

Case Series

# Endoscopic Laryngopharyngeal Surgery Combined with Endoscopic Submucosal Dissection as a Treatment Option for Superficial Hypopharyngeal Cancer with Suspected Synchronous Lymph Node Metastasis

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## Keywords

Laryngopharyngeal cancer · Endoscopic laryngopharyngeal surgery · Endoscopic submucosal dissection · Synchronous lymph node metastasis · Lymph node dissection

## Abstract

We report 4 cases of hypopharyngeal cancer preoperatively suspected with synchronous lymph node metastases. Pathologic lymph node metastasis was confirmed in three of the four cases. All 4 cases underwent endoscopic laryngopharyngeal surgery (ELPS) combined with endoscopic submucosal dissection (ESD) and subsequent lymph node dissection as an optional treatment rather than the standard treatment. Peroral resection for primary site was selected because of the expected decline in quality of life (QoL) after radical surgery. Among 4 patients, one developed local recurrence; however, the other three remained recurrence-free and survived without any additional treatment. Furthermore, the patient who developed local recurrence had a recurrence-free survival for more than 5 years, with additional chemoradiation therapy. No

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disorders in speech, swallowing, or breathing was observed during the follow-up period. ELPS combined with ESD is generally indicated for laryngopharyngeal cancer without synchronous lymph node metastasis. However, this can be a treatment option for patients may wish to preserve a greater QoL after treatment. In the future, when more data on the results and long-term prognosis of this treatment are accumulated, it may be possible to discuss its validity further.

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## Introduction

The laryngopharynx is an important organ for swallowing, speech, and breathing; therefore, clinicians are required to take into consideration the patients' quality of life (QoL) after treatment of malignancies in this area. Fortunately, the recent widespread availability of narrow-band imaging (NBI) with magnifying endoscopy has resulted in an increased detection rate of asymptomatic early stage laryngopharyngeal cancers [1, 2]. Endoscopic laryngopharyngeal surgery (ELPS) [3], endoscopic submucosal dissection (ESD) [4], and ELPS combined with ESD [5] are all excellent treatment procedures for early stage hypopharyngeal cancers in terms of QoL and curability. However, these endoscopic transoral resections exclude patients with synchronous lymph node metastases. In contrast, transoral laser microsurgery (TLM), transoral robotic surgery (TORS), and transoral videolaryngoscopic surgery (TOVS) have been used in combination with lymph node dissection to treat hypopharyngeal cancers with synchronous lymph node metastasis [6]. However, a common disadvantage of TLM, TORS, and TOVS is that they require specialized hardware and technical preparation; therefore, these treatments are not versatile and cannot be performed at most facilities. In this case series, we present cases of hypopharyngeal cancer preoperatively diagnosed as positive for synchronous lymph node metastasis in patients who underwent ELPS combined with ESD. The purpose of this report is to suggest new strategies for QoL maintenance, curability, and versatility in the treatment of hypopharyngeal cancer. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see [www.karger.com/doi/10.1159/000528424](http://www.karger.com/doi/10.1159/000528424)).

## Methods

### *Patients*

In our institution, 32 patients with laryngopharyngeal cancer (28 patients without synchronous metastasis and 4 patients diagnosed preoperatively with synchronous lymph node metastases) underwent ELPS combined with ESD between March 2017 and June 2022. According to Japanese clinical practice guidelines for head and neck cancer [7], surgical resection including peroral resection, chemotherapy, and radiation therapy is indicated for hypopharyngeal cancer with synchronous lymph node metastasis. Currently, there is no fixed protocol on the combination of these treatments. In general, cases with synchronous lymph node metastases are excluded from endoscopic peroral resection [8]. For the 4 patients with suspected synchronous cervical lymph node metastasis on preoperative examination, we initially recommended open procedures (with or without radiation) or platinum-based chemoradiotherapy as standard treatment. However, they rejected standard treatment as initial therapy owing to expected adverse effects and underwent lymph node dissection following ELPS combined with ESD. This study was approved by the hospital Ethics Committee.

## *Treatment Protocol*

In accordance with the Japanese clinical practice guidelines for head and neck cancer [7], the basic treatment strategy for superficial hypopharyngeal cancer at our institution was as follows: (a) ELPS combined with ESD is indicated for cases in which lymph node metastasis is not suspected on preoperative imaging studies, (b) radical surgery with lymph node dissection or chemoradiotherapy is indicated for patients with suspected lymph node metastasis on preoperative imaging, (c) if the patient does not agree to these standard treatments, the individual treatment plan is discussed at a conference with a head and neck surgeon, a radiation therapist, and a gastrointestinal endoscopist. ELPS combined with ESD and subsequent lymph node dissection for suspected simultaneous lymph node metastases, as described below, was an optional treatment proposed at the conference.

