant to surgery (pre or post op). A dose of 66 to 70Gy in 33 to 35 fractions in 2Gy daily fraction over six to seven weeks.T1 and T2 cancers can be controlled using surgery or radiotherapy. The choice is influenced by tumor site, accessibility, histological grade, patient performance status, vocation or preference.T3 and T4 – combination of surgery and radiotherapy is used in combination with chemotherapy. Machines used to administered radiotherapy include Cobalt 60, linear accelerators, IMRT. IGRT. SRS.

Indications for post op radiotherapy

1. Close or inadequate resection margin
2. Poorly differentiated cancers
3. Extensive involvement of lymphatics including cervical nodes.

Role of Chemotherapy in Head and Neck Cancers

Chemotherapy is useful in adjuvant setting. It can be given as an induction chemotherapy or adjuvant or concurrently with radiation (chemoradiation). Chemotherapy given alone is not curative but when given in combination improves the rate of curability.[77]

Effective agents

Cisplatin, Carboplatin, 5-fluorouracil (5-fu), bleomycin, mitomycin, epirubicin, methotrexate, topotecan, vinorelbine, gemcitabine, Capecitabine, Docetaxol and paclitaxel are active single agents each achieving significant tumor reduction in 15-30% of previously untreated patients. Cisplatin is clearly the most effective drug; it is a potent radio sensitizer. A meta-analysis examining various chemotherapy regimen indicated that platinum containing regimens might provide a survival advantage compared with non cisplatin containing regimen.[78]

Concurrent Chemotherapy with Radiation Therapy (CCRT)

This is the administration of chemotherapy and radiation therapy simultaneously. This is done to increase the efficacy of radiation i.e radiation sensitization in other to achieve synergistic DNA damage, inhibition of repair of sublethal radiation damage, hypoxic cell sensitization, cell cycle synchronization, inhibition of rapid repopulation of tumor cells, decreasing tumor mass which leads to improved blood supply and reoxygenation. This improves both local/regional control and overall survival for patient with high risk, locally advanced cancers of oral cavity, larynx, oropharynx, hypopharynx and nasopharyngeal carcinoma compared with postoperative radiotherapy alone. The greater benefit of chemoradiation is observed in those at highest risk for recurrence. The patient

nutritional status, performance status and co-morbid conditions greatly affect the significance of the response. Chemoradiation is considered for patients in good general condition and with good performance status because it can be associated with substantial toxicity. Two important ongoing CCRT studies that have shown significant impact on disease outcome are the European Organization for Research and Treatment of Cancer [EORTC22931] and the Radiation Therapy Oncology Group [RTOG 9501]. The three years survival rate has improved from 50% to 55% for treatment with radiotherapy alone to about 65% for concurrent chemotherapy with radiotherapy.

Chemotherapy regimen used with radiotherapy (chemoradiation)

Cisplatin alone is used in many clinical trials involving Chemo radiation including in high doses in EORTC 22931 and RTOG 9501.

Examples of regimens are:

1. High dose regimen: cisplatin 100mg/m^2iv given for 3 cycles every 21 days concomitantly with about 66-70Gy radiation in 33-35 fractions in 2.0Gy daily fraction over 6-7 weeks. This regimen causes severe toxic effects such as nephrotoxicity, ototoxicity and neurotoxicity as well as severe mucositis which make the treatment suitable for only patient with normal creatinine clearance and good performance status. Locoregional failure rates are 35-65% depending on stage, tumor location and resectability[79, 80, 81].
2. Weekly regimen: cisplatin 40mg/m^2 iv given weekly concomitantly with radiotherapy described as being well tolerated since there is less toxic effect, there was no nephropenia were prominent.

3. Infusional regimen: cisplatin 40mg/m2/day, plus 5-fu, 600mg/m2/day is given by continuous iv infusion given days 1-4 during the first and sixth weeks of radiotherapy and then two more monthly cycles (also well tolerated). A randomized trial established the use of Cisplatin based chemotherapy. The trial reported by Adelstein et al[82] randomized 295 patients with unresectable locoregional advanced disease to one of three groups: 70Gy radiation administered in conventional daily 2Gy fraction, the same radiation regimen with 100mg/m2 of cisplatin concurrently on days 1, 22 and 43 during radiotherapy and unconventional split courses of radiation with chemotherapy. A median follow up of 41 month showed that single agent cisplatin based chemotherapy was significantly more efficacious, increasing the overall survival at 3 years (37%) for concurrent chemotherapy versus 23% for radiotherapy alone. Despite this, overall survival remained poor. In a later trial by Adelstein et al[83] the addition of 5 flurouracil to Cisplatin appeared to increase the efficacy further with 65.7% of patients alive at 5 years.

Concurrent Cetuximab and Radiotherapy

A marked increase in median survival from 29.3months to 49months was seen when radiation was combined with cetuximab. The 3years survival[84] was 45% for radiotherapy alone and 55% for those receiving combination chemotherapy. This regimen is used in elderly and patients with poor performance status who cannot withstand chemotherapy.

Side effects of Radiotherapy

1. Erythema of skin
2. Conjunctivitis

3. Mucositis in oral cavity, oropharynx, nasopharynx, larynx
4. Epilating involving scalp, facial hair, eyebrows (these are dose related)
5. Edema laryngeal is most serious
6. Alteration of taste
7. Xerostomia
8. Infection most frequent in candidiasis
9. Blurring of vision
10. Inability to sleep
11. Hearing loss
12. Pain on swallowing

Long term Complication

1. Altered taste for salt or sweet
2. Cataract
3. Osteoradionecrosis
4. Cervical myelopathy
5. Skin cancer
6. Epilation

Toxicity of Chemoradiation

Moderate to severe toxicities particularly those affecting swallowing and eating are experienced by the majority of patients undergoing chemoradiation (CCRT). The incidence of mucositis is doubled with chemoradiation compared with radiotherapy alone. The use of gastrostomy tubes for feeding and hydration are usually necessary.[82]

a) Xerostomia develop in 75% of patients and persists in 60% at 1 year after chemoradiation treatment. Persistent problems with sticky saliva, swallowing, chewing or tasting develop in 25% to 35%.

b) At 12 months following treatment, half of patients are still able to eat only soft foods or liquids. Feeding tubes continue to be necessary after 2 years in 25% of patients treated with radiotherapy alone and in 50% treated with concurrent chemotherapy and radiotherapy (CCRT).

c) Because of toxicity, compliance with treatment protocol is often compromised. About 40% of patients do not undergo the third course of high dose cisplatin and 30% require delays in radiotherapy schedule.[82]

Supportive care

1. Acute mucositis – analgesics
2. Opportunistic infections – antibiotics
3. Adequate nutrition
4. Dental care

Prognostic Factors

The most important prognostic factors for patients with primary cancers of the head and neck are primary tumor site, size and extent, and regional/distant metastases. Histological differentiation of epidermoid carcinomas is less important. A major risk factor is a previous head and neck cancer. Continued cigarette smoking and consumption of alcoholic beverages expose the mucosa to known carcinogens. Prognosis correlates strongly with stage at diagnosis

CHAPTER THREE

MATERIALS AND METHODS

3.1 STUDY SITE

The study was carried out in the radiotherapy and oncology department, National Hospital Abuja. The national hospital is located in the central area of the Federal Capital Territory. It is a 200 bedded hospital established in 1999 and initially built for women and children before it was converted to care for all patients and serves as a referral centre for oncology services from all over Nigeria especially from the Northern Nigeria. The Federal Capital territory has an estimated population of 1,406,239 (National population commission 2006) with a population projection of 2,759,829 in 2013.

The radiotherapy and oncology department has been running since the inception of the hospital in 1999. It houses a multiple energy Linear Accelerator, conventional simulator, two brachytherapy machine (low dose rate) and office blocks.

