SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 15: 7355-7361, 2018

Swallowing disorder following salvage total pharyngo-laryngo-esophagectomy with free jejunum reconstruction

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Received October 18, 2017; Accepted January 25, 2018

DOI: 10.3892/ol.2018.8213

Abstract. For recurrent cases or residual cases following concomitant chemo-radiation therapy (CCRT), salvage surgery is a frequently used treatment options. A swallowing disorder is one of the major complications of CCRT. The purpose of the present study was to evaluate the effect of CCRT on swallowing function in patients who underwent salvage total pharyngo-laryngo-esophagectomy (TPLE), and to evaluate the importance of pharyngeal constriction in patients who underwent TPLE. Between 2008 January and 2014 May, 54 patients were treated with salvage TPLE following CCRT or TPLE at the National Cancer Center Hospital East, Chiba, Japan and were included in the present study. A total of 14 patients underwent salvage TPLE following CCRT for recurrence or residual tumor (the salvage TPLE group), and 40 patients underwent TPLE as initial treatment (the TPLE group). The pharyngeal constriction score and the post-swallowing oropharyngeal residue rate were evaluated, and inadequate velopharyngeal closure was assessed by videofluorography. The pharyngeal constriction score of the salvage TPLE group was poorer than that of the TPLE group ($P<0.05$). The bolus residue in the oropharynx was significantly larger in the salvage TPLE group than in the TPLE group ($P<0.05$). With regards to inadequate velopharyngeal closure, there was no significant difference between the TPLE group and the salvage TPLE group ($P>0.99$). The results of the present study indicate that the swallowing function of patients who undergo salvage TPLE may be affected by CCRT.

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Key words: salvage surgery, total pharyngo-laryngo-esophagectomy, dysphagia, pharyngeal construction, chemoradiotherapy

Introduction

Concomitant chemo-radiation therapy (CCRT) is a standard treatment for head and neck cancer (1,2). For recurrent cases or residual cases following CCRT, salvage surgery is one of the important treatment options (3). With the increasing use of CCRT in the treatment of head and neck cancer (4), salvage surgery following failed CCRT will be increasingly prominent. Higher rates of acute and long-term toxicity following CCRT could result in higher rates of postoperative morbidity and mortality (5,6). Swallowing disorders are major complications of CCRT that can directly affect the quality of life of the patient. Previous studies have shown that the major complications of CCRT are xerostomia, reduced mobility of the tongue base, reduced mobility of the larynx, reduced pharyngeal and laryngeal sensation (incomplete protection of the airway) and trismus (7,8). These complications can result in the reduction of pharyngeal construction and inadequate laryngeal closure. Pharyngeal constriction, which presses the bolus to the esophagus, and laryngeal closure, which prevents bolus invasion to the lungs, serve major roles in swallowing function. In this sense, it seems that total laryngectomy and total pharyngo-laryngo-esophagectomy (TPLE) with free jejunal graft reconstruction cannot cause dysphagia because the larynx is removed. However, the incidence of dysphagia following total laryngectomy has been reported to range between 10 and 60% (9). Similarly, the overall reported incidence of dysphagia following pharyngolaryngectomy with free jejunal graft reconstruction is reported to range between 2 and 58% (10). Previous studies (9,10) have reported a higher incidence of dysphagia at discharge and at long-term follow-up in patients that underwent laryngectomy or pharyngolaryngectomy. We therefore hypothesized that pharyngeal constriction is strongly associated with swallowing function following TPLE. Furthermore, swallowing function following salvage TPLE is poorer than that following TPLE as an initial treatment, because the pharyngeal membrane of the patients who received salvage TPLE has already been affected by initial CCRT. To the best of our knowledge, there have been

no reports concerning dysphagia following salvage surgery, particularly salvage TPLE.

The purpose of the present study was to evaluate the influence of CCRT on pharyngeal constriction by comparing swallowing function between the salvage TPLE group and the initial TPLE group, and to confirm the role of pharyngeal constriction following TPLE.

Materials and methods

Study design and patients. The present study was a retrospective study conducted in a single institute in the National Cancer Research Center Hospital East (Kashiwa, Japan). The present study was approved by the Research Ethics Committee of the National Cancer Research Center Hospital East, and the research outline is open to the public.

Eligible patients were those who received salvage TPLE following CCRT or received TPLE as initial treatment for hypopharyngeal cancer, those whose clinical records were available and those who presented for treatment between 2008 January and 2014 May in the National Cancer Research Center Hospital East. CCRT in the current study was defined as at least one course of chemotherapy with >60-Gy radiation.

