

Head and Neck Squamous Cell Carcinoma in Western Uganda: Disease of Uncertainty and Poor Prognosis

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objectives. Patients with head and neck squamous cell carcinoma (HNSCC) have symptoms that masquerade as benign conditions, resulting in late presentations. The objective is to describe characteristics and stages of patients with HNSCC and document their prognosis from clinical experience in western Uganda.

Study Design. Cross-sectional study with clinical follow-up.

Setting. Mbarara Regional Referral Hospital.

Subjects and Methods. Fifty-one participants were recruited from February to July 2016. A questionnaire was used for patient characteristics, and staging, serologic studies, biopsy for histopathology, and immunohistochemistry were investigated. Staging was subclassified as early (stage I and II) and late (stage III and IV). Analysis was done with Fisher's exact test.

Results. Of 51 participants, 44 (86.5%) were male; the group had a mean age of 57.7 years, and 41 (80.1%) presented with late stage. Of 10 participants who presented with early stage, 6 (60%) had laryngeal HNSCC. The pharynx was ranked as the highest subsite ($n = 19$, 37.3%), followed by the oral cavity ($n = 9$, 17.6%), the larynx ($n = 9$, 17.6%), an unknown primary ($n = 8$, 15.7%), and sinonasal area ($n = 6$, 11.8%). Tobacco smoking, alcohol consumption, and prior use of traditional remedy were common characteristics among participants. Moderate differentiation was the most common grade ($n = 23$, 45.1%). *Helicobacter pylori*, Epstein-Barr virus, human immunodeficiency virus, and human papilloma virus type 16 were identified among 51 participants. However, none could afford referral for radiotherapy; hence, 1-year survival was 4%.

Conclusion. The majority of our patients with HNSCC present at late stage, and the prognosis is poor. There is great need for preventative community-based education and early screening services to save our population.

Keywords

head and neck squamous cell carcinoma, Uganda

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Head and neck squamous cell carcinoma (HNSCC) is the sixth-most common type of cancer affecting the upper digestive tract, representing approximately 6% of all new cancer cases.¹ HNSCC is thought to account for 350,000 cancer deaths worldwide per year, with males affected significantly more than females at a ratio of 4:1.² Reliable data from Africa are absent, and most information is from hospital-based registries or case series, as opposed to population-based data.² The few available reports provide data from Nigeria,³ Egypt,⁴ and Kenya.⁵ A Ugandan report indicated that between 1989 and 1999 at Mulago Hospital, 1298 neoplastic orofacial cases were identified in by oromaxillofacial department, of which 15% were HNSCC.⁶ In addition, 16% of 1292 patients treated in the radiation department with Chinese GWGP80 cobalt unit had HNSCC.⁷

Despite advances in diagnostic tools and treatment modalities, almost two-thirds of patients with HNSCC present with advanced disease (stages III and IV).⁸ In the early stages of the disease (I and II), patients with HNSCC have a 5-year survival rate of 70% to 90%, independent of the sublocation or treatment.⁹ In contrast, in advanced stages of the

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disease, patients display different survival rates, depending on the tumor.

In Uganda, the incidence of cancers has been on the rise over the past 20 years,^{10,11} and it appears that patients present with late disease. A report from Kampala covering the time frame 2004 to 2009 reported that 219 patients had HNSCC, of which 56.2% had lymph node involvement and 6.8% had distant metastases at diagnosis.^{12,13}

We aimed to describe the characteristics and stages of patients with HNSCC and document their prognosis from clinical experience in a rural setting in western Uganda.

Methods

We conducted a cross-sectional study with clinical follow-up of patients with HNSCC at Mbarara Regional Referral Hospital in the outpatient departments of the ENT (ear, nose, and throat), surgery, and dental clinics. Patients with suspected HNSCC were consecutively recruited between February 2016 and July 2016 for a total of 54 cases.

A questionnaire captured patient demographics, socioeconomic characteristics, and presenting complaint. Complete clinical examination and flexible nasopharyngolaryngoscopy were performed, and patients were staged through the American Joint Committee on Cancer staging system (tumor, node, and metastasis [TNM]).

Biopsies were later taken for histology from all participants with suspected HNSCC. Routine hematoxylin and eosin staining was used to confirm diagnosis and typing of tissues into well, moderately, and poorly differentiated carcinoma. Additionally, lymphovascular permeation and perineural invasion assessment were performed, and P16 immunohistochemistry was done to determine the human papilloma virus (HPV) status of the biopsies.

Participants underwent chest radiography for assessment of lung metastases. Routine blood investigations for human immunodeficiency virus (HIV), *Helicobacter pylori*, and Epstein-Barr virus were performed for each participant.