3.2 STUDY POPULATION

The study population include outcome of head and neck cancer patients managed at the radiotherapy department, NHA from January 2009 to December 2013

3.3 SAMPLE SIZE

The study included all histologically diagnosed head and neck cancer cases who met the study criteria that were seen at the radiotherapy department, N.H.A from January 2009 to December 2013. Only those that met the study criteria were evaluated. The research is a

retrospective descriptive study on all patients with histopathology confirmed malignancy of head and neck cancer from January 2009 to December 2013.

3.4 INCLUSION CRITERIA

Patients with histopathology confirmed head and neck cancer from a standard histopathology laboratory managed at the Radiotherapy Dept of National Hospital Abuja.

Patients must have been followed up regularly.

Result and documentation of radiological tests and other relevant investigations must be available.

Patients must have been managed with chemoradiation protocol using weekly cisplatin, 5FU, docetaxel and paclitaxel.

3.5 EXCLUSION CRITERIA

All patients whose tumour had not been histopathologically confirmed or Suspected head and neck cancer cases without histologic diagnosis or with conflicting histology.

3.6 DATA DESCRIPTION AND METHOD OF COLLECTION

All available radiotherapy case notes and treatment records cards of head and neck cancer patients seen from January 2009 to December 2013 were retrieved. Information obtained from radiotherapy case notes and treatment records were patients' bio-data including age at presentation, sex, duration of symptoms, anatomical site, clinical staging, histopathological type grade either as well differentiated (G1), moderately differentiated (G2), or poorly differentiated (G3), The patients were staged at time of presentation using the 2010 edition of the American Joint Committee on Cancer (AJCC). The details of treatment received was taken into consideration; chemoradiation, radiotherapy, type of

surgery and chemotherapy. The status of patients was determined. The time of completion of treatment, time of first locoregional recurrence and/or metastasis after completion of treatment were also noted. The above information was extracted from records using a data extraction form.

3.7 DATA MANAGEMENT

The data were carefully entered, cleaned and analyzed using SPSS version 20. Regular cleaning and editing were done to detect and correct errors. Frequency tables were done for all the variables collected, the sample size was compared with the number for each variable to ensure they coincided in number.

3.8 DATA ANALYSIS

Demographic and treatment variables of patients were presented in tables, histogram and bar charts using frequency, percentage. Independent variables such as age, sex, stage of disease, clinical presentation, metastasis, histology, grade and treatment outcome.

3.9 DATA MANAGEMENT

The data obtained was analysed using the Statistical Package for Social Sciences version 20 (SPSS). Data analysed was presented using percentages, tables and charts.

3.10 ETHICAL CONSIDERATIONS

Ethical clearance to conduct the study was sought from the Joint Ethical Review Committee of the National Hospital Abuja.

3.11 CONFIDENTIALITY OF THE DATA

All information collected in this study were coded serial numbers and hospital numbers with no names of patients used to maintain confidentiality. The numbers cannot be linked

to the patients in anyway and names and any identifier will not be used in any publication or reports from this study. The data extraction forms were kept in a locked cupboard, the data entered on the computer was password protected and was accessible to the researcher only.

3.12 BENEFICENCE TO PATIENTS

The results of this study will increase the body of knowledge on survival of patients with head and neck cancer for the use of stakeholders in head and neck cancer management, patients and general public.

3.13 NON-MALEFICENCE TO PATIENTS

The study was non-invasive and without any harm to the patients.

CHAPTER FOUR

RESULTS

The results of this study are presented below.

Three hundred and eighty four patients were eligible during the study period. Figure1 showed age ranged between >1-90 years with the mean age being 47.2 (SD=11.5) years. Two hundred and fourty eight patients (64.6%) presenting with head and neck cancer were men and one hundred and thirty six patients were women. (35.4%). Male to female ratio was 2:1. (62.3%) had formal levels of education, while the rest had no formal levels of education (37.7%). Majority were married (70.8%) and employed (71.1%) at the time of presentation in the hospital. More than one third of the patients were civil servants (41.8%). Head and neck cancer patients presenting at the clinic had a distribution that cut across the geographical zones in the country with South East constituting the majority 34.5%. and South West has the lowest.

Table 1 showed various clinical symptoms at presentations multiple symptoms-31.7%, neck mass 15.7%, pain 10.6%, headache 7.6%, nasal obstructions 6.8%, nasal discharge and difficulty in breathing 6.0% and 5.6%.

Table 2 showed nasopharynx to be the commonest anatomical site 26.6%, larynx 12.0%, oral cavity 13.5%, sinonasal region12.5%, oropharynx 5.2%, orbit 11.5% and salivary gland 8.3%, Table 3 showed moderately differentiated squamous carcinoma (23.2%) as the most prevalent histology seen, followed by well differentiated squamous cell carcinoma (16.7%), poorly differentiated squamous cell carcinoma (15.5%) sarcoma (9.9%), mucoepidermoid(5.5%), adenocarcinoma and non Hodgkin lymphoma (3.6%), Other histology types were not common.

Figure 2 was stage of disease at presentation. Majority of the patients presented in the late stage of the disease. Stage IV(42%), stage III (29%). Few patients (11%) presented with stage I and

(18%) with stage II. more than two thirds of the patients (72.1%) presented with metastatic disease, 34.9% of them had multiple sites of metastasis. Table 5 shows single agent chemotherapy administered to the patients. More than half of the patients 173(54.7%) had 40mg of weekly cisplatin, 69(21.8%) had 1g of weekly 5FU, 45(14.2%) had 20mg/m^2 of weekly docetaxel and 29(9.1) had 80mg of weekly paclitaxel. Table 6 shows external beam radiotherapy offered to the patients. 224(64.5%) received 66Gy over the period of six and half weeks, 95(25.6%) had 60Gy over the period of six weeks, while 31(9.8%) had 54Gy over five and half weeks. Figure 3 shows nature of response to treatment at six months of follow up. 70% of patients had complete response, 23% partial response and 7% no response. Table 8 shows outcome of concurrent chemoradiation at two years of treatment to different anatomical site. Patients with nasopharynxgeal cancer had local recurrence of 18%, distant metastases 6.7%, recurrence and metastases 4.5%. Patients with cancer of the larynx, 15.2% had local recurrence, 6.5% distant metastases, 6.5% recurrent and metastases. Sino nasal cancer patients, 25.6% had local recurrence, 12.8% distant metastases, Patients with cancer of the oral cavity 19% had local recurrence and 11.9% had distant metastases. 22.2% had local recurrence of orbital cancer and 7.4% had distant metastases. while patients with oropharyngeal cancer 26.7% had local recurrence and 20% distant metastases . Table 9 shows outcome of concurrent chemoradiation at two years of follow up to different anatomical site.

For patients with cancer of the nasopharynx, , 40.5% were disease free, 48.3% alive with the disease, while 11.2% died of the disease. , 39.1% of laryngeal cancer patients were disease free, 54.3% alive with the disease and 6.5% died of the disease. 30.8% of Sino nasal cancer were disease free, 56.4% alive with the disease, and 12.8% died of disease. 33.3% of patients with cancer of the oral cavity were disease free, 66.7% alive with the disease, while 16.7% died

of disease. , 40.7% of orbital cancer were disease free, 44.4% live with disease, and 14.8% died of the disease. 64% of salivary gland tumours were disease free, 28%, alive with disease, while 8% died of disease. 36.7% of oropharyngeal cancer patients were disease free, 46.7% alive with disease and 16.7% died of disease. Figure 4 shows overall survival for concurrent chemoradiation at two years of follow up. Out of the 316 patients . 124(39.2%) were disease free, 136 (43.3%) alive with the disease, 40 (12.6%) died of the disease, 16 (5.6%) were lost to follow-up. Table 10 shows outcome to single agent chemotherapy at five year of follow up. More than half of the patients 179(56.6) received 40mg 0f weekly cisplan with good response than 5FU, docetaxel and paclitaxel, At five year of follow up, 41(23.6%) of patients that received weekly cisplatin were disease free. 16(23.1%) of patients that had weekly 5FU were disease free while 8(27.5%) of patient that received paclitaxel were disease free.