## *ELPS Combined with ESD and Subsequent Lymph Node Dissection*

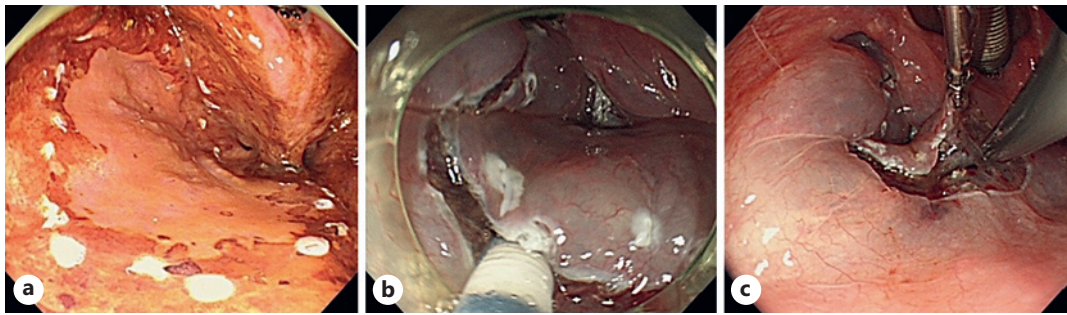
Under general anesthesia, an esophagogastroduodenoscope with NBI magnification (GIF-H260Z; Olympus Medical Systems, Tokyo, Japan) was inserted transorally to visualize the surgical field. NBI-magnifying endoscopy and endoscopic iodine staining were used to delineate lesion margins. Markings for the incision line were placed outside the margin of the lesion using a Flush knife BT-S (diameter: 2.2 mm, length: 2,000 mm, Fujifilm Co., Tokyo, Japan) with a high-frequency generator (VIO300D; ERBE Elektromedizin, Tübingen, Germany) set at 15 W for forced coagulation mode (shown in Fig. 1a). To obtain mucosal elevation, glycerol (Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) tinged with an indigo carmine solution was injected into the submucosa under and around the lesion (the subepithelial tissue of the hypopharynx is called the submucosa). After achieving sufficient mucosal elevation, a circumferential mucosal incision was made around the lesion with a Flush knife BT-S, and the submucosal tissue (part of the oral side of the lesion) was cut by grasping with curved grasping forceps (this procedure is called “creating the mucosal flap”). Procedures until the creation of the mucosal flap (shown in Fig. 1b) were performed by a gastroenterologist. Subsequently, subepithelial tissue dissection was performed by the head and neck surgeon using an electric needle knife (KD-600, Olympus Medical Systems) with orally inserted curved grasping forceps (for grasping the mucosal flap). Dissection was then performed using a high-frequency generator set at 40 W in the swift coagulation mode (shown in Fig. 1c). We have previously reported on these procedures in detail [9]. The subsequent lymph node dissection margin was determined according to the site of lymph node metastasis diagnosed by preoperative contrast-enhanced computed tomography, positron emission tomography-computed tomography (PET-CT), cervical ultrasound, and magnetic resonance imaging examination. The dissection was performed mainly on the internal deep cervical lymph nodes.

## *Follow-Up*

After resection, each patient underwent laryngoscopy and physical examination by a head and neck surgeon every 3–4 months. In addition, CT and esophagogastroduodenoscopy were also performed every 6 months. The follow-up period was defined as the period from ELPS combined with ESD to the date of the most recent examination.

## **Results**

The preoperative demographic details of the 4 patients are provided in Table 1. The pathological findings and postoperative course are summarized in Table 2.



**Fig. 1.** **a** Markings for the incision line are placed outside the margin of the lesion using a Flush knife BT-S. **b** Creating the mucosal flap for grasping with the orally inserted curved grasping forceps. **c** Subepithelial tissue dissection is performed by the head and neck surgeon using an electric needle knife.

**Table 1.** Characteristics and preoperative findings of 4 patients

	Case 1	Case 2	Case 3	Case 4
Age, years	68	84	53	81
Gender	Male	Male	Male	Male
Endoscopic findings of primary lesion				
Location of lesion	Posterior wall of hypopharynx	Posterior wall of hypopharynx	Left arytenoid	Posterior wall of hypopharynx
Macroscopic type	Protruded	Protruded	Protruded	Protruded
Preoperative findings of lymph node				
Imaging findings diagnosed as LNM	CT, PET-CT	CT, PET-CT	CT, PET-CT	CT, PET-CT, MRI
Location of LNM	Right internal deep cervical LN	Left internal deep cervical LN	Left internal deep cervical LN	Right internal deep cervical LN
Preoperative N factor	N1	N1	N1	N1

SEP, tumor invading the subepithelial layer; Ly+, lymphatic invasion positive; LN, lymph node; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging; ELPS, endoscopic laryngopharyngeal surgery; LNM, lymph node metastasis.

## Case Presentations

### Case 1

A 62-year-old male was referred to our institution with complaint of discomfort during swallowing. Esophagogastroduodenoscopy revealed a thick, flat, elevated lesion with ulcerative changes in the posterior wall of the hypopharynx (shown in Fig. 2a, b). A biopsy specimen revealed well-differentiated squamous cell carcinoma (SCC). Additionally, contrast-enhanced computed tomography revealed right internal deep cervical lymph node swelling, and intense fluorodeoxyglucose (FDG) uptake was observed in the swollen lymph nodes (shown in Fig. 2c). Therefore, we preoperatively diagnosed SCC in the hypopharynx with lymph node metastasis (clinical T3N1M0 in accordance with the Union for International Cancer Control tumor-node-metastasis (UICC/TNM) classification (8th edition) of head and neck cancer) and recommended that the patient undergo radical surgery accompanied with lymph node dissection or platinum-based chemoradiotherapy as standard treatment. However, he did not accept our treatment strategy as initial treatment because of expected swallowing, speech, or respiratory dysfunction and opted to prioritize function