A total of 212 patients underwent TPLE with free jejunal reconstruction for laryngeal cancer and hypopharyngeal cancer between 2008 January and 2014 May in the National Cancer Research Center Hospital East, Chiba, Japan. A total of 60 patients were eligible for the current study, with the remaining patients excluded because they lacked videofluorography (VF) records. A further 6 of these 60 patients with laryngeal cancer: Glottic cancer and subglottic cancer, were excluded as the range of radiotherapy for glottic cancer and subglottic cancer was different from hypopharyngeal cancer and supraglottic cancer; thus, 54 patients (48 males, 6 females; median age 66.3 years; age range, 36-81 years) with hypopharyngeal cancer were included in the present study. Overall, 14 patients received salvage TPLE following CCRT for recurrence or residual tumor (the salvage TPLE group), and 40 patients received TPLE as initial treatment (the TPLE group) (Table I). The TNM stage of eligible patients was defined by Union Against Cancer and American Joint Committee on Cancer staging system for head and neck cancer, seventh edition (11).

Table I. Chemotherapy regimens.

Regimen	Patients, n
CDDP	11
Cetuximab	2
5-FU + CDDP	3
Total	16

CDDP, cisplatin; 5-FU, 5-fluorouracil.

Table II. Patient characteristics (n=60).

Characteristic	TPLE, n	Salvage TPLE, n
Total	44	16
Sex		
Male	40	14
Female	4	2
Tumor site		
Hypopharynx	40	14
Larynx (supraglottic)	4	2
Clinical T classification		
T2	8	2
T3	9	7
T4a	25	4
T4b	2	1
Clinical N classification		
N0	11	6
N1	6	2
N2	24	8
N3	3	0
Combined resection of the oropharynx[a]	13	1

[a]The superior margin is set to the tonsils. TPLE, total pharyngo-laryngo-esophagectomy; T, tumor; N, node (11).

Chemoradiotherapy. Chemoradiotherapy was performed for all patients in the salvage TPLE group. The chemotherapy regimens are depicted in Table II.

Following CT simulation in the treatment position, the radiation dose plan was made for each individual patient. A conventional fractionation schedule of 2 Gy/day was used. Only patients who received a total radiation dose that was >60 Gy were included in this study. The field of radiation is shown in Fig. 1.

Surgery. All surgery was performed at the National Cancer Research Center Hospital East by a single surgical team. All patients in the present study received TPLE with free jejunal reconstruction. With regards to primary resection, the superior margin was set based on the degree of cancer progression. For 40 patients, the superior margin was set to over the hyoid bone, and for the remaining 14 patients, it was set to the tonsil. The anal side margin was also set based on cancer progression, and it was set at the same level as tracheostomy for all patients. No patients exhibited a tumor extension to an area lower than cervical esophagus, and no patients required mediastinal tracheostomy.

Level 2-4 neck dissection (ND) was performed for the bilateral neck in the TPLE group. In the salvage TPLE group, ND was not performed. Retropharyngeal lymph node dissection was not performed for either group.

Reconstruction surgery. Following jejunal trimming on the oral side, pharyngojejunostomy was performed according to the Gambee technique (12), with 4-0 absorbable monofilament sutures. The anal side of the jejunal conduit was then trimmed