The outcome of chemoradiation at five years of follow up to different anatomical site were showed in table 11. 22.4% of patients with cancer of the nasopharynx were disease free,41.6% alive with disease, and 36% died of disease. 23.9% of cancer of the larynx were disease free, 47.8% alive with disease and 28.3% died of disease. 23.1% of sino nasal cancer were disease free, 35.9% alive with disease and 41% died of disease. 16.7% of oral cavity cancer were disease free, 45.2% alive with disease and 38.1% died of disease. Patients with orbital cancer, , 33.3% free of disease, 5.9% alive with disease, while 40.7% died of disease. Almost half of patients with salivary gland tumour, 48% were disease free, 24% alive with disease, 28% died of disease. Majority of patients with oropharyngeal cancer died of disease 43%, 36.7% alive with disease, 20% were free of the disease.

Figure 5 shows overall survival at 5 years follow up. Out of the 316 patients managed with chemoradiation. At five years 78 (24.6%) were disease free, 99 (31.3%) alive with the disease, 114 (36.7%) died of the disease, 25 (7.9%) were lost to follow-up.

Figure 6 shows overall survival at 5 years follow up for patients who had radiotherapy alone. A total 97 patients had radiotherapy alone. 14 (14.4%) were disease free, 36 (37.1%) alive with the disease, 30 (30.9%) died of the disease, 17 (17.5%) were lost to follow-up, probably on account of either complications of treatment, financial constraint, disease progression or unreported deaths.

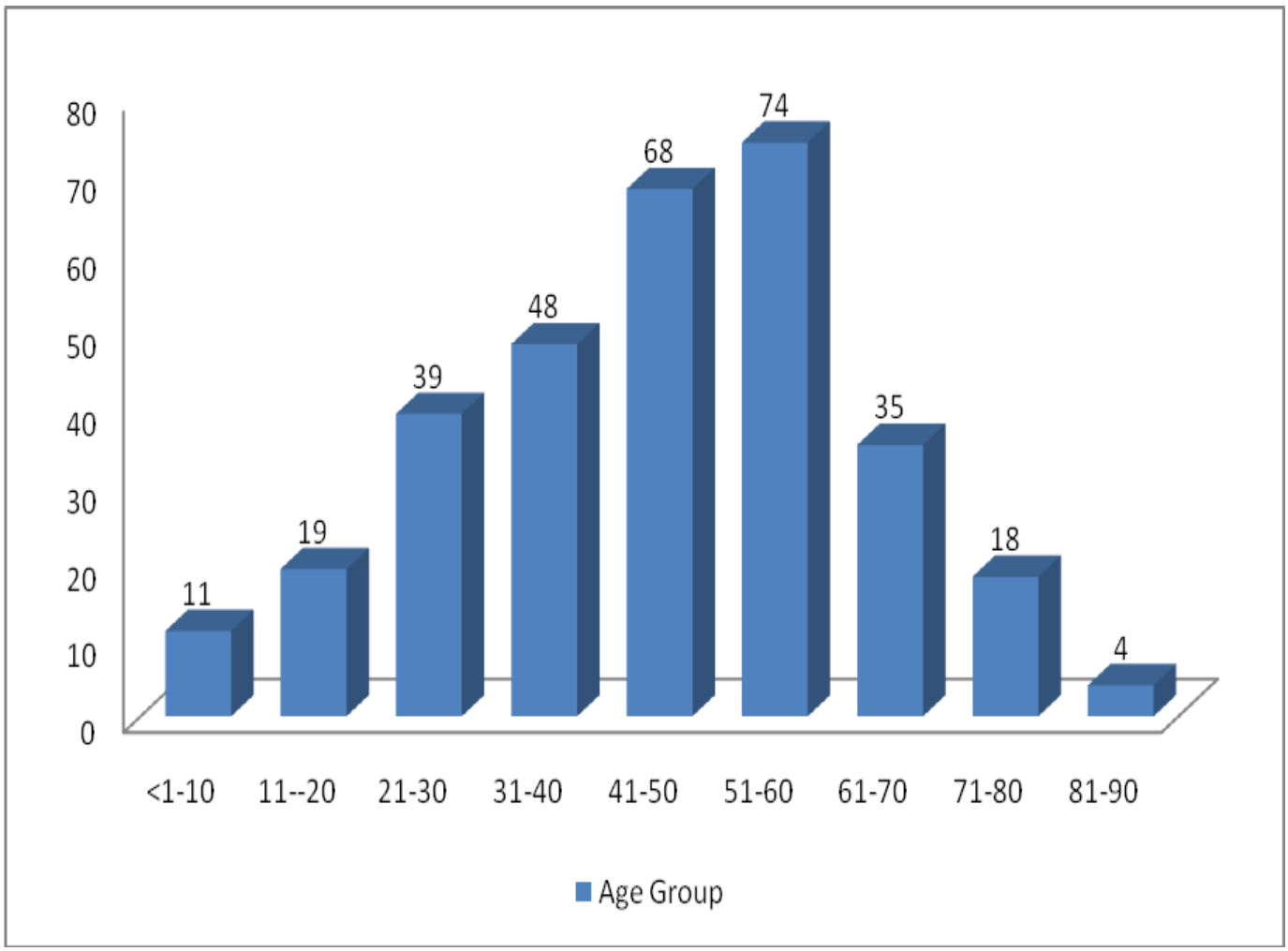

Figure 1: Age Distribution of all the Patients

Table 1: Pattern of Clinical Presentations

Clinical features	Frequency	Percentage
Neck mass	248	15.7
Pain	168	10.6
Headache	125	7.9
Nasal Obstruction	107	6.8
Nasal Discharge	95	6.0
Difficulty in Breathing	88	5.6
Dysphagia	79	5.0
Aural symptoms	78	4.9
Epistasis	76	4.8
Loss of vision	72	4.6
Sore throat	65	4.1
Decreased hearing	53	3.4
Tinnitus	48	3.0
Hoarsiness of voice	47	3.0
Ear pain	36	2.3
Trisinus	36	2.3
Neurologic symptoms	35	2.2
Ulcer at primary site	35	2.2
Distant metastasis	32	2.0
Leukokoria	28	1.8
Diplople	14	0.9
Ear discharge	10	0.6
Strabismus	6	0.4
Total	1581	100.0

Table 2: Anatomical location of the tumours

Anatomical site	Number of patients	%
Nasopharynx	102	26.6
Oral cavity	52	13.5
Sinonasal region	48	12.5
Larynx	46	12.0
Orbit	44	11.5
Salivary Gland	32	8.3
Others	21	5.5
Oropharynx	20	5.2
Thyroid Gland	19	4.9
Total	384	100.0

Table3: Histological types of head and neck cancer

Histopathology	Frequency	Percentage
SCC Moderately differentiated	89	23.2
SCC well differentiated	64	16.7
SCC poorly differentiated	52	13.5
Sarcoma	38	9.9
Muroepidermoid	21	5.5
Undifferentiated	14	3.6
Adenocarcinoma	14	3.6
Non Hodgkins	13	3.4
Carcinosarcoma	10	2.6
Hodgkins lymphoma	8	2.1
Lymphoepithelioma	8	2.1
Pleiomorphic adenoma	6	1.6
Anaplasttic	4	1.0
Others	43	11.2
Total	384	100.0

Table 4: Variants of squamous cell carcinoma

Types	No. of patients	%
SCC Moderately differentiated	78	36.4
SCC well differentiated	61	28.5
SCC poorly differentiated	47	22.0
Undifferentiated	14	6.5
Lymphoepithelioma	8	3.7
Anaplastic	4	1.9
SCC Baseloid	2	0.9
Total	214	100.0

