Degree of pharyngeal deformation caused by pharyngeal endoscopic submucosal dissection is associated with the incidence of aspiration pneumonia

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ABSTRACT

Background and study aims Endoscopic submucosal dissection (ESD) is one of the most minimally invasive treatments for superficial squamous cell cancer of the pharynx. However, aspiration pneumonia (AsP) associated with postoperative deformity of the pharynx may occur. The purpose of this study was to investigate the frequency of AsP and the degree of pharyngeal deformity after pharyngeal ESD.

Patients and methods This was a retrospective observational study of patients who underwent pharyngeal ESD at Okayama University Hospital between 2006 and 2017. The degree of pharyngeal deformation was assessed using the pharyngeal deformation grade (PDG). The primary endpoint was the frequency of AsP as a long-term adverse event.

Results Among the 52 patients enrolled, nine developed aspiration pneumonia, with a 3-year cumulative incidence of 9.0% (95% confidence interval [CI], 3.3%–22.0%). There were 16, 18, 16, and two patients that had PDG 0, 1, 2, and 3, respectively. Patients with a history of radiotherapy, as a treatment of head and neck cancer (44.4% vs. 11.6%; P= 0.02) and the high PDG group (PDG 2 and 3) (77.8% vs. 25.6%; P=0.005) had a significantly higher incidence of AsP. The 3-year cumulative incidence rate of AsP after ESD in the high PDG group was significantly higher than that in the low PDG group (PDG 0 and 1) (23.9% [95%CI, 9.2.–49.5%] vs. 0%; P=0.03).

Conclusions The incidence of aspiration pneumonia in the long-term course after pharyngeal ESD was revealed. The incidence of aspiration pneumonia may be associated with pharyngeal deformity, but further studies are needed.

Introduction

In recent years, with the development of endoscopic imaging technology, there has been an increase in early detection of squamous cell cancer of the head and neck. Transoral resection is increasingly used as a minimally invasive technique for the early detection of superficial squamous cell cancer. Transoral resections include endoscopic resection (endoscopic mucosal resection [EMR], endoscopic submucosal dissection [ESD],

endoscopic laryngo-pharyngeal surgery [ELPS], and transoral video laryngoscopic surgery [TOVS]), which have been reported to have good tumor control and long-term survival rates [1–9]. On the other hand, patients with superficial cancer of the pharynx have been reported to have a high incidence of heterogeneous multiple cancers in the head and neck region, and they often have to be treated multiple times for various head and neck cancers [4]. Because the pharynx is involved in swallowing, treatment of the pharynx may cause a decrease in swallowing function, but it has also been reported that patients who undergo transoral resection are less likely to require tube feeding [2, 7, 8, 10, 11].

Patients often experience frequent hospitalization for aspiration pneumonia (AsP) during follow-up after transoral resection, and there is reluctance to treat patients with multiple heterogeneous head and neck cancers, which can lead to further deterioration of swallowing function. The occurrence of AsP may be related to the decline in swallowing function associated with the initial treatment; however, not much is known about the incidence of AsP during follow-up after transoral resection. In addition, deformities of the pharynx that occur as the ulcer heals after transoral resection (▶ **Fig. 1**) may be associated with a decrease in swallowing function, but little is known about how often this occurs and to what extent it is associated with the development of AsP.

Therefore, we conducted a retrospective observational study to determine the association between the incidence of AsP and treatment-associated pharyngeal deformity during follow-up in patients who had undergone pharyngeal ESD and who were available for long-term follow-up.

