

## Survival of the patients treated for Head and Neck Cancer in a Low resource country - A retrospective study

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### Abstract

**Background:** Worldwide Head and Neck cancer- HNC is the 6th most frequent cancer, with an estimated world incidence of over 600,000 new cases per year and 300,000 deaths yearly. Despite successful primary therapy of advanced local and regional disease, 50-60 % of head and neck cancer patients die from local recurrences, while 20 – 30 % of them die from distant metastases, and 10 – 40 % die from secondary malignancy due to treatment.

**Methods:** This was a retrospective descriptive study conducted at ORCI, the only Centre for treatment of cancer in Tanzania at the time of the data collection. A total of 200 randomly selected files of the patients with a diagnosis of Squamous Cell Carcinoma of Head and Neck treated from 1st January 2009 to 31st December 2011 were used for the study. A standardized data collecting tool was used to obtain socio-demographic characteristics, clinico-pathological characteristics, and different treatment modalities that were used in the treatment of the patients.

**Results:** The majority of HNC patients studied were above 56 years; The overall survival was 59%. The factors seen to be associated with survival in this study were; stage at diagnosis P-value =0.003, anatomical site of the tumor P-value =0.038 and total amount of radiation dose given P-value = 0.043.

**Conclusion:** Early stages of HNC, anatomical sites of the disease, and standard high radiation doses of >40Gy are associated with more prolonged survival in patients with HNC.

**Keywords:** Head, Neck Neoplasms, Survival, Kaplan-Meier estimate

Head and neck cancers - HNC constitute 5 – 6% of all cancers globally and 5 – 8% in Europe and America alone. In the developing world, estimates from India are as high as 30% of all cancers, data from Africa lacks due to the lack of registry and limitations in infrastructure for diagnosis and treatment [1]. Tobacco use is the most significant carcinogen with a relative risk of more than 25 times [2, 3]. Furthermore, human papillomavirus - HPV types 16 and 18 especially for oropharyngeal cancer, and the Epstein Barr Virus - EBV for nasopharyngeal cancer have also been shown to carry an increased risk [4].

Mortality from this cancer is still high despite advances in treatment; more than half of patients dying from local recurrence, a quarter from distant metastasis and secondary malignancies related to treatment [4]. The treatment outcome of HNC in sub-Saharan African setting, where the management might be suboptimal together with late presentation, has not been well investigated hence the need for such studies.

Apart from late presentation, tobacco use and related non-cancer comorbidities might also affect the treatment outcome of this population of patients. The most commonly encountered are cardiovascular and respiratory complications affecting performance status and hence, treatment tolerance, especially where radiotherapy is involved [5, 6]. The overall survival – OS; has been shown to differ across the countries and regions according to economic statuses, being high in Europe at 59% and low in India at 42.8% [7, 8]. Patients demography, tumor characteristics, the presence of co-morbidities, treatment modality offered and presence of HPV virus have all been shown to influence

survival [9]. Africa lacks data on determinants of HNC patient's survival, this study, therefore, aimed to describing HNC treatment and outcomes at Ocean Road Cancer Institute which is the National referral cancer Centre in Tanzania. We found out that disease characteristics, and treatment options contributes to the survival of HNC patients.

### MATERIALS AND METHODS

We conducted a retrospective, descriptive study. ORCI is the only cancer center in Tanzania, serving a population of 50 million people and from neighboring countries. It receives patients with confirmed histological diagnosis mainly from the Muhimbili National Hospital, where diagnosis and staging of patients is done. It welcomes about 4000 new cancer patients yearly, with 10% being HNCs. ORCI is a suitable center to carry out the study as it is where the follow up of patients is carried out following treatment. The center can provide chemotherapy and external beam radiation therapy.

