

RESEARCH ARTICLE

Clinico-Epidemiologic Patterns of Laryngeal Cancer: 5-year Results from a Regional Cancer Centre in Northeastern India

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Abstract

Purpose: To determine the risk factors, clinical symptoms and patterns of spread in laryngeal cancer. **Materials and Methods:** A cross sectional study was carried out in the Regional Cancer Centre, Imphal, Manipur, India. One hundred and sixteen patients with laryngeal cancer were retrospectively reviewed for epidemiological data and descriptive statistics were reported for various variables. **Results:** Median age at presentation was 65 years and 32.8% were undernourished at presentation. The male to female ratio was 5.4:1. Heavy smoking and tobacco chewing was associated in 91.4% and 33.6% of patients respectively. Tracheostomy was required in 21.5% leading to diagnosis of laryngeal cancer. Almost all were squamous cell carcinoma with neuroendocrine and verrucous carcinoma accounting for less than 2%. Supraglottic, glottic and trans-glottic tumors were 56.9%, 36.3% and 6.9% respectively. Nodal metastases were seen in 81.8% of supraglottic cancers and 31.6% of glottic cancers with supraglottic involvement. Level II neck nodes were the commonest site followed by level III. Distant metastases (only liver) were apparent in 1.7% at presentation. Including these liver metastases, unresectable cases were limited to 6% of the patients. **Conclusions:** Tobacco use is implicated in almost all of the cases and the sex ratio has also decreased due to increased female smokers. The supraglottis remains the commonest site and incidence of nodal metastases is higher than in other countries. There is also a higher requirement for tracheostomy at presentation in this region.

Keywords: Laryngeal carcinoma - epidemiology - risk factors - tracheostomy - clinicopathology - Northeast India

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Introduction

Laryngeal cancer constitutes around 1.7% of all cancers in Manipur, a state in north eastern part of India (Singh et al., 2013). People of this state are different from the rest of India varying in ethnic, social, dietary and environmental factors. However established risk factors of laryngeal cancer like the use of tobacco and alcohol are common like the rest of India. There seems to be an increased use of tobacco either in the smoked or smokeless form among women. Diet containing salted or fermented meat/fish is a regular habit in most households. This inherent difference in the people of this region leads to varied epidemiologic presentation of malignancies. There is a need to document the epidemiology and trends in cancer occurrence pertaining to this region. Periodic evaluation and assessment of epidemiological characteristics needs to be done to plan for any community intervention at the earliest.

Also the clinical characteristics and patterns of spread vary within different sub-sites of larynx. Recently, more countries report a higher incidence of glottic tumors

(Makitie et al., 1999; Markou et al., 2013; Peller et al., 2016). In the United States, the ratio of glottic to supraglottic tumor ratio is 3:1 (Medenhall et al., 2013). Larynx had the most male to female ratio among other malignancies but there has been a rise in the incidence of female cancers in the recent past (De Rienzo et al., 1991; Gallus et al., 2003). On the contrary, the male to female ratio in India is still around 9:1 (Section of Cancer Surveillance, 2012) Trends in pattern of spread of the disease is noted to change with time and various geographical locations. The purpose of this study is to conduct a detailed evaluation of the risk factors, clinical symptoms and patterns of spread in laryngeal cancer at presentation in this part of Northeast India.

Materials and Methods

A cross sectional study of patients registered at the Outpatient Department, Regional Cancer Centre, Regional Institute of Medical Sciences, Imphal, Manipur, India was undertaken. Patient records were examined and all cases of laryngeal cancer between the period of January

2011 and December 2015 were analysed retrospectively. Two patients with previous treatment for laryngeal cancer outside our centre were excluded from analysis.

All patients had histopathologically proven laryngeal cancer and tissue biopsy from the primary was mandatory. Computed Tomography (CT) scans of the neck, direct laryngoscopic evaluation and physical examination findings were used in all cases to assess the primary tumor and the draining lymph nodes. Those with enlarged nodes on clinical examination or imaging were assessed with FNAC.

