of the current study was to determine the endoscopic features of BCH in the pharynx using NBI and to clarify how neoplastic lesions, such as SCC, can be discriminated from other lesions that are recognized as brownish areas so as to enable endoscopic diagnoses. The construction of new diagnostic criteria based on the NBI-ME findings in the present study may contribute to appropriate decisions regarding whether superficial squamous epithelial lesions should be treated or followed up carefully.

Materials and Methods

Patients. Patients who were pathologically diagnosed as having BCH based on endoscopic biopsy samples of the pharynx obtained between January 2008 and July 2012 at our institute were included in the present study. Endoscopic images of superficial-type HNSCC that had been diagnosed pathologically were also used to compare the endoscopic findings for BCH and SCC of the pharynx. For all cases, clear images were obtained using NBI with or without magnification using a GIF H260Z (Olympus, Tokyo, Japan) or in some cases using a GIF Y0002 (Olympus) for a much higher-power magnification (maximum of 380-fold magnification). Cases without NBI-ME images or with only unsuitable images (blurry or unfocused) were excluded from this study. All the biopsy samples were diagnosed pathologically based on the World Health Organization classification of tumors (head and neck tumors)[8]; BCH with IPCL atypia was diagnosed based on the criteria reported by our group.[7] Finally, 26 cases of BCH and 37 cases of HNSCC were analyzed in the current study.

Methods. The endoscopic images for each case were examined in detail with respect to location, macroscopic type, size, sharpness of the margin, intervascular transparency, and IPCL-findings including dilatation, tortuosity, shapes and distribution. Intervascular transparency and intervascular color changes in which the transparency was preserved or slightly impaired were also examined except in elevated lesions, which were hard to evaluate and compare.

The sizes of the BCH were estimated using forceps with a width of 6 mm when open (Radial Jaw [Boston Scientific, MA, USA]); the sizes of the SCC were measured pathologically.

The margin of each lesion was categorized into two groups: clear or ambiguous. We classified intervascular transparency into three categories: (i) preserved; (ii) slightly impaired (not completely transparent, but easily recognizable subepithelial vessels); and (iii) impaired (difficult or impossible to recognize subepithelial vessels). In cases where the lesion exhibited both preserved and (slightly) impaired intervascular transparency, the type of transparency was re-evaluated as "(slightly) impaired". We classified the intervascular color changes into "positive" for apparently brownish areas and "negative" for areas that were not apparently brownish.

The caliber changes in the IPCL, which are a major characteristic of IPCL observed in SCC, were not examined in the present study because the GIF H260Z did not enable a magnification sufficient for measuring and comparing the calibers of the capillaries of the IPCL. Therefore, only IPCL dilatation was examined. The shapes of the IPCL were classified into three categories as follows: monotonous (most IPCL were composed of two to four loop-shaped capillaries), variable (IPCL were composed of various shapes including one-loop, two-to-four loop or non-loop capillaries) and intermediate (the shapes of the IPCL were regular).

In cases where the IPCL were distributed regularly between avascular or loosely vascular areas, we defined the appearance as a regular distribution of IPCL.

In cases where follow-up endoscopies were performed, the changes in the endoscopic findings were evaluated.

Statistical analysis. The lesion size and the endoscopic findings were statistically analyzed to clarify the features of BCH. Cases in which the sizes were not available were excluded from this analysis. The categorical data regarding endoscopic findings were compared using the Fisher exact test or the χ^2-test, as appropriate. SPSS version 11 (SPSS Inc., Chicago, IL, USA) was used for all the statistical analyses. All the statistical tests were two-tailed, and the statistical significance was defined as $P < 0.05$.

This study was approved by the institutional review board of our hospital on 29 January 2013 (approved clinical study number 2012-298) and was undertaken in conformity with the provisions of the Declaration of Helsinki in 1995 (as revised in Tokyo in 2004).

Results

The characteristics of the BCH patients and those of the BCH and SCC lesions are shown in Tables 1 and 2, respectively.

