Factors predicting survival after diagnosis of laryngeal cancer

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S U M M A R Y
Survival in patients with laryngeal cancer has not increased remarkably within the last years. It is presumed that a variety of factors act jointly in predicting survival after diagnosis: tumour stage, tumour site, treatment approaches, age and comorbidities. The aim of this German clinical multi-centre study is to present results from multivariate analysis. A retrospective cohort study was conducted in four hospitals in South-West Germany. Incident cases with laryngeal squamous cell carcinoma were included for the years 1998 to 2004, resulting in a population sample of 594 patients. Multivariate regression analysis was performed using the Cox proportional hazards model. Patients were followed up for 64.1 months on average. Overall 5-year survival was 66% (95% confidence interval (CI): 62–70%). The strongest risk factors in multivariate analysis were age at first diagnosis (hazard ratio (HR): 1.5; 95% CI: 1.5–1.7 per each additional 10 years), tumour stage, and the development of recurrences (HR 3.1; 95% CI: 2.3–4.2) or second primary carcinomas (HR 2.1; 95% CI: 1.4–3.1). A somewhat weaker effect was shown for patients with comorbidities (using Charlson’s comorbidity index). The choice of treatment did not strongly affect survival when adjusting for other factors, possibly because the optimal treatment approach was applied for the specific constitution and requirements of each patient. For future research it would be desirable to study the effect of treatment on quality of life in multivariate analysis as well as other modifiable risk factors as smoking and drinking reduction or cessation after diagnosis.

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Introduction

During the recent years, the incidence of laryngeal cancer was relatively stable with about 160,000 new cases per year. The disease predominantly affects men; hence the age-standardised incidence rate varies strongly between the sexes, with 5.1 and 0.6 new cases per 100,000 per year, respectively. In men, laryngeal cancer comprises about 2.4% of all cancer cases and 2.1% of all cancer deaths worldwide.1 In Germany, about 4000 new cases of laryngeal cancer are diagnosed every year, causing more than 1,500 deaths. While the age-standardised incidence and mortality rates in men slowly decreased during the recent years, the rates in women rather increased.2

The most important risk factors for laryngeal cancer are the lifestyle factors tobacco smoking and alcohol consumption,3−5 while there are also occupational substances like asbestos, polycyclic aromatic hydrocarbons, dust and solvents, promoting the development of laryngeal cancer.4,6−10 There is some evidence for an influence of genetic factors, as people with a family history of head and neck cancer were shown to have an increased risk of developing laryngeal cancer.11 Despite this knowledge, it is not well determined up to which extent survival time after diagnosis of laryngeal cancer is influenced by the above mentioned factors.12

Five-year overall survival of all Europeans diagnosed with laryngeal cancer between 1995 and 1999 was 55%, slightly worse than survival rates for the German population (59%).13 It is presumed that a variety of factors act jointly in predicting survival after diagnosis of head and neck cancers: Research has shown that survival time after diagnosis of head and neck cancers14,15 and specifically laryngeal cancer16 mainly depends upon the tumour stage and the age of the patient. However, early diagnosis of laryngeal cancer is often complicated by unspecific symptoms.
Tumour site has also been identified as a prognostic factor for survival after diagnosis of laryngeal cancer. Patients diagnosed with supraglottic tumours had poorer survival times than patients with glottic tumour sites, 70% and 81% five-year disease-specific survival, respectively. However, these figures do not take into account that patients with supraglottic tumours are on average diagnosed with later tumour stages than patients with glottic tumours.

Several studies have focused on the influence of different treatment approaches on survival, but comparability of results is difficult, as the choice of treatment depends on a variety of factors, like tumour size, location and tumour stage (number and localization of positive neck nodes, presence of distant metastases). Based on the currently largest German patient cohort investigated, showing an effect in univariate analysis, were included. Therefore, primary concurrent or sequential chemoradiation for organ preservation in advanced but still resectable stages is recommended and currently still under investigation within clinical trials. However, a decisive superiority of one or another therapeutic approach has not been demonstrated due to its dependence on the patient's and the disease-specific characteristics. Additionally, the general health aspects of the patients play a role, as the presence of comorbidities significantly decreases disease-specific survival time of patients with head and neck cancers. Besides present comorbidities, the occurrence of second primary carcinomas (SPCs) is assumed to reduce survival time in patients with head and neck cancer. Considering the variety of the previously mentioned factors, multivariate models are needed to gain insight into this complex relation. The aim of this study is to present results from a multivariate analysis based on the currently largest German patient cohort diagnosed with laryngeal cancer.

