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Efficacy of endoscopic surveillance for pharyngeal mucosa during endoscopic resection for pharyngeal carcinoma: a multicenter prospective study

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Abstract

Introduction Since patients with pharyngeal squamous cell carcinoma (SCC) often have multiple pharyngeal lesions, evaluation of pharyngeal lesions before endoscopic resection (ER) is important. However, detailed endoscopic observation of the entire pharyngeal mucosa under conscious sedation is difficult. We examined the usefulness of endoscopic surveillance with narrow band imaging (NBI) and lugol staining for detection of pharyngeal sublesions during ER for pharyngeal SCC under general anesthesia (endoscopic surveillance during treatment; ESDT).

Methods From January 2021 through June 2022, we examined 78 patients who were diagnosed with superficial pharyngeal SCC and underwent ER. They underwent the ESDT and for patients who were diagnosed with new lesions of pharyngeal SCC or high-grade dysplasia (HGD) that were not detected in the endoscopic examination before treatment, ER were performed simultaneously for new lesions and the main lesions. The primary endpoint of this study was the detection rate of new lesions of pharyngeal SCC or HGD in the ESDT.

Results Fifteen of the 78 patients were diagnosed as having undetected new pharyngeal lesions in the ESDT and 10 (12.8%) (95% CI 6.9–22.2%) were histopathologically confirmed to have new lesions of pharyngeal SCC or HGD. Among the 13 lesions of SCC or HGD, 8 were found by NBI observation; however, 5 were undetectable using NBI but detectable by lugol staining. All of the 13 lesions had endoscopic findings of pink color sign on lugol staining.

Conclusions Endoscopic surveillance for pharyngeal sublesions during ER for pharyngeal SCC is feasible and useful.

Keywords Endoscopic resection · Endoscopic surveillance · Lugol staining · Narrow band imaging · Pharyngeal carcinoma

Due to the recent technological developments in endoscopic diagnosis such as narrow band imaging (NBI), superficial squamous cell carcinoma (SCC) of the pharynx is being detected more frequently [1–14]. Many of the patients with such early lesions can be treated with endoscopic resection (ER) including endoscopic submucosal dissection (ESD) and endoscopic laryngopharyngeal surgery (ELPS) with minimal invasiveness. Good long-term outcomes for patients with superficial pharyngeal SCC who underwent ER have been reported and ER has become increasingly popular as an alternative to surgical treatment or chemoradiotherapy in such patients [5–14]. Since patients with pharyngeal SCC often have multiple pharyngeal lesions [6, 7, 9, 10], pretreatment evaluation of pharyngeal lesions is important. Patients in whom pharyngeal SCC is diagnosed by endoscopic screening and are considered to be candidates for ER usually undergo further detailed endoscopic observation for precise

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diagnosis and determination of the indication for ER before treatment. The presence of other pharyngeal lesions is also examined in the detailed endoscopic observation. However, detailed endoscopic observation of the entire pharyngeal mucosa under the condition of conscious sedation is difficult because of the gag reflex induced by pharyngeal stimulation. Moreover, washing out pharyngeal mucus and saliva using water involves a risk of aspiration. The stimulus from lugol staining, which is known to be a useful method for detection of superficial esophageal SCC [15–18], is too strong for observation of the pharynx under the condition of conscious sedation. Therefore, some pharyngeal lesions might be overlooked in pretreatment endoscopic examination.

ER for superficial pharyngeal SCC is usually performed under general anesthesia, and lugol staining around the lesions is also performed to delineate the lesion demarcation [5–13]. Detailed endoscopic observation of the pharyngeal mucosa with washing out of mucus using water and lugol staining for the entire pharyngeal mucosa are, therefore, possible during the treatment procedure. Some pharyngeal lesions that could not be found in pretreatment endoscopic examination would be found by endoscopic surveillance with lugol staining just before resection. In this study, we evaluated the feasibility and usefulness of endoscopic surveillance for pharyngeal sublesions during ER for superficial pharyngeal SCC.

