Radiotherapy and Oncology 100 (2011) 108–115

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Laryngeal carcinoma

Development and validation of a nomogram for prediction of survival and local control in laryngeal carcinoma patients treated with radiotherapy alone: A cohort study based on 994 patients

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ARTICLE INFO

Article history:
Received 20 May 2010
Received in revised form 11 June 2011
Accepted 11 June 2011
Available online 23 July 2011

Keywords:
Prediction
Nomogram
Laryngeal carcinoma
Radiotherapy

ABSTRACT

Introduction: To advise laryngeal carcinoma patients on the most appropriate form of treatment, a tool to predict survival and local control is needed.

Materials and methods: We performed a population-based cohort study on 994 laryngeal carcinoma patients, treated with RT from 1977 until 2008. Two nomograms were developed and validated. Performance of the models is expressed as the Area Under the Curve (AUC).

Results: Unfavorable prognostic factors for overall survival were low hemoglobin level, male sex, high T-status, nodal involvement, older age, lower EQD_{2T} (total radiation dose corrected for fraction dose and overall treatment time), and non-glottic tumor. All factors except tumor location were prognostic for local control. The AUCs were 0.73 for overall survival and 0.67 for local control. External validation of the survival model yielded AUCs of 0.68, 0.74, 0.76 and 0.71 for the Leuven ($n = 109$), the VU Amsterdam ($n = 178$), the Manchester ($n = 403$) and the NKI cohort ($n = 205$), respectively, while the validation procedure for the local control model resulted in AUCs of 0.70, 0.71, 0.72 and 0.62. The resulting nomograms were made available on the website www.predictcancer.org.

Conclusions: For patients with a laryngeal carcinoma treated with RT alone, we have developed visual, easy-to-use nomograms for the prediction of overall survival and primary local control. These models have been successfully validated in four external centers.

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In laryngeal carcinoma patients, treatment decisions are usually made by a multidisciplinary team based on guidelines. Patient- and tumor-related factors that are taken into consideration in this decision-making process are the TNM-stage, the functionality of the larynx, and the general condition of the patient (WHO performance status or Karnofski score) [1]. Though new developments are appearing in therapy, the primary treatment for early stage laryngeal carcinomas is radiotherapy (RT), laser surgery, or limited surgery. RT, open surgery (with or without postoperative radiotherapy), or a combination with systemic therapy are the current treatment options for more advanced cancers. Guidelines are used in the treatment decision process, and assessment of prognosis and preserved function are also taken into consideration. Doctors often predict the prognosis fairly poorly [2–4], and so it is questionable whether this has an additional value.

Besides the widely used predictors TNM-stage and general condition, other clinical factors are investigated for their prognostic and predictive value. An example of this is the pretreatment hemoglobin level. It is well established that patients with lower pretreatment hemoglobin levels have worse overall survival and local control than patients with normal hemoglobin levels [5–8]. Other prognostic factors that are investigated are sex and age [9–12], with indications that women and younger patients have a better prognosis than men and elderly people.

Thus, to assist the doctor in deciding on the most appropriate treatment form, a tool to predict survival and local control is needed [13]. We, therefore, aimed to investigate which clinical

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0167-8140
doi:10.1016/j.radonc.2011.06.023

and imaging factors are prognostic for the laryngeal carcinoma patients we have treated since 1977 with radiotherapy alone. We hypothesized that it is possible to develop nomograms for the prediction of survival and local control of laryngeal carcinoma patients treated with radiotherapy alone performing better than a nomogram based on TNM classification alone. We tried to validate these models with four external datasets from the University Hospital of Leuven (Belgium), the VU University Medical Center of Amsterdam (The Netherlands), the Christie Hospital, Manchester (UK) and the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam (The Netherlands). These models will allow for improvement of the information given to patients about their prognosis. In the long term the models will allow for tailoring of the treatment to individual patients (e.g., for the choice surgery-radiotherapy), when combined with models predicting outcome after other therapies.

Materials and methods

Patient population

The patient and treatment characteristics of 1051 consecutively treated patients with a squamous cell laryngeal carcinoma were recorded in a database from January 1977 to December 2008. All patients were treated with radiotherapy alone at the MAASTRO Clinic. Patients with a carcinoma in situ or distant metastasis at presentation (seven patients) were excluded from the study. Other exclusion criteria were treatment with Cobalt radiation (nine patients) and the use of chemotherapy (41 patients, three of whom had concurrent chemoradiation; 24 neoadjuvant chemotherapy; and 14 of whom were treated according to the ARCON-trial with carbogen and nicotinamide). A total of 994 patients were included in our cohort study. 528 (53.1%) of these patients had a T1 tumor, 264 (26.6%) a T2, 131 (13.2%) a T3, and 71 patients (7.1%) had a T4 tumor. Most of the patients (894, 89.9%) did not have positive lymph nodes. 45 patients (4.5%) had a N1 status, 42 (4.2%) a N2, and eleven (1.1%) patients had a N3 status. The trial is registered on ClinicalTrials.gov with registration number 2263.

