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## Magnifying Endoscope With NBI to Predict the Depth of Invasion in Laryngo-Pharyngeal Cancer

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**Objectives/Hypothesis:** To examine if macroscopic classification with a magnifying gastrointestinal endoscope with narrow band imaging (ME-NBI) is useful in predicting pathological depth of tumor invasion in laryngo-pharyngeal cancer.

**Study Design:** Retrospective study.

**Methods:** Preoperative endoscopy reports and postoperative pathological reports on 139 laryngo-pharyngeal cancer lesions were retrospectively reviewed, and the association between macroscopic findings in the lesions and the depth of tumor invasion was analyzed statistically.

**Results:** The ratios of lesions macroscopically classified as 0-I (superficial and protruding), 0-IIa (slightly elevated), 0-IIb (true flat), 0-IIc (slightly depressed), and 0-III (superficial and excavated) in the preoperative endoscopy reports were 3%, 25%, 71%, 1%, and 0%, respectively. Regarding the depth of tumor invasion in the postoperative pathological reports, the ratios of lesions classified as EP (carcinoma in situ), SEP (tumor invades subepithelial layer), and MP (tumor invades muscularis propria) were 73%, 26%, and 1%, respectively. The ratios of subepithelial invasion or muscular invasion in 0-I, 0-IIa, and 0-IIb were 100%, 54%, and 14%, respectively, and showed significant difference ( $P < 0.0001$ ). Only one of 139 lesions invaded the muscularis propria.

**Conclusions:** This study is the first one to show that macroscopic findings by ME-NBI predict the depth of tumor invasion in superficial laryngo-pharyngeal cancer. It was indicated that there is a little chance of muscular invasion if the lesion is endoscopically diagnosed as 0-I or 0-II. A new T stage classification based on the depth of tumor invasion may be needed in order to adapt the classification to include transoral surgery.

**Key Words:** Magnifying endoscopy, narrow band imaging, endoscopic laryngo-pharyngeal surgery, transoral robotic surgery, TNM classification.

**Level of Evidence:** 4

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### INTRODUCTION

Transoral surgery is a less invasive treatment that is becoming a major strategy in the treatment for laryngo-pharyngeal cancer. Since the 1990s, transoral laser microsurgery (TLM) has been recognized as an organ preservation strategy that reportedly has good

oncological control and functional results,<sup>1</sup> although it has not been widely used because of its technical difficulty. Recently, transoral robotic surgery (TORS) is becoming popular as a new treatment modality for laryngo-pharyngeal cancer, and surgical robots are widely used in the United States.<sup>1</sup> To date, several methods have been reported as less invasive transoral surgical approaches, such as TLM, TORS,<sup>2–4</sup> and transoral videolaryngoscopic surgery.<sup>1</sup> These surgical methods have great advantages over the conventional open surgery, especially in functional outcomes such as swallowing and use of voice, and are creating a paradigm shift in the treatment strategy for laryngo-pharyngeal cancer.

One of the most important factors for achieving success in transoral surgery is the ability to determine properly whether there is indication for transoral surgery and especially the ability to estimate the depth of tumor invasion precisely at the preoperative examination. Cancer lesions that invade bone or cartilage are contraindications for this technique. In addition, the preoperative estimation of the depth of tumor invasion strongly influences functional outcomes, such as swallowing and use of voice, whereas the extent of resection in the laryngo-pharynx directly affects swallowing and

Additional Supporting Information may be found in the online version of this article.

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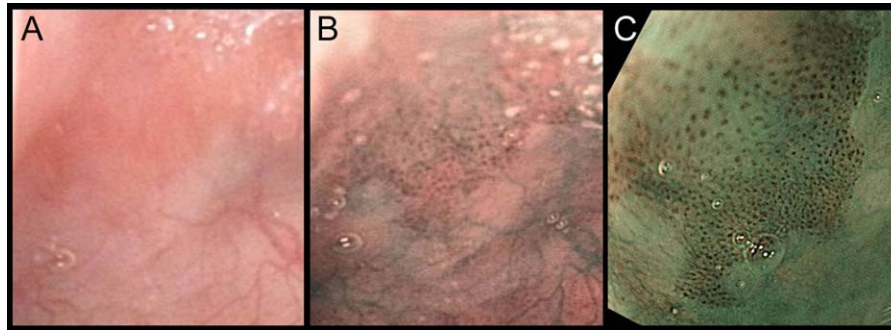


