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WILEY
Complications After Endoscopic Laryngopharyngeal Surgery

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Objectives/Hypothesis: Endoscopic laryngopharyngeal surgery (ELPS), a hybrid of head and neck surgery and gastrointestinal endoscopic treatment, has been attracting attention as a new therapeutic modality for superficial laryngopharyngeal cancers. Although this technique is less invasive than traditional open procedures, some complications including postoperative bleeding, subcutaneous emphysema, or aspiration pneumonia can occur after treatment. The purpose of this study was to investigate the complications associated with ELPS to better understand the indications for this procedure.

Study Design: Retrospective medical chart review.

Methods: One hundred five patients with 159 laryngeal or pharyngeal lesions were treated with ELPS between August 2009 and September 2015 at Kyoto University Hospital. In total, 147 resections were performed, and complications after the resections were reviewed.

Results: Of the 147 resections, postoperative bleeding, subcutaneous emphysema, and aspiration pneumonia were observed in 10, 17, and 10 cases, respectively. All cases with postoperative bleeding and aspiration pneumonia occurred in patients over 65 years of age. A history of taking anticoagulation/platelet medications, and macroscopic 0–IIa lesions were shown to correlate with postoperative bleeding after ELPS. Resection of lesions in the pyriform sinus was found to be associated with subcutaneous emphysema.

Conclusions: All complications after ELPS were safely managed. A history of taking anticoagulation/platelet medications and macroscopic 0–IIa lesions were identified as risk factors for postoperative bleeding, whereas resection of pyriform sinus lesions was found to be a risk factor for subcutaneous emphysema. These risk factors should be carefully considered when treating pharyngeal and laryngeal lesions by ELPS.

Key Words: ELPS, transoral, pharyngeal cancer, laryngeal cancer.

Level of Evidence: 4.

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INTRODUCTION

Recent innovations in optical technology, such as narrow band imaging (NBI) or magnifying endoscopy (ME), have enabled very early stage detection of laryngopharyngeal cancers.1,2 Although traditional open neck surgery and radiation therapy are established therapeutic options for laryngeal/pharyngeal cancers, they cause scar formation and damage to muscular and neural structures, and can contribute to the development of swallowing and speech dysfunction. Given that impairments in these functions are directly linked to a decrease in patient quality of life, less-invasive transoral surgery is becoming a major strategy for early and superficial laryngopharyngeal lesions as a means of avoiding post-therapeutic complications.

Endoscopic submucosal dissection (ESD) is a widely used gastrointestinal endoscopic procedure for superficial cancers in the upper tract performed by a gastroenterologist. In this procedure, the mucosa containing the lesion is resected at the subepithelial level using a coagulator and forceps inserted through a flexible endoscope. Initially, it was introduced to treat pharyngeal lesions by Muto et al. and achieves good oncological outcomes3; however, it was a one-arm procedure and had limitations due to its technical difficulties.4

To overcome the limitations of pharyngeal ESD, endoscopic laryngopharyngeal surgery (ELPS) was developed to treat superficial laryngeal and pharyngeal cancers by modifying the procedure for ESD. During ELPS, a curved rigid laryngoscope is inserted under general anesthesia to create sufficient working space in the pharyngeal lumen, and an ME-NBI is inserted transorally by a gastroenterologist to visualize the surgical field. An excellent view of the oropharynx, hypopharynx, and larynx is achieved with this approach, enabling the lesions to be grasped with forceps and resected via
electrocautery by a head and neck surgeon. Thus, unlike transoral laser microsurgery (TLM), ELPS is a hybrid of head and neck surgery and gastrointestinal endoscopic treatment. Safe and precise resection with less damage to the surrounding tissues is achievable with the aid of a flexible ME-NBI and specially fabricated curved instruments. Initially, ELPS was indicated for carcinoma in situ or invasive laryngopharyngeal cancer without muscular invasion; however, with the establishment of these procedures and the development of surgical devices and techniques, the indications for ELPS have become broader including T1, T2, and select T3 cases.

Although ELPS is less invasive than conventional open procedures, some complications including postoperative bleeding, subcutaneous emphysema, or aspiration pneumonia can occur after treatment. However, the risk factors for these complications have not been previously studied. The purpose of this study was to investigate the complications and risk factors associated with ELPS to gain a better understanding of the indications for this procedure.

