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Original Research Article

The two-year survival rate of laryngeal squamous cell carcinoma patients treated at Dr. George Mukhari academic hospital South Africa

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ABSTRACT

Background: The study was conducted to assess the outcome of patients diagnosed with laryngeal squamous cell carcinoma (LSCC) treated at a tertiary level hospital in South Africa. The focus was the two-year disease-specific survival (DSS) rate after diagnosis as a measuring tool for the outcomes of the disease.
Methods: A retrospective cross-sectional descriptive study was conducted at Dr. George Mukhari academic hospital (DGMAH) from 1 January 2010 to 31 December 2015. The data was collected from files of patients who were identified by clinical laryngeal symptoms, pan-endoscopy and biopsy. A total of 37 files of patients diagnosed as LSCC were included in the study.
Results: 166 hospital records were retrieved. After application of inclusion and exclusion criteria, the study excluded 129 files because of benign lesions, malignancies other than SCC on histology report, SCC from upper aero-digestive sites other than the larynx or files with incomplete information. Therefore, 37 records were considered for the study.
Conclusions: The study found the two-year DSS to be 43.2%. A significant contributing factor to the low two-year DSS was the advanced stage of the disease (III and IV) at the time of the presentation that was managed by palliative treatment. Advanced disease was likely due to delayed presentation to the hospital influenced by a low level of patient health knowledge, the negative impact of religious and cultural beliefs, low disposable household income coupled with high distance from home to the nearest hospital, and suboptimal screening at the primary health care level.

Keywords: LSCC, DSS, Treatment modality

INTRODUCTION

Laryngeal squamous cell carcinoma (LSCC) is a significant public health problem worldwide.[1] LSCC is a preventable head and neck malignancy that has a considerable impact in poor socio-economic communities.[1] According to global cancer statistics 2018, there were 177,422 new LSCC cases and 94,771 deaths worldwide.[2] In South African male population, incidence rate of LSCC stood at 2.64 per 100,000 people.[6]

Laryngeal carcinoma is the second most common cancer of the upper aero-digestive system.

Most of these carcinomas are squamous cell carcinomas (SCC) and they account for 85% to 95% of laryngeal tumours.[7] LSCC is one of the ten most prevalent malignancies in South African black male population.[8]

The risk factors for developing LSCC include smoking, alcohol consumption, synergistic effect of smoking and alcohol consumption, male gender (especially above 40 years of age), human immunodeficiency virus (HIV) infection, human papilloma virus (HPV) infection, and African descent.[8-10]

LSCC symptoms differ depending on whether or not cancer involves the vocal cords causing changes in voice

quality or creating swallowing problems. Possible symptoms patients will present include:[1,8,11,12] Hoarseness, pain when swallowing, sensation of a lump in the throat, pain over the larynx, chronic cough that does not settle, referred earache, shortness of breath and stridor, which can culminate in upper airways obstruction requiring an emergency tracheostomy.

In advanced stages, difficulty in swallowing, haemoptysis, neck mass, fetor and cachexia can appear.

The treatment approach depends upon tumour extent and location, patient-specific factors such as age, comorbidity, performance status and psychosocial support, physician expertise and the availability of treatment and rehabilitation services.[13,14]

LSCC treatment modalities are:[13,15-19] Single modality, surgery-Radiotherapy (RT), double modality, surgery plus RT, chemotherapy plus RT (CRT), triple modality: Surgery, chemotherapy and RT.

LSCC is one of the most common head and neck malignancies encountered at Dr George Mukhari academic hospital (DGMAH).

DGMAH is a large tertiary referral hospital located in Ga-Rankuwa, Gauteng province of South Africa, largely servicing patients from low socio-economic households. Data from 2018 revealed that the ENT out-patients department received 7,516 patients with different otorhinolaryngologic ailments of whom 1,106 were admitted to the hospital. The statistics showed that patients originate from the surrounding peri-urban and rural areas of northern Gauteng province and others came from the neighbouring provinces of Limpopo and North West.

LSCC is diagnosed by a pan-endoscopy and biopsy for histology. The type of tumour, as well as the differentiation, is confirmed by the pathology report. The treatment option is chosen based on the clinical, radiological and pathological staging at a multidisciplinary head and neck oncology clinic.