Fig. 1. The same superficial cancer lesion in the hypopharynx observed by endoscope for otolaryngology (ENF type VQ) with white light (A), endoscope for otolaryngology (ENF type VQ) with NBI (B), and magnifying endoscope for upper gastrointestinal tract (GIF TYPE H260Z) with NBI (C). (A) The lesion cannot be identified by ENT endoscope with white light. (B) The lesion can be identified by ENT endoscope with NBI, although the contrast is poor. (C) The lesion is clearly identified as a brownish area with scattered dots of abnormal vessels, and the margin of the lesion is easily traceable. ENT = ear, nose, and throat; NBI = narrow band imaging.

voice functions. Although computed tomography and magnetic resonance imaging are widely accepted as useful modalities for estimating the extent of tumor growth, different preoperative invasion staging techniques may help estimating the depth of tumor invasion more accurately. Therefore, developing a method to predict the depth of tumor invasion is needed in transoral surgery.

Narrow band imaging (NBI) is an innovative optical technology that can increase contrast of the precise morphological changes in the mucosal surface. When combined with magnifying endoscopy, NBI clearly visualizes microvascular structures.<sup>5</sup> In the head and neck region, we have previously reported that magnifying gastrointestinal endoscopy with NBI function (ME-NBI) provides high-resolution images and is useful in detecting early superficial laryngo-pharyngeal cancers, which are difficult to detect by standard endoscopy.<sup>6–8</sup> In addition to the detection, ME-NBI is useful in predicting the depth of tumor invasion in the upper gastrointestinal tract.<sup>9</sup> For example, esophageal cancer is classified in detail in terms of macroscopic morphology and the pathological depth of tumor invasion according to the Japanese Classification of Esophageal Cancer (10th edition),<sup>10</sup> and correlations between endoscopic findings and the depth of tumor invasion have been reported.<sup>11</sup> Nevertheless, although Kikuchi et al.<sup>12</sup> reported correlation between microvascular characteristics and the depth of tumor invasion in superficial pharyngeal cancer, no reports have been published regarding the correlation between macroscopic findings and the depth of tumor invasion in head and neck cancer.

Since 2007, the departments of otolaryngology head and neck surgery and gastroenterology and hepatology in our university hospital have been collaborating and have been screening the laryngo-pharyngeal region of all patients who have a history of esophageal cancer or head and neck cancer by using ME-NBI. Detected lesions were macroscopically classified and were then biopsied. If a lesion was diagnosed as superficial cancer, it was treated by either endoscopic submucosal dissection (ESD)<sup>13,14</sup> or endoscopic laryngo-pharyngeal surgery (ELPS), which was developed to treat laryngo-pharyngeal superficial cancer.<sup>15</sup>

The purpose of this study is to examine if the preoperative macroscopic classification with ME-NBI is useful in predicting pathological depth of tumor invasion in laryngo-pharyngeal cancer. Endoscopic report data on the screening and postoperative pathological results were retrospectively reviewed, and the correlation between the macroscopic endoscopic classification and the pathological depth of tumor invasion was statistically analyzed.

## MATERIALS AND METHODS

### *Patients and Lesions*

During the period from February 2007 to January 2014, 176 consecutive laryngo-pharyngeal lesions in 106 patients were treated with ELPS or ESD under general anesthesia at Kyoto University Hospital, Japan. Among them, 139 fresh lesions of carcinoma in situ or squamous cell carcinoma in 91 patients who had no history of radiation therapy to the neck or surgery to the same site are included in this study. The 15 patients excluded from the study include four patients with a history of surgery on the same site, four with a history of neck radiation, one with a spindle cell carcinoma, and six with nonmalignant lesions.

Patients were predominantly male (86 cases, 95%) and the median age was 67 years (range 33–85 years). Written informed consent for the treatment was obtained from all patients; and this study was approved by the institutional review board of the Graduate School of Medicine, Kyoto University.