The study was approved by the Research Ethics Committee at the Mbarara University of Science and Technology. Anonymity and confidentiality were ensured by identification numbers on questionnaires (ie, no names or initials). Participants' identities were known only to the principal investigator, who was their primary health care provider. Written informed consent was obtained from the participants with suspected HNSCC. Privacy was ensured during the interviews.

Data Analysis

A total of 54 participants were recruited to participate in study; of these, 3 were excluded per their histology results, which included rhabdomyosarcoma, basal cell carcinoma, and adenocystic carcinoma. Data from completed questionnaires were entered into Microsoft Excel 2007 and exported to STATA/IC 13.0 (StataCorp LLC, College Station, Texas) for analysis.

The dependent variable was stage. The following independent variables were assessed for their confounding effects on stage: demographics (age, sex, income, occupation),

Table 1. Demographic and Socioeconomic Characteristics of 51 Patients Aged 20 to 90 Years with Head and Neck Squamous Cell Carcinoma.

| Characteristics | Mean \pm SD or n (%) |
|------------------------------------------|------------------------|
| Age, y | 57.7 \pm 14.0 |
| Age category, y | |
| <55 | 12 (23.5) |
| \geq 55 | 39 (76.5) |
| Sex | |
| Female | 7 (13.7) |
| Male | 44 (86.5) |
| Monthly income, Uganda shillings | |
| <144,100 | 33 (64.7) |
| \geq 144,100 | 18 (35.3) |
| Level of education | |
| None | 15 (29.4) |
| Primary | 28 (54.9) |
| Secondary | 4 (7.6) |
| Tertiary | 4 (7.6) |
| Occupation | |
| Manual laborer | 3 (5.9) |
| Professional | 3 (5.9) |
| Business | 3 (5.9) |
| Peasant | 42 (82.4) |
| Ever smoked tobacco | |
| No | 9 (17.6) |
| Yes | 42 (82.4) |
| Ever taken alcohol | |
| No | 10 (19.6) |
| Yes | 41 (80.4) |
| Family history of cancer | |
| No | 46 (90.2) |
| Yes | 5 (9.8) |
| Duration of symptoms to presentation, mo | 11.4 \pm 10.4 |

socioeconomic characteristics (smoking status, alcohol status, marital status, family history of cancer), and serologic and histologic characteristics (HPV, HIV, Epstein-Barr virus, *H pylori*, and histology types).

Age was grouped into <55 or \geq 55 years, based on the 2016 Uganda demographic profile, which stated that the total population life expectancy in Uganda is 55.4 years. Income was categorized as \geq 144,100 and <144,100 Uganda shillings (about US \$40). This was adapted from the Uganda Bureau of Statistics, which stated that the 2016 average household monthly income is 144,100 Uganda shillings in rural setting. Staging of HNSCC was subclassified as early (stage I and II) and late (stage III and IV).

For the descriptive statistics, we used chi-square analysis and adjusted for the Fisher's exact method in univariate analysis, with data represented in tables and graphs. A significance level of $P \leq .05$ was used.

Table 2. Distribution of Stage and AJCC Classification for 51 Participants with HNSCC Seen at the Mbarara Regional Referral Hospital (February-August 2016).

| AJCC | Participants, n (%) | | | | | P Value |
|------------|---------------------|-----------|-----------|-----------|------------|---------|
| | Overall | Stage I | Stage 2 | Stage 3 | Stage 4 | |
| Tumor | | | | | | .0001 |
| 1 | 4 (9.1) | 4 (100.0) | 0 | 0 | 0 | |
| 2 | 7 (15.9) | 0 | 6 (100.0) | 1 (25.0) | 0 | |
| 3 | 5 (11.4) | 0 | 0 | 2 (50.0) | 3 (10.0) | |
| 4 | 28 (63.6) | 0 | 0 | 1 (25.0) | 27 (90.0) | |
| Nodal | | | | | | .0001 |
| 0 | 17 (33.3) | 4 (100.0) | 6 (100.0) | 2 (50.0) | 5 (13.5) | |
| 1 | 4 (7.8) | 0 | 0 | 1 (25.0) | 3 (8.1) | |
| 2 | 14 (27.5) | 0 | 0 | 1 (25.0) | 13 (35.1) | |
| 3 | 16 (31.4) | 0 | 0 | 0 | 16 (43.2) | |
| Metastases | | | | | | .0001 |
| 0 | 44 (86.3) | 4 (100.0) | 6 (100.0) | 4 (100.0) | 30 (100.0) | |
| 1 | 7 (13.7) | 0 | 0 | 0 | 7 | |

Abbreviations: AJCC, American Joint Committee on Cancer; HNSCC, head and neck squamous cell carcinoma.