Materials and methods

Study design

This study was a prospective multicenter observational study. During the period from January 2021 to June 2022, we recruited patients from 5 hospitals throughout Japan (Hokkaido University Hospital, National Hospital Organization Hokkaido Medical Center, Dokkyo Medical University, The Jikei University School of Medicine and Keiyukai Sapporo Hospital). The ethics committee of each hospital approved the study protocol, and all participants gave written informed consent based on the Helsinki Declaration (1964, 1975, amended in 1983, 2003, 2008 and 2013) of the World Medical Association (UMIN Clinical Trials Registry ID: UMIN000045230).

Patients

Patients in whom a diagnosis of pharyngeal SCC was made by endoscopic screening and were scheduled to undergo further detailed endoscopic examination for precise diagnosis and determination of the indication for ER were candidates for this study. Patients with lesions that were suspected to be superficial pharyngeal SCC based on the findings of redness and an irregular surface on WLI and/or a brownish area on NBI (without histpathological confirmation for a biopsy specimen) who were referred to the participating institutions were also included. Detailed endoscopic examination was performed for patients who gave consent for participation in the study. The endoscopic examination was performed by using a GIF-H290Z endoscope (Olympus Medical Systems Corp., Tokyo, Japan) under conscious sedation using pethidine hydrochloride, midazoram or diazepam. White light imaging (WLI) and NBI (with magnification) were performed for precise diagnosis of the indication for ER and to determine whether the presence or absence of other pharyngeal lesions in that examination. Laryngoscope and a physical examination were also performed by an otolaryngologist. The valsalva method was used for observation of the postcricoid area [4]. Patients with lesions that were diagnosed to be confined to the subepithelial layer and with indication for ER were finally enrolled in this study.

The following patients were excluded from this study: (1) patients who had history of total laryngectomy, (2) patients with recurrent or residual pharyngeal SCC after radiotherapy or chemoradiotherapy, (3) patients with a history of allergy for iodine, (4) patients who did not have a sufficient understanding after receiving an explanation for participation in this study, and (5) patients who the investigator considered were unsuitable as subjects.

Procedures

All of the patients underwent ER within 4 weeks after enrollment. All procedures of ER for superficial pharyngeal SCC were performed with the patient in the supine position under general anesthesia. A curved-type rigid laryngoscope (Nagashima Medical Instruments Co., Ltd. Tokyo, Japan) was inserted to widen the pharyngeal space. Detailed endoscopic observation with WLI and then NBI for the pharyngeal mucosa after washing out of mucus using water was performed. Lugol staining using 1.5% lugol solution on the pharyngeal mucosa (including the pyriform sinus, postcricoid area, posterior wall of the hypopharynx, posterior wall of the oropharynx and lateral wall of the oropharynx) was finally performed (we defined these procedures as the endoscopic surveillance during treatment; ESDT). If new lesions diagnosed to be SCC or high-grade dysplasia (HGD) were found, marking by using a needle knife was performed at any timing. For patients who were diagnosed as having new lesions of pharyngeal SCC or HGD that were not detected in the endoscopic examination before treatment, ER was performed simultaneously for new lesions and the main lesions. Since diagnostic criteria for superficial pharyngeal SCC have not yet been established, we made a diagnosis of superficial esophageal SCC based on

criteria including redness and an irregular surface on WLI, a brownish area and background coloration on NBI [15, 19] and an unstained area and pink color sign on lugol staining [16, 20] (pink color sign was defined as reported by Shimizu et al. If a light pink part appeared in the lugol-unstained area within 3 min after lugol staining, the lesion was regarded as being pink color sign-positive). If one of these findings was confirmed, we diagnosed the lesions to be SCC or HGD.

