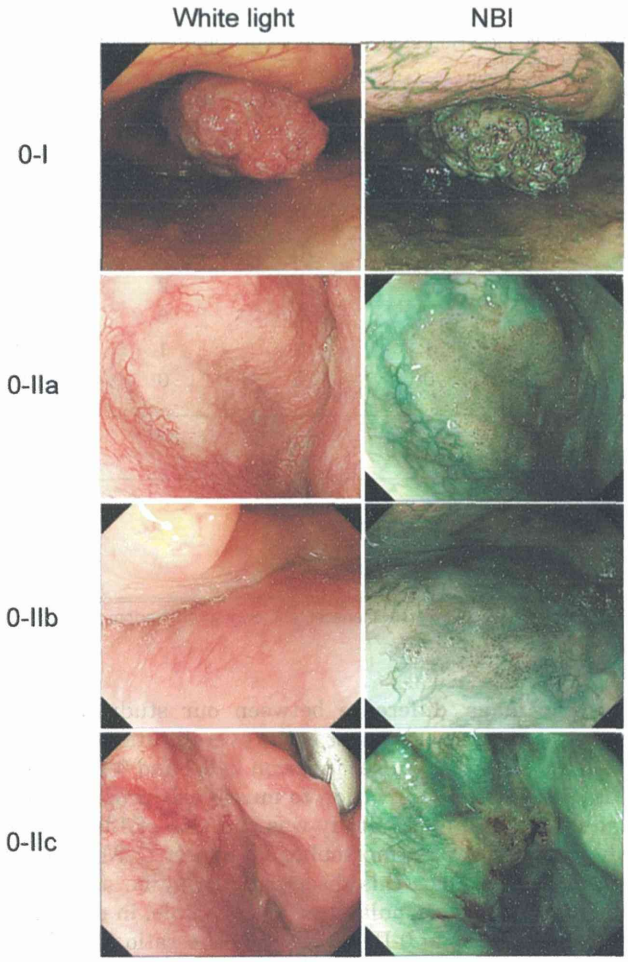

Fig. 4. Representative endoscopic images of each macroscopic subtype by magnifying endoscope for upper gastrointestinal endoscope with NBI (GIF TYPE H260Z). NBI = narrow band imaging.

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,[10] 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 muscular 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.

Acknowledgment

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

BIBLIOGRAPHY

1. Tomifuji M, Araki K, Yamashita T, Shiotani A. Transoral videolaryngoscopic surgery for oropharyngeal, hypopharyngeal, and supraglottic cancer. *Eur Arch Otorhinolaryngol* 2014;271:589–597.
2. O'Malley BW Jr, Weinstein GS, Hockstein NG. Transoral robotic surgery for tongue base neoplasms. *Laryngoscope* 2006;116:1465–1472.
3. Weinstein GS, O'Malley BW Jr, Snyder W, Hockstein NG. Transoral robotic surgery: supraglottic partial laryngectomy. *Ann Otol Rhinol Laryngol* 2007;116:19–23.
4. Park YM, Byeon HK, Chung HP, Choi EC, Kim SH. Comparison study of transoral robotic surgery and radical open surgery for hypopharyngeal cancer. *Acta Otolaryngol* 2013;133:641–648.
5. Muto M, Horimatsu T, Ezoe Y, Morita S, Miyamoto S. Improving visualization techniques by narrow band imaging and magnification endoscopy. *J Gastroenterol Hepatol* 2009;24:1333–1346.
6. Muto M, Katada C, Sano Y, et al. Narrow band imaging: a new diagnostic approach to visualize angiogenesis in superficial neoplasia. *Clin Gastroenterol Hepatol* 2005;3(suppl 1):S16–S20.
7. Muto M, Minashi K, Yano T, Saito Y, et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. *J Clin Oncol* 2010;28:1566–1572.
8. Muto M, Nakane M, Katada C, Sano Y, et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. *Cancer* 2004; 101:1375–1381.
9. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. *Gastrointest Endosc* 2003;58(suppl 6):S3–S43.
10. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, tenth edition: part I. *Esophagus* 2009;6:1–25.
11. Jang JY. The usefulness of magnifying endoscopy and narrow-band imaging in measuring the depth of invasion before endoscopic submucosal dissection. *Clin Endosc* 2012;45:379–385.
12. Kikuchi D, Iizuka T, Yamada A, Furuhata T, et al. Utility of magnifying endoscopy with narrow band imaging in determining the invasion depth of superficial pharyngeal cancer. *Head Neck* 2014 Mar 12. doi: 10.1002/hed.23683. Epub ahead of print.
13. Muto M, Satake H, Yano T, et al. Long-term outcome of transoral organ-preserving pharyngeal endoscopic resection for superficial pharyngeal cancer. *Gastrointest Endosc* 2011;74:477–484.
14. Okami K, Ebisumoto K, Sakai A, et al. Transoral en bloc resection of superficial laryngeal and pharyngeal cancers. *Head Neck* 2013;35:1162–1167.
15. Sato Y, Omori Y, Tagawa M. Surgical treatment for hypopharyngeal superficial cancer: endoscopic laryngo-pharyngal surgery. *Nihon Jibiinkoka Gakkai Kaiho* 2006;109:7:581–586.
16. Kumagai Y, Inoue H, Nagai K, Kawano T, Iwai T. Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial oesophageal carcinoma. *Endoscopy* 2002;34:369–375.
17. Japan Society for Head and Neck Cancer. *General Rules for Clinical Studies on Head and Neck Cancer.* 5th Edition, Tokyo, Japan: Kanehara Publishing Group; 2012. 58–65.
18. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma–2nd English *Edition. Gastric Cancer* 1998;1:10–24.
19. Sobin, LH, Gospodarowicz, and Wittekind C, eds. *TNM Classification of Malignant Tumours*, 7th edition. Hoboken, NJ: Wiley-Blackwell; 2009.
20. Kodama M and Kakegawa T. Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. *Surgery* 1998;123:432–439.

Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer

Authors Hironaga Satake[1], Tomonori Yano[1], Manabu Muto[2], Keiko Minashi[1], Yusuke Yoda[1], Takashi Kojima[1], Yasuhiro Oono[1], Hiroaki Ikematsu[1], Ikuo Aoyama[3], Shuko Morita[3], Shinichi Miyamoto[3], Satoshi Fujii[4], Akihiko Yoshizawa[5], Atsushi Ochiai[4], Ryuichi Hayashi[6], Kazuhiro Kaneko[1]

Institutions Institutions are listed at the end of article.

submitted
3. December 2013
accepted after revision
17. July 2014

Bibliography
DOI http://dx.doi.org/10.1055/s-0034-1378107
Published online: 30.9.2014
Endoscopy 2015; 47: 11–18

ISSN 0013-726X

Corresponding author
Tomonori Yano, MD
Department of Gastroenterology, Endoscopy Division
National Cancer Center Hospital East
6-5-1, Kashiwanoha
Kashiwa 277-8577
Japan
Fax: +81-4-71314724
toyano@east.ncc.go.jp

Background and study aims: The curability of endoscopic resection for superficial pharyngeal squamous cell carcinoma (SPSCC) has not been fully elucidated, particularly for lesions invading the subepithelial layer, which carry the risk of metastasis. The aim of this study was to evaluate the curative potential of endoscopic resection for SPSCC invading the subepithelial layer.

Patients and methods: From June 2002 to July 2010, 198 SPSCCs in 176 consecutive patients were treated by endoscopic resection at two tertiary referral centers. Selection criteria were initial endoscopic resection, histologically proven squamous cell carcinoma invading the subepithelial layer, no lymph node or distant metastasis before endoscopic resection, and no prior treatment for pharyngeal squamous cell carcinoma. Endoscopic resection was performed under general anesthesia. Long-term survival and clinical outcomes were retrospectively evaluated.

Results: Among 176 consecutive patients, 50 lesions in 47 patients (all male; median age 64 years) were histologically diagnosed from endoscopic resection specimens as having subepithelial invasion. Median tumor thickness was 1000 µm (range 200–10 000 µm). Six patients developed local recurrence (13%; 95% confidence interval [CI] 3.1%–22.4%), and all were cured with organ-preserving intervention. After a median follow-up period of 71 months (range 27–116 months), one patient (2%; 95%CI 0–6.3%) developed neck lymph node metastasis. A total of 14 patients (30%) were followed for 5 years or more, and 5-year overall survival and disease-specific survival rates were 84.5% (95%CI 73%–96%) and 100%, respectively.

Conclusions: Endoscopic resection has curative potential as a minimally invasive treatment option for SPSCC that invades the subepithelial layer.

Introduction

The majority of patients with pharyngeal squamous cell carcinoma (SCC) are diagnosed at an advanced stage, at which point the prognosis is poor [1,2]. Even if detected at an operable stage, extensive surgical resection or chemoradiotherapy (CRT) frequently results in loss of swallowing, disturbance of salivary secretion or speaking functions, and possible cosmetic deformities, and markedly degrades quality of life [3–6]. Early detection of superficial pharyngeal squamous cell carcinoma (SPSCC) by conventional white-light endoscopy is markedly hampered by an almost complete lack of morphological changes [7–9].

The narrow-band imaging (NBI) system is an innovative optical image-enhanced technology that uses narrow-bandwidth filters [10]. The 415-nm light is well absorbed by hemoglobin, and NBI in combination with magnifying endoscopy allows the microvascular structure of the organ surface to be clearly visualized [10]. Any surface microvascular irregularities detected are useful landmarks of early neoplasms in the head and neck region [8,9,11,12]. In a multicenter prospective study of patients with esophageal cancer, NBI with magnifying endoscopy demonstrated significantly better detection of SPSCC than conventional white-light endoscopy [9].

Recent major advances in diagnostic techniques such as magnifying endoscopy and NBI have produced a dramatic increase in the detection of SPSCCs that can be successfully treated by endoscopic resection [8,13–18]. We previously reported the long-term results of endoscopic resection for patients with SPSCC [19]. Theoretically at least, squamous intraepithelial neoplasia (dysplasia or carcinoma in situ) can be cured by endoscopic resection, because it has no risk of lymph node or distant metastasis. Only one small case series has been reported [20], however; in particular, the risk of lymph node metastasis after

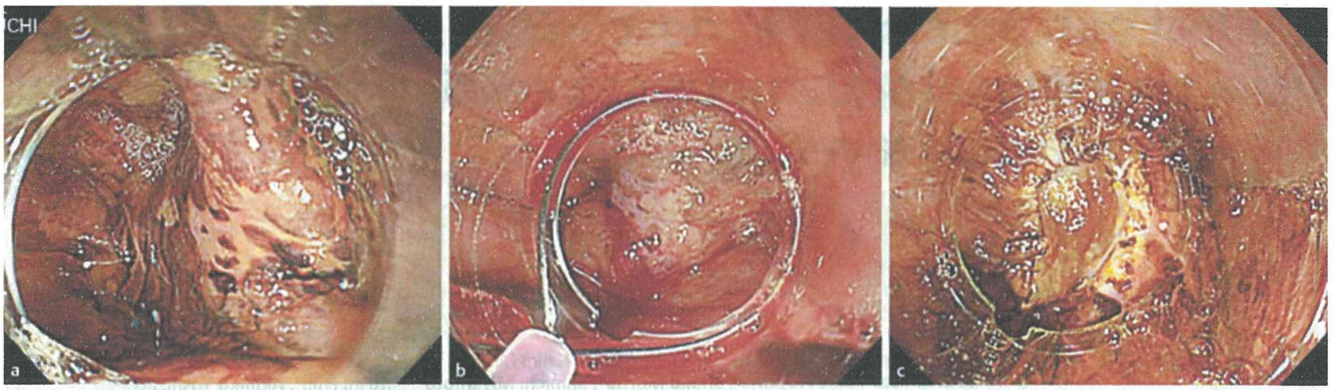

Fig. 1 Schema of endoscopic mucosal resection procedure using a cap-equipped panendoscope (EMR-C). **a** An adequate volume of 0.9% saline solution mixed with low-volume epinephrine is injected into the subepithelial layer beneath the lesion. **b** Placement of the snare at the cap. **c** Induced ulcer after removal of the lesion.

endoscopic resection of SPSCC is unclear in patients whose resected endoscopic resection specimens histologically show subepithelial invasion. Accordingly, the use of additional treatments such as CRT or preventive neck lymph node dissection in these patients is controversial.

The aim of this study was to retrospectively evaluate the curative potential of endoscopic resection alone for SPSCC invading the subepithelial layer.

