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Clinical Profile and Treatment Outcome of Laryngeal Cancer Patients. A Single-Institution Retrospective Analysis

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Abstract

Background

In Tanzania, cancer of the larynx is second in occurrence among head and neck cancers. Laryngeal cancer is increasing in developing countries and most patients present at advanced stages. Management of laryngeal cancer in developing countries is complicated by the late presentation and lack of health care resources. There is little documented information about the profile of laryngeal cancer patients in Tanzania. This study aimed to determine the clinical-pathological profile and treatment outcome of laryngeal cancer patients treated at the Ocean Road Cancer Institute (ORCI) from 2010 to 2014.

Methods

This was a retrospective study done at the ORCI by reviewing medical charts of 82 laryngeal cancer patients.

Results

About half of the patients had a history of smoking and alcohol consumption. The male to female ratio was 10:1 and the mean age at diagnosis was 61 years. Hoarseness of voice was the most common symptom (90.2%) and the mean duration of symptoms was 14.4 months. The majority (73.1%) of the patients had advanced stages. Glottis was the most common site (62.2%). The tracheostomy rate was 75%. The most common (98.8%) histology was squamous cell carcinoma. The most common (60%) primary therapy was radiotherapy alone. Around 84% of the patients were treated with palliative intent with a radiotherapy dose in 2 Gy fractions (EQD2) of less than 60 Gy and the majority (60%) of patients (60%) received only radiotherapy without concurrent cisplatin. The mean EQD2 was 46 Gy for the whole cohort. The mean duration of treatment waiting time was 55.7 ± 72 days for the whole cohort. The mean duration of radiotherapy was 32.8 ± 19.8 days and the mean duration of treatment interruption was 7.4 ± 15 days. Only 13% of the patients were treated with radical concurrent chemo-radiation. None of the patients were treated by either upfront or salvage surgery. The 5 years the overall survival rate (OS) was 26%.

Conclusion

Laryngeal cancer is more common among elderly males than females in Tanzania**.** The majority of patients had advanced stages and were treated with low radiotherapy doses without concurrent chemotherapy. The 5 years OS rate was 26%.

Keywords: *Clinical profile, Laryngeal cancer, Treatment outcome.*

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Background

Worldwide laryngeal cancer accounts for nearly 1% of all malignancies and approximately 22% of head and neck tumors (1). Several recent studies have suggested that the incidence of laryngeal cancer and other smoking-related cancers is declining in North America and Europe(2) reflecting achievement in the antismoking effort (3). However, in developing countries, the incidence of laryngeal cancer is on the increase. The reason for this is unknown, but may not be unconnected to frequent exposure to inhalational irritants at workplaces, homes as well as malnutrition (4). Other people have attributed the increased incidence of laryngeal cancer in developing countries to due to increased use of alcohol and smoking as the risk factors (5).There are a variety of malignant tumors arising in the laryngeal epithelial and non-epithelial tissues. Squamous cell carcinoma is the most common and accounts for more than 90% of all malignancies (5). There is a geographical difference in the occurrence of laryngeal cancer among the head and neck cancers in East Africa. Laryngeal cancer is the most common head and neck cancer in Nairobi (6) and In Mwanza, Tanzania it is third in occurrence after oral cavity and pharyngeal cancers (7). At Muhimbili National Hospital in Dar es salaam, laryngeal cancer is second in occurrence after sinonasal cancer among the head and neck cancers (8). According to a report from the World Health Organization, it is the second most common malignancy of the head and neck region (9).

Malignant laryngeal tumors could involve any or all of the three laryngeal subsites, namely, the Supraglottis, Glottis, and Subglottis. The tumor in the glottis is associated with hoarseness and as a result, patients tend to present early to clinicians. In developing countries, most patients with laryngeal cancer are still present in the advanced disease stage. Other symptoms of laryngeal tumors include difficulty with breathing, noisy breathing, cough, referred otalgia, hemoptysis, neck swelling, and dysphagia (4).

Early laryngeal cancers (Stages I and II) are usually treated with single modality therapy, whereas advanced cancers (Stages III and IV) are treated with combined modality therapy. Treatment modalities for laryngeal carcinoma include surgery, chemotherapy, and radiotherapy. The successful management of malignant laryngeal tumors requires accurate diagnosis, tumor stage, and selection of appropriate treatment modalities (4). In developing countries, the major challenges of management are late disease presentation and acceptance of treatment by patients and their families. This study, therefore, presented the epidemiology, clinical presentation, pathologic profile treatment modalities, and treatment outcome of laryngeal tumors in a tertiary health institution in Tanzania from 2010 to 2014.