Diagnosis and staging were always undertaken according to the Dutch guidelines, including endoscopia under anesthesia and biopsy of the tumor. Also recommended in the latest Dutch guidelines are a computed tomography (CT) scan of the head and neck, a chest X-ray, ultrasonography of the neck (if necessary with punction), and blood tests.

Radiotherapy treatment

All patients were treated at the MAASTRO Clinic with a continuous course of radiotherapy delivered by a 4–6 MV linear accelerator after either a traditional simulation (patients before 1996) or a CT simulation (patients treated from 1996 onwards). During simulation and treatment, all patients were immobilized by a thermoplastic mask. Sixteen patients received a palliative radiation dose of less than 60 Gy. Patients were treated in line with the state-of-the-art practices. T1–2 glottic tumors and T1 supraglottic tumors were treated with 60–66 Gy in fractions of 2–2.40 Gy, and other tumors were treated with 70 Gy over seven weeks in daily fractions of 2 Gy, and after 2000 with 68 Gy, the first 23 fractions 2 Gy daily, and the last 11 fractions twice daily in fractions of 2 Gy.

To correct for differences in radiation scheme, the biological equivalent dose in fractions of 2 Gy and corrected for overall treatment time was calculated, using the following formula:

$$EQD_{2T} = D \times ((d + \alpha/\beta)/(2 + \alpha/\beta)) - \gamma(T - T_k)$$

D is the total radiation dose, d is the fraction dose, α/β is 10 Gy, T is the overall treatment time, accelerated repopulation kick-off time (T_k) is 28 days, and loss in dose due to repopulation (γ) is 0.6 Gy/d [14]. As EQD_{2T} is not easily calculated in daily clinical practice, EQD_{2T} values for the most common radiation schemes are given in Table 1. If the overall treatment time for a patient differs from the anticipated value, it is possible to recalculate EQD_{2T} after completing the treatment and thus to obtain an adjusted prediction.

The follow-up for all patients consisted of regular visits to the head and neck oncology department over five years after the curative radiotherapy treatment. These visits took place every second month for the first six months, then every third month for two years, every fourth month during the third year, then twice yearly until the end of follow-up (five years). At every visit, the medical history was taken and physical examination carried out. Thereafter, information was gathered from the general practitioner and the Dutch Registry of Births, Deaths, and Marriages (“Gemeentelijke Basis Administratie”, or “GBA”).

PET–CT analysis

Features of the PET–CT scans were analyzed for a subgroup of patients. ^{18F}FDG-PET-scans were available since 2004, and 115 of these scans were available and assessable. Contoured tumor volumes were available for 124 patients, mostly patients with a T3 or T4 tumor. The gross tumor volume (GTV) was measured as contoured in our radiotherapy treatment planning system by a radiation oncologist (Computerized Medical Systems, INC, St. Louis, MO). Several features were extracted from the pretreatment PET-scans. A circle was drawn around the region of interest c.q. the larynx. Within this region of interest the maximal Standard Uptake Value (SUV_{max}) is given. Dedicated software (TrueD; Siemens Medical, Erlangen, Germany) was used to calculate SUV_{max} per patient. Furthermore, the SUV of the deltoid muscle was calculated. The SUV_{max} of the tumor and the SUV of the background was used to calculate a source-to-background ratio according to the following formula:

$$78.13 * (SUV_{tumor}/SUV_{background})^{(-0.2988)}$$

The output of the formula is expressed as a percentage, which was used as the contouring percentage to determine the metabolic volume, i.e., the volume of the tumor that has higher FDG uptake than the contouring percentage of the SUV_{max}.

Statistical analysis

The prognostic factors tested were age at start of radiotherapy, sex, tumor location (glottic or non-glottic), pretreatment hemoglobin level, EQD_{2T}, T-stage, and N-stage (N0 or N+). Age, hemoglobin level, and EQD_{2T} were analyzed as continuous values. The endpoints of the study were overall survival and local control, both calculated from the start of radiotherapy. Patients were followed for at least 1 month up to a maximum of 72 months. Failure of local control was defined as persistent or recurrent local disease after the start of radiotherapy (i.e., the first relapse after therapy).

The Kaplan–Meier method was used for univariate survival analysis. For overall survival, data were considered right-censored if patients were still alive at the time of evaluation. For local control, data were considered right-censored if patients did not have recurrent local disease at the time of evaluation. Groups were compared using the log rank test. The Cox proportional hazards model was applied to perform a multivariate analysis. The proportional hazards assumption was tested by adding time-dependent covariates to the model. In addition, linearity of the variables was assessed. Missing values were imputed using predictive mean matching. A stepwise backward method was used to select a relevant set of variables ($p < 0.2$). Hazard ratios and 95% confidence intervals were reported. Performance of the models was expressed

Table 1
EQD_{2T} of the most common radiotherapy schemes.

