

Clinicopathological Features and Outcomes of Endoscopic Submucosal Dissection for Superficial Cancer of the Pharynx

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The efficacy and safety of endoscopic submucosal dissection (ESD) for superficial cancer of the pharynx are still unclear. To identify clinicopathological features of superficial pharyngeal cancer, and the efficacy and safety of ESD, we retrospectively assessed 70 pharyngeal cancers in 59 patients who underwent ESD. Of these patients, 61.0% and 50.8% had a history of esophageal cancer and head and neck cancer, respectively. The median tumor size was 15 mm, and 75.7% of the lesions were located at the piriform sinus. The en bloc resection rate was 94.9%. Treatment-related adverse events occurred in 8 cases, but there was no treatment-related death. The lateral margin was positive for neoplasm in 3 lesions (4.3%) and inconclusive in 27 lesions (38.6%), but no local recurrence was observed. Cervical lymph node metastasis was observed in 6 patients, and was successfully treated by cervical lymph node dissection. The three-year overall survival rate was 91.5% (95%CI: 76.6-97.3%) and the cause-specific survival rate was 97.6% (95%CI: 84.9-99.7%). In conclusion, ESD for superficial pharyngeal cancer was safe and effective. "Resect and watch" is probably a feasible and rational strategy for treatment of patients with superficial pharyngeal cancer.

Key words: endoscopic submucosal dissection, superficial cancer, pharynx, endoscopic resection

In recent years, the number of pharyngeal cancer patients has been increasing. At the same time, the development of endoscopic imaging technology has contributed to an increase in the rate of superficial neoplasms among pharyngeal cancer patients [1-3]. For superficial cancers, transoral surgeries such as endoscopic mucosal resection (EMR) [4,5], endoscopic submucosal dissection (ESD) [6,7], endoscopic laryngo-pharyngeal surgery (ELPS) [8], and transoral video-laryngoscopic surgery [9] have been performed rather than open surgery or radiation chemotherapy, because

these procedures are minimally invasive, can preserve the physical function, and do not impair the patient's quality of life. Historically, ESD has frequently been adopted for the treatment of esophageal, gastric, and colonic neoplasms, although the number of institutions performing ESD for superficial cancer of the pharynx is increasing in Japan. Nonetheless, there have been only a few reports on the efficacy and safety of pharyngeal ESD, partly due to the rarity of superficial cancers. In this study, we retrospectively assessed the efficacy and safety of ESDs performed at our institution for the treatment of pharyngeal neoplasms.

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Patients and Methods

We assessed 70 lesions of early cancers in the oropharynx or hypopharynx in 59 patients who underwent ESD between September 2006 and February 2017 at the Okayama University Hospital. Prior to ESD, all patients underwent esophagogastroduodenoscopy and cervical ultrasound or computed tomography (CT). ESD was conducted as one of the treatment options for lesions with a preoperative diagnosis of either severe dysplasia or a possible node-negative squamous cell carcinoma without invasion to the muscle layer. The Ethical Committee of the Okayama University Hospital approved this study (no. 1804-012), which also adhered to the Declaration of Helsinki.

ESD procedures. All procedures were performed by one of the 2 endoscopists who had previously performed > 500 ESDs for esophageal, gastric, and colonic neoplasms. Patients were placed in a supine position and intubated. ESD was performed under general anesthesia. To make an adequate working space, an otorhinolaryngologist lifted the larynx with a direct laryngoscope and fixed it on the ventral side of the intubation tube (Fig. 1). Using a Q260J scope (Olympus, Tokyo) with a lucent hood (F-030; Top, Tokyo) on its tip, the endoscopist confirmed the location of the lesion and the operability of the scope. The extent of the lesion was demarcated using iodine dye, and the margin was circumferentially marked with a Dual knife (KD650; Olympus) and an electrosurgical generator unit (VIO 300D; ERBE, Tübingen, Germany) set at 40 W for a soft coagulation mode.

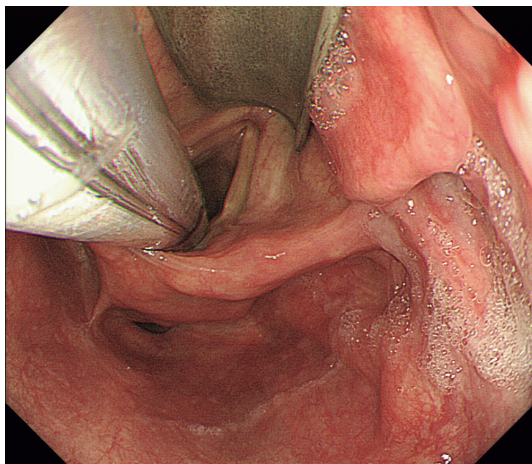


Fig. 1 To make an adequate working space, an otorhinolaryngologist lifted the larynx with a direct laryngoscope and fixed it on the ventral side of the intubation tube.

