

The Usefulness of Total Laryngectomy in Sarcopenic Patients With Hypopharyngeal and Laryngeal Cancer

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Abstract. *Background/Aim:* Sarcopenia has an adverse effect on postoperative complications and prognoses in head and neck cancer. This study focused on hypopharyngeal and laryngeal cancer patients with sarcopenia and analyzed the body composition following treatment when the larynx was preserved and when total laryngectomy was performed to examine the usefulness of laryngectomy. *Patients and Methods:* We retrospectively reviewed 88 primary hypopharyngeal and laryngeal cancer patients aged 65 years or older with cT2N0M0 or higher who visited our department. *Results:* There were no significant differences in the 3-year overall survival rate and the 1-year local control rate between the laryngeal preservation group and laryngectomy group. The average change one year following treatment in the laryngeal preservation group, when compared to prior to treatment, was a significant decrease in the body weight (BW) of -0.035, skeletal muscle mass (SMM) of -0.030, skeletal muscle mass index (SMI) of -0.026, body mass index (BMI) of -0.034, and grip strength (GS) of -0.066. The average change one year following treatment in the laryngectomy group, compared with prior to treatment, was an increase in BW of +0.028, SMM of +0.026, SMI of +0.008, BMI of +0.032, and GS of +0.026. Although no changes in serum biochemical testing after treatment were observed in the laryngeal preservation group, albumin, transferrin, and

transthyretin all exhibited significant improvement or a tendency toward improvement in the laryngectomy group. The patients with sarcopenia before treatment in the laryngeal preservation group had a significantly higher incidence of aspiration pneumonia. *Conclusion:* The presence or absence of sarcopenia before starting treatment is considered to be an index for selecting total laryngectomy.

Sarcopenia is a general term for pathological conditions in which muscle mass decreases due to aging or disease, and is a concept that was proposed by Rosenberg in 1989 (1). In the case of cancer patients with sarcopenia, there have been many reports indicating that sarcopenia has an adverse effect on postoperative complications and prognoses in gastrointestinal cancer (2-5) and head and neck cancer (6-9). The important point in the treatment of head and neck cancer is how to preserve the larynx, an organ involved in swallowing and vocalization, while enhancing cancer curability. However, if the larynx is preserved in a state of poor laryngeal function, dysphagia and aspiration pneumonia may occur, potentially resulting in death as the worst-case scenario. Therefore, in general, if laryngeal preservation, including function preservation, is possible, treatment aimed at preservation is desirable. However, even if the degree of progression is the same, when posttreatment difficulty in oral intake or aspiration pneumonia is expected to occur at a high rate, upon evaluating pretreatment performance status (PS), swallowing function, physical strength, *etc.*, total laryngectomy may be performed in some cases, with the patient's consent, once laryngeal preservation is deemed inappropriate.

Therefore, this study focused on hypopharyngeal and laryngeal cancer patients with sarcopenia and analyzed the body composition following treatment when the larynx was preserved and when total laryngectomy was performed to examine the usefulness of laryngectomy.

Patients and Methods

We retrospectively reviewed 88 primary hypopharyngeal and laryngeal cancer patients aged 65 years or older with cT2N0M0 or higher who visited our department from October 2016 to March 2021. Of the 88 patients, those who underwent laryngectomy as the

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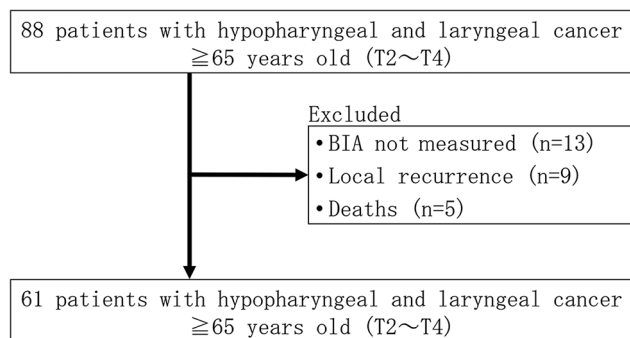


