The epidemiology of laryngeal cancer in a country on the esophageal cancer belt

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Abstract

Objective Laryngeal cancer is one of the most common malignant neoplasms of the head and neck and occurs predominantly in males. Squamous cell carcinomas arising in the glottic region are the most common of all laryngeal cancers and more prevalent than the supraglottic ones. But this pattern is reverse in some countries. This study was done to investigate the epidemiologic aspect of this subject in Iran.

Study design Cross-sectional study

Subjects and methods During a ten-year period from 1997 to 2007, all patients referred to two tertiary referral hospitals with a diagnosis of laryngeal cancer were enrolled in this study.

Results Laryngeal cancer was diagnosed in a total of 453 patients and confirmed histologically. The average patient age was 59.92 years. Men outnumbered women (9.5:1). Four hundred patients (88.5%) were tobacco smokers. The primary location of the tumor was supraglottic in 221 (49%) cases, followed by glottic in 163 (36.2%), transglottic (the tumor involved all regions of the larynx and the origin was unspecified) in 60 (13.3%), and subglottic in 7 (1.6%).

Conclusion In our series, although we excluded transglottic tumors, the supraglottic tumor was dominant and the ratio of supraglottic to glottic tumors was 1.36. This is compatible with results from countries with a reverse ratio.

Keywords Laryngeal neoplasms · Larynx · Anatomy · Iran · Esophageal cancer · Epidemiology

Introduction

Laryngeal cancer is one of the most common malignant neoplasms of the head and neck and the most common malignant tumor in the upper aerodigestive tract [1–3]. It exists in a number of well-known variations in different countries [3, 4]. Moreover, laryngeal cancer has been reported to account for approximately 1% of all new cancer diagnoses in recent years [5]. The total incidence of this disease has been reported to be rising, especially among women [3, 6], although currently the incidence of the disease is significantly higher in male patients. It represents 2.3% of all malignant tumors in males and 0.4% of all malignant tumors in females; the overall male-to-female ratio is about 4:1 to 10:1 [7, 8]. There is a strong relationship between laryngeal cancer and lifestyle and environmental factors [2]. Histologically, the most common form is squamous cell carcinoma, comprising more than 90% of laryngeal cancers [5, 9].

As regards the classification of tumors, the larynx is divided into three anatomical regions of the supraglottis, glottis, and subglottis. Involvement of the glottis has generally been reported to be more common than the supraglottis [10], but in some Mediterranean and Latin American countries, supraglottic carcinomas have been found to be more prevalent [3–5, 11]. Tumors originating from different regions of the larynx have their own clinical behaviors and are also associated with different risk factors [1, 5]. Proposed explanations for this relatively high proportion of supraglottic carcinomas include disparity among patients in their smoking, drinking and dietary habits [1, 4, 12].

Iranian population has the highest rates of esophageal squamous cell carcinoma in the world [13, 14]. The cause of these extraordinary rates has been investigated [15]. The main risk factors suggested by these studies included a poor diet (marked by a reliance on tea and bread and a deficiency

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in fresh fruits, vegetables, and meat), genetic susceptibility, and opium consumption [15–18]. These risk factors are common between esophageal cancer and supraglottic carcinoma [18–20]. Considering the high rate of esophageal cancer in Iran and its correlation with supraglottic cancer, this study was designed to investigate the epidemiologic pattern of laryngeal cancer and its treatment in Iran.