Table 1. Patient characteristics

n = 26	
Median age (range) in years	70 (53–83)
Sex: Male/female	24/2
Past or current history of SCC	
ESCC	22
HNSCC	13
Without SCC	3

ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; SCC, squamous cell carcinoma.

Table 2. Lesion characteristics

	BCH (*n* = 26) Number (%)	SCC (*n* = 37) Number (%)
Location		
Oropharynx	20 (73)	14 (38)
Posterior wall	15 (58)	7 (19)
Lateral wall	3 (8)	3 (8)
Uvula	1 (4)	0 (0)
Vallecula	1 (4)	4 (11)
Hypopharynx	8 (27)	23 (62)
Posterior wall	5 (15)	2 (5)
Piriform sinus	3 (12)	18 (49)
Postcricoid area	0 (0)	3 (8)
Macroscopic type		
Depressed	0 (0)	3 (8)
Elevated	7 (19)	11 (30)
Flat	19 (73)	23 (62)
Mixed with flat and elevated	2 (8)	0 (0)
Size		
1–5 mm	23 (88)	3 (8)
6–10 mm	1 (4)	13 (35)
>10 mm	2 (8)	18 (49)
NA		3 (8)

BCH, basal cell hyperplasia; NA, not available; SCC, squamous cell carcinoma.

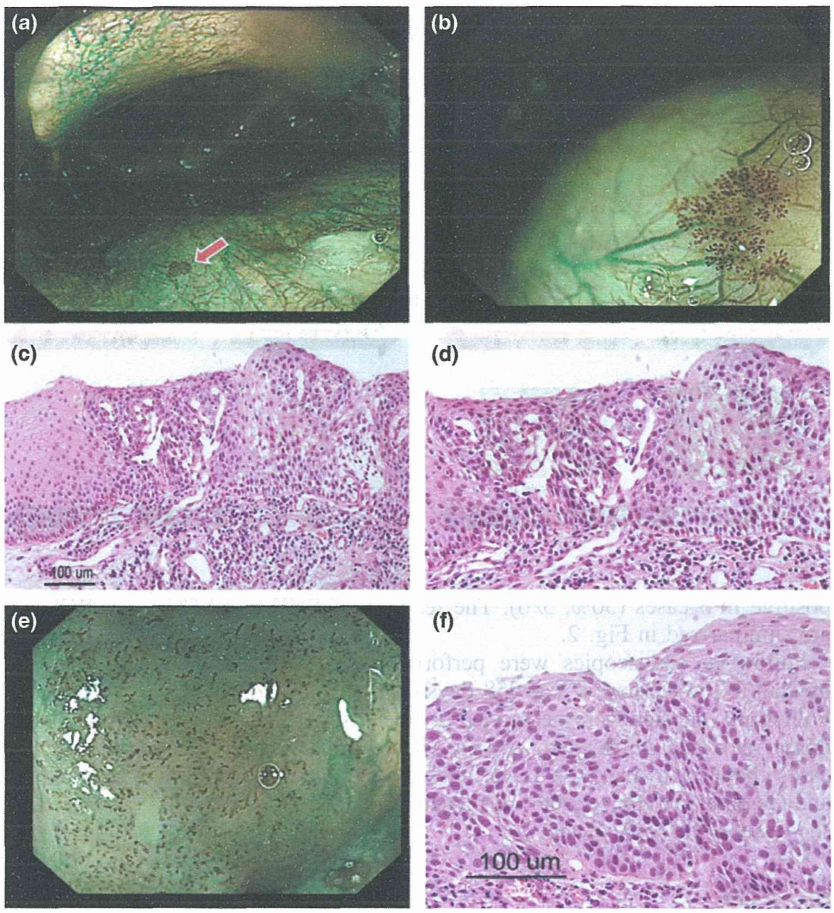

Fig. 1. Narrow-band imaging (NBI) view and pathological findings of basal cell hyperplasia (BCH) and head and neck squamous cell carcinoma (HNSCC). (a) NBI view of BCH (arrowhead) without magnification. (b) NBI view of BCH with magnification. (c,d) (c) Pathological findings of BCH. Basal cell hyperplasia is visible within the area around the dilated IPCL, and the maturation of superficial cells is preserved. (d) The area around IPCL in figure (c) was enlarged. (e) NBI view of HNSCC with magnification. (f) Pathological findings of HNSCC, H.E. The whole epithelial layer is occupied by atypical cells.