Radiotherapy scheme	EQD_{2T}
60 Gy in fractions of 2 Gy in 6 weeks	$60 \times ((2 + 10)/(2 + 10)) - 0.6\ (40 - 28) = 52.8$ Gy
66 Gy in fraction of 2 Gy in 6.5 weeks	$66 \times ((2 + 10)/(2 + 10)) - 0.6\ (45 - 28) = 55.8$ Gy
68 Gy, 23 fractions of 2 Gy once daily, and 11 fractions of 2 Gy twice daily, in 6 weeks	$68 \times ((2 + 10)/(2 + 10)) - 0.6\ (39 - 28) = 61.4$ Gy
70 Gy in fractions of 2 Gy in 7 weeks	$70 \times ((2 + 10)/(2 + 10)) - 0.6\ (47 - 28) = 58.6$ Gy
55 Gy in fractions of 2.2 Gy in 5 weeks	$55 \times ((2.2 + 10)/(2 + 10)) - 0.6\ (33 - 28) = 53.9$ Gy

as the C-statistic (Harrell's C), which is comparable to the Area Under the Curve (AUC). The maximum value of the C-statistic is 1.0; indicating a perfect prediction model. A value of 0.5 indicates that 50% of the patients are correctly classified (i.e., as good as chance). Bootstrapping techniques were used to validate the models; that is, to adjust the estimated model performance for over-optimism or overfitting. The results of the multivariate analysis were used to develop a nomogram. These nomograms will be, after publication, publicly available on the website www.predictcancer.org. The MAASTRO cohort was split into four subgroups according to quartiles of the risk score. To assess for differences in survival of the subgroups, Kaplan–Meier curves were made. In addition, the performance of the multivariate model was assessed using four external validation sets [15]. Analyses were performed using SPPS for Windows (version 17.0; SPSS Inc., Chicago) and Matlab 7.11.0 (The MathWorks Inc., Natick, MA, USA).

Validation datasets

Patient characteristics of the validation cohorts are shown in Table 2. The validation cohort of Leuven consisted of 109 laryngeal carcinoma patients, treated with radiotherapy alone between March 2000 and January 2006. 45 of these patients (40.9%) had a T1 tumor, and 83 patients (75.5%) did not have nodal involvement. None of the patients received chemotherapy. Two thirds of the patients received 2 Gy fraction until a total dose of 66–72 Gy. Most other patients were treated with 25 fraction of 2.2 Gy, to reach a total dose of 55 Gy.

Table 2
Patient characteristics.

	MAASTRO cohort Number (%)	Leuven cohort Number (%)	VU Amsterdam cohort Number (%)	NKI/AVL Amsterdam cohort Number (%)	Manchester cohort Number (%)
Age					
18–60 years	360 (36.2)	40 (36.7)	62 (34.8)	75 (36.5)	154 (38.2)
>60 years	634 (63.8)	69 (63.3)	116(65.2)	130 (63.5)	249 (61.8)
Gender					
Male	883 (88.8)	99 (90.8)	154 (86.5)	162 (79.1)	357 (88.6)
Female	111 (11.2)	10 (9.2)	24 (13.5)	43 (20.9)	46 (11.4)
T-classification					
T1	528 (53.1)	45 (41.3)	67 (37.6)	86 (41.9)	252 (62.5)
T2	264 (26.6)	30 (27.5)	91 (51.1)	119 (58.1)	124 (30.8)
T3	131 (13.2)	24 (22.0)	16 (9.0)	0 (0.0)	27(6.7)
T4	71 (7.1)	10 (9.2)	4 (2.2)	0 (0.0)	0 (0.0)
N-classification					
N0	894 (89.9)	82 (75.2)	165 (92.7)	184 (89.8)	398 (98.8)
N1	45 (4.5)	6 (5.5)	5 (2.8)	6 (2.9)	1 (0.2)
N2	42 (4.2)	18 (16.5)	6 (3.4)	11 (5.4)	3 (0.7)
N3	11 (1.1)	3 (2.8)	0 (0)	4 (1.9)	1 (0.2)
Missing	2 (0.2)	0 (0)	2 (1.1)	0 (0.0)	0 (0.0)
Location tumor					
Glottic	729 (73.3)	64 (58.7)	127 (71.3)	149 (72.7)	403 (100.0)
Supraglottic	245 (24.6)	39 (35.8)	43 (24.2)	56 (27.3)	0 (0.0)
Subglottic	13 (1.3)		2 (1.1)		
Transglottic	7 (0.7)		6 (3.4)		
Other		6 (5.5)			0 (0.0)
Hemoglobin level					
Low[a]	168 (16.9)	20 (18.3)	44 (24.7)	35 (17.1)	90 (22.3)
Normal-high	667 (67.1)	46 (42.2)	123 (69.1)	145 (70.8)	255 (63.3)
Missing	159 (16.0)	43 (39.4)	11 (6.2)	25 (12.1)	58 (14.4)
Total radiation dose					
<60 Gy	16 (1.6)	45 (41.3)	1 (0.6)	2 (0.9)	402 (99.8)
60–66 Gy	437 (44.0)	12 (11.0)	69 (38.8)	94 (45.9)	1 (0.2)
>66 Gy	541 (54.4)	52 (47.7)	108 (60.7)	109 (53.2)	0 (0.0)
Fraction dose					
1.6–2.0	677 (68.1)	65 (59.6)	116 (65.2)	0 (0.0)	1 (0.2)
>2.0	317 (31.9)	44 (40.4)	62 (34.8)	205 (100)	402 (99.8)
Overall treatment time					
<40 days	321 (32.3)	43 (39.4)	164 (92.1)	162 (79.1)	401 (99.5)
40–50 days	595 (59.9)	41 (37.6)	11 (6.2)	38 (18.5)	2 (0.5)
>50 days	78 (7.8)	25 (22.9)	3 (1.7)	5 (2.4)	0 (0.0)

