

## Modified TALK Score for Japanese Patients with Laryngeal and Hypopharyngeal Cancers to Predict the Possibility of Laryngeal Preservation by Concurrent Chemoradiotherapy

NAOKI OTSUKI<sup>1\*</sup>, MIO MATSUI<sup>2</sup>, MIKI TAKAHASHI<sup>1</sup>,  
RYOHEI SASAKI<sup>3</sup>, NAOMI KIYOTA<sup>4</sup>, MAKOTO USAMI<sup>5</sup>  
and KEN-ICHI NIBU<sup>1</sup>

<sup>1</sup> Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, Kobe, Japan;

<sup>2</sup> Department of Nursing, Faculty of Health Sciences, Kobe University School of Medicine, Kobe, Japan;

<sup>3</sup> Department of Medical Radiation Oncology, Kobe University Graduate School of Medicine, Kobe, Japan;

<sup>4</sup> Department of Oncology and Hematology, Kobe University Graduate School of Medicine, Kobe, Japan;

<sup>5</sup> Division of Surgical Metabolism, Faculty of Health Sciences, Kobe University School of Medicine, Kobe, Japan;

\*Corresponding Author

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**Key Words:** TALK score, laryngeal cancer, hypopharyngeal cancer, laryngeal preservation, chemoradiotherapy

**Objective:** TALK score has been developed as an index for predicting the possibility of larynx preservation and prognosis of the patients with advanced laryngeal and hypopharyngeal cancers treated by concurrent chemoradiotherapy (CCRT). In this study, we validated the original TALK score in our clinical setting and modified the score for Japanese population.

**Methods:** The subjects were 21 patients with laryngeal cancer and 50 patients with hypopharyngeal cancer who underwent CCRT at Kobe University Hospital between April 2007 and August 2012. Data regarding T stage, serum albumin level just before treatment, maximum alcohol use, Karnofsky Performance Status (KPS), 3-year overall survival rate and 3-year larynx-preservation rate were collected from medical records. In the revised TALK score (JTALK), the following scoring criteria were modified to adjust Japanese population: T stage of the primary tumor ( $\geq T3$ ), serum albumin level ( $<3.5$  g/dl), maximum alcohol use ( $\geq$  one 350-ml can of beer/day or an equivalent amount), and KPS ( $<80\%$ ).

**Results:** The original TALK score was not significantly associated with the larynx preservation rates or survival rates for laryngeal cancer or hypopharyngeal cancer. Instead, JTALK score was significantly associated with the 3-year larynx preservation rates and 3-year survival rates of the patients with hypopharyngeal and laryngeal cancer.

**Conclusion:** These results indicate that JTALK score could be a useful index for predicting the possibility of larynx preservation and prognosis of Japanese patients with advanced laryngeal and hypopharyngeal cancer treated by CCRT.

### INTRODUCTION

Concurrent chemoradiotherapy (CCRT) for advanced head and neck cancer (stage III/IV) has been demonstrated to yield a comparable survival rates to surgery and has become widely used with the aim of improving larynx preservation and survival rates (1,2). However, it is becoming increasingly clear that patients who undergo CCRT experience complications such as pain, edema, xerostomia and trismus as well as sequelae such as chewing difficulty, dysphagia, dyspnea and articulation disorders (3,4).

In addition, while many studies have shown that CCRT yields a higher rate of organ preservation, some retrospective studies showed that the 5-year overall survival rate of T3/T4 cancer decreased and surgery yielded better survival than non-surgical treatment (5). Thus, in the decision of the treatment strategy for individual patient with advanced laryngeal cancer and hypopharyngeal cancer, one must carefully determine whether it is possible to preserve pharyngeal function by non-surgical treatment.

Given such backgrounds, Sherman et al. proposed the TALK score index as a predictive model for use with patients with advanced laryngeal and hypopharyngeal cancers (6). They performed univariate analysis of pretreatment factors, namely, age, sex, race, tumor site, T classification, N classification, M classification, clinical stage, Karnofsky Performance Status (KPS), tracheotomy status, gastrostomy status, hematology,

smoking habit, alcohol use, rate of weight loss, symptoms (fever, dysphagia, otalgia, neck mass, dyspnea, pharyngeal pain), and Charlson comorbidity index (7). They found that scoring criteria for four of these factors, T classification ( $\geq T4$ ), serum albumin level ( $<4$  g/dl), maximum alcohol use (6 drinks/day:  $\geq$  six 350-ml cans of beer/day or an equivalent amount), and KPS ( $<80\%$ ), were independent significant variables associated with larynx preservation rate. The name "TALK" score came from the first letters of each of these four criteria. One point is added for each criterion, making the total score range 0 to 4 points for evaluation.

In this study, we validated the original TALK score and found that it did not reflect laryngeal preservation rates. Accordingly, we developed a modified TALK score for Japanese population (JTALK) and validated its usefulness to predict possibility of larynx preservation and prognosis.

