Symptoms of Laryngeal Carcinoma and their Prognostic Significance

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Symptoms of 301 patients with laryngeal squamous cell carcinoma were evaluated. Tumour site affected the symptom profile significantly. Hoarseness was more common among patients with glottic and subglottic tumours, but was also the leading symptom in supraglottic patients. Other symptoms were mainly associated with supraglottic tumours and more advanced glottic lesions. There was a positive correlation between the number of symptoms and stage, regardless of tumour site. Patients with a supraglottic tumour had significantly more symptoms (median 2) than those with a glottic lesion (median 1). The median duration of the symptoms was significantly longer in stages III–IV (4.7 months) than in stages I–II (3.8 months). In the multivariate analysis, tumour stage was the only variable showing prognostic significance.

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Symptoms of laryngeal cancer vary according to location, size and degree of invasion of the tumour. Although it is a relatively rare malignancy, the high cure rate of early cases emphasizes the importance of early detection of this disease. Hoarseness is the main symptom and in glottic cases it occurs even with small tumours, in which the treatment results are particularly good. Supraglottic and more advanced glottic tumours may cause miscellaneous symptoms such as sore throat, globus sensation, dysphagia, and dyspnoea, which is also common in subglottic cases. A neck mass caused by nodal metastasis or direct extension of the tumour may also be present. Although the symptomatology of laryngeal cancer is well known, there is relatively little detailed quantitative data of the symptoms and their real prognostic value. In order to evaluate the symptoms of laryngeal squamous cell carcinoma and their prognostic significance, we have reviewed all cases of laryngeal cancer diagnosed during a 30-year period from 1962 to 1991 in the Tampere University Hospital area, covering a population of about 400000.

MATERIAL AND METHODS

The medical records of all 312 patients with histologically verified squamous cell carcinoma of the larynx diagnosed during the study period were retrospectively reviewed. During the primary evaluation of the disease, the symptoms and their duration reported by the patient had been registered in the patient records. Eleven patients whose symptoms were not recorded were excluded from this study. The median age of the remaining 16 female and 285 male patients was 63.0 (range 20–87) years. 126 (41.9%) tumours were supraglottic, 165 (54.8%) glottic and 10 (3.3%) subglottic. During the study period, the annual age-adjusted incidence in males decreased from 6.7 to 2.6 per 100000 and the proportion of supraglottic tumours decreased from 2/3 to 1/3 (1).

The tumours were staged according to the 1987 UICC TNM classification (2). There was a significant difference in stage distribution between the laryngeal sites, so that stage I tumours were distinctly most common and higher stages more infrequent among the glottic cases (Table 1). The proportion of stage I–II tumours decreased from 72.3% to 61.2% and that of stage III–IV lesions increased from 27.7% to 38.8% from the first to the last 10-year period. This change was found in both glottic and supraglottic disease, but it was not statistically significant. At the time of diagnosis, regional lymph node metastases were clinically present in 20.6% of supraglottic, 1.8% of glottic and 10.0% of subglottic cases; 166 patients (55.1%) were primarily treated with radiotherapy, 38 (12.6%) with surgery, 93 (30.9%) received combined therapy and 4 (1.3%) were not given any curative treatment. All patients

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Table 1

Stage distribution by tumour site

Tumour site	Stage			
	I n (%)	II n (%)	III n (%)	IV n (%)
Supraglottic	18 (14.3)	51 (40.5)	29 (23.0)	28 (22.2)
Glottic	85 (51.5)	40 (24.2)	34 (20.6)	6 (3.6)
Subglottic	0 (0.0)	4 (40.0)	3 (30.0)	3 (30.0)
All sites	103 (34.2)	95 (31.6)	66 (21.9)	37 (12.3)

$p < 0.0001$.

were followed up for at least 5 years or until death, the median follow-up time being 5.6 years.

Symptom duration was calculated from the beginning of the earliest symptom reported by the patient to the date of the diagnostic biopsy and the length of each symptom was also recorded separately. In 16 patients the duration was not known and these patients were excluded from the respective analyses. Five patients were excluded from the survival analyses because of insufficient follow-up data. Because of the small number of subglottic cases, most analyses were not performed separately among them. The statistical analyses were carried out by SPSS for Windows 6.1 software using the χ^2-test, the Mann-Whitney *U*-test, the Kruskall-Wallis analysis of variance and the Cox regression model. A p-value < 0.05 was accepted as statistically significant.

