

**A STATISTICAL ANALYSIS OF LARYNGEAL MALIGNANCIES AT OUR INSTITUTION**Bharathi Mohan Mathan<sup>1</sup>, Elango Kuppuswamy Mohanraj<sup>2</sup>, Kalidass Muthukrishnan<sup>3</sup>, Sumeer Venkatesan<sup>4</sup>, Inan Madheswaran<sup>5</sup><sup>1</sup>Associate Professor, Department of ENT, Government Vellore Medical College and Hospital, Tamil Nadu.<sup>2</sup>Senior Assistant Professor, Department of ENT, Government Vellore Medical College and Hospital, Tamil Nadu.<sup>3</sup>Senior Assistant Professor, Department of ENT, Government Vellore Medical College and Hospital, Tamil Nadu.<sup>4</sup>Speech Therapist, Department of ENT, Government Vellore Medical College and Hospital, Tamil Nadu.<sup>5</sup>Tutor, Department of ENT, Government Vellore Medical College and Hospital, Tamil Nadu.**ABSTRACT****BACKGROUND**

Malignancies of larynx are an increasing global burden with a distribution of approximately 2-5% of all malignancies with an incidence of 3.6/1,00,000 for men and 1.3/1,00,000 for women with a male-to-female ratio of 4:1. Smoking and alcohol are major established risk factors. More than 90-95% of all malignancies are squamous cell type. Three main subsite of laryngeal malignancies are glottis, supraglottis and subglottis. Improved surgical techniques and advanced chemoradiotherapy has increased the overall 5 year survival rate. The above study is statistical analysis of laryngeal malignancies at our institution for a period of one year and analysis of pattern of distribution, aetiology, sites and subsites and causes for recurrence.

**MATERIALS AND METHODS**

Based on the statistical data available in the institution for the period of one year from January 2016-December 2016, all laryngeal malignancies were analysed with respect to demographic pattern, age, gender, site, subsite, aetiology, staging, treatment received and probable cause for failure of treatment. Patients were followed up for 12 months period during the study.

**RESULTS**

Total number of cases studied are 27 (twenty seven). Male cases are 23 and female cases are 4, male-to-female ratio is 5.7:1, most common age is above 60 years, most common site is supraglottis, most common type is moderately-differentiated squamous cell carcinoma, most common cause for relapse or recurrence is advanced stage of disease and poor differentiation.

**CONCLUSION**

The commonest age occurrence at the end of the study is above 60 years and male-to-female ratio is 5.7:1, which is slightly above the international standards. Most common site is supraglottis and not glottis. The relapse and recurrences are higher compared to the international standards.

**KEYWORDS**

Laryngeal Cancer, Tobacco, Alcohol, Staging, Grading, Glottis, Epidemiology, Aetiological Factor.

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**BACKGROUND**

Incidence of laryngeal malignancies despite continual efforts by the government all over the globe to make public awareness, continue to persist with only minimal demographic and epidemiological variations for the past 40-50 years.

Incidence of laryngeal malignancies are relatively low compared with the malignancies of all other sites with only 2-5% of all malignancies worldwide.

Laryngeal carcinomas are more prevalent in heavy smokers, present earlier and are less likely with the exception of supraglottic malignancies to metastasise early to the adjacent lymph nodes. On the other hand, hypopharyngeal carcinomas present late have a high association with alcoholism and other disorders and commonly present with cervical metastatic disease. Most importantly, because of the early presentation and lack of rich lymphatic drainage of the larynx, tumours confined to the laryngeal framework have a substantially better prognosis. Their early detection in warning patients of the need for evaluation of persistent hoarseness and an easier in office endoscopic examination allows for the earlier detection and treatment. In addition, studies reported in this chapter will show that conservative treatment when not effective still permits reasonable salvage by more radical surgery.<sup>1</sup>

Tobacco is a major risk for the development of larynx cancer. Many studies show that risk increases with

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increasing tobacco use. People who smoked 40 or more cigarettes daily had an age-adjusted death rate of 15/1,00,000 compared with 0.6/1,00,000 person-years among nonsmokers. The death rate for pipe and cigar smoking was 5/1,00,000 persons-years. This accumulation of evidence indicates that tobacco acts as a promoter and an initiator in carcinogenesis.<sup>1</sup>