## PATIENTS AND METHODS

### 1. Patients

One hundred eighty six patients with laryngeal cancer and 168 patients with hypopharyngeal cancer were treated at Kobe University Hospital between April 2007 and August 2012. Among the patients with laryngeal cancer, the clinical stage was I in 65 patients, II in 58 patients, III in 36 patients, IVA in 21 patients, IVB in 3 patients and IVC in 3 patients. Among the patients with hypopharyngeal cancer, the clinical stage was I in 16 patients, II in 22 patients, III in 26 patients, IVA in 81 patients, IVB in 13 patients and IVC in 10 patients. Seventy-one patients who had CCRT as an initial treatment for laryngeal or hypopharyngeal cancer were enrolled in this study. The clinical features of these patients were shown in Table II. Each fraction dose of radiation was 2 Gy/day and total radiation dose ranged from 60 to 70 Gy. Eighty mg/m<sup>2</sup> of cisplatin was basically administrated every 3 weeks during irradiation period. Induction chemotherapy was administered in the patients with clinical stage IVB using cisplatin based multi-agents regimens. For the patients with moderate renal impairment (estimated glomerular filtration rate (eGFR): 40-59ml/min/1.73m<sup>2</sup>), other platinum chemotherapy agents (carboplatin Area Under the Curve (AUC) 1.5 weekly, nedaplatine 70mg/m<sup>2</sup> every 3 weeks or satraplatin 30mg/m<sup>2</sup> given daily over 5 days during irradiation period) were used. Dose and the number of cycles were adjusted in consideration of general condition, such as renal function and myelosuppression. In particular, 64mg/m<sup>2</sup> (80%) of cisplatin was administrated for the patients with moderate renal impairment (eGFR: 40-59ml/min/1.73m<sup>2</sup>) and chemotherapy agent administration was postponed for the patients with severe renal impairment (eGFR  $<40$  ml/min/ 1.73m<sup>2</sup>) or severe neutropenia ( $<1500$  cells/ $\mu$ l).

Data regarding age, sex, primary site, T classification, N classification, M classification, clinical stage, maximum alcohol use, KPS, serum albumin level, prognosis, survival time, larynx preservation, and survival time with larynx preservation were collected from medical records during March 2015 to November 2015. Overall survival rate and larynx preservation rate were determined as the period of time from the start of treatment until the death of a patient, regardless of the cause of death and the period of time from the start of treatment until loss of laryngeal function due to laryngectomy, tracheotomy, or other such reasons, respectively. "Larynx preservation" was defined as not having lost laryngeal function. The larynx was not considered as "preserved" in patients who required tracheotomy or could no longer speak or eat, even if they had not undergone total laryngectomy. The 3-year overall survival rate was used as the metric for survival and survival time was sequentially updated during the study period.

As mentioned above, Sherman set the threshold of scoring criterion for alcohol at 6 cans of 350-ml beer/day or an equivalent amount (6). Following formula was used to convert the amount of alcoholic beverage to pure alcohol: Volume of liquor (ml)  $\times$  [alcohol content (%)  $\div$  100]  $\times$  0.8. According to this formula, 6 cans of 350-ml beer convert to 84 g of pure alcohol. For those whose records had been made using the PS classification of the Eastern Cooperative Oncology Group (ECOG), KPS of less than 80% was considered equivalent to ECOG PS of 2, 3, or 4.

### 2. JTALK score and Statistical Analysis

We validated the original TALK score and found that it did not reflect laryngeal preservation rates in the cohort of this study. Accordingly, we developed a modified TALK score for Japanese population (JTALK score). In JTALK score, the following thresholds were changed: 1) T classification: 4 to 3, 2) Alcohol use: 6 cans to 1 can, 3) Serum albumin level: 4g/dl to 3.5g/dl. Associations of TALK score and JTALK score with larynx preservation rates and survival rates were evaluated. In addition, patients were categorized into "low-risk group (JTALK score of 0 or 1) and "high-risk group" (JTALK score of 2, 3, or 4) and the associations of these two groups with larynx preservation rate and survival rate were tested. (Table I) Larynx preservation and survival rates were calculated using Kaplan-Meier method and the log-rank test was used for statistical analysis. Statcel 2 in "4 Steps Excel Statistics Ver. 2"(OMS Ltd.) and JMP (SAS Institute Japan) were used to perform the

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Kaplan-Meier method and log-rank test. The significance level was set at  $<0.05$ . This study has been approved by the ethical committee of Kobe University Hospital (No. 1589).

TABLE I. Comparison of TALK Score and JTALK Score

Criteria	TALK Score	JTALK score
T stage	T4	T3 and T4
Albumin	$<4.0$ g/dl	$<3.5$ g/dl
Alcohol	$\geq 6$ drinks/day	$\geq 1$ drinks/day
KPS	$<80\%$	$<80\%$

### Risk staging

Point	0	1	2	3	4
TALK score	Good	Intermediate		Poor	
JTALK score	Low risk		High risk		

KPS= Karnofsky performance status.

6 drinks/day= alcohol users or liquor users drinking 6 canned beer and more.

1 drinks/day= alcohol users or liquor users drinking 1 canned beer and more.