Materials and methods

Patients with laryngeal malignant neoplasm treated at Imam Khomeini and Amir Alam Hospital, Department of Otolaryngology, Head and Neck Surgery, Medical University of Tehran from 1997 until 2007 were included in this study. All patients who participated in this study filled the appropriate consent forms. The study protocol was approved by the Ethic Committee of Tehran University of Medical Sciences (IRB). Medical reports of patients with confirmed diagnoses were registered during the study period. There was no randomization in this study, and all eligible patients were enrolled during the study period. All patients had direct laryngoscopy, staging and biopsy. Information regarding the patients' age, sex, habit history, occupation, chief complaint, associated diseases, primary tumor location, pathologic type, tumor stage, tumor grading, type of treatment and complications were recorded. The histology of the tumors was classified with reference to the Histological typing of tumors of the upper respiratory tract and ear by the World Health Organization (WHO). Tumor staging was performed according to TMN criteria (WHO). The histological grading of squamous cell carcinomas was performed according to G1±3 scale. [7] Tumors were categorized based on their location, and when the origin was unspecified because of tumor bulk, it was categorized as transglottic and not included in supraglottic and glottic subgroups.

Patients were asked about their smoking and drinking habits. Smokers were defined as someone who use to smoke in their entire lifetime or having regularly smoked cigars/cigarillos or pipes. Because of the prevalence of Islamic culture in Iran, we rarely encountered heavy drinkers or alcoholics. Therefore we used light drinkers as the reference group. Each patient was asked to recount his drinking of beer, wine and spirits in a typical week during specific age periods.

Treatment in this report represents the first course of cancer-directed therapy used to manage the tumor. Information on subsequent therapy to address recurrences was unavailable for this report. Initial cancer-directed therapy may include a combination of modalities and may span many weeks or several months if irradiation or multiple cycles of chemotherapy are included in the original treatment plan. Treatment is presented for all laryngeal subsites. The recording of specific data addressing type, timing and

dose of chemotherapy and irradiation was not sufficiently complete to permit detailed analysis of these parameters for the years under review. Data addressing the type of primary site surgery was enough to permit the analysis of the extent of surgery for all laryngeal cancer sites.

The statistical analyses of the data were performed using the SPSS (VER 14). Relations between different parameters were determined by analysis of variance Chi-square test, Fisher's exact test and Mann-Whitney test.

Results

A total of 453 cases of laryngeal cancer, diagnosed at our hospital and confirmed histologically, were recruited into the study. The average patient age was 59.92 (SD, 9.55; median, 61; range, 19 to 87) years. Men outnumbered women 9.5:1 (410 men, 43 women). No statistical difference was found between the mean age of males and females, but the age range was much narrower in women than in men. Most patients (72.4%) were in the 5th and 6th decades of their life.

Four hundred (88.5%) patients were tobacco smokers (Table 1). Average pack-year of smoking was 25 (range, 17 to 35) pack-years. 97 (21.4%) patients (21.2% of men and 23.2% of women) patients stated that they consume alcohol, and 165 (36.4%) mentioned that they had been using opium regularly (Table 1). Symptoms of gastroesophageal reflux disease (heart burn and acid regurgitation) were mentioned by 149 (33%) patients. Twenty-two patients (18 men and 4 women) had a history of radiation to the head and neck, and 25 (5.5%) patients had a positive family history of laryngeal cancer. Patients' occupational data is presented in Table 2.

According to TNM staging, 83 (18.3%) cases were in stage T1, 114 (25.2 %) in stage T2, 159 (35%) in stage T3, and 97 (21.4%) were in stage T4. In 65.9% of patients no lymph node involvement was noted (N0), and among the rest, 13%, 2.9%, 10.1%, 5.1%, and 2.9% were in stages N1, N2a, N2b, N2c, and N3, respectively. The incidence of neck node metastases increased with a higher T stage ($P<0.001$). Distant metastasis was detected in 11 (2.4%) patients. The most common site was the lung. There was no statistically significant relationship between the sex and age of the patients and the T stage, lymph node involvement, or distant metastasis.

Table 1 Gender distribution (percentage) of smoking, alcohol and opium usage among the patients

	Male	Female	Total
Tobacco smoking	88	90	88.5
Alcohol consumption	21.2	23.2	21.4
Tobacco and alcohol use	19.1	18.2	19
Opium use	38.8	18.6	36.4
Negative substance history	3.9	14.6	5

The primary location of the tumor was supraglottic in 221 (49%) cases, followed in the order of frequency by glottic 163 (36.2%), transglottic (the tumor involved all regions of the larynx and it was impossible to determine the origin) 60 (13.3%), and subglottic 7 (1.6%). The mean age of the patients at the time of diagnosis for each subsite was 61.8, 61, 60.5, and 58.3 years for glottic, transglottic, subglottic, and supraglottic tumors, respectively. There was no statistically significant relationship between age and subsites.