CT scans of the thorax and abdomen were done to rule out primary/secondaries in the lung and secondaries in the abdomen. Any other site was assessed for distant metastases only on clinical suspicion. FNAC was done to confirm metastatic sites. Staging was done according to the AJCC Cancer Staging Manual 2010. Trans-glottic tumors involving the supraglottis, glottis and subglottis were reported. They were not considered for statistical analysis of the individual sub sites because a proper identification of the tumor origin could not be made out. Surgical staging of the neck or primary was not done and conclusions made from this study are based only on clinical evaluation.

All records contained sufficient data and none were excluded on the basis of insufficient data. 116 eligible patients were identified. Records of the outpatient registry were maintained after signed consent of the patient and collective data could be published without identifier. Patients' identity and personal information were not collected. Collected data were kept anonymous and ethical issues were none.

Data including age, sex, personal habits like tobacco and alcohol abuse, medical history, physical examination findings and results of diagnostic procedures at presentation were used for analysis. Obtained data were checked for completeness and consistency. Data were entered in IBM® SPSS® Statistics software for Windows® version 21. Descriptive statistics like mean, median, range, frequency and percentages were calculated for individual variables. No analytical tests for statistical significance were used.

Results

The median age at presentation was 65 years (Range: 37 – 85 years) maximum belonging to the seventh decade. Performance status at presentation and age groups are summarised in the Table 1. Male sex was predominant with a male to female ratio of 5.4:1 (98 males and 18 females).

Table 1. Patient Distribution by Age and Performance Status (n=116)

Age (years)	Frequency (%)	KPS*	Frequency (%)
30-9	1 (0.86)	100	1 (0.86)
40-9	6 (5.17)	90	20 (17.2)
50-9	20 (17.2)	80	45 (38.8)
60-9	47 (40.5)	70	41 (35.3)
70-9	33 (28.4)	60	3 (2.58)
80-9	9 (7.75)	≤ 50	6 (5.17)
Total	116(100.0)	Total	116(100.0)

*Karnofsky performance score

32.8% (n = 38) were undernourished at presentation with a body mass index (BMI) < 18.5. Overweight (BMI=25.0-29.9) and class I obesity (BMI=30.0-34.9) were seen in 4.31% (n=5) and 3.44% (n=4) respectively and the rest of them (59.5%, n=69) had a normal BMI (BMI=18.5-24.9) (Table not shown).

Tobacco smoking was associated with 92.2% (n=107) and a majority of them (91.4%, n=106) consumed more than 15 pack years of cigarettes (89.8% of males and 100% of females). One male patient (0.86%) was a light smoker with a pack year of 0.37. Most of them used non-filter cigarettes, cigarettes with small filters and beedis and were not confined to one type of cigarette to smoke. Consumption of alcohol and use of oral tobacco were seen in 63.8% and 33.6% respectively. When history of cigarette smoking was present, additional use of alcohol consumption and oral tobacco were seen in 60.3% (n=70) and 30.2% (n=30) respectively. Presence of all three risk factors were seen in 22.4% (n=26). Among never smokers, 3.4% (n=4) consumed alcohol and 3.44% (n=4) consumed oral tobacco. Only 4.31% (n=5) did not have exposure to any form of tobacco. Two patients (1.72%) were not exposed to any of tobacco/alcohol and among them one had a neuroendocrine carcinoma and the other was a squamous cell carcinoma. 97.4% (n=113) of the patients consumed fermented and salted fish/meat on a regular basis. On an average, they consumed salted/fermented foods at a minimum of four times per week.

