TALK Score: Development and Validation of a Prognostic Model for Predicting Larynx Preservation Outcome

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Objectives/Hypothesis: To develop and validate a simple prognostic tool that would help predict larynx preservation outcome.

Study Design: A retrospective review of 3 prospective studies.

Methods: We reviewed consecutive chemotherapy/radiation protocols for patients (n = 170) with advanced, resectable, squamous cell, larynx, or pharynx cancer treated at Memorial Sloan-Kettering Cancer Center from 1988 to 1995 with larynx preservation intent. The outcome was successful larynx preservation. Model validation used data from U. S. Department of Veterans Affairs larynx preservation study.

Results: The developed model added one point for each poor prognostic covariate present (show in parentheses) and was given the acronym TALK: T stage (T4), albumin (<4 g/dL), maximum alcohol/liquor use (≥6 drinks/day or heavy drinking), and Karnofsky performance status (<80%). The 3-year larynx preservation rates by TALK score were 65% (0), 41% (1–2), and 6% (3–4), $P < .0001$; on validation, the TALK 3–4 group was particularly well demarcated.

Conclusions: The TALK score is an easily applied and valid tool that should assist treatment selection.

Key Words: Laryngeal neoplasms, decision making, prognosis, speech, combined modality therapy.

Level of Evidence: 2c.

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INTRODUCTION

Most advanced cancers of the larynx and surrounding structures require total laryngectomy if managed with primary surgery. This operation is among those most feared by patients.[1] Both voice alteration and related communication challenges, as well as the presence of a stoma may adversely affect quality of life.[2,3] Voice rehabilitation strategies exist, but many patients feel totally or partly dissatisfied with the options and continue to feel restricted in their daily lives.[4] Accordingly, the development of treatment programs intended to preserve laryngeal function without compromising survival is an important priority within head and neck oncology and of great interest to patients.

Historically, conservation surgery[5,6] and radiation[7] as a single modality had been the principal larynx preservation options. In the last 15 years, integrated chemotherapy/radiotherapy has established itself as a broadly applicable larynx preservation strategy. Randomized trials have shown that such an approach offers voice preservation and improved quality of life without compromise in survival.[8–10]

When successful organ preservation is achieved, chemotherapy/radiation is generally viewed as having been the appropriate treatment choice for the patient; unfortunately, in some patients the strategy will fail. In this setting, a patient would have experienced the potential toxicities of chemotherapy (e.g., neuropathy, hearing loss) and definitive-dose radiation therapy (e.g., increased risk of severe mucositis, feeding tube) and the potential added morbidity associated with surgery after those treatments without any apparent benefit and many added costs. Arguably, such patients would have been better served by proceeding directly to primary total laryngectomy. Understandably, knowing whether a given patient has a higher or lower likelihood of success with chemotherapy/radiation therapy would be useful to both physicians and patients.

There is currently no validated methodology available to help separate better from poorer risk patients before the initiation of larynx preservation therapy. Therefore, treatment choice is often subjective and may use widely varying, difficult-to-reproduce criteria. Our

TABLE I.		
Induction Chemotherapy Regimens.		
Drugs	Dosage	Days
Protocol 1988–1990 (n = 70)		
Cisplatin	100 mg/m^2 IV	1, 29, 57
5-fluorouracil	1,000 mg/m^2 CIV	1–5, 29–33, 57–61
Protocol 1991–1995 (n = 103)		
Cisplatin (n = 22)	100 mg/m^2 IV	1, 22, 43
5-fluorouracil (n = 22)	800 mg/m^2 CIV	1–5, 22–26, 43–47
Leucovorin calcium (n = 22)	100 mg PO every 4 hr	1–5, 22–26, 43–47
Cisplatin (n = 81)	100 mg/m^2 IV	1, 22, 43
5-fluorouracil (n = 81)	1,000 mg/m^2 CIV	1–5, 22–26, 43–47

IV = intravenous; CIV = continuous intravenous; PO = orally.

objective was to create a simple prognostic tool using readily available clinical data that would help predict successful and, perhaps more importantly, unsuccessful larynx preservation outcome to facilitate treatment decision making in this setting.