Figure 1. Flow diagram (n=61).

main treatment were classified as the laryngectomy group, while those who underwent radiotherapy (with or without chemotherapy) and preserved the larynx were classified as the laryngeal preservation group. All patients were able to engage in oral ingestion prior to treatment. The radiation therapy dose was 66-70 Gy, and cisplatin (80-100 mg/m²) and cetuximab (400 m² for the first dose and 250 m² for subsequent doses) were used for combined chemotherapy. First, we analyzed the 3-year survival rate and 1-year local control rate by treatment in 88 patients. Next, we analyzed the posttreatment body composition of 61 patients among the 88 patients who had no local recurrence 1 year after treatment and for whom measurements by bioelectrical impedance analysis (BIA) as well as grip strength (GS) were possible for more than 1 year (Figure 1). The reasons why BIA and GS measurements could not be conducted in some cases included poor measurement, inability to maintain a standing position, and placement of a pacemaker. Body measurements (body weight: BW, skeletal muscle mass: SMM, body mass index: BMI) were performed using InBody370 (InBody Japan Co., Ltd., Tokyo, Japan) as the BIA method. The AWGS2019 diagnostic criteria (10) announced in 2019 by the Asian Working Group on Sarcopenia (AWGS) were used as the diagnostic criteria for sarcopenia. In other words, sarcopenia was defined as 1) GS of less than 28 kg for men and less than 18 kg for women and 2) skeletal muscle mass index (SMI) (skeletal muscle mass of limbs/height²) of less than 7.0 kg/m² for men and less than 5.7 kg/m² for women. A commonly used digital grip dynamometer was used to measure the left and right grip twice the same day, with the maximum value being used (if the GS of the right hand was 25 kg and 27 kg, while the GS of the left hand was 20 kg and 22 kg, then the maximum value would be 27 kg). Furthermore, albumin (Alb), transferrin (Tf), transthyretin (TTR), C-reactive protein (CRP) and zinc (Zn) were measured in the blood before and after treatment as a nutritional evaluation.

The TNM classification was determined before treatment in accordance with the “TNM Classification of Malignant Tumours 8th Edition”.

The values were expressed as the mean±SD and SE, with Fisher’s exact test and Mann-Whitney *U*-test used for the statistical analysis. The Statistical Package for Social Sciences (SPSS; version 25) software (IBM, New York, NY, USA) was used for the analysis. A statistically significant difference was defined as a risk rate of less than 5%. For ethical considerations, approval was obtained from the Ethics Committee of Kindai University Hospital (receipt number R04-063). This study was conducted in accordance with the Declaration of Helsinki.

Table I. Demographic characteristics of the participants (n=88).

	Total (n=88)	Preservation of larynx (n=51)	Laryngectomy (n=37)	<i>p</i> -Value
Age	74.9±6.9	73.8±7.1	76.6±6.6	0.035
Sex				0.196
Male	80	48	32	
Female	8	3	5	
Subsite				0.059
Hypopharynx	53	35	18	
Larynx	35	16	19	
Stage				<0.001
II	26	23	3	
III IV	62	28	34	
T				<0.001
1 2	45	41	4	
3 4	43	10	33	
PS				0.333
0 1	86	49	37	
2	2	2	0	

p-Values in bold indicate statistical significance.

Results

Table I shows the background of the 88 patients in the laryngeal preservation group and the laryngectomy group. There were 51 cases in the laryngeal preservation group and 37 cases in the laryngectomy group. Although there were no differences in terms of sex, tumor site, and PS between the two groups, the laryngectomy group was significantly older (*p*=0.035), with more advanced cases in the stage classification (*p*<0.001) and the T classification (*p*<0.001). However, the 3-year overall survival rate was 80.5% in the laryngeal preservation group and 70.6% in the laryngectomy group, with no significant difference between the two groups (Figure 2). The 1-year local control rate was 83.7% in the laryngeal preservation group and 94.3% in the laryngectomy group, with no significant difference between the two groups (Figure 3).