Histologic analysis

ER specimens were paraffin-embedded, cut into longitudinal slices of 2 mm in width, and stained with hematoxylin–eosin. The pathologist, who was blinded to the clinical characteristics of the patients, made the diagnosis based on the three-tiered grading system (low-grade dysplasia (LGD), HGD and SCC in situ) used for dysplasia/squamous intraepithelial lesion proposed by the World Health Organization [21].

Endpoints

The primary endpoint was the detection rate of new lesions of pharyngeal SCC or HGD in the ESDT (per patient analysis). The secondary endpoints were the additional advantage of lugol staining compared with NBI observation and safety of lugol staining on the pharyngeal mucosa.

Statistical analysis

A previous study showed that cumulative development of multiple SCC in the pharyngeal mucosa after ER for superficial pharyngeal SCC at 3 years was 20% (95% CI 10–29%) [10]. Assuming an expected detection rate of 15% for ESDT in this study and a threshold detection rate of 5%, the number of superficial pharyngeal SCC cases to yield 80% power at a significance level of 5% (one-sided) was calculated to be 67 based on the binomial test (normal approximation). The target number of patients was set at 75, taking into account the occurrence of dropouts and ineligible cases. The detection rate in the ESDT including the 95% confidence interval was calculated. Age and lesion size were expressed as mean ± standard deviation (SD) values. SPSS statistics version 19 (IBM, Armonk, NY, USA) was used for data analyses.

Results

Study population

From January 2021 through June 2022, we examined 78 patients who were diagnosed with superficial pharyngeal SCC and underwent ER. Table 1 shows the characteristics of the patients who were enrolled in this study. The patients included 70 men and 8 women with a mean (± SD) age of 68.4 ± 8.9 years. Eleven patients had multiple lesions. The locations of the main lesions (largest lesions) were the pyriform sinus for 37 lesions, posterior wall of the hypopharynx for 19 lesions, postcricoid area for 8 lesions and oropharynx for 14 lesions. Among the 78 patients, 72 underwent ELPS and 6 underwent ESD. As a major adverse event caused by treatment, laryngeal edema (requiring temporary tracheostomy) occurred in 2 patients (2.6%). The mean (± SD) lesion size was 19.8 ± 11.8 mm.

Table 1 Characteristics of the 78 patients with pharyngeal cancer who were registered in the study and underwent endoscopic resection

Age, mean ± SD, years	68.4 ± 8.9
Sex, male (%)	70 (89.7%)
Multiple lesions	11/67
Yes/no	
Location (main lesion)[a]	
Hypopharynx	
Pyriform sinus	37
Posterior wall	19
Postcricoid area	8
Oropharynx	
Posterior wall	4
Superior wall	3
Lateral wall	4
Anterior wall	3
Treatment methods	
ESD/EMR/ELPS	6/0/72
Adverse events	
Perforation	0
Subcutaneous emphysema	0
Laryngeal edema	2
Delayed bleeding	0
Lesions, size (mm), mean (± SD)	19.8 ± 11.8
Histopathological diagnosis (main lesion)	
Cancer/HGD/LGD/non-tumor	71/4/2/1
Depth of the invasion (cancer)	
CIS/SEP/Muscle layer	46/25/0

ESD endoscopic submucosal dissection, *EMR* endoscopic mucosal resection, *ELPS* endoscopic laryngopharyngeal surgery, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia, *CIS* carcinoma in situ, *SEP* subepithelial invasion

[a]The largest lesions were defined to be main lesions

Histopathologically, 71 lesions were diagnosed as SCC (including 25 lesions with subepithelial invasion), 4 were diagnosed as HGD, 2 were diagnosed as LGD and 1 was diagnosed as non-tumor.