MATERIALS AND METHODS

Patients

One hundred twenty-two ELPS procedures (117 male and five female), totaling 147 resections, were performed on 105 patients with 159 laryngeal or pharyngeal lesions between August 2009 and September 2015 at Kyoto University Hospital. All lesions were diagnosed as high-grade dysplasia, carcinoma in situ, or squamous cell carcinoma based on pathological examination. Written informed consent was obtained in all cases, and this study was approved by the institutional review board of the Graduate School of Medicine, Kyoto University.

After summarizing the patients' clinical information, any complications that occurred after the resections were reviewed, and data on independent and dependent variables were collected by retrospective chart review and subjected to statistical analyses.

Macroscopic Classification

Observations of the lesions were made by ME, and macroscopic morphology was classified according to the Japanese Classification of Esophageal Cancer (11th Edition) (Fig. 1). Although this classification is designed for the evaluation of lesions in the gastrointestinal tract, it is also applied to head and neck cancer in the General Rules for Clinical Studies on Head and Neck Cancer (5th Edition) of the Japan Society for Head and Neck Cancer. Briefly, superficial type lesions have the prefix 0 and are classified into 3 subtypes: 0-I (superficial and protruding), 0-II (superficial and flat), or 0-III (superficial and excavated). Type 0-II (superficial and flat) is further classified into 0-IIa (slightly elevated: less than 1 mm in height), 0-IIb (true flat), and 0-IIc (slightly depressed).

Surgical Procedures

All procedures were performed as previously reported. Under general anesthesia, a curved rigid laryngoscope (Nagashima Medical Instruments Company, Ltd., Tokyo, Japan) was inserted to provide a working space, then a ME-NBI (GF-H260Z or Q240Z, Olympus Medical Systems, Tokyo, Japan) was inserted transorally to visualize the surgical field (Fig. 2). The extent of the lesions and the exact margins were determined by NBI and iodine staining. A mixed solution of epinephrine (0.02 mg/mL) and saline was injected into the subepithelial layer beneath the lesion to raise it up. Lesions were resected using transorally inserted curved forceps (Nagashima Medical Instruments Company, Ltd.) and a curved electrosurgical needle knife (KD-600; Olympus Medical Systems). In cases where multiple adjacent lesions were detected, a maximum of four lesions were removed with a single resection.

Pathological Evaluation

After measuring the size of the resected specimens, all specimens were fixed and cut into longitudinal slices and subjected to pathological examination. Specimens were microscopically evaluated in accordance with the World Health Organization Classification, and T staging was performed according to the Union for International Cancer Control tumor-node-metastasis (UICC/TNM) classification (7th Edition) of head and neck cancer.

We assigned a mucosal resection greater than 30 mm as a dependent variable in the analysis, because multiple lesions were treated in one resection in some cases and it was difficult to use T stage as a dependent variable. The 30-mm measurement was employed assuming cases of T2 (20 mm) lesions resected with 5-mm safety margins.

Statistical Analyses

Clinical information pertaining to the patients, lesions, and resections is presented using descriptive statistics for continuous variables and frequencies for categorical variables. The relationship between age and complications was examined by a \( \chi^2 \) test. Univariate and multivariate logistic regression analyses were performed to identify the risk factors for complications after ELPS. All statistical analyses were performed with JMP version 12.1.0 (SAS Institute Inc., Cary, NC).
RESULTS

Clinical information pertaining to the patients is summarized in Table I. Their ages ranged from 44 to 85 years (average, 67.0 years). In 13 patients, new lesions were found in other parts of the pharynx during the follow-up period; nine patients underwent ELPS twice, and four patients underwent the procedure three times. Multiple simultaneous lesions were detected and treated in 28 out of 122 ELPS cases.

A total of 159 lesions consisting of 111 hypopharyngeal lesions, 43 oropharyngeal lesions and five laryngeal lesions were investigated. Out of 147 resections, five, 39, 101, and two specimens were macroscopically diagnosed as 0-I, 0-IIa, 0-IIb, and 0-IIc, respectively. As for T classification, 86 lesions were pathologically diagnosed as Tis, 46 lesions as T1, 21 lesions as T2, and six lesions as T3.

ELPS is a relatively safe procedure, and lesion resection was successfully completed in all cases. As possible outcomes, postoperative bleeding, subcutaneous emphysema, aspiration pneumonia, and simultaneous/metachronous multiple lesions were selected for analyses.

Postoperative bleeding, subcutaneous emphysema, and aspiration pneumonia were observed in 10, 17, and 10 cases out of 147 resections, respectively. Although all the bleeding cases needed endoscopic hemostasis in the operating room, all complications were safely managed.