[a] Male < 8.5 mmol/L, female < 7.5 mmol/L.

The VU Amsterdam cohort consists of 178 patients, which were treated between December 2001 and January 2007. 67 (37.6%) had a T1 tumor and 165 patients (92.7%) were N0. 97 patients were treated with two lateral fields and 19 patients with an IMRT technique. All patients were treated with radiotherapy alone, with most patients treated with 2 Gy fraction, until 68–70 Gy or 60 Gy in 2.5 Gy fractions.

The NKI/AVL Amsterdam cohort consisted of 205 patients with early larynx cancer (T1 tumors in 42% of cases, T2 tumors in 58% of cases) treated with primary radiation treatment between March of 2000 and July 2008. 184 patients (89.8%) were N0 at presentation. Patients with T1N0 glottic cancer were treated with 2 lateral opposing beams to the larynx only. The standard fractionation scheme for these patients was 25 fractions of 2.4 Gy to a total dose of 60 Gy in 5 weeks. Patients with T2 glottic cancers or with supraglottic cancer received radiation treatment to the larynx including prophylactic neck irradiation. The fractionation schedule for this latter group was 35 fractions of 2 Gy to a total dose of 70 Gy in 6 weeks, according to the DAHANCA schedule [16]. None of the patients received chemotherapy.

The Manchester cohort consists of 403 patients, which were treated between January 1998 and January 2005. All these patients had a glottic tumor and most of these tumors were small (252 (62.05%) T1 tumors and 124 (30.8%) T2 tumors). All but four patients (1.2%) were N0. 189 patients received radiation through two lateral opposing fields and 240 patients were treated with an anterior oblique technique. The majority of patients with treated with 50–55 Gy, in 16 fractions (3.1–3.4 Gy per fraction).

Results

MAASTRO cohort

Analyses were carried out for 994 patients of the MAASTRO cohort. The majority of the patients were male (88.8%) and the median age at the start of radiotherapy was 65.0 years (range 31–91 years). Pretreatment hemoglobin level was available for 835 patients; this value was missing in 16.0% of cases. For more patient information, see Table 2.

At the time of analysis, 476 patients were alive (47.9%). Median follow-up for surviving patients was 72 months (range 2–72 months). Two-year overall survival was 82.8%, and five-year overall survival was 67.7%. Primary local control was 71.0% at two years and 54.0% at five years after the start of treatment. A total of 220 local failures were observed. Most of these (179/220, 81.4%) occurred within the first two years after treatment, and no local failures were recorded after five years as they are assumed to be second primary tumors.

Prognostic factors

Univariate Cox regression was carried out on the following factors: age at the start of radiotherapy, sex, tumor location, pretreatment hemoglobin level, EQD_{2T}, T-stage, and N-stage (N0 or N+). All factors were statistically significant for overall survival ($p < 0.05$). In the multivariate analysis, independent unfavorable prognostic factors for overall survival were low hemoglobin level, male sex, high T-status, presence of nodal involvement, older age, lower EQD_{2T}, and non-glottic tumor. See Table 3 for the hazard ratios, confidence intervals and p-values.

The year of therapy had no prognostic significance for either survival ($p = 0.28$) or local control ($p = 0.48$). In order to test the hypothesis that modern radiotherapy (3D, in vivo dosimetry) would perform better than 2D radiotherapy, the cohort was split before ($n = 532$) and after January 1996 ($n = 462$). In the univariate analysis there was no difference between the two groups ($p = 0.14$), but in the Cox regression analysis there was a trend ($p = 0.077$) with a hazard ratio of 1.3 in favor of modern radiotherapy.

The clinical factors investigated for local control were the same as for overall survival. Tumor location (i.e., glottic vs non-glottic) was significant in the univariate analysis ($p < 0.001$), but not in the multivariate analysis ($p = 0.93$). All other factors were significant both in the univariate and in the multivariate analysis. Unfavorable prognostic factors for local control were low hemoglobin level, male sex, high T-status, nodal involvement, older age, and lower EQD_{2T}. See Table 3 for the hazard ratios, confidence intervals and p-values.

PET–CT scans

Tumor volume was measured in only 124 patients. The GTV ranged between 0.0 and 128.2 cc with a median of 4.7 cc. In a subgroup analysis with these patients, the volume was a statistically significant predictor for overall survival ($p < 0.001$) and local control ($p < 0.001$). In the Cox regression analysis, we tested the prognostic value of tumor volume, sex, and N-status. None of these factors was statistically significant for either overall survival, or for local control. This subgroup is possibly too small to detect influences on overall survival or local control.