LSCC treatment outcome can be measured by the DSS after completion of oncology treatment. The DSS is the percentage of people in a study group, with a specific type and stage of cancer, who did not die from any cause during a particular period after diagnosis.[20] No study on LSCC survival rate or into the factors that could have played a role in the survival of patients has been conducted in South Africa. The high incidence of LSCC, coupled with the scarcity in the literature regarding the outcome, prompted a decision to undertake a retrospective study on LSCC seen at DGMAH. The study was conducted, taking into consideration demographics, tumour site, type and stage, treatment options and DSS.

Aim

To establish the outcome of patients diagnosed with LSCC at DGMAH in terms of the two-year DSS rate after diagnosis.

Objectives

Objectives were to determine the incidence of LSCC, taking into consideration patient demographics (age, gender, race and marital status), to determine the HIV status in LSCC patients at the otorhinolaryngology-head and neck department at DGMAH, to determine the two-year DSS rate of LSCC patients treated at DGMAH over six years dating from 1st January 2010 to 31st December 2015, to determine the effect of risk factors (smoking, drinking and HIV) on the two-year DSS rate and to determine the effect of site, type and stage of the tumour, and treatment modality on the two-year DSS rate.

METHODS

Ethics

The study was approved by SMU research and ethics committee (SMUREC), and the DGMAH management team.

Study design

A retrospective cross-sectional descriptive study was performed at DGMAH. Otorhinolaryngology out-patient's department over 5 years from 01 January 2010 until 31 December 2015. The data was collected from files of all patients who were identified as having laryngeal symptoms and taken to theatre for direct laryngoscopy or pan-endoscopy and biopsy.

The data collection form included the following variables: Age, ID number, gender, race and marital status, file number, smoking, drinking, HIV status (positive/negative), tumour site (supraglottic, glottic, subglottic), tumour staging (TNM, clinical oncological), histology subtype, date of diagnosis, date of treatment (initiation), treatment modality (surgery and/or chemotherapy and/or RT), date of the last contact and alive at the two-year limit

Calculation of two-year DSS was conducted according to a patient's latest follow-up visit at DGMAH.

All files with complete demographic information, clinical information and pathologically confirmed LSCC at DGMAH operated and, or referred to the radio-oncology department at Steve Biko academic hospital (SBAH) from 1 January 2010 to 31 December 2015.

Exclusion criteria

Patients with incomplete information such as no histology report available, incomplete clinical data, uncaptured South African identity number or passport number, patients with recurrence LSCC or synchronous tumours, patients with laryngeal carcinoma other than LSCC and patients with squamous cell carcinoma not arising from the larynx.

Data analysis

In consultation with a Statistician, descriptive statistical analysis was conducted for all data collected and used to describe the sample group. The mean and standard deviation or median and interquartile range were applied where appropriate. Continuous variable group means were compared using unpaired t-tests for normally distributed data. Results were presented in tables and graphs.

Study bias

Selection bias was minimized as all LSCC patients diagnosed during this period and whose files were available from the active as well as dead patients' sections of the filing room were included in the study. Sample bias was of concern as DGMAH is an academic hospital linked to a tertiary institution where the majority of patients arrived at advanced stages of the disease, constituting a sample that is not representative of the condition in the general population. Observer bias can also be a concern as the study is retrospective over six years with different clinicians involved in the management of patients included in the study.

RESULTS

Theatre records at DGMAH identified 305 patients taken for pan-endoscopy or direct laryngoscopy from 1 January 2010 to 31 December 2015. Of the 305 identified files, 139 files were missing, and only 166 files were retrieved. After application of inclusion and exclusion criteria, the study excluded 129 files because of benign lesions, malignancies other than SCC on histology report, SCC from upper aero-digestive sites other than the larynx, or files with incomplete information. Ultimately, only 37 patients were considered for the study. All of the demised patients died of cancer-related complications.

Table 1 summarises the demographics of the study cohort. The mean age of patients who demised was 59.3 years, whereas for those who survived was 56.2 years. The average waiting time before diagnosis was 2.8 months and 2.7 months, respectively. There were 8 females (21.6%) and 29 males (78.3%).

Table 2 illustrates the risk factors identified in the study cohort. Cigarette smoking was identified in 40.5% of demised and 27.0% of survived patients. Alcohol use was reported in 37.8% of patients who passed away and 24.3% of patients who survived after 2 years. The HIV serology status revealed that 16.2% of the patients were HIV-positive, 48.6% were HIV-negative and unknown HIV-status identified in 35.1%.