300D; ERBE, Tübingen, Germany) set at 40 W for the soft coagulation mode (Fig. 2). For submucosal injection, a solution of indigo carmine with glycerol was used. A mucosal incision was made around the lesion with the Dual knife in VIO endo cut I mode (effect 1; Fig. 3), and submucosal dissection was performed using the Dual knife and a Mucosectom (Pentax Medical, Tokyo) in swift coagulation mode at 40 W (effect 3; Fig. 4). In cases with difficult maneuverability, an otorhinolaryngologist inserted a nasopharyngo-

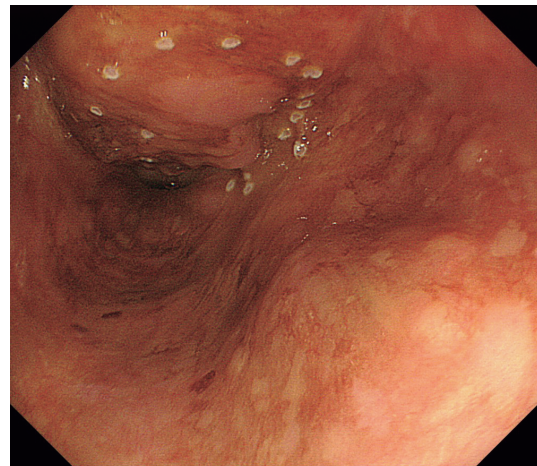


Fig. 2 The extent of the lesion was demarcated using iodine dye, and the margin was circumferentially marked with a Dual knife (KD650; Olympus) and an electrosurgical generator unit (VIO 300D; ERBE, Tübingen, Germany) set at 40 W for a soft coagulation mode.

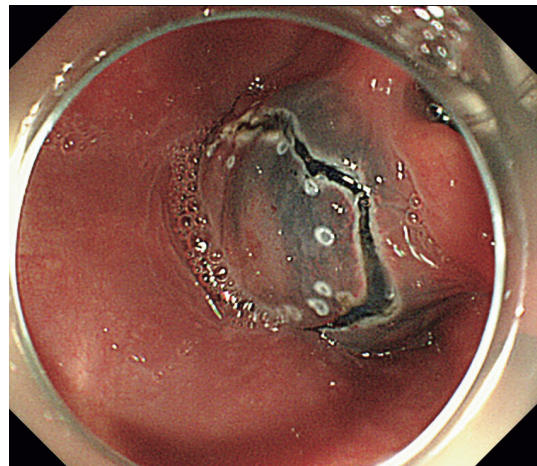


Fig. 3 For submucosal injection, a solution of indigo carmine with glycerol was used. Incision of mucosa was made around the lesion with a Dual knife in VIO endo cut I mode (effect 1).

laryngoscope to grasp and tow the lesion (Fig. 5).

Histological evaluations. Resected specimens were extended on a board, fixed in 10% formalin for 24 hours and sectioned at 2-mm intervals. The tumor size, specimen size, lateral and vertical margins for neoplasm, and lymphovascular invasion were assessed.

Management after ESD. After removal of the endotracheal tube, a swallowing function test was performed by an otorhinolaryngologist on a daily basis before starting oral intake. CT scanning and endoscopic surveillance were performed every 6 months to detect lymph node metastasis, local recurrence, and metachronous cancers of the mouth, pharynx, larynx, and

esophagus. Metachronous cancer was defined as a lesion detected 12 months or more after ESD.

Statistical analysis. The primary outcomes of this study were the incidence of short-term adverse events and long-term cause-specific and overall survival rates. In this study, we included the cases who received subsequent ESD for metachronous cancer in the analysis of short-term outcomes because frequent occurrence and repetition of ESD is characteristic of pharyngeal cancer. Long-term outcomes were analyzed by using the Kaplan-Meier method.