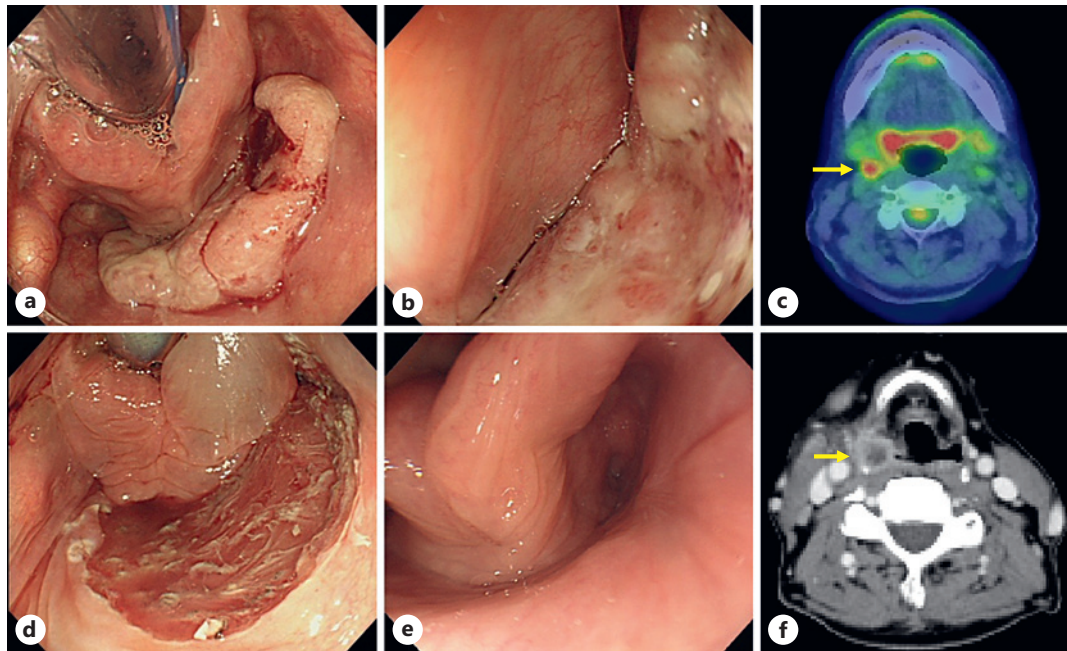
**Table 2.** Pathological findings and postoperative clinical course

	Case 1	Case 2	Case 3	Case 4
Pathological findings of primary lesion				
Size, mm	45	34	32	45
Tumor thickness, $\mu\text{m}$	8,000	8,000	10,000	6,000
Depth of invasion	SEP	SEP	SEP	SEP
Lateral margin	–	$\pm$	+	$\pm$
Vertical margin	–	–	–	–
Lymphovascular involvement	Ly +	–	–	Ly +
Timing of LN dissection	6 months after ELPS	1 month after ELPS	1 month after ELPS	Simultaneous excision with ELPS
Procedure of LN dissection	Removal of right internal deep cervical LN	Removal of left internal deep cervical LN	Removal of left internal deep cervical LN	Removal of right internal deep cervical LN
Pathological findings of LNM	+	+	–	+
Postoperative N factor	N1	N1	N0	N1
Follow-up periods, months	62	42	39	30
Adverse Events				
Post-ELPS bleeding	–	–	–	–
Subcutaneous emphysema	–	–	–	–
Aspiration pneumonia	–	–	–	–
Swallowing dysfunction, dysphagia score	0	0	0	0
Speech dysfunction	–	–	–	–
Recurrence	+	–	–	–
Type of recurrence	Submucosal local recurrence before lymph node dissection	–	–	–
Additional treatment for recurrence	IMRT and intra-arterial chemotherapy	–	–	–
Current status	Alive with complete Remission	Alive without recurrence	Alive without recurrence	Alive without recurrence

LN, lymph node; ELPS, endoscopic laryngopharyngeal surgery; IMRT, intensity-modulated radiotherapy.

preservation over higher curability. He insisted that standard therapy be considered when the disease relapses after optional therapy, which has fewer side effects. The reasons for the patient's desire for optional therapy are almost the same in the other 4 cases and are omitted from the following case presentations. A sufficient explanation was provided to the patient, and consent was obtained to perform lymph node dissection following ELPS combined with ESD. In our facility, we employed this treatment strategy for the first time, and we found it difficult to estimate the duration of the procedure; hence, we performed the



