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A predictive model for recurrence in patients with glottic cancer implemented in a mobile application for Android

Ana Gabriela Jover-Esplá[a,1], Antonio Palazón-Bru[b,1,*], David Manuel Folgado-de la Rosa[a], Guillermo Severá-Ferrándiz[a], Manuela Sancho-Mestre[a], Joaquín de Juan-Herrero[c], Vicente Francisco Gil-Guillén[b]

[a] Department of Otolaryngology, General University Hospital of Alicante, Alicante, Alicante, Spain
[b] Department of Clinical Medicine, Miguel Hernández University, San Juan de Alicante, Alicante, Spain
[c] Department of Biotechnology, University of Alicante, San Vicente del Raspeig, Alicante, Spain

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ABSTRACT

Objectives: The existing predictive models of laryngeal cancer recurrence present limitations for clinical practice. Therefore, we constructed, internally validated and implemented in a mobile application (Android) a new model based on a points system taking into account the internationally recommended statistical methodology.

Materials and methods: This longitudinal prospective study included 189 patients with glottic cancer in 2004–2016 in a Spanish region. The main variable was time-to-recurrence, and its potential predictors were: age, gender, TNM classification, stage, smoking, alcohol consumption, and histology. A points system was developed to predict five-year risk of recurrence based on a Cox model. This was validated internally by bootstrapping, determining discrimination (C-statistics) and calibration (smooth curves).

Results: A total of 77 patients presented recurrence (40.7%) in a mean follow-up period of 3.4 ± 3.0 years. The factors in the model were: age, lymph node stage, alcohol consumption and stage. Discrimination and calibration were satisfactory.

Conclusion: A points system was developed to obtain the probability of recurrence of laryngeal glottic cancer in five years, using five clinical variables. Our system should be validated externally in other geographical areas.

Introduction

Cancer of the larynx is one of the most frequent cancers of the head and neck [1–3]. Its incidence adjusted for age is estimated in the United States at 5.4 cases per 100,000 inhabitants in men and 1.1 cases per 100,000 inhabitants in women [4]. These figures are slightly higher in men in Europe, where there are 8.8 incident cases per 100,000 inhabitants, while in women the figure is slightly lower, at 0.8 cases per 100,000 inhabitants [5,6]. Survival at five years is approximately 60% in both the United States and Europe [4,7]. Regarding recurrence, cancer of the larynx has a higher risk of re-appearance in the first three years after treatment [8], and for glottic cancer its incidence at five years is between 12 and 49%, depending on the stage [9,10]. After this window of time, recurrences are infrequent and often represent new primary malignancies [8]. For the standard treatment of this cancer, the therapeutic options are surgery, radiotherapy and chemotherapy [11].

In cancer, as in other types of diseases, prediction models are available to determine the risk a patient has of developing an adverse event (mortality and recurrence) based on the clinical situation of the patient, that is, from his or her risk factors for this event [12]. In addition, a prediction model should be easy to apply in clinical practice (immediate calculation of risk), have an EPV greater than 10 (otherwise the model would have overfitting), study the functional form of the continuous predictors (not a linear analysis or categorizations), perform multiple imputations with the missing data (not only complete cases), select the predictors considering the goodness of fit of the model (not by bivariate or convenience analysis) and perform validation by bootstrapping (resampling) taking into account both discrimination and calibration [13,14].

Regarding prediction models for recurrence of laryngeal cancer published in the scientific literature (Table 1) [15,16], only two studies were found, neither of which fulfilled all the requirements for a

Abbreviations: EPV, events-per-variable; CI, confidence interval

* Corresponding author at: Department of Clinical Medicine, Miguel Hernández University, Carretera de Valencia-Alicante S/N, 03550 San Juan de Alicante, Alicante, Spain.
E-mail address: apalazon@umh.es (A. Palazón-Bru).

[1] Equal contribution.

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Table 1
Published predictive models for recurrence in laryngeal cancer patients.