## RESULTS

### 1. Patients characteristics

Characteristics of the patients are shown in Table II. There were 64 men and 7 women. The age ranged from 49 to 79 years (average 65.7 years). Among the patients with hypopharyngeal cancer, the subsite was piriform sinus in 41 patients, posterior wall in 5 patients, and postcricoid in 4 patients. The clinical stage was III in 12 patients, IVA in 31 patients, and IVB in 7 patients. Among the patients with laryngeal cancer, the subsite was glottis in 14 patients and supraglottis in 7 patients. The clinical stage was III in 17 patients, IVA in 3 patients, and IVB in 1 patient.

TABLE II. Demographic Characteristics

	No. of Patients (%)
No. analyzed	71
Age $<65/\geq 65$	31/40
KPS $<80\%/\geq 80\%$	6 /65
Male/Female	64/7
Site	
Larynx	21 (30)
Hypopharynx	50 (70)
Stage	
T1/T2/T3/T4	8/28/29/6 (11/39/41/9)
N0/N1/N2/N3	16/16/34/5 (22/23/48/7)
Stage I / II / III / IV	0/0/29/42 (0/0/41/59)
Current/former alcohol users ( $\geq 6$ drinks)	18 (25)
Current/former alcohol users ( $\geq 1$ drinks)	64 (90)

KPS= Karnofsky performance status.

6 drinks/day= alcohol users or liquor users drinking 6 canned beer and more.

1 drinks/day= alcohol users or liquor users drinking 1 canned beer and more.

Six patients (8%) had KPS of 80% or lower. Eighteen patients (25%) consumed at least 6 drinks/day and 63 patients (90%) consumed at least 1 drink/day. The drugs used for chemotherapy were cisplatin in 64 patients, carboplatin in 4 patients, nedaplatin in 1 patient, and satraplatin in 1 patient, respectively. Among the patients who were treated by cisplatin, the number of chemotherapy cycles was one in 12 patients, two in 24 patients and three in 29 patients. The total dose of cisplatin was <100mg/m<sup>2</sup> in 12 patients, 100-200 mg/m<sup>2</sup> in 27 patients and >200mg/m<sup>2</sup> in 26 patients. Nine patients with Stage IVA or IVB underwent multi-agent induction chemotherapy consisting of 5 cisplatin, 5-FU and docetaxel (TPF) and 4 cisplatin and 5-FU (FP).

### 2. Hypopharyngeal Cancer

The numbers of patients with TALK score of 0, 1, 2, 3, and 4 were 5, 27, 16, 2, and 0, respectively (Table III). The 3-year overall survival rates of patients with TALK score of 0, 1, 2, and 3 was 100%, 59.0%, 63.6%, and 100.0%, respectively, while 3-year larynx preservation rates were 80.0%, 89.6%, 71.1%, and 100%, respectively. The 3-year overall survival rate and 3-year larynx preservation rate of all patients were 65.3% and 81.0%, respectively (Table IV).

The numbers of patients with JTALK score of 0, 1, 2, 3, and 4 were 3, 18, 23, 6, and 0, respectively (Table III). The 3-year overall survival rate for patients with JTALK score of 0, 1, 2, and 3 were 100%, 73.8%, 56.5%, and 66.7%, respectively, while the 3-year larynx preservation rate was 100%, 91.7%, 78.7%, and 25%, respectively (Table IV).

Original TALK scores did not reflect laryngeal preservation rates. Contrary to expectation, laryngeal preservation rate was higher in patients with TALK score of 3 than in patients with TALK score of 0, (Fig.1A). In contrast, JTALK scores significantly reflected the larynx preservation rates (Fig.1B). In addition, the larynx preservation rate was significantly lower in the high-risk group than in the low-risk group (P=0.012, Fig.1C).

Neither TALK scores nor JTALK scores reflect the survival rates (Fig.2A, 2B). However, the survival rate was significantly lower in the high-risk group than in the low-risk risk group (P=0.012, Fig.2C).

TABLE III. TALK Score Groups and Stage

	TALK Score	No. (%)	T stage				Clinical Stage			JTALK Score	No. (%)	T stage				Clinical Stage		
			T1	T2	T3	T4	III	IVA	IVB			T1	T2	T3	T4	III	IVA	IVB
Hypopharynx	0	5 (10)	1	2	2	0	2	3	0	0	3 (6)	1	2	0	0	0	3	0
	1	27 (54)	4	14	7	2	8	15	4	1	18 (36)	5	13	0	0	5	12	1
	2	16 (32)	3	8	2	3	1	13	2	2	23 (46)	2	9	6	6	7	12	4
	3	2 (4)	0	1	0	1	1	0	1	3	6 (12)	0	1	5	0	0	4	2
	4	0	—	—	—	—	—	—	—	4	0	—	—	—	—	—	—	—
	Total	50 (100)	8	25	11	6	12	31	7	Total	50	8	25	11	6	12	31	7
Larynx	0	7 (33)	0	2	5	0	5	1	1	0	0	—	—	—	—	—	—	—
	1	11 (52)	0	1	10	0	10	1	0	1	6 (29)	0	3	3	0	4	2	0
	2	3 (15)	0	0	3	0	2	1	0	2	12 (57)	0	0	12	0	11	0	1
	3	0	—	—	—	—	—	—	—	3	3 (14)	0	0	3	0	2	1	0
	4	0	—	—	—	—	—	—	—	4	0	—	—	—	—	—	—	—
	Total	21 (100)	0	3	18	0	17	3	1	Total	21	0	3	18	0	17	3	1
Overall	0	12 (17)	1	4	7	0	7	4	1	0	3 (4)	1	2	0	0	0	3	0
	1	38 (54)	4	15	17	2	18	16	4	1	24 (34)	5	16	3	0	9	14	1
	2	19 (27)	3	8	5	3	3	14	2	2	35 (49)	2	9	18	6	18	12	5
	3	2 (2)	0	1	0	1	1	0	1	3	9 (13)	0	1	8	0	2	5	2
	4	0	—	—	—	—	—	—	—	4	0	—	—	—	—	—	—	—
	Total	71	8	28	29	6	29	34	8	Total	71	8	28	29	6	29	34	8