Three BCH cases had tiny satellite lesions adjacent to the main lesions. Each of these cases was considered as one lesion that included the satellite lesions. In three SCC cases, accurate sizes were unknown because of a piecemeal resection. The sizes of the BCH were significantly smaller ($P < 0.001$) than those of the SCC.

Typical BCH and HNSCC cases are shown in Fig. 1. Both lesions were recognized as brownish areas on the NBI images; however, intervascular transparency and a regular distribution were only observed in the BCH lesion. The endoscopic findings for the BCH and SCC lesions are shown in Table 3. The typical findings for BCH were defined as a regular distribution of IPCL composed of 2–4 loop-shaped ("lasso-like") capillaries, with all the cases except for one exhibiting this typical finding (Fig. 1). As a result, the BCH were significantly smaller ($P < 0.001$), had a more preserved intervascular transparency (flat type) ($P < 0.001$), had fewer variations in IPCL shapes ($P < 0.001$) and had a more regular distribution of IPCL ($P < 0.001$) than the SCC. In contrast, no significant difference in the sharpness of the margin was seen between the BCH and SCC lesions ($P = 0.17$), and the IPCL of both of them were dilated and tortuous. Among the 21 cases of non-elevated (flat or mixed with flat and elevated) BCH, the intervascular transparency was not impaired in any of the cases (i.e. preserved or slightly impaired) and the intervascular color changes were positive in two cases (10%, 2/21). Among the 26 cases of non-elevated (flat or depressed) SCC, 20 cases (77%) had an impaired intervascular transparency, and among the remaining 6 cases, the intervascular color change was

Table 3. Endoscopic findings

	BCH ($n = 26$) Number (%)	SCC ($n = 37$) Number (%)	*P*-value
Border of the margin			
Clear	24 (92)	37 (100)	0.17
Ambiguous	2 (8)	0 (0)	
Intervascular transparency	($n = 21$)	($n = 26$)	
Preserved	15 (71)	3 (12)	<0.001
Slightly impaired	6 (29)	3 (12)	
Impaired	0 (0)	20 (77)	
IPCL findings			
Dilatation			
Yes	26 (100)	37 (100)	NA
No	0 (0)	0 (0)	
Tortuosity			
Yes	26 (100)	37 (100)	NA
No	0 (0)	0 (0)	
Shapes			
Monotonous	25 (96)	1 (3)	<0.001
Intermediate	1 (4)	4 (11)	
Variable	0 (0)	32 (86)	
Distribution			
Regular	26 (100)	4 (11)	<0.001
Irregular	0 (0)	33 (89)	

BCH, basal cell hyperplasia; IPCL, intra-epithelial papillary capillary loop; NA, not available; SCC, squamous cell carcinoma.