MATERIALS AND METHODS

Patients

From 1988 to 1995, 173 patients with histologically confirmed squamous cell carcinoma of the larynx, hypopharynx, or oropharynx were treated on one of two consecutive, institutional review board–approved protocols at Memorial Sloan-Kettering Cancer Center with the primary intent of preserving the larynx. Seventy patients participated in the first protocol (1988–1990), and 103 patients participated in the second protocol (1991–1995). Three patients were found to be ineligible (2 with nonsquamous cell histology; 1 with M$_1$ disease before initial treatment) and were excluded. Therefore, a total of 170 patients were included in this study. All histologic material was reviewed by the department of pathology at Memorial Hospital. Entry criteria were similar among the studies and have been previously described.[11–13] All patients gave informed consent after the studies were approved by the local human investigations committee.

Treatment

The details of treatment have been previously discussed[11–13] and are summarized in Table I and II. In both studies, three cycles of induction cisplatin-based combination chemotherapy were planned with appropriate supportive measures.[14] The decision whether to proceed to radiation-based treatment or primary surgical management depended on the extent of response to chemotherapy. In general, patients with a major response at the primary site and no progression in the neck proceeded to radiation-based treatment; for lesser response categories and progression, surgical intervention was recommended. The patients on the first protocol received conventional external-beam radiation that was delivered in 1.8- to 2-Gy fractions to a planned total dose of 66 to 70 Gy to the primary site and other sites of gross disease. The patients on the second protocol received delayed accelerated external-beam radiation therapy that was delivered in 1.8-Gy daily fractions during weeks 1 to 4, followed by twice-daily fractions (1.8 Gy in the

morning and 1.6 Gy in the afternoon) during weeks 5 to 6, for a total planned dose of 70 Gy, with planned concurrent cisplatin 100 mg/m^2 administered intravenously on days 1 and 22. On both studies, selected patients with base of tongue cancer received a brachytherapy[15] boost, and surgery was pursued for suspected disease persistence or relapse.

Larynx Preservation Outcome

Prospective functional data were not available for these patients. As a surrogate measure, successful larynx preservation outcome for this study was defined as local control without any surgery (except biopsy) to the primary site and without a permanent tracheostomy or gastrostomy. Such an endpoint has been successfully used previously.[9] Overall survival was not included as part of this outcome.

Prognostic Variables

T stage, N stage, and overall TNM stage (by clinical exam alone and with the use of imaging studies to potentially address stage migration concerns[16,17]) as well as age, sex, race, primary site, and Karnofsky performance status had all been collected prospectively. After a comprehensive review of the literature, our data set was expanded to include other potential pretreatment prognostic factors, which were collected retrospectively from patient charts. These pretreatment factors included weight loss,[18] symptoms,[19–22] comorbidity[23] (Charlson comorbidity index[24]), performance status,[25] alcohol use,[18,20] cigarette use,[26–28] albumin,[18] alanine aminotransferase,[29] hemoglobin,[29] platelets,[30] mean corpuscular volume, lactic acid dehydrogenase,[31] serum albumin,[32] and pretreatment tracheostomy[21,33] and gastrostomy status. All variables were dichotomized before any modeling applying either cutoff points used in the medical literature or based on the frequency distribution in the dataset.

Validation Dataset

The U.S. Department of Veterans Affairs (VA) Laryngeal Study Group performed a prospective randomized study in patients with stage III or IV larynx cancer.[8,33] The protocol and informed consent procedures were approved by the institutional review boards at all participating institutions. A total of 332 patients were randomized to receive either standard treatment (surgery and postoperative radiation therapy) or investigational treatment (larynx preservation with sequential standard cisplatin/5-fluorouracil chemotherapy followed by radiation therapy, with primary site surgery reserved for disease persistence or salvage). The full details of treatment plan and outcome have been previously described.[8,34] Data from the 166 subjects who were randomized to the investigational treatment were used as the validation dataset.