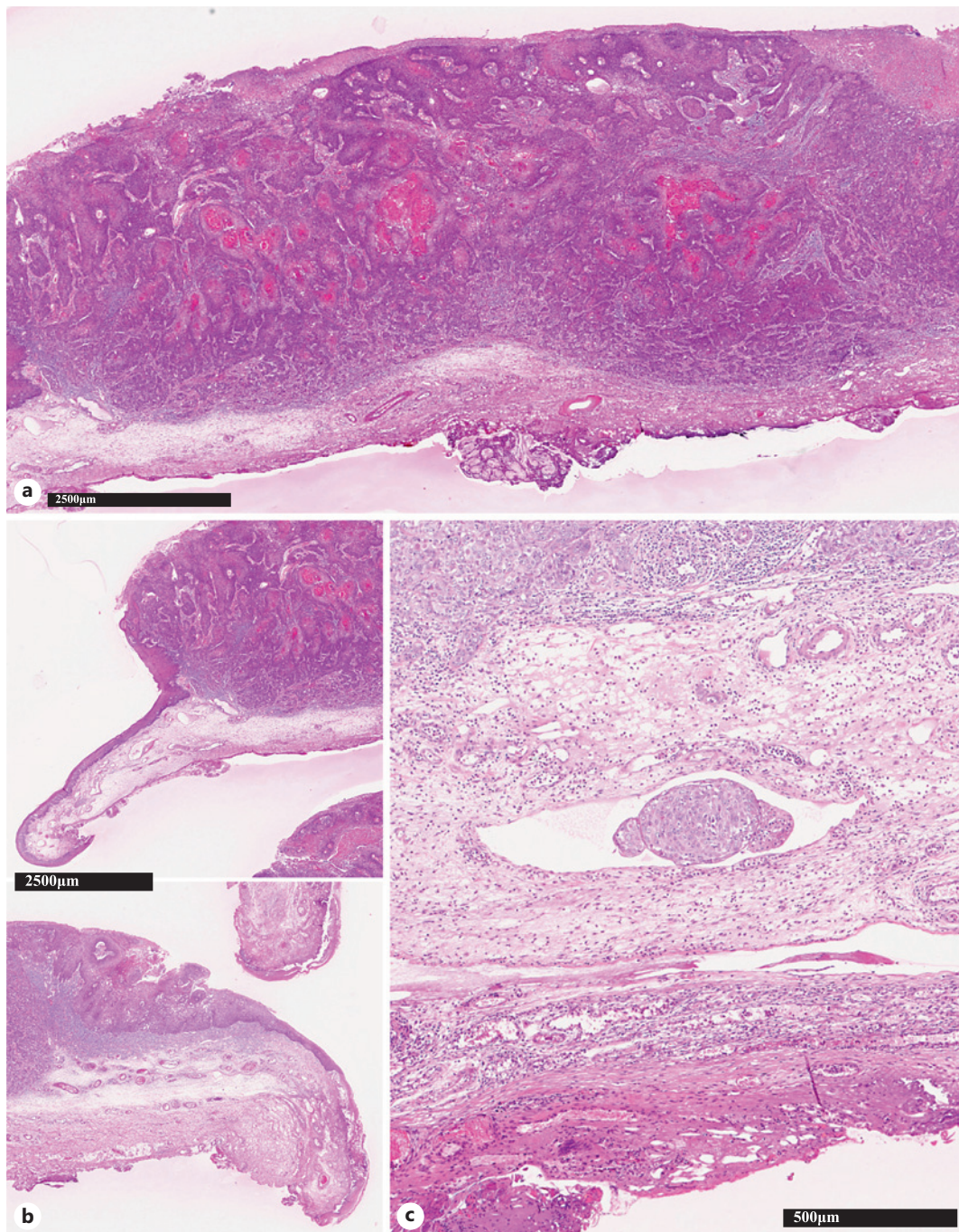


**Fig. 2.** **a** Intraoperative endoscopic images after tracheal intubation show a thick, elevated lesion at the posterior wall of the hypopharynx. **b** At the apex of the lesion, the mucosa disappears, forming an ulcer. **c** A PET-CT shows a right internal deep cervical lymph node swelling, and there is intense FDG uptake (SUV max 4.1) (Yellow arrow). **d** The primary site, immediately after ELPS combined with ESD. The lesion is completely resected. **e** Two months following ELPS combined with ESD. The ulcer has completely healed without significant deformation. **f** Two months following ELPS combined with ESD. Endoscopy confirms no residual recurrence, but contrast-enhanced CT shows submucosal mass formation in the primary site (Yellow arrow).

procedure twice: first to remove the primary lesion and second to dissect the lymph nodes. After the preoperative examination was completed, the patient's hypopharyngeal cancer was first removed within 150 min by ELPS combined with ESD (shown in Fig. 2d). Pathologic evaluation of the resected specimen confirmed that a well-differentiated SCC invaded subepithelial layer (invasion depth 8,000  $\mu$ m) with negative lateral and vertical resection margins (shown in Fig. 3a, b). A cluster of SCC was found in the lymph vessels in the subepithelial layer (shown in Fig. 3c). The patient was scheduled to undergo lymph node dissection after complete wound healing. Two months following ELPS combined with ESD, the sore throat associated with resection alleviated, and the mucosal defect healed completely (shown in Fig. 2e), while a preoperative examination for lymph node dissection revealed submucosal local recurrence (shown in Fig. 2f). The planned treatment strategy was altered, and he was administered a combination of intensity-modulated radiotherapy (IMRT; 30.6 gray irradiated in 17 fractions) and platinum-based intra-arterial chemotherapy (cisplatin 70 mg was administered for a total of 8 courses). After chemoradiation therapy, 6 months after ELPS combined with ESD, the local recurrence tumor disappeared, and we finally performed lymph node dissection. The pathological findings revealed residual SCC in the resected lymph node. Since then, no additional treatment has been administered, and the patient has been alive with complete remission for 62 months.