Table 3
Multivariate analysis of potential prognostic factors.

	Overall survival			Local control		
	Hazard ratio	Confidence intervals	p-Value	Hazard ratio	Confidence intervals	p-Value
Age	1.04	1.03–1.05	<0.0001	1.02	1.01–1.03	0.0012
Gender			0.0002			<0.0001
Female	1.00			1.00		
Male	2.30	1.49–3.55		2.47	1.69–3.60	
T-stage			<0.0001			<0.0001
T1	1.00			1.00		
T2	1.22	0.91–1.63		1.52	1.20–1.92	
T3	2.22	1.56–3.14		2.48	1.87–3.28	
T4	4.29	2.85–6.47		4.28	3.05–6.02	
N-stage			0.034			0.0059
N0	1.00			1.00		
N-positive	1.46	1.03–2.06		1.51	1.13–2.03	
Location tumor			0.0725			
Glottic	1.00			1.00		
Non-glottic	1.31	0.98–1.75		–		0.93
Hemoglobin level	0.67		<0.0001	0.75	0.67–0.85	<0.0001
EQD_{2T}	0.97	0.94–0.99	0.0037	0.97	0.95–0.99	0.0011

One-hundred and fifteen PET-scans were assessable and evaluable. SUV_{max} ranged between 1.9 and 23.8, with a median of 6.1. The metabolic volume ranged between 1.1 and 73.3 cc, with a median of 7.9 cc. The SUV_{max} and metabolic volume were not statistically significant for survival ($p = 0.093$ and $p = 0.93$, respectively), but SUV_{max} was a statistically significant predictor for local control ($p = 0.019$, metabolic volume: $p = 0.70$). In the Cox Regression analyses, the SUV_{max} lost significance, when corrected for T-status, N-status and GTV. GTV, T-status and the SUV_{max} are highly correlated.

Nomograms

Two nomograms were built, one for prediction of survival (Fig. 1) and one for local control (Fig. 2). The AUCs of the models were 0.73 and 0.67, respectively. The AUC corrected for overfitting by the bootstrap procedure was 0.73 for overall survival and 0.67 for local control. For the purpose of comparison, we analyzed the predictive value of the TNM-stage alone. The AUC of the model for overall survival was 0.62, which means that the model predicted overall survival correctly in only 62% of patients. The AUC of the model for local control was 0.62 too.

The MAASTRO cohort can be split into four subgroups, according to the quartiles of the risk score. The prognoses of the high- and low-risk groups are distinctive, but the other two groups have overlapping 95% confidence intervals. They are, therefore, merged into one patient group with a medium risk score. The two- and five-year survival rates were 82.1% (95% CI, 76.8–87.4%) and 76.3 (95% CI, 70.4–82.2%) for the low-risk group, 72.1% (95% CI, 67.8–76.4%) and 53.3% (95% CI, 48.6–58.4%) for the medium-risk group, and 47.3% (95% CI, 40.4–54.2%) and 28.3% (95% CI, 21.8–34.8%) for the high-risk group, respectively ($p < 0.001$). See Fig. 3 for the Kaplan–Meier curve.

We validated these models with the datasets of Leuven, VU and NKI Amsterdam and Manchester. Validation of the survival model yielded AUCs of 0.68, 0.74, 0.71 and 0.76, while the validation procedure for the local control model resulted in AUCs of 0.70, 0.71, 0.62 and 0.72, respectively. We validated the TNM model on the other datasets. The AUCs of the survival TNM model were 0.70 for the Leuven database, 0.65 for the VU Amsterdam database, 0.57 for the NKI database and 0.63 for the Manchester database. The local control TNM model yielded AUCs of 0.62, 0.64, 0.56 and 0.63, respectively. Confidence intervals are shown in Table 4.

Discussion

We have developed visual, ready-to-use nomograms for overall survival and primary local control in laryngeal carcinoma patients to predict outcome following radiotherapy alone. We did so after a multivariate analysis of several easily assessable clinical factors in a large group of unselected laryngeal cancer patients. The survival rates in this study are comparable with other studies and with those in the Dutch Cancer Registration (Nederlandse Kankerregistratie) [17], which observed a two- and five-year overall survival of 81% and 69%, respectively. The models we developed for both