TABLE II.			
Radiation Therapy Regimens.			
Radiation Therapy		Cisplatin	
Target total dose	Fractionation	Dosage	Days
Protocol 1988–1990 (n = 70)			
6,600–7,000 cGy	1.8 Gy/d, wk 1–6	None	
Protocol 1991–1995 (n = 103)			
7,000 cGy	1.8 Gy/d, wk 1–4	100 mg/m^2 IV	1, 22
	1.8 Gy/AM, wk 5–6		
	1.6 Gy/PM, wk 5–6		

IV = intravenous.

TABLE III. Demographic Characteristics.		
	No. of Patients	%
No.	173	—
No. analyzed	170	—
Age, median (range), yr	59 (25–84)	—
KPS, median (range)	80 (60–90)	—
Male/female	123/47	72/28
Pretreatment tracheostomy	31	18
Weight loss ≥10%	28	16
Charlson comorbidity >3*	25	15
Site		
Larynx	96	56
Hypopharynx	47	28
Oropharynx	27	16
Stage		
T2/T3/T4	21/73/76	12/43/45
N0/N1/N2/N3	57/30/77/6	34/18/45/4
Stage II/III/IV	6/47/117	11/34/55
Current/former smokers	158	93
Current/former alcohol users	53	68

*Because of the diagnosis of cancer, all patients had a minimum score of 2.

KPS = Karnofsky performance status.

Statistics

Larynx preservation times were calculated from the start of treatment and assigned a value of 0 if local control was never achieved. Univariate analyses of potential prognostic covariates were done using the Kaplan-Meier method. Variables with $P < .10$ by the log-rank test were included in the multivariate analysis. Multivariate analysis used Cox's proportional-hazards model,[35] doing the regression in a forward stepwise manner with a threshold significant value of .10. P values of .10 were used in the early phases of the modeling so that potentially predictive factors with borderline P values were not immediately excluded from the analysis; however, only variables with $P < .05$ after multivariate analysis were included in the final model. Because previous data suggested that patients in the second protocol (1991–1995) had better outcomes than those in the first protocol (1988–1990),[36] all of the univariate and multivariate analyses were stratified by the protocol in which the patient had participated. The candidate variables for the prognostic tool were derived from the results of the multivariate analysis (2-sided P values < .05). Discrimination was evaluated using the concordance index.[37,38] A concordance index of 1 indicates that a model performs perfectly in predicting success or failure in an individual subject.

Median follow-up for both datasets was computed using the inverse Kaplan-Meier method.[39] Median as well as actuarial larynx preservation and survival times were reported. For subgroup comparisons of larynx preservation rates, Kaplan-Meier curves were also presented.

RESULTS

Memorial Sloan-Kettering Cancer Center Development Dataset

Patient characteristics. The baseline characteristics for those 170 evaluable patients are listed in Table III. The median age was 59 years (range, 25–84), and me-

dian Karnofsky performance status was 80 (range, 60–90). The majority of primary sites were of the larynx (56%); 45% had N_2 disease or greater, and 32% had T_4 disease. Fifteen percent of the subjects had significant comorbidity as per the Charlson comorbidity criteria.[24] A larger proportion were either current/former consumers of tobacco (93%) or alcohol (68%).

Outcomes. The median follow-up of the patients was 82.5 months (range, 0.4–141.5 months). Fifteen (9%) were censored before 3 years; 28 (17%) before 5 years. The median overall survival and time to larynx preservation failure were 54.5 months and 15 months, respectively. The 3-year overall survival rate was 59%. The 3-year larynx preservation rate was 44%.