### 3. Laryngeal Cancer

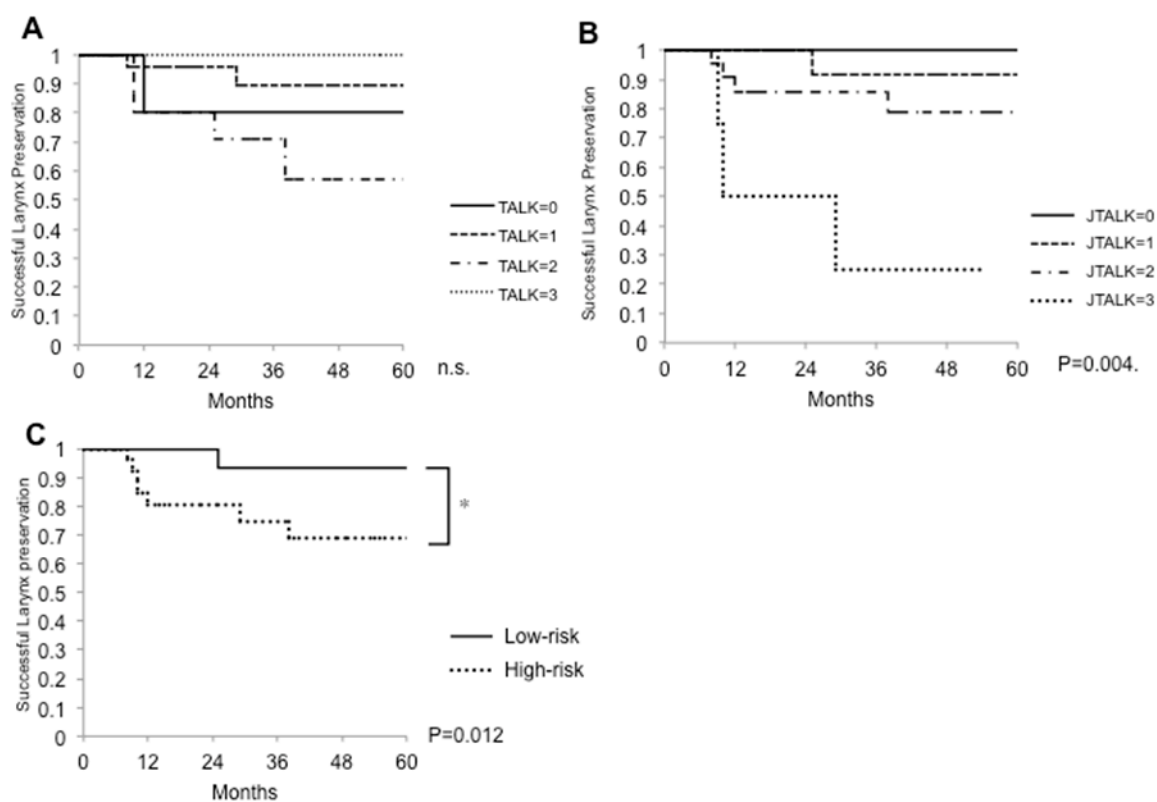
The numbers of patients with TALK score of 0, 1, 2, 3, and 4 were 7, 11, 3, 0, and 0, respectively (Table III). The 3-year overall survival rate of patients with JTALK scores of 0, 1, and 2, were 83.3%, 91.7%, and 100%, respectively, while the 3-year larynx preservation rates of those patients were 100%, 69.2%, and 100%, respectively. The 3-year survival and 3-year larynx preservation rates of all patients were 90.5% and 80.9%, respectively (Table IV).

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Neither TALK score nor JTALK score reflected the larynx preservation rates (Fig.3A, 3B). However, there was a trend that the larynx preservation rate was lower in the high-risk group than in the low-risk group (Fig.3C), while the difference was not statistically significant.