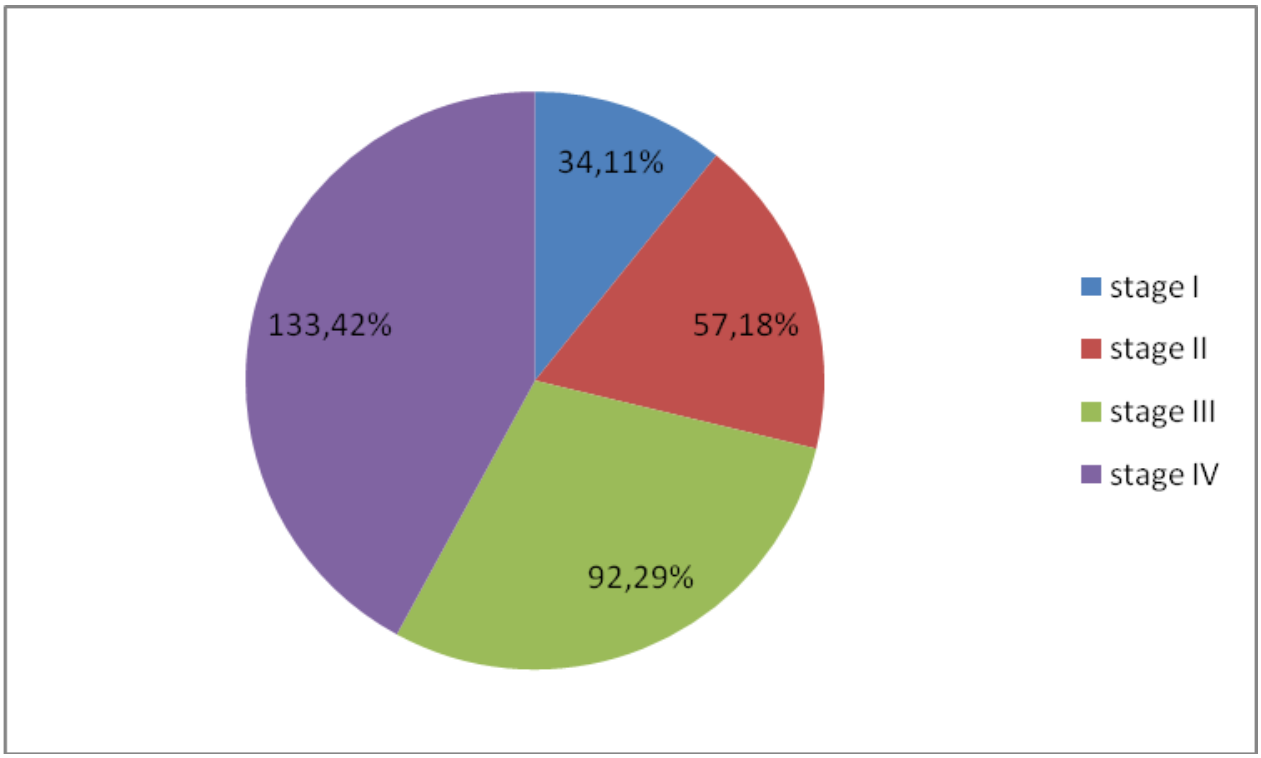

Figure 2: Stages of Disease at time of presentation

Table 5: Single agent chemotherapy administered to patients for chemoradiation**.**

Single agent chemotherapy	No. of patients	Percentage (%)
Cisplatin 40mg weekly	173	54.7
5FU 1000mg weekly	69	21.8
Docetaxel 20mg/m^2 weekly	45	14.2
Paclitaxel 80mg weekly	29	0.1
Total	316	100.0

Table 6 External beam radiotherapy offered to the patients

Dose of radiotherapy	No. of patient	Percentage
66Gy/33#/6.5 weeks	224	64.5
60Gy/30#/6 weeks	95	25.6
54Gy/27#/5 weeks	32	9.8
Total	351	100.0

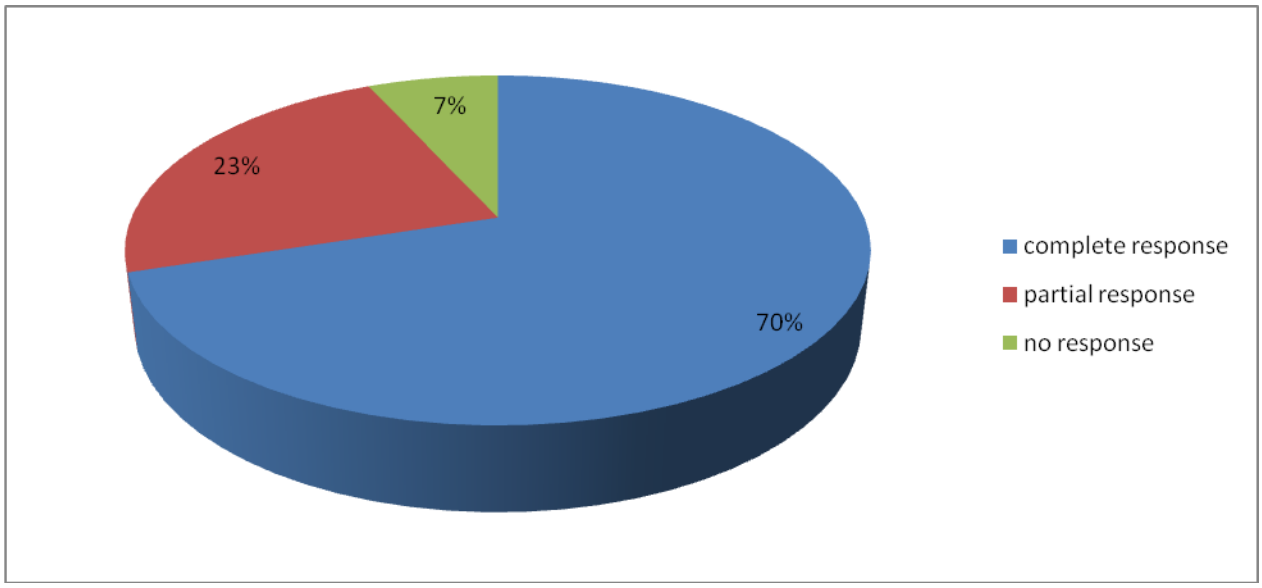

Figure 3 : Nature of response to chemoradiation at six month of follow up

Table 7: Types of treatment modalities for the anatomical site

No. of Patients	Primary tumour site	Chemodiation %	Radiotheraphy alone %	Chemotherapy alone %	Radiotheraphy before Chemotherapy	Chemotherapy before Radiotheraphy
102	Nasopharynx	75(73.5)	10(9.8)	8(7.8)	7(6.9)	2(2.0)
52	Larynx	29(55.8)	17(32.7)	4(7.7)	2(3.8)	-
48	Sinonasal	26(54.2)	13(27.1)	2(4.2)	6(12.5)	1(2.1)
46	Oral cavity	38(82.6)	5(10.9)	3(6.5)	-	-
44	Orbit	11(25.0)	24(54.5)	6(13.6)	-	3(6.8)
32	Salivary	5(15.6)	16(50.0)	4(12.5)	2(6.3)	5(15.6)
20	Oropharynx	16(80.0)	1(5.0)	-	3(15.0)	-
19	Thyroid grand	-	11(57.9)	3(15.8)	5(26.3)	-
21	Others	13(61.9)	4(19.0)	1(4.8)	1(4.8)	2(9.5)

Table 8: Outcome of chemoradiation at two year of treatment to different anatomical site