Methods

This was a 5-year retrospective descriptive study conducted at the Ocean Road Cancer Institute (ORCI). The study center is a tertiary health institution that manages patients referred from primary, secondary, and other tertiary health institutions in Tanzania and East African countries because of its radiotherapy facilities for head and neck oncologic therapy. Approximately 5000 new cancer patients are seen at ORCI annually out of which approximately 4% have laryngeal cancer. Medical charts of patients with laryngeal carcinoma who presented to ORCI from January 2010 to December 2014 were reviewed.

Patients who were above 18 years of age and with histological confirmed laryngeal carcinoma were included in the study. Patients whose histopathology was not carcinoma and those without follow-up records were excluded from the study.

Neck scars and the tracheostomy (if present) were wired. Patients were immobilized in a mask in a supine position and neck in extension. A conventional simulation was used to delineate the part to be treated. Fields were delineated according to the extent of the disease. Cobalt-60 teletherapy unit used for treatment. The curative radiation dose was 62Gy/31 fractions to 66Gy/33 fractions concurrent with chemotherapy. The chemotherapy that was used was cisplatin given weekly during radiotherapy and the dose was 40 mg/m^2.

Data were extracted from medical charts by using a structured questionnaire. Patients were staged according to the American Joint Committee on Cancer (AJCC) cancer staging manual, seventh edition. We collected information on age, sex, smoking status, alcohol intake status, level of education, occupation, stage, location of the tumor, histology, duration of treatment waiting time, treatment intention, type of treatment, and total radiotherapy dose. Treatment intention was either curative intention when the total radiotherapy dose was more than 60 Gy or palliative intention when the total radiotherapy dose was less than 60 Gy. EQD2 was calculated using an alpha-beta ratio of 10 to compare different radiotherapy fractionations. The five years overall survival (OS) was estimated from the date of completion of treatment. Patients who were lost to follow-up or alive at the end of the follow-up period were censored.

SPSS version 21 (SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous variables were summarized and presented as frequencies and means and categorical variables were summarized as proportions .X^2 test and Fisher's exact test were used to compare proportions and an independent sample t-test was used to compare means. A P-value of less than 0.05 was considered statistically significant. The survival curve was drawn by using Kaplan Meir. Ethical approval with reference number MU/PGS/SAEC/Vol.XI/29 for

this study was obtained from the Ethical Clearance Board (IRB) of the Muhimbili University of Health and Allied Sciences (MUHAS).

Results

One hundred and thirty-nine patients with cancer of the larynx treated at ORCI between January 2010 and December 2014 were reviewed and 82 patients were found to be eligible for inclusion in the study.

The mean age at diagnosis was 61 years with a range of 41 to 84 years and a standard deviation of 10.8 years. The male to female ratio was 10:1. Hoarseness of voice was the most common (90.2%) presenting symptom. The current smoking rate was 57.3% and the current alcohol consumption rate was 53.7%. One-third of the patients were current smokers and current alcohol consumers. About half of the patients were peasants with primary school education (Table 1).

Table 1: Social-demographic characteristics (n=82)

Variable		Frequency	(%)
Age	31-60	45	54.9
	>61	37	45.1
Sex	Male	75	91.5
	Female	7	8.5
Current smokers	Yes	47	57.3
	No	35	42.7
Alcohol	Yes	44	53.7
	No	38	46.3
Level of education	Primary	38	46.3
	Secondary	19	23.2
	College	25	30.5
Occupation	Peasants	43	52.4
	Civil servants	16	19.5
	Petty business	11	13.4
	Retired	12	14.6

The most common (90%) presenting symptom was hoarseness of voice. The mean duration of symptoms was 14.4 ± 11.3 months. All patients had Squamous cell carcinoma except one patient who had anaplastic carcinoma. The majority (75%) of the patients (75%) had advanced T stages (T3 and T4) and only 33% had positive neck nodes. Glottis was the

commonest (62%) tumor site. Most (73.1) of the patients (73.1%) had advanced TNM stages (stage 3 and stage 4). (Table 2).

