

Pattern and outcome of radiotherapy management of oral cancers in a Nigerian Teaching Hospital: a twenty four year experience

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Abstract

Introduction: The incidence of oral cavity cancer is on the increase. Most cases present late resulting in poor prognosis of the disease. In the last few decades there has been an increasing trend of use of radiotherapy to treat oral cancers with improvement in survival. This retrospective study was aimed at determining the pattern of oral cancers seen at Radiotherapy Department of University College Hospital Ibadan and also to assess outcome of treatments offered over a period of 24 years.

Methodology: Data extraction form was designed to obtain information from case notes and treatment records of patients with histologically diagnosed oral cavity cancer from 1987 to 2011 at the Radiotherapy clinic. The outcome of treatment at 6 months follow up was determined as either complete or partial/ no clinical response. Symptom free interval was also determined for each patient.

Results: A total of 88 patients with histologically diagnosed oral cavity cancer were analysed. The mean age of presentation was 51.8 years with M: F ratio 1.8: 1. The mean duration of symptoms was 13.4 months. All the patients in this study had radiotherapy. Complete clinical response was seen in 35 patients (39.8%) while partial and no response was observed in 53 (60.2%) patients. Patients who had radical doses of radiotherapy, early stage at presentation and multimodality treatment were found to have better outcome.

Conclusion: Oral cancer patients present late in our environment, Radiotherapy in combination with other modalities of treatment have been found to have better outcome.

Keywords - Radiotherapy Management, clinical response, symptom free interval

Résumé

Contexte : L'incidence du cancer de la cavité buccale est en augmentation. La plupart des cas se présentent tardivement, ce qui entraîne un mauvais pronostic

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de la maladie. Dans les dernières décennies il ya eu une tendance croissante de l'utilisation de la radiothérapie pour traiter les cancers oraux avec une amélioration de survie. Cette étude rétrospective visait à déterminer le schéma des cancers oraux observés au département de radiothérapie du Collège Hospitalier Universitaire d'Ibadan et aussi évaluer les résultats des traitements offerts sur une période de 24 ans.

Méthodologie: Le formulaire d'extraction de données a été conçu pour obtenir des informations à partir des notes de cas et des dossiers de traitement des patients atteints d'un cancer histologique de la cavité buccale de 1987 à 2011 à la clinique de radiothérapie. L'issue du traitement à 6 mois de suivi a été déterminée comme complète ou partielle / pas de réponse clinique. L'intervalle libre de symptômes a également été déterminé pour chaque patient.

Résultats: Un total de 88 patients ayant un cancer histologique de la cavité buccale ont été analysés. L'âge moyen de présentation était de 51,8 ans avec un rapport M:F de 1,8:1. La durée moyenne des symptômes était de 13,4 mois. Tous les patients de cette étude avaient une radiothérapie. Une réponse clinique complète a été observée chez 35 patients (39,8%) alors que la réponse partielle et aucune réponse n'a été observée chez 53 (60,2%) patients. Les patients qui ont reçu des doses radicales de radiothérapie, au stade précoce de la présentation et au traitement multimodal ont été jugés à avoir de meilleurs résultats.

Conclusion: Les patients atteints d'un cancer buccal se présentent tardivement dans notre environnement, la radiothérapie en association avec d'autres modalités de traitement s'est révélée avoir de meilleurs résultats.

Mots-clés - Gestion de la radiothérapie, Cancer buccal, survie

Introduction

According to the American joint committee on cancer (AJCC) the oral cavity is defined as the region extending from the mucocutaneous border of the lips to the junction of the hard and soft palate superiorly and inferiorly to the line of the circumvallate papillae

of the tongue [1]. The oral cavity consists of the lips, buccal mucosa, alveolar gingivae, oral tongue, and floor of the mouth (FOM), hard palate, and retromolar region.

Cancer of the oral cavity is said to be uncommon, it is the sixth most common cancer worldwide [2] with over 274,000 new oral cavity cancers diagnosed annually, out of which two-thirds occur in developing countries [3]. There is a worldwide geographic variation in the prevalence of oral cancers ranging from only a few percent in most Western countries to over 40% in South and South-East Asia [4]. Data from Africa are limited to a few hospital cancer registries. It is therefore difficult to extrapolate the true incidence in these countries; however reported rates do not show evidence that oral cancer is a serious problem in the African continent [5]. Elumelu et al (2011) [6] at the Radiotherapy department University College Hospital (UCH), Ibadan found that oral cavity cancer consists about 12% of all head and neck cancers and squamous cell carcinoma is the most common histology.