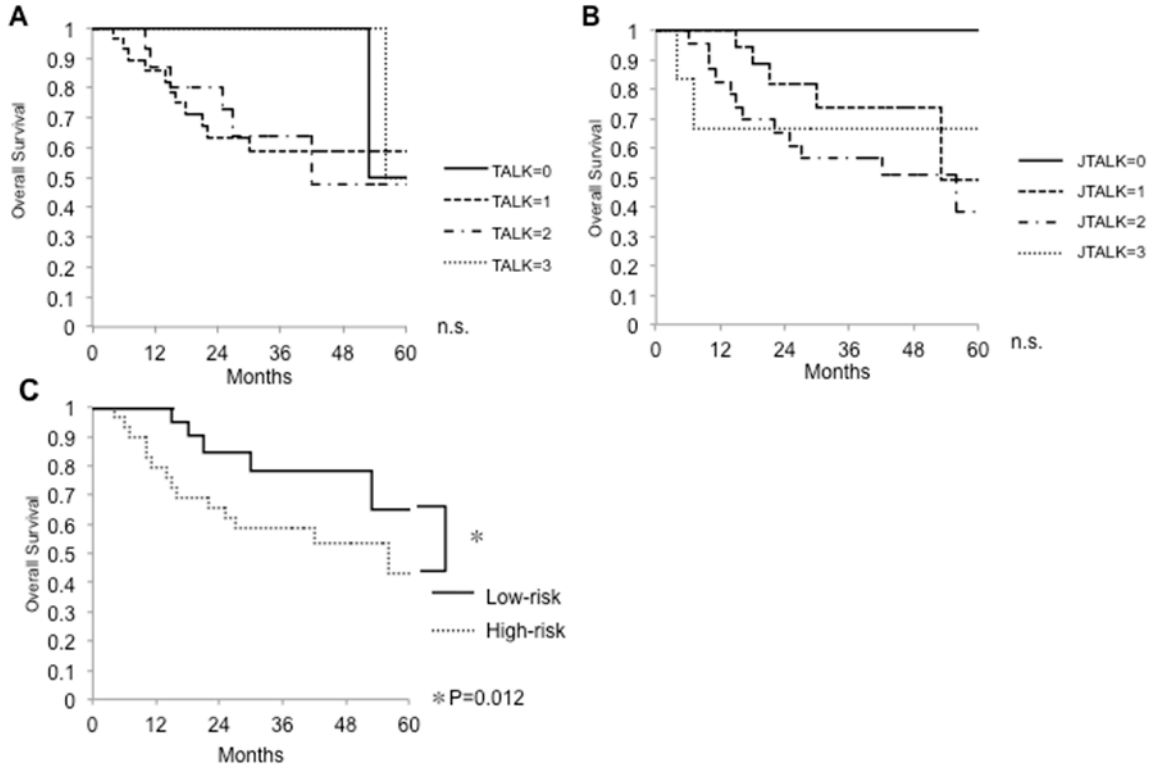
TABLE IV. TALK Score groups and outcomes

	TALK Score	No. (%)	3-Year OS Rate, %	3-year LP Rate, %	JTALK Score	No. (%)	3-Year OS Rate, %	3-Year LP Rate, %
Hypopharynx	0	5 (10)	100	80.0	0	3 (6)	100	100
	1	27 (54)	59.0	89.6	1	18 (36)	73.8	91.7
	2	16 (32)	63.6	71.1	2	23 (46)	56.5	78.7
	3	2 (4)	100	100	3	6 (12)	66.7	25
	4	0	-	-	4	0	-	-
	<b>Total</b>	<b>50</b>	<b>65.3</b>	<b>81</b>	<b>Total</b>	<b>50</b>	<b>65.3</b>	<b>81</b>
Larynx	0	7 (33)	80.0	57.1	0	0	-	-
	1	11 (52)	92.3	90.9	1	6 (29)	83.3	100
	2	3 (15)	100	100	2	12 (57)	91.7	66.7
	3	0	-	-	3	3 (14)	100	100
	4	0	-	-	4	0	-	-
	<b>Total</b>	<b>21</b>	<b>90.5</b>	<b>80.9</b>	<b>Total</b>	<b>21</b>	<b>90.5</b>	<b>80.9</b>
Overall	0	12 (17)	83.3	66.7	0	3 (4)	100	100
	1	38 (54)	71.0	90.8	1	24 (34)	76.0	93.8
	2	19 (27)	70.3	76.4	2	35 (49)	67.6	79.4
	3	2 (2)	100	100	3	9 (13)	87.5	57.1
	4	0	-	-	4	0	-	-
	<b>Total</b>	<b>71</b>	<b>74.1</b>	<b>82.1</b>	<b>Total</b>	<b>71</b>	<b>74.1</b>	<b>82.1</b>