Table II shows the breakdown of the 61 cases in which body composition and GS measurements using BIA were possible for more than one year. There were 36 cases in the laryngeal preservation group and 25 cases in the laryngectomy group. The laryngectomy group was older (*p*=0.026), with significantly more advanced cases in the stage classification (*p*=0.012) and the T classification (*p*<0.001) (Table II). However, there were no differences between the two groups in terms of sex, site, and PS, in addition to no significant differences in terms of the rate of sarcopenia between the laryngeal preservation group (19.4%) and the laryngectomy group (32%).

Serum biochemical tests before treatment indicated significant differences in CRP, Alb, Hb, Tf, and TTR between the laryngeal preservation group and the laryngectomy group; however, no differences were observed in terms of physical

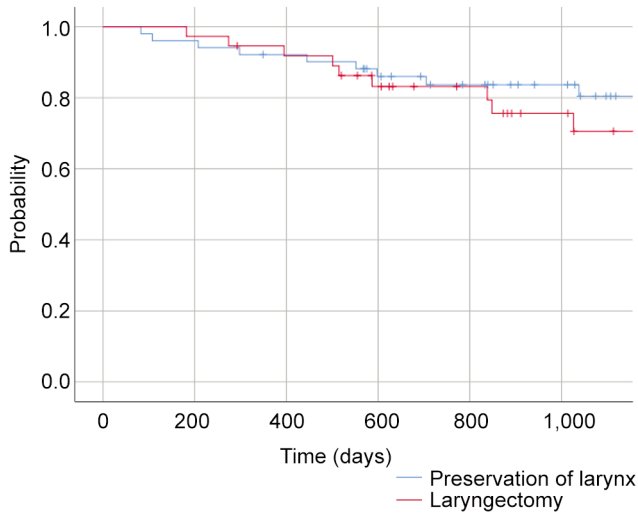


Figure 2. Kaplan-Meier curves of the overall survival rate (n=88). There was no significant difference between the two groups (p=0.714).

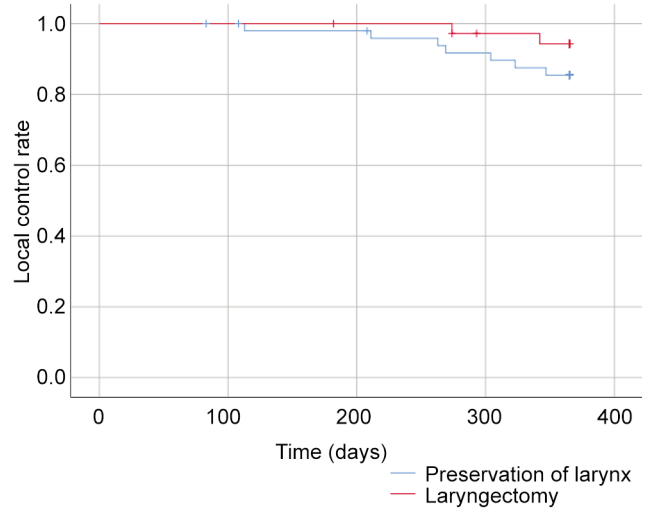


Figure 3. Kaplan-Meier curves of the local control rate (n=88). There was no significant difference between the two groups (p=0.194).

Table II. Demographic characteristics of the participants (n=61).

	Total (n=61)	Preservation of larynx (n=36)	Laryngectomy (n=25)	p-Value
Age	74.2±6.0	72.8±6.0	76.1±5.6	0.026
Sex				0.092
Male	54	34 (94.4%)	20 (80%)	
Female	7	2 (5.6%)	5 (20%)	
Subsite				0.145
Hypopharynx	36	24 (66.7%)	12 (48%)	
Larynx	25	12 (33.3%)	13 (52%)	
Stage				0.012
II	18	15 (41.7%)	3 (12%)	
III IV	43	21 (58.3%)	22 (88%)	
T				<0.001
1 2	33	30 (83.3%)	3 (12%)	
3 4	28	6 (16.7%)	22 (88%)	
PS				0.590
0 1	60	35 (97.2%)	25 (100%)	
2	1	1 (2.8%)	0 (0%)	
Sarcopenia				0.263
Yes	15	7 (19.4%)	8 (32%)	
No	46	29 (80.6%)	17 (68%)	

p-Values in bold indicate statistical significance.

