Letter to the editor

A preliminary Bayesian network model to identify factors associated with treatment outcome in T2 and T3 laryngeal carcinoma

Introduction

The outcome of early stage (T1-2) laryngeal squamous cell carcinoma (LSCC) is generally good. However, the case of T2 LSCC specifically, is exceptional. Despite it being an early stage tumor by definition, some studies have shown it to have a prognosis comparable to a locally advanced T3 LSCC [2,5,6]. Factors underlying this finding remain elusive, although several factors, including faulty T classification (i.e. T3 tumors classified as T2) and subsequent undertreatment have been suggested.

Materials, methods and results

We utilized a nationwide, comprehensive, and earlier published cohort of LSCC patients diagnosed and treated at the five Finnish university hospitals during 2001–2005, published earlier [5,6]. Patient demographic data, such as age, gender, previous cancers, LSCC characteristics and treatment as well as follow-up data including recurrences and causes of death were gathered. All patients had a minimum follow-up of five years or until death. The data were first narrowed down to include only patients with curative treatment intent (n = 340). We chose to analyze T2 and T3 LSCCs (n = 174) for which the optimal treatment is currently undecided according to the literature.

The aim of this study was to assess the direct causal effect of treatment decision (surgery vs. radiotherapy/chemoradiotherapy) on the outcome (*locoregional failure*) in patients having T2 or T3 LSCC. We did this assessment by using a Bayesian network model derived from observational data. The dataset consisted of 18 pre-treatment variables from 174 patients with T2 or T3 LSCC.

We performed the statistical analysis by using the Bayesialab 8.0 tool (Bayesia, USA). The visual form of a Bayesian network uses DAG (Directed Acyclic Graph), from which direct and indirect effects, common causes and effects can be discovered and mathematically expressed. A DAG consists of nodes presenting variables, and arcs or bars presenting associations between them. The network can be fixed to one or several variable values to demonstrate their effect on the target variable. The outcome variable, *locoregional failure (meaning cancer recurrence at the primary site or in the neck)*, was set to be the target variable. The research data contained 2% missing data, whose type was missing at random. We imputed the missing values by using an Expectation-Maximization (EM) algorithm.

The learning algorithm was perturbed Augmented Naive Bayes. The result was a non-causal augmented naïve Bayes network model with 16 independent variables, one dependent variable (*locoregional failure*) set as the target variable, and the variable *primary treatment* which was an intervention variable (Fig. 1.). We used all independent values in the model to have all possible confounders to be present. The variables with

their values, definitions, and discretizations are presented in Table 1. The predictive performance of the model as Area Under ROC Curve (AUC) was 77.3%.

Direct effects are based on Jouffe's proprietary Likelihood Matching Algorithm, which allowed us to estimate the independent variables' causal effect on the target while holding the others constant [3]. These direct effects are presented in Table 1.

Following the disjunctive confounder criterions by vanderWeele and Shpitser [9], we examined the effect of intervention (surgery vs. radiotherapy/chemoradiotherapy) separately in T2 and T3 LSCC fixing marginal distributions of all other independent variables except *primary treatment* and *T class*. We fixed manually these two variables to different combinations.

Results

In patients with T2 LSCC, locoregional failure was seen in 28.6% of the patients after surgery, and in 37.2% of the patients after radiotherapy/chemoradiotherapy. The corresponding figures in patients with T3 LSCC were 26.4% after surgery and 34.1% after radiotherapy/chemoradiotherapy. The difference between these treatment approaches in all patients was 8.9 percentage points favoring surgical treatment, as indicated in direct effect on target for the outcome variable (Table 1).

Discussion

The current series represents the comprehensive data on all T2-3 LSCC patients treated at the five Finnish university hospitals during a five-year period. Because these neoplasms are treated almost exclusively at the university hospitals in Finland, it may be regarded as a nationwide cohort.

To our knowledge, this is the first study utilizing the Bayesian network model to analyse factors predictive of locoregional failure in LSCC in a such cohort. In our analysis, we found that for T2-3 LSCC, T class was not a major predictive factor in determining locoregional control. Furthermore, surgical treatment appears to be associated with a significantly better locoregional control.