Outcome of the endoscopic surveillance during treatment

Among the 78 patients, 15 were found to have new pharyngeal lesions (20 lesions) that were not detected in prior endoscopic examination by the ESDT, and additional ER was performed simultaneously with the main lesions. Table 2 shows the characteristics of all of the pharyngeal lesions that were found by the ESDT. No lesion was found by WLI observation, 8 lesions were found by NBI observation and 12 lesions were found by lugol staining (All lesions that were found by NBI had findings of a lugol-unstained area. Histopathologically, 6 lesions were diagnosed as SCC (including 4 with subepithelial invasion), 7 were diagnosed as HGD, 6 were diagnosed as LGD and 1 was diagnosed as non-tumor. As the results, 10 of the 78 patients (12.8%) (95% CI 6.9–22.2%) were diagnosed as having undetected new lesions of pharyngeal SCC or HGD. Table 3 shows the characteristics of the 13 pharyngeal lesions (10 patients) that were found by the ESDT and were histopathologically confirmed to be SCC or HGD. Nine of the 13 lesions were located in the pyriform sinus, 2 were located in posterior

Table 2 Characteristics of the lesions that were found by endoscopic surveillance of the pharynx during treatment

	20 lesions (15 patients)
Lesions, size (mm), mean (± SD)	13.8 ± 11.0
Location	
Hypopharynx	
Pyriform sinus	11
Posterior wall	4
Postcricoid area	0
Oropharynx	
Posterior wall	3
Superior wall	1
Lateral wall	0
Anterior wall	1
Larynx	0
Others	0
Modality of detection	
WLI/NBI/Iodine staining	0/8/12
Endoscopic findings (WLI)	
Redness ±	0/0
Surface irregular ±	0/0
Endoscopic findings (NBI)	
Brownish area ±	8/0
Background coloration ±	6/2
Endoscopic findings (Iodine staining)	
Unstained area ±	20/0
Pink color sign ±	17/3
Endoscopic diagnosis	
Cancer/dysplasia/others	14/6/0
Treatment methods	
ESD/EMR/ELPS	2/0/18
Histopathological diagnosis	
Cancer/HGD/LGD/non-tumor	6/7/6/1

WLI white light imaging, *NBI* narrow band imaging, *ESD* endoscopic submucosal dissection, *EMR* endoscopic mucosal resection, *ELPS* endoscopic laryngopharyngeal surgery, *HGD* high-grade dysplasia, *LGD* low-grade dysplasia

Table 3 Characteristics of the lesions that were found by endoscopic surveillance of the pharynx during treatment and were histologically confirmed to be carcinoma or high-grade dysplasia

	13 lesions (10 patients)
Lesions, size (mm), mean (± SD)	17.7 ± 11.3
Location	
Hypopharynx	
Pyriform sinus	9
Posterior wall	2
Postcricoid area	0
Oropharynx	
Posterior wall	1
Superior wall	1
Lateral wall	0
Anterior wall	0
Larynx	0
Others	0
Modality of detection	
WLI/NBI/Iodine staining	00/8/5
Endoscopic findings (WLI)	
Redness ±	0/0
Surface irregular ±	0/0
Endoscopic findings (NBI)	
Brownish area ±	8/0
Background coloration ±	6/2
Endoscopic findings (Iodine staining)	
Unstained area ±	13/0
Pink color sign ±	13/0
Endoscopic diagnosis	
Cancer/dysplasia/others	11/2/0
Treatment methods	
ESD/EMR/ELPS	1/0/12
Depth of invasion	
HGD/CIS/SEP/muscle layer	7/2/4/0

WLI white light imaging, *NBI* narrow band imaging, *ESD* endoscopic submucosal dissection, *EMR* endoscopic mucosal resection, *ELPS* endoscopic laryngopharyngeal surgery, *CIS* carcinoma in situ, *SEP* subepithelial invasion

wall of the hypopharynx and 2 were located in the oropharynx. Regarding the modality of detection, 8 lesions were found by NBI observation; however, 5 were undetectable using NBI but were detected by lugol staining. Endoscopic findings of the lesions were a brownish area in 8 lesions and background coloration in 6 lesions on NBI, and an unstained area and pink color sign on lugol staining were found in all of the 13 lesions. The mean (± SD) lesion size was 17.7 ± 11.3 mm. Four lesions had subepithelial invasion. As for the characteristics of the 7 pharyngeal lesions (5 patients) that were found by the ESDT and were histopathologically confirmed to be LGD or non-tumor, all lesions were undetectable using NBI but were detected by lugol staining. The mean (± SD) lesion size was 5.3 ± 2.5 mm.