Materials and methods

Study population

This retrospective cohort study was conducted in the South-West of Germany, comprising four cities of the Rhein-Neckar-Odenwald region. Ascertainment of all incident cases of histological confirmed cancer of the larynx began on May 1, 1998 up to December 2004. Treatment of laryngeal cancer is exclusively done in the clinics from which cases were obtained. Local practitioners were additionally contacted to check for possible cases sent to other more distant clinics and to verify complete case ascertainment.

Data analysis

Demographic data and clinical information were extracted from the medical records of the hospitals, using a standardised form. Vital status, date and cause of death were requested from the local record sections. Overall and disease-specific survival rates were calculated using the Kaplan–Meier method. A total of 11 patients had to be omitted from the calculation of disease-specific survival rates, as the cause of death could not be determined. All possible explanatory variables were initially studied in univariate analysis.

Regression analysis with endpoint overall survival was performed using the proportional hazards model, in which all variables, showing an effect in univariate analysis, were included. Both univariate and multivariate analyses were stratified by hospital. Survival time was measured as time from first diagnosis until death or until first December 2008. For analysis, patients who migrated out of Germany were censored at the middle of the time span between first diagnosis and end of follow-up of the study. As explanatory variables, age at first diagnosis, tumour location, TNM classification, comorbidities, recurrences and second primary carcinomas as well as therapy approach were included into analysis. Proportional hazards assumption was checked by adding a time-dependent version of all variables in the model. The assumption was met for all variables apart from lymph node status, for which we kept the time-dependent additional variable in both the univariate and the multivariate regression models. For categorization purposes, tumour location was entered into the model in four different groups, where ‘supraglottic’, ‘transglottic’ and ‘carcinomas without defined site of origin’ were compared to ‘glottic’ carcinomas. Subglottic carcinomas were added to the group of glottic carcinomas.

T and N status were included as binary variables, where T3 and T4 were classified as advanced stage of the primary site and patients with N1 to N3 status belonged to the group with advanced stage of the lymph nodes. The metastatic status could not be evaluated, as only six patients could be assigned to M1 status with certainty. Comorbidity conditions were determined using Charlson’s comorbidity index (CCI), which assigns values between one and six to 18 different comorbidities and sums them up to a single score, taking into account the number as well as the severity of comorbidities. For this analysis we considered the binary form of the variable, which was set to one for values of the CCI of two or higher. Developments of a local or regional recurrence or a second primary carcinoma (SPC) were included into the model as time-dependent covariates. From the date of diagnosis of a recurrence or an SPC, the corresponding variable was set to one. The different therapy approaches that patients received were considered for the model in six different categories. The reference group (i) comprises patients who received partial laryngectomy (PL) by laser surgery or open partial laryngectomy and did not receive any non-operative treatment like radio-, chemo- or radiochemotherapy (RC). Patients of this group were compared to (ii) patients who received PL with adjuvant RC, (iii) patients who received total laryngectomy (TL) without RC, (iv) patients who were treated with TL and adjuvant RC, (v) patients who received primary RC and (vi) patients who did not receive any treatment at all. All analyses were performed with SAS (version 9.2).

Results

Sample characteristics

Mean age of the 538 men and 56 women in this study was 63 years, ranging from 33 to 91 years (Table 1). The majority of patients (62%) presented with a glottic carcinoma, while 23% suffered from a supraglottic and further 15% from a transglottic (35 patients) or subglottic (11 patients) carcinoma or a carcinomas without defined site of origin (43 patients). Of the 594 patients in this study, 29% had advanced T stage and 19% had affected lymph nodes.

Of all patients, 440 (74%) had neither a recurrence nor an SPC. Recurrences were more frequent than SPFs with a maximum number of four recurrences (two patients) and three SPFs (one patient). Of all 594 patients, 78 received primary RC, compared to 500 patients who were treated by initial surgery. The majority of these patients were treated with laser surgery (317 patients), while open partial laryngectomy (57 patients) and total laryngectomy (126 patients) were less frequently used. Adjuvant RC was applied for 114 patients.

Survival

Patients were followed up for 64.1 months on average, ranging from two weeks to about 10.5 years. A total of seven patients were lost to follow-up, due to emigration. Overall five-year survival was
66% with a 95% confidence interval (CI) of 62% to 70% and disease-specific survival was 83% (95% CI: 79%, 86%) after five years of observation.