Table III. Demographic characteristics of the participants (n=61).

	Preservation of larynx (n=36)	Laryngectomy (n=25)	p-Value
CRP (mg/dl)	0.4±0.7	0.7±0.8	0.002
Alb (mg/dl)	3.9±0.4	3.6±0.6	0.025
Zn (µg/dl)	70.0±12.7	65.6±14.8	0.205
Hb (g/dl)	13.3±1.4	12.4±1.8	0.041
Total lymphocyte count (cells/mm ³)	1,694.5±542.4	1,490.2±455.6	0.147
Tf (mg/dl)	223.8±47.0	196.1±40.3	0.078
TTR (mg/dl)	23.7±6.3	19.3±6.4	0.011
Body weight (kg)	56.5±7.5	53.2±12.7	0.495
SMM (kg)	24.4±3.3	22.2±5.5	0.200
Body fat amount (kg)	11.6±4.5	12.1±5.7	0.639
Body mass index (kg/m ²)	20.1±2.2	20.3±3.6	0.971
Body fat percentage	20.2±6.2	22.0±8.0	0.256
SMI (kg/m ²)	6.7±0.7	6.3±1.4	0.446
Handgrip strength (kg)	32.9±7.4	27.9±9.8	0.067

Results are expressed as a mean±standard deviation (SD). SMM: Skeletal muscle mass; SMI: skeletal muscle index; Alb: albumin; CRP: C reactive protein; Hb: hemoglobin; Tf: transferrin; TTR: transthyretin. p-Values in bold indicate statistical significance.

measurements, including BW, SMM, SMI, BMI, and GS (Table III).

Figure 4 shows the amount of change in physical measurements (BW, SMM, SMI, BMI, and GS) between the laryngectomy group and the laryngeal preservation group. The average change one year following treatment in the laryngeal preservation group, when compared to prior to treatment, was a significant decrease in BW of -0.035, SMM of -0.030, SMI of -

0.026, BMI of -0.034, and delete grip GS of -0.066. The average change one year following treatment in the laryngectomy group compared to prior to treatment was an increase in BW of +0.028, SMM of +0.026, SMI of +0.008, BMI of +0.032, and GS of +0.026. Although no changes in serum biochemical testing after treatment were observed in the laryngeal preservation group, Alb, Tf, and TTR exhibited significant improvement or a tendency toward improvement in the laryngectomy group (Table