Surgery, radiotherapy, chemotherapy, or combination of these modalities are classical treatment options for patients with cancers of the oral cavity. The choice of treatment modality depends on the stage of the disease and patient factors such as toxicity, performance status, co morbid disease, and convenience. Broadly speaking, single modality treatment is preferred for early stage lesions and combined modality for more advanced lesions [7].

The change in trend in the management and outcome of oral cancers over the years was demonstrated in a study by Carvalho et al (2004) [8]; in the 1950s only 29.1% of oral cancer patients were treated by surgery alone, 54.5% by radiotherapy and 16.4% by combined treatment; while in the 1990s there was increased use of multimodality treatment with 39.7% treated with surgery alone, 9.7% with radiotherapy alone and 50.6% by combined treatment. They also reported a significant increase in the 5-year survival rates from 28.7% for patients treated in the 1950s to 43.2% in the 1990s.

This study was therefore designed to determine the pattern of oral cancer in our environment, evaluate the role of radiotherapy in its management and outcome.

Materials and methods

This was a retrospective study of all patients with histologically diagnosed oral cavity cancer who received external beam radiotherapy at the

Department of Radiotherapy, University College Hospital (UCH), Ibadan, from November 1987 to December 2011. Patients with tumours of the jaw bones, facial skin, major salivary gland tumours, tonsils and oropharynx, children (age <15 years) with oral cancer and patients who did not receive radiotherapy in Ibadan were excluded. All available records of oral cavity cancer patients treated during the study period were retrieved and analysed. Information obtained include patients' bio-data (age, gender and occupation), duration of illness prior to presentation, stage at presentation and histology. Socioeconomic class was classified according to Boroflka and Olatawura (1976) [9]. The details of treatment received were also taken into consideration e.g. dose and mode of radiotherapy, surgery, chemotherapy regimen. Lesions were classified according to primary site as described in the WHO International Classification of Diseases+ for Oncology ICD-10 2010 [10]. Tumour involving more than one site or multiple simultaneous primary tumours was classified as multiple sites. The patients were retrospectively restaged using the 2010 edition of the American Joint Committee on Cancer (AJCC).

The role of radiotherapy was assessed using the number of patients that received radiotherapy as part of their treatment, the mode of radiotherapy (adjuvant, neo adjuvant or radical), the intent of radiotherapy as either curative or palliative, and the outcome between radical radiotherapy with adjuvant radiotherapy. The outcome of radiotherapy was also compared between radiotherapy alone or in combination with surgery and/or chemotherapy. Response to treatment was documented from 6 months' follow-up clinic as either complete, partial or no remission. Complete response (CR) was considered as disappearance of irradiated tumour on clinical examination within 6 months of completion of prescribed treatment, while partial response (PR) is greater than 50% reduction in size of the tumour at 6 months of completion of prescribed treatment and no response (NR) when there is no reduction in size or a reduction in size of less than 50% of the irradiated tumour or disease progression at 6 months of completion of prescribed treatment. The symptom free interval at 6 months, 12 months and beyond 12 months were used for assessing response to treatment as a result of high default rate during follow ups. Symptom free interval (SFI) was defined as the duration that the patient stayed clinically free of signs and symptoms associated with the disease after treatment. Patients who had partial or no remission were considered to have SFI of zero (0) months. The

above information was extracted using a data extraction form. The data were carefully entered and analysed using SPSS version 17.0.

Results

A total of 117 oral cavity cancer patients were seen over the study period out of which 88 patients met the selection criteria and were analysed. The other 29 patients were not analysed due to scanty records and/or did not receive radiotherapy as part of their treatment, and/or had radiotherapy outside Ibadan. This formed 0.4% of the 32,009 patients seen at the UCH cancer registry and 0.8% of the estimated 13,979 patients seen at the Radiotherapy Department over the same period. The mean age of the patients was 51.8 years (SD±16.5), ages ranged from 18-98 years. The peak age range was 40-49 (22.7%) years. There were 56 males (63.6%) and 32 (36.4%) females giving a male to female ratio of approximately 1.8: 1. The distribution according to the social classes were class I- 4 (4.5%), class II- 11(12.5%), class III- 11(12.5%), class IV-9(10.2%), class V- 20(22.7%), class VI- 21(23.9%) and retired- 12 (13.6%). The yearly distribution of patients is shown in table 1.