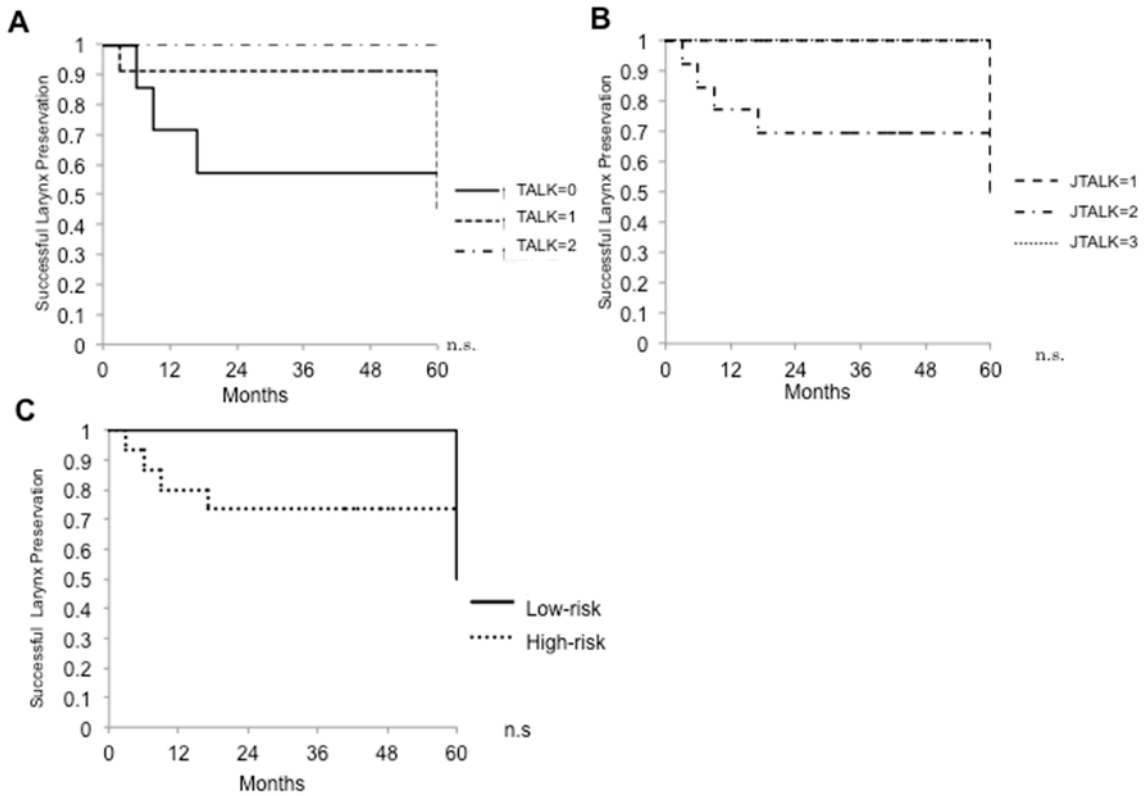
**Figure 1. Larynx preservation rate in Hypopharynx cancer patients**

A: Kaplan-Meier curves by Sherman Score value. B: Kaplan-Meier curves by JTALK. C: Low-risk group (JTALK=0, 1) and High-risk group (JTALK=2, 3)



**Figure 2. Overall Survival rate in Hypopharynx cancer patients**

A: Kaplan-Meier curves by Sherman Score value. B: Kaplan-Meier curves by JTALK. C: Low-risk group (JTALK=0, 1) and High-risk group (JTALK=2, 3).



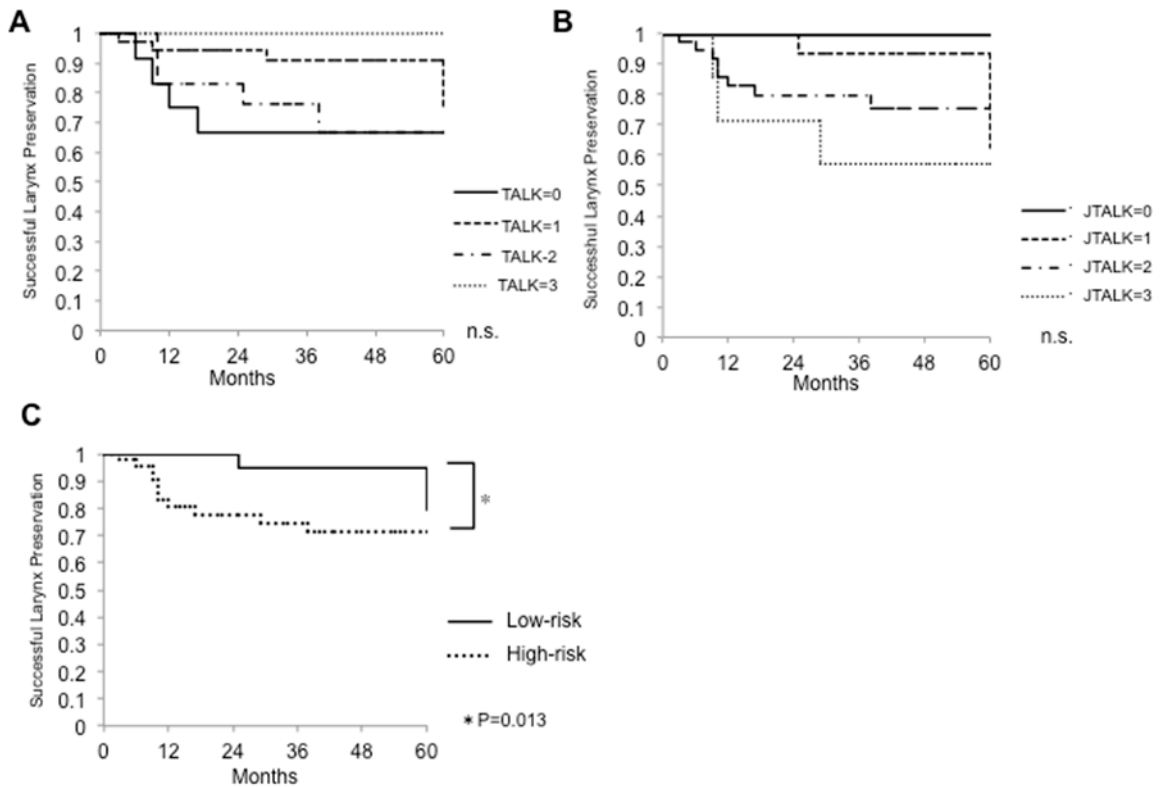
**Figure 3. Larynx preservation rate in larynx cancer patients**