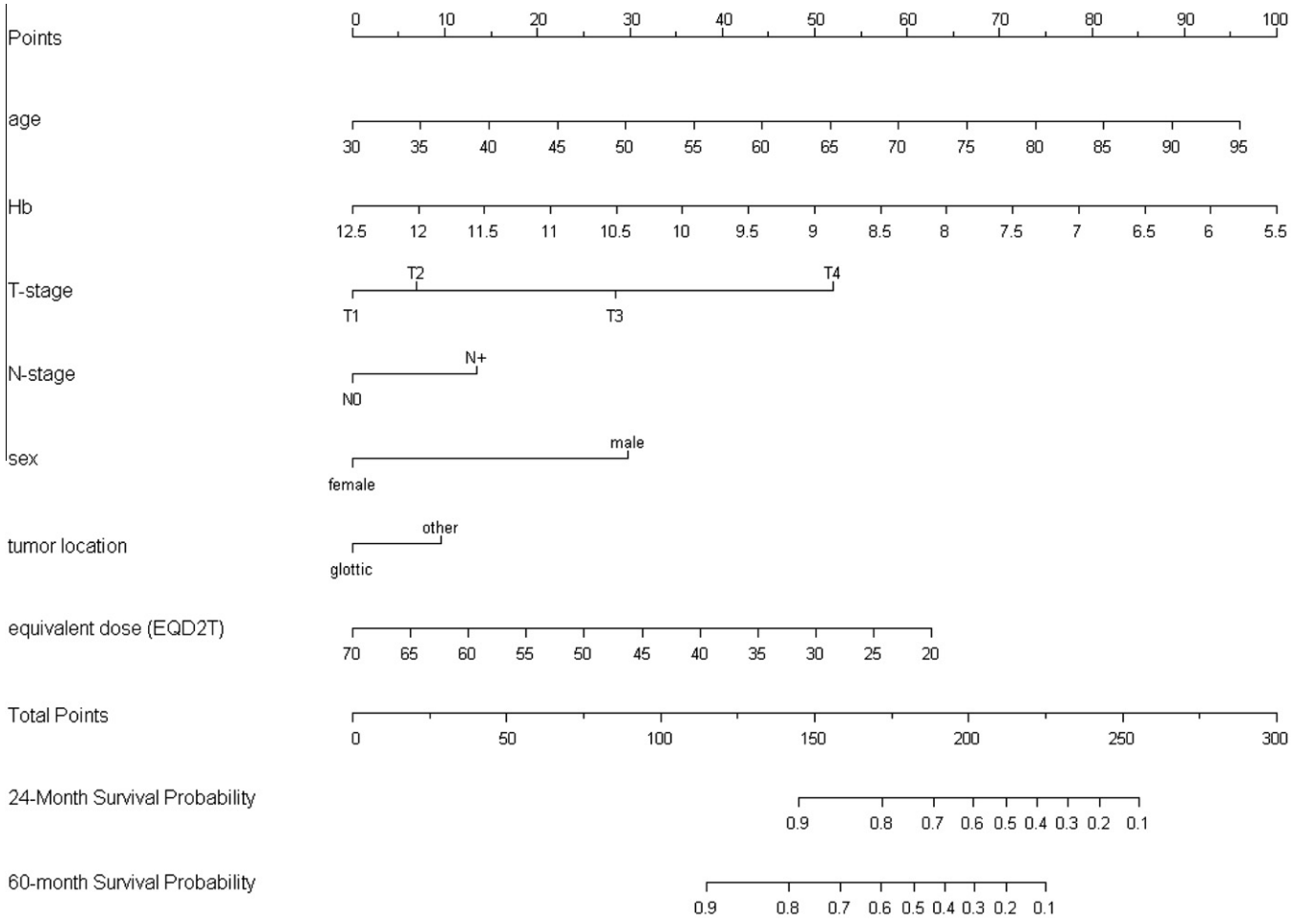

Fig. 1. Nomogram for the prediction of 2-year and 5-year overall survival.