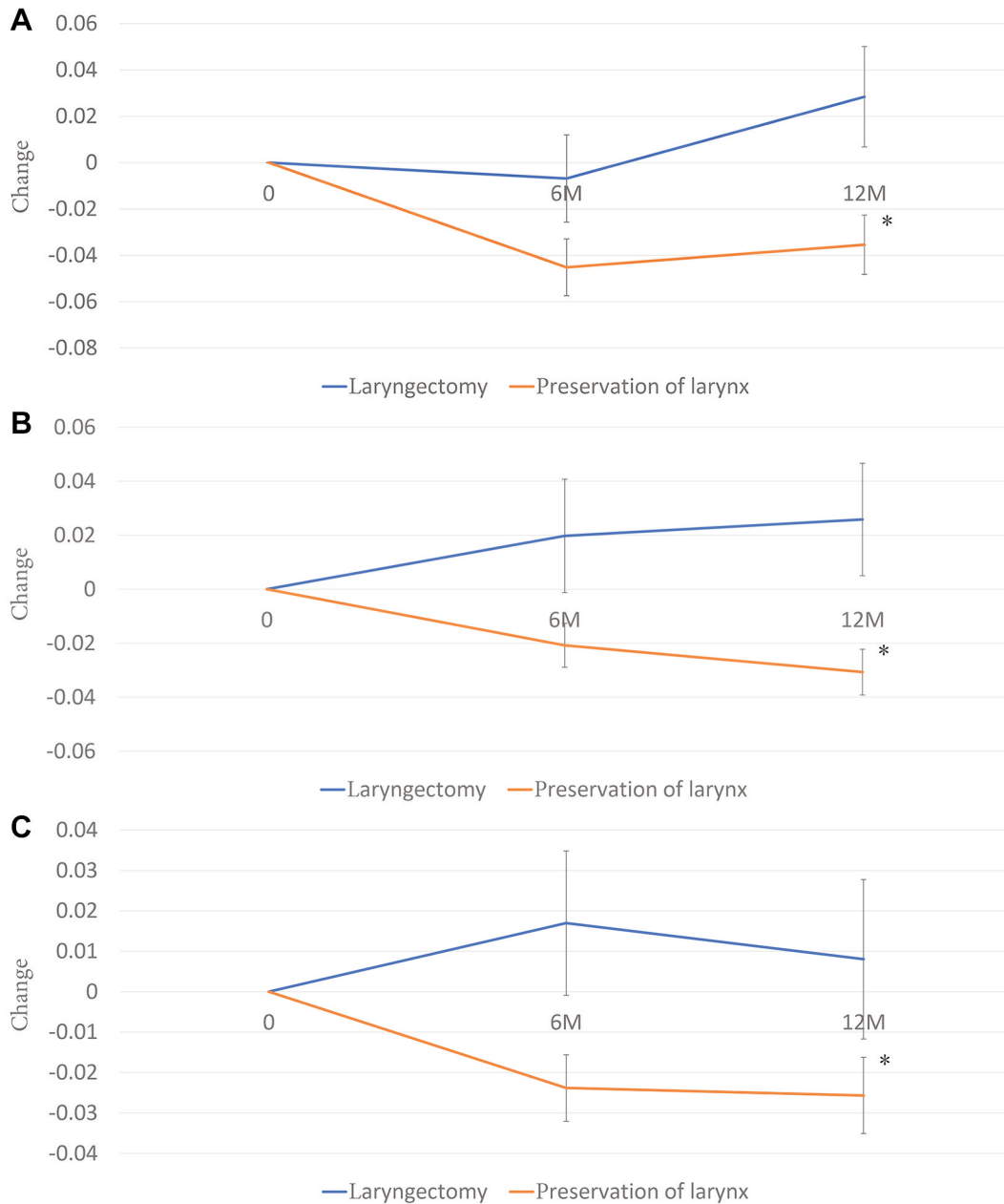


Figure 4. *Continued*

IV). Furthermore, improvement in sarcopenia was observed in only 2 out of 8 cases in the laryngectomy group (Table V).

A follow-up study of 36 patients in the larynx-preserving group up to one year after treatment indicated that the patients with sarcopenia before treatment had a significantly higher incidence of aspiration pneumonia (Table VI).

Discussion

The National Comprehensive Cancer Network (NCCN) guidelines (11) specify laryngectomy as one of the recommended

treatments for hypopharyngeal cancer and laryngeal cancer of T2 or higher. This study indicated that although there were significantly more advanced laryngeal and hypopharyngeal cancers of T2 or higher in the laryngectomy group than in the laryngeal preservation group in terms of T and stage classification, the 3-year survival rate and 1-year local control rate were nearly the same. While chemoradiotherapy (larynx preservation) is generally often selected to preserve voice function (12), surgical resection, including laser cordectomy and laryngectomy, is considered to have the same or better therapeutic results as radical chemoradiotherapy (13-16).