#### Case 2

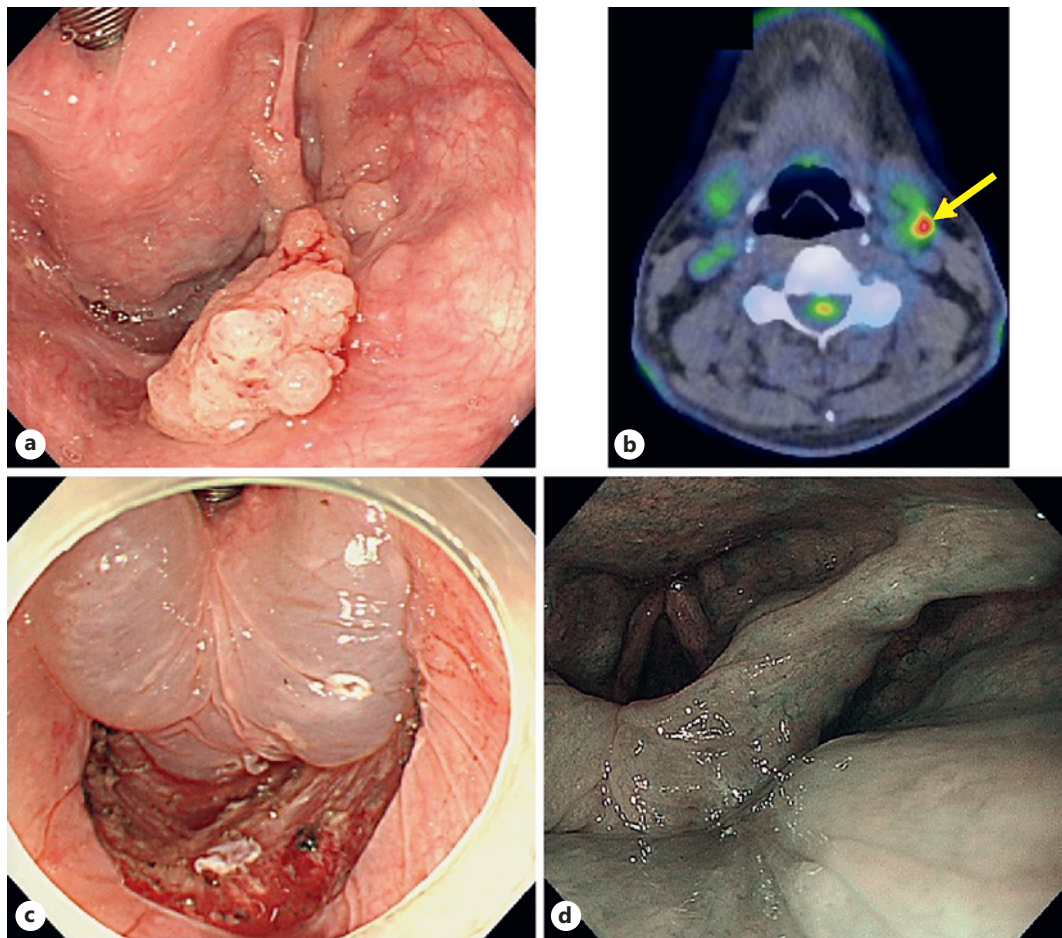
An 84-year-old male was referred to our institution for hypopharyngeal cancer that was accidentally discovered during screening endoscopy. Esophagogastroduodenoscopy revealed



**Fig. 3.** **a** Histology of the resected specimen shows the tumor invading the subepithelial layer (invasion depth 8,000 µm) with negative vertical resection margin. **b** Histology of the resected specimen also shows that the lateral margins were negative. **c** A cluster of squamous cell carcinoma was found in the lymph vessel.

a distorted elevated lesion in the posterior wall of the hypopharynx (shown in Fig. 4a), and the biopsy specimen revealed a well-differentiated SCC. PET-CT showed left internal deep cervical lymph node swelling. In addition, there was intense FDG uptake in the swollen lymph node (shown in Fig. 4b). Lymph node dissection following ELPS combined with ESD was