Results

Patients and lesion characteristics. We performed ESD for 70 lesions in 59 patients during the study period (Table 1). The mean age of the patients was 66.0 years. Thirty-six patients (61.0%) had esophagus squamous cell carcinoma (ESCC), which was previously diagnosed or treated in 22 patients (37.3%) and synchronously diagnosed in 15 patients (25.4%). Head and neck squamous cell carcinoma (HNSCC), other than early cancers in the oropharynx or hypopharynx treated with ESD, was found in 30 patients (50.8%). Twenty-nine patients (49.2%) had previously diagnosed or treated HNSCCs, and 4 patients (7.0%) had synchronous HNSCC. In 27 patients (45.8%), oropharyngeal and hypopharyngeal cancers were found during a follow-up examination of ESCC or a preoperative examination for ESCC. The median tumor size of the oropharyngeal and hypopharyngeal cancers was 15 mm, and 53 lesions (75.7%) were located in the piriform sinus.

Procedure outcomes. The en bloc resection rate was 94.9% (Table 2). The median fasting period was 4 days. Treatment-related adverse events occurred in 8 cases. Aspiration pneumonia developed in 6 cases and was treated with antibiotics. One patient who underwent laryngopharyngectomy prior to ESD developed hypopharyngeal stenosis and was treated by balloon dilation. There were no treatment-related deaths.

Histopathological outcomes. Of the 70 lesions, the horizontal margin was positive for neoplasm in 3 lesions (4.3%) and inconclusive in 27 lesions (38.6%) (Table 3). The vertical margin was positive in 2 lesions (2.9%). Subepithelial invasion was observed in 27 lesions (38.6%). Three lesions had vascular invasion, and 4 lesions had lymphatic invasion. One lesion had

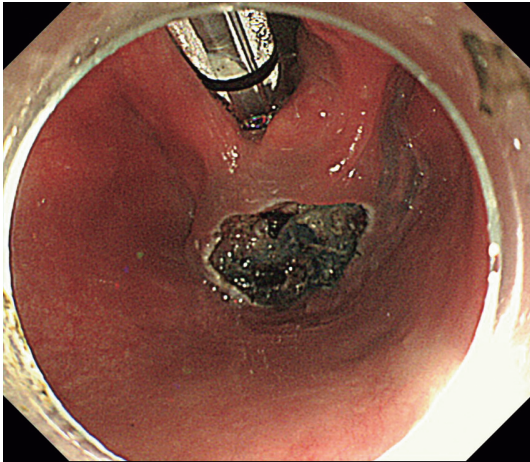


Fig. 4 Submucosal dissection was performed using a Dual knife with Mucosectom in swift coagulation mode at 40 W (effect 3).

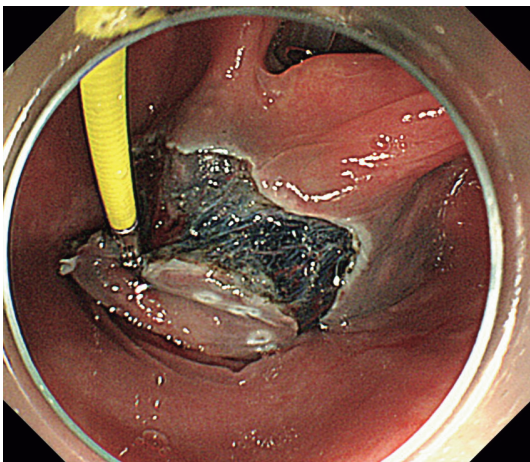


Fig. 5 In cases with difficult maneuverability, an otorhinolaryngologist inserted a nasopharyngolaryngoscope to grasp and tow the lesion.

Table 1 Characteristics of patients and lesions

	n	%
Median age (range in years)	66 (41-91)	
Sex		
Male	57	97
Female	2	3
History of ESCC	36	61
Previous ESCC	22	37
Synchronous ESCC	15	25
History of HNSCC	30	51
Previous HNSCC	29	49
Synchronous HNSCC	4	7
The purpose of examination		
Follow-up after treatment or preoperative examination of HNSCC	19	32
Follow-up after treatment or preoperative examination of ESCC	27	46
Follow-up after treatment or preoperative GI cancer	5	9
Follow-up after treatment of benign disease	3	5
Screening	5	9
Symptom	5	9
Lesions	70	
Tumor size, mm (range)	15 (2-40)	
Location		
Hypopharynx	61	87
Piriform sinus	53	76
Posterior wall	4	6
Postcricoid	2	3
Oropharynx	8	11
Posterior wall	6	9
Lateral wall	2	3
Other	1	1

ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; GI, gastrointestinal.