Clinical symptoms are summarised in the Figure 1. One patient (0.86%) never had any symptoms and his diagnosis was made incidentally during endoscopy for a stomach problem. Median duration of these symptoms were four months (Range: 0 – 36 months). In all, certain symptoms like pain, swelling and dysphagia were reported in 29.3%, 28.4% and 36.2% respectively (Table not

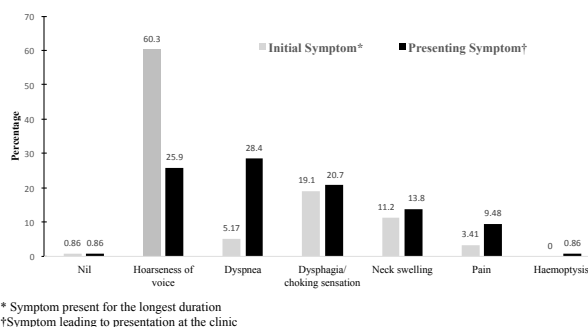


Figure 1. Clinical Symptoms (n=116)

Table 2. Clinical Stage Distribution (n=116)

Stage*	Supraglottic carcinoma	Glottic carcinoma	Trans-glottic carcinoma	Total (%)
I	0	13	0	13 (11.2)
II	6	11	2	19 (16.4)
III	22	11	3	36 (31.0)
IV A	32	5	2	39 (33.6)
IV B	5	1	1	7 (6.03)
IV C	1	1	0	2 (1.72)
Total	66	42	8	116 (100.0)

*American Joint Committee on Cancer Staging 7th edition, 2010

shown). Some of them had severe breathlessness with stridor and airway obstruction on presentation and a tracheostomy was needed in 21.5% to establish the airway.

The histological characteristics of the tumors are summarised in the Figure 2. Verrucous carcinoma was found in one patient causing complete airway obstruction at the supraglottis with a one month duration of clinical symptoms and he required tracheostomy at presentation. Histologically grade one or two squamous cell carcinoma was more common and in particular all glottic tumors were either grade one or two.

Stage wise presentation of the patients are summarised in the Table 2. Among the sites of larynx, supraglottis was the commonest (56.9%, n=66) followed by glottis (36.2%, n=42). Trans-glottic tumors were seen in 6.89% (n=8) and carcinoma of the subglottis was never seen. Presence of multiple lesions were seen in 2.58% (n=3) and they include two separate epiglottic lesions in the first, lesions of the glottis and supraglottis in the second and lesions involving two sites at epiglottis and the nasal cavity in the third who had neuroendocrine carcinoma. None of them had any previous malignancies in the past. Tumor volume

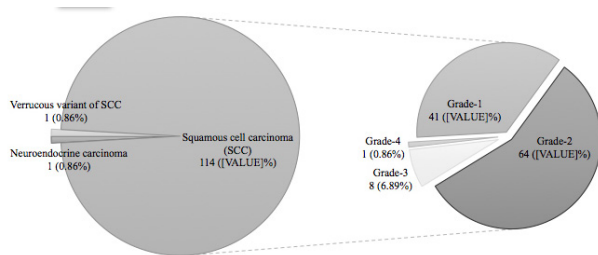


Figure 2. Histopathologic Characteristics (n=116)

Table 3. Clinically Evident Lymphatic Spread (n=116)

Cervical lymph	Supraglottic cancer	Glottic cancer	Trans-glottic cancer	Total Frequency (%)
Node level	n	n	n	
IB	4	0	0	4 (3.45)
II	48	7	4	59 (50.9)
III	29	6	1	36 (31.0)
IV	5	2	0	7 (6.03)
V	3	2	1	6 (5.17)
No nodes	10	34	4	48 (41.4)

Table 4. Tumor Extension to Individual Subsites (n=116)

Subsite	Supraglottic carcinoma	Glottic carcinoma	Trans-glottic carcinoma	Frequency (%)
	n	n	n	
Pyriiform fossa	28	3	3	34 (29.3)
Paraglottic space	13	6	4	23 (19.8)
Pre-epiglottic space	9	2	1	12 (10.3)
Thyroid cartilage	4	4	4	12 (10.3)
Strap muscles	1	1	2	4 (3.4)
Prevertebral space	2	1	1	4 (3.4)
Carotid space	1	1	0	2 (1.7)

was estimated from the CT images and they had a median volume of 11 cc (Range: 1.3 – 105 cc). Largest diameter of the lesion was a median of 29 mm (Range: 7 – 70 mm).