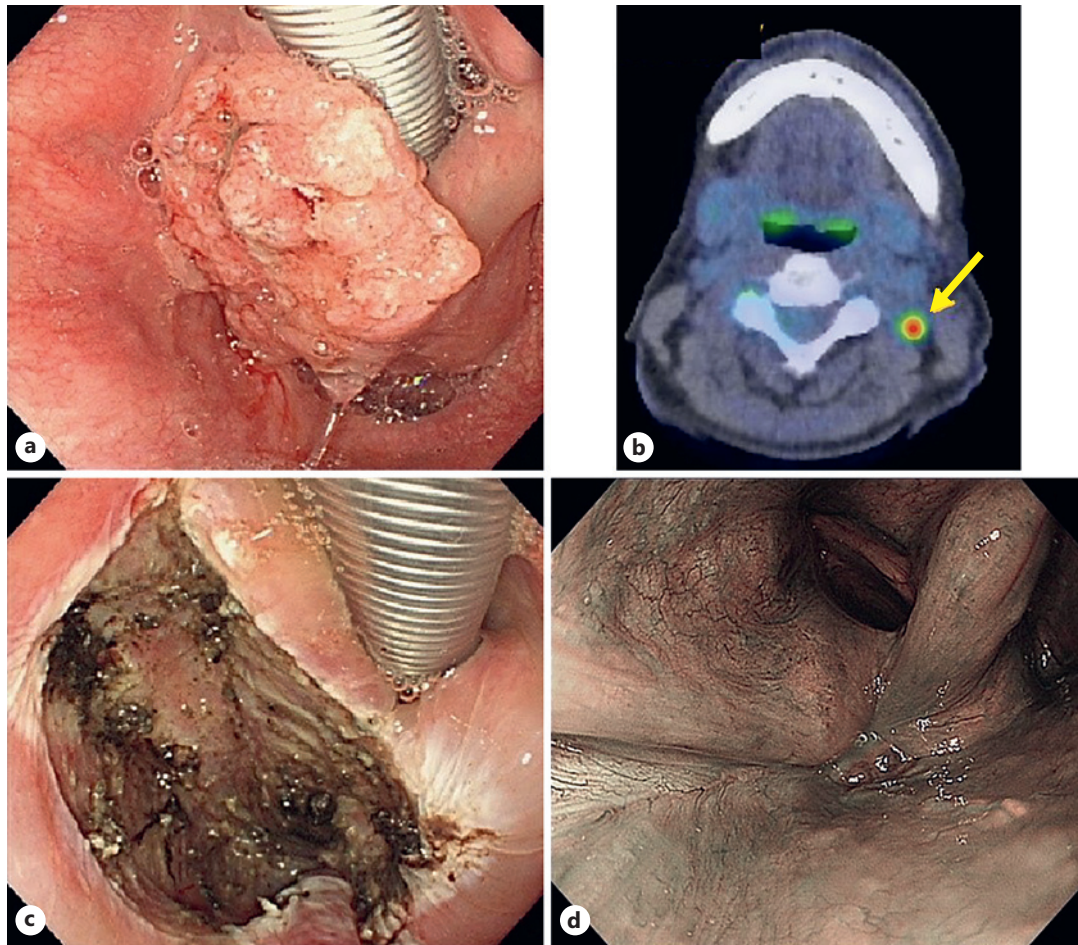
**Fig. 4.** **a** Intraoperative endoscopic images after tracheal intubation show a thick, partially flat elevated lesion at the posterior wall of the hypopharynx. **b** A PET-CT shows a left internal deep cervical lymph node swelling, and there is intense FDG uptake (Yellow arrow). **c** The primary site, immediately after ELPS combined with ESD. The lesion is completely resected. **d** Two months following ELPS combined with ESD. The ulcer has completely healed without significant deformation.

planned. During the 9-day hospital stay, the primary lesion was resected without adverse events in ELPS combined with ESD (shown in Fig. 4c). In addition, lymph node metastasis was resected without adverse events during the second 9-day hospitalization period. The mucosal defect after ELPS combined with ESD was completely covered by normal mucosa 2 months after resection (shown in Fig. 4d). Forty-two months after the treatment, the patient was recurrence-free and survived without any additional treatment.

### Case 3

A 53-year-old male was referred to our institution complaining of pain during swallowing. Esophagogastroduodenoscopy showed a distorted protruding lesion on the left arytenoid (shown in Fig. 5a), and the biopsy specimen revealed a well-differentiated SCC. PET-CT showed left internal deep cervical lymph node swelling and intense FDG uptake in the swollen lymph node (shown in Fig. 5b). A well-experienced therapeutic radiologist (N.F.) opined that chemoradiotherapy alone would not suffice for such a large-volume protruding cancer. It took approximately 140 min to remove the primary lesion by ELPS combined with ESD with a negative vertical margin during a 19-day hospitalization (shown in Fig. 5c). Pathologic evaluation of the