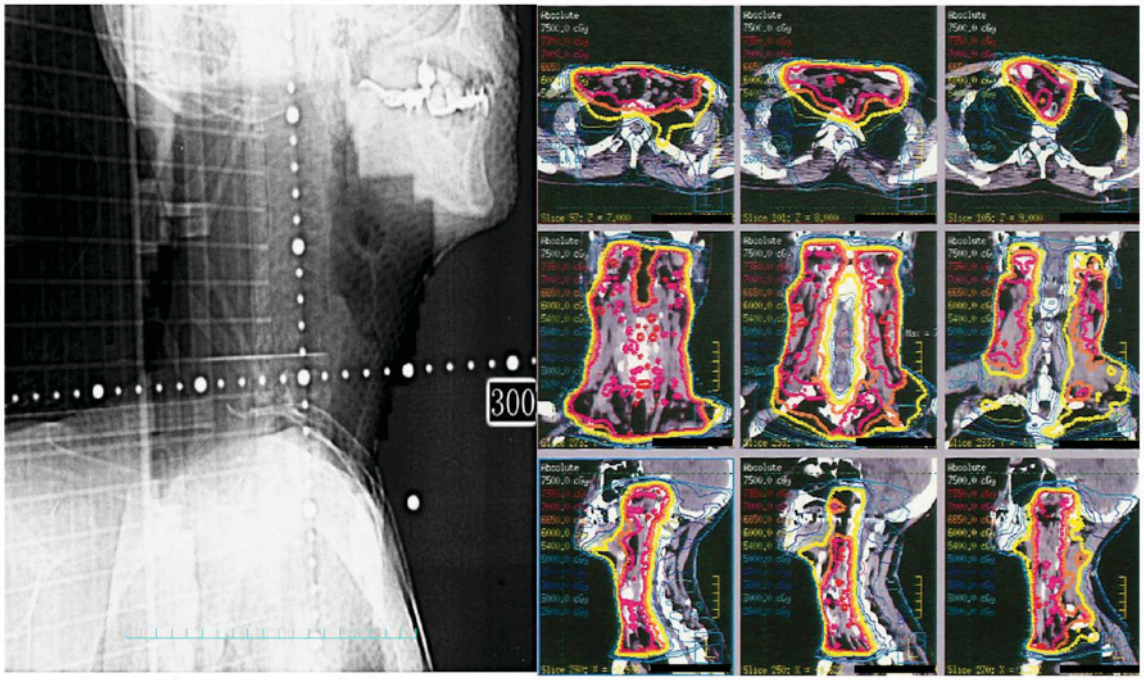

Figure 1. Radiation range for laryngeal cancer and hypopharyngeal cancer. The radiation range is approximately the same for all patients who received chemoradiation. The most cranial area of the radiation range is the top of the oropharynx, and the caudal end of the radiation range is the supraclavicular area.

so that the jejunal graft would be pulled straight following complete enteric anastomosis. When relaxed, the trimmed jejunum was approximately two-thirds the length of the defect. Jejunoesophagostomy was performed using the Gambee technique, using 4-0 absorbable monofilament sutures. Following complete enteric anastomosis, the microscopic vascular anastomoses were established (13).

Swallowing assessment. Swallowing was assessed by VF using a modified barium swallow procedure (MBS). The contrast medium was 40% barium sulfate, and a digital video recorder was used to record the images observed from the lateral and frontal perspectives (30 frames/sec). The MBS protocol included swallowing boluses of 5 ml of thin liquid barium. Postoperative VF examination was performed at 7 days after surgery in the TPLE group and at 14 days in the salvage TPLE group.

Swallowing function was evaluated using the pharyngeal constriction score (14), the post-swallow pharyngeal residue rate and velopharyngeal regurgitation on VF. Pharyngeal constriction has been proposed as a parameter to distinguish functional from impared swallows (15-19). The parameters for evaluation of swallowing function were then determined, and those parameters were measured at the first swallow in the first VF study following surgery by one investigator. The first swallow was used to measure the parameters more easily than the second and subsequent swallows, because there was no bolus residue remaining from the previous examination.

With regards to the pharyngeal constriction score, the pharyngeal constriction ratio (PCR) is a well-established tool for measuring and monitoring pharyngeal constriction (16). It has been validated as a surrogate measure of strength and is associated with manometric findings (17,20). In the present study, the pharyngeal constriction score was determined using the VF evaluation criteria of the Japanese Society of Dysphagia Rehabilitation (14). This score is based on the data from VF analysis. The pharyngeal constriction score ranges from 1 to 3, with a higher score indicating a better contact of the front and back of the pharynx. Score 3 is normal (complete contact of the front and back and elimination of the air space of the pharynx); score 2 is inadequate contact of the front and back of the pharynx; and score 1 is abnormal (no contact of the front and back of the pharynx). In this analysis, a score of 3 was defined as normal, and a score of 2 or 1 demonstrated that patients had constriction disorder. VF finding criteria that are matched with the pharyngeal constriction score are depicted in Fig. 2. The pharyngeal score was estimated based on these criteria.

With regards to the post-swallow oropharyngeal residue rate, the residue rate was defined as the proportion of the oropharyngeal residue of the total bolus. The proportion of the oropharyngeal residue was estimated by comparing the thinness of the bolus in the oropharynx prior to and following swallowing using the following formula: Post-swallowing oropharyngeal residue rate = Oral-pharyngeal residue/total bolus x100 (%) (Fig. 3). The volume of residue was measured in the same way as the oropharyngeal swallow efficiency (OPSE). OPSE is a global measure of swallowing function used to quantify the interaction between the speed of bolus movement and the safety/efficiency of the mechanism in clearing material from the oropharynx (21).