In cancer of the supraglottis (n=66), tumor was seen to originate from the aryepiglottic fold and supraglottic tissues in 81.8% (n=54). Another 16.7% (n=11) had epiglottic origin and in 0.86% (n=1) it could not be made out clearly. Extension of the supraglottic tumors to glottis and pyriform fossa were seen in 48.5% and 42.4% respectively. In glottic tumors (n=42), 97.6% (n=41) involved the vocal cords and one patient purely had carcinoma of the anterior commissure. Anterior commissure involvement from vocal cords were seen in 33.3% (n=14). Extension to the supraglottic and the subglottic tissues were seen in 45.2% (n=19) and 11.9% (n=5) of the glottic tumors respectively.

Involvement of the cervical lymph nodes were seen in only 58.6% (n=68) of all patients and bilaterality was seen in 18.1% (n=21). Contralateral node alone involvement was never seen. Among node-positive patients (n=68), the largest node involved was found to be at level IB in 1.5%, level II in 69.1% and level III in 29.4%. Mean largest diameter of the involved nodes was 24 mm (Range: 8- 80 mm). Various levels of lymph node involvement are summarised in the Table 3. Level II was the commonest and was not involved in 13.2% (n=9) of node-positive patients. In these nine patients, eight had level III as the largest node and one had bilateral involvement of the level IB alone. Level III was found to be larger than level II in another 17.6% (n=12) node-positive patients. Number of nodes involved were one node in 42.6%, two nodes in 23.5%, three nodes in 16.2%, four nodes in 11.8% and five or more in 6.03% in all of the 116 patients (Table not shown).

Lymph nodes were involved in 84.8% of supraglottic cancers and were bilateral in 24.2%. Stage I was never seen in supraglottic cancer. Most of the patients had a unilateral disease and extension to glottis and pyriform fossa was seen in around half of the patients. Nodal spread was seen in 19.0% (n=8) of all glottic cancers. Among them seven had extension to the supraglottis and one had subglottis extension and the involvement was more often bilateral (62.5%). Level III was the largest involved node in 62.5% of them and level IB was never involved in a glottic tumor.

Involvement of the individual sub sites are summarised in Table 4. Involvement of the pre-epiglottic space and the pyriform fossa was more common among supraglottic cancer. Involvement of the thyroid cartilage, paraglottic space, prevertebral space and the carotid space did not differ significantly among supraglottic and glottic tumors. 37.5%, 50.0% and 50.0% of the paraglottic tumors involved the pyriform fossa, paraglottic space and thyroid cartilage respectively as well. Unresectable disease with involvement of either the prevertebral space or carotid space or distant organs were seen in 6.03% (n=7).

Discussion

Smoking and alcohol consumption has been the two primarily implicated risks of any head and neck cancer.

Among our patients it was seen that 96.5% had been exposed to tobacco either in the smoked or smokeless forms. Almost all of them regularly consumed salted and fermented fish/meat known to contain N-nitrosamines which has been implicated with certain types of cancer particularly the nasopharyngeal and gastric carcinoma (Tricker and Preussmann, 1991; Mirvish, 1995; Song et al., 2015) This seems to correlate with the higher incidences of these cancers in this part of the world (Barad et al., 2014; Sharma et al., 2011). Zheng W et al (Zheng et al., 1992) in their case control study estimated that consumption of salted fish or meat increased the risks of laryngeal cancer also. However a clear relationship between dietary factors and laryngeal cancer could not be established. According to the population based cancer registry report of the National Cancer Registry Programme of India in 2012, the age-adjusted rates of laryngeal cancer are 2.35 and 0.64 per 100,000 Manipuri males and females respectively. These rates are well below most other rural and urban regions of the country (Population based cancer registry, 2013) Hence it still remains unanswered whether these dietary habits results in carcinogenesis of the larynx. For now it is safe to assume that they do not increase the incidence of laryngeal cancer and does not play an important role in its etiology.