Several retrospective institutional series have been published regarding treatment outcome in T2-3 LSCC [7,4,8]. Similar outcomes have been reported for various approaches including RT, CRT, open partial resection, TLS and total laryngectomy. However, as institutional series often focus on certain treatment approaches, selection bias plays a crucial role.

In lack of randomized controlled trials, several registry studies utilizing the Surveillance, Epidemiology and End Results (SEER) registry data have been published to support our observation. Zhan et al. [10] observed better cancer-specific survival for T1-2N0 LSCC patients
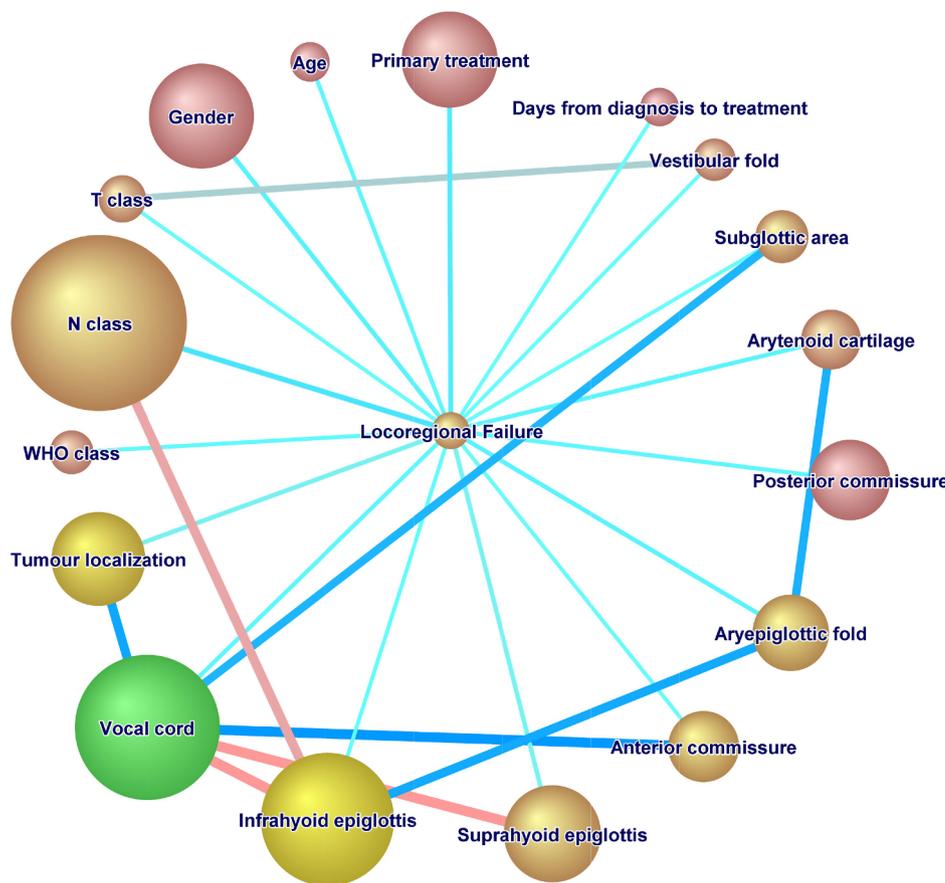
Fig. 1. An augmented naïve Bayes network model of factors associated the outcome variable *locoregional failure*. Size of nodes represents direct effect on target node, color indicates node force (green highest, red lowest, yellow in-between). Lines between the nodes indicate Pearson's correlation (blue color is positive, red color negative). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Variables, their distributions and direct effects on the target variable.