Table 1: Yearly distribution of the 88 patients with oral cavity cancer that had radiotherapy from 1987-2011

| Years | Number of cases | Percent |
|-------|-----------------|---------|
| 1987 | 1 | 1.1 |
| 1988 | 6 | 6.8 |
| 1989 | 8 | 9.1 |
| 1990 | 6 | 6.8 |
| 1991 | 0 | 0.0 |
| 1992 | 5 | 5.7 |
| 1993 | 0 | 0.0 |
| 1994 | 5 | 5.7 |
| 1995 | 3 | 3.4 |
| 1996 | 4 | 4.5 |
| 1997 | 1 | 1.1 |
| 1998 | 7 | 8.0 |
| 1999 | 1 | 1.1 |
| 2000 | 2 | 2.3 |
| 2001 | 1 | 1.1 |
| 2002 | 3 | 3.4 |
| 2003 | 1 | 1.1 |
| 2004 | 3 | 3.4 |
| 2005 | 1 | 1.1 |
| 2006 | 3 | 3.4 |
| 2007 | 4 | 4.5 |
| 2008 | 12 | 13.6 |
| 2009 | 3 | 3.4 |
| 2010 | 3 | 3.4 |
| 2011 | 5 | 5.7 |
| Total | 88 | 100.0 |

Average of 3.5 patients per year.

Twenty patients (22.7%) had complaints of less than 6 months' duration at presentation, while 46 (52.3%) had presenting complaints of 6-12 months and 22 (25.0%) had complaints above 12 months. The commonest site of involvement was hard palate in 32 (36.4%) of the patients. Other sites were; lips-13 (14.8%), buccal mucosa- 4 (4.5%), alveolar gingivae- 3 (3.4%), oral tongue- 22 (25.0%), floor of the mouth- 9 (10.2%), and multiple sites- 5 (5.7%). The most common histological type was squamous cell carcinoma in 64 (72.7%) patients. The other histological types included, minor salivary gland tumours 16 (18.2%) which consisted of adenoid cystic carcinoma [10], mucoepidermoid carcinoma [4] and one each of adenocarcinoma and papillary adenocarcinoma. About 62.5% of the minor salivary gland tumours were adenoid cystic carcinoma. The remaining 8 (9.1%) included basal cell carcinoma [2], melanoma [1], intraepithelial carcinoma [1], lymphoma [1], sarcoma [1], Kaposi sarcoma [1], and adenosquamous carcinoma [1]. Stage distribution is shown in figure 1 below.

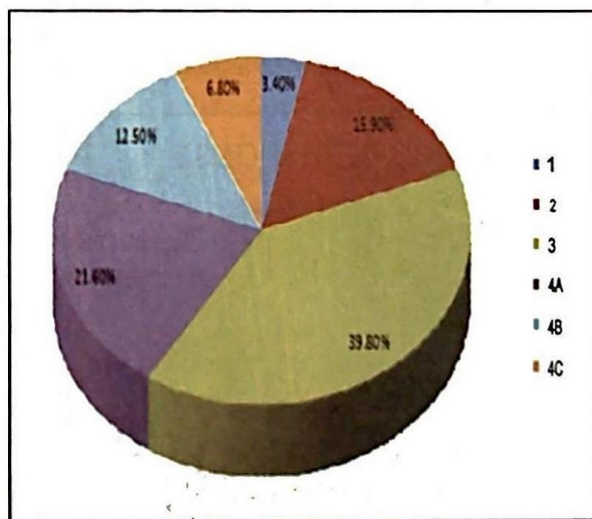


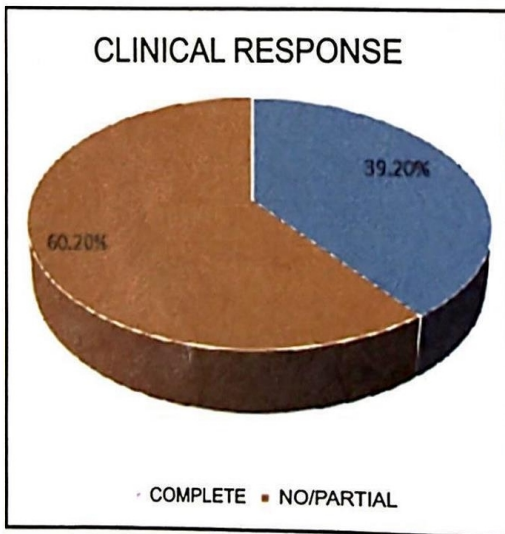
Fig. 1: Distribution of stage at presentation

All patients in this study had radiotherapy. Fifty-four patients (61.4%) received curative doses from a Co-60 teletherapy machine, a dose of 60-66Gy in 30-33 fractions or hypo-fractionated 45Gy in 12 fractions, while 34 patients (38.6%) who had advanced disease received palliative doses of either 15Gy in 5 fractions, 20Gy in 6 fractions or 30Gy in 10 fractions in order to control pain, bleeding and local disease. Twenty-seven (30.7%) had radiotherapy alone, 35 (39.8%) had chemotherapy and radiotherapy, 7 (8.0%) had surgery and radiotherapy, while 19 (21.6%) had all the 3 modalities. The distribution of radiotherapy treatment is shown in table 2.