Table 1: Demographics, (n=37).

Variables		Patients who demised (%)	Patients who survived (%)
Age (Years)	Mean ± SD	59.3±13.5	56.2±9.9
The time delay before diagnosis	Mean (months)	2.8	2.7
Gender	F (8)	5 (13.5)	3 (8.1)
	M (29)	16 (43.2)	13 (35.1)
Race	Black African	21	16
Marital status	Single (5)	2 (5.4)	3 (8.1)
	Married (12)	8 (21.6)	9 (10.8)
	Unknown (20)	11 (29.7)	9 (24.3)

Table 2: Risk factors, (n=37).

Variables		Patients who demised (%)	Patients who survived (%)
Cigarette smokers only	Yes (25)	15 (40.5)	10 (27.0)
	No (8)	6 (16.2)	2 (5.4)
	Unknown (4)	0 (0.0)	4 (10.8)
Alcohol users only	Yes (23)	14 (37.8)	9 (24.3)
	No (8)	7 (18.9)	1 (2.7)
	Unknown (6)	0 (0.0)	6 (16.2)
Cigarette smokers and alcohol users	Yes (23)	14 (37.8)	9 (24.3)
	No (8)	7 (18.9)	1 (2.7)
	Unknown (6)	0 (0.0)	6 (16.2)
HIV status	Positive (6)	3 (8.1)	3 (8.1)
	Negative (18)	11 (29.7)	7 (18.1)
	Unknown status (13)	7 (18.9)	6 (16.2)

Table 3 above shows that the tumour with glottis epicentre was the most common at 54.0%, followed by supraglottic (45.9%). The subglottic epicentre was not identified. The Oncological staging demonstrated that more patients presented with advanced tumour (stage III-IV) at 75.6% than early tumour stage (stage I-II) at 24.3%. The poorly differentiated tumour was the most common histological differentiation at 43.2%, followed

by Moderate differentiation (27.0%) and well differentiation at 16.2%. About 13.5% had unspecified tumour differentiation.

Table 3: Tumour characteristics, (n=37).

Variables		Demised patients (%)	Survived patients (%)
Epicentre	Supraglottic (17)	16 (43.2)	1 (2.7)
	Glottic (20)	5 (13.5)	15 (40.5)
	Subglottic (0)	0 (0)	0 (0)
Oncology staging	I-II (early) (9)	0 (0)	9 (24.3)
	III-IV (Advanced) (28)	21 (56.8)	7 (18.9)
Histology differentiation	Well (6)	0 (0)	6 (16.2)
	Moderately (10)	3 (8.1)	6 (18.9)
	Poor (16)	14 (37.8)	2 (5.4)
	Unspecified (5)	4 (10.8)	1 (2.7)
Treatment	Surgery + PORT (3)	0 (0)	3 (8.1)
	CRT (5)	2 (5.4)	3 (8.1)
	RT only (12)	2 (5.4)	10 (27)
	Palliative care (17)	17 (46)	0 (0)

Different treatment modalities were offered to this cohort. Surgery and PORT were offered to 3 patients (8.1%). Combined chemo-radiation was given to 5 patients (13.5%) and curative radiotherapy was given to 12 patients (32.4%) of the patients. Palliative and supportive care were given to 17 patients (46%).

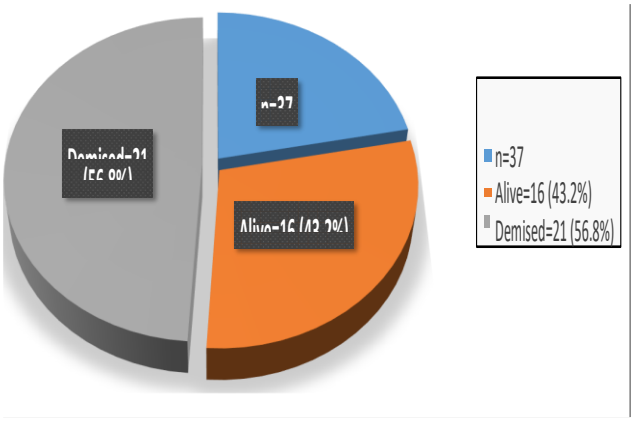

Figure 1: Two-year survival rate.

The final analysis revealed that 16 patients (43.2%) were alive and 21 patients (56.8%) had demised after two years of diagnosis (Figure 1).