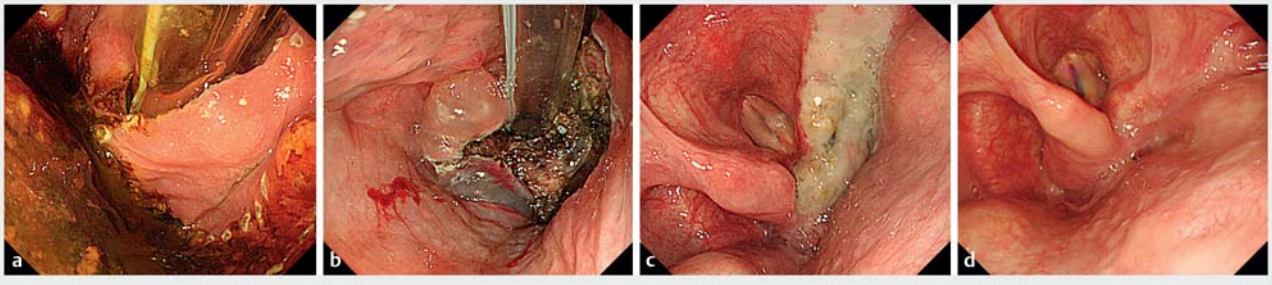
Patients and methods

We assessed 74 consecutive patients who underwent ESD for early cancers of the oropharynx or hypopharynx between September 2006 and December 2017 in the Department of Gastroenterology at Okayama University Hospital. The medical records of these 74 patients were reviewed, and the following information was collected: age, sex, lesion location, lesion size, date of pharyngeal ESD, duration of follow-up, date of most recent endoscopy, history of head and neck cancer or esophageal cancer, comorbidities, and occurrence of AsP. We excluded patients who did not undergo endoscopic follow-up for more than 1 year, and those who had undergone pharyngeal and/or laryngeal surgery pre- or post-ESD. We also excluded those who could not confirm a history of AsP occurrence during follow-up.

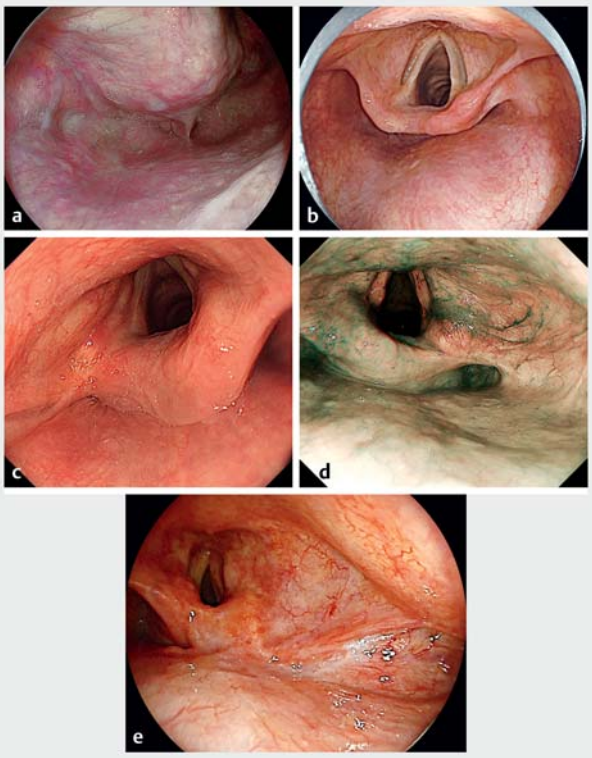
ESD was conducted for lesions with a preoperative diagnosis of severe dysplasia or possible node-negative squamous cell cancer without invasion to the muscle layer. ESD was performed as previously described [1].

After ESD, in our postoperative surveillance, endoscopy was performed every 6 months. We then asked questions about swallowing function using the functional outcome of swallowing scale (FOSS) format, and also checked for development of pneumonia [12]. These questions were asked over the phone if the patient did not visit the hospital. AsP was defined as the presence of imaging findings suggestive of AsP and requiring antibiotic treatment. To exclude AsP as an early adverse event of the treatment, AsP occurring within 2 months postoperatively until when the post-ESD ulcer scarred was not counted as an event.