With regards to inadequate velopharyngeal closure, the bolus flowing backward in the velopharynx was defined as a positive finding.

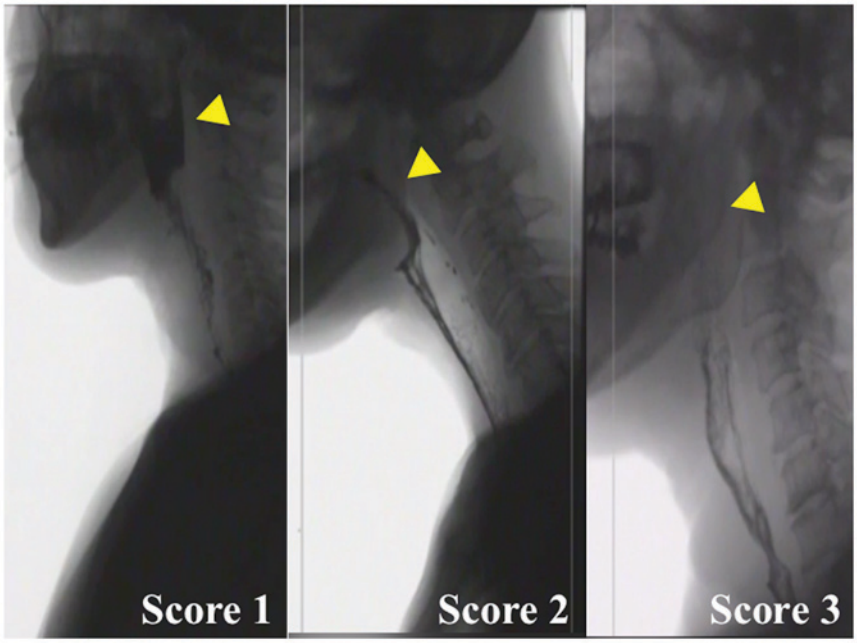

Figure 2. The pharyngeal constriction score from the videofluorography evaluation criteria of the Japanese Society of Dysphagia Rehabilitation. Score 3, Normal (complete contact of the front and back and elimination of the air space of the pharynx); score 2, inadequate contact of the front and back of the pharynx; score 1, abnormal (no contact of the front and back of the pharynx). A score of 3 is normal, and a score of 2 or 1 shows that patients have constriction disorder.

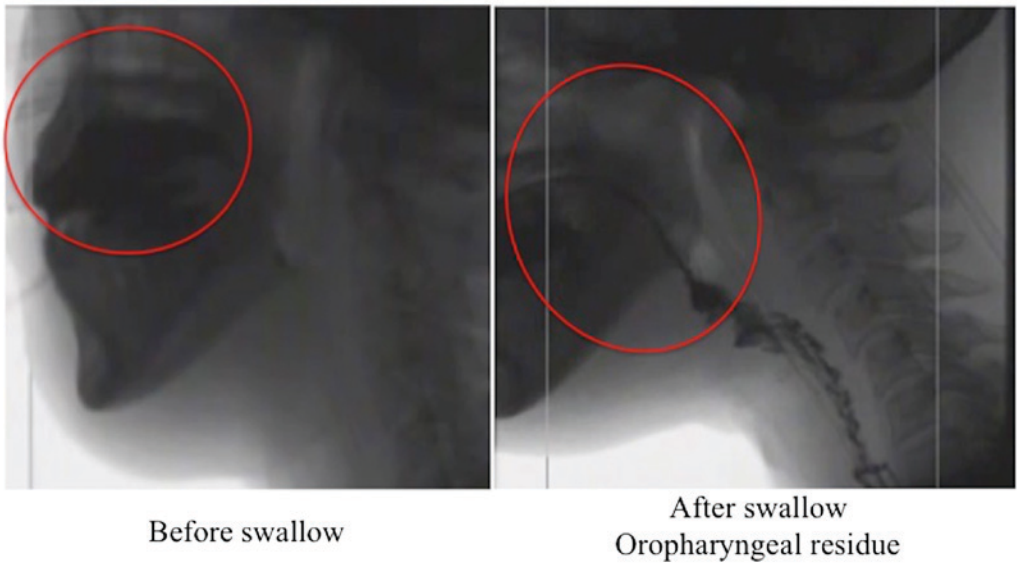

Figure 3. The volume of oropharyngeal residue is defined as the residual bolus volume in the oral and pharyngeal space after swallowing. The total volume is the bolus volume in the oral phase prior to swallowing.