DISCUSSION

Laryngeal cancer is the second most common cancer of the upper aero-digestive tract.[1] Most of the laryngeal cancers are SCC, accounting for 85% to 95% of malignant laryngeal neoplasms.[21] In a Tanzanian study done by Peter et al and a South African study done by De Villiers et al the glottis was the most common subsite.[1,8] These findings are similar to the DGMAH study, where the common subsite of the tumour epicentre was glottis at 54.0%, followed by supraglottic (45.9%) and zero subglottic subsites were found. The supraglottic epicentre was however the commonest in a study done by Sharma et al.[7]

Histopathological diagnosis of malignant tumours differs from one centre to another. In the DGMAH study, poorly differentiated histopathology was common at 43.2%, followed by moderate-differentiation (27.0%) and well-differentiation (16.2%). The DGMAH study differs from a study done by Sharma et al., which found well-differentiated SCC (50%), moderately differentiated SCC (26.6%), and poorly differentiated SCC was (10%).[7] LSCC variants account for less than 10% of all Laryngeal SCC and three of the most common and important of these are basaloid, verrucous, and papillary SCC.[22] There were no SCC variants identified in the DGMAH study.

The oncological staging in the DGMAH study showed that 75.6% of the patients presented with advanced disease (Staged III and IV) and 24.3% were staged I-II. The advanced cases (8.1%) were offered surgery followed by PORT and 13.5% of the advanced disease who declined surgery received combined chemo-radiation.

Of 3 advanced patients who were offered surgery and PORT, all of them (8.1%) were alive after 2 years. Of the 5 advanced patients who declined surgery but opted for combined chemoradiation, only 3 (8.1%) were alive after 2 years. The remaining patients with advanced disease (46.0%) were considered too progressed for any intervention and were therefore treated with palliative care.

A total of 12 patients (32.4%) receives curative radiotherapy as a form of treatment. Nine of these patients were early-stage (24.3%) and 3 patients (8.1%) had advanced disease. The outcome for this cohort showed 10 patients who had curative radiotherapy were alive after 2 years. These findings show that curative radiotherapy for the early stage gave a better 2-year survival in the DGMAH study.

Surgery followed by PORT and combined chemoradiation for stage III-IV had an equal 2-year survival of 8.1% in our study. The DGMAH outcome differs significantly with two studies, veterans' affairs and the Guangdong studies which had far much better two-year DSS 86% and 97% respectively.[23,24] A low

sample size contributed to the low DSS in the DGMAH study of 43.2%.

Age

The survival of LSCC depends on the age of the patient. In our study, the mean age of LSCC is 62.3 years. The youngest patient was 31 years old and the oldest 94 years old. A Turkish study done by Akduman et al documented the age of LSCC patients to be between 34-84 years (mean: 57.6). In the city of Jos in Nigeria, Adoga et al noted the age of LSCC patients to be 30-70 years with a mean of 56.14 years.[18] In Cameroon, Oyono et al found that the mean age of LSCC was 53 years.[19] In the Free State province of South Africa, a study done by De Villiers et al. reported LSCC cases ranging from 41-87 years (mean: 61.9 years).[8] The finding of a mean of 62.3 years by the DGMAH study suggests that LSCC patients in South Africa present in their sixties on average, corroborating the finding by De Villiers et al (61.9 years) and Roos et al (60.1 years).[8,25] These mean ages are higher compared to the average in other studies where LSCC patients are generally reported to appear in their fifties for the rest of the African continent.[12,17-19,26]

The average age of patients that demised in the DGMAH study was 59.3 years, and those that survived was 56.2. These results may suggest that younger patients have a better chance of survival compared to older ones.

Marital status

In their US study, Megwalu et al reported that marital status positively affects the survival of LSCC.[21] Inverso et al found in their research that marriage had a protective effect against the presence of metastases at presentation and that married patients are more likely to seek medical treatment early.[27]

In the DGMAH study, married patients constitute 32.4% and single patients represent 13.5%. The patients with unknown marital status constituted 54%. The married patients who survived after two years were 10.8%, the singles were 8.1% and the unknown marital status was 24.3%. The DGMAH study indicates that marital status has no significant benefit in the 2-year survival rate. This outcome concurs with the Michigan study done by Choi et al.

which ruled out the relationship between marital status and cancer stage.[28] There were no African studies reporting survival rates about marital status.