An overview of this study is shown in Fig. 1. Cases for which hypopharyngeal SCC or HGD were newly found by endoscopic surveillance with lugol staining during treatment for superficial pharyngeal SCC are shown in Figs. 2 and 3.

Discussion

Multiple development of SCC in the upper aero-digestive tract is known as the "field cancerization phenomenon" [22, 23]. This concept indicates that exposure to carcinogens, such as alcohol and cigarettes, leads to multiple cancer onset in the mucosa of the esophagus and of the head and neck [24]. Muto et al. studied outcomes for 104 patients with superficial pharyngeal SCC who underwent ER and reported that the cumulative rate of development of metachronous multiple SCC in pharyngeal mucosal sites at 5 years was 22% with a median follow-up period of 43 months [10]. Close follow-up examination is, therefore, required for patients who have undergone ER for superficial pharyngeal SCC. However, some pharyngeal sublesions that were overlooked at the time of initial treatment and became larger during the follow-up period are thought to be included in such metachronous multiple lesions.

In this study, we could safely perform detailed endoscopic observation of the entire pharyngeal mucosa including washing out of mucus using water and lugol staining for the entire pharyngeal mucosa in all of the 78 patients. As a result, 10 (12.8%) of the 78 patients were diagnosed with undetected new lesions of pharyngeal SCC or HGD and underwent ER of the new lesions simultaneously with main lesions. We suppose that such patients could receive not only benefits of avoiding the risk for delayed detection of multiple SCC at the developed stage during the follow-up period but also social and economic benefits of conclusive single treatment under general anesthesia for multiple lesions. The pyriform sinus was the most frequent site of newly detected lesions. The pyriform sinus includes organs with narrow lumens, in which stricture and dysphagia are common problems following ER. Even if such adverse events do not occur with the initial treatment, repeated ER causes multiple scars following resection, which may consequently lead to dysphagia and aspiration pneumonia. We, therefore, consider that sublesions should be found as early as possible when they are small. Laryngeal edema as a major adverse event occurred in 2 patients (2.6%) in this study. However, its prevalence is