Table 2 Procedure outcomes

	n	%
Number of procedures	59	100
En bloc resection	56	94.9
Adverse event	8	13.6
Aspiration pneumonia	6	10.2
Hematoma	1	1.7
Stenosis	1	1.7
Pharyngitis	1	1.7
Fasting period, median (range), d	4	(1-28)
Hospital stay, median (range), d	11	(9-52)

both the vascular and lymphatic invasions. Sub-epithelial invasion was observed in all of the 6 lesions that had lymphovascular invasion.

Clinical course of the patients and long-term out-

comes. The median follow-up period was 35.5 months (range 2-119 months). No patients with a positive or inconclusive horizontal margin received radiation therapy postoperatively. However, none of the patients developed local recurrence. Among the 2 patients with a positive vertical margin, one patient received radiation therapy postoperatively. However, the patient died of primary pharyngeal cancer after 23 months. The other patient did not develop local recurrence. Seven patients developed cervical lymph node metastasis 1.2 to 54 months (median 8.5 months) after endoscopic resection of hypopharyngeal cancers. These patients were successfully salvaged with lymph node dissection. Eight patients died during the follow-up period. Only one patient died of pharyngeal cancer. Nine patients developed metachronous pharyngeal cancer at 24 months (range 13-52 months) after endoscopic

Table 3 Histopathological outcomes

	n	%
Number of lesions	70	100
Histology of specimens		
Squamous cell carcinoma	68	97.1
High grade dysplasia	1	1.4
Low grade dysplasia	1	1.4
Lateral margin		
Positive	3	4.3
Negative	40	57.1
Inconclusive	27	38.6
Vertical margin		
Positive	2	2.9
Negative	68	97.1
Vascular invasion		
Positive	3	4.3
Negative	67	95.7
Lymphatic invasion		
Positive	4	5.7
Negative	65	94.3
Specimen size, mm (range)	24	(7-55)
Tumor depth		
Epithelium	43	61.4
Subepithelium	27	38.6

resection. The 3-year overall survival rate was 91.5% (95%CI: 76.6-97.3%) and the cause-specific survival rate was 97.6% (95%CI: 84.9-99.7%).

Discussion

In this study, we evaluated patients who underwent pharyngeal ESD and found that the 3-year overall survival rate was 91.5% and the cause-specific survival rate was 97.6%. Short-term adverse events were observed in 13.6% of cases. ELPS is one of the treatment methods that can be used to safely perform en bloc resection of early pharyngeal cancers. ESD is conducted with endoscopy devices through the forceps hole of an endoscope and is mainly performed by gastroenterologists, whereas otorhinolaryngologists directly manipulate the surgical devices in ELPS. Tateya *et al.* reported that the 3-year overall and disease-specific survival rates of patients who underwent ELPS for 104 superficial laryngopharyngeal cancers were 90% and 100%, respectively, which were similar to our results [9]. ESD or ELPS is conducted as one of the treatment options for lesions with a preoperative diagnosis of a possible node-negative superficial laryngopharyngeal cancer based on the morphology of the lesion. Therefore,

indications are not different between ESD and ELPS. Radiation therapy is another modality that allows for laryngeal preservation in patients with head and neck cancer. Radiation can be applied to locally advanced oropharyngeal cancers, in addition to superficial lesions. Nakamura *et al.* reported the results of radiation therapy for early hypopharyngeal cancer; the overall and disease-specific 5-year survival rates for 95 patients without synchronous malignancies were 66.0% and 77.4%, respectively [10]. However, because there have been no studies comparing the effectiveness of ESD, ELPS, and radiation therapy for the treatment of early pharyngeal cancers, the treatment strategies have tended to differ among institutions. Future studies investigating the efficacy and safety of these procedures will be needed.

In the present study, 50.8% of the patients had a previous history of or synchronous HNSCC. Moreover, 61.0% of the patients had a previous history of or synchronous ESCC. It has been reported that synchronous or metachronous HNSCC and ESCC are identified in 7.8-44.1% and 39.2-85.6%, respectively, of patients with pharyngeal cancers [5,11-13]. It is noteworthy that 70.0% of the lesions were detected during a follow-up period after the treatment or preoperative screening of HNSCC or ESCC. These results reinforce the importance of a strict follow-up examination of newly developed pharyngeal superficial cancers in patients with esophageal cancer or head and neck cancer. Drinking, smoking and alcohol flushing have been reported as risk factors for developing pharyngeal cancers [14-17]. Morimoto *et al.* reported that pharyngeal screening was useful to detect early pharyngeal cancers in patients who underwent ESD for superficial esophageal cancers [18]. Careful observation of the pharynx in these patients is considered important.