### *Macroscopic Classification by Magnifying Endoscopy With Narrow Band Imaging*

All procedures were performed using a ME-NBI (GIF TYPE H260Z, Q240Z, or Q260J; Olympus Medical Systems, Tokyo, Japan), as reported previously.<sup>5</sup> In short, each patient was sedated with 35-mg pethidine hydrochloride before the examination. A nonmagnifying observation with NBI was performed to identify abnormal mucosal areas. If abnormal mucosal areas (e.g., well demarcated brownish lesions) were identified, photographs of the nonmagnified NBI view were taken. Subsequently, the lesion and surrounding normal mucosa was observed under magnification. ME-NBI has the capabilities of both standard video endoscopy and adjustable image magnification over a continuous range up to a magnification factor of 80, and it provides higher resolution images with higher

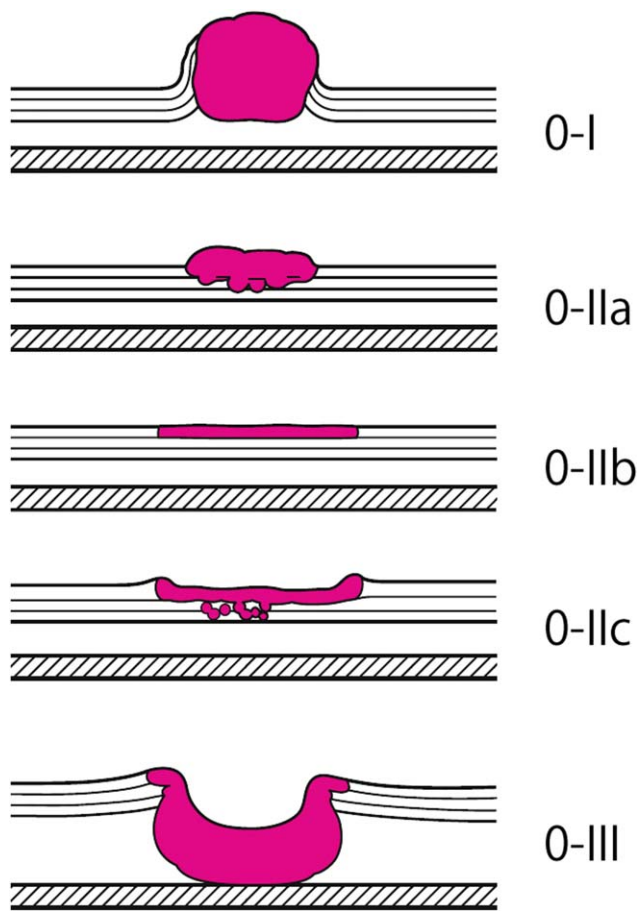


Fig. 2. Schematic view of the macroscopic classification of superficial esophageal cancer in the Japan Classification of Esophageal Cancer (10th edition), modified from reference 10. This classification is applied for head and neck cancer in the General Rules for Clinical Studies on Head and Neck Cancer (5th edition) of the Japan Society for Head and Neck Cancer<sup>17</sup> and used for this study. 0-I (superficial and protruding type: more than 1 mm in height), 0-IIa (slightly elevated type: less than 1 mm in height), 0-IIb (flat type), 0-IIc (slightly depressed type: less than 0.5 mm in depth), 0-III (superficial and excavated type).

contrast compared to endoscopes with NBI used in otolaryngology, such as ENF-VQ and ENF-VH (Olympus Medical Systems) (Fig. 1).

If scattered brownish dots were observed within the lesion under ME-NBI, the lesion was clinically diagnosed as malignant, as has previously been reported for lesions in the esophagus.<sup>16</sup> Biopsy was performed to pathologically confirm the malignancy after the observation.

Macroscopic morphology of the lesion was classified quickly after the examination and reported in accordance with both the Japanese Classification of Esophageal Cancer (10th edition)<sup>10</sup> and the General Rules for Clinical Studies on Head and Neck Cancer (5th edition) of the Japan Society for Head and Neck Cancer<sup>17</sup> by at least two experienced gastroenterologists who had no information regarding the pathology. According to the Japanese Classification of Esophageal Cancer (10th edition),<sup>10</sup> superficial cancer is defined as a lesion with no invasion to the muscularis propria, and tumors in which invasion is diagnosed to extend to the muscularis propria or beyond are