Reference	Patients	Time (years)	Variables	Applicability of the model	EPV ≥ 10	Continuous predictors	Missing data	Selection of predictors	Validation
Egelmeer et al., 2011 [15]	LCP treated with RT	2 and 5	Age, hemoglobin, T, N, gender, location, RT dose	Nomogram and mobile application	Yes	Linear analysis without explanation	Multiple imputations	Stepwise method based on a statistical test (unknown)	C-statistics and bootstrapping, but no calibration
Yang et al., 2016 [16]	LCP	4.6 (mean)	N and CISD2 expression	Scoring system based on risk groups	Yes	Categorization	Complete cases	Significant predictors in the bivariate analysis	C-statistics and bootstrapping, but no calibration

Abbreviations: CISD2, CDGSH iron sulfur domain2; EPV, events-per-variable; LCP, Laryngeal carcinoma patients; RT, radiotherapy.

Table 2
Descriptive characteristics and adjusted hazard ratios for predicting recurrence in patients with laryngeal carcinoma.

Variable	Total n = 189 n(%)/x ± s	Adjusted HR[b] (95% CI)	p-value
Recurrence	77(40.7)	N/A	N/A
Age (years)[a]	62.9 ± 10.9	0.16(0.03–0.79)[c]	0.024
Age^2 (years^2)	N/A	1.16(1.02–1.32)[c]	0.023
Male gender	182(96.3)	1.94(0.46–8.14)	0.363
T[a]:			
1a	65(34.4)	N/M	N/M
1b	27(14.3)		
2	49(25.9)		
3	34(18.0)		
4	14(7.4)		
N[a]:			
0	176(93.1)	1.98(1.27–3.10)	0.003
1	7(3.7)		
2	5(2.6)		
3	1(0.5)		
Stage[a]:			
I	92(48.6)	11.81(2.96–47.18)	< 0.001
II	48(25.4)		
III	35(18.5)		
IV	14(7.4)		
Stage^2	N/A	0.58(0.42–0.80)	< 0.001
Smoking[a]:			
No	9(4.8)	N/M	N/M
Former	142(75.1)		
Yes	38(20.1)		
Alcohol consumption[a]:			
No	58(30.7)	1.68(1.12–2.51)	0.013
Former	107(56.6)		
Yes	24(12.7)		
Epidermoid carcinoma	179(94.7)	N/M	N/M
Microsurgery	152(80.4)	N/M	N/M
Chemotherapy	14(7.4)	N/M	N/M
Radiotherapy	27(14.3)	N/M	N/M

Abbreviations: CI, confidence interval; HR, hazard ratio; n(%), absolute frequency (relative frequency); N/A, not applicable; N/M, not in the multivariate model; x ± s, mean ± standard deviation.

[a] Analyzed as quantitative variables [T (*1a* → 0, *1b* → 1, *2* → 3, *3* → 4 and *4* → 5), N (*0* → 0, *1* → 1, *2* → 2 and *3* → 3), stage (*I* → 1, *II* → 2, *III* → 3 and *IV* → 4), smoking and alcohol consumption (*No* → 0, *Former* → 1 and *Yes* → 2)]. We determined whether the variables had a non-linear association with the recurrence risk (p-values for the score test): quadratic [age, 0.009; T, 0.151; N, 0.294; stage, < 0.001; smoking, 0.454; and alcohol consumption, 0.905], cubic [age, 0.893; and stage, 0.129].

[b] The variables in the multivariate model are those with HR.

[c] Per 10 years. Goodness-of-fit of the model: $\chi^2 = 40.1$, $p < 0.001$, C-statistic = 0.68 (standard error 0.034). Number of tested combinations: 5811.

prediction model to be considered valid for use in clinical practice [13,14]. Consequently, we decided to conduct a study to construct and internally validate a predictive model of recurrence in patients with glottic cancer. An additional aim was to integrate the model into a points system and a mobile application for Android with which the clinician could immediately calculate the risk and thereby improve decision-making in patients with glottic cancer.

Material and methods

Study population

The study population comprised patients diagnosed with glottic cancer in the Health Department of Alicante, which covers a total of 268,425 inhabitants (figures for 2015). The Department is made up of 16 primary care centers, two specialized care centers and a single hospital. It is located in the province of Alicante (southeast of Spain) and, as in the rest of Spain, the health system is free and universal, including patients with this type of cancer.