RESULTS

Tumour site affected the symptom profile significantly (Table 2). Hoarseness was more commonly associated with glottic and subglottic tumours, although it was the most frequent symptom also in supraglottic disease. Supraglottic tumours caused a markedly higher occurrence of sore throat, dysphagia, globus, otalgia and haemoptysis. Dyspnoea was most common in patients with subglottic tumours. These findings were independent of the differences in stage distribution between tumour sites. About 10% of patients having a supra- or subglottic lesion presented with a neck mass detected by the patient, which was the only symptom in two cases. The frequency of all other symptoms except hoarseness increased significantly along with stage. This association was stronger in glottic than in supraglottic disease. In patients with a supraglottic tumour the prevalence of hoarseness was significantly higher (96.7%, $p = 0.0002$) when the tumour extended to the vocal cord(s). Among stage I supraglottic cases, sore throat was even more prevalent (55.6%) than hoarseness (44.4%).

The 301 patients reported a total of 447 symptoms ranging from 0 to 6 (median 1) per patient. Of the five asymptomatic patients, three had a supraglottic stage I tumour, one a supraglottic stage II and one a glottic stage I lesion. Supraglottic tumours caused significantly ($p < 0.0001$) more symptoms (median 2) than glottic lesions (median 1). This difference was also present inside stages II and III but not in stages I and IV. The number of symptoms increased along with stage, regardless of tumour site. The median duration of the symptoms was 4.2 months and this was not significantly affected by tumour site. The symptom duration was significantly longer in stage III–IV cases (median 4.7 months) than in stages I–II (median 3.8 months, one-tailed $p = 0.0379$, Mann-Whitney *U*-test). A parallel but non-significant trend was also present separately in glottic and supraglottic disease. About 2/3 of the patients had had symptoms for longer than 3 months and 1/3 for longer than 6 months. The proportion of patients with symptom duration longer than 1 year was 13.2% among those with a stage I–II tumour and 24.0% among those with a stage III–IV lesion ($p = 0.0221$). A similar difference was also found separately in glottic and supraglottic cases. The median lengths of individual symptoms ranged from 1.0 month of haemoptysis to 4.1 months of hoarseness (Table 3). The median dura-

Table 2

Occurrence of symptoms by tumour site

Symptom	Tumour site				
	Supraglottic n (%)	Glottic n (%)	Subglottic n (%)	All sites n (%)	p-value
Hoarseness	88 (69.8)	164 (99.4)	10 (100.0)	262 (87.0)	<0.0001
Sore throat	58 (46.0)	9 (5.5)	0 (0.0)	67 (22.3)	<0.0001
Dyspnoea	17 (13.5)	16 (9.7)	4 (40.0)	37 (12.3)	0.0156
Dysphagia	30 (23.8)	5 (3.0)	0 (0.0)	35 (11.6)	<0.0001
Globus	13 (10.3)	1 (0.6)	0 (0.0)	14 (4.7)	0.0004
Neck mass	12 (9.5)	1 (0.6)	1 (10.0)	14 (4.7)	0.0012
Otalgia	10 (7.9)	1 (0.6)	0 (0.0)	11 (3.7)	0.0035
Haemoptysis	7 (5.6)	0 (0.0)	0 (0.0)	7 (2.3)	N.E.

N.E. = not evaluable.

Table 3

Duration of individual symptoms

Symptom	Duration (months)	
	Median	Range
Hoarseness	4.1	0.1–48.0
Globus	3.7	1.0–13.0
Dysphagia	3.6	0.1–18.0
Sore throat	3.1	0.1–24.0
Otalgia	2.2	1.0–13.0
Neck mass	2.1	0.5–24.0
Dyspnoea	2.0	0.1–25.0
Haemoptysis	1.0	0.1–9.0

tion of hoarseness was longer in glottic (4.2 months) than in supraglottic (3.4 months) disease. The frequency, duration or quality of the symptoms did not change significantly during the study period.

Five-year disease-specific survival was 85.4% in stage I, 74.0% in stage II, 55.7% in stage III and 33.5% in stage IV. In the univariate Cox regression analysis, higher stage, multiple symptoms, and presence of dyspnoea, globus, neck mass or haemoptysis indicated a significantly poorer prognosis. However, when these variables were analysed by tumour site and stage, they lost their significance, which indicates that their impact on survival was merely due to the association with site and stage. The duration of the symptoms did not have a significant effect on prognosis. In the multivariate Cox regression analysis, only stage ($p < 0.0001$) affected the disease-specific survival significantly.

DISCUSSION

Our finding of the symptom pattern of laryngeal cancer is rational from the anatomical and functional points of view and it is consistent with most previous reports (3–6). Hoarseness was distinctly the most common symptom regardless of tumour site. It was more prevalent in glottic and subglottic cases but also in supraglottic disease it was the leading symptom. Spread of the tumour to vocal cord(s) increased the frequency of hoarseness in supraglottic disease. Other symptoms were associated with supraglottic tumours and more advanced glottic lesions. Sore throat was the second most common symptom in supraglottic disease, and among stage I cases it was even more prevalent than hoarseness.