Statistical analysis. Data were analyzed to evaluate differences between the salvage TPLE group and the TPLE group using Fisher's exact test, Wilcoxon rank sum test and Pearson's χ test, as appropriate. $P<0.05$ was considered to indicate a statistically significant difference. All analyses were performed using JMP 11 (SAS Institute, Inc., Cary, NC, USA).

Results

Pharyngeal constriction score. The pharyngeal constriction scores are depicted in Table III; this score is defined in Fig. 2, and a high score is indicative of good constriction. In the TPLE group, 35 patients had a score of 3 and 9 patients had a score of 2; no patients had a score of 1. In the salvage TPLE group, 8 patients had a score of 3, 5 patients had a score of 2, and 3 patients had a score of 1. Scores of 2 and 1 were defined as inadequate pharyngeal constriction, and a score of 3 was defined as normal constriction. Inadequate pharyngeal constriction was observed in 9 patients in the TPLE group and 8 patients in the salvage TPLE group. Normal pharyngeal constriction was observed in 35 patients in the TPLE group and 8 patients in the salvage TPLE group. Using a Pearson's

Table III. Pharyngeal constriction scores by group.

Score	TPLE, n	Salvage TPLE, n
3	35	8
2	9	5
1	0	3

TPLE, total pharyngo-laryngo-esophagectomy.

Table IV. Comparison of pharyngeal constriction.

Group	Inadequate, n	Normal, n	P-value
TPLE	9	35	0.0247[a]
Salvage TPLE	8	8	
Total	17	43	

[a]TPLE group vs. salvage TPLE group. TPLE, total pharyngo-laryngo-esophagectomy.

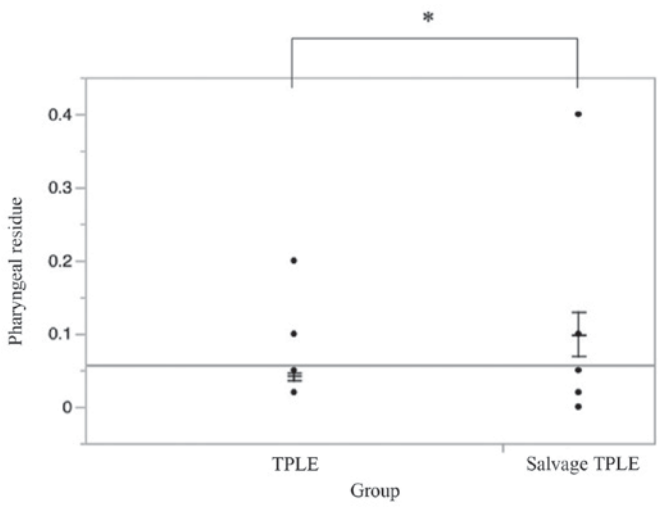

Figure 4. Comparison of pharyngeal residue between TPLE and salvage TPLE. The vertical axis depicts the residual rate and the horizontal axis depicts each groups. A plot of the same residual rate is overlaid. *P<0.05. TPLE, total pharyngo-laryngo-esophagectomy.

χ^2 test, the association between pharyngeal constriction type (normal or inadequate) and surgery type (salvage or initial) was investigated. There was a significant difference between the TPLE group and the salvage TPLE group. The pharyngeal constriction score was poorer in the salvage TPLE group than in the TPLE group (P<0.05) (Table IV).

Post-swallow oropharyngeal residue. The bolus residue rate in the oropharynx is depicted in Fig. 4. There was a significant difference in this rate between the TPLE group and the salvage TPLE group using Wilcoxon rank sum test (P=0.0263). However, there were outliers in the salvage TPLE group.

Table V. Comparison of velopharyngeal closure.

Group	Inadequate	Normal	P-value
TPLE	5	39	>0.99[a]
Salvage TPLE	2	14	
Total	7	53	

[a]TPLE group vs. salvage TPLE group. TPLE, total pharyngo-laryngo-esophagectomy.

Velopharyngeal closure. The proportion of patients that experienced inadequate velopharyngeal closure is depicted in Table V; there was no significant difference between the TPLE group and the salvage TPLE group (P>0.99).