The most common adverse events after ESD of pharyngeal cancers are aspiration pneumonia and subcutaneous emphysema. It has been reported that aspiration pneumonia and subcutaneous emphysema occur in 4-14.3% and 2-6%, respectively, of patients [11-13,19,20]. In this study, treatment-related adverse events developed in 13.6% of patients. Among these events, aspiration pneumonia was most frequent, accounting for 10.2% of cases (6 patients). It is likely that pharyngeal ESD adversely affects swallowing function. Therefore, physicians should be aware of the potential for aspiration pneumonia after pharyngeal

ESD. As a long-term adverse event, deterioration of swallowing function is a concern after transoral surgery. Tomifuji *et al.* reported that although the percutaneous endoscopic gastrostomy dependency rate is quite low in transoral surgery, resection of the piriform sinus and arytenoid, pulmonary dysfunction, and large mucosal defect were associated with postoperative dysphagia [21]. Because there has been no report on the swallowing function observed long after ESD or ELPS, further studies are anticipated.

The en bloc resection rate of our institution was 94.9%. A similar rate (77.4-100%) has been reported from other institutions [11-13, 19, 20]. Although the horizontal margin was positive in 4.3% and inconclusive in 38.6% of the lesions, local recurrence was not observed even in patients who did not undergo adjuvant therapy. The relatively higher rate of lesions with an inconclusive horizontal margin might have resulted from our attempt to resect the lesions as minimally as possible in order to reduce a postoperative adverse event. An unclear tumor margin sometimes occurs owing to crush or burn damage during the ESD procedure. In such cases, a close observation for possible burn effects from the ESD is acceptable. In this study, local recurrence was not observed in patients with a positive horizontal margin, suggesting that our strategies—that is, determining the extent of the lesion based on iodine staining and resecting the specimen as minimally as possible—are appropriate.

Cervical lymph node metastasis occurred in 6 patients (7 lesions) during the follow-up period (median 35.5 months). In all 6 of these patients, the pharyngeal lesion that had been resected by ESD had infiltrated to the subepithelium. Moreover, 4 lesions had lymphovascular invasion. Conversely, lesions with carcinoma *in situ* had no lymphovascular invasion or emergence of lymph node metastasis during the follow-up period. All patients with cervical lymph node metastasis were successfully treated by the cervical lymph node dissection. These results indicate that early pharyngeal cancers with subepithelial invasion or lymphovascular invasion should be strictly followed up for metastatic tumors [22]. It is also important to perform an en bloc resection of pharyngeal superficial cancers by oral surgery, including ESD, and a thorough histopathological evaluation in order to investigate the risk of lymph node metastasis.

For superficial pharyngeal cancers, a “resect and

watch” strategy has been proposed as an option after endoscopic resection of the lesions. In the “resect and watch” approach, patients with a possible incomplete endoscopic resection are observed until the development of secondary diseases, such as local recurrence, neck lymph node metastasis, and metachronous pharyngeal cancer without receiving additional treatments such as radical surgical resection and radiation therapy. Imai *et al.* applied this strategy and reviewed 32 patients with 47 lesions of superficial pharyngeal cancer [23]. The authors reported that, during the median follow-up period of 43 months, local recurrence (n=4), neck lymph nodes metastasis (n=5), and metachronous pharyngeal cancers (n=6) were observed and these lesions were successfully treated by a local resection or neck dissection. The 5-year overall survival rate was 84.4% and the cause-specific survival rate was 100%. In our present series, we similarly found that the 3-year overall survival rate was 91.6% and the cause-specific survival rate was 97.6%, indicating that the “resect and watch” strategy is feasible for the treatment of superficial pharyngeal cancers.

This study has several limitations. First, this is a single-centered, retrospective study. Second, although the surgeons who performed the ESD had considerable experience with endoscopic tumor resection of the gastrointestinal tract, they were only two in number. Therefore, multi-centered, prospective studies will be needed to determine the usefulness and safety of ESD for superficial pharyngeal cancers.

In conclusion, we revealed that ESD for superficial pharyngeal cancers resulted in a 3-year overall survival rate of 91.5% and a cause-specific survival rate of 97.6%. Although physicians must be mindful of the potential for short-term adverse events such as aspiration pneumonia, “resect and watch” is probably a feasible and rational strategy for the treatment of patients with superficial pharyngeal cancers.

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