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Influence of anemia and BMI on prognosis of laryngeal squamous cell carcinoma: Development of an updated prognostic model

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ABSTRACT

Objective: evaluating the impact of anemia and body mass index (BMI) on survival, and development of a prognostic model for overall survival for patients with laryngeal squamous cell carcinoma (LSCC).
Materials and methods: A retrospective cohort study was performed including all consecutive patients with LSCC diagnosed and treated at the Erasmus Medical Center between January 2006 and December 2013. Patient- and tumor-specific data were collected using data from the Netherlands Comprehensive Cancer Organization and supplemented with data from patient records available in the Erasmus MC. All comorbidities were scored at the time of diagnosis.
Results: in total 788 patients were included. Mean follow-up time was 50 months (SD: ± 30), during which 298 patients (37.8%) died. In both univariate and multivariate analysis BMI and anemia were significant predictors for overall survival. Multivariate analysis was performed using known predictors such as age, TNM-stage and comorbidity (ACE-27). The hazard ratio of anemia was 1.41 (95% CI: 1.05–1.90) and of BMI was 0.97 (95% CI: 0.94–0.99). BMI had an inverse association with overall survival in both univariate and multivariate survival analysis. Updating and validating an existing prognostic model with addition of anemia and BMI enhanced the performance of the prognostic model (C-statistic) from 0.77 (95% CI: 0.74–0.79) to 0.79 (95% CI: 0.77–0.82).
Conclusion: anemia and BMI are predictors of overall survival for LSCC, independent of other known predictors of overall survival. Adding anemia and BMI to an existing prognostic model provides better prediction of overall survival.

Introduction

In the Netherlands, over 38% of all head and neck squamous cell carcinoma (HNSCC) originates from the larynx [1]. Also, laryngeal squamous cell carcinoma (LSCC) has a favorable prognosis compared to HNSCC as a whole [1]. Treatment of LSCC can impair speech, swallowing and breathing, which have a profound impact on the quality of life [2,3]. Prognosis and morbidity of LSCC are therefore significant topics in communication between physicians and their patients.

In the recent past, our research group developed prognostic models to estimate patients' individual prognosis to support decision making [4,5]. In these models, besides cTNM stage and age, comorbidity, scored with the Adult Comorbidity Evaluation 27 (ACE-27], turned out to be an important prognostic factor for overall survival [6,7].

However, more recent studies show that presence of anemia and low Body Mass Index (BMI) also negatively impact patient survival of HNSCC [8,9]. A systematic review on the impact of BMI on survival shows better survival for patients with a BMI above 25.0 [9]. However, other comorbidities (as measured by ACE-27) or weight loss were not addressed in this study. In addition, presence of anemia is known to negatively impact the efficacy of radiotherapy [10], but the effect of anemia on overall survival of patients with HNSCC treated otherwise is presently not known. Furthermore, anemia is not taken into account in comorbidity indexes nor in existing prognostic models.

As prognosis is an important factor during patient counseling, insight in the influence of anemia and BMI amongst other comorbidities on survival of head and neck malignancies is needed. Therefore, the purpose of this study is to report on the impact of anemia and BMI on overall survival of LSCC, independent of other comorbidities. The secondary objective is to determine whether adding anemia and BMI improves the existing prognostic model.

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Methods

This study was approved by the ethics committee of the Erasmus Medical Center (Erasmus MC) (MEC number: MEC-2016-751). Patients with glottic and supraglottic squamous cell carcinoma who were diagnosed and treated at the Erasmus MC between January 1st, 2006 and December 31st, 2013, were included in this retrospective study. Patients were excluded in case of a synchronous primary tumor in the head and neck region, when a patient died before completion of diagnostics or when records were incomplete.

Primary outcome of this study was overall survival and the secondary outcome was Harrell's concordance statistic for internal validation of an updated prognostic model.

Data collection

Tumor- and patient-specific data regarding these patients were obtained from the Netherlands Comprehensive Cancer Organization (NCCO) and merged with corresponding data from the patient records of Erasmus MC. Subsequently, the data were manually checked for each patient using available data from the patient records. Incorrect or missing data was either revised or supplemented by the research staff. A log was kept in which the inclusion of patients was recorded.

Definitions

Both patient- and disease specific data was scored at the time of diagnosis. Comorbidity was scored using the Adult Comorbidity Evaluation-27 (ACE-27). This ACE-27 index consists of 27 different endpoints in 9 organ systems. Severity of comorbidity was classified into four categories: none, slight, moderate and severe (ACE-27 score 0, 1, 2, and 3 respectively) [5,10].

Anemia was defined as hemoglobin levels below 8.5 mmol/L for men and below 7.5 mmol/L for woman, which corresponds to 13.7 and 12.1 g/dL respectively. Length and weight was used to calculate the Body Mass Index (BMI).