A: Kaplan-Meier curves by Sherman Score value. B: Kaplan-Meier curves by JTALK. C: Low-risk group (JTALK=0, 1) and High-risk group (JTALK=2, 3).

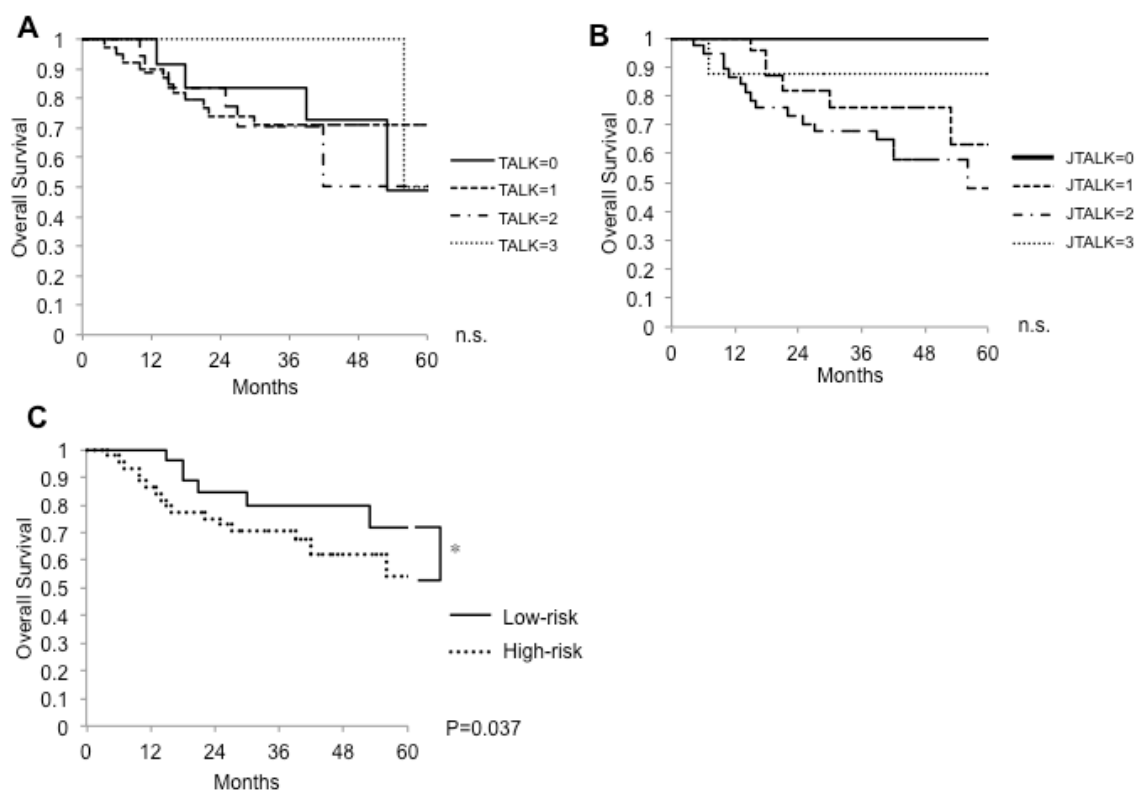
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4. Laryngeal and Hypopharyngeal Cancers

The numbers of patients with TALK score of 0, 1, 2, 3, and 4 were 12, 38, 19, 2, and 0, respectively (Table III). The 3-year overall survival rates for patients with TALK score of 0, 1, 2, and 3 were 83.3%, 71.0%, 70.3%, and 100%, respectively, while the 3-year larynx preservation rates were 66.7%, 90.8%, 76.4%, and 100%, respectively. The 3-year overall survival rate and 3-year larynx preservation rate of all the patients were 74.1% and 82.1%, respectively (Table IV). The numbers of patients with JTALK score of 0, 1, 2, 3, and 4 were 3, 24, 35, 9, and 0, respectively (Table III). The 3-year overall survival rates of the patients with JTALK of 0, 1, 2, and 3 were 100%, 76.0%, 67.6%, and 87.5%, respectively. The 3-year larynx preservation rates were 100%, 93.8%, 79.4%, and 57.1%, respectively (Table IV). While TALK scores did not reflect the larynx-preservation rate (Fig.4A), JTALK scores reflect the survival rates. With increasing score, larynx-preservation rate decreased (Fig.4B). The larynx-preservation rate was significantly lower in high-risk group than in low-risk group ( $P = 0.013$ ) (Fig.4C). Neither TALK scores nor JTALK scores did not reflect the survival rates (Fig.5A, 5B). However, the survival rate was significantly lower in the high-risk group than the low-risk group ( $P=0.037$ ) (Fig.5C).