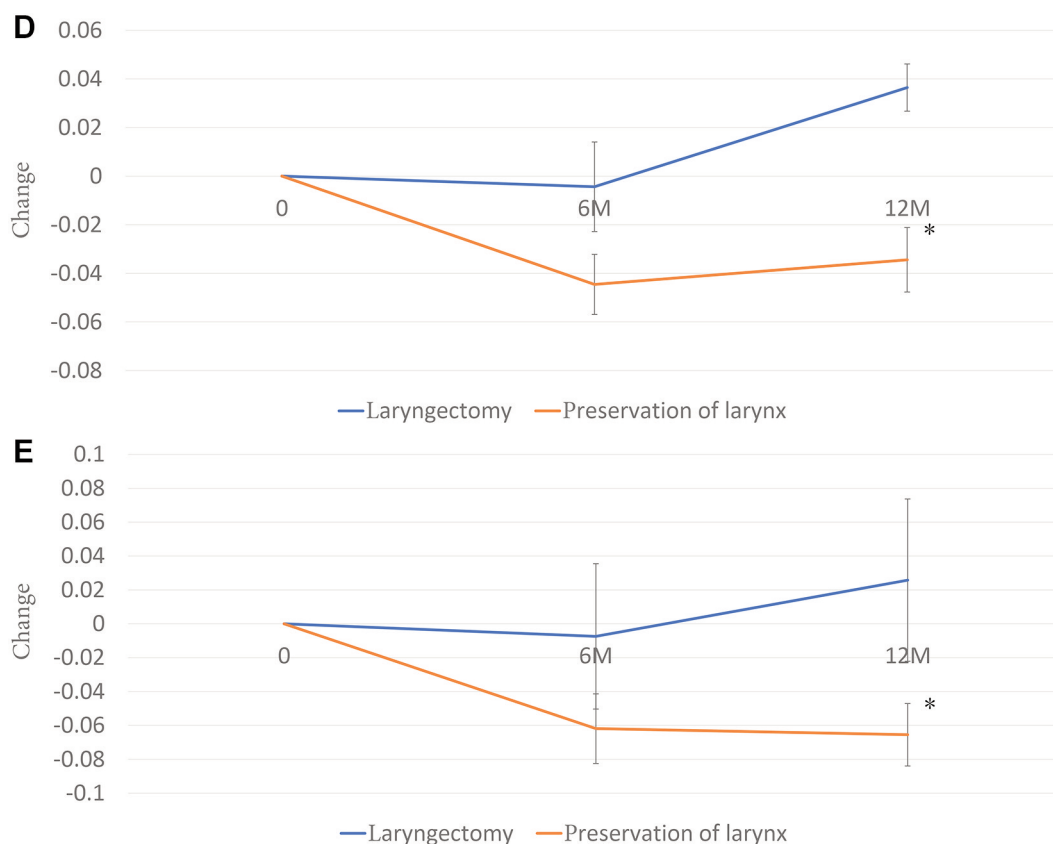


Figure 4. The amount of change in physical measurements between the laryngectomy group and the laryngeal preservation group. The amount of change in the laryngeal preservation group remained significantly decreased before treatment and 1 year after treatment. Results are expressed as a mean±standard error. A. Body weight (* $p=0.005$). B) Skeletal muscle mass (* $p<0.001$). C) Skeletal muscle mass index (* $p=0.03$). D) body mass index (* $p=0.005$). E) Grip strength (* $p=0.001$).

Table IV. Changes in biochemical testing (n=61).

		Before treatment	6 months after treatment	1 year after treatment	p-Value
Laryngectomy (n=25)	Al (mg/dl)	3.6±0.6	3.9±0.4	3.9±0.5	0.053
	Tf (mg/dl)	196.1±40.3	218.8±44.2	231.6±40.9	0.010
	TTR (mg/dl)	19.3±6.4	21.0±5.7	23.1±7.7	0.080
Preservation of larynx (n=36)	Alb (mg/dl)	3.9±0.4	4.0±0.4	4.0±0.4	0.756
	Tf (mg/dl)	223.8±47.0	226.9±47.9	234.1±54.0	0.365
	TTR (mg/dl)	23.7±6.3	23.2±5.9	23.2±6.9	0.696

Alb: Albumin; Tf: transferrin; TTR: transthyretin. p-Values in bold indicate statistical significance.