Univariate analyses. After analyzing the breakdown of each variable and considering clinically relevant values, each factor was dichotomized as listed in Table IV. Each of the potential prognostic covariates listed in Table IV underwent univariate analysis for larynx preservation outcome. T stage, alcohol use, Karnofsky performance status, lactate dehydrogenase, albumin, platelets, weight loss, pretreatment tracheostomy, and overall stage ($P < .05$ by log-rank test) as well as the symptom of dyspnea ($P < .1$) were all significant covariates. Cigarette use, either as a dichotomous variable or a continuous variable by pack years (data not shown), was not a significant predictor. The times of last cigarette or alcohol used were also examined both as a continuous variable as well as a dichotomous variable (using 1 month and 1 year as break points), and neither was found to significantly predict successful larynx preservation in our data set.

Multivariate analysis. Two variables that were significant on univariate analysis were excluded from the multivariate analysis. Lactate dehydrogenase was excluded because less than 10% of the subjects had an abnormally high value pretreatment. Weight loss was excluded owing to concerns about the accuracy of the data using only chart review, particularly the time over which weight loss occurred. All of the other eight variables that were found to predict successful larynx preservation ($P < .10$) were entered in the Cox's proportional-hazards model. Because of missing data, three subjects (all with larynx cancer as the primary) were excluded from all subsequent analyses. As noted in Table V, four of the variables remained independently significant ($P < .05$): T stage ($\leq T_3$ vs. T_4), serum albumin level (<4 g/dL vs. ≥4 g/dL), Karnofsky performance status (<80% vs. ≥80%), alcohol/liquor use (described as minor or no alcohol use in the past or <6 cans of beer, or the equivalent alcohol, per day during maximum alcohol use vs. described as major alcohol use in the past or ≥6 cans of beer, or the equivalent alcohol, per day during maximum alcohol use). Pretreatment albumin levels had the highest risk ratio (2.55); the risk ratios are similar among the other three variables (1.60-1.77).

TALK score. The risk of unsuccessful larynx preservation was characterized by summing the number of risk factors present at time of diagnosis (Table V). Even though the risk ratio for pretreatment albumin was higher than the other variables, this approach was taken

TABLE IV.

TABLE IV.
Univariate Analysis of Pretreatment Factors.

Pretreatment Factors	Dichotomization	P < .10
Age, yr	<60 vs. ≥60	*
Sex	Male vs. female	*
Race	Caucasian vs. non-Caucasian	*
Primary site	Larynx vs. hypopharynx or oropharynx	*
T stage	<T4 vs. T4	<.001
N stage	<N2 vs. ≥N2	*
Overall stage	II or III vs. IV	.037
Karnofsky performance status, %	<80 vs. ≥80	<.001
Tracheostomy	Yes vs. no	.004
PEG	Yes vs. no	*
Laboratory serum tests		
Lactic acid dehydrogenase	Normal vs. higher than ULN	.027
Albumin, g/dL	<4 vs. ≥4	<.001
Mean corpuscular volume, fl	<100 vs. ≥100	*
Alanine aminotransferase	Normal vs. higher than ULN	*
Hemoglobin, g/dL	<10 vs. ≥10	*
Platelets	Normal vs. higher than ULN	.002
Cigarette use	Yes vs. no	*
>40 pack years	<40 vs. ≥40	*
Alcohol use	Described as minor or no alcohol use in the past or <6 cans of beer/d, or the equivalent, during maximum alcohol use vs. described as major alcohol use in the past or ≥6 cans of beer/d, or the equivalent, during maximum alcohol use	.032
Weight loss, %	<10 vs. ≥10	.002
Symptoms		
Dysphagia	Yes vs. no	*
Otalgia	Yes vs. no	*
Neck mass	Yes vs. no	*
Dyspnea	Yes vs. no	.081
Sore throat	Yes vs. no	*
Charlson comorbidity index	<4 vs. ≥4	*

*P > .10.
PEG = percutaneous endoscopic gastrostomy; ULN = upper limits of normal.