Table 2: Distribution of radiotherapy treatment

| | Number of patients | Percent |
|----------------------------------|--------------------|---------|
| Palliative | 34 | 38.6 |
| Radical | 54 | 61.4 |
| <i>Radiotherapy modality</i> | | |
| Combined (+surgery/chemotherapy) | 61 | 68.2 |
| Alone | 27 | 31.8 |
| <i>Radiotherapy form</i> | | |
| Neoadjuvant | 1 | 1.1 |
| Adjuvant | 25 | 27.3 |
| Radiotherapy alone | 27 | 34.1 |
| Chemo-radiation | 35 | 37.5 |

Only 54 patients had chemotherapy, the combinations include Cisplatin/5-FU (24) for squamous cell carcinomas, patients with minor salivary gland tumours and adenocarcinomas had Vincristine/Bleomycin/Methotrexate-VBM [9] or Cyclophosphamide/Methotrexate/ Vincristine CMV [14] combinations, while others [7] had different regimens depending on the histological type. All the 54 patients had 4-6 courses of chemotherapy. Treatment outcome is shown in figure 2.

**Fig. 2:** Clinical outcome at 6 Months

Fifty-three patients (60.2%) had SFI of less than 6 months, while 11 (12.5%) had an SFI of 6-12 months and 24 (27.3%) had SFI of greater than 6 months. About 66.6% of the patients in stage 1 and 71.5% of the patients in stage 2 had SFI of greater than 12 months while 17.2% and 15.8% of patients in stage 3 and 4 respectively had a SFI beyond 12 months. As the dose of radiotherapy increases so also the SFI, it was found that for lower doses of equal to or less than 30Gy none of the patients had an SFI of

greater than 12 months while at doses of about 60Gy SFI after 12 months was seen in 40% of the patients. In those that received radical radiotherapy, 40.8% had a SFI greater than 12 months compared to those that received palliative radiotherapy with only 5.9% having an SFI greater than 12 months. Forty eight percent of patients who had adjuvant radiotherapy had an SFI beyond 12 months compared to radiotherapy alone with only 22.2%, neoadjuvant radiotherapy and concurrent chemo-radiation groups had 0.0% and 17.2% of patients with SFI beyond 12 months respectively. However these differences were not statistically significant (table 3; mode of radiotherapy).

Those patients that had all the 3 modalities had the best outcome with 59.7% having SFI of more than 12 months, while it was 22.2%, 17.1% and 14.3% of those who had radiotherapy alone, chemotherapy + radiotherapy, and surgery + radiotherapy respectively. SFI for social class, duration of illness were not statistically significant. The variables and their statics significance in relation to SFI are summarised in table 3.

Table 3: Symptom Free Interval for Socio-demographic and clinical Characteristics

| Factor | Pearson's Chisquare (X ²) | P-Value |
|-------------------------------------|---------------------------------------|---------|
| Social Class | 6.099 | 0.911 |
| Duration of Illness at presentation | 5.132 | 0.274 |
| Stage | 27.398 | 0.002 |
| Dose (Increasing dose) | 28.730 | 0.004 |
| Aim (Radical/Palliative) | 22.158 | 0.000 |
| Treatment Combination | 14.672 | 0.023 |
| Mode of Radiotherapy | 10.474 | 0.106 |

Discussion

Most studies put the mean age of patients with oral cancer around the 5th or 6th decade. The mean age in this study was 51.8 (SD±16.5) years which is similar to the mean age of 52.8 years reported by Olusanya and colleagues in Ibadan [11]. A lower mean age at presentation of 37.1 years has also been reported in a local study [12] while others found a slightly higher figure [13, 14]. The peak age group was 40-49 years which is a decade or two lower than most local studies [11, 14-16]. Oral cancers are said to be more common in males than in females. Arotiba and colleagues [17] reported a M: F of 1.5:1, researchers at the Base Hospital Yaba reported M:F of 2:1 [18], in a study in Zimbabwe 1.9:1 was documented [19],

white 2.4:1 was reported in another study from Ibadan [16]. This study found a male to female ratio (M: F) of 1.8:1. Majority of the patients in our study belonged to the low socioeconomic class, this is in line with claims by some authors on the increase risk in those of the low socioeconomic class [20]. There is however uncertainty and limited recognition of the association between socioeconomic class and oral cancer. In a study by Adeyemi and others in Ibadan they failed to demonstrate any significant statistical association between them [14]. The high number of low socioeconomic status in these group studied may also be associated with risk factors such as poor oral hygiene and infections, ignorance, difficulty in accessing care and lack of adequate medical screening to detect premalignant conditions also contribute to increase number of cases in this vulnerable group.