The degree of pharyngeal deformation was assessed with the pharyngeal deformation grade (PDG) under endoscopic examination using the image of the pharynx from the most recent endoscopic examination of the patient. PDG was classified into four grades according to the degree of pharyngeal deformation observed during endoscopic observation, the operability of the endoscope, and treatment history for stenosis after pharyngeal ESD: grade 0, no observable deformation of the pharynx (▶ **Fig. 2a**); grade 1, mild deformation associated with treatment observed, and the original shape of the pharynx was maintained (▶ **Fig. 2b**); grade 2, an obviously deformed pharynx due to adhesions or scarring (e. g. a piriform sinus with more than half of depression have adhered, not passing through the scarred side of pharynx during the examination with normal diameter endoscope, bilateral deference of the larynx), and the original shape of the pharynx was slightly or not observed (▶ **Fig. 2c,** ▶ **Fig. 2d**); and grade 3, needing a narrow-diameter endoscope for insertion into the esophagus or history of balloon dilation for stricture of the pharynx (▶ **Fig. 2e**). The operability of the scope was judged only by whether it could be inserted into the esophagus through the piriform sinus on the resected side of the le-



▶ **Fig. 1** **a** Superficial squamous cell cancer of the pharynx located in the right piriform sinus to aryepiglottic fold. **b** Dissection and resection of the lesion. **c** Hypopharynx at 14 days after ESD. **d** Hypopharynx at 40 days after ESD. The right piriform sinus and larynx were severely deformed by scarring.



▶ **Fig. 2** **a** Post-ESD scar of posterior wall of the hypopharynx. No deformation was observed (PDG 0). **b** Post-ESD scar of the right piriform sinus. The deformation was observed, but the original shape of the pharynx was maintained (PDG 1). **c** Post-ESD scar of the left aryepiglottic fold. The bilateral deference of the larynx was observed (PDG 2). **d** Post-ESD scar of the right piriform sinus with more than half of depression have adhered (PDG 2). **e** Stenosis of the hypopharynx after ESD (PDG 3).

sion. This judgment was made by an endoscopist who performed the examination at our hospital. Only if the examination report indicated difficulty in passing through the piriform sinus was the patient considered inoperable. The PDG was determined by a majority vote, with each of the three experienced endoscopists making the decision.

The Ethics Committee of the Okayama University Hospital approved this study (no. 1804–012), which also adhered to the Declaration of Helsinki.

Statistical analyses

The primary outcome was the incidence of AsP that developed during the follow-up period. The group that developed AsP (AsP group) and the group that did not develop AsP (non-AsP group) were compared. Secondary outcomes were the incidence and degree of pharyngeal deformation after ESD. The low PDG (PDG of 0 or 1) and high PDG groups (PDG of 2 or 3) were compared for incidence of AsP. The The Kaplan-Meier method was used to calculate the cumulative incidence of AsP, and Pearson' s correlation coefficient, chi-square test, Fisher's exact test, and log-rank test were used to compare the two groups. $P < .05$ was considered statistically significant.

▶ **Table 1** Patient demographics.

Patients, n	52
Male/female, n	50/2
Median age (range), years	66 (41–86)
Median follow-up period (range), days	1221 (432–4120)
Multiple treatments, n	10
Multiple lesions, n	18
Previous radiation therapy, n	9
Previous esophagectomy, n	7
Lesion, n	72
Location of the lesions	
▪ Oropharynx, n	9
▪ Hypopharynx, n	58
▪ Larynx, n	5
Median lesion size (range), mm	15 (3–40)

Results

ESD was performed in 74 patients with 99 lesions determined to be early cancer in the oropharynx or hypopharynx between September 2006 and December 2017. We excluded 22 patients for the following reasons: surgery in the pharynx area was performed before or after ESD (n = 5); the latest endoscopy was performed within 1 year after ESD (n = 12); and the patient could not confirm the occurrence or history of AsP (n = 8). Finally, 52 patients (median follow-up period was 36 months) were assessed.

Characteristics of the patients are shown in ▶ **Table 1**. Twenty patients were treated for esophageal cancer; six underwent subtotal esophagectomy, and 14 underwent esophageal ESD.