First, we investigated the relationship between age and ELPS complications, as advanced age over 65 years has been reported as a risk factor for various complications including hemorrhage, fistula, and aspiration pneumonia in transoral robotic surgery (TORS), and similar results were expected for ELPS cases. All cases of postoperative bleeding and aspiration pneumonia occurred in patients over 65 years of age, and $\chi^2$ tests revealed a significant relationship between age and complications (Table II).

The effects of other independent variables on the outcomes were analyzed with univariate and multivariate logistic regression analyses (Table III).

Postoperative Bleeding

Hemostatic treatments under general anesthesia were needed in two cases. Univariate analyses showed that the use of anticoagulant/antiplatelet medications, mucosal resection greater than 30 mm, and macroscopic appearance classified as 0-IIa were associated with

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of cases</td>
<td>122</td>
</tr>
<tr>
<td>Age, yr, range, mean ± SD</td>
<td>44–85; 67.0 ± 7.47</td>
</tr>
<tr>
<td>Gender, no. of cases</td>
<td>Female 5 (4.1%), Male 117 (95.9%)</td>
</tr>
<tr>
<td>Lesions, cases, no. (%)</td>
<td>1 94 (77.0%), 2 22 (18%), 3 3 (2.5%), 4 3 (2.5%)</td>
</tr>
<tr>
<td>Total no. of lesions</td>
<td>159</td>
</tr>
<tr>
<td>Sites, lesions, no. (%)</td>
<td>Larynx 5 (3.1%), Oropharynx 43 (27.0%), Hypopharynx 111 (69.8%)</td>
</tr>
<tr>
<td>T stages, lesions, no. (%)</td>
<td>In situ 86 (54.1%), 1 46 (28.9%), 2 21 (13.2%), 3 6 (3.8%)</td>
</tr>
<tr>
<td>Total no. of resected sites, resections</td>
<td>147</td>
</tr>
<tr>
<td>Macroscopic classification, resections</td>
<td>0-I 5 (3.4%), 0-IIa 39 (26.5%), 0-IIb 101 (68.7%), 0-IIc 2 (1.4%)</td>
</tr>
<tr>
<td>Lesions, resections, no. (%)</td>
<td>1 140 (95.2%), 2 4 (2.7%), 3 1 (0.7%), 4 2 (1.4%)</td>
</tr>
</tbody>
</table>

SD = standard deviation.
postoperative bleeding. Furthermore, multivariate analyses revealed that the use of anticoagulant/antiplatelet medications and 0-IIa lesions were statistically independent factors associated with postoperative bleeding.

**Subcutaneous Emphysema**

All cases of emphysema were managed conservatively. Univariate and multivariate analyses identified that lesion resection in the pyriform sinus is correlated with subcutaneous emphysema.

**Aspiration Pneumonia**

Percutaneous endoscopic gastrostomy dependence due to intractable dysphagia occurred in only one case, and others eventually received nourishment by mouth. No independent variables were shown to be associated with aspiration pneumonia.

**DISCUSSION**

ELPS is a hybrid of head and neck surgery and gastrointestinal endoscopic treatment used for pharyngeal and laryngeal cancer, with demonstrated advantages over laryngeal microsurgery traditional open surgery, and radiation therapy. A flexible gastrointestinal endoscope inserted with the aid of a curved laryngoscope offers a good surgical view and allows the precise resection of lesions with less damage to the surrounding tissues. Given these benefits, its general safety and reduced invasiveness have been emphasized, and complications have rarely been discussed.

In this study, three major complications of ELPS—postoperative bleeding, subcutaneous emphysema, and aspiration pneumonia—were reviewed to clarify the risk factors of these complications. Results identified some factors that correlated with these postoperative ELPS complications.

Postoperative bleeding occurred in 6.8% of the resections after ELPS, and it was equivalent to other transoral procedures. Although postoperative hemorrhage was

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**TABLE II.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Postoperative Complications After Endoscopic Laryngopharyngeal Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;65 Years, No. (%)</td>
<td>&lt;65 Years, No. (%)</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

---

**TABLE III.**

Univariate and Multivariate Logistic Regression Analyses of the Variables Associated With Postoperative Bleeding, Subcutaneous Emphysema, and Aspiration Pneumonia in Patients Who Underwent Endoscopic Laryngopharyngeal Surgery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resections</td>
<td>Events</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>Use of anticoagulant/platelet</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>PT-INR ≥ 1.2</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>HT</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Diameter of the resected specimen ≥ 30 mm</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Subepithelial invasion</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Macroscopic classification; 0–IIa</td>
<td>39</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>DM</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Diameter of the resected specimen ≥ 30 mm</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Subepithelial invasion</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Macroscopic classification; 0–IIa</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Site: pyriform sinus</td>
<td>82</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>DM</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Diameter of the resected specimen ≥ 30 mm</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Subepithelial invasion</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Site: pyriform sinus</td>
<td>103</td>
</tr>
</tbody>
</table>