Table 2: Clinical-pathological characteristics (n=82)

Variable		Frequency	(%)
Presenting symptoms	Voice change	74	90.2
	Dyspnea	43	52.4
	Cough	16	19.5
	Neck mass	14	17.1
	Dysphagia	8	9.8
Duration of symptoms (months)	<12	55	67.1
	>12	27	32.9
Histology	SCC	81	98.8
	Anaplastic carcinoma	1	1.2
Neck Nodes	Positive	27	33.0
	Negative	55	67.0
M stage	M0	80	97.6
	M1	2	2.4
TNM Stage	1	16	19.5
	2	6	7.3
	3	28	34.1
	4	32	39.0
Location of tumor	Supraglottis	30	36.6
	Glottis	51	62.2
	Subglottis	1	1.2

About 62 patients (75%) had a tracheostomy. Tracheostomy was more common (82%) among patients with advanced TNM stages (Stages 3 and 4) (than those with early stages and this difference was statistically significant by the Chi-Square test (P=0.014). Around 84% of the patients were treated with palliative intent with EQD2 of less than 60 Gy and the majority of patients (60%) received only radiotherapy without concurrent cisplatin. The mean EQD2 was 46 ± 12.6 Gy. Around two-thirds of the patients had radiotherapy waiting times of less than 30 days. The mean duration of treatment waiting time was 55.7 ± 72 days for the whole cohort. The mean duration of radiotherapy was 32.8 ± 19.8 days and the mean duration of treatment interruption was 7.4 ± 15 days. The mean hemoglobin level was 11.2 g/dL (Table 3).

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Table 3: Treatment modalities among patients with laryngeal cancer (n=82)

Variable		Frequency	%
Tracheostomy	Yes	62	75.6
	No	20	24.4
Initial treatment	RT	49	59.8
	CRT	33	40.2
Treatment intention	Curative	13	15.9
	Palliative	69	84.1
Radiotherapy waiting time (days)	<30	49	59.8
	31-60	15	18.3
	>61	18	22.0
EQD2 (Gy)	<60	69	84.5
	>60	13	15.9
Treatment interruption (days)	<3	42	51.2
	>3	40	48.8
Radiotherapy duration	<30	42	51.2
	>30	20	48.8
Hemoglobin level (g/dL)	<9	7	8.6
	>9	74	91.4

The five years overall survival rate (OS) was 29% and the median survival time was 23 months (Figure 1).

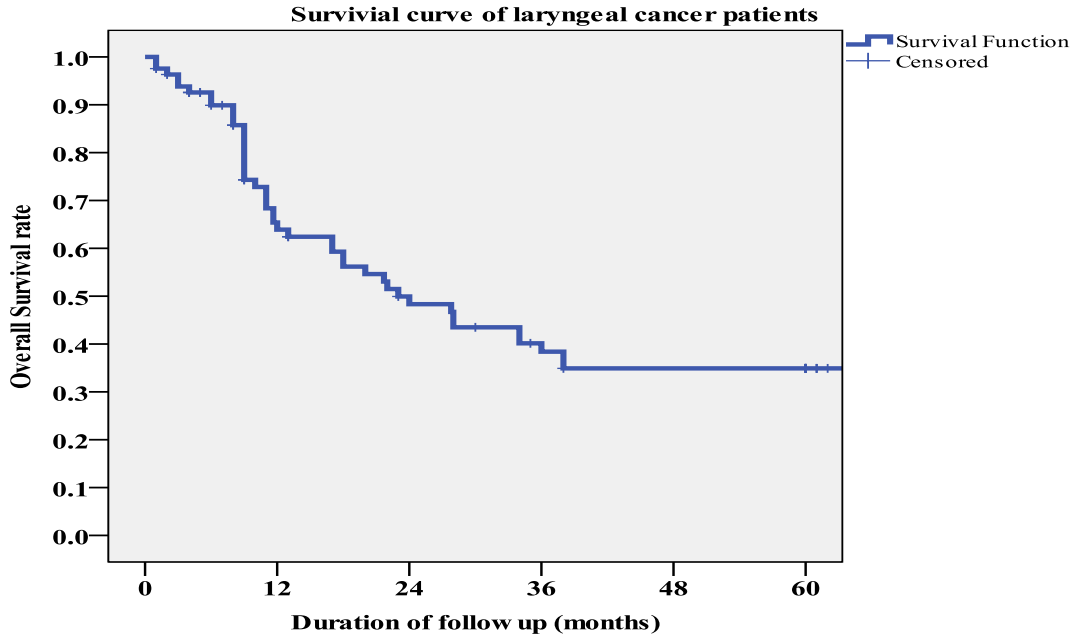

Figure 1. Survival curve of laryngeal cancer patients

No. at risk	82	44	31	23	19	19

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Discussion

In this study, the mean and median ages at diagnosis were 61 and 60 years with a range of 41 to 84 years. This finding is in keeping with other studies which have shown that laryngeal cancer is a disease of elderly people (10). The mean age at diagnosis of laryngeal cancer in Lebanon is 64 (10).