Patients and methods

Patients

From June 2002 to July 2010, 198 SPSCC lesions in 176 consecutive patients were treated by endoscopic resection at the National Cancer Center Hospital East and Kyoto University Hospital. All lesions were detected by NBI endoscopy in high-risk patients, who were mainly patients with prior or synchronous esophageal squamous cell carcinoma, which was histologically diagnosed as squamous cell carcinoma according to criteria proposed by the World Health Organization (WHO) using biopsy specimens before the endoscopic resection procedure [21].

Indications for endoscopic resection for SPSCC were: 1) histological confirmation of SCC lesion by NBI-targeted biopsy specimens; 2) no highly protruding areas or ulceration beyond suspected minor invasion to the subepithelial layer; 3) no involvement of the pharyngeal space bilaterally or spread into the deep laryngeal space (i.e. no lesions >4 cm); 4) no distant or lymph node metastasis on physical examination or on computed tomography (CT); and 5) provision of written informed consent. Selection criteria for this study were initial endoscopic resection, histologically proven SCC invasion of the subepithelial layer in resected specimens, and no prior treatment for head and neck cancer.

Case comparability regarding diagnosis, endoscopic treatment, and pathological diagnosis of SPSCC was assured by frequent meetings of all endoscopists and pathologists involved in the study, during which criteria for treatment decisions and pathological diagnosis were determined. Characteristics of resected lesions, patient characteristics, and clinical results were compared between subepithelial invasion and SCC in situ lesions. Pathological results and long-term outcome were evaluated with regard to subepithelial invasion. The study protocol was approved by the institutional review committee of both hospitals (study number 2011–019).

Endoscopic resection procedure

Endoscopic resection involved endoscopic mucosal resection using a cap (EMR-C), the endoscopic submucosal dissection (ESD) technique (with dissection from the subepithelial layer), and endoscopic laryngopharyngeal surgery. Before 2006, all endoscopic resection procedures were performed by the EMR-C method. From 2006, the ESD method was adopted, and endoscopic laryngopharyngeal surgery was used for large lesions to achieve en block resection. All procedures 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 by a head and neck surgeon to widen the pharyngeal space. A single-channel upper gastrointestinal endoscope with a water-jet system was used (GIF-H260Z, Q240Z; Olympus Medical Systems Co., Tokyo, Japan), and a high-frequency generator with automatically controlled system (Endo Cut mode, 120 W, effect 2 for circumference incision/Forced coagulation 50 W for dissection by ICC 200; ERBE Elektromedizin GmbH, Tübingen, Germany). The seven endoscopists who participated in the study had at least 5 years' specialist experience in NBI examination for the head and neck region, and were highly experienced in endoscopic resection in the upper gastrointestinal tract and in ESD procedures. Lesion extent was confirmed by NBI endoscopy and 2.0% iodine staining, and lesions were clearly recognized as unstained areas under iodine solution chromoendoscopy.

The EMR-C method was conducted as follows (**Fig. 1**) [22]. A cap (D206–06, diameter 18.1 mm; Olympus Medical Systems Co.) was fitted to the tip of the endoscope. A fine semilunar snare wire (SD-7P; Olympus Medical Systems Co.) was passed through the biopsy channel of the endoscope and pre-looped around the gutter at the tip of the cap. Under endoscopic suction, the lesion area was drawn into the cap, strangulated by closure of the snare wire, and resected by high-frequency electrocautery. The resected specimen was drawn into the cap and withdrawn, together with the endoscope.

Details of the ESD procedure using a Dual knife (Olympus Medical Systems Co.) (**Fig. 2**) or endoscopic laryngopharyngeal surgery (**Video 1**) were as follows. Marking spots were made around the circumference of the lesion using the Dual knife. Saline solution (concentration 0.9%) was injected into the subepithelial layer to create a subepithelial cushion. The initial incision was made just outside of a marking spot, and a circumferential incision around the lesion was made using the Dual knife. Addi-

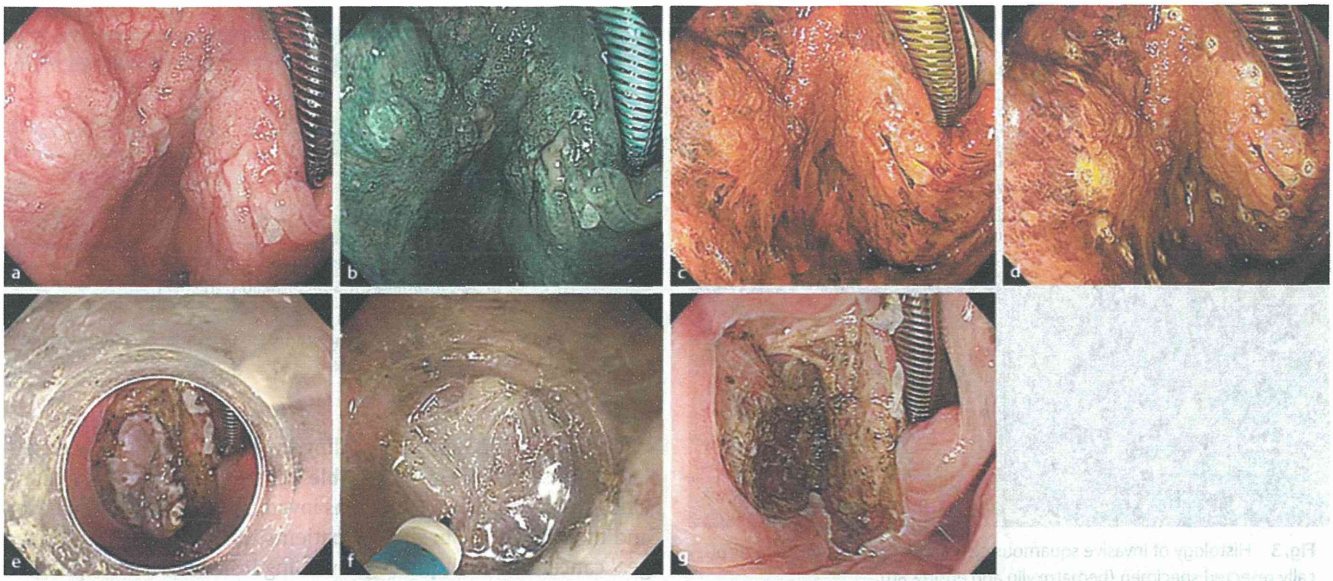

Fig. 2 Endoscopic subepithelial dissection method using a Dual knife. **a** Reddish and protruded lesion of the left pyriform sinus on conventional endoscopy with white light. **b** Brownish neoplastic area on endoscopy with narrow-band imaging. **c** Chromoendoscopy with 2.0% iodine staining to demarcate the lesion. **d** Marking around the lesion with a Dual knife. **e** Circumferential incision made using a Dual knife. **f** Dissection of the subepithelial layer after subepithelial injection. **g** Induced ulcer after removal of the lesion.

tional saline solution was then injected into the subepithelial layer, and dissection of the subepithelial layer was performed using the same device. After the lesion had been resected, vessels were coagulated to prevent delayed bleeding.