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A total of 200 case files of HNC patients treated in the specified period 2009 to 2011 were randomly selected and reviewed. The sample size was derived based on estimated Hazard rates of 0.4 and 0.7, respectively, among SCC Head and Neck Cancer patients. A double-sided test, the P-value significance is  $P = 0.05$  and a power of 90% with a duration of 3 years, a sample size of 178 patients was estimated to be adequate for analysis. To take care of loss to follow up, then the sample size was increased to 200. The inclusion criteria were confirmed histology of Squamous Cell Carcinoma - SCC, with no history of prior cancer treatment, with either chemotherapy, radiation therapy, surgery, or a combination of these modalities, and with contact information in the file. The patients excluded are with histology other than squamous cell carcinoma, HNC of the thyroid gland, parathyroid glands, ocular cancers, skin cancers, lymphomas, and brain cancers. A structured data sheet was used to extract relevant information from the patients' files that included socio-demographic factors, clinical-pathologic factors, primary site, stage of the disease and any comorbidities. Details of management received included the intention of the treatment either curative, or Palliative treatment; with outcome measures as dead, alive, or lost to follow up. Patients were called using the contact mobile number on the file to determine if they were still alive or dead.

All data sheets were checked for completeness and accuracy by the investigator; then dully filled data sheets checklists were given an identification number and coded before entering into the computer using statistical package for social science - SPSS. Data management was done by the software using SPSS Version 19. Frequency distribution and two-way tables were used to summarize the data. Chi-square and Kaplan Meyer tests were the determinants of the association between independent and dependent categorical variables. A statistical significance of the data was when a P-value is  $< 0.05$ . During analysis, the anatomic site categorized as pharynx, larynx, nasal cavity, paranasal sinuses, and oral cavity.

### Results

Participant's ages ranged from 17 to more than 76 years, with the majority aged 56 to 76years, which was 49.5%. Out of the total 200 participants, there were more males than females with a ratio of approximately 3:1. The majority of the study population were married 84.5%. The distribution of the education levels of the study population was; primary/none 38%, secondary 45% and tertiary 17percentage. Most of the patients had used tobacco 74.5% or alcohol 72.5%. Table 1.

**TABLE 1: Social demographic characteristics of the study participants**

Variable	Frequency	Percentage
<b>Age</b>		
16-35	39	19.5
36-55	62	31.0
56-75	86	43.0
>76	13	6.5
<b>Sex</b>		
Male	153	76.6
Female	47	23.4
<b>Marital status</b>		
Single	20	10
Married	169	84.5
Divorced	6	3.0
Widowed	5	2.5
<b>Education level</b>		
Primary/ none	76	38
Secondary	150	75
University	34	17
<b>Ever Tobacco use</b>		
Yes	149	74.5
No	51	25.5
<b>Ever Alcohol use</b>		
Yes	145	72.5
No	55	27.5

Most of the patients had used tobacco 74.5% or alcohol 72.5%

### Clinical – pathologic characteristics

The mean values of hemoglobin level before the start of treatment was 11.27 +/- 1.67 g/dl respectively, and 57.5% of the patients had a hemoglobin level of equal or more than 11g/dl. We found that 53% of the patients had advanced HNC clinical stage III and IV. Staging information was missing in 19.5% of case files.

Most of the patients had oral and pharyngeal cancers 41.5%, and that included cancers of the lower lip, tonsils, gingival, mandible, retromolar, tongue, soft palate, and hard palate, the floor of the mouth, lower jaw and buccal mucosa. Table 2.

**TABLE 2: Clinical – pathologic characteristics of the study population n=200**

Variable	Frequency	Percentage
<b>Hemoglobin level</b>		
<11	85	42.5
≥11	115	57.5
<b>Stage</b>		
One	27	13.5
Two	28	14.0
Three	31	15.5
Four	75	37.5
Unstaged	39	19.5
<b>Anatomical site</b>		
Nasopharynx	34	17.0
Oropharynx	8	4.0
Orocavity	83	41.5
Hypopharynx	11	5.5
Larynx	48	24.0
Nasal cavity and Paranasal sinuses	16	8.0

53% of the patients had advanced HNC clinical stage III and IV

### Treatment modalities delivered to different sites in HNC

Majority of the patients with HNC did not receive any surgical procedure, except for patients with hypopharynx in which 63.6% had surgery - Table 3. Chemoradiation was used mainly in nasopharyngeal and oro-pharyngeal cancers 64.7% and 75%, respectively. Most patients with diseases of the oral cavity, hypopharynx, larynx, nasal and paranasal sinus received radiotherapy alone.