Variable	Explanation	Values n (%)	Direct effect to target
Outcome: Locoregional failure	The recurrence of cancer in the larynx or in the regional lymph nodes of the neck	no = 112 (64.4%); yes = 62 (35.6%)	–
Intervention: Primary treatment	The primary treatment of the tumor. Surgical = primary treatment includes surgery; radiotherapy = primary treatment doesn't include surgery	surgical = 56 (32.3%); radiotherapy = 118 (57.8%)	0.089
Age	Patient's age on the day of histological laryngeal carcinoma diagnosis	age ≤ 64 yrs = 89 (51.2%); age > 64 yrs = 85 (48.9%)	0.002
Gender	Patient's gender	male = 159 (91.4%); female = 15 (8.6%)	0.102
T class	TNM classification T class (UICC 7th edition)	T2 = 91 (52.3%); T3 = 83 (47.7%)	−0.014
N class	TNM classification N class (UICC 7th edition)	N0 = 135 (77.6%); N+ = 39 (22.4%)	0.211
WHO performance status	WHO performance status classification	0 = 30 (17.2%); 1 = 118 (67.8%); 2 = 5 (2.9%); 3 = 6 (3.4%); 4 = 2 (1.1%); not known = 13 (7.5%)	0.008
Tumour localization	The main localization of the tumor in the larynx	glottic = 113 (64.9%); supraglottic = 55 (31.6%); subglottic = 3 (1.7%); undefinable = 3 (1.7%)	−0.085
Vocal cord	Tumor growth in the vocal cords	yes = 134 (77.0%); no = 38 (21.8%); missing = 2 (1.1%)	0.164
Infrahyoid epiglottis	Tumor growth in the part of epiglottis situated below the level of the hyoid bone	yes = 35 (20.1%); no = 133 (76.4%); missing = 6 (3.4%)	0.145
Suprahyoid epiglottis	Tumor growth in the part of epiglottis situated above the level of the hyoid bone	yes = 20 (11.5%); no = 151 (86.8%); missing = 3 (9.2%)	−0.090
Anterior commissure	Tumor growth in the anterior commissure of the vocal cords	yes = 91 (52.5%); no = 72 (41.4%); missing = 11 (6.3%)	−0.050
Aryepiglottic fold	Tumor growth in the aryepiglottic fold	yes = 34 (19.5%); no = 132 (75.9%); missing = 8 (4.6%)	0.058
Posterior commissure	Tumor growth between the posterior ends of the vocal cords	yes = 14 (8.0%); no = 144 (82.4%); missing = 16 (9.2%)	0.065
Arytenoid cartilage	Tumor growth in the arytenoid cartilage	yes = 36 (20.7%); no = 129 (74.1%); missing = 9 (5.2%)	0.033
Subglottic area	Tumor growth below the level of the vocal cords	yes = 64 (36.8%); no = 104 (59.8%); missing = 6 (3.4%)	−0.022
Vestibular fold	Tumor growth in the false vocal cords (vestibular folds)	yes = 109 (62.6%); no = 59 (33.9%); missing = 6 (3.4%)	−0.006
Days from diagnosis to treatment	The time in days between the day of cancer diagnosis and the first day of primary treatment (the day of surgery or the day of the first radiotherapy fraction)	delay ≤ 40 days = 107 (61.5%); delay 41–80 days = 53 (30.5%); delay > 60 days = 6 (4.1%); missing = 8 (4.6%)	−0.001

treated with surgery compared with those treated with radiotherapy. Similarly, Al-Gilani et al. [1] reported improved overall survival for T3 LSCC patients who underwent surgery compared with non-surgical treatment methods.

Our study suffers a few weaknesses. For a predictive model, our cohort is quite small. The model was intentionally overfit to cover all confounders, and the model's predictive performance is therefore limited. Use of disjunctive confounder criterion requires, besides the use of pre-treatment variables only, that no unmeasured confounder has a direct effect on treatment selection, outcome, or both. Genetic and toxic factors, biology of tumor cells, as well as tumor growth speed are examples of potential unmeasured confounders. We consider them to be mostly parent variables to the presently measured confounders in DAG, and therefore there is no need to control them. However, we cannot conclusively rule out a potential role of an unmeasured confounder.

We consider the current method promising in measuring effectiveness using observational data and future research is warranted also in other contexts.

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Declaration of Competing Interest

None declared.

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