The incidence of laryngeal cancer is relatively low compared with that of carcinomas of all sites comprising about 2 to 5% of all cancers worldwide. The relative incidence is similar to that for all sites in the oral cavity as a group and is similar to that of thyroid cancer. Over the years, there has been a male preponderance noted. As more women have taken up smoking in recent decades, a shift in this ratio can be expected. A study at Ben Taub General Hospital revealed that comparing the two 15-year periods 1959 to 1973 and 1947 to 1988, the ratio of male-to-female incidence of laryngeal cancer dropped from 5.6 to 1 to 4.5 to 1. Another study revealed an increase in the incidence of supraglottic lesions in women.<sup>2</sup>

There is an increased reported incidence of laryngeal cancer occurs in the fifth, sixth and seventh decades (more than 80%). The largest number of cases occurs in the sixth decade (approximately 40% of all cases), with the average age for the occurrence of laryngeal carcinoma appearing to be approximately 59 years. Laryngeal cancer in children and adolescents is rare and tends to be papillary-lymphocytic and non-keratinising. There is an increased reported incidence of laryngeal malignancies in industrialised areas with a relative increase from 8-12% more than the non-industrialised areas.<sup>2</sup>

Alcoholics who smoke are thought to carry a 25 to 50 fold increase in risk of laryngeal cancer over nonsmokers. Other aetiologic factors include gastroesophageal reflux and exposure to wood dust, asbestos, volatile chemicals, nitrogen mustard and ionising radiation. Persons with various types of immunodeficiency states are also thought to be at higher risk for developing laryngeal cancer. An underlying genetic susceptibility to this type of cancer may also exist and has been theorised as a potential cofactor in oncogenesis.<sup>2</sup>

A growing body of evidence from molecular genetic studies supports this hypothesis. Such a theory might explain why some individuals smoke heavily and never develop cancer, whereas others may smoke lightly or not at all and develop laryngeal cancer. The role of "passive smoking" in the development of laryngeal cancer remains unknown. Human Papillomavirus (HPV) is also considered to be an important cofactor in the development of laryngeal cancers.<sup>2</sup>

Variations in the occurrence of laryngeal cancers are seen among countries and ethnic groups, but generally reflect the prevalence of tobacco use in those countries. There are also wide variations geographically in the distribution of laryngeal cancers among the various subsites. Clearly, genetic influences are important in determining the occurrence and site of involvement; however, this is a complex issue and other factors. Deficiencies in certain

nutrients particularly the B vitamins, vitamin A, beta-carotene and retinoids are considered to be important in the development of squamous cell cancer in general.<sup>2</sup>

Heavy alcohol use and lower socioeconomic deficiencies or to a higher incidence of gastroesophageal reflux disease and could account for some of the differences noted between different countries, cultures and ethnic groups.

Over 95% of all malignant laryngeal tumours are squamous cell carcinomas. These tumours arise from the surface epithelium, which is a stratified squamous lining, except at the free edge of the vocal fold where the mucosa consists of a pseudostratified squamous layer. Areas of hyperkeratosis, dysplasia and CIS are often found adjacent to the primary invasive lesion. With proper orientation, it is usually possible to define a transition from normal epithelium, to dysplastic epithelium, to invasive carcinoma. Islands, tongues and clusters or cords of invasive atypical cells within the underlying stroma characterise the tumour. The cells show squamous differentiation including keratinisation of individual cells, keratin pearl formation or intercellular bridging.<sup>2</sup>

Over 70 large case-control studies covering most of the world populations have examined the aetiology of squamous cell laryngeal cancer. Tobacco (relative risk 6-60) and alcohol (RR 2-6) are so dominant in these studies that the quantification of risk due to other possible factors is difficult. Good case-control studies have repeatedly shown that these factors have a multiplicative effect. Alcohol is thought to promote carcinogenesis through acetaldehyde exposure, malnutrition and desiccation of mucosa.<sup>3</sup>

Tobacco acts via polycyclic aromatic hydrocarbons like benzopyrene whose products wind directly to DNA and RNA. Molecular changes include upregulation of myeloid cells. However, family history (RR 4) and 'high-risk' subtypes of HPV infection stand out as other possible agents. A host of dietary (e.g., regional hot drinks) and occupational (e.g., asbestos exposure) risk factors have been examined in this way with even weaker associations detected. Patients who have no exposure to alcohol and tobacco may still develop laryngeal cancers, but this is usually a decade later and there are a higher proportion of glottic tumours.<sup>3</sup>