PDG of the latest endoscopic observation was as follows: 16 patients were grade 0, 18 patients were grade 1, 16 patients were grade 2, and two patients were grade 3 (▶ **Table 2**). Among the 16 patients with grade 2 deformity, nine had adhesions of the piriform sinus and 11 had deformities of the larynx. Of the two patients with grade 3 deformity, one required a small-diameter endoscope to pass through the pharynx, and the other had to undergo balloon dilation for pharyngeal stenosis. Six patients underwent only oropharynx resection, all of whom belonged to the low PDG group. Lesion size was significantly larger in the high PDG group (15 mm vs. 20 mm [median], $P = 0.04$). All patients in the high PDG group had resected lesions larger than 10 mm in size in the hypopharynx. A history of hypopharyngeal and/or laryngeal radiotherapy was significantly associated with high PDG ($P < 0.05$).

Three endoscopists with more than 10 years of endoscopic experience were asked to determine the PDG by presenting endoscopic images and treatment sites of 50 cases, excluding the two PDG 3 cases. PDGs with two or more concordant judgments were designated as the PDGs of the cases. The results

▶ **Table 2** Comparison of patient demographics based on degree of pharyngeal deformity.

	Low PDG n = 34	High PDG n = 18	*P* value
PDG (0/1/2/3)	16/18/0/0	0/0/16/2	
Male / female, n	32/2	18/0	n.s
Median age at the first ESD (range), years	68 (41–86)	66 (53–86)	n.s
Median follow-up period (range), days	1046 (432–3722)	1724 (489–4120)	n.s
Location of the lesion			
▪ Oropharynx, n	6	3	n.s
▪ Hypopharynx, n	36	22	n.s
▪ Larynx, n	2	3	n.s
▪ Median tumor size (range), mm	15 (2–40)	20 (5–37)	0.04
▪ Multiple times ESD, n	5	5	n.s
▪ Previous radiation therapy, n	3	6	0.04
▪ Aspiration pneumonia, n	2	7	<0.01
FOSS			
▪ 0–2, n	29	14	n.s
▪ 3–4, n	1	2	n.s

ESD, endoscopic submucosal dissection; PDG, pharyngeal deformation grade; FOSS, functional outcome of swallowing scale.

showed that in 23 cases (46 %), all endoscopists agreed on the PDG, and in 27 cases (54 %), one endoscopist made a different decision. In no case were three different judgments made by each of the three endoscopists. In 84.6 % (11 of 13) of PDG 2 cases, all endoscopists agreed on the PDG determination, and in 15.4 % (2 of 13), one endoscopist determined the PDG as PDG 1. On the other hand, in cases with PDG 0 and 1, all endoscopists agreed on the PDG in 27 % of cases (10 of 37), and one endoscopist made a different decision in 73 % of cases (27 of 37). Although variability occurred in PDG 0 and 1 judgments, all judgments agreed on the classification of the high PDG or the low PDG in 92 % of cases (46 of 50).

During the follow-up period, nine patients were diagnosed with AsP and required antibiotic treatment. Details of the patients and their comorbidities that may be related to dysphagia are shown in ▶ **Table 3**. The median age of patients at the time of onset of AsP was 67 years, which occurred, on average, 46 months after the initial ESD. There were no significant differences in age, follow-up period, lesion size, number of ESD sessions, and history of multiple lesion resection between the AsP and non-AsP groups. Patients with a history of radiotherapy as a treatment of head and neck cancer (44.4 % vs. 11.6 %; $P = 0.02$) and the high PDG group (77.8 % vs. 25.6 %; $P = 0.005$) had a significantly higher incidence of AsP. The cumulative incidence of AsP at 3 years was 9.0 % (95 % CI, 3.3 %-22.0 %) (▶ **Fig. 3a**). The 3-year cumulative incidence rates for AsP after ESD in the high PDG and low PDG groups were 23.9 % (95 % CI, 9.2–49.5 %) and 0 %, respectively. A Kaplan-Meier curve of incidence of AsP was significantly higher in the high PDG group ($P = 0.02$) (▶ **Fig. 3b**).