Primary tumour site	No. of Patients	Local recurrence n(%)	Metastases n(%)	Recurrent and metastases n(%)
Nasopharynx	89	16(18.0)	6(6.7)	4(4.5)
Larynx	46	7(15.2)	3(6.5)	3(6.5)
Oral cavity	42	8(19.0)	5(11.9)	4(9.5)
Sinonasal	39	10(25.6)	5(12.8)	3(7.7)
Oropharynx	30	8(26.7)	6(20.0)	5(16.7)
Orbit	27	6(22.2)	2(7.4)	2(7.4)
Salivary	25	2(8.0)	2(8.0)	1(4.0)
Others	18	5(27.8)	1(5.6)	2(11.1)
Total	316	62	30	24

Table 9: Outcome of chemoradiation at two years of follow up to different anatomical site

Primary tumour site	No. of patients	Died of Disease %	Alive with Dx %	Disease free %
Nasopharynx	89	10(11.2)	41(48.3)	31(40.5)
Larynx	46	3(6.5)	25(54.3)	18(39.1)
Sinonasal	39	5(12.8)	22(56.4)	12(30.8)
Oral cavity	42	7(16.7)	28(66.7)	14(33.3)
Oropharynx	30	5(16.7)	14(46.7)	11(36.7)
Orbit	27	4(14.8)	12(44.4)	11(40.7)
Salivary	25	2(8)	7(28)	16(64)
Others	18	4(22.2)	5(27.8)	9(50.0)
Total	316	40	154	122

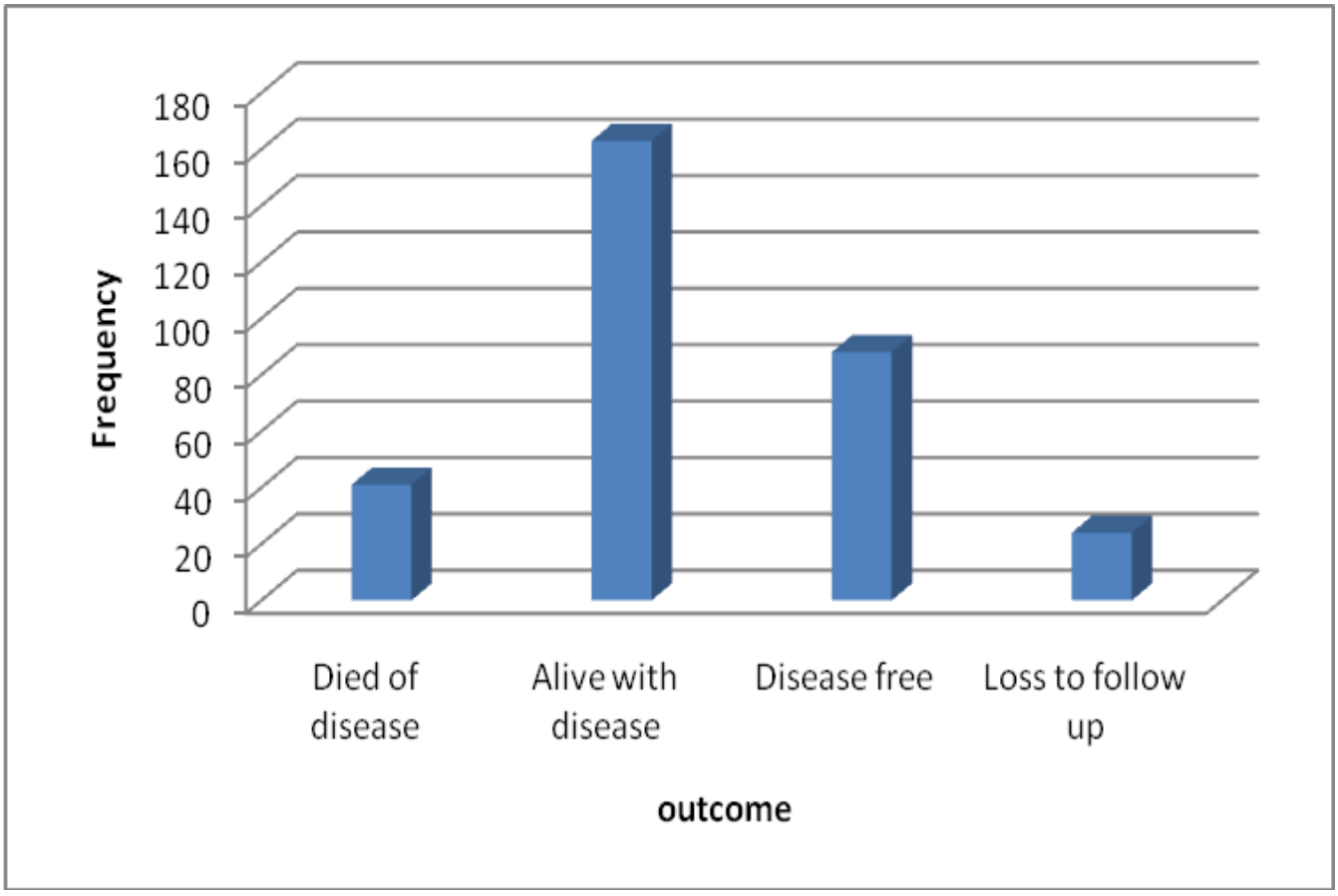

Figure 4: Overall survival at two years of treatment with chemoradiation.

Table 10: Outcome of single agent chemotherapy at 5 year of follow up

Chemotherapy agent	No of patients	Died of disease %	Alive with DX %	Disease free
Cisplatin	179	53(30.6)	79(45.6)	41(23.6)
5FU	69	24(34.7)	29(42.0)	16(23.1)
Docetaxel	45	21(46.6)	11(24.4)	13(28.8)
Paclitaxel	29	18(62.0)	3(10.3)	8(27.5)
Total	316	116	122	78

Table11: Outcome of chemoradiation at five years of follow up to different anatomical site

Primary tumour site	No. of Patients	Died of Disease %	Alive with Dx %	Disease free %
Nasopharynx	89	32(36.0)	37(41.6)	20(22.4)
Larynx	46	13(28.3)	22(47.8)	11(23.9)
Sinonasal	39	16(41.0)	14(35.9)	9(23.1)
Oral cavity	42	16(38.1)	19(45.2)	7(16.7)
Oropharynx	30	13(43.3)	11(36.7)	6(20.0)
Orbit	27	11(40.7)	7(25.9)	9(33.3)
Salivary	25	7(28.0)	6(24.0)	12(48.0)
Others	18	8(44.4)	6(33.3)	4(22.2)
Total	316	116	122	78