classified as advanced type. The superficial type has the prefix 0 and is classified into 0-I (superficial and protruding type), 0-II (superficial and flat type), or 0-III (superficial and excavated type). Type 0-II (superficial and flat type) is classified into 0-IIa (slightly elevated type: less than 1 mm in height), 0-IIb (true flat type), and 0-IIc (slightly depressed type). The utility and clinical relevance of the Japanese endoscopic classification of superficial neoplastic lesions of the gastrointestinal (GI) tract, including esophagus, stomach, and colon, were explored by an international group of endoscopists, surgeons, and pathologists in an intensive workshop in Paris in 2002, and the results<sup>9</sup> were published in 2003. This endoscopic classification of the GI tract is globally accepted and is also called the Paris endoscopic classification.<sup>9</sup> Clinically, the height and depth of a lesion are evaluated by placing a single cup of the opened biopsy forceps (approximately 1.2 mm in height) next to the lesion as a calibrating gauge. Lesions protruding above the level of the cup are classified as 0-I; and protruding lesions that have a thick pedicle with a broad base<sup>18</sup> and restricted mobility are classified as type 1, an invasive tumor. Lesions that are depressed by more than half the level of a single cup are classified as 0-III. Entirely flat lesions with neither protrusion nor depression observed with ME-NBI are classified as 0-IIb. The 0-IIb lesions are detectable only with NBI. This classification has been applied for head and neck cancer by the Japan Society for Head and Neck Cancer as the General Rules for Clinical Studies on Head and Neck Cancer (5th edition).<sup>17</sup> Schema views of each of the subtypes of the superficial cancer are shown in Figure 2.

### Surgical Procedure

If the lesion was clinically diagnosed as superficial cancer, ELPS or ESD was indicated as a minimally invasive treatment under general anesthesia. ELPS was developed to treat laryngopharyngeal superficial cancer. The concept of ELPS is the same as that of ESD in that both are performed as en bloc resection of a cancer lesion following submucosal injection, but it differs from ESD in that the resection procedure is performed by a head and neck surgeon with both hands (Supp. Fig. S1). After starting the use of ELPS in August 2009, all lesions have generally been treated with ELPS except those that invaded the cervical esophagus beyond the entrance of the esophagus. In brief, a curved rigid laryngoscope (Nagashima Medical Instruments Company, Ltd, Tokyo, Japan) was inserted to provide a working space in the pharyngeal lumen, and a ME-NBI was inserted transorally by a gastroenterologist to visualize the surgical field (Supp. Fig. S2). The extent of the lesion 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 in order to lift the lesion above the surrounding mucosa and to create a safety space. Specially designed curved forceps<sup>13</sup> (Nagashima Medical Instruments Company, Ltd, Tokyo, Japan) and a curved electrosurgical needle knife (Olympus Medical Systems) were orally inserted and the tumor was resected. Thirty-five lesions were treated with ESD, and 104 lesions were treated with ELPS in this study.

### Pathology and Evaluation of the Invasion of the Tumor

All resected specimens were cut into longitudinal slices 2 mm in width after fixation. The slices were embedded in paraffin and stained with hematoxylin-eosin. All specimens were microscopically evaluated according to the World Health Organization Classification. T staging was performed according to the Union for International Cancer Control tumor-node-

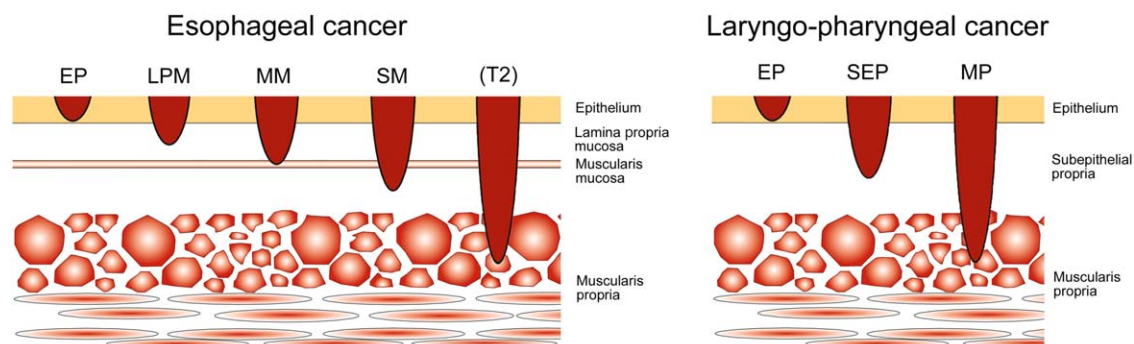


Fig. 3. Schematic view of the pathological classification for the superficial cancer of the esophageal cancer and the head and neck cancer, in the Japan Classification of Esophageal Cancer (10th edition)<sup>10</sup> and the General Rules for Clinical Studies on Head and Neck Cancer (5th edition) of the Japan Society for Head and Neck Cancer,<sup>17</sup> respectively, modified from reference 10.