**Regression analysis**

Table 2 shows the influence of variables on survival time according to univariate and multivariate analysis. The presented factors age, T and N stage, tumour site, comorbidity, therapy, recurrences and SPTs showed highly significant effects on overall survival in univariate analysis. Sex of the patients did not have a significant effect, while M stage could not be evaluated due to very small numbers.

Among the strongest risk factors for overall survival in multivariate analysis were age at first diagnosis, N stage, and the development of recurrences/metastases or second primary carcinomas. The hazard ratio for overall mortality increased by 50% for each ten additional years of age at first diagnosis. Patients who developed a recurrence after diagnosis were three times more likely to die than patients without recurrences, while the development of a second primary carcinoma doubled the risk of dying.

Tumour stage was a strong risk factor in our study group, with stage T3 and T4 patients having an about doubled risk of dying compared to the patients with lower stages. The increase in mortality risk by lymph node status (N1–N3) was very strong in the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>N (%)</th>
<th>5-Year overall survival (%)</th>
<th>5-Year disease-specific survival (%)</th>
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<td>85.0</td>
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<td>78.6</td>
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<td>1+</td>
<td>57 (9.6)</td>
<td>57.8</td>
<td>82.9</td>
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</tbody>
</table>

Table 1


Discussion

Considering the results of our analysis it becomes apparent that survival after diagnosis of laryngeal cancer depends on a variety of factors, which act jointly. Five-year overall survival in our study population was 66%, which is considerably higher than shown for the whole of Germany (59%) and Europe (55%) between 1995 and 1999 and the survival rates found in a large population-based study from the United States (overall survival: 52%, relative survival: 63%). Generally, comparability of survival rates is difficult, as most studies focusing on survival with laryngeal cancer recruited patients according to specific criteria, rather than selecting them as a population sample.

The most prominent risk factor for mortality in our analysis was the development of local or regional recurrence. The same was true for the development of second primary carcinomas, even if this effect was weaker in multivariate analysis. While the development of SPCs after diagnosis of laryngeal and hypopharyngeal cancer seems to depend upon the age at first diagnosis with cancer, an additional effect of the SPCs on overall survival could be shown in the present regression analysis.

Tumour stage was a strong risk factor in our study group, with stage T3 and T4 patients having an about doubled risk of dying compared to the patients with lower stages. The increase in mortality risk by lymph node status (N1–N3) was very strong in the
time directly after diagnosis and levelled off after the first three years. The effect of the presence of distant metastases (M stage) could not be evaluated in our analysis due to the small number of patients with M1 stage. However, five of the six patients with M1 stage died within the first three years after diagnosis. The proportion of patients with advanced T or N stages, about 40% of our study population, is very similar to the distribution found among the majority of transglottic tumour stage and progression of disease, which could not be captured with the categorization of T and N stage in the regression model. Other studies ended up with similar results concerning the effect of therapy on overall survival, but found differences between therapeutic approaches, when studying the effect on larynx preservation rate or locoregional control.16,19 Additionally, research has shown that the choice of treatment has an effect on the quality of life of patients diagnosed with laryngeal cancer.27–29

Data on disease-specific characteristics, socio-demographic variables of the study population and any events after diagnosis had to be obtained from hospital records. Especially concerning the presence of comorbidities and the disease-specific survival, interpretation of data was difficult, as the completeness of records did not always match our requirements and validity could not be verified. Hence, the five-year disease-specific survival of 83% and the absence of comorbidities in 53% of the patients are likely to be an overestimation. However, as comorbidities are recorded at time of diagnosis, they should present a non-differential bias at the most and therefore should not have led to an overestimation of the real effect or have interfered with the other variables in our analysis.

There is some evidence that smoking and alcohol consumption are important risk factors, not only for the development of disease, but also for survival after diagnosis of laryngeal cancer.4,14,30,31 Data on lifestyle factors were only available for a subset of our study population (159 patients), for whom we performed a sensitivity analysis including pack years smoked and alcohol intake prior to diagnosis. Despite their individual effect, inclusion of these lifestyle factors did not notably change the results described above.

To our knowledge, our study is the first multi centre study in Germany to report results from a comprehensive multivariate analysis concerning survival after diagnosis with laryngeal cancer.16,19 Data on lifestyle factors were only available for a subset of our study population (159 patients), for whom we performed a sensitivity analysis including pack years smoked and alcohol intake prior to diagnosis. Despite their individual effect, inclusion of these lifestyle factors did not notably change the results described above.
Conflict of interest

None declared.

References