In the endoscopic laryngopharyngeal surgery method, a circumferential incision was made, and a curved-type retention forceps (Nagashima Medical Instruments Co., Ltd. Tokyo, Japan) and electrosurgical knife were inserted orally. The retention forceps allowed counter-tension to be exerted, under which the lesion was resected using the electrosurgical knife under endoscopic observation.

Finally, the head and neck surgeon evaluated the degree of laryngeal edema. If severe bilateral laryngeal edema was present, a temporary tracheostomy was performed to prevent airway obstruction.

Patients who complained of severe symptoms such as sore throat, high fever, and dyspnea underwent check-up endoscopy the day after endoscopic resection in order to assess the degree of laryngeal edema and to exclude visible bleeding vessels. If the edema was mild and the absence of bleeding was confirmed, patients were allowed to drink water 2 days after endoscopic resection and to eat semi-solid food thereafter.

Video 1

Endoscopic laryngopharyngeal surgery procedure.

Online content including video sequences viewable at: www.thieme-connect.de

Pathological evaluation and postendoscopic resection follow-up

All resected specimens were cut into longitudinal slices measuring 2 mm in width, fixed in 10% formalin, and embedded in paraffin wax. The tissue specimens were sectioned at a thickness of 2 µm and stained with hematoxylin and eosin. All sections were subjected to routine pathological evaluation and checked for lymphatic and venous invasion.

Diagnosis was made according to the criteria proposed by WHO [21], by one of three experienced pathologists (S.F., A.Y., or A.O.), each of whom had specialized for more than 10 years in gastroenterological evaluation. Pathological T staging was based on the surface dimensions of the tumor, the most important parameter for primary tumor staging in pharyngeal cancer, in which T1 tumors were 2 cm or less in greatest dimension, T2 tumors were more than 2 cm but not more than 4 cm in greatest dimension, and T3 tumors were more than 4 cm in greatest dimension. Although there are no accepted definitions of SPSCC, the guidelines for esophageal cancer proposed by the Japan Esophageal Society define superficial esophageal SCC as a tumor limited to the submucosal layer regardless of lymph node or distant metastasis [23]. In the present study, SPSCC was defined as a tumor limited to the subepithelial layer regardless of lymph node and distant metastasis. Moreover, subepithelial invasion is difficult to diagnose because there is no lamina muscularis mucosae in the pharyngeal field. Accordingly, subepithelial invasion was defined in the present study by the observation of at least one solitary carcinoma cell nest in the subepithelial region [24]. Tumor thickness was measured from the tumor surface to the base of the malignant tissue in the thickest tumor section (**Fig. 3**).

No additional treatment, such as CRT was performed after endoscopic resection regardless of pathological results. All patients were enrolled in a strict follow-up program in collaboration with the referring head and neck surgeon. Follow-up examinations were performed every 3 months within the first year after treatment, followed by check-up examinations at 6-month inter-

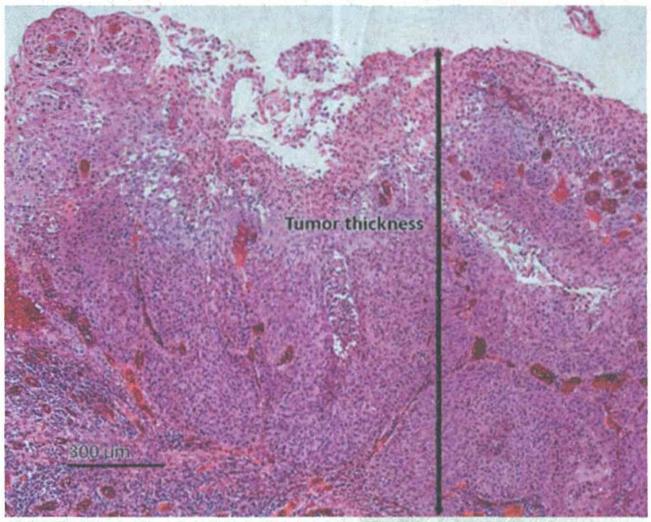

Fig. 3 Histology of invasive squamous cell carcinoma from an endoscopically resected specimen (hematoxylin and eosin × 80).

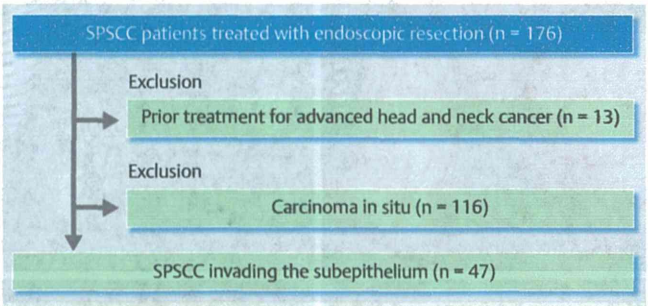

Fig. 4 Patient enrollment flow of the study. SPSCC, superficial pharyngeal squamous cell carcinoma.

vals thereafter. Each check-up examination included NBI endoscopy, physical examination, and CT scan.

When any follow-up examination revealed residual neoplastic tissue or secondary malignant lesions (metachronous or recurrent lesions), local endoscopic resection or partial resection was repeated after the patient had been provided with appropriate information. Lesions occurring near the primary site, for example at the margin of a scar after endoscopic resection, were defined as local recurrence.

Statistics

Long-term outcome was analyzed using the Kaplan–Meier method. Continuous data were compared using the Mann–Whitney U test. The Pearson chi-squared test or Fisher's exact test was used to analyze categorical data and to compare proportions.

All statistical analyses were performed using SPSS 22.0 (IBM Corp., Armonk, New York, USA). All statistical tests were two tailed, and statistical significance was defined as $P<0.05$.