In the esophageal cancer, superficial cancers are classified as EP (carcinoma in situ), LPM (tumor invades lamina propria mucosa), MM (tumor invades muscularis mucosa), and tumor invades submucosa (T1b), depending on the depth of tumor invasion. In the laryngo-pharynx, because muscularis mucosa is absent in the laryngo-pharynx, the lesion was classified as EP (carcinoma in situ), SEP (tumor invades subepithelial layer), and MP (tumor invades muscularis propria).<sup>17</sup>

metastasis (UICC/TNM) classification (7th edition) of the head and neck cancer.<sup>19</sup>

Evaluation of the invasion of the tumor was also made according to the General Rules for Clinical Studies of Head and Neck Cancer (5th edition) by the Japan Society for Head and Neck Cancer<sup>17</sup> and the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society (10th edition).<sup>10</sup>

In the esophageal cancer, superficial cancers are pathologically classified as EP (carcinoma in situ), LPM (tumor invades lamina propria mucosa), MM (tumor invades muscularis mucosa), and tumor invades submucosa (T1b), depending on the depth of tumor invasion.<sup>10</sup> In the laryngo-pharynx, because muscularis mucosa is absent in the laryngo-pharynx, the lesion was classified into EP (carcinoma in situ), SEP (tumor invades subepithelial layer) and MP (tumor invades muscularis propria), according to the General Rules for Clinical Studies on Head and Neck Cancer by the Japan Society for Head and Neck Cancer (5th edition).<sup>17</sup> In this study, all lesions were classified as EP, SEP, or MP in accordance with the rule by the Japan Society for Head and Neck Cancer.<sup>17</sup> Schematic views of pathological classi-

fication of the depth of tumor invasion in the esophageal cancer and head and neck cancer are shown in Figure 3.

### Data Analysis

Macroscopic classification with a ME-NBI, pathological classification regarding the depth of tumor invasion, lymphatic invasion, vessel invasion, and recurrence was reviewed. The association between macroscopic classification (0-I /0-IIa/0-IIb) and the depth of tumor invasion (EP/SEP + MP) was statistically analyzed using the Cochran–Mantel–Haenszel test (degree of freedom = 1). Because of the small sample size (N = 1), 0-IIc was excluded from the statistical analysis. SAS for Windows 9.3 (SAS Institute Inc., Cary, NC) was used for the analysis.

### RESULTS

Lesion characteristics are shown in Table I. Of the 139 lesions resected, the total number of lesions in the oropharynx, hypopharynx, and larynx was 41 (30%), 95 (68%), and three (2%), respectively. In the oropharynx, the numbers of lesions in the anterior, posterior, superior, and lateral walls were five (12%), 19 (46%), nine (22%), and eight (20%), respectively. In the hypopharynx, the numbers of lesions in the piriform sinus, post-cricoid, and posterior walls were 76 (80%), three (3%), and 16 (17%), respectively. In the larynx, all lesions were in the supraglottic area. Regarding the T classification, 101 lesions were pathologically diagnosed as Tis, 16 lesions as T1, 18 lesions as T2, and four lesions as T3.

Macroscopic classification, pathological classification regarding the depth of tumor invasion, lymphatic invasion, vessel invasion, and the number of recurrences are shown in Table II. The numbers of lesions classified macroscopically as 0-I, 0-IIa, 0-IIb, 0-IIc, and 0-III were 4 (3%), 35 (25%), 99 (71%), one (1%), and 0(0%), respectively. Representative images of each subtype are shown in Figure 4. Regarding the depth of tumor invasion, the numbers of lesion classified as EP, SEP, and MP were 101 (73%), 37 (26%), and one (1%), respectively.

In the 0-I lesions, all lesions showed subepithelial invasion (SEP). In the 0-IIa lesions, 18 lesions (51%) were SEP;

TABLE I.  
Lesion Characteristics.