because there exists overlap of the 95% confidence intervals of the risk ratios. For example, a patient who had a T4 tumor (a risk factor), serum albumin level of 3 g/dL (a risk factor), a Karnofsky score of 90% (NOT a risk factor), and never drank alcohol (NOT a risk factor) would have a score of 2 (due to 2 risk factors). Kaplan-Meier curves for each possible TALK score with successful larynx preservation as the outcome are shown in Figure 1. The curves for TALK scores of 1 and 2 were close by visual inspection, so they were combined to represent an intermediate risk for successful larynx preservation. Similarly, the curves for TALK scores of 3 and 4 were close by visual inspection and were therefore combined. Thus, a patient was defined as at good risk if no risk factors were present, intermediate risk if one or two risk factors were present, and poor risk if three or four factors were present.

Furthermore, it was noted that the first letter of each risk factor (T stage, albumin, alcohol/liquor use, Karnofsky performance status) made up the acronym TALK. The prognostic model was renamed the TALK score to facilitate the ability to remember the risk factors.

Figure 2A and Table VI summarize larynx preservation rates over time for each prognostic group. The 3-year larynx preservation rates for the good (TALK score = 0), intermediate (TALK score = 1 or 2), and poor (TALK score = 3 or 4) risk groups were 65%, 41%, and 6%, respectively. The median time to larynx preservation failure (and the 95% confidence intervals) for the good-, intermediate-, and poor-risk groups were not reached (117 months: not reached), 14 months (10–37), and 0 months (0–2), respectively. These differences were significant (P < .0001 by log-rank test). All but one patient's cancer in the poor-risk group had larynx preservation failure by 3 years. In the studied population, the majority of the patients (57%) fell into the intermediate-risk group; 18 patients (11%) were in the poor-risk group.

In the developmental dataset, the concordance index of the TALK score was 0.65.

TALK score for larynx cancer only. Because only laryngeal cancer patients were part of the validation set, the TALK score model was also applied only to the larynx cancer patients in the Memorial Hospital dataset.

Variables	Condition	$Pr > \chi^2$	Hazard Ratio	95% Confidence Interval	TALK Score
T stage*	T_4	.008	1.76	1.16-2.68	1
Albumin	<4 g/dL	.001	2.55	1.44-4.51	1
Alcohol use (or liquor use)	Major alcohol use or >6 cans of beer/d	.023	1.60	1.07-2.41	1
Karnofsky performance status	<80%	.025	1.77	1.08-2.90	1

*Staging with the use of radiologic evaluation.
TALK = T stage, albumin, alcohol/liquor use, Karnofsky performance status.

Overall, there were 93 evaluable subjects with larynx cancer. The 3-year larynx preservation rates (Table VI) for the good- (35 subjects), intermediate- (50 subjects), and poor-risk (8 subjects) groups were 68%, 41%, and 13%, respectively. The median time to larynx preservation failure (and the 95% confidence intervals) for the good-, intermediate-, and poor-risk groups were not reached (lower interval not reached-upper interval not reached), 14 months (9–73), and 0 months (0–8), respectively. These differences were significant (P < .0001 by log-rank test). The larynx preservation Kaplan-Meier curves for the patients with larynx cancer only are illustrated in Figure 2B.

The concordance index of the TALK score in the larynx cancer subgroup was also 0.65.

Department of Veterans Affairs Laryngeal Cancer Study - Validation Dataset

Patient characteristics. There were a total of 166 evaluable patients in this population. All subjects in the VA Laryngeal Cancer Study had larynx cancer as the primary site. Of the subjects in this dataset, 26% had T4 disease; 28% had N2 or N3 disease; and 44% had stage IV disease.

Overall outcomes. The median follow-up was 52 months. The actuarial 3-year overall survival rate was 52%. The 3-year larynx preservation rate was 44%. The median time to larynx preservation failure was 21 months. Compared to the Memorial Hospital data, there were more patients censored early: 25 (15%) before 3 years and 49 (30%) before 5 years.