Results

Patients and lesions

Of 176 consecutive patients, 13 were excluded because of prior treatment for advanced head and neck cancer and 116 because of histological confirmation of carcinoma in situ, leaving 47 patients with 50 SCC lesions invading the subepithelial layer enrolled in the study (**Fig. 4**). **Table 1** compares patient characteristics between those with lesions invading the subepithelial layer and those with SCC in situ. All patients with a history of esophageal cancer had multiple Lugol-voiding lesions of the esophageal mucosa, which is considered to indicate a very high risk of multiple cancers in the region from the head-and-neck to the esophagus [25].

Baseline characteristics of lesions with subepithelial invasion (n=50) and SCC in situ (n=148) are compared in **Table 2**. Lesions with subepithelial invasion had a significantly larger median tumor size than SCC in situ (20 vs. 13 mm; $P=0.002$). With regard to macroscopic type, lesions with subepithelial invasion included a significantly larger number of cases with protrusion (0-I or 0-IIa; $P<0.001$). Most lesions were located in the hypopharynx, with the pyriform sinus being the most frequent primary site in both groups.

Clinical outcome of endoscopic resection

Clinical results of the endoscopic resection procedures are listed in **Table 3**. En bloc resection was performed in 66% with subepithelial invasion and in 75% with SCC in situ. The median size of lesions resected by EMR-C was 14 mm (range 2–50 mm). Of the lesions resected by EMR-C, 20% were over 20 mm, indicating that the en bloc resection rate in this study might have been low. All complications were successfully treated by conservative therapy. All patients were ultimately discharged without any loss of swallowing or speaking function.

Pathology results are shown in **Table 4**. Pathological T stage was pT1 in 31 patients, pT2 in 18, and pT3 in 1 patient.

Table 1 Patient characteristics (n = 163).

	Subepithelial invasion (n=47)	SCC in situ (n=116)	*P* value
Age, median (range), years	64 (45–88)	63 (42–88)	0.388
Sex, n (%)			0.267
Male	47 (100)	113 (97)	
Female	0 (0)	3 (3)	
Prior or synchronous esophageal cancer, n (%)			0.584
Present	36 (77)	84 (72)	
Multiple Lugol-voiding lesions, n (%)			0.128
Positive	38 (81)	109 (94)	
Negative	7 (15)	6 (5)	
Unknown	2 (4)	1 (1)	

SCC, squamous cell carcinoma.

Table 2 Baseline characteristics of lesions (n = 198)

	Subepithelial invasion (n = 50)	SCC in situ (n = 148)	*P* value
Lesion size, median (range), mm	20 (3 – 56)	13 (2 – 50)	0.002
Macroscopic type, n (%)			< 0.001
0-I	7 (14)	1 (1)	
0-IIa	25 (50)	24 (16)	
0-IIb	16 (32)	94 (63)	
0-IIc	2 (4)	29 (20)	
Location, n (%)			0.559
Hypopharynx	43 (86)	122 (82)	
Pyriform sinus	37 (74)	96 (65)	
Posterior wall	4 (8)	15 (10)	
Postcricoid area	2 (4)	11 (7)	
Oropharyx	7 (14)	24 (16)	
Posterior wall	4 (8)	14 (9)	
Lateral wall	1 (2)	6 (4)	
Upper wall	1 (2)	1 (1)	
Epiglottis	1 (2)	2 (1)	
Tonsil	0 (0)	1 (1)	
Oral cavity	0 (0)	2 (1)	

0-I, protruded type; 0-IIa, slightly elevated type; 0-IIb, flat type; 0-IIc, slightly depressed type; SCC, squamous cell carcinoma.

Table 3 Clinical results of endoscopic resection procedures (n = 198).

	Subepithelial invasion (n = 50)	SCC in situ (n = 148)	*P* value
Endoscopic resection method, n (%)			
EMR-C	26 (52)	85 (57)	
ESD	17 (34)	53 (36)	0.329
ELPS	7 (14)	10 (7)	
Endoscopic resection type, n (%)			
En bloc resection	33 (66)	111 (75)	0.218
Piecemeal resection	17 (34)	37 (25)	
No. of resected segments, median (range)	3 (2 – 9)	3 (2 – 9)	
Major complications, n (%)	8 (16)	9 (6)	0.031
Delayed bleeding	2 (4)	0 (0)	
Dysphasia	2[1] (4)	3[2] (2)	
Laryngeal edema	1[1] (2)	2[2,3] (1)	
Aspiration pneumonia	1 (2)	0 (0)	
Subcutaneous emphysema	1 (2)	0 (0)	
Trismus	1 (2)	0 (0)	
Perforation	0 (0)	5[3] (3)	
Temporary tracheostomy, n (%)	10 (20)	21 (14)	0.330

EMR-C, endoscopic mucosal resection using a cap-equipped panendoscope; ESD, endoscopic subepithelial dissection; ELPS, endoscopic laryngopharyngeal surgery.
[1] One patient had both dysphagia and laryngeal edema.
[2] Two patients had both dysphagia and laryngeal edema.
[3] One patient had both dysphagia and perforation.

Table 4 Pathology results of endoscopic resection specimens of subepithelial invasion (n = 50).

Depth of invasion, median thickness (range), µm	**1000 (200 – 10000)**
Invasion of vessels	
Lymphatic invasion, n (%)	
Present	4 (8)
Absent	46 (92)
Venous invasion, n (%)	
Present	4 (8)
Absent	46 (92)
Pathological T stage, n (%)	
pT1	31 (62)
pT2	18 (36)
pT3	1 (2)
pT4	0 (0)

Follow-up

Median follow-up period was 71 months (range 27 – 116 months) for subepithelial invasion. Among the 14 patients (30 %) who were followed for 5 years or more, 6 developed local recurrence (13 %; 95 % confidence interval [CI] 3.1 % – 22.4 %) and 1 developed neck lymph node metastasis (2 %; 95 %CI 0 – 6.3 %). Median time to local recurrence after endoscopic resection was 13 months (range 3 – 24 months). All recurrent lesions could be treated with curative intent. In total, four of the six local recurrent lesions underwent repeat endoscopic resection. Of the remaining two lesions, one was treated with partial resection, and the other was treated with CRT consisting of cisplatin with concurrent radiotherapy. One case of neck lymph node recurrence detected 6 months after endoscopic resection was pathologically diagnosed from the endoscopic resection specimen as a hypopharyngeal lesion with subepithelial invasion (pT2 stage, tumor thickness 1750 µm, no lymphatic or venous invasion). This pa-

Table 5 Clinical course after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer (n = 47).