FOSS was measured in 47 patients to assess swallowing function. It was measured between January 2017 and December 2018; therefore, five patients who had already completed their follow-up were not included. Among the remaining patients, 60 %, 11 %, 23 %, 2 %, 0 %, and 4 % had FOSS stages 0, 1, 2, 3, 4, and 5, respectively. The group of patients with a FOSS of 2 or more had a significantly higher incidence of AsP (35.7 % vs. 6.3 %; $P = 0.01$) and a significantly higher rate of belonging to the high PDG group (57.4 % vs. 25 %; $P = 0.04$) compared to the group of patients with a FOSS of 0 or 1. Only three patients had a FOSS of 3 or higher, which was an extremely small number. Those three patients had good eating habits after the initial treatment. However, two patients had multiple ESDs, and one patient had ELPSs three times in the hypopharyngeal region after ESD in 2014, and the eating situation gradually deteriorated. Of the nine patients with AsP, FOSS was available in seven. Two patients had a FOSS of 5, one was 3, two were 2, and two were 0. Two patients were placed on percutaneous endoscopic gastrostomy feeding (FOSS 5) due to repeated AsP. Of the 43 patients who did not develop AsP, FOSS was available in 40 cases, but none developed dysphagia with a FOSS of 3 or higher.

Discussion

Patients who have undergone transoral resection, including ESD, have been reported to have long-term survival, but there are no reports about swallowing function or the development of aspiration pneumonia in the long postoperative period. In this study, the 3-year cumulative incidence rate of AsP after

▶ **Table 3** Comparison of patient demographics in groups with and without aspiration pneumonia.

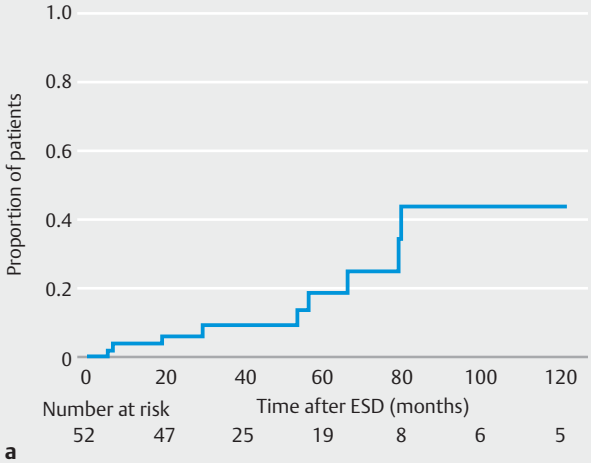
	AsP group n = 9	Non-AsP group n = 43	*P* value
Male/female, n	9/0	41/2	ns
Median age at first ESD (range), years	63 (60–75)	67 (41–86)	ns
Median follow-up period (range), days	1667 (377–4120)	727 (363–3648)	ns
Location			
▪ Oropharynx, n	2	7	
▪ Hypopharynx, n	12	46	
▪ Larynx, n	3	2	
Median tumor size (range), mm	15 (4–37)	15 (2–40)	ns
ESD for multiple lesions, n	4	6	ns
Previous esophageal surgery, n	1	6	ns
Previous radiation therapy, n	4	5	0.02
PDG (0/1/2/3), n	0/2/6/1	16/16/10/1	
High PDG, n	7	11	< 0.01
FOSS			
▪ 0–2, n	4	40	< 0.01
▪ 3–4, n	3	0	