Histopathological analysis revealed that 432 (95.4%) of tumors were squamous cell carcinomas; 242 (56.5%) well differentiated, 112 (26 %) moderately differentiated, and 78 (18%) poorly differentiated carcinomas. Other types of histopathology are summarized in Table 3. There was no correlation between sex and age of the patients and histopathologic grading of the tumors.

After diagnosis, 23 patients signed out of our center against medical advice without receiving any treatment, perhaps to seek care at another center. Of the remaining 430 patients, 145 had radiotherapy as a single modality and 285 patients were treated surgically; 205 patients underwent total laryngectomy, and 23 and 57 patients had partial laryngectomy and laryngopharyngectomy, respectively.

Table 2 Patients' occupation distribution

Occupation	Percentage
Farmer	25
Factory worker	14
Office clerk	11
Housekeeper	7
Stonemason	4
Carpenter	3
Driver	2
Greengrocer	2
Street vendor	2
Cook	2
Retired	5
Other	23

Table 3 Histopathologic distribution of laryngeal tumor

Histopathology	Number of patients	Percentage
Squamous cell carcinoma	432	95.4
Verrucous cell carcinoma	10	2.2
Chondrosarcoma	3	0.6
Malignant fibro histiocytoma	1	0.2
Other sarcomas	2	0.4
Other (neurofibroma, spindle-cell carcinoma)	2	0.4
Unspecified	3	0.7

Tracheostomy was performed on 30 patients before other treatments. The most common complication after surgical treatment was fistula, which was noted in 54 (18.9%) patients. The surgical mortality rate was 3.5%. There was a statistically significant correlation between complications and the T stage ($P=0.047$). Also the correlation between mortality and T stage was significant ($P=0.016$). We found no significant relationships between age, sex, subsite, tumor grading and complications or mortality.

Discussion

The larynx is the most common site of primary squamous cell carcinomas of the head and neck. There is a great geographical variation in the epidemiology of laryngeal cancer in different parts of the world, with especially high rates of occurrence in Brazil, France, Italy, Spain, India and parts of south-east Asia [7]. Worldwide, glottic carcinoma is more common than supraglottic cancer, but for example, in southern Europe, supraglottic carcinoma is more common than carcinoma of the glottis, whereas the reverse is true for north-western Europe. Tumors of the glottis are predominant in Anglo-Saxon populations, whereas in France, India and among the African-American populations of the United States, the number of glottic and supraglottic tumors are approximately equal [4, 8, 11].

Compared to the rest of world, Iran has some special distinctions. First, it is located in the region with the highest rates of esophageal cancer [13, 14]. Second, the rate of alcohol consumption in Iran is low because of different social mores (mainly religious beliefs). Finally, there is a high rate of opium addiction among laryngeal cancer patients. To our knowledge, the epidemiology of laryngeal cancer in Iran has not yet been thoroughly studied. The present study was conducted at Imam Khomeini Hospital, the nation's largest university-affiliated referral center to which most cases of laryngeal cancer are treated in it. The study of 453 new cases at this center during the study period can acceptably represent the epidemiologic pattern in Iran.

The association between esophageal cancer and laryngeal cancer is well-known [18, 20], but the association with different laryngeal subsites is not understood [18]. From the embryological point of view, the glottis and supraglottis originate from completely different structures so they have different biologic behavior [5]. Supraglottic tumors are more similar to hypopharyngeal and esophagus tumors than glottic tumors. The reason is more direct exposure with carcinogens [1, 4].