Worldwide, males had 7.3 times more incidence of cancer of the larynx than females according to the GLOBOCAN 2012 statistics (Section of Cancer Surveillance, 2012). In our study, this ratio has decreased. One reason for this could be due to the increased abuse of tobacco among Manipuri women and in fact all of the female patients were heavy smokers and 22.2% chew oral tobacco. In an earlier report from our centre, we have seen that the males and females report almost equal incidences of lung cancer (Mandal et al., 2013) Changes in the epidemiological characteristics are expected to change with time in the future mostly attributable to tobacco use.

Hoarseness of voice was the most common initial symptom at all sub sites. Dysphagia, neck swelling and throat pain was commoner among supraglottic cancers while hoarseness of voice was more common in glottic cancers. It is well known that glottic cancers cause hoarseness early in the presentation and this led to an increased number of early stage glottic cancers (Raitiola and Pukander, 2000). However on the other end of the spectrum one fifth required tracheostomy at presentation. Fang et al found that around 70% of emergent tracheostomies done in the otolaryngology clinic are due to laryngeal carcinoma and almost half of them are diagnosed only after tracheostomy (Fang et al., 2015) We did not find any studies reporting the rates of tracheostomy in laryngeal cancer at presentation. Yet we think our number to be alarmingly high and it is probably due to the late presentation in many patients. Both supraglottic and glottic cancer patients had similar requirements of tracheostomy.

Supraglottic to glottic tumor ratio was 1.6:1 in our study. A reversal of this trend has been seen worldwide primarily attributed to lifestyle modifications pertaining to smoking habits in the developed countries (Makitie et al., 1999) Commoner use of filtered cigarettes has been

suggested as a reason (Virtaniemi et al., 2000). In the developing countries, the use of non-filter cigarettes and beedis are expected to produce a harsher taste of smoke making them less easily inhaled. Although not directly proven in any study, this causes the smoke to stay for a longer duration in the pharynx exposing the supraglottic structures (De Stefani et al., 1987). Beedi is a type of an Indian cigarette in which tobacco is rolled on a small leaf and smoked. It is found to deliver a higher quantity of nicotine, carbon monoxide and tar than traditional cigarettes (Rahman and Fukui, 2000)

The lymphatic dissemination was mainly identified in supraglottic tissue involvement, with 84.8% of supraglottic tumors and 31.6% of glottic tumors with supraglottic extension having regional node metastases. Even stage-I supraglottic tumors were found to harbour nodal metastases similar to other stages. Similarly other studies reported a higher chance of nodal metastases with supraglottic cancers (Moe et al., 1996; Tomik et al., 2001; Pfreundner et al., 1996). But the rates at which these tumors metastasised to the regional nodes are higher than other studies. A longer duration of symptoms prior to presentation could be a possible factor. Symptoms like throat pain or foreign body sensation common in supraglottic tumors are vague and many present to the clinician after a serious disability to eat or breathe.

Distant metastases were rarely encountered in our patients with liver metastases seen in 1.72% and both also had multiple nodes at presentation. Being rare at presentation, could metastatic workup be avoided at presentation needs to be answered. CT imaging of the thorax is anyhow mandatory with almost all head and neck cancers having a risk of second primary in the lung. CT abdomen may be required to rule out spread in the abdominal nodes or liver. In a study for nodal metastases in head and neck cancer, N+ laryngeal cancer was found to be associated with retroperitoneal adenopathy in 4% (McLaughlin et al., 1995). The veteran affairs study group also concluded that the presence of three or more lymph nodes resulted in significantly high distal recurrence rates Moe et al., 1996). So in less developed regions like ours, CT screening of the abdomen could be limited only to cases with multiple neck nodes.

In conclusions, Use of tobacco either in the smoked or smokeless form is implicated in almost all of the cases. Widespread use of fermented and salted fish/meat in this region did not increase the incidence of laryngeal cancers. Gender gap is lesser than other countries and also other regions in India possibly due to increased tobacco use among women. Supraglottic cancer still remains the commonest site in larynx. There is also a higher incidence of regional nodal spread than the western countries and a higher requirement of tracheostomy at presentation.

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