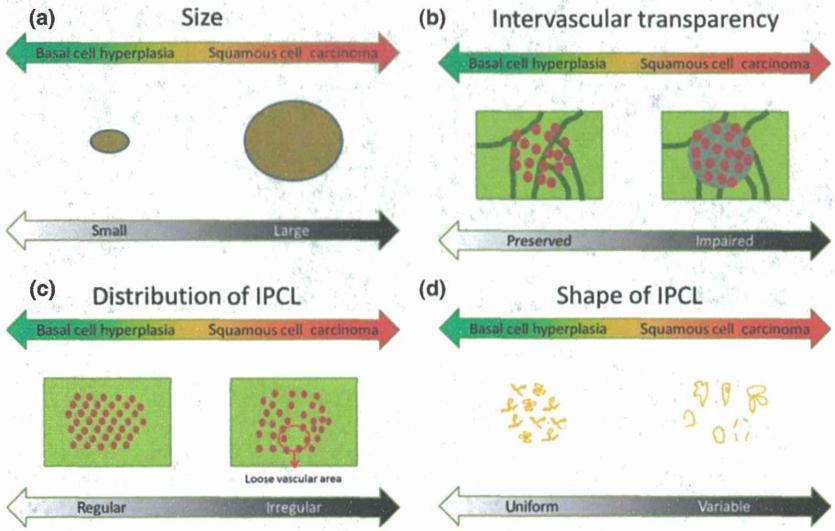

Fig. 2. Schema of the four parameters (size, a; intervascular transparency, b; distribution of intraepithelial papillary capillary loop (IPCL), c; shape of IPCL, d) for the differential diagnosis of basal cell hyperplasia (BCH) and squamous cell carcinoma (SCC). BCH tend to have the features on the left side of the schema, whereas SCC tend to have those on the right side.

positive in 3 cases (50%, 3/6). The features of BCH and SCC are summarized in Fig. 2.

Follow-up endoscopies were performed for 13 cases. The median follow-up period was 958 days (range: 182–2263 days). Follow-up biopsies were performed in five cases, and the diagnoses remained unchanged. Among them, the lesions in two cases changed in size, with 1 case showing a slight enlargement and the other showing a slight shrinkage. The other cases did not show any endoscopic changes.

Discussion

Basal cell hyperplasia in the pharynx was shown to exhibit characteristic NBI findings. The fact that some lesions that are clearly recognized as brownish areas in the pharynx turn out to not be carcinomas but BCH is clinically important, as accurate diagnosis can reduce unnecessary endoscopies or treatments. Muto *et al.* report 148 lesions resected using peroral endoscopic laryngopharyngeal mucosal resection.[9] All of these patients were treated under general anesthesia, and 17 patients (16%) required a temporary tracheostomy. This treatment is minimally invasive but does place physical and economic burden on the patient. Consequently, an accurate diagnosis is important to reduce unnecessary treatment. Lesions diagnosed as BCH are thought to have a low potential to change into cancer. Therefore, BCH is categorized as a non-cancerous entity.

For accurate diagnosis, we were able to obtain more information regarding brownish areas using NBI-ME than using NBI without magnification. In this study, we found that the color of the epithelium (in this study we used the term "intervascular color change") in HNSCC observed using NBI varied from light green to brown, and color changes were difficult to evaluate objectively; instead, it was somewhat easier to evaluate intervascular transparency objectively. We analyzed intervascular transparency as one of the important features, while intervascular color changes were analyzed when the transparency was not impaired because the impaired transparency might strongly affect the color change.

Based on our data, we defined the typical findings of BCH as a regular distribution of IPCL composed of 2–4 loop-shaped ("lasso-like") capillaries; all the cases in this series except for one had these typical findings. However, some minor variations existed with regard to intervascular transparency, intervascular color changes and macroscopic type. Consequently, the lesions with typical BCH findings are likely to have various genetic backgrounds. Based on the statistical analyses, the key points for differentiating BCH and SCC are