**Figure 4. Larynx preservation rate in all patients**  
 A: Kaplan-Meier curves by Sherman Score value. B: Kaplan-Meier curves by JTALK. C: Low-risk group (JTALK=0, 1) and High-risk group (JTALK=2, 3).



**Figure 5. Overall Survival rate in all patients**  
 A: Kaplan-Meier curves by Sherman Score value. B: Kaplan-Meier curves by JTALK. C: Low-risk group (JTALK=0, 1) and High-risk group (JTALK=2, 3).

## DISCUSSION

In this study, TALK score was not associated with the larynx preservation rates or survival rates, suggesting that thresholds of original TALK score criteria are not well suited to Japanese population. On the other hand, present results showed that JTALK score could potentially be a useful tool for predicting the possibility of larynx preservation and prognosis of the patients with laryngeal and hypopharyngeal cancers.

Generally, in the treatment of laryngeal cancers, we recommend our patients radiotherapy for T1 and T2 diseases, CCRT for T3 disease and surgery for T4 disease at our department. For advanced hypopharyngeal cancer, we recommend CCRT for T2 and T3 diseases, and surgery for T4 disease. Thus, although sometimes we employed treatment options contrary to this treatment policy as required by the patient's general condition or preferences, there were only few patients with T4 diseases treated by CCRT in this study, which resulted in few patients with TALK score of 3 or 4. This is the most possible reason why JTALK score in which criterion threshold of T classification was changed to T3 and higher, was significantly associated with larynx-preservation rates and survival rates.

The scoring criterion for alcohol use in TALK score was based on findings from studies conducted in Western countries. However, the median alcohol use of the subjects of this study was much lower than the scoring criterion of 84 g for "alcohol use", which skewed the distribution of results. Alcohol consumption levels are believed to be associated with aldehyde dehydrogenase (ALDH) polymorphisms. While most Caucasians have ALDH2\*1/ALDH2\*1 genotype, almost half of Japanese population have ALDH2\*1/ALDH2\*2 genotype and are prone to developing symptoms such as facial flushing and tachycardia with excessive alcohol consumption. This commonly found heterozygous ALDH polymorphism in Japanese population has been reported to be associated with high prevalence of hypopharyngeal and esophageal cancers in Japan (8). This is probably why it was appropriate to change the scoring criterion for maximum alcohol use for Japanese to 14 g/day, the equivalent of 1 can of 350 ml beer/day, from the original scoring criterion, which was based on the alcohol consumption level of subjects in Western countries and would be too high for the Japanese subjects of this study.

The scoring criterion for serum albumin level was also based on results from Western studies. However, Japanese serum albumin levels might be also different from Caucasians probably due to differences in diet



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between Japan and Western countries (9). Nutrition Improvement Manual published by the Japanese study group supported by Japanese Ministry of Health, Labour and Welfare defined that a serum albumin level of 3.5 g/dl or less is an evidence of undernutrition in elderly adults and physical functions in this condition improve as nutritional status improves (10). Therefore, a serum albumin level of 3.5 g/dl or less can be considered to be a suitable scoring criterion for Japanese population.

Efforts have been made to select patients properly based on tumor characteristics, clinical aspects, imaging, and molecular biology with the primary goal of curing the patient and secondarily to preserve laryngeal function as well as form. Suzuki et al. reported that tumor location and pretreatment hemoglobin levels are important prognostic factor for progression-free survival (PFS) of the patients who underwent non-surgical multimodal treatment for laryngeal preservation (11). Chen et al. also reported that a high rate of laryngopharyngeal dysfunction occurred in T4a patients with hyoid bone invasion and in the patients with large primary tumor volume (12, 13). Meanwhile, 18F-FDG PET metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were reported to be prognostic predictors of outcome in patients with head and neck cancer (14). In addition, some studies have identified biological markers that may help predict the outcome of larynx preservation. Bradford et al. evaluated biomarker expression in pretreatment biopsy specimen using tissue microarray and determined their correlations with outcome (15). Although the results from these studies on blood examination data, imaging and biomarkers have had no impact on clinical practice so far, the indexes to select patients suitable for larynx preservation strategies with advanced laryngeal and hypopharyngeal cancers might be identified in further studies.

Limitation of this study is a retrospective study in a single institution, consisting of relatively limited number of patients. Since the results of this study are influenced by the course of treatment, it will be necessary to conduct a multi-institutional study including a large number of patients treated by various protocols.

### CONCLUSION

JTALK, the modified TALK score, was found to be associated with the 3-year larynx preservation rate and 3-year survival rate in patients with hypopharyngeal cancer and in patients with hypopharyngeal or laryngeal cancer. JTALK score could be a useful index for predicting the possibility of larynx preservation and prognosis of the patients with laryngeal and hypopharyngeal cancers treated by concurrent chemoradiotherapy (CCRT).

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### DISCLOSURE STATEMENT

All authors have no conflict of interest to declare.

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