TALK score for the VA dataset. When TALK was applied to the VA Laryngeal Cancer Study dataset, 27 subjects (16%) were in the good-risk group, 109 (66%) were in the intermediate-risk group, and 30 (18%) were in the poor-risk group (Table VI). The 3-year larynx preservation rates were 54%, 47%, and 25% for the good-, intermediate-, and poor-risk groups, respectively. The median time to larynx preservation failure (and the 95% confidence intervals) for the good-, intermediate-,

Fig. 2. (A) TALK score model; Memorial Sloan-Kettering Cancer Center data set—all patients. (B) TALK score model; Memorial Sloan-Kettering Cancer Center data set—larynx cancer patients only. TALK = T stage, albumin, alcohol/liquor use, Karnofsky performance status.
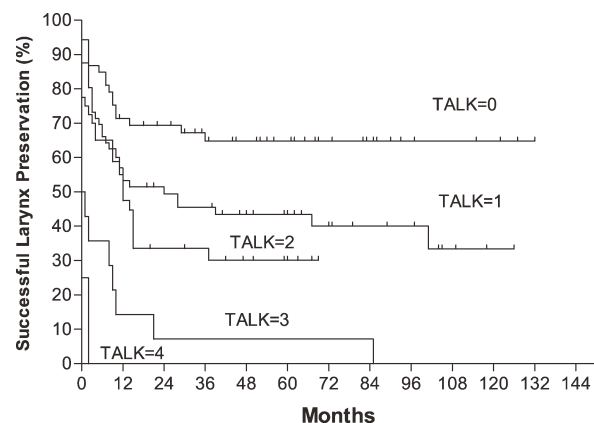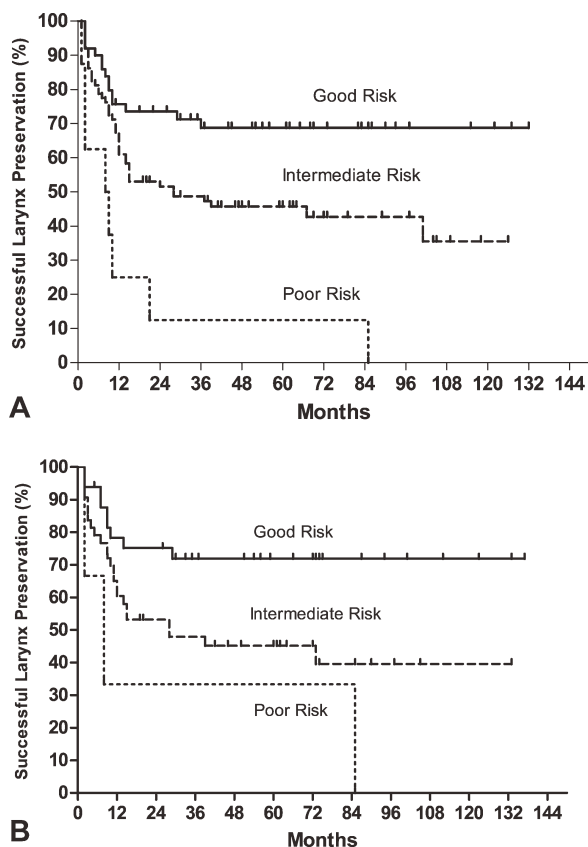

Fig. 1. Kaplan-Meier curves describing larynx preservation rates for each TALK score value. TALK = T stage, albumin, alcohol/liquor use, Karnofsky performance status.

TABLE VI.
TALK Score Groups.