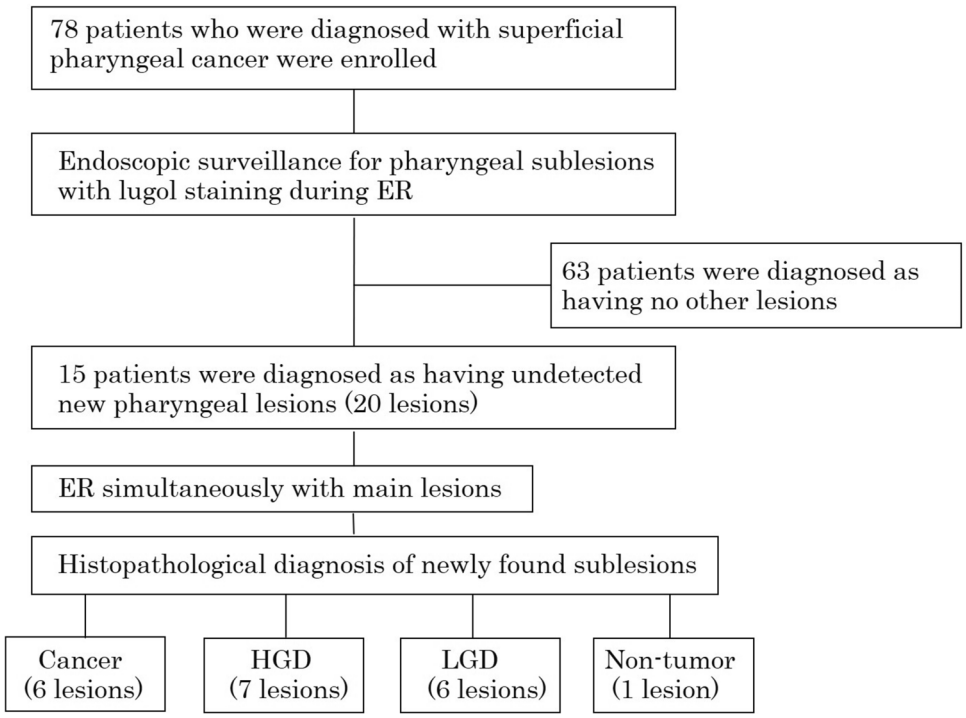

Fig. 1 Overview of this study. *ER* endoscopic resection, *HGD* high-grade dysplasia; *LGD* low-grade dysplasia