The male to female ratio in this study was 10:1. Most previous studies have shown that there is a preponderance of laryngeal cancer among males as compared to females (11). This is due to different levels of exposure to the main risk factors of laryngeal cancer, such as tobacco smoking and alcohol consumption (11).

Tobacco and alcohol consumption are important risk factors for laryngeal carcinoma (5)(9). About half of the patients in the current study had a history of current tobacco and alcohol consumption. The majority (52.4 %) of the patients were peasants and their main source of fuel for cooking is firewood and charcoal. The prolonged exposure to smoke emanating from either the firewood/charcoal or power plants (generators) might have contributed to the development of malignant laryngeal cancer. Smoke contains carcinogenic substances such as formaldehyde, benzene, and benzo(a)pyrene which, when inhaled, might irritate laryngeal mucosa and induce neoplastic changes (12)

In the current study, the most common (90.2%) initial symptom was hoarseness of voice. This finding is in keeping with the study done by Pukander et al.(13) which showed that hoarseness of voice was present in 87% of all patients and almost 100% of patients with glottic cancer. In this study, dyspnea (27%) had a higher frequency than in the study done by Pukander et al.(10) In Finland, where dyspnea was present in only 12% of all patients. This may be explained by the fact that dyspnea is a relatively late symptom in laryngeal cancer and about two-thirds of patients in the current study had advanced stages compared to only one-third of patients who had advanced stages in the study by Pukander et al.(13).

Most clinicians are not well informed about laryngeal cancer because of the uncommon nature of the disease. Hence, patients presenting with noisy breathing, cough, and hoarseness are likely to be initially treated for common medical conditions such as laryngitis, chest infection, and asthma. Most of the time, otorhinolaryngologists are only invited as the last consideration for laryngoscopy when there is no improvement in the clinical conditions of the patients. At this stage, the disease would have advanced, and tracheostomy becomes inevitable to save lives (4).

The median duration of treatment waiting time was 55.7 days for the whole cohort. There was no statistical difference in treatment waiting time between patients treated with curative and palliative intentions. This duration of treatment waiting is much longer than the recommended duration of 20-30 days (14). A study by Fortin et al. suggested that a delay of more than 40 days to start radiotherapy was significantly associated with an increased risk of local and neck failure and poorer survival relative to patients treated in less than 30 days or between 31 and 40 days (14).

In the current study, the majority of the study participants (75%) had advanced T stages (T3 and T4). Similar findings were in seen Nigeria whereby 92.8% were diagnosed in stages three and four (4) The reasons for this late presentation in developing countries included self-medication, wrong advice from relations/friends to consult a traditional herbalist or quacks for treatment and traditional & religious beliefs contributed to delay in presentation to hospitals (15). The high cost of medical treatment, unwelcoming attitudes of some hospital staff, and lack of confidence in orthodox medicine, poverty, and illiteracy, still prevail in our society. About 52 % of patients in the current study were peasants from rural communities where there is no oncologic clinic.

Only one-third of the study participants had enlarged neck nodes and 2 patients had distant metastasis. The observation that most of the patients had no palpable neck nodes and very few patients had distant metastasis could be due to inaccurate clinical staging as all of the study respondents had neither CT scan nor MRI to exclude nodal or distant metastasis.

The current glottis was the most common tumor site. About two-thirds of patients with supraglottic cancer had neck nodal metastasis and about one-third, of patients with glottic cancer had neck nodal metastasis. Almost all of the patients with supraglottic cancers were in T3 and T4 stages while only two-thirds of glottic cancers were in T3 and T4 stages. Other studies have also shown that glottis is the most common site and supraglottic cancer is usually in the advanced stage at diagnosis (16). The supraglottic region has a rich capillary lymphatic plexus. There is essentially no capillary lymphatic of the glottis region. The subglottic area has relatively few capillaries lymphatic. This explains why supraglottic laryngeal cancer is usually in the advanced stage at diagnosis compared to glottic laryngeal cancer(17).

The present study showed that two-thirds of patients needed tracheostomy before initial treatment. Out of these patients who needed tracheostomy, the majority had advanced laryngeal cancer. The late presentation also necessitated emergency tracheostomy in about 92% of patients in a study done in Nigeria. The tracheostomy rate demonstrated in the

current study is so high compared to that in the US (18) which was about 34% among patients with laryngeal cancer. This finding could be because most of the cases diagnosed in developing countries are usually in advanced stages compared to those in the developed world.