Even though one may think that oral cavity is readily accessible to visual inspection, however most reports from Nigeria had patients presenting late [21, 22]. Most tumours of the oral cavity are not diagnosed until at least T2 stage as initial symptoms may be vague and painless [23]. Patients in this study presented late with 77.3% of the patients presenting at 6 months and beyond. Ignorance, poverty, low socioeconomic class, marital problems, sense of despair and delay in referral has been suggested by the aforementioned studies as reasons for delayed presentation. In this study the characteristics of most patients fit into these. Also the lack of radiotherapy facilities in most states may have also contributed, as patients will have to travel long distances and may require to pay for accommodation and feeding so the patients take a long time to prepare before coming for radiotherapy. Similarly, the incompetence of some primary physicians in detecting early disease and delayed referral by the primary physicians may have contributed. The mean duration of symptoms at presentation in North Central Nigeria for tongue cancers is 13 ± 13.3 months and lips 23 ± 22.9 months [24].

The commonest site for oral cancer varies from region to region, Olusanya and colleagues in Ibadan found hard palate to be the most common site over a 25 year period [11]. At the Ahmadu Bello University Zaria floor of the mouth was reported as the commonest [15], in another report from Zimbabwe it was the gingivae [19], in the US at the M.D Anderson Cancer Centre it was oral tongue [25] and in most studies in Southeast Asia the buccal mucosa [5, 25]. This suggests that there may be difference in risk factors according to region, for

instance cancer of the floor of the mouth is more strongly associated with smoking than cancer of the gingivae [26], and practice of reverse smoking (smoking with the light end of cigar in the mouth) in India has been associated with increased risk of cancer of the hard palate [27].

Over 80% of the patients presented at late stages 3 and 4. It is well documented that oral cavity cancer in most cases remain localised until late in the course of the illness. Late stage at presentation may be as a result of the fact that most of the patients are of low socioeconomic class with high level of poverty and ignorance which may hinder accessing care at early stages. The most common histology in this study and in most local and international studies [19, 24, 28, 29] is squamous cell carcinoma. It is reported that adenoid cystic carcinoma accounts for 30-40% of minor salivary gland tumours in the oral cavity [30]. The relative high occurrence of minor salivary gland tumours in this study can be explained by the fact that most minor salivary glands tumours arise in the hard palate and the commonest site in this study was the hard palate.

SFI was used to assess the outcome as a result of high default rate and late presentation of the patients. The patients presented with late stage disease whereby the prognosis is already poor, most of the patients were from low socioeconomic position and had delay in presentation, all of which may contribute to the poor outcome in these patients. The study found a significant association between stage and SFI (P value=0.002). Patients with early stage disease have a higher proportion of patients that were symptom free beyond 12 months than those in late stage. Staging has also been found to be vital on prognosis of patients with oral cancer by Guerra and colleagues [31], Gonzales-Moles and others [32], and Nguyen and Yuch [33] which all demonstrated a better outcome at early stages than late stages. The lower SFI in stage 1 compared to stage 2 in this study may be attributed to the few number of patients in stage 1 compared to stage 2 (3 vs 14 patients). However from the analysis no patient in stage 1 (0.0%) had an SFI less than 6 months while three (21.4%) patients in stage 2 had a lower SFI of 6 months which still points to a better outcome in the patients in stage 1. Other factors that may have contributed in this variation include the site of the tumour and the histological type as these are also known to affect prognosis in oral cavity cancer.

The advanced nature of the disease in most patients require multimodality treatment. This may have contributed to better outcome in patients who had all the 3 modalities. This is further buttressed

by the findings of Carvalho and colleagues [8]. They showed that with increased use of multimodality treatment over 5 decades brought about a significant increase in the 5-year survival rates from 28.7% for patients treated in the 1950s to 43.2% in the 1990s. This study did not suggest any statistically significant improve outcome of in patients that had adjuvant radiotherapy over those that had radiotherapy alone or vice versa, but only showed improved outcome if radiotherapy is combined with chemotherapy and surgery.

Conclusion

Patients with oral cavity cancer present with advanced disease. Adjuvant radiotherapy is not superior to radiotherapy alone, however radiotherapy in combination with surgery and chemotherapy has been found to have better outcome.

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