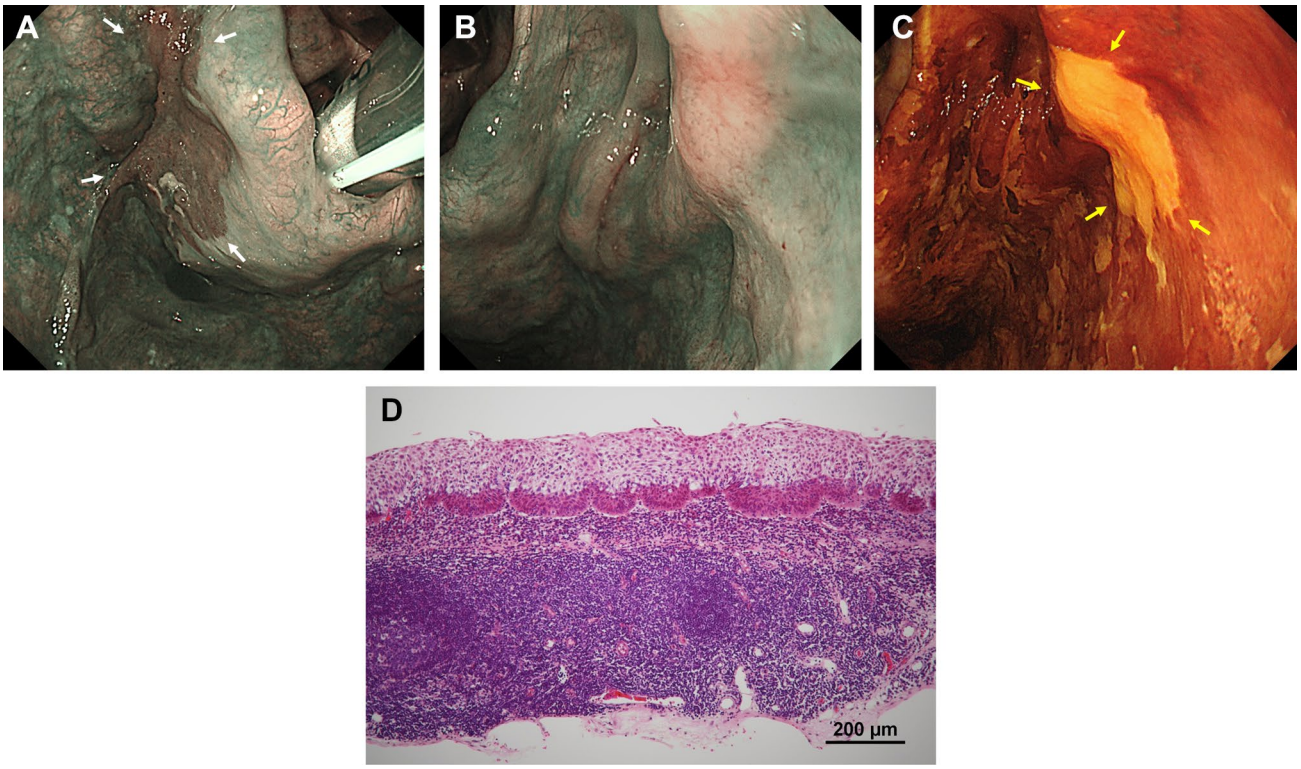

Fig. 2 A representative case for which a pharyngeal sublesion was newly found by endoscopic surveillance with lugol staining during treatment for superficial pharyngeal SCC. **A** An endoscopic image just before resection with narrow band imaging showing superficial pharyngeal SCC on the left pyriform sinus (white arrows). **B** An endoscopic image just before resection with narrow band imaging showing the right pyriform sinus. Although an area with color change was found, findings of a demarcated brownish area (like a main lesion shown in **A**) were not confirmed, and we, therefore, could not diagnose this area to be SCC (we could not find any other lesions in pretreatment endoscopic examination). **C** An endoscopic image just before resection with lugol staining. A sublesion was detected as a demarcated lugol-unstained area (yellow arrows) on the right pyriform sinus. **D** Photomicrograph of the resected specimen of the newly found sublesion revealed SCC with subepithelial invasion (H&E, orig. mag. × 40) (Color figure online)

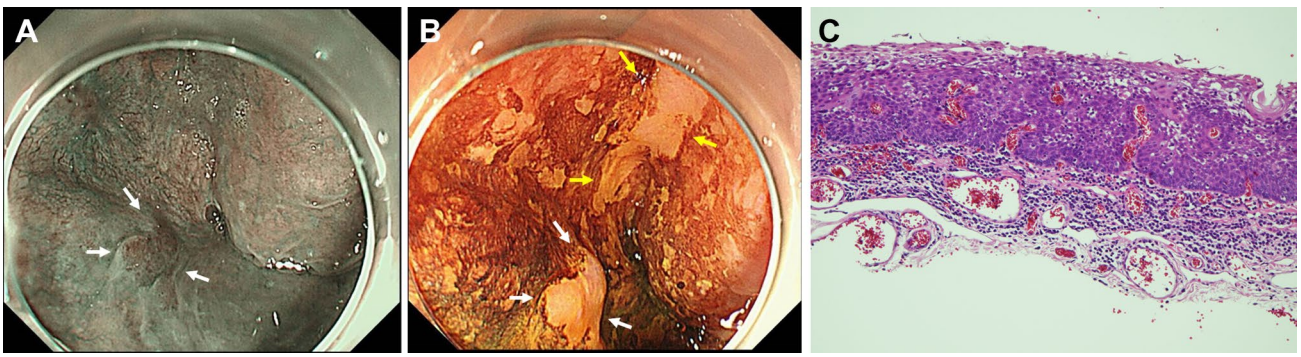

Fig. 3 A representative case for which a pharyngeal sublesion was newly found by endoscopic surveillance with lugol staining during treatment for superficial pharyngeal SCC. **A** An endoscopic image just before resection with narrow band imaging showing superficial pharyngeal SCC on the posterior wall of hypopharynx (white arrows). We could not find any other lesions around this main lesion (we could not find any other lesions in pretreatment endoscopic examination). **B** An endoscopic image just before resection with lugol staining. A sublesion was detected as a lugol-unstained area with the finding of a pink color sign (yellow arrows) near the main lesion that was indicated by white arrows on the left pyriform sinus. **C** Photomicrograph of the resected specimen of the newly found sublesion revealed HGD (H&E, orig. mag. × 40) (Color figure online)

the same as that in previous studies [8, 12] and we, therefore, consider that lugol staining for the pharyngeal mucosa does not increase the risk of adverse events.