Results

From February to July 2016, 51 participants with confirmed HNSCC at Mbarara Regional Referral Hospital were enrolled into the study. The majority (n = 42, 82.4%) were peasant farmers with a diet composed of plantain (locally referred to as *matooke*), millet bread, maize flour, beans, green vegetables, and occasional meat without spices and oils; they had no prior exposure to radiotherapy; and they were naïve of oral sexual practices.

Table 1 presents the sociodemographic characteristics of all study participants. The mean age was 57.7 years; 39 participants were ≥ 55 years old; and the lowest limit was 20 years. The group had a male:female ratio of 6:1. The majority of the participants earned <144,100 Uganda shillings annually. Among the participants, 42 (82.4%) had a history of tobacco smoking and alcohol intake, and 5 (9.8%) had a family history of aerodigestive cancers.

Table 2 and **Figure 1** illustrate that among the participants in the study, 41 (80.1%) presented with late stage according to the American Joint Committee on Cancer staging system.

Of 10 patients who presented in early stage, 6 (60%) had laryngeal HNSCC. Pharynx ranked highest for HNSCC subsite (n = 19, 37.3%), followed by the oral cavity (n = 9, 17.6%), the larynx (n = 9, 17.6%), an unknown primary (n = 8, 15.7%), and sinonasal area (n = 6, 11.8%), as shown in **Figure 2**.

Patient Characteristics

The majority of patients who presented with late-stage disease were aged ≥ 55 years (n = 30, 73.2%), were men (n = 36, 87.8%), and earned <144,100 Uganda shillings (n = 26, 63.4%). Among them, 33 (80.5%) had no education or a

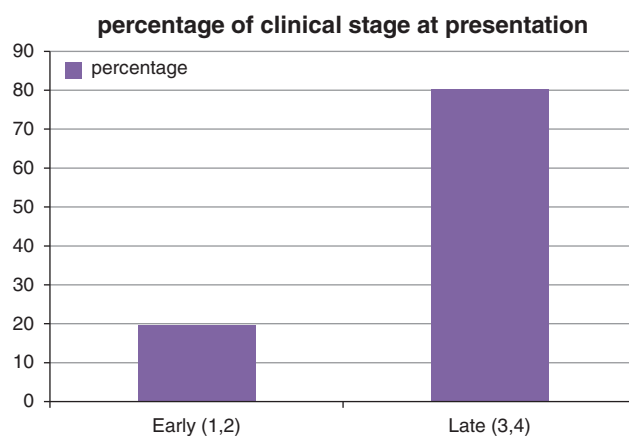


Figure 1. Clinical stage distribution among 51 study participants with head and neck squamous cell carcinoma.

primary level of education; 32 (78.1%) were peasant farmers; and 33 (80.5%) admitted to use of traditional remedy (*Bishaka* in the local language) for different traditional diagnoses (*enfumbi* and *ebinyoro* in local language) prior to presentation to the hospital. Among those presenting with late-stage disease, 32 (78.1%) and 31 (75.6%) had a history of tobacco smoking and alcohol intake, respectively (**Table 3**).

Serologic and Histologic Characteristics in Relation to Stage

Among all the participants who tested positive for HIV, 6 presented with late clinical stage; however, *H pylori* tested positive for 30 participants, of whom 24 presented with late stage. Epstein-Barr virus immunoglobulin M tested positive for 4 participants. These participants had nasopharyngeal keratinizing carcinoma, of which 3 presented with late

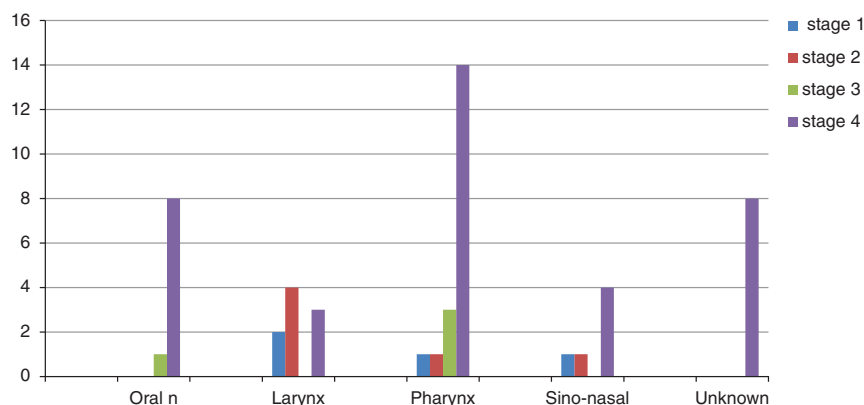


Figure 2. Number of participants distributed across head and neck squamous cell carcinoma sites by clinical stage at presentation (N = 51).