**TABLE 3: Treatment modalities to different sites in HNC**

Variable	Surgery	Chemoradiation	Radiation alone
Nasopharynx (n=34)	2 (5.8%)	22 (64.7%)	9 (26.5%)
Oropharynx (n=8)	0 (0%)	6 (75%)	2 (25%)
Orocavity (n=83)	2 (2.4%)	23 (27.7%)	57 (68.7%)
Hypopharynx (n=11)	7 (63.6%)	4 (36.4%)	7 (63.6%)
Larynx (n=48)	12 (25%)	16 (33.3%)	32 (66.7%)
Nasal & PNS* (n=16)	2 (12.5%)	2 (12.5%)	14 (87.5%)

\*PNS: Paranasal Sinuses  
Most patients with diseases of the oral cavity, hypopharynx, larynx, nasal and paranasal sinus received radiotherapy alone.

The association between clinical, pathologic characteristics and survival

The 3 years observation of HNC patients showed that 70.9% of patients with the early disease i.e. Stage 1&2 were still alive, compared to 57.5% with advanced disease - Table 4. The difference observed is statistically significant  $p= 0.003$ . Survival of patients with oral cavity cancers is shown to be 68.7% and 58.5% for laryngeal cancers, while those with pharyngeal cancers and nasal/paranasal cancers had more reduced survival of 49% and 43.7% respectively. These differences observed in the anatomical sites of origin were found to be statistically significant  $p=0.038$ .

The higher survival rate of 68.2% showing in those that received a higher total radiation dose of > 40 Grays; Whereas 54.5% were alive in the group that received a total radiation dose of < 40 Grays. The difference observed is statistically significant  $p=0.043$ , but the association between the different treatment modalities and survival was not statistically significant.

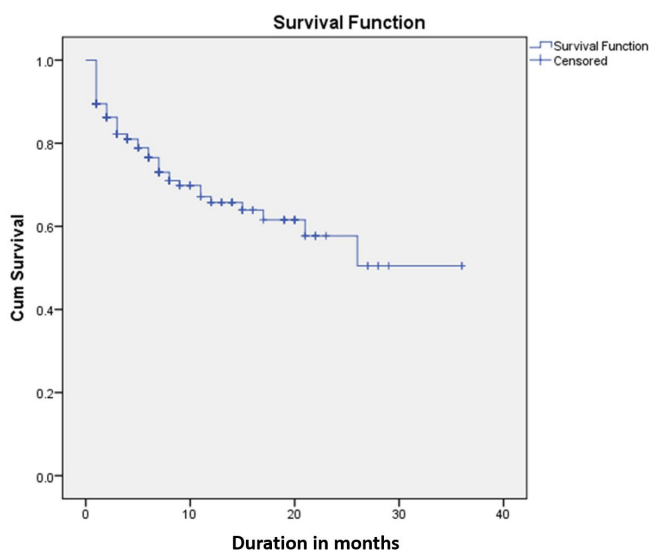
**TABLE 4: Association between clinical-pathologic factors; treatment modalities and survival**