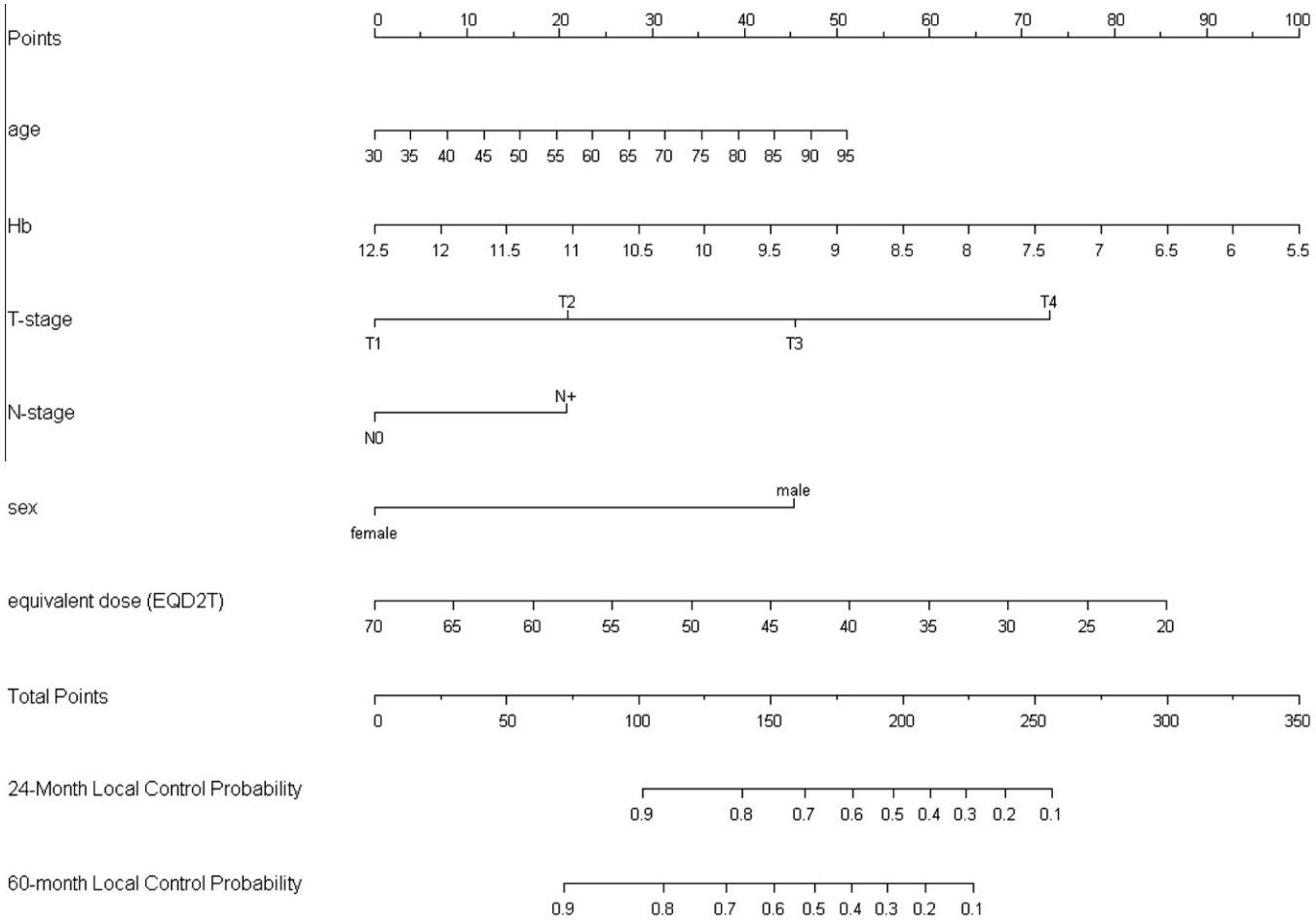

Fig. 2. Nomogram for the prediction of 2-year and 5-year local control.

survival and local control yielded similar results in three other patient populations in hospitals in Leuven (Belgium), Amsterdam (The Netherlands), and Manchester (UK). The models perform better than models based on TNM staging alone.

Johansen et al. [18] performed a multivariate analysis on 1127 patients with a laryngeal carcinoma treated with curative radiotherapy alone. This group of patients is comparable to ours with respect to age, sex, TNM-stage and tumor location. As in our patient population, they found sex, T-stage, N-stage, and hemoglobin level to be statistically significant for overall survival. They also found differentiation grade to be significant for survival, but this value was not available for our patients. And unlike our data, the hemoglobin level was not prognostic for local control.

In 2001 a study was published about a prediction model for head and neck cancer patients [19]. This model was based on 1662 head and neck cancer patients, using age, sex, cTNM-status, tumor (sub)site, and history of tumor as predictors for survival. However, because the performance of the model is not indicated, its accuracy is unknown. Other studies with smaller groups of patients found correlations between outcome and T-site [20], low pretreatment hemoglobin level [5–7], and tumor volume [20–22]. Along with clinical factors, imaging features [23–25], serum markers [26,27] and other biomarkers [28–30] also have a predictive value for laryngeal carcinoma.

Several studies have been published with different findings about the predictive value of the PET–CT scan in head and neck cancer [31,32]. In contrast to earlier studies, our population consists exclusively of patients with a laryngeal carcinoma. Even though there are similarities between the different tumors in the head and neck region, there are also a number of differences. Therefore, it is not possible to perform prognostic and predictive studies without adequate stratification for location of the tumor. In the group of patients in this study, GTV was a significant prognostic factor for survival in the univariate analysis. The prognostic factors for local control in the univariate analysis were SUV_{max} and GTV.

This study is an observational – "population-based" cohort study, which included all laryngeal carcinoma patients treated with radiotherapy alone at our hospital. There is a potential selection bias, because treatment choice was made before inclusion in the study. During the inclusion period there were changes in diagnostics, staging methods, and treatment choice, which imply that there might be stage migration. Although treatment quality and control have improved in recent decades, we observed no significant improvement of overall survival over the course of this study. A possible explanation for this is that co-morbidity in laryngeal carcinoma patients is high and influences overall survival more than the cancer itself. Data on WHO performance status or Karnofski score were missing in our population, thus we were not able to incorporate the effect of co-morbidity on the predictive nomogram which may limit its predictive performance. Although co-morbidity would certainly influence the estimation of overall survival, our estimation based on the predictive nomogram yielded similar AUCs on the external datasets and was significantly superior to TNM for overall survival prediction. Co-morbidity might be an important predictor and should be investigated in future studies.