Generally, glottic cancer is by far the most common site for primary malignant tumours in the larynx. It is vitally important to specifically designate the site of origin of the primary lesion with its local extension to adjacent sites within the same region of the larynx or from one region to the other regions. Bulky lesions may extend beyond the larynx into the adjacent base of the tongue, piriform sinus, pharyngeal wall or postcricoid region.<sup>4</sup>

Nearly, 75% of patients with glottic carcinoma have localised disease at the time of diagnosis in contrast to nearly 70% of patients with supraglottic carcinoma who have advanced disease at presentation.<sup>4</sup>

Alcohol has been implicated as well as an important risk factor in the pathogenesis of laryngeal cancer. Indeed, the relation between alcohol consumption and the development of laryngeal carcinoma is proportional to the dose and duration of exposure.<sup>15</sup> Chronic inflammation of the lining of

the larynx from ethanol causes a series of mutations at gene level that disturb cell proliferation and promote carcinogenesis. The precise mechanism of cancer development is not fully defined. Ethyl alcohol is not considered a carcinogen, but acts as a co-factor, which affects the local or systemic carcinogenesis through different mechanisms and at different stages, especially during initiation or promotion of carcinogenesis.<sup>5</sup>

As more women are smoking in recent decades, a change in the male-to-female ratio has occurred. The ratio of male-to-female incidence of laryngeal malignancies dropped from 5.6:1 to 4:1. Another study has revealed the increase in supraglottic malignancies in women population.

There is an increased reported incidence of such malignancies in areas with close proximity to chemical factories (such as arsenic, leather) and radioactive materials such as plutonium.

Laryngeal malignancies are relatively less common in children and adolescents, if at all it is present, it is found to be papillary-lymphocytic and non-keratinising malignancies rather than squamous cell malignancies.

Squamous cell carcinomas comprise over 95% of all the primary malignancies of larynx.

### Aim of the Study

Aim of the study is statistical analysis of laryngeal malignancies at our institution with regards to occurrence, percentage of occurrence, subsites, percentage of distribution among subsites, most common subsite, male and female distribution and analysis of aetiology and survival rate.

### Investigations

Computed Tomography (CT), ultrasound of abdomen and neck, chest x-ray, direct laryngoscopy- biopsy and positron emission tomography (for recurrences).

### MATERIALS AND METHODS

Based on the statistical data available in the institution for the period of one year from January 2016-December 2016, all laryngeal malignancies are analysed with respect to demographic pattern, age, gender, site, subsite, aetiology, staging, treatment received and probable cause for failure of treatment. Patients are followed up for 12 months period during the study.

1. Patients are categorised above the age group of 30 based on statistical data available in the institution.
2. Patients are categorised into male and female and with age wise distribution in the order of every 10 years distribution.
3. Patients are categorised into 3 different subsites of larynx with percentage wise distribution of each subsite.
4. Patients are categorised into different stage wise distribution and percentage wise distribution of each stages.
5. Patients are categorised on the treatment that they obtained into surgical group with the indication of type

of surgery and nonsurgical group with the indication of type of chemoradiation available.

6. Patients are followed up for 12 months duration.
7. Other aetiological factors for nonsmokers and woman population if available are analysed.

### Inclusion Criteria

1. All laryngeal malignancy with the age limit of 30 and above were taken into consideration.
2. All laryngeal malignancies for both the sexes were taken into consideration.
3. All laryngeal malignancies at any stage of disease were taken into consideration (stage I, II, III, IV).

### Exclusion Criteria

1. Children and adults below the age limit 30 were not included in study group.
2. Patients with benign tumours of larynx were not included in the study group.
3. Patients with malignant tumours of non-laryngeal structures spreading to larynx (not a true laryngeal tumour) are not included in the study group.