It should be noted that among the 13 lesions of SCC and HGD that were newly found in the ESDT, only 8 lesions were detected as a demarcated brownish area in NBI. Although the usefulness of NBI for diagnosis of superficial esophageal SCC is well known [2, 19, 25], several investigators reported higher sensitivity of lugol staining than that of NBI [15, 26, 27]. Ono et al. evaluated the characteristics of superficial esophageal SCC lesions that were undetectable using NBI but were detected by lugol staining [27]. Multivariate analysis in their study revealed independent factors for NBI-undetectable lesions including anterior wall position and numerous lugol voiding lesions on background mucosa. They speculated that detailed observation of the anterior wall of the esophagus would be difficult due to its tangential view and that numerous lugol voiding lesions that were considered to be induced by chronic inflammation associated with smoking and alcohol consumption would hinder diagnosis of the brownish area (because chronic inflammation induce dilated micro vessels on background mucosa in NBI observation). The pharynx has a complex structure that often restricts endoscopic observation to a tangential view. The pharyngeal mucosa would be affected more strongly than the esophageal mucosa by chronic inflammation associated with smoking and alcohol consumption. We, therefore, recommend the use of lugol staining during the endoscopic surveillance.

We used "pink color sign" on lugol staining as an index of pharyngeal SCC or HGD. In the squamous epithelium, SCC and HGD hardly react with lugol due to the small number of glycogen-containing cells and are, therefore, seen as completely unstained areas with a reddish color after the brown color of lugol solution has faded. This finding was named pink color sign and it was reported to be useful for diagnosis of superficial esophageal SCC [15, 16, 20]. In our study, all of the 13 lesions of SCC and HGD were positive for pink color sign, suggesting that pink color sign would also be useful for diagnosis of superficial pharyngeal SCC. On the other hand, among the 20 lesions that were found by the ESDT and additionally resected, histopathologically, 6 were diagnosed as LGD and 1 was diagnosed as non-tumor. The effectiveness of ESD for pharyngeal LGD is controversial. Kuwabara et al. studied clinical features of 51 patients with pharyngeal intraepithelial neoplasia and outcomes of treatment by ESD [7]. They performed ESD not only for patients with HGD or carcinoma in situ but also for patients with LGD and concluded that ESD is an effective treatment for pharyngeal intraepithelial neoplasia. However, our 5 patients who had sublesions of LGD or non-tumor might have undergone unnecessary treatment. None of them were found by NBI observation and they were small lesions. Although the sensitivity of lugol staining was very high, the specificity of lugol staining was insufficient in this study. Course observation might be better for the small lesions (about 5 mm in size) that were undetectable using NBI but were detected by lugol staining. A precise diagnostic procedure for superficial pharyngeal SCC has not yet been established. Further examination and evaluation in this field are, therefore, required to improve diagnostic specificity.

There are two other limitations in this study. First, evaluation of the diagnostic criteria including pink color sign depended on the individual investigator and was subjective. Second, since we did not examine the long-term outcomes of patients, the contribution of ESDT for the prognosis of patients with superficial pharyngeal SCC is not yet confirmed. Further examination of the long-term outcomes of the patients in our study is needed to obtain a firm conclusion.

Conclusions

In the procedure of ER for superficial pharyngeal SCC under general anesthesia, lugol staining around the lesions is often performed to delineate the lesion demarcation. We recommend detailed endoscopic observation for the pharyngeal mucosa including washing out of mucus using water, NBI observation and lugol staining for the entire pharyngeal mucosa at that time to find lesions that could not be found in pretreatment endoscopic examination.

Author contributions YK, YS and AW contributed to conception and design, MT, SI, AD, KG, YN and KY contributed to collection and analysis of the data, SI performed histopathological diagnosis.

Declarations

Disclosures Yuki Kimura, Yuichi Shimizu, Masanobu Taniguchi, Suguru Ito, Akira Dobashi, Kenichi Goda, Yusuke Nishimura, Keiko Yamamoto, Shin Ichihara and Akihito Watanabe declare that they have no conflicts of interest or financial ties to disclose.

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