Origin	Subsite	
Oropharynx	Anterior wall	5
	Posterior wall	19
	Superior wall	9
	Lateral wall	8
Hypopharynx	Piriform sinus	76
	Post cricoid	3
	Posterior wall	16
Larynx	Supraglottic	3
<hr/>		
T stage		
Tis	101	
T1	16	
T2	18	
T3	4	

TABLE II.  
Macroscopic Classification by Magnifying Endoscope, Pathological Classification Regarding the Depth of Tumor Invasion, Lymphatic Invasion, and Vessel Invasion.

Preoperative Macroscopic Classification	Number of Lesions	Pathology				
		Depth of Tumor Invasion				
		EP	SEP	MP	ly (+)	v (+)
0-I	4	0	4	0	0	0
0-IIa	35	16	18	1	2	1
0-IIb	99	85	14	0	0	0
0-IIc	1	0	1	0	1	0
0-III	0	0	0	0	0	0

Preoperative Macroscopic Classification	Ratio of SEP + MP*
0-I	100%
0-IIa	54%
0-IIb	14%

\*The ratios of SEP + MP in 0-I, 0-IIa, and 0-IIb showed significant difference ( $P < 0.0001$ ; Cochran-Mantel-Haenszel test: degree of freedom = 1).

one lesion (3%) was MP; and vessel invasion was observed in three lesions (9%). In the 0-IIb lesions, most lesions (86%) were EP and there was no vessel invasion. Only one lesion was classified as 0-IIc; and the lesion was pathologically classified as SEP with lymphatic duct invasion.

The ratios of subepithelial invasion or muscular invasion (SEP + MP) in 0-I, 0-IIa, and 0-IIb were 100%, 54%, and 14%, respectively, and showed significant difference ( $P < 0.0001$ ).

## DISCUSSION

The present study showed strong correlation between macroscopic classification by ME-NBI and pathological depth of tumor invasion. This is the first report to show that macroscopic findings by ME-NBI predict the depth of tumor invasion in superficial laryngo-pharyngeal cancer.

Correlations between endoscopic macroscopic type and invasion depth have been reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas in the Paris endoscopic classification,<sup>9</sup> which was made based on the Japanese endoscopic classification of superficial neoplastic lesions of the GI tract. In the multicenter analysis of superficial esophageal squamous cell carcinoma conducted in Japan on the basis of 2,418 patients from 143 institutions,<sup>20</sup> the total risk for submucosal invasion is high (90%) in type 0-I lesions. The highest risk occurs in type 0-I and in type 0-III lesions, and the lowest risk is in type 0-IIb lesions. Ratios of invasion deeper than EP in 0-I, 0-IIa, 0-IIb, and 0-IIc were 99% (259/262), 89% (270/303), 47% (104/221), and 80% (567/707), respectively. In our study, the highest risk for subepithelial invasion occurred in type 0-I (100%); and the lowest risk was in type 0-IIb lesions (14%), which were similar to the results in esophageal cancer.

The major difference between our study and the report on esophageal cancer is the overall ratio of submucosal (muscularis propria) invasion in 0-I and 0-II lesions. The overall ratio of invasion to muscularis propria in 0-I and 0-II lesions in our study was only one of 139 lesions, whereas it was 52% in esophageal cancer.<sup>20</sup> We suggest that one reason for this discrepancy may be associated with the different populations. For example, in our study there was just one 0-IIc lesion, but the ratio of 0-IIc in esophageal cancer was 47%. Although it is unclear if the population difference is due to a natural characteristic of laryngo-pharyngeal cancer or to an institutional bias, the results indicate that there is a little chance of muscular invasion in the laryngo-pharyngeal cancer as long as the lesions are diagnosed as 0-I and 0-II.