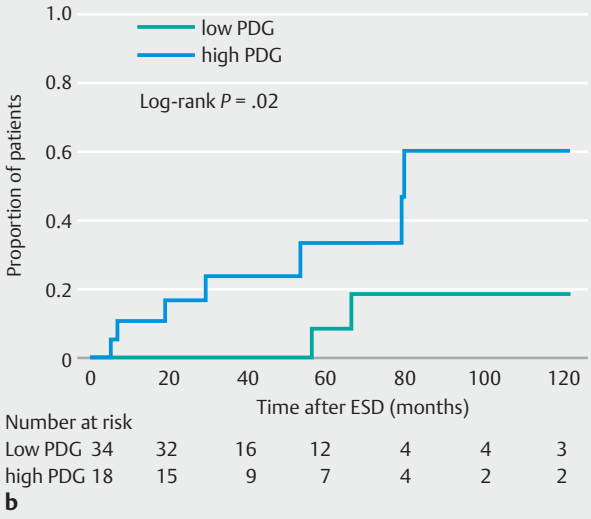
ESD, endoscopic submucosal dissection; PDG, pharyngeal deformation grade; AsP, aspiration pneumonia; FOSS, functional outcome of swallowing scale.

ESD was 9.0% (95%CI, 3.3%-22.0%) (▶ **Fig. 3a**). The 3-year cumulative incidence rates of AsP after ESD in the high PDG and low PDG groups were 23.9% (95%CI, 9.2–49.5%) and 0%, respectively. The cumulative incidence of AsP in the high PDG group was significantly higher than that in the low PDG group ($P = 0.02$) (▶ **Fig. 3b**). Among the nine patients who developed AsP, two were in the low PDG group, but both developed AsP at the age of 80 and were considered to be affected by age-related decline in swallowing function. In addition, one patient had a comorbid disease of amyotrophic lateral sclerosis, which causes swallowing impairment. On the other hand, seven patients in the high PDG group developed AsP at an average age of 65 years and were significantly younger ($P < 0.001$). High PDG and history of radiotherapy for head and neck cancer were considered to be risk factors for the development of AsP.

Because baseline swallowing function was not measured in almost all patients in this study, it was difficult to directly address the association between swallowing function and the degree of deformity of the pharynx and the development of AsP. To eliminate differences in preoperative swallowing function, we calculated the cumulative incidence of AsP in the high and low PDG groups in 30 patients after excluding all patients who may have already had impaired swallowing function before ESD (history of head and neck cancer surgery, previous radiotherapy for head and neck cancer, and history of AsP, or comorbidity that may lead to impaired swallowing function) using the Kaplan-Meier curves. The incidence of AsP was 0% (0/23) and 42.9% (3 of 7) in the low and high PDG groups, respectively, and the Kaplan-Meier curve showed a significantly higher incidence of AsP in the high PDG group (log-rank, $P = 0.0384$). However, to clarify the association between pharyngeal deformity and development of AsP, further studies measuring baseline swallowing function are needed.

PDG 3 or 4 was observed in 35% of patients in this study. In all cases, hypopharyngeal lesions larger than 10 mm in diameter were resected, which was considered to be a risk factor for deformity. On the other hand, in resection of the oropharyngeal lesion, no visible deformation was observed by endoscopic observation. However, in this study, only nine oropharyngeal lesions (13%) were resected, so further study is required. Tomifuji et al. reported that in TOVS, a history of resection of piriform sinus lesions, arytenoid lesions, pulmonary dysfunction, and large mucosal defects were risk factors for postoperative dysphagia [10]. Although it is not possible to make a simple comparison because the target lesions differed between TOVS and ESD, in this study, 89% of patients in the high PDG group and 68% in the low PDG group had a piriform sinus lesion. The rate was higher in the high PDG group, but no significant difference was observed. In this study, five patients underwent resection of the arytenoid lesion. Of the five patients, three were classified into the high PDG group, and two of them developed AsP. The remaining two were classified into the low PDG group, and one of them developed AsP. Patients with a resected arytenoid lesion had a significantly higher incidence of AsP than pa-





▶ **Fig. 3** **a** Cumulative incidence of aspiration pneumonia after pharyngeal ESD. **b** Cumulative incidence of aspiration pneumonia after pharyngeal ESD by degree of pharyngeal deformity.

tients without a resected arytenoid lesion. Patients with severe deformity after excision of the arytenoid lesion were considered to be at high risk of developing AsP.