Dataset	TALK Score	Risk Grouping	No.*	Median LP Rate, mo	3-Year LP Rate, %
MSKCC (all)					
	0	Good	53	Not reached	65
	1–2	Intermediate	96	14	41
	3–4	Poor	18	0	6
	Total		167	15	44
MSKCC (larynx only)					
	0	Good	35	Not reached	68
	1–2	Intermediate	50	14	41
	3–4	Poor	8	0	13
	Total		93	28	49
VA					
	0	Good	27	47	54
	1–2	Intermediate	109	24	47
	3–4	Poor	30	7	25
	Total		166	21	44

TALK = T stage, albumin, alcohol/liquor use, Karnofsky performance status; LP = larynx preservation; MSKCC = Memorial Sloan-Kettering Cancer Center; VA = Department of Veterans Affairs Laryngeal Study Group.

and poor-risk groups were 47 months (11; upper interval not reached), 24 months (10; upper interval not reached), and 7 months (2–13), respectively. These differences were significant ($P < .01$ by log-rank test). It should be noted in the actuarial larynx preservation curves provided in Figure 3 that the demarcation at 3 years in the larynx preservation between the good (TALK score = 0) and intermediate (TALK score = 1 or 2) groups did not persist beyond 48 months. Furthermore, seven of the 30 patients in the poor-risk group were censored before the 3-year mark (only 3 patients were censored after 3 years).

In the validation dataset, the concordance index of the TALK score was 0.57.

DISCUSSION

The goal of this project was to develop and validate a simple tool that supplies health-care providers and
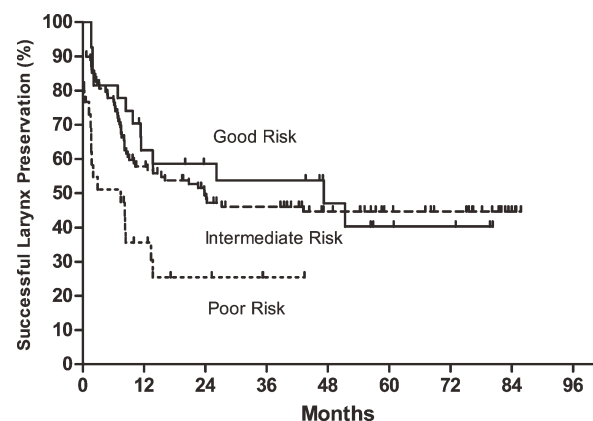

Fig. 3. TALK score model; the Department of Veterans Affairs larynx preservation study. TALK = T stage, albumin, alcohol/liquor use, Karnofsky performance status.

patients with added prognostic data to assist decision making in the larynx preservation setting. The result of our analysis is the TALK score, which demarcated a significant prognostic gradient in larynx preservation outcome in both our (development) and the VA Laryngeal Cancer Study (validation) datasets. The inclusion of the validation step distinguishes our report from other prognostic analyses intended to assist prediction of larynx preservation outcome available in the literature. Numerous clinical factors were analyzed as potential candidates for the prognostic model. Many of these factors, such as comorbidity, symptoms, and alcohol/smoking history, are not routinely collected during the analyses of the management options in patients with cancer. The TALK score consists of T stage, serum albumin level, alcohol/liquor use, and Karnofsky performance status.

Not surprisingly, the development dataset demonstrated a large gradient between groups. In the validation dataset from the VA Laryngeal Cancer Study, the TALK score's ability to select a poor-risk group, representing nearly 20% of patients in the study, is also well demonstrated. However, a durable separation of larynx preservation rates between the good- and intermediate-risk groups was not delineated. Potential explanations to consider include a smaller proportion of VA Laryngeal Cancer Study patients in the good-risk group compared to our population (16% vs. 37%) and the impact of approximately 30% of the VA Laryngeal Cancer Study subjects being censored before 5 years of follow-up compared to 17% in the Memorial Hospital dataset. Future work will need to identify ways to further delineate between these groups. Arguably, however, the true value of the TALK score is the ability to predict unsuccessful, not successful, larynx preservation. In general, costs and morbidity are higher in subjects who undergo and fail larynx preservation treatment, as they are exposed to additional, potentially toxic, treatments

that would have been avoided with upfront surgery and adjuvant radiation therapy. Because studies have shown patients to strongly prefer avoiding surgery if possible,[10,40] particularly if survival is not compromised, we anticipate that the majority of patients would choose a larynx preservation option if there exists a reasonable chance of success. Therefore, the clinical impact on decision-making between the good- and intermediate-risk groups is likely much smaller than between the intermediate- and poor-risk groups. The TALK score's ability to identify a poor-risk group is its strength.