Finally, the correlation between macroscopic morphological classification and the depth of tumor invasion shown in this study may contribute to modify the T stage classification in head and neck cancer. The T stage classification of head and neck cancer, especially in the pharynx, is based on the diameter of the tumor. This is probably because radiotherapy or open neck surgery are two standard modalities, and the volume or the area of the tumor are important for them. The T staging system is the gold standard in evaluating a primary lesion and its prognostic importance is widely accepted. However, the limitation of the current T staging system is becoming evident with the development of new treatments and diagnostic modalities. For example, NBI enables detection of superficial pharyngeal cancer lesions that are barely visible by conventional methods, and excellent long-term oncological outcome for endoscopic resection of such lesions is reported with the 5-year cause-specific survival rate of 97%.<sup>13</sup> According to the current T staging system, a pharyngeal superficial cancer with micro invasion, such as SEP, is diagnosed as T3 when it is

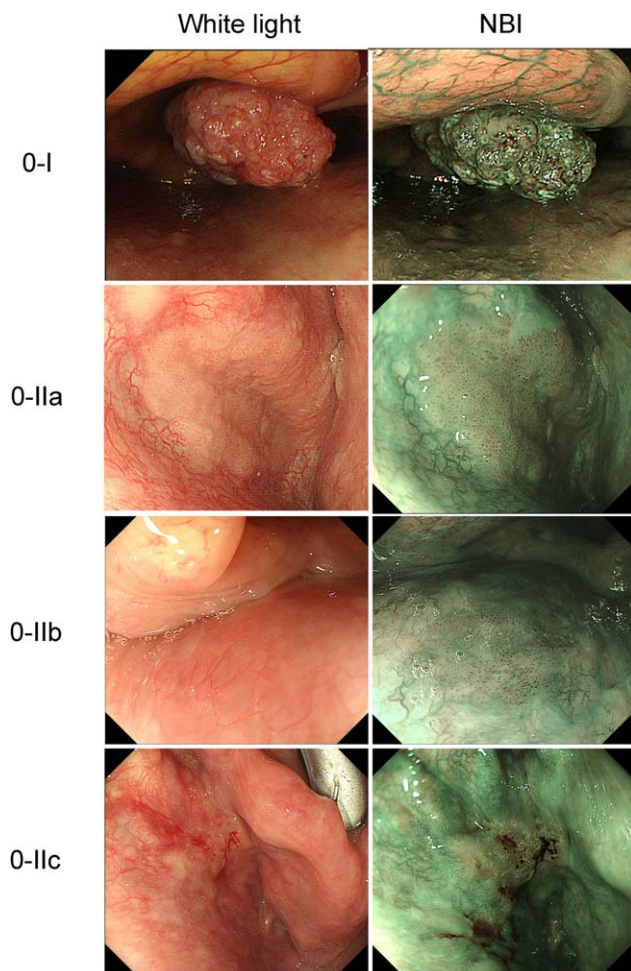


Fig. 4. Representative endoscopic images of each macroscopic subtype by magnifying endoscope for upper gastrointestinal endoscope with NBI (GIF TYPE H260Z). NBI = narrow band imaging.

more than 4 cm in diameter or when it invades to the entrance of the esophagus, although it is a superficial lesion with excellent prognosis. In esophageal cancer, transoral endoscopic resection is a standard treatment, and T stage classification is based on the depth of tumor invasion because the depth is an important factor in determining whether there is indication for endoscopic treatment. Indeed, in esophageal cancer,<sup>10</sup> EP, LPM, and MM lesions are classified as T1a; a SM lesion is classified as T1b; and a lesion with invasion to the muscularis propria is classified as T2. Faced with the paradigm shift in treatment modality from open surgery to transoral surgery, it may be necessary to adapt a change in T stage modification based on the depth of tumor invasion in the laryngo-pharyngeal cancer. The findings shown in this study will help to develop the new T stage classification based on the depth of tumor invasion.

There are two limitations in this study. One is the small number of invasive lesions. There was no 0-III lesion in the study because 0-III lesions were primarily treated with radiation or concurrent chemoradiotherapy, and pathological information other than biopsy results was not obtained. The other limitation is that the study

was a retrospective study. A prospective, randomized, controlled multi-institutional trial should be conducted in the future to validate the results.

## CONCLUSION

This study is the first to show that macroscopic findings by ME-NBI predict the depth of tumor invasion in superficial laryngo-pharyngeal cancer. The highest risk for subepithelial invasion was present in type 0-I (100%), and the lowest risk was in type 0-IIb lesions (14%). Only one out of 139 lesions of 0-I and 0-II invaded muscularis propria; and it was indicated that there is a little chance of muscular invasion in the laryngo-pharyngeal cancer as long as the lesions are diagnosed as 0-I and 0-II.

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Ichiro Tateya, MD, PhD, and Shuko Morita, MD, contributed equally to this study.

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