Weight loss was defined as the percentage of weight patients lost within 6 months prior to diagnosis of the tumor. It was subdivided in no- to mild weight loss (0–5%), moderate weight loss (5–10%) and severe weight loss (> 10%).

Intoxications were defined as tobacco- and alcohol use. Data on (former) use at the time of diagnosis was collected. If tobacco use had occurred in any time in the past, the total pack years was registered. Marital status was defined as having a partner (either married or having a durable long term relationship), or being either single or widowed. Finally, we recorded if the received therapy was in accordance with standard treatment protocol at the time of diagnosis.

Data on patient follow-up was obtained using the Dutch Civil Registry and data available in the Erasmus MC. Final day of follow-up time for a patient was defined as the final date that the patient was confirmed to be alive. Follow-up ended on the 31st of December 2015, resulting in a minimum follow-up duration of 2 years.

Statistical analysis

The data was analyzed using IBM SPSS (version 21.0) and R (version 3.4.0) statistical software. Descriptive statistics were performed for all variables and, if applicable, the assumption of a Gaussian distribution was verified. Associations between the collected covariates were studied using the Pearson Chi-square test for categorical data and Student *t*-test or Wilcoxon rank test for continuous data. During univariate analysis, BMI was analyzed as both a continuous and categorical variable. Univariate analysis of overall survival was performed on all available variables by applying Kaplan-Meier analysis (log-rank test) and the Cox proportional hazard regression model was used to calculate the univariate hazard ratios.

Table 1
Demographics of the total patient population (n = 788).

Variables		No. of patients (%)	Missing (%)
Gender	Men	651 (82.6)	–
	Woman	137 (17.4)	
Mean age at time of diagnosis (years)		66 ± 10	–
Tumor localization	Glottis	530 (67.3)	–
	Supraglottis	258 (32.7)	
T-stage	1	19 (2.4)	–
	1A	260 (33.0)	
	1B	52 (6.6)	
	2	183 (23.2)	
	3	192 (24.4)	
	4A	82 (10.4)	
N-stage	0	661 (83.9)	–
	1	55 (7.0)	
	2	68 (8.6)	
	3	4 (0.5)	
M-stage	0	786 (99.7)	–
	1	2 (0.3)	
Treatment given	Yes	765 (97.1)	–
	No	23 (2.9)	
Treated according to protocol	Yes	698 (88.6)	–
	No	90 (11.4)	
Smoking	Current	477 (60.5)	5 (0.6)
	Former	266 (33.8)	
	Non-smoker	40 (5.1)	
Mean pack years		41 ± 22	183 (23.2)
Alcohol	Current	545 (69.2)	6 (0.8)
	Former	178 (22.6)	
	Non-drinker	59 (7.5)	
ACE-27 total score	0 (none)	224 (28.4)	–
	1 (mild)	273 (34.6)	
	2 (moderate)	204 (25.9)	
	3 (severe)	87 (11.0)	
Marital status	With partner	542 (68.8)	35 (4.4)
	No partner	211 (26.8)	
Body Mass Index	< 18.5	28 (3.6)	65 (8.1)
	≥18.5 and < 25	294 (37.3)	
	≥25 and < 30	275 (34.9)	
	≥30 and < 38	106 (13.5)	
	≥38	21 (2.7)	
Weight loss	< 5%	526 (66.8)	158 (20.0)
	≥5% and < 10%	56 (7.1)	
	≥10%	48 (6.1)	
Anemia	Yes	121 (15.4)	55 (7.0)
	No	612 (77.7)	

Some data were missing for the variables anemia, BMI, weight loss and variables related to intoxications, see Table 1. After analyzing patterns of our missing data, data were considered missing at random (MAR) [11]. Since the MAR assumption was plausible, we found multiple imputation (MI) to be the best way to handle our missing data. We performed MI using the Markov Chain Monte Carlo (MCMC) function in SPSS and used 5 iterations to account for possible simulation errors. Multivariate statistical analysis was performed by using the pooled data of all five iterations in a Cox proportional hazard regression model. Multiplicative interaction terms were taken into account. Covariate selection was performed using all available variables and subsequently eliminating variables using backward stepwise elimination until all variables left had a p-value below 0.10. Continuous variables used were age at time of diagnosis, pack years and BMI. All other variables used were categorical. For both univariate and multivariate analysis, a p-value lower than 0.05 was considered significant.

After performing multivariate Cox proportional hazard regression analysis of overall survival, we created a prognostic model using variables previously defined as prognosticators by our study group (Datema et al. in 2010 and van der Schroeff in 2012 [4,5]). The following