Clinical course	No. of patients (%)
Local recurrence	6 (13)
Treatment	
Salvage endoscopic resection	4
Partial resection	1
Chemoradiotherapy	1
Neck lymph node metastasis	1 (2)
Treatment	
Neck lymph node dissection	1
Death	7 (15)
Cause of death	
Esophageal squamous cell carcinoma	3
Colorectal cancer	1
Lung cancer	1
Cardiac disease	1
Unknown cause	1

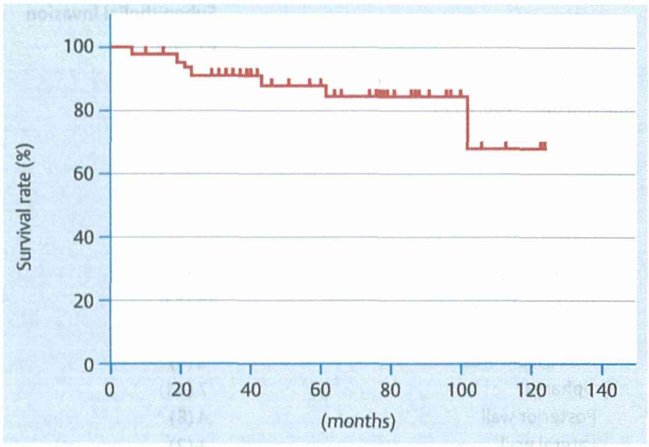

Fig. 5 Overall survival time after endoscopic resection for superficial head and neck squamous cell carcinoma invading the subepithelium.

tient was treated by neck lymph node dissection with organ preservation. No patient with recurrence underwent extensive surgery such as total pharyngolaryngoesophagectomy, and laryngeal function was accordingly preserved in all.

To date, 7 of the 47 patients have died, but all deaths were due to other diseases.

Clinical course after endoscopic resection for SPSCC invading the subepithelial layer is summarized in ● **Table 5**.

The overall survival rate is presented in ● **Fig. 5**. At a median follow-up of 71 months, overall survival rate at 5 years was 84.5% (95%CI 73%–96%). Disease-specific survival rate at 5 years was 100%.

Discussion

In this study, endoscopic resection for SPSCC lesions invading the subepithelial layer demonstrated excellent curability with preservation of laryngeal function, and without the need for additional treatment such as CRT. These findings indicate that endoscopic resection has curative potential as a minimally invasive treatment option for SPSCC that invades the subepithelial layer.

In general, primary treatment for early-stage pharyngeal cancers is either surgical resection or definitive radiation therapy. Conservative medical surgery (i.e. partial pharyngectomy), provides an excellent functional outcome (93% laryngeal preservation rate) and local control (79.6% 5-year local control rate), but the perioperative death rate is relatively high (9%) and 3-year overall survival rate is only 40% [26]. Curative radiation therapy is generally the preferred treatment option for patients with T1–2 pharyngeal tumors. The 5-year cause-specific survival of patients with T1-N0 lesions and T2-N0 lesions after curative radiation therapy is more than 90% and 70%, respectively [27]. However, the majority of patients experience predictable side effects during the course of head and neck radiation therapy, namely mucositis, fatigue, loss of taste acuity, radiation dermatitis, and xerostomia. Infrequent (9%) serious late toxicities are chondritis of the larynx, prolonged dysphagia requiring chronic enteral tube feeding, persistent mucosal ulceration, webbing of the pharynx requiring dilation, and laryngeal edema requiring tracheostomy. To date, we have observed a number of complications associated with endoscopic resection, including subcutaneous emphysema, aspiration pneumonia, trismus, dysphagia, edema of the larynx, and delayed bleeding, but all patients recovered rapidly with conservative treatment, and all were discharged without permanent functional disorders. On this basis, endoscopic resection appears to be less invasive for patients with SPSCC than partial surgical resection or radiation therapy. Endoscopic resection is compared with other treatments in ● **Table 6**.

Histological evaluation of endoscopic resection specimens has been found to be feasible and useful. Numerous studies of esophageal SCC have shown that lesions confined to the lamina propria of the mucosa have minimal risk of lymph node or distant metastasis. In contrast, lymph node metastasis occurs in 1.9%–15% of cases with invasion of the muscularis mucosa or upper third of the submucosa [28–30]. Even with the same kind of cancer (i.e. SCC), the pathological characteristics of the esophageal and pharyngeal areas differ due to the absence of the muscularis mucosa in the pharynx. We previously reported that the microvascular density of intraepithelial SCC is correlated with the thickness of intraepithelial squamous cell carcinoma. Furthermore, invasive

Table 6 Historical comparison of endoscopic resection and other treatments.

	Endoscopic resection (n=47)	Partial pharyngectomy (n=30) [26]	Radiotherapy (n=115) [27]
Age, mean, years	64	59	67
TNM stage 1–2, %	98	40	100
5-year overall survival rate, %	84.5	23.3	66.0
5-year disease-specific survival rate, %	100	N/E	77.4
Failure patterns, %			
Local	13	13.3	26.1
Nodal	2	N/E	12

N/E, not evaluated.

SCC shows significantly higher microvascular density than intraepithelial SCC, and the thickness of intraepithelial SCC significantly correlates with subepithelial invasion [12]. In contrast, data about the relationship between tumor depth and lymph node metastases for pharyngeal SCC are lacking. In the present study, subepithelial invasion was defined by the observation of at least one solitary carcinoma cell nest in the subepithelial region. Median tumor thickness was 1000 µm, and only one case of lymph node metastasis after endoscopic resection for SPSCC invading the subepithelial layer was encountered (1/47, 2%; 95% CI 0–6.3%).

More than three-quarters of patients with primary tumors of the hypopharynx will have metastases to regional lymph nodes during the course of their disease. The necessity of additional preventive CRT or neck lymph node dissection after endoscopic resection for SPSCC should be discussed. In esophageal SCC, although adjuvant CRT after extended EMR for lesions invading the submucosal layer might be considered to prevent lymph node metastasis or distant metastasis [14], radiation therapy for the pharyngeal space is an invasive treatment with both acute and late toxicity, as described above. Moreover, lymph node metastasis is easily diagnosed by physical examination of the neck, compared with the more difficult diagnosis of locoregional lymph node metastasis of esophageal cancer. We therefore consider that strict follow-up and observation is a reasonable option for patients who achieve endoscopic resection, and have negative clinical examination and radiographic results. Although a suitable follow-up period has yet to be determined, such regular periodic examination resulted in the early detection of local recurrent lesions or locoregional neck lymph node metastasis, with local recurrence detected in six patients (13%) within 2 years of endoscopic resection, of whom four were cured following repeat endoscopic resection.