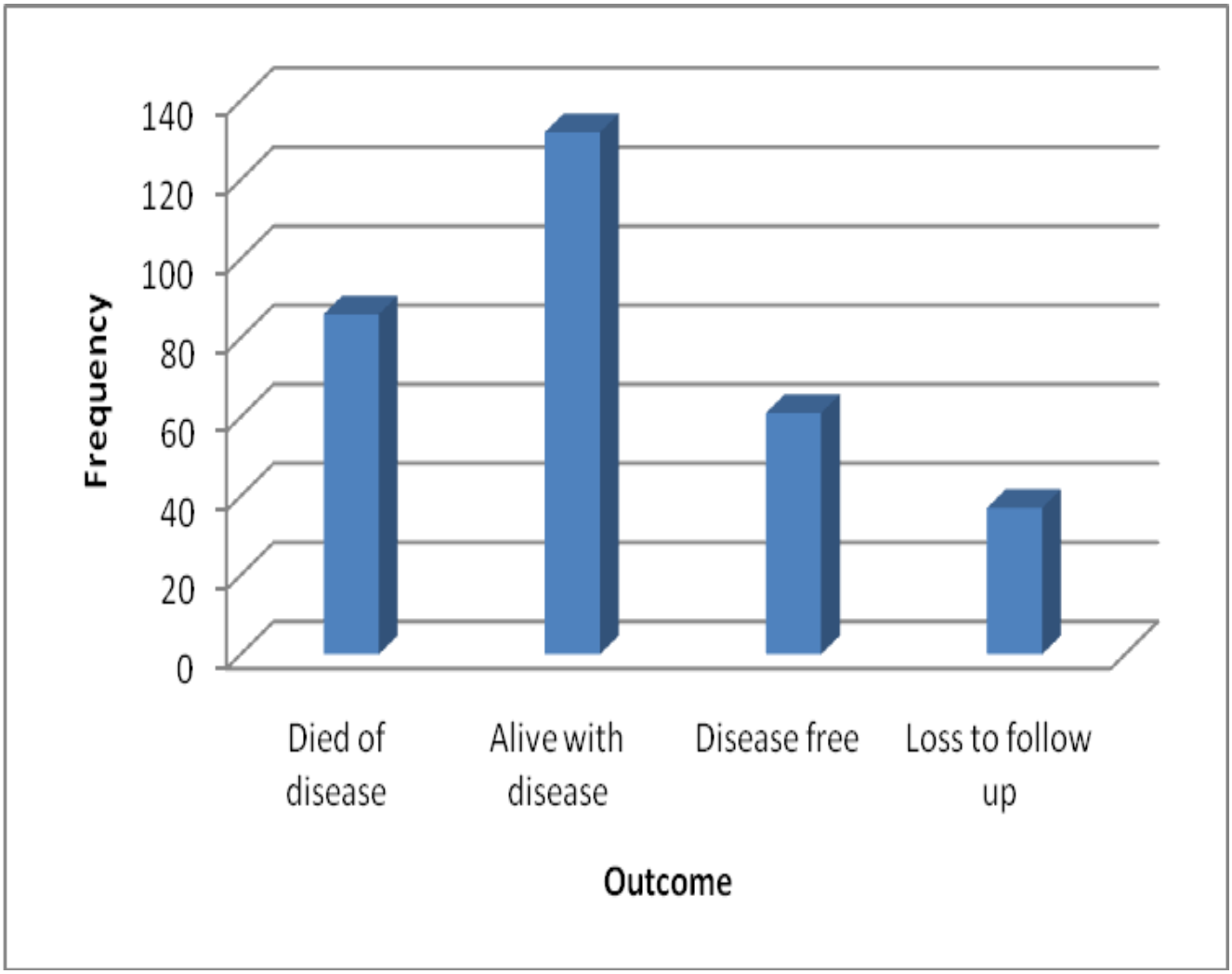

Figure 5: Overall survival at five years of treatment with chemoradiation

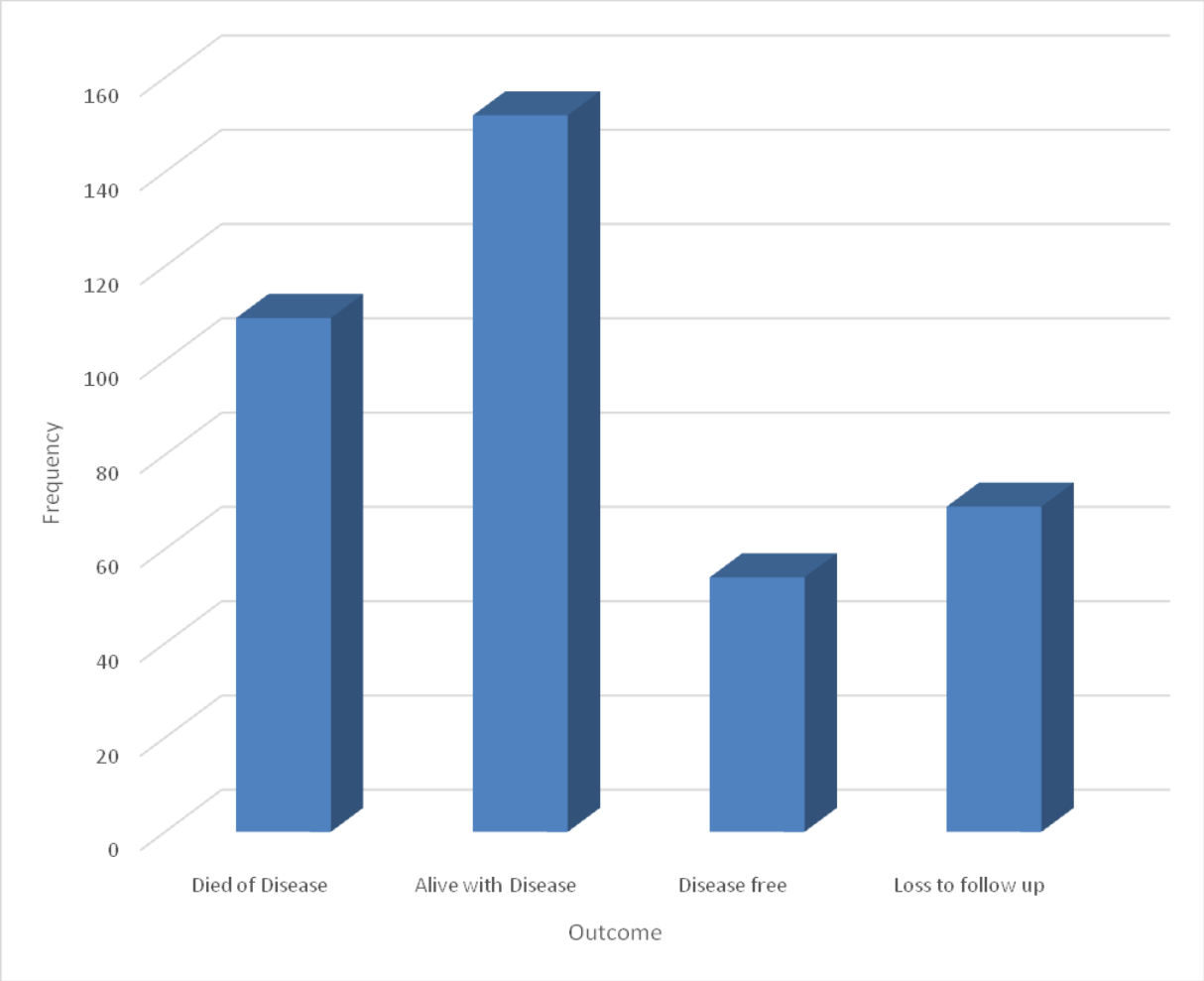

Figure 6: Overall survival at five years of treatment with external beam radiotherapy.

DISCUSION

In this study, the mean age of head and neck cancer patients was 43.5 (SD 18.6), ranging from <1-90 years, with the peak age range at 41-50 years. There were only very few patients at the extremes <1-10 and 80+ years. This is similar to other studies in the country[5,34,22].These findings is contrary with studies done in United Kingdom which show an increasing incidence of Head and Neck cancers with age[83,84].The relatively low cases seen within the first decade in this study is a reflection of how seldom Paediatricians refer their patients for Radiotherapy in NHA. This is because most paediatric tumours seen, e.g. Burkitt's Lymphoma, are highly chemosensitive and cytotoxic chemotherapy is usually administered by Paediatricians without referral to the Radiotherapy Department.

The Male: Female ratio is 2:1. This is similar to the studies done worldwide which show a male preponderance of Head and Neck cancers [3,10, 34,60]. The Male: Female ratios from previous studies done in Nigeria ranged from 1:1-2.3:1 [5, 1, 12, 23, 34,] . This is contrary to the study by Ologe et al in Ilorin[80] which showed a higher incidence in females compared to males.