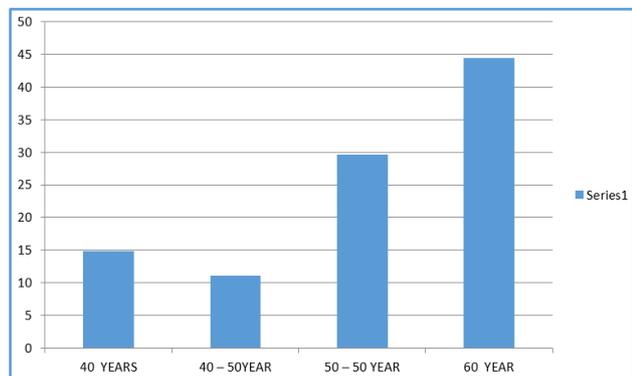
### RESULTS

- Total number of cases studied are 27 (twenty seven).
- Among the total number of cases of 27, male cases are 23 with a percentage of 85.19% and female cases are 4 with a percentage of 14.81% with a male and female ratio of 5.7:1.
- All the cases are above the age of 30 years with % wise distribution for every 10 years is;
  - <40 yrs. - 14.82%.
  - 40-50 yrs. - 11.12%.
  - 50-60 yrs. - 29.62%.
  - >60 yrs. - 44.44%.
 The most common age is above 60 years.
- The most common site is supraglottis with percentage-74.01%.
  - Glottis - 22.22%.
  - Subglottis - 3.77%.
- Most of them are smokers and alcoholics - 62.96%.
- Only isolated smokers are - 7.40% and nonsmokers are - 29.62%.
- Most common histopathological type is moderately differentiated squamous cell carcinoma - 59.25% followed by well-differentiated type - 29.02% and poorly-differentiated type - 11.11%.
- Most common presenting symptoms are hoarseness of voice, foreign body sensations and dysphagia. Two cases who presented with stridor underwent emergency tracheostomy to secure the airway.
- Most common stage at the type presentation is stage III- 62%, following stage II- 20% and stage IV- 18%.
- Most of the patients are treated with curative chemoradiotherapy and only two patients underwent total laryngectomy.

- On follow up, seven patients had residual growth or recurrence, which is 25.92%. Causes for failure of treatment are late diagnosis, advanced stage of disease, poor differentiation and decreased response to curative chemoradiotherapy.

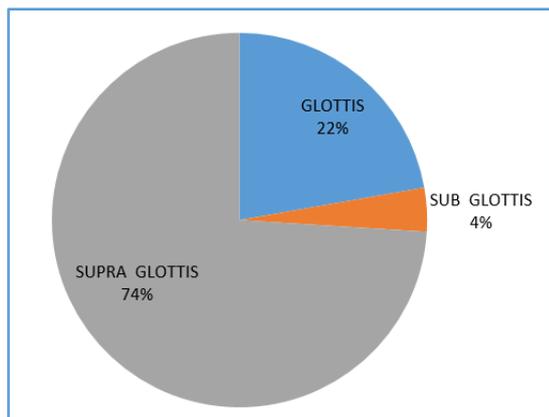
**Age Wise Distribution (Bar Chart)**

40 years	14.82%
40-50 years	11.12%
50-50 years	29.62%
60 years	44.44%



**Site Wise Distribution (Pie Chart)**

Glottis	22.22%
Subglottis	3.77%
Supraglottis	74.01%



**DISCUSSION**

The effect of tobacco smoking is similar in relation to the risks involved for all the subsites compared, but the risks associated with alcohol varies with different sites, which is more for supraglottis than glottis and subglottis.

The relative risks of alcohol and tobacco consumption together has an additive or stimulant effect, increasing the oncogenesis with relation to the constituents such as nitrosamine, polycyclic hydrocarbons, acelyene, benzene and ethylene oxide increasing the risk variability (RR value) to more that 0.5.

Epigenetics emerged as an important field in understanding the biology of the human malignancies. Epigenetic alterations refer to the dysregulation of gene,

which do not involve the alterations of the DNA sequence. Major epigenetic changes including methylation imbalance, histone modification and small RNA dysregulation could play a role in the development of human malignancies.<sup>6</sup>

There is wide regional variation in the incidence of laryngeal cancer in India. Survival rates of laryngeal carcinoma are much lower as compared to other Asian countries. Studies conducted in India to identify important risk factors of laryngeal cancer are very limited, especially on diet and indoor air pollution. Hence, more research is required for identifying the aetiological factors and development of scientifically sound laryngeal cancer prevention programs.<sup>7</sup>

There are more than 20 proved carcinogens in tobacco (cigarette/beedi) smoking and more than 2 proved carcinogens with alcohol consumption increasing the positive predictive value more than 50%.