The length of individual symptoms varied considerably. In accordance with some earlier findings, hoarseness had the longest (4, 5, 7), and more alarming symptoms like haemoptysis, dyspnoea and neck mass had the shortest median durations. The proportion of advanced-stage lesions was distinctly higher among patients with a supraglottic tumour, but there was no great difference in symptom duration between supraglottic and glottic cases. This supports the general opinion that the symptoms appear late in supraglottic cancer (8). Contrary to several previous reports (4–7, 9, 10), our patients showed a significant, positive association between symptom duration and tumour stage at diagnosis. However, as in previous studies (4–7, 9, 10), the duration of the symptoms did not have any prognostic significance. In addition to differences in intrinsic aggressiveness of the neoplasms (4, 7, 10), recall bias by the patients and inaccurate recording of the symptoms are likely contributors to the usual lack of association between symptom duration and the stage of the disease at the time of diagnosis (4, 6, 7). It is easy to understand that a patient presenting with an advanced tumour with prominent symptoms does not always remember the onset of the minor early symptoms. Consequently, symptom duration reported by the patient, especially in advanced cases, may be unreliable and does not indicate the real duration of the disease. Furthermore, the symptom pattern of rapidly advancing tumours may differ from that of less aggressive lesions (5, 11).

High number of symptoms has been found to predict poor prognosis in neuroblastoma (12), and in colorectal (13), lung (14) and nasopharyngeal (15) cancers, but to the best of our knowledge analyses of the number of symptoms in patients with laryngeal cancer have not been published. We found a positive correlation between the number of symptoms and tumour stage, furthermore, the patients with glottic carcinoma had fewer symptoms than those with supraglottic lesions. The survival analysis revealed that the higher the number of symptoms, the poorer the prognosis, but in the multivariate Cox regression analysis, symptom number lost its prognostic significance because of the strong correlation with tumour site and stage.

Screening of laryngeal carcinoma, or even of all head and neck cancers together, seems not to be rational because of the relatively low incidence, even if focused to the high-risk population (8). The lack of correlation between symptom duration and stage at diagnosis has also led to scepticism concerning possibilities to increase the proportion of cases found at an early stage and thus improve the cure rate (4, 6, 10). It has also been stated that the early detection of vocal cord carcinoma has improved considerably but seems to have reached a plateau, and further progress in early diagnoses is restricted by the fact that only a proportion of the tumours can be diagnosed early because of the differences in their intrinsic aggressiveness (8). The same author considers that supraglottic carcinomas are symptomless over a long period and continue to be diagnosed in an advanced stage, with only occasional and rare early diagnoses. According to our results, the proportion of glottic tumours diagnosed at stages I–II was about 75% and even in supraglottic cases this proportion was over 50%. The fact that our percentage of early stage cases decreased during the study period, despite improved standard of living and increased availability of healthcare services, supports the opinion that the early detection of laryngeal cancer is difficult to improve. However, 1/3 of

our patients had had symptoms for over 6 months and 1/4 of advanced (stages III–IV) cases for over one year. Even though there will always be a proportion of the population that rejects all advice, the delay by at least the patients with long duration of symptoms could probably be shortened by intensive education of the high-risk group, i.e. middle-aged (male) smokers. Furthermore, the importance of prompt and adequate laryngeal examination of patients with prolonged hoarseness and other symptoms typical of laryngeal cancer should be emphasized to primary healthcare physicians.

In conclusion, our results show that there are marked differences in the symptom pattern of laryngeal cancer, depending on tumour site and stage. Presence of certain individual symptoms and a higher number of symptoms indicated poorer prognosis, but this impact was mainly due to the association with stage and it was not found in the multivariate analysis. Thus the independent role of the symptoms in treatment planning and evaluation of prognosis seems to be minor. Hoarseness is the main symptom of laryngeal carcinoma and its presence even with small vocal cord tumours is a major contributor to early detection and good treatment results in glottic cancer. However, a substantial proportion of laryngeal malignancies and also of glottic tumours is diagnosed at an advanced stage when the cure rate is distinctly lower. There is undoubtedly considerable variation in the intrinsic aggressiveness of laryngeal carcinomas and the proportion of tumours that can be diagnosed early may be limited. Nevertheless, the relatively high proportion of patients with a long symptom duration emphasizes the importance of increasing the awareness among both the general public and primary healthcare physicians of the symptoms of laryngeal cancer.

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