Discussion

The present study demonstrated that pharyngeal constriction in patients who underwent salvage TPLE was more severe than that in patients who underwent TPLE, and that the pharyngeal residue rate of patients who underwent salvage TPLE was higher than that of patients who underwent TPLE.

Ward *et al* (22) demonstrated that there was a high incidence of dysphagia at discharge and during long-term follow-up in laryngectomy and pharyngolaryngectomy groups. Previous studies have shown that the major complications of CCRT are xerostomia, reduced mobility of the tongue base, reduced mobility of the larynx, reduced sensitivity (incomplete protection of the airway) and trismus (7,8). Eisbruch *et al* (23) demonstrated that conformal radiation reduced the radiation dose to the pharyngeal constriction. The present study revealed that the pharyngeal constriction scores of the patients who underwent salvage TPLE were poorer than those of patients who underwent TPLE. This result indicates that the adverse effects of CCRT affect pharyngeal constriction following TPLE. However, it is possible that the range of resection, reconstruction method, and the scar and edema (skin and pharyngeal mucosa) from surgery also affected swallowing function following TPLE. The present study was retrospective, so the background characteristics of the patients were not stratified, and other factors may also have affected this result. Further, the current study only evaluated the movement of the pharynx and did not evaluate pressure. It is possible that postoperative edema also affected this result.

With regards to pharyngeal residue, there was a significant difference between the TPLE group and the salvage TPLE group. The residue rate of the salvage TPLE group was higher than that of the TPLE group. Pharyngeal constriction in the salvage TPLE group may have been reduced by the initial CCRT treatment. However, there were outliers in the results of the current study, which may have affected this result. Furthermore, only the first VF examination following surgery was evaluated. It is possible that the residue rate may change with recovery, as the progress of recovery may differ for each patient. Post-swallow residue should be evaluated several times during the postoperative period.

With regards to inadequate velopharyngeal closure, there was no significant difference between the salvage TPLE group and the TPLE group. It was possible that the range of resection was not suitably wide in the present study. If the upper resection margin was over the tonsil and included soft palate resection, soft palate movement may be limited, causing inadequate velopharyngeal closure. In the present study, the bolus flowing backward in the velopharynx was defined as a positive finding, so when the amount of bolus flowing backward in the velopharynx was too small to bed captured and objectively analyzed, the reflex may not be captured correctly.

There were limitations to the present study. Since the current study was retrospective, the number of patients in the salvage TPLE group and the TPLE group may not have been adequate for the appropriate analysis of the differences. Particularly in the TPLE group, there were a number of ineligible patients, who lacked VF records; thus, the present study may be biased as a result. The quality of life of the patients was not evaluated, and it is possible that VF findings do not associate with the subjective perceptions of patients. Finally, the present study measured only motor response; the pressure of constriction, and pharyngeal and laryngeal sensation were not analyzed. In a future study, the pressure of constriction should be evaluated directly, and the associations between the findings of examinations and the subjective perceptions of patients will require evaluation.

However, the results of thecurrent study indicated the importance of pharyngeal constriction following TPLE. Stokely *et al* (24) reported that pharyngeal constriction was associated with pharyngeal residue; however, pharyngeal constriction was not the only factor involved in explaining pharyngeal residue. Treatments that improve pharyngeal constriction should result in less residue. It is possible that rehabilitation, bringing about improvements such as reduced pharyngeal constriction, can reduce pharyngeal residue. Thus, rehabilitation following TPLE, such as tongue-strengthening exercises and the Masako maneuver (25) may improve swallowing function and the patient's quality of life. Therefore, a future study should also evaluate the effect of rehabilitation.

In conclusion, the swallowing function of patients who underwent salvage TPLE may be affected by CCRT. Pharyngeal constriction may be due to complications of CCRT. The results of the current study may indicate that pharyngeal constriction has a crucial role in swallowing ability following TPLE.

Acknowledgements

We are grateful to Dr Fujimoto (Department of Otorhinolaryngology, Nagoya University Graduate School of Medicine) for helpful discussions.

Funding

No funding was received.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TM designed the study, and wrote the initial draft of the manuscript. TM contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to publish

The present study was approved by the Research Ethics Committee of the National Cancer Research Center Hospital East, Chiba, Japan (No. 2016-380), and the research outline is open to the public.

Consent for publication

All patients have consented to the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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