Nasopharynx was found to be the commonest site 102(26.6%) of head and neck cancers. This is similar to other studies, [6, 18 ,19-21] followed by oral cavity (13.5%), and larynx (12.0%) In this study, carcinoma of the lip was observed to be 6:1 female to male ratio which is contrary to reports in the literature review where lip was 8:1 male to female ratio. Cancer of the ear was also observed to be few which is similar to what was obtained in reports from Ibadan [6, 18, 22 . 21,]

The majority of Head and Neck cancers seen in this studies were epithelial in origin (>90%).This predominance is similar to that seen in previous studies carried out in Nigeria [19,8132-34] ,as well as worldwide literature[1,3,4,5,].Like this study, all these studies cited above show Squamous Cell Carcinoma as the commonest cancer type. In this study (0.4%) presented with lymphomas both occurring in the nasopharynx. This is contrary to the findings in many centres in Nigeria, where lymphomas were the second most frequent cell type seen. [22,23]. Sarcomas were the second commonest histological type seen in this study, in agreement with Nwawolo et al in Lagos, Lilly-Tariah in Jos and Okoye et al in Port-harcourt who also found sarcomas to be the second most occurring histologic type in their centres[6,22,34].

Irrespective of anatomical site, the most common clinical feature seen among the patients with Head and Neck cancer was neck mass (15.7%).Every other clinical feature seen varied with the specific anatomical site under consideration. Although none of the previous studies on Head and Neck cancers done in Nigeria gave a detailed analysis of patients' presenting symptoms/clinical features, all the features noted are in consonance with published literature worldwide[1,4,6,9 13 15)]

Majority of the patients presented in the late stage of the disease, stage IV 42% and stage III 29%. Few patients 11% presented with a Stage 1 disease and 18% stage II. These findings are similar to others studies in Nigeria, where late presentation was a common feature in most reports from different parts of the country[(6,,9 21,2238,48.)]. Late presentation is a common feature of cancer patients in the developing parts of the world, for various reasons. One of them is that the early symptoms of cancer are rather vague and non specific. Because these symptoms do not produce functional limitation or

cosmetic problems at the initial stage, they are often ignored or not suspected. Also, the high level of ignorance and poverty greatly affect the people's health seeking behavior, with many preferring to seek Spiritual help or the services of Traditional-medical Practitioners prior to seeing Orthodox Doctors. Even for patients who seek help early in peripheral Primary Health Centres, a lot of primary physicians are not familiar with these symptoms and end up delaying before eventually referring the patients to Specialist Centres. At that point, the disease is usually advanced. The unavailability of trained personnel (Otorhinolaryngologists, maxillofacial surgeons, general surgeons, and family physicians) at the first point of contact to make proper diagnosis and referral contribute to the dismal state of late presentation. The diagnosis of Head and Neck cancer requires a good knowledge of the disease pattern as well as a high index of suspicion. Most parts of the aerodigestive tract are not readily visible or palpable .Thus, they need examination under anaesthesia. Videoendoscopic examination of mucosal surfaces, imaging technique, multiple biopsies of suspected primary sites and histological diagnosis are some of the requirements for diagnosis. The skill and materials for all these are not readily available in most of the hospitals of first contact.

The treatment modality for patients with head and neck cancers depend on tumour extent. Many tumours of the head and neck are not surgically accessible and in some cases where surgery may play a role, late presentation makes it unsuitable or cosmetic reason taken into consideration. As a result, surgical treatment will be limited to biopsy alone. Chemoradiation is the main stay of treatment in most head and neck tumours. Chemotherapy can be used to down stage the disease in those with locally advanced disease. Adding concurrent chemotherapy to radiotherapy (chemoradiation) is now

recognized to improve outcome in advanced head and neck cancer patients compared with once-daily radiotherapy alone and has become a standard approach for non-metastatic disease.

The commonest RTH dose and fractionation used for HNC in this study was 66Gy in 33 fractions over six and half weeks, which was administered to 224 patient constituting 64.5% of all cases, followed by 60Gy in 30 fractions over 6 weeks given to 95 patients (25.1%) and 31(9.8%) of the patients had 54Gy in 27 fractions over five and half weeks. This is similar to other studies in the literature review.[41, 78,85]

The commonest single agent chemotherapy administered to patients in this study was cisplatin. More than half of the patients 173(54.7%) had 40mg of weekly cisplatin, 69(21.8%) had 1g of weekly 5FU, 45(14.2%) had $20mg^2$ of weekly docetaxel and 29(9.1) had 80mg of weekly paclitaxel. The various single agent chemotherapy used for the patients are in concordance with recommended regimens from published literature.[85],[86],[87] Many of the patients had to be given supportive therapy in the form of analgesics and antibiotics for pain and various super imposed infections. Moderate to severe anaemia had blood transfusions while patients with mild anaemia received haematinic.

At six months' follow-up, (238) 70% of patients had complete response, (57) 23% had partial response, and (21) 7% of the patients had no response. Factors found to be associated with complete response in this study were early stage of disease, short duration of illness to presentation, SCC of the larynx, lymphomas, multi-modal treatment (combination of Platinum based chemotherapy and RTH in particular) and RTH dose of 66Gy in 33 fractions over six and half weeks weeks. On the contrary, the most important

factors for partial or no response was advancement of the disease stage at the time of presentation and long RTH treatment gaps. This posed a great challenge for recurrence, metastases and as well the employment of palliative measures as the intent of treatment. At Second year of follow-up, 62 (19.6%) had recurrence, 30 patients (9.4%) developed distant metastases and 24(7.5%) had recurrence and metastases, 124(39.2%) were disease free, 136 (43.3%) alive with the disease, 40 (12.6%) died of the disease, 16 (5.6%) were lost to follow-up,

At five years of follow up 78 (24.6%) were disease free, 99 (31.3%) alive with the disease, 114 (36.7%) died of the disease, 25 (7.9%) were lost to follow-up,
probably on account of either complications of treatment, financial constraint, disease progression, unreported deaths or the seldom incomplete documentation in the patients' records. In this study, it was observed that patients with head and neck cancers treatments outcomes are usually based on stage and tumor location and thus showed similar report with other studies reported in the literature review [10,11,77,78] The overall survival at 5 years of follow up was 24.6% for concurrent chemoradiation and 14.4% for radiotherapy alone, thus showed similar report with other studies reported in the literature review [10,11, 15,77,78.82,85].

This study also showed, despite late presentation there was improved out comes in patients with head and neck cancer who had chemoradiation .This is similar to finding by Adenipekun et al[9], and other studies reported in the literature review[24,27,28,30,

CONCLUSION

The mean age at presentation was 47.2 years (SD 11.5). Most patients presents at late stage of the disease, poor educational background and belong to the low socioeconomic class. Cisplatin was the commonest radiosesitizer used in this study which is similar in developed countries. In this study, it was observed that the outcome of treatment of patients with head and neck cancers depend on stage of disease and tumor location.

The overall survival at 5 years of follow up was 24.6% for concurrent chemoradiation and 14.4% for radiotherapy alone, thus showed similar report with other studies reported in the literature review [10,11, 15,77,78.82,85,]

RECOMMENDATIONS TO THE FEDERAL MINISTRY OF HEALTH

Head and neck cancers are not uncommon in Nigeria. Reports from centers across the country showed that cancers of the nasopharynx, oral cavity and larynx are the most frequently seen. Most patients present late at diagnosis and treatment; and subsequently prognosis of HNC in our environment is poor. The WHO reported that a third of all cancers are preventable, and therefore:

1.The provision of basic social amenities as well as better employment policies will improve socioeconomic condition and standard of living of the population at risk of head and neck cancer. Since higher disease burden is seen in countries with low standard of living.

2.There is a need for equipping of existing hospitals in all states of the federation with facilities in cancer treatment and establishment of a national cancer institute with regional units to champion the course for the reduction of cancer morbidity and mortality in Nigeria.

3.There is need for the Federal government to supports head and neck cancer awareness campaigns and education by several groups and organisations in the country on screening methods, risk factors and symptoms of head and neck cancer. This will encourage early presentation and subsequently adherence with treatment and follow-up.

4.Provision of facilities and expertise for immunohistochemistry will help in adequate care for the patients

5. There is need for government to include all chemotherapy drugs and radiotherapy in NHIS scheme and also to subsidize cancer treatment especially for the indigent patients. It is believed that these effort will reduce the present high incidence of late presentation and loss to follow up.