The majority of the patients (60%) were treated with definitive radiotherapy alone using palliative doses of less than 4 Gy. The mean radiotherapy dose in 2 Gy fractions for the whole cohort was only 46.9 Gy. However, this radiotherapy dose was so low and could be attributed to the frequent breaking down of the conventional simulator. Moreover, very few patients were treated by radical systemic concurrent chemo-radiation (6%). Studies have shown that an optimum radiotherapy dose of 60-70 Gy is necessary for better curative treatment outcomes (19). In a retrospective study done in Egypt to assess the outcome of patients with advanced laryngeal cancer who were treated with surgery followed by adjuvant concurrent chemoradiation, the mean total dose delivered to the primary tumor and involved lymph nodes was 66 Gy (range 60-66Gy) (20).

Among the patients treated with curative intention, the mean duration of overall treatment time was 45 days, which is within the recommended 49 days, but the mean duration of treatment interruption was 7 days, which is much longer than the recommended treatment interruption of fewer than 3 days(21). Fast tumor cell repopulation has been suggested as the main reason why prolonging the overall treatment time (OTT) by interrupting treatment negatively affects local control (LC) and overall survival (OS) in many human tumors(21)

The five years overall survival rate (OS) in the index study was 29% and the median survival time was 23 months. This finding contradicts the by Fasunla et al. In Nigeria whereby the 5 years OS rate was 52.2%. Surprisingly, the majority of patients (92%) in the study by Fasunla et al. had stage 3 and 4 diseases compared to the 73.1 % in the current study. The low 5 years survival rate in our study could be attributed to the non-surgical management of laryngeal cancer in Tanzania. In our study, none of the patients was treated by either upfront laryngectomy or salvage laryngectomy whereas in the study by Fasunla et al about half of the patients were treated by total laryngectomy followed by adjuvant chemoradiotherapy (4). For patients with advanced laryngeal cancer, the traditional treatments have included radical surgery—total or near-total laryngectomy—and intensive radiation and/or chemotherapy combined with radiation. Because of the morbidity associated with these cancers and their multimodality treatment, the emphasis of clinical research over the past 25 years has focused on efforts to preserve laryngeal function by the use of combinations of chemotherapy and radiation in the majority of patients with advanced disease as an

alternative to total laryngectomy. Unfortunately, these efforts have not met with improvements in overall survival rates, even though the preservation of laryngeal function can be achieved in 50% of patients. No larynx-preservation approach offers a survival advantage compared with total laryngectomy and appropriate adjuvant treatment (22). Based on SEER data for the period of 2006 to 2012, the estimated overall 5-year survival rate for patients with larynx cancer is 60.7% in the USA and has not changed appreciably during the past several decades (23). This has been achieved by careful selection of patients who may benefit from laryngeal perseveration therapy and the availability of salvage laryngectomy.

Limitations

This study if of retrospective nature with a lot of missing information and most of the patients were lost to follow up. Quantification of alcohol and cigarette consumption was not possible.

Conclusion

The mean age at presentation was 61 years and the male to female ratio was 10:1. The most common symptom was hoarseness of voice and the mean duration of symptoms was 14.4 months. The majority of the patients had advanced TNM stages (73.1%). Glottis was the most common site. The tracheostomy rate was 75%. The mean duration of treatment waiting time was 55 days. Most patients were treated with definitive radiotherapy alone without concurrent chemotherapy (60%). The majority of the patients (60%) were treated with palliative radiotherapy doses and the mean radiotherapy dose for the whole cohort was 46 Gy in conventional fractions. None of the patients was treated by laryngectomy. The 5 years the overall survival rate was 26%. This is the only study, to describe the clinical-pathological profile of laryngeal cancer patients in Tanzania.

Recommendation

The successful management of malignant laryngeal tumors depends on accurate diagnosis, tumor stage, and selection of appropriate treatment modality with close postoperative follow-up. Thus, targeted and well-coordinated health education on awareness of laryngeal cancers and their prevention program towards avoidance of alcohol and smoking at the community level should be pursued through appropriate organizations and relevant agencies.

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Abbreviations

ORCI	Ocean Road Cancer Institute
EBRT	External beam radiotherapy
EQD2	Mean total biologically equivalent dose in 2 Gy fractions
TNM	Classification of malignant tumors

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Author contributions

ELL contributed to conception and design of the study, acquisition of ethical clearance, data collection and analysis, and writing the final report. NJD, ASM and SI participated in data analysis and preparing the manuscript for publication.

Competing Interests

The authors declare no competing interests.

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