The male-to-female ratio in our study is 5.7:1, while the male-to-female ratio according to international standards is 4:1 for laryngeal malignancies showing increased incidence of laryngeal malignancies in male population than the female population as compared with international standards, probably due to chronic smoking and alcoholism, delayed presentation, poor awareness among the study population analysed.

Laryngeal malignancies unlike other malignancies has a direct correlation with chronic smoking and alcoholism with an increased RR factor of more than 0.5.

The most common subsite in our case is supraglottis as compared to international analysis, which indicate glottic malignancies as the commonest site.

In supraglottic malignancies, there is involvement of aryepiglottic folds either right or left with an extension either to arytenoids or adjacent piriform sinus.

The second most common subsite involved is glottis involving one or both vocal cords with or without fixation of the involved vocal cord.

Only one case is found to be a pure subglottic growth, which is a circumferential growth with an extension to the glottis.

Two cases are found to be transglottic growth with the involvement of glottis, supraglottis and subglottis.

Hypopharyngeal malignancies extending to the larynx are not included in the study.

Of the presenting symptoms hoarseness of voice, dysphagia and foreign body sensation in the throat are the primary symptoms. Two such cases presented with stridor at the time of diagnosis and they underwent emergency tracheostomy to secure the airway with subsequent direct laryngoscopy, biopsy and further management.

The most common histopathological type is found to be squamous cell carcinoma in almost all cases. The most common differentiation was found to be moderately-differentiated squamous cell carcinoma, followed by well-differentiated squamous cell carcinoma and only few cases presented with poorly-differentiated squamous cell carcinoma.

Among the gender distribution, only 4 out of the total study group are females, but still this is found to be different from the international standards.

The most common age group is found to be above 60 yrs., which coincides with the international statistics. Increased age may have a direct implication in the production of oncogenesis especially for laryngeal malignancies.

Among the stages, the commonest stage at the time of presentation is found to be stage III and stage IV indicating the poor awareness among the study group in the involved region.

Majority of the patients underwent curative chemoradiotherapy, which is in coherence with the international standards of preserving the laryngeal functions with a curative intent.

Patterns of initial management across this same period indicated the increase in the use of chemoradiation with a decrease in the use of surgery despite an increase in the use of endoscopic resection.<sup>8</sup>

Most patients responded well to chemoradiotherapy and only few cases had either residual growth or recurrence on follow up. The probable cause maybe poor differentiation, advanced stage at the time of presentation with either local or distant metastasis and reduced response to curative chemoradiotherapy.<sup>9</sup>

Young patients and female patients even presented with poorly-differentiated squamous cell carcinoma who were nonsmokers and alcoholics indicating other factors influencing growth (oncogenesis), such as viral aetiology, i.e. human papilloma virus and Epstein-Barr virus, environmental factors and genetic factors.

One such patient had multiple papillomas earlier and was treated by surgery few years back indicating the role of viruses in predisposition of laryngeal malignancies.

Other than that, no other premalignant conditions turning into malignancy are documented.

Two such patient underwent total laryngectomy as a curative procedure who presented with stage III malignancy without any extension to adjacent structures and both are glottic malignancies. On followup, both the patients had no recurrence indicating the efficacy of surgery in providing improved 5 year survival rate in stage III or stage IVa glottic malignancies.

Such statistical analysis with regards to various aspects of laryngeal malignancies has got aetiological as well as regional significance.

Increased risk of recurrence was observed in patients with supraglottic cancer, younger patients, those with T2-T3 tumours and in patients treated in the earlier part of the study period. Significant factors for recurrence in glottic carcinomas were age, treatment in the earlier part of the study and T-status, whereas age was a significant factor in supraglottic cancer.<sup>10</sup>

## CONCLUSION

At the end of our study in our institution for a period of one year, laryngeal malignancies are more common in male population with ratio of 5.7:1, which is slightly above the international standards. Supraglottis is the most common subsite and not glottis, which varies from international distribution site. Most cases are above the age of 60, which is coherent with international statistics. Smoking and alcoholism are common aetiological factors. Moderately-differentiated histopathological type is the commonest. Most common stage at the time of presentation is stage III and above. Most patients responded well with curative chemoradiotherapy and causes for failure were advanced stage at time of presentation and poor differentiation. Recurrence rate is found to be more when compared with the international results indicating delayed presentation and poor awareness of the study population about the disease studied and public awareness to the ill effects caused by chronic smoking and alcoholism has to be signified more effectively.

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