Treatment delay

The waiting time for treatment significantly influenced OS in a Danish study as reported by Lyhne et al.[29] Bhattacharjee et al corroborated this finding and concluded that an average waiting time of 20 to 45 days is ideal for maximal survival benefit.[30] Naghavi et al found in a US study that black patients who had more than 45 days lapse between diagnosis and treatment had a lower three-year OS.[31] The average waiting time from diagnosis to treatment in the DGMAH study was 2.62 months.

Cigarette smoking and alcohol use

Smoking remains a public health issue in South Africa and globally. The use of tobacco with the roll-your-own-cigarette habit has been increasing especially in rural areas of South Africa.[32] This increase explains the higher risks of smoking-associated malignancies.[32] A Canadian study concluded that smoking during treatment of Head and Neck Cancer is associated with a poor prognosis.[33] The DGMAH study could not prove whether patients were smoking during treatment as the research is retrospective. The records revealed that 25 patients (67.5%) were cigarette smokers only, 23 patients (54%) were alcohol users only and 23 patients (54%) were using both alcohol and smoking. The two-year survival for the smokers was 27.9%, for the alcohol consumers only was 24.3% and for the combined smoking and alcohol consumers was 24.3%. The outcome shows that there was no statistical difference in the 2-year DSS between smoking alone, alcohol use alone or combined consumption.

HIV status

HIV statistics show that South Africa has one of the highest prevalence of HIV infection with an estimated 8,409,000 people HIV infected in 2016.[34] McLemore et al found a link between HIV infection and LSCC.[35] The authors reported that, in the presence of HIV infection, the adjusted relative risk to develop LSCC after the diagnosis of AIDS is 10.6 for females and 2.0 for males compared to the general population. HIV infection in LSCC patients is significantly associated with younger age at diagnosis.[35] HIV-infected patients have an increased risk of developing non-AIDS cancers, particularly those associated with infections and smoking.[36]

The DGMAH study found that 16.2% of the patients were HIV-positive, which is similar to the prevalence in the healthy population. From the LSCC patients that were HIV-positive, 8.1% demised and 8.1% were still alive within two years. Of the HIV-Negative patients, 29.7% demised and 18.1% survived after 2 years. In the DGMAH study, more HIV-negative patients were demised from cancer-related complications.

Our conclusion, therefore, shows that HIV status played no role in the survival of LSCC patients at DGMAH. The DGMAH study differs from a US study done by Coghill et al that concluded that HIV-infected patients with cancer have higher cancer-specific mortality than HIV-Negative cases and a Danish study that suggested that

HIV increases the risk of HNSCC, especially in HPV-related SCC.[37,38]

Limitations

The study faced some limitations in its fulfilment. The limitations included: The DGMAH study was a retrospective study and shortcomings are often encountered in this type of study.

CONCLUSION

This dissertation investigated the two-year DSS of LSCC at DGMAH, which renders service for a population that is mostly of low-income households. From the 72 patients considered in the DGMAH research, the study managed to trace the two-year survival for 37 patients only.

Twenty-one of 37 patients were confirmed dead within two years, whereas 16 of them survived.

The study observed the two-year DSS be 43.2%. The two-year DSS of LSCC varies between 64% and 91.7%, according to the literature perused.[21,23,24] Most of the perused studies on DSS are from developed countries due to the dearth of literature on the two-year survival of LSCC in developing countries.

The low two-year DSS outcome of LSCC patients at DGMAH is multifactorial. Factors favourable to the two-year survival included younger age at presentation (mean=56.2), early tumour (I and II) and glottic epicentre. This low two-year DSS is due to the majority of LSCC patients presenting at an advanced stage of disease (III) or very advanced stage of disease (IV) and most probably requiring palliative treatment or best supportive care. The results can be a consequence of the low level of education in the target population, weak screening system at Primary Health care centres, lifestyle habits such as roll-your-own-cigarette smoking and alcohol consumption, cultural and religious beliefs and late presentation.

Recommendations

Finding the link of causality between the factors and survival rate will require a prospective study and a bigger sample size over a more extended period. A prospective study would curtail the limitations of the current study.

Poor record capturing and keeping remain an issue at DGMAH and most institutions in developing countries. Conversion to paperless data capturing can be a valuable adjunct to improve clinical trials, studies and research within the institution.

The department of otorhinolaryngology at DGMAH should prepare a standard protocol for early diagnosis and prompt referral for better management of all head and neck cancers.

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