Several limitations of the present study relate to selection bias. First, lesions larger than 4 cm (T3) were excluded from endoscopic resection, as well as those suspected of having deep invasion to the subepithelial layer. In addition, all patients evaluated in the study were clinically N0-M0 before endoscopic resection. The present lesions might therefore have been at lower risk than the targets of other treatment, such as surgical resection or radiation therapy, even though all were classified as invasive SPSCC. Second, although the study included survival data for a relatively large population of patients with SPSCC invading the subepithelial layer and with more than 5 years' follow-up, it was conducted at only two expert centers. Thus, a conclusive answer to the curability of endoscopic resection for SPSCC invading the subepithelial layer will require prospective randomized controlled trials at multiple institutions with a larger number of patients and longer follow-up.

In conclusion, this study shows that endoscopic resection for SPSCC that invades the subepithelial layer has curative potential as a minimally invasive treatment option.

Competing interests: None

Institutions
[1] Department of Gastroenterology, Endoscopy Division, National Cancer Center Hospital East, Kashiwa, Japan
[2] Department of Clinical Oncology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[3] Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[4] Pathology Division, Research Center for Innovative Oncology, National Cancer Center, Kashiwa, Japan
[5] Department of Laboratory Medicine, Shinshu University Hospital, Nagano, Japan
[6] Department of Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan

Acknowledgments

This study was presented in part at the 21st United European Gastroenterology Week, Berlin, Germany (14 October 2013).

References

1 *Pesko P, Sabljak P, Bjelovic M* et al. Surgical treatment and clinical course of patients with hypopharyngeal carcinoma. Dis Esophagus 2006; 19: 248–253
2 *Triboulet JP, Mariette C, Chevalier D* et al. Surgical management of carcinoma of the hypopharynx and cervical esophagus: analysis of 209 cases. Arch Surg 2001; 136: 1164–1170
3 *Kraus D, Zelefsky M, Brock H* et al. Combined surgery and radiation therapy for squamous cell carcinoma of the hypopharynx. Otolaryngol Head Neck Surg 1997; 116: 637–641
4 *Wahlberg P, Andersson K, Biörklund A* et al. Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. Head Neck 1998; 20: 714–719
5 *Johansen L, Grau C, Overgaard J.* Hypopharyngeal squamous cell carcinoma – treatment results in 138 consectively admitted patients. Acta Oncol 2000; 39: 529–536
6 *Eckel H, Staar S, Volling P* et al. Surgical treatment for hypopharynx carcinoma: feasibility, mortality, and results. Otolaryngol Head Neck Surg 2001; 124: 561–569
7 *Erkal H, Mendenhall W, Amdur R* et al. Synchronous and metachronous squamous cell carcinoma of the head and neck mucosal sites. J Clin Oncol 2001; 19: 1358–1362
8 *Muto M, Nakame M, Katada C* et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer 2004; 101: 1375–1381
9 *Muto M, Minashi K, Yano T* et al. Early detection of superficial squamous cell carcinoma in the head and neck region and esophagus by narrow band imaging: a multicenter randomized controlled trial. J Clin Oncol 2010; 28: 1566–1572
10 *Gono K, Obi T, Yamaguchi M* et al. Appearance of enhanced tissue feature in narrow-band endoscopic imaging. J Biomed Opt 2004; 9: 568–577
11 *Muto M, Ugumori T, Sano Y* et al. Narrow band imaging combined with magnified endoscopy for the cancer at the head and neck region. Dig Endosc 2005; 17: 23–S24
12 *Fujii S, Yamazaki M, Muto M* et al. Microvascular irregularities are associated with composition of squamous epithelial lesions and correlate with subepithelial invasion of superficial-type pharyngeal squamous cell carcinoma. Histopathology 2010; 56: 510–522
13 *Iizuka T, Kikuchi D, Hoteya S* et al. Endoscopic submucosal dissection for treatment of mesopharyngeal and hypopharyngeal carcinomas. Endoscopy 2009; 41: 113–117
14 *Shimizu Y, Tsukagoshi H, Fujita M* et al. Long-term outcome after endoscopic mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper. Gastrointest Endosc 2002; 56: 387–390
15 *Shimizu Y, Yamamoto J, Kato M* et al. Endoscopic submucosal dissection for treatment of early stage hypopharyngeal carcinoma. Gastrointest Endosc 2006; 64: 255–259
16 *Suzuki H, Saito Y, Oda I* et al. Feasibility of endoscopic mucosal resection for superficial pharyngeal cancer: a minimally invasive treatment. Endoscopy 2010; 42: 1–7
17 *Iizuka T, Kikuchi D, Hoteya S* et al. Clinical advantage of endoscopic submucosal dissection over endoscopic mucosal resection for early mesopharyngeal and hypopharyngeal cancers. Endoscopy 2011; 43: 839–843
18 *Okada K, Tsuchida T, Ishiyama A* et al. Endoscopic mucosal resection and endoscopic submucosal dissection for en bloc resection of superficial pharyngeal carcinomas. Endoscopy 2012; 44: 556–564
19 *Muto M, Satake H, Yano T* et al. Long-term outcome of transoral organ-preserving pharyngeal endoscopic resection for superficial pharyngeal cancer. Gastrointest Endosc 2011; 74: 477–484