Variable	Alive	$\chi^2$ (df)	P-value
<b>Stage</b>			
1 & 2(55)	39(70.9%)	11.905(2)	0.003
3 & 4(106)	61(57.5%)		
<b>Anatomical site (n)</b>			
Pharynx (53)	26(49.0%)	13.351(6)	0.038
Oroavity (83)	57(68.7%)		
Larynx (48)	28(58.3%)		
Nasal & Paranasal sinuses (16)	7(43.7%)		
<b>Dose (grays)</b>			
0 -40(134)	73(54.5%)	6.277(2)	0.043
>40(66)	45(68.2%)		
<b>Radiation alone</b>			
Yes (121)	67(55.4%)	2.498(2)	0.287
No (79)	51(64.5%)		
<b>Surgery</b>			
Yes (25)	12(48%)	2.077(2)	0.354
No (175)	106(60.6%)		
<b>Chemoradiation</b>			
Yes (73)	49(67.1%)	3.226(2)	0.199
No (127)	69(54.3%)		

Early stages of HNC ( $P=0.003$ ), anatomical sites of the disease( $P=0.038$ ), and standard high radiation doses of >40Gy( $P=0.043$ ) are associated with more prolonged survival in patients with HNC.

**Overall Survival of HNC patients**

The median overall survival duration was six months and ranged from 1 to 36 months. At the end of the three years follow up period, the overall survival rate was 59%. Figure 1.



**Discussion**

This was a retrospective descriptive study conducted at ORCI, the only Centre for treatment of cancer in Tanzania at the time of the data collection. A total of 200 randomly selected files of the patients with a diagnosis of Squamous Cell Carcinoma of Head and Neck treated from 2009 to 2011 were used for the study.

Findings from this study do not differ from other studies done in different parts of the world; whereby increasing age confers an increased risk to HNC. Nearly three quarter 74% of HNC patients were in the middle to older age groups and 50% of patients that were more than 56 years were alive at the end of our study period. Similar findings are seen elsewhere [10, 11], whereby the majority of the patients are in the middle to older age groups. However, a study done by Gugic and Strojan [11] shows a better survival in patients with <65 years compared to older patients, with 40% of the older patients surviving with no evidence of the disease.

Even though our study showed no statistical difference in survival between young and adults after receiving different modalities of treatment, this shows the advantage of therapy in advanced age regardless of the disease-free survival. In this study, women showed better three-year survival of 65.9% compared to men 56.8%. This finding does agree with a majority of epidemiologic studies, that shows poor overall survival among men compared to women. Similar hospital-based studies are demonstrating that women have better survival rates than men [12, 13].

In our study, the survival difference between patients with none/low education to highly educated patients was not statistically significant. Contrarily to our study Chu et al. [14] is describing that levels of social economic status are significantly associated with disease-specific survival -DSS and overall survival; this association may be a sign of a lack of preventative care in the lower SES populations, as well as barriers to health care that may delay treatment after diagnosis. Future research on HNC management should control for the disparity in SES. Also, future education efforts on HNC risk and management should target lower SES patients to improve the overall outcome of this debilitating disease [14].

While tobacco and alcohol use are primary risk factors for HNC, our results did not show a survival difference between the two groups. However, in one study which aimed at examining smoking and second primary tumor development - SPT; it shows that smoking increases the risk of developing SPT [15]. Smoking and drinking pre-diagnosis have previously been linked with more reduced survival in patients with HNC [16].

In general, a strong correlation existed between stage at diagnosis and relative patients-survival, with cancers that are at lower stages having higher relative survival. In our study, patients with early-stage i.e. stage I & II disease had a better survival rate; unfortunately, most of our patients had advanced disease at diagnosis.

The anatomical site of the tumor can also predict the survival of HNC [17]. In our study, patients with oral cavity cancers had better survival than patients with pharyngeal cancers  $P=0.025$ . Similarly, as was documented by SEER [7] patients with oral cavity cancers are surviving better than other HNC subtypes, the reason being oral cavity cancers are detected and diagnosed in early stages while hypopharyngeal diseases are anatomically hidden and therefore difficult to access for early diagnosis.

The mainstay of treatment for the early-stage disease is either radiotherapy or surgery. Advanced disease is treated either by surgery with postoperative radiotherapy or by definitive radiotherapy, with operation in reserve for salvage if necessary [18].