Patients treated with chemotherapy were excluded from this analysis, as they constituted only a small group of patients. Most

Table 4
Nomograms performance in external datasets.

	Survival		Local control	
	Model based on multiple variables	Model based on TNM	Model based on multiple variables	Model based on TNM
MAASTRO (n = 994)	0.73	0.62	0.67	0.62
(95% CI)	(0.70–0.77)	(0.58–0.63)	(0.64–0.71)	(0.55–0.63)
Leuven (n = 109)	0.68	0.70*	0.70	0.62
(95% CI)	(0.50–0.82)	(0.45–0.81)	(0.50–0.78)	(0.49–0.72)
VU Amsterdam (n = 178)	0.74	0.65	0.71	0.64
(95% CI)	(0.69–0.87)	(0.57–0.75)	(0.66–0.81)	(0.57–0.74)
NKI/AVL Amsterdam (n = 205)	0.71	0.57	0.62	0.56
(95% CI)	(0.60–0.82)	(0.52–0.69)	(0.55–0.75)	(0.49–0.63)
Manchester (n = 403)	0.76	0.63	0.72	0.63
(95% CI)	(0.72–0.81)	(0.58–0.69)	(0.67–0.78)	(0.58–0.69)
Pooled external datasets	0.71	0.60	0.65	0.60
	(0.70–0.76)	(0.57–0.62)	(0.62–0.68)	(0.58–0.61)

* Confidence intervals were obtained in a bootstrap procedure (n = 1000). The obtained AUCs were significantly different for the multivariate model compared with the TNM based model for every cohort ($p \ll 0.001$), except for survival prediction in the Leuven cohort where no significant differences were found.

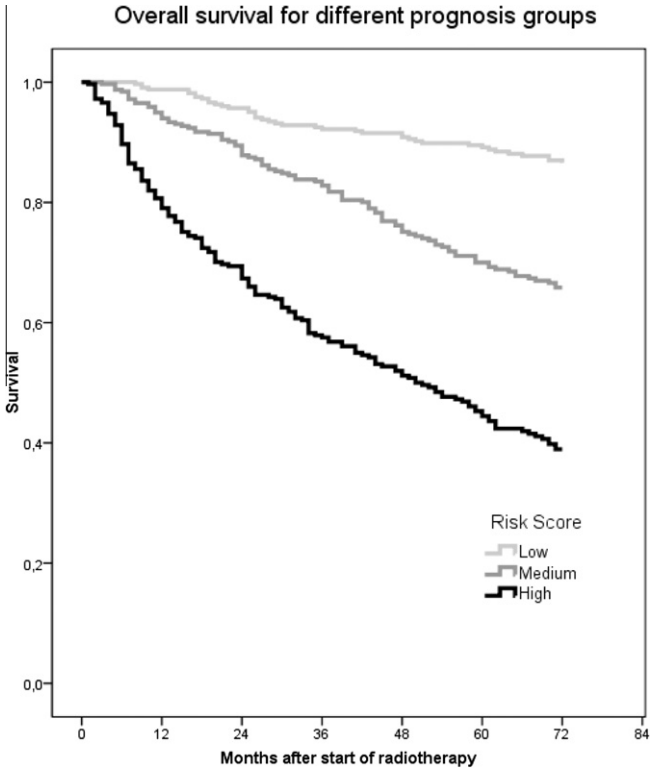

Fig. 3. Kaplan Meier curve for overall survival according to the different prognosis groups.

of them received chemotherapy as a palliative treatment or within a study protocol. A recent meta-analysis demonstrates the benefit of concurrent chemotherapy [33–36], with an absolute benefit of 6.5% at five years for head and neck cancer patients. In subgroup analyses this effect seems stronger for younger patients (<60 years old) and patients with good performance status and locally advanced disease.

To allow for adequate decision making regarding treatment for laryngeal cancer patients, we are currently analyzing our data on patients with a laryngeal carcinoma treated with laser surgery or surgery, and patients treated with surgery and postoperative radiotherapy. By making nomograms for these patients too, we can create a useful tool for the treatment decision-making process. A model consisting of solely clinical features is still too limited to allow clinical decision making. There is a need for adding biological and imaging data [29]. There is a need for a prospective multicentric randomized trial, preferably with banking of tissues, to validate and extend the results. A prognostic study of that kind would make it possible to collect data on biomarkers and imaging features, along with clinical data. Normal tissue reactions should then also be taken into account [37–39]. The availability of several validated nomograms for the different therapeutic options for laryngeal carcinoma consisting of clinical, biological, and imaging features will make a potent decision support model. The risk groups illustrated in Fig. 3 can also be used for stratification in clinical trials or to customize more aggressive strategies to the risk of relapse.

Conclusions

We have built visual, ready-to-use nomograms for the prediction of survival and primary local control with several easy assessable clinical factors, for use on patients with laryngeal carcinoma treated with radiotherapy alone. The performance of these nomograms is significantly better than the predictive value of the TNM-classification alone, but still need additional data before being used in clinical practice.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.radonc.2011.06.023.

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