*P < .05. CI = confidence interval; DM = diabetes mellitus; HT = hypertension; OR = odds ratio; PT-INR = prothrombin time-international normalized ratio.
not associated with long prothrombin time-international normalized ratio, a history of hypertension or subepithelial invasion and the use of anticoagulant/antiplatelet medications were correlated with hemorrhage. Previous studies reporting on the potential for postoperative bleeding in association with antithrombotic medications in patients undergoing transoral resection, such as TORS or TLM for head and neck cancers, have been consistent with our results.\textsuperscript{7,8,10} In addition, we found that postoperative hemorrhage was associated with macroscopic 0-IIa lesions. More than half of the 0-IIa lesions have been reported to show subepithelial or muscular invasion\textsuperscript{1}; it is likely that the deeper resections required for these deeper lesions might contribute to the occurrence of postoperative hemorrhage.

Subcutaneous emphysema was observed in 17 cases (11.6%), and it was relatively high compared to other transoral procedures.\textsuperscript{9,10} All the emphysemas were not severe requiring no additional treatments and disappeared shortly. One assumed reason is the use of insufflation treatment of gastrointestinal endoscope. Because of the insufflation to make the lens clear, emphysema might be formed around the surgical site. Furthermore, subcutaneous emphysema occurred more frequently after ELPS for lesions in the piriform sinus. A possible explanation is that the pyriform sinus consists of relatively weak structures; only loose connective tissues are found beneath the mucosa of the pyriform sinus, and it lacks any underlying muscles.\textsuperscript{12} Consistent with this, perforation of the pyriform sinus after sneezing has been reported,\textsuperscript{13} and the pyriform sinus mucosa is assumed to be weak. Moreover, swallowing pressure peaks at the hypopharynx to cervical esophagus,\textsuperscript{14} and thus, postoperative emphysema around the hypopharynx could easily expand with swallowing movements.

After transoral resection of laryngeal/pharyngeal lesions, scarring or impaired movement of the larynx/pharynx is often observed. Swallowing impairment is typically not severe; however, aspiration pneumonia occasionally occurs in some cases. The correlation between aspiration pneumonia and resection size/site was not significant in this study, and aspiration pneumonia was only observed in elderly patients. In a multicentric study conducted in France on the complications from TORS for head and neck cancers, tumoral stage, laryngeal location, and advanced age over 65 years were identified as risk factors for aspiration pneumonia.\textsuperscript{7} Resection size was not correlated with aspiration pneumonia as an increase in cases was not observed even after wide resections. In our study, subepithelial injection during the procedure was thought to minimize excessive resection and contribute to a reduction in unnecessary damage to surrounding tissues and subsequent scar formation.\textsuperscript{15} In contrast, it was expected that aspiration pneumonia would tend to occur after resection of laryngeal lesions due to anatomical and functional causes. However, only a limited number of laryngeal cancers was included in our study population, and thus, differences between previous studies and our results might be attributed to differences in the distribution of the subjects. We did, however, observe a similar tendency with age (over 65 years) and aspiration pneumonia after ELPS. Pulmonary complications were often observed in aged patients due to their lowered respiratory function,\textsuperscript{16} suggesting that extra care should be taken when treating aged patients.

The limitations of this study include the small sample size of patients who experienced postoperative complications, a bias in the distribution of lesions, and the study’s retrospective nature. A multicentric prospective study is warranted to confirm the risk factors for postoperative complications after ELPS, and to clarify the appropriate indications for this procedure.

**CONCLUSION**

This study reviewed the complications after ELPS. All complications after ELPS were safely managed. All cases of postoperative bleeding and aspiration pneumonia occurred in patients over 65 years of age. A history of taking anticoagulation or antiplatelet medications and macroscopic 0-IIa lesions were shown to be correlated with postoperative bleeding after ELPS. In addition, the resection of lesions in the pyriform sinus was found to be associated with subcutaneous emphysema. It is thus recommended that these risk factors should be considered when deciding on an indication for ELPS, and extra care should be taken in the treatment of patients with these factors.

**BIBLIOGRAPHY**