20 *Shimizu Y, Yoshida T, Kato M* et al. Long-term outcome after endoscopic resection in patients with hypopharyngeal carcinoma invading the subepithelium: a case series. Endoscopy 2009; 41: 374–376
21 *Barnes D, Eveson JW, Reichart P* et al. eds. World Health Organization Classification of Tumors. Pathology and genetics. Head and neck tumors. Lyon: IARC Press; 2005
22 *Tani M, Sakai P, Kondo H.* Endoscopic mucosal resection of superficial cancer in the stomach using the cap technique. Endoscopy 2003; 35: 348–355
23 Japan Esophageal Society. Japanese classification of esophageal cancer. 10th edn. Tokyo: Kenehara Co., Ltd; 2008
24 *Fujii S, Yamazaki M, Muto M* et al. Microvascular irregularities are associated with composition of squamous epithelial lesions and correlate with subepithelial invasion of superficial-type pharyngeal squamous cell carcinoma. Histopathology 2010; 56: 510–522
25 *Muto M, Hironaka S, Nakane M* et al. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc 2002; 56: 517–521
26 *Holsinger FC, Motamed M, Garcia D* et al. Resection of selected invasive squamous cell carcinoma of the pyriform sinus by means of the lateral pharyngotomy approach: the partial lateral pharyngectomy. Head Neck 2006; 28: 705–711
27 *Nakamura K, Shioyama Y, Kawashima M* et al. Multi-institutional analysis of early squamous cell carcinoma of the hypopharynx treated with radical radiotherapy. Int J Radiat Oncol Biol Phys 2006; 65: 1045–1050
28 *Katada C, Muto M, Momma K* et al. Clinical outcome after endoscopic mucosal resection for esophageal squamous cell carcinoma invading the muscularis mucosae – a multicenter retrospective cohort study. Endoscopy 2007; 39: 779–783
29 *Kodama M, Kakegawa T.* Treatment of superficial cancer of the esophagus: a summary of responses to a questionnaire on superficial cancer of the esophagus in Japan. Surgery 1998; 123: 432–439
30 *Nagawa H, Kaizaki S, Seto Y* et al. The relationship of macroscopic shape of superficial esophageal carcinoma to depth of invasion and regional lymph node metastasis. Cancer 1995; 75: 1061–1064

Cancer Science
Japanese Cancer Association JCA
Open Access

Endoscopic findings using narrow-band imaging to distinguish between basal cell hyperplasia and carcinoma of the pharynx

Atsushi Yagishita,[1] Satoshi Fujii,[2] Tomonori Yano[1] and Kazuhiro Kaneko[1]

[1]Endoscopy Division, Department of Gastroenterology, National Cancer Center Hospital East, Chiba; [2]Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan

Key words

Basal cell hyperplasia, head and neck cancer, intra-epithelial papillary capillary loop, narrow-band imaging, pharynx

Correspondence

Tomonori Yano, Department of Gastroenterology, Endoscopy Division, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan.
Tel: +81-4-7133-1111; Fax: +81-4-7131-4724;
E-mail: toyano@east.ncc.go.jp

Funding Information

National Cancer Center Research and Development Fund (23-A-15).

Received March 14, 2014; Revised April 20, 2014; Accepted May 6, 2014

Cancer Sci **105** (2014) 857–861

doi: 10.1111/cas.12440

Narrow-band imaging (NBI) has been reported to be useful for detecting superficial-type esophageal or head and neck squamous cell carcinoma (SCC), and in the present study we have used NBI to detect non-carcinomatous lesions, such as basal cell hyperplasia (BCH) accompanied by microvascular irregularities; these non-carcinomatous lesions were pathologically discriminated from squamous cell carcinoma of the pharynx. The aim of the present study was to clarify the endoscopic characteristics of BCH that contribute to the discrimination of superficial-type head and neck SCC (HNSCC). We examined the key endoscopic findings capable of distinguishing BCH from SCC using 26 BCH and 37 superficial-type SCC of the pharynx that had been pathologically diagnosed at our institution between January 2008 and July 2012. The clinicopathological factors were also compared. The size of the BCH lesions was significantly smaller ($P < 0.001$), and their intervascular transparency was more clearly observed ($P < 0.001$). Intra-epithelial papillary capillary loop (IPCL) shapes were less variable and monotonous ($P < 0.001$), and the distribution of the IPCL was more regular with an interval comparable to that of SCC ($P < 0.001$), although no significant differences in the sharpness of the lesion border, dilatation of IPCL and tortuosity of the IPCL were seen between the BCH and SCC lesions. This study revealed that BCH was an independent entity in terms of not only pathological findings, but also endoscopic findings observed using NBI, such as the regular distribution of IPCL and the preserved intervascular transparency.

New innovations in endoscopic modalities have enabled more lesions, such as small or flat-type lesions in the mucosa of the gastrointestinal tract and the head and neck region, to be detected at an early phase. One of these revolutionary modalities is narrow-band imaging (NBI), which makes it possible to visualize microvascular irregularities, also known as intra-epithelial papillary capillary loop (IPCL) abnormalities, of the squamous epithelium. Superficial-type squamous epithelial lesions have been identified using NBI in combination with magnifying endoscopy (NBI-ME).[1–5] The strategy behind this method is to recognize the characteristics of IPCL in neoplastic lesions, such as dilatation, tortuosity, caliber changes in one IPCL, variations in multiple IPCL and color changes in the background mucosa, which are completely different from those seen in normal squamous epithelium.[1] The sensitivity and specificity of NBI endoscopy for the detection of esophageal squamous cell carcinoma (SCC) and high-grade intraepithelial neoplasia are reported to be 90.9 and 95.4%, respectively, suggesting that NBI may be a useful and reliable method of screening for early neoplastic lesions in the esophagus.[4] Muto *et al.* (2004) first reported that it was possible to identify superficial HNSCC during an early phase as a "brownish area" using NBI-ME, although, up to then, it had been possible to detect only advanced SCC using the conventional modality in the head and neck region.[6]

Thus, early-phase superficial-type SCC, which cannot be detected by an ordinary endoscopy examination, can be detected using NBI-ME. Patients with superficial-type SCC can benefit from early detection through the preservation of important organs, such as the pharynx and larynx, associated with critical and physiological functions including swallowing and vocalization, because since such lesions can be completely resected endoscopically. However, superficial and flat lesions are sometimes recognized in the pharynx as brownish areas using NBI but are not pathologically diagnosed as SCC or dysplasia when a biopsy specimen is examined pathologically. Most of these lesions are pathologically diagnosed as basal cell hyperplasia (BCH) with IPCL atypia.[7] BCH accompanied by microvascular abnormalities was recently reported.[7] BCH exhibit IPCL abnormalities, such as upward extension, dilatation and branching, but do not fulfill the criteria for dysplasia with regard to structural and cellular atypia, which are clearly observed in neoplastic lesions arising in squamous epithelium.[7,8] As described above, the squamous epithelial lesions that are recognized as brownish areas using NBI-ME can include BCH as well as neoplastic lesions. Therefore, the aim