The TALK score is simple to use. All variables were dichotomized to facilitate its application. Also, all of the variables are routinely collected by physicians before the initiation of treatment and, for the most part, are independent of high technology. The sole exception to this is the T stage, which was measured with the aid of a computerized axial tomography scan or magnetic resonance imaging. T stage, based on clinical exam but not imaging, was significant in predicting local control with a functional larynx after multivariate analysis (data not shown) but with a lower relative risk ratio. Nevertheless, most physicians do get a pretreatment imaging study of the primary site. The TALK score provides an objective and valid method to predict the likelihood of successful larynx preservation and an alternative to more subjective, likely less reproducible approaches.

There exist several potentially important applications of the TALK score. First, the TALK score can be used to compare larynx preservation rates from separate nonrandomized larynx preservation trials by allowing investigators to compare the baseline prognostic risks of patients entered in different studies. Second, it will give the patient and clinician additional prognostic data to make an informed decision. However, the health-care provider should not use this model to make a clinical decision independent of the patient. Evidence suggests that health-care providers often gauge patient preferences or quality of life inaccurately.[2,41–43] Third, if a patient falls into the poor-risk category but truly wishes to pursue a larynx preservation option, an investigational, instead of a standard, larynx preservation approach may be a better treatment choice.

There are certain limitations to this model. The TALK score was created and validated on protocol data sets. Patients participating in clinical trials are required to pass stricter inclusion criteria (see Methods section) than those receiving noninvestigational therapy. Clinical factors that may have importance in a less-selected population may not have been reflected in this clinical trial setting. An example is comorbidity. Although many patients with high comorbidity are excluded from clinical trials, this will not be the case for the head and neck cancer population at large, especially considering the influence of cigarette smoking[44] and alcohol use[45] as risk factors for these diseases.

A limitation to the study is the lack of data pertaining to human papillomavirus (HPV) status. It was not until after these studies were completed that HPV was found to be associated with a subset of squamous cell carcinomas of the head and neck.[46–48] More recent work has shown that HPV-related squamous cell cancers of the head and neck have a favorable prognosis compared to HPV-negative tumors.[49,50] However, the risk of HPV in non-oropharynx tumors is very low.[49,51] Considering only 16% of our development dataset consisted of oropharynx tumors, and there were no oropharynx tumors in our validation dataset, it is unlikely that HPV status is a confounder in our model, although the model is most likely relevant only for HPV-negative tumors.

In addition to HPV, other studies have identified biological markers[27,52–56] as well as other clinical characteristics[8,33,56] that may help predict larynx preservation outcome. Examples include the presence of p53 mutations, vascular endothelial growth factor levels, and epidermal growth factor receptor expression. Although the addition of these factors to the TALK score will be considered in future models, the TALK score model in its current form represents a simple and easy to apply model that supplies important information quickly without the aid of difficult, time-consuming, and/or expensive investigations.

The concordance index of 0.57 for the TALK score when applied to the validation dataset indicated that the model performed better than pure chance in this population but was well below an index of 1 associated with a perfect model. A concordance index in this range is nonetheless consistent with clinical utility. For example, the Gail model,[57] which is widely used to predict breast cancer risk, has a reported concordance index of 0.58.[58]

CONCLUSION

The TALK score represents a beginning, a backbone for further prognostic model development in this clinical setting, for which tools to guide management are solely needed. It is likely most relevant to HPV-negative squamous cell cancers of the head and neck. We anticipate further refinement in the scale. For example, other studies have identified biologic markers[27,52–56] as well as other clinical characteristics[8,33,56] that may help predict larynx preservation outcome. The addition of selected prognostic factors with the intent of creating a better predictive model while preserving ease of use is being considered for future investigations.

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