Table 3. Demographic and Socioeconomic Characteristics in Relation to Stage for 51 Participants with Head and Neck Squamous Cell Carcinoma.

| Demographic/Socioeconomic | Participants, n (%) | | | P Value |
|----------------------------------------|---------------------|-------------|------------|---------|
| | Overall | Early Stage | Late Stage | |
| Age, y | | | | .261 |
| <55 | 12 | 1 (10.0) | 11 (26.8) | |
| ≥55 | 39 | 9 (90.0) | 30 (73.2) | |
| Sex | | | | .520 |
| Female | 7 | 2 (20.0) | 5 (12.2) | |
| Male | 44 | 8 (80.0) | 36 (87.8) | |
| Income, Uganda shillings | | | | .1527 |
| <144,100 | 33 (100) | 7 (70.0) | 26 (63.4) | |
| ≥144,100 | 18 (100.0) | 3 (30.0) | 15 (36.6) | |
| Level of education | | | | .289 |
| None | 15 | 4 (40.0) | 11 (26.8) | |
| Primary | 28 | 6 (60.0) | 22 (53.7) | |
| Secondary/tertiary | 8 | 0 | 8 (19.5) | |
| Occupation | | | | .446 |
| Manual laborer | 3 | 0 | 3 (7.3) | |
| Professional | 3 | 0 | 3 (7.3) | |
| Business | 3 | 0 | 3 (7.3) | |
| Peasant | 42 | 10 (100.0) | 32 (78.1) | |
| Ever smoked tobacco | | | | .103 |
| No | 9 | 0 | 9 (21.9) | |
| Yes | 42 | 10 (100.0) | 32 (78.1) | |
| Ever taken alcohol | | | | .082 |
| No | 10 | 0 | 10 (24.4) | |
| Yes | 41 | 10 (100.0) | 31 (75.6) | |
| Use of traditional/herbal remedy prior | | | | .128 |
| No | 8 | 0 | 8 (19.5) | |
| Yes | 43 | 10 (100.0) | 33 (80.5) | |

stage, including the youngest participant in the study (a 20-year-old man).

Histologically, there was a proportional distribution of squamous cell cancer differentiation: well (n = 9, 22.0%), moderate (n = 20, 48.8%), and poorly (n = 12, 29.2%). Of

the 51 participants, only 6 were positive for HPV type 16 on P16 immunohistochemistry. Among the 5 who presented with late stage, their lesions were oropharyngeal in origin, whereas the participant who presented with early stage had a laryngeal lesion. Regarding histology, keratinization was

Table 4. Serologic and Histologic Characteristics in Relation to Stage for 51 Participants with Head and Neck Squamous Cell Carcinoma.

| Serologic-Histologic | Participants, n (%) | | | P Value |
|-------------------------------------------|---------------------|-------------|------------|---------|
| | Overall | Early Stage | Late Stage | |
| Human immunodeficiency virus | | | | 1.6585 |
| Negative | 45 | 10 (100.0) | 35 (85.4) | |
| Positive | 6 | 0 | 6 (14.6) | |
| <i>Helicobacter pylori</i> | | | | .0071 |
| Negative | 21 | 4 (40.0) | 17 (41.5) | |
| Positive | 30 | 6 (60.0) | 24 (58.5) | |
| Epstein-Barr virus immunoglobulin M | | | | .0801 |
| Negative | 47 | 9 (90.0) | 38 (92.7) | |
| Positive | 4 | 1 (10.0) | 3 (7.3) | |
| P16 (human papilloma virus) | | | | .0373 |
| Negative | 45 | 9 (90.0) | 36 (87.8) | |
| Positive | 6 | 1 (10.0) | 5 (12.2) | |
| Squamous cell carcinoma differentiation | | | | .093 |
| Well | 15 | 6 (60.0) | 9 (22.0) | |
| Moderate | 23 | 3 (30.0) | 20 (48.8) | |
| Poor | 13 | 1 (10.0) | 12 (29.2) | |
| Squamous cell carcinoma keratinizing type | | | | .030 |
| No | 23 | 8 (80.0) | 15 (36.6) | |
| Yes | 28 | 2 (20.0) | 26 (63.4) | |

present in 28 biopsies, of which 26 were among participants with late-stage disease (Table 4).