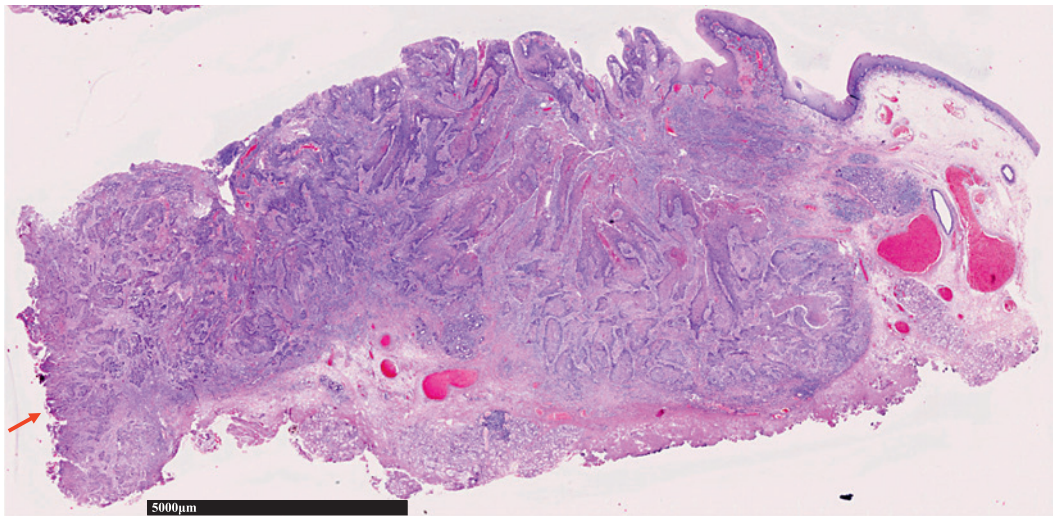


**Fig. 5.** **a** Intraoperative endoscopic images after tracheal intubation show a distorted protruded lesion on the left arytenoid. **b** A PET-CT shows a left internal deep cervical lymph node swelling, and there is intense FDG uptake (SUV max 4.7) (Yellow arrow). **c** The primary site, immediately after ELPS combined with ESD. The lesion is completely resected. **d** Two months following ELPS combined with ESD. The ulcer has completely healed without significant deformation.

resected specimen confirmed that a well-differentiated SCC invaded subepithelial layer (invasion depth 10,000  $\mu\text{m}$ ) with negative vertical resection margins. The lateral margin was difficult to determine because of the effect of burning during resection. However, the final pathology diagnosis was positive because of the presence of tumor at the margins (shown in Fig. 6). Lymphatic and venous invasions were negative which assessed by D2-40 staining and Elastica van Gieson staining, respectively. After 38 days of the initial treatment, we resected the left internal deep cervical lymph node during a 10-day hospitalization. No pathological metastatic findings were confirmed in the resected lymph node specimens. The mucosal defect was completely covered by normal mucosa 2 months after resection (shown in Fig. 5d). Thirty-nine months after the treatment, the patient was recurrence-free and survived without any additional treatment. However, pathologic lymph node metastasis could not be confirmed in this case.

#### Case 4

An 81-year-old male was referred to our institution complaining of discomfort during swallowing. Esophagogastroduodenoscopy revealed a flat elevated lesion of 25 mm in size



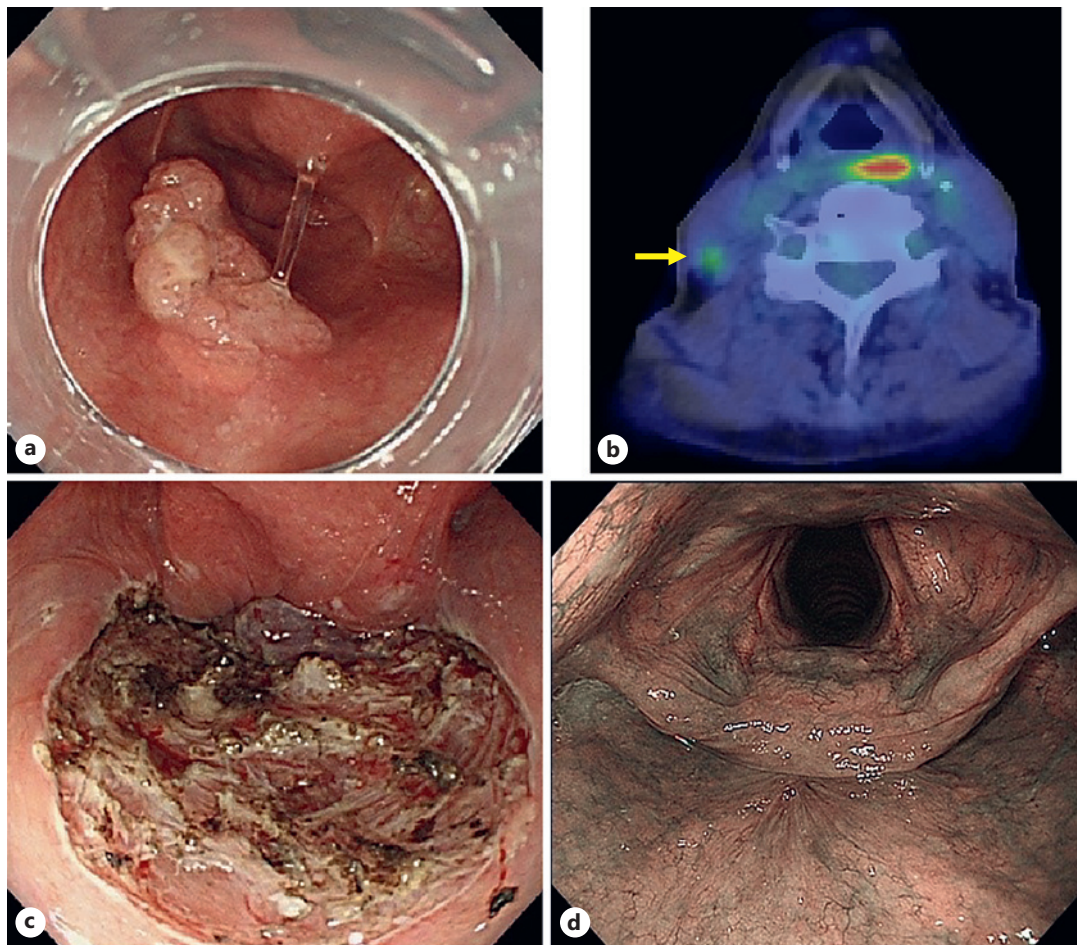
**Fig. 6.** Pathologic evaluation of the resected specimen confirmed that a well-differentiated squamous cell carcinoma invaded subepithelial layer (invasion depth 10,000  $\mu\text{m}$ ) with negative vertical resection margins. The lateral margin was difficult to determine because of the effect of burning during resection (red arrow).

in the posterior wall of the hypopharynx (shown in Fig. 7a). PET-CT showed right internal deep cervical lymph node swelling with FDG uptake (shown in Fig. 7b). ELPS combined with ESD and subsequent lymph node dissection was performed in one session (shown in Fig. 7c). The patient was hospitalized for only 14 days for treatment. The mucosal defect was completely covered by normal mucosa 2 months after resection (shown in Fig. 7d). The patient did not experience recurrence in the following 30 months without any additional treatment.