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APPENDIX I

TNM Staging of Head and Neck Tumors

[a]Parapharyngeal extension denotes posterolateral infiltration of tumor beyond the pharyngobasilarfascia.

[b]Central compartment of soft tissues includes prelaryngeal strap muscles and subcutaneous fat.

[c]Midline nodes are considered ipsilateral nodes.

[d]Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (a) the superior margin of the sternal end of the clavicle, (b) the superior margin of the lateral end of the clavicle, (c) the point where the neck meets the shoulder. Note that this would include the caudal portions of levels IV and V. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

Definition of TNM

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis	Carcinoma *in situ*
Nasopharynx	
T1	Tumor confined to the nasopharynx
T2	Tumor extends to soft tissue
T2a	Tumor extends to the oropharynx and/or nasal cavity without parapharyngeal extension[a]
T2b	Any tumor with parapharyngeal extension[a]
T3	Tumor involves bony structures and/or paranasal sinuses
T4	Tumor with intracanial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space
Oropharynx	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Hypopharynx	

T1	Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx
T4a	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue[b]
T4b	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

Regional Lymph Nodes (N)

Nasopharynx

The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[c]

N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[c]

N3 Metastasis in a lymph node(s)[c]>6 cm and/or to supraclavicular fossa

N3a Greater than 6 cm in dimension

N3b Extension to the supraclavicular fossa[d]

Oropharynx and Hypopharynx

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T2a	N1	M0
	T2b	N0	M0
	T2b	N1	M0
Stage III	T1	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N0	M0
	T3	N1	M0

	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Stage Grouping: Oropharynx, Hypopharynx

Stage 0	Tis	N0	M0
Stage 1	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0

	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

APPENDIX II

(Data Extraction Form)

OUT COME 0F HEAD AND NECK CANCERS PATIENTS MANAGED WITH CHEMORADIATION AT NATIONAL HOSPITAL ABUJA

(FIVE-YEARS RETROSPECTIVE STUDY)

1. Serial no: .....
2. Hosp. No: .....
3. Initials: .....
4. Age (yrs.): .....
5. Sex: (1) Female (2) Male
6. Marital Status: (1) Single (2) Married (3) Widowed (4) Divorced
7. Level of Education: (1) Non formal (2) Formal
8. Employment status (1)Employed (2) Unemployed
9. Occupation: .....
10. Ethnic group: .....
11. State of origin: .....
12. Height (M) …….
13. Weight (Kg) ……..
14. BMI (Kg/M^2) …….
15. Hypertension: (1) No (2) Yes

16. Diabetes: (1) No (2) Yes

17. History of other chronic illness: (1) No (2) Yes

    If yes specify.....

18. Smoking: (1) No (2) Yes

19. Alcohol: (1) No (2) Yes

20. Histological Diagnosis:

    Squamous Cell Carcinoma ……., Lymphoma ……..……,

    Adenocarcinoma ……., Adenocystic Carcinoma …….....,

    Lymphoepithelioma ..……..…., Sarcoma …….……,

    Poorly Differentiated Carcinoma……., Others (specify) ……..,

21. Anatomic site:

    Nasopharynx …….., Oral cavity ……., Oropharynx ……..,

    Larynx …….…, Sinonasal Region ……., Salivary Gland ……..……,

    Thyroid gland ……., Skin ..……, Others (specify) ……..……..

22. HIV Status:

    Positive …..…….……, Negative …….……..…..

23. Clinical Features

- Headache Yes ( ) No ( )
- Neck mass Yes ( ) No ( )
- Swelling Yes ( ) No ( )

- Nasal

  Discharge Yes ( ) No ( )

  Bleeding Yes ( ) No ( )

  Obstruction Yes ( ) No ( )

  Others Specify ……..

- Swelling (at primary site) Yes ( ) No ( )
- Aural

  Tinnitus Yes ( ) No ( )

  Hearing loss Yes ( ) No ( )

  Pain Yes ( ) No ( )

  Discharge Yes ( ) No ( )

  Others Specify ……

- Ophthalmic

  Diplopia Yes ( ) No ( )

  Strabismus Yes ( ) No ( )

  Leukoria Yes ( ) No ( )

- Pain Yes ( ) No ( )
- Sore throat Yes ( ) No ( )
- Hoarseness of voice Yes ( ) No ( )

- Dysphagia Yes ( ) No ( )
- Trismus Yes ( ) No ( )
- Distant metastasis, Specify site ……..
- Others(specify) ……

24. Stage of presentation (1) I (2) II (3) III (4) IV

25.Grade (1)Well (2)Moderate (3)Poorly

26.Definitive Treatment

- Radiotherapy + Chemotherapy Only ……..
- Radiotherapy only …….
- Surgery only …….……
- Chemotherapy only ……..……..
- Radiotherapy + Surgery Only ……..
- Surgery + Chemotherapy Only ……
- Radiotherapy + Chemotherapy + Surgery ……..
- Other Definitive treatment specify) ……

27.*Supportive treatment*

I. Blood Transfusion Yes ( ) No ( )

II. Analgesics Yes ( ) No ( )

III. Haematinics Yes ( ) No ( )

IV. Antibiotics Yes ( ) No ( )

V. Others (specify) ……

……

28.If Radiotherapy was given, state:

Dose of Radiation ……

Number of Fractions ……

Duration of Treatment ……..

29.If Chemotherapy given, state:

Regimen used ……

Number of cycles……

30.Side effects of Chemoradiation

- Nausea Yes ( ) No ( )
- Vomiting Yes ( ) No ( )
- Diarrhea Yes ( ) No ( )
- Loss of hair Yes ( ) No ( )
- Erythema of skin Yes ( ) No ( )
- Conjunctivitis Yes ( ) No ( )
- Mucositis Yes ( ) No ( )

- Epilating Yes ( ) No ( )
- Alteration of taste Yes ( ) No ( )
- Xerostomia Yes ( ) No ( )
- Blurring of vision Yes ( ) No ( )
- Inability to sleep Yes ( ) No ( )
- Hearing loss Yes ( ) No ( )
- Pain on swallowing Yes ( ) No ( )

31.Long term Complication

- Altered taste for salt or sweet Yes ( ) No ( )
- Cataract Yes ( ) No ( )
- Osteoradionecrosis Yes ( ) No ( )
- Cervical myelopathy Yes ( ) No ( )
- Skin cancer Yes ( ) No ( )

Epilation Yes ( ) No ( )

NATIONAL HOSPITAL

(Established by Act No 36 of 1999).

ABUJA

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NHA/ADMIN/236/V.VII/

7th October, 2015

RE: STUDY OF CHEMORADIATIO IN HEAD AND NECK CANCER IN NATIONAL HOSPITAL ABUJA A-5 YEAR RETROSPECTIVE STUDY

Health Research Ethics Committee (HREC) Assigned number: **NHA/EC/047/2015**

Name of Principal Investigator: **Dr. Fatima Uba**

Address of Principal Investigator: Department of Radiotherapy & Oncology
National Hospital
Abuja

Date of Receipt of Valid Application: 3Rd September, 2015

Notice of Approval

This is to inform you that the research described in the submitted protocol, the consent forms, and other changes stated in the submitted research protocol addendum have been reviewed and *given full approval by the Institute Review Board (IRB) Committee, National Hospital Abuja.*

This approval dates from **7th October 2015** to 6th **October, 2017.** If there is delay in starting the research, please inform the HREC National Hospital Abuja so that the dates of approval can be adjusted accordingly. Note that no participant accrual or activity related to this research may be conducted outside of these dates. *All informed consent forms used in this study must carry the HREC assigned number and duration of HREC approval of the study.*

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the HREC. No changes are permitted in the research without prior approval by the HREC except in circumstances outlined in the Code. The HREC reserves the right to conduct compliance visit to your research site without previous notification.

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