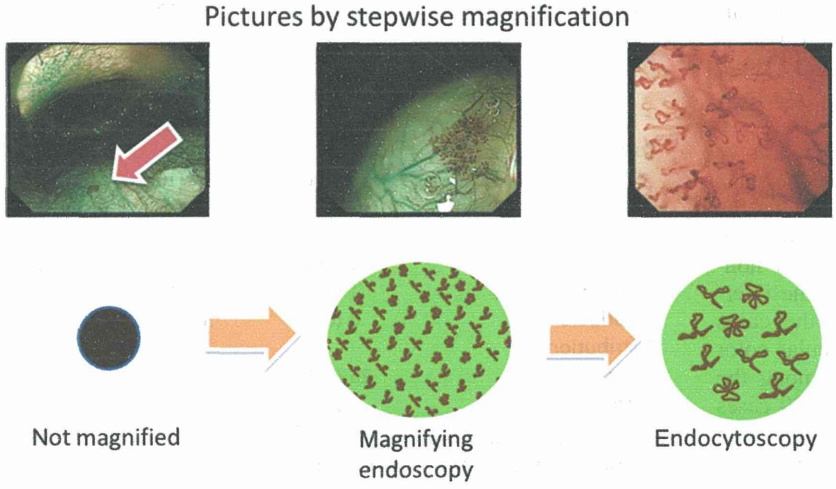

Fig. 3. Narrow-band imaging view of basal cell hyperplasia with stepwise magnification and its schema. The left image is without magnification, the middle image is with magnification, and the right image is with magnification using an endocytoscope.

shown in Fig. 2. Most of the BCH were small but were relatively easily recognizable, probably because they had a clear margin and a dense and regular distribution of dilated IPCL; however, we could not evaluate the IPCL density. In addition to these features, the IPCL of BCH were dilated and tortuous, causing the BCH to be misdiagnosed endoscopically as SCC in our previous endoscopic studies. No superficial HNSCC with both preserved transparency and the typical findings of BCH were observed. In contrast, 11 BCH cases exhibited both of these features without an intervascular color change, which was a finding of early ESCC. Thus, this type of BCH is unlikely to require intensive follow up. The long-term changes remain uncertain, however, so some follow up may be needed.

There are several limitations in the present study, including its retrospective design and the fact that it is a single-center study. We need to validate the outcome of this study in a prospective study.

For further understanding and clinical use, we have presented the images of a case with stepwise magnification in a schema shown in Fig. 3. An endocytoscope is not indispensable, but is helpful for understanding the features of BCH and SCC. In daily clinical situations, it may be difficult to magnify the pharynx adequately because of the gag reflex or the lack of magnifying endoscopes at some institutes. Even if it is impossible or difficult to magnify the images, the evaluation of intervascular transparency alone should be helpful, to some extent, in making a differential diagnosis.

Finally, several points require further clarification. Whether BCH has malignant potential or not remains unclear, and whether BCH consists of a sole entity or includes several entities also remains uncertain. Long-term follow up or a gene analysis may resolve these questions.

In summary, we have presented the features of BCH in the pharynx as observed using NBI-ME; these findings are expected to be useful in the differential diagnosis of brownish areas in the pharynx as either BCH or SCC.

Acknowledgments

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Disclosure Statement

The authors have no conflict of interest.

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頭頸部外科学領域

下咽頭早期癌に対して経口的手術がどこまで可能かわからない！

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● Key Words ●下咽頭早期癌，NBI ビデオスコープ，表在癌，腫瘍伸展範囲●

症例提示

〔症例 1〕 67 歳，男性。

主　訴：食道癌術後の咽喉頭領域の検査目的。

経　過：食道癌内視鏡治療後に頭頸部癌スクリーニング目的で受診した。NBI ビデオスコープを用いた内視鏡検査で下咽頭輪状後部に内部に点状異型血管を有する茶褐色の領域がみられ表在癌を疑う所見であった（図 1）。通常検査では腫瘍の尾側への広がりの範囲が見えなかった。そこで，バルサルバ法を用いて下咽頭観察範囲を広げたが尾側の断端は十分に見えなかった。次に modified Killian 法を用いて下咽頭を広く展開し腫瘍伸展範囲が確認できたことで経口的手術可能と判断した（図 2）。