## Discussion

Among 4 patients, one developed local recurrence (case 1); however, the other three remained recurrence-free and survived without any additional treatment. Despite local recurrence, case 1 had a recurrence-free survival for more than 5 years, with additional treatment. In terms of QoL, in all patients, the mucosal defect after ELPS combined with ESD was completely covered by normal mucosa within 2 months after surgery. No disorders in speech, swallowing, or breathing were observed during the follow-up period. Based on the above clinical course, the 4 patients treated in this study showed excellent results in both curability and QoL. Transoral surgery for superficial laryngopharyngeal cancer is a less invasive and effective treatment for patients' QoL. As with several transoral surgeries, in ESD [8] and ELPS combined with ESD [5], the gastrointestinal endoscopist collaborated with a head and neck surgeon. ESD is the standard treatment strategy for early gastrointestinal tumors and is not indicated in patients with synchronous lymph node metastases, regardless of the organ [10, 11]. Therefore, even in laryngopharyngeal cancer, lesions with synchronous lymph node metastases are excluded from the indications for ESD and ELPS combined with ESD. In contrast, TLM, TORS, and TOVS treat patients with synchronous lymph node metastasis; however, there is no established protocol for the treatment of such cases [6]. In addition to TLM, TORS, and TOVS, the strategy of local excision of the primary tumor is common in all peroral resections, and data on cases with lymph node metastases are expected to accumulate for ESD and ELPS combined with ESD. In our routine ELPS combined with ESD





**Fig. 7.** **a** Intraoperative endoscopic images after tracheal intubation show a distorted protruded lesion on the posterior wall of hypopharynx. **b** A PET-CT shows a right internal deep cervical lymph node swelling, and there is slight FDG uptake (Yellow arrow). **c** The primary site, immediately after ELPS combined with ESD. The lesion is completely resected. **d** Two months following ELPS combined with ESD. The ulcer has completely healed without significant deformation.

for patients without synchronous lymph node metastases, we did not provide additional treatment after resection until the recurrence was confirmed. This was considered the “resect and watch strategy” [12]. Similarly, after local excision and lymph node dissection, no additional treatment was administered to the 4 patients in this study until metachronous recurrence was confirmed. This is because salvaging ELPS for local recurrence or new lesions within the irradiation field would be difficult [13]. In addition, it would be beneficial to preserve radiation therapy, which is a powerful treatment for laryngopharyngeal cancer, until the extent and dose of radiation could be adequately determined. In case 1, the patient developed local recurrence. This case was negative for both vertical and horizontal resection margins. On the other hand, the positive lymphatic invasion suggests a local recurrence via vasculature (shown in Table 2). The location, size, and the number of organs with recurrence were identified, which allowed us to add IMRT and platinum-based intra-arterial chemotherapy and achieve recurrence-free survival for 5 years. In case 3, pathological results confirmed that the lymph node diagnosed with synchronous metastasis by preoperative PET-CT did not have metastasis, and correct TNM staging could be performed. It has been reported that it is sometimes difficult to reliably diagnose cancer metastasis even by the pathological diagnosis of



resected lymph nodes, although this is the case for breast and colorectal cancer [14, 15]. Therefore, careful follow-up is necessary for case 3, considering the limitations of the pathological diagnosis. As all 4 patients in this study did not accept the proposed standard treatments (surgical resection and chemoradiotherapy) due to risk of complications and decreased QoL after treatment, we performed ELPS and lymph node dissection. More data on the results and long-term prognosis are required to discuss the validity of this treatment strategy.

## Statement of Ethics

Written informed consent was obtained from all 4 patients for publication of this case series and any accompanying images. Information revealing the subject's identity is to be avoided. All patients should be identified by numbers or aliases and not by their real names. This study protocol was reviewed and approved by the internal review board at Ise Red Cross Hospital, approval number ER2022-41.

## Conflict of Interest Statement

The authors declare no conflicts of interest.

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## Author Contributions

Shinya Sugimoto wrote the initial draft of the manuscript. Tomohito Fuke, Daisuke Kobayashi, Mamika Kaneko, Taishi Temma, Tatsuma Nomura, Nobuyuki Tsuda, Mayu Kawabata, Ryutaro Matsushima, Hirohisa Hisada, Satoshi Hayashi, Toji Murabayashi, Jun Oyamada, Akira Kamei, Nobukazu Fuwa, Tadashi Yabana, Hiroyuki Yamada, and Hayato Nakagawa critically reviewed and approved the final version of the manuscript.

## Data Availability Statement

All data that support the findings of this study are included in this article.

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