In our series, although we excluded transglottic tumors, the supraglottic tumor were dominant, and the ratio of supraglottic tumors to glottic ones was 1.36. This is compatible with results from other countries with this reverse ratio. Interestingly in some reports from Europe, such as France and Spain, the high rate of supraglottic tumors is associated with higher rates of esophageal cancer [1, 13].

The main risk factors of esophageal cancer are smoking, drinking, a poor diet (marked by a reliance on tea and bread and a deficiency in fresh fruits, vegetables, and meat), opium consumption, and genetic susceptibility [7, 9, 15, 16, 18, and 21]. All these can cause supraglottic tumors [1, 6, 12, 18]. In the present study, 88% of cases had a history of smoking; this is compatible with results of other studies [11, 22]. The role of alcohol has been considered important in the etiology of supraglottic carcinoma [1, 4, 7, 19]. This is supported by studies in France, Italy, Spain and Uruguay where the consumption of alcohol, especially wine, is high. However, our patients showed a low rate of alcohol drinking (21.4%) with a high rate of opium consumption (36.4%), which is a unique finding compared to that in other countries. It has been shown that long-term opium consumption not only has a strong relation to laryngeal cancer but also reduces the age of onset of the disease [17].

The male to female ratio was 9.5, indicating a higher prevalence of risk factors among men. This rate is approximately in the middle of the global range [7, 8, 11, 23] that can be as high as 3.8 in the black population of New Orleans and as low as that in Basque country [3, 11, 24]. In terms of age, the peak incidence was between the 5th and 6th decades of life, which compared to other reports [7, 11, 17, 24], is ten years earlier.

Occupational exposure is another risk factor. Contact with asbestos increases the risk of laryngeal cancer. A number of other exposures, including mustard gas, sulphuric acid, nickel, isopropyl alcohol, steam and fumes [7, 11, 21, 25, and 26] have been implicated as risk factors that were not prominent in our series; only 14% of our patients may have had such exposures.

Twenty-five (5.5%) patients had a positive family history of laryngeal cancer. Genetic susceptibility is another risk factor mentioned in the literature. Several factors have to be considered in estimating the true risk for developing cancer [7, 15, 17, 25].

The last evaluated risk factor was gastroesophageal reflux disease (GERD) which is weakly, but consistently correlated with laryngeal cancer [25, 27, 28]. It may play an important role in the non-smoker group [27, 28]. Symptoms of GERD (heart burn and acid regurgitation) were mentioned by 149 (33%) patients. Considering the high rate of extraesophageal reflux without gastrointestinal problems, this data shows a high rate of GERD in our series. In some series lower rates are reported [27]. However, as a limitation of our study, 24 h pH monitoring should have been done to detect the incidence of GERD [28] more accurately.

The majority of malignant tumors of the larynx are squamous cell carcinomas. Similar to other reports [5, 7], they accounted for 95.4% of all neoplasms in our study and also the majority of squamous cell carcinomas of the larynx were well-differentiated and that the differentiation was related

to age and sex [24]. However, in our series, 43.5% of patients had moderately and poorly differentiated carcinomas, that showed a relatively higher rate of moderately and poor differentiated grading. There was no relationship between sex, age and differentiation. This contradictory pattern may be due to the higher rate of supraglottic tumors.

Nearly 50% of our patients were diagnosed at T1 and T2 stages; this can be comparable with results of developed countries where 60% are detected in T1 and T2 stages. This is probably again because of the high rate of supraglottic tumors in our patients [8, 10].

In terms of treatment, 32% of the cases had radiotherapy as the first treatment, which shows surgery plays a more important role in treatment of laryngeal cancer in our country. This result is contradictory with some countries where radiotherapy is the first option. [8]

In conclusion, the pattern of laryngeal cancer, risk factors, and rate of esophageal cancer in Iran are completely different from other parts of the world, and therefore more detailed analyses are required to understand the descriptive epidemiology of laryngeal cancer and its correlation with the epidemiology of esophageal cancer.

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