The incidence of AsP as a perioperative complication after pharyngeal ESD has been reported to range from 4% to 14.3%. This study is the first to mention the incidence of AsP after postoperative ulcer healing. There are reports that swallowing rehabilitation after radiotherapy for head and neck cancer is effective in reducing dysphagia [12–14]; therefore, a similar effect may be expected after pharyngeal ESD, but there are no reports on the usefulness of swallowing rehabilitation for dysphagia after pharyngeal ESD. Further research is needed on the details of swallowing dysfunction after pharyngeal ESD and how to prevent it.

In Japan, covering the mucosal defect with a polyglycolic acid sheet [15] and local injection of triamcinolone acetonide [16–18] have been tried to prevent scarring or stenosis after transoral resection of superficial carcinoma of the pharynx, but the effects have not been clearly evaluated because there is no index for the degree of pharyngeal deformation.

To our knowledge, this is the first study to mention the risk of developing AsP in the long term or the degree of pharyngeal deformity after ESD. The degree of pharyngeal deformation was set as a classifiable index based on the images obtained by endoscopy for ordinary screening purposes. However, as the deformity of the pharynx becomes more severe, it becomes more difficult to obtain an appropriate endoscopic image of the pharynx. Therefore, the opinion of the practitioner regarding the operability of the scope in the pharynx was also added as a factor for determining the degree of deformation. Therefore, although it was not possible to obtain an image that can determine that the deformation was grade 2, there might have been a patient who was classified as having a mild deformation because the comment of the practitioner that the scar made it difficult to pass through the piriform sinus on that side was missing.

In the current study, only tumor size (>20 mm) and previous radiotherapy were identified as factors that contribute to high PDG. Further study with a larger number of patients may identify other risk factors for postoperative high PDG. ESD is recommended in cases where low PDG is expected. On the other hand, radiotherapy has a reported incidence of AsP of 25.4% to 62% and various other complications [19–21]. Therefore, there is no clear reason to avoid ESD even in cases in which high PDG is expected. Further studies are needed to directly compare ESD with radiotherapy in cases of expected high PDG. By analyzing a large number of patients using the classification of pharyngeal deformities used in this study, risk factors for cases with severe deformities may be clarified, which may be useful in selecting indications and treatment methods for lesions with the potential for severe postoperative deformities.

This study has several limitations. First, this retrospective study has a small sample size and was conducted at a single center. Second, there is no clear indication of ESD in the pharyngeal area, and the indicative lesion differs according to a hospital's internal guidelines. Third, this study examined ESD in the context of oral resection only; ESD is often performed on hypopharyngeal lesions, and there were few oropharyngeal lesions included in this study. Fourth, objective assessment of swallowing function, such as video fluoroscopic swallowing examinations, was not examined in this study. In fact, most of the patients enrolled did not have an objective swallowing function assessment performed, but a swallowing function test may help clarify the relationship between pharyngeal deformity and swallowing function. Fifth, the degree of pharyngeal deformation caused by a single oral resection has not been studied. Further studies are required. Sixth, in many cases, endoscopic examination was performed within 6 months after surgery, but because the purpose of the examination was to confirm residual recurrence, many close-up images were recorded, and images appropriate for judging pharyngeal deformity were missing. In recent years, the pharyngeal observation technique of endoscopists has improved, and many images of the pharynx have been recorded, making it easy to determine the deformation of the pharynx. Although pharyngeal deformity and dys-

phagia should have been identified in the early postoperative period, in this study, we used the latest endoscopic images to determine pharyngeal deformity. Finally, there was no specific rule regarding the endoscopic image-capturing method used for PDG determination. However, sufficient images were taken to determine PDG in all cases.

Conclusions

In conclusion, the PDG used in this study was considered to be useful as a visual indicator of potential decline in swallowing function. Severe pharyngeal deformity is considered to be associated with a potential decrease in swallowing function and the development of AsP, and patients who have already experienced pharyngeal deformity are considered to be at a high risk of developing AsP.

Competing interests

The authors declare that they have no conflict of interest.

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