Among the 51 participants, none were able to afford referral to the neighboring country for radiotherapy; hence, the 1-year survival rate was 4%.

Discussion

The diagnosis of HNSCC in western Uganda takes a turmoil on both caregiver and patient. As the world advances in diagnostic tools and treatment modalities, HNSCC remains a major source of morbidity and mortality, with almost two-thirds of patients with HNSCC presenting with advanced disease (stages III and IV).¹⁴ In Africa, published clinical experience at Kenyatta National Hospital showed that most patients presented with late disease, and this is a setting where variable treatment¹⁵ options and countrywide screening programs are in place. Our study showed that 80.1% of patients with HNSCC presented with late stage. These results also indicate that more participants in western Uganda presented with late stage as compared with other patient populations with oropharyngeal cancer, who have documented rates of 60% and 77%.^{16,17}

The American Joint Committee on Cancer TNM staging system was applicable and readily adapted in our setting. Among patients who had tumor stage 4 at presentation, 80% had late stage, and 31.4% had nodal spread on clinical examination. There was statistical significance between TNM staging and stage. However, assessment of participants with metastatic neck lymph nodes with an unknown

primary was a challenge per financial constraints, despite flexible nasopharyngolaryngoscopy and bimanual palpation.

We also found a statistically significant relationship between stage at presentation and site of the tumor. The majority of the patients who presented with late stage had HNSCC lesions in the oral cavity and pharynx (50.7%); however, an additional 15.6% of participants with an unknown primary brought this percentage to 66.3%. Participants who presented with early stage mostly had HNSCC in the larynx. In our study, laryngeal involvement resulted in difficulty in breathing, prompting patients to present earlier than those with HNSCC in other sites. These findings are similar to research conducted in India, where patients who presented in early stage had laryngeal HNSCC.¹⁸

For age in general, our results are also similar to research conducted in India,¹⁸ where the age range was 25 to 85 years, although we differ by having an age range of 20 to 90 years with a mean (SD) of 57.7 (14.0) years. The participant with the lowest age was a 20-year-old man with nasopharyngeal carcinoma, who tested positive for Epstein-Barr virus immunoglobulin M and negative for P16, while the oldest participant was a 90-year-old man with metastatic neck lymph nodes and an unknown primary.

Participants whose socioeconomic characteristics included being a peasant farmer, low income, and low educational status were more inclined to present with late-stage disease. Thus, patients with low socioeconomic status are more likely to present with late stage, and more attention ought to be paid to them as a vulnerable population.¹⁹

Use of traditional/herbal remedy prior to presentation to the hospital was reported among 84.3% of participants, with a mean of 11.4 months from experience of the first symptom to hospital presentation. Traditional herbalists in western Uganda are affordable and easy to access, and they understand cultural beliefs. Although they play a role in delay in hospital presentation, the pharmacokinetics of traditional herbal medicine in the diagnosis and management of HNSCC are still unknown.

Our study demonstrated that the majority of patients with HNSCC had a history of tobacco smoking and alcohol intake, and a few were positive for HIV, Epstein-Barr virus, *H pylori*, and HPV subtype 16. These are established risk factors for HNSCC. However, our study also reveals the shortage of countrywide preventative and early screening interventions for HNSCC in Uganda.

According to a recent National Cancer Database report, approximately 822,000 cancers of the head and neck are HNSCC. Histological typing in our study showed 20 (82.6%) participants with moderately differentiated HNSCC and 12 (84.6%) with poorly differentiated HNSCC presenting with late stage ($P = .03$; likewise for keratinization). As recently shown, biological tumor behavior may be independent of anatomic staging, and keratinizing HNSCC lesions may be more aggressive in nature; as such, knowledge of a given squamous cell carcinoma tumor's grade remains a critical factor in the construction of an accurate prognosis.²⁰ Among the 51 participants, none were able to afford referral to the neighboring country for radiotherapy, and the 1-year survival rate was 4% from clinical experience.

Limitations

Genetic assays would have added information on risk factors for HNSCC; however, this was not done because of financial constraints.

Conclusion

The majority of our patients with HNSCC present with late stage, and the prognosis is poor. There is a need for preventative community-based education and early screening services to save our population.

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Author Contributions

Jamilah Nabukenya, conceived the study and participated in data collection and analysis and manuscript writing; **Tessa A. Hadlock**, participated conceptualization of the topic, manuscript revision, and writing guidance; **Wilfred Arubaku**, supervisor and guided in proposal development and manuscript preparation proofreading.

Disclosures

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