In this study, surgery was to only 25 out of 200 patients 12.5%, most of them being patients with hypopharyngeal and laryngeal cancers. Tracheostomy was the commonest palliative surgical procedure done

due to advanced disease to relieve obstructive tracheal symptoms. Another surgical procedure done was debulking of the tumor mass; no curative surgery performed. There was no survival difference between those having palliative surgery and those who did not. It is also reported on by another study [19] whereby the two groups of patients with imminent airway obstruction had their airways managed either by tracheotomy or by emergency laryngectomy. The survival advantage between the two groups was not significant.

A combination of radiotherapy with a cisplatin-based regimen shows to improve survival at 5years by 11% in HNC patients and to locally advanced disease by 5% at 2 to 5 years [20]. Among the 87 trials reviewed, the use of chemotherapy is associated with a survival advantage of 5% at 5years [21]. In our study, 73 patients received combination therapy, oral pharyngeal cancer 75%, and nasopharyngeal carcinoma 64.7%. However, no survival benefit established.

The difference in the results of our study and previous ones could be due to the mode of delivery of the cisplatin and dose prescribed. In this study participants received cisplatin 50mgs/m<sup>2</sup> or 100mgs/m<sup>2</sup> weekly for six cycles concurrently with radiotherapy, while in other studies, cisplatin was given concurrently with radiation 100mgs/m<sup>2</sup> 3 weekly for three times-cycles [21]

The more significant proportion of patients in this study received radiation alone 60.5%, given in single daily fractions of 1.8 – 2Gy for five days per week. No survival difference demonstrated in those that received radiotherapy alone. However, those who received a total dose of >40Gy survived longer than those that received a full dose of <40Gy p=0.001. The patients received a treatment of <40Gy, treated as palliative patients due to the presence of either/or advanced disease, debilitating comorbidities, and advanced age.

Radiotherapy delivered for the reason of being adjuvant therapy to improve local control following surgery and also as palliative therapy to provide symptomatic relief Cooper et al. [22] also found what corresponds with our results that adjuvant radiotherapy improves disease-free local control and even the overall survival.

This study found that the overall survival rate of 200 diagnosed HNC patients treated at ORCI, between 2009- 2011, was 59% with the median survival of 6 months, this was not overly different from what is found in SEER [7], that 3 years and 5 years relative survival rate was 64% and 57% respectively. In other studies, done in Europe and America for all patients with HNC, the overall five-year relative survival rate was 57%, while in India it is about 42.8% [8, 23]. Our study was retrospective, the data collection was from the files, and there was a poor recording of some of the factors needed for analysis, this limited the extraction of the data, and hence the difficulty in assessing some factors.

### Conclusion

Our study showed that the overall survival of HNC was 59%, with the median survival of 6 months and that clinicopathologic and treatment factors affected the survival of patients with HNC. Our study was retrospective, the data collection was from the files, where some of the data were missing that needed for analysis, and this limited the assessment of some of the factors. Therefore, there is a need of further studies to confirm these finding especially now where the hospital data management have moved to computer data systems.

### What already known on this topic?

- HNC treatment including surgery, Radiation therapy and Chemotherapy

- Five -year survival rate 57% for Europe and America and 42.8% in India
- Common histopathology is Squamous cell carcinoma due to cigarette smoking

### What is this study adding?

- In a low resource country, the 3 years overall survival was 59%
- Mobile phones can be used to follow up cancer patients after treatment
- Few HNC patients receive curative surgery in a low resource country

### Conflict of interest:

The authors declare no competing of interest.

### Author's contributions

CVM: designed the study, collected the data, made the analysis and wrote the first draft of the manuscript

LS: assisted in data analysis and manuscript writing.

SSO: a critical analysis of the script

LA: a critical review of the document

KM: supervised study designing, critical revision of the manuscript

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