Next, compared to before treatment, there was a significant decrease in body composition and GS in the larynx-preserving group one year after treatment; however, there was no significant difference in the laryngectomy group, although a tendency toward improvement was observed. In fact, of the 36 patients in the laryngeal preservation group, seven of the seven patients who had sarcopenia before treatment showed no improvement, while two of the eight patients in the

laryngectomy group became non-sarcopenic after 6 months. Poor nutrition is one cause of sarcopenia. Undernutrition causes weight loss and leads to decreased muscle strength through loss of muscle mass (original meaning of sarcopenia) (17, 18). Based on the blood data, a significant improvement in nutritional status was observed in the laryngectomy group, resulting in improvements in undernutrition and sarcopenia with weight gain.

Table V. Presence or absence of sarcopenia after 6 months (n=61).

	Sarcopenia → Non-sarcopenia	Sarcopenia → Sarcopenia	Non-sarcopenia → Non-sarcopenia	Non-sarcopenia → Sarcopenia
Laryngectomy (n=25)	2	6	15	2
Preservation of larynx (n=36)	0	7	26	3

Alb: Albumin; Tf: transferrin; TTR: transthyretin. *p*-Values in bold indicate statistical significance.

It has also been noted that in patients with sarcopenia, swallowing dysfunction may occur due to decreased motor function (19), and a relationship between sarcopenia and aspiration pneumonia was previously reported (20). The analysis of the laryngeal preservation group also indicated that the incidence of aspiration pneumonia in the sarcopenia group was 57.1%, which was significantly higher than that in the non-sarcopenia group ($p=0.016$). Judging from the above, total laryngectomy is also an aspiration prevention technique and should be selected as a therapeutic method, taking into consideration the fact that aspiration pneumonia may occur after treatment even if laryngeal preservation is possible with chemoradiotherapy. In particular, the presence or absence of sarcopenia before starting treatment is considered one of the indicators for selecting total laryngectomy as a treatment method.

In general, exercise and nutritional therapies are said to be important for improving sarcopenia (21-23). If the disease can be treated on an elective basis, even if sarcopenia is present, exercise and nutritional therapies can be performed, and treatment of the primary disease can be initiated once the sarcopenia has improved (24). However, it is difficult to wait for treatment until sarcopenia has improved in the case of malignant disease, so the means of selecting a treatment method is important in the case of sarcopenia. In this study, we were able to demonstrate the advantages of total laryngectomy in hypopharyngeal and laryngeal cancer of T2 or higher: 1) prevention of aspiration; 2) improvement of nutritional status; and 3) good local control.

The limitations of this study include that it is performed in a single center, number of cases is small and its retrospective design. While we believe that further accumulation of cases and an observation period are essential, this study clarified the usefulness of total laryngectomy in selecting laryngeal preservation and laryngectomy, making it useful in selecting treatment methods for sarcopenia patients and contributing to reducing complications and improving prognoses.

Conclusion

The advantages of total laryngectomy in hypopharyngeal and laryngeal cancer of T2 or higher include 1) prevention of

Table VI. Swallowing pneumonia and sarcopenia (n=36).

	Non-sarcopenia (n=29)	Sarcopenia (n=7)	<i>p</i> -Value
Swallowing pneumonia			0.016
Yes	3	4	
No	26	3	

aspiration; 2) improvement of nutritional status; and 3) good local control. The presence or absence of sarcopenia before starting treatment is considered to be an index for selecting total laryngectomy.

Conflicts of Interest

The Authors declare no conflicts of interest associated with this manuscript.

Authors' Contributions

RY and MK substantially contributed to the study conceptualization. SK, HT, SI, KM, NO, TK and MS were involved in data acquisition. MK and TK significantly contributed to data analysis and interpretation. MK wrote the manuscript text and prepared the figures. All Authors critically reviewed and revised the manuscript draft and approved the final version for submission.

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