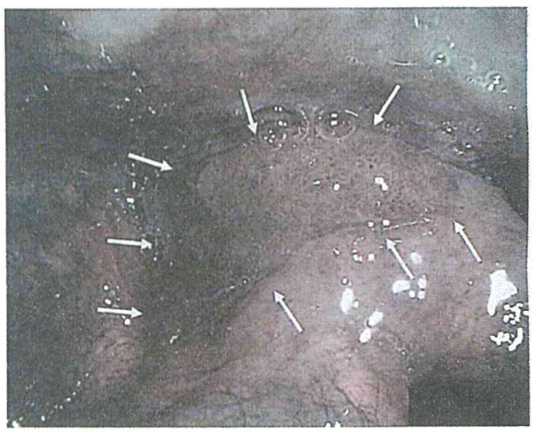

図 1　症例 1 の NBI 画像
下咽頭輪状後部に茶褐色の病変を認める（矢印）。

手術は全身麻酔下に経口手術として内視鏡的咽喉頭手術（endoscopic laryngo-pharyngeal surgery：ELPS）を選択した。この方法は彎曲喉頭鏡を用いることで下咽頭を広く展開でき，輪状後部の腫瘍に対しても十分に対応可能であった（図 3）。切除標本では腫瘍は水平断端陰性，深部断端陰性で完全切除できていた。

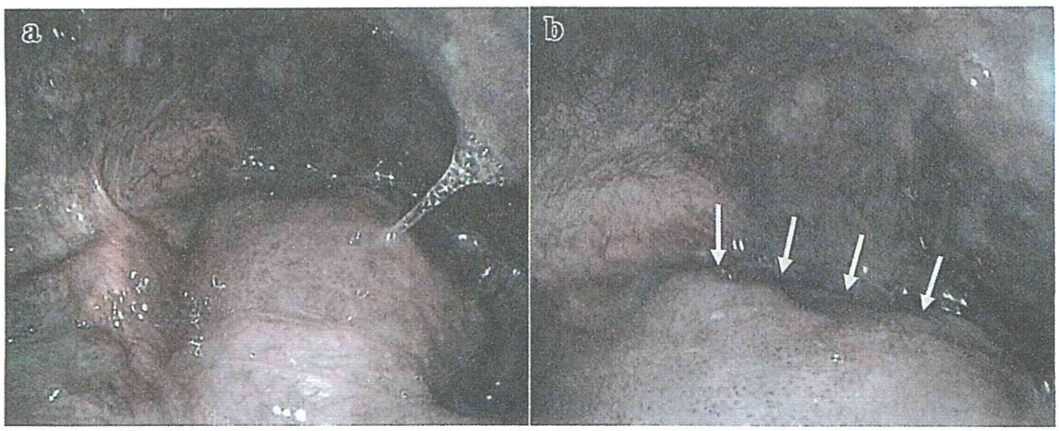

図 2　症例 1 の NBI 画像（modified Killian 法）
a：下咽頭輪状後部が広く展開された。b：尾側の伸展範囲が確認された（矢印）。

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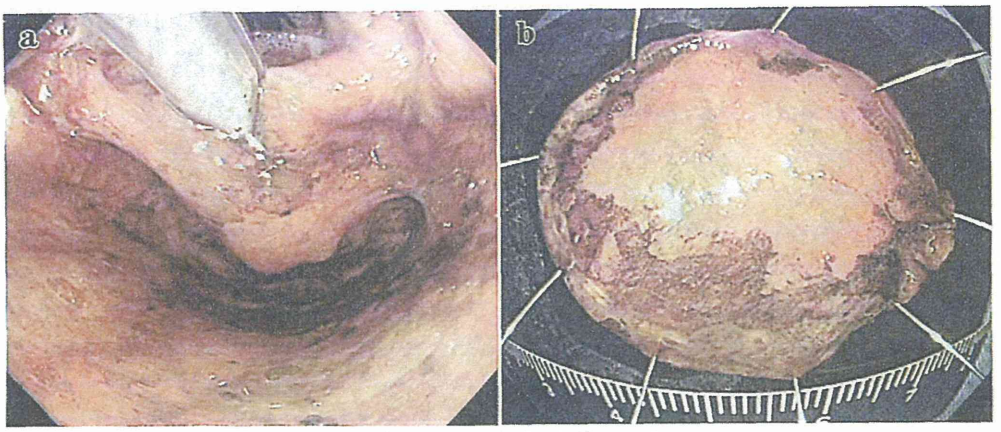

図 3　症例 1 の NBI 画像（ELPS 時）
a：腫瘍の伸展範囲はヨード染色後に不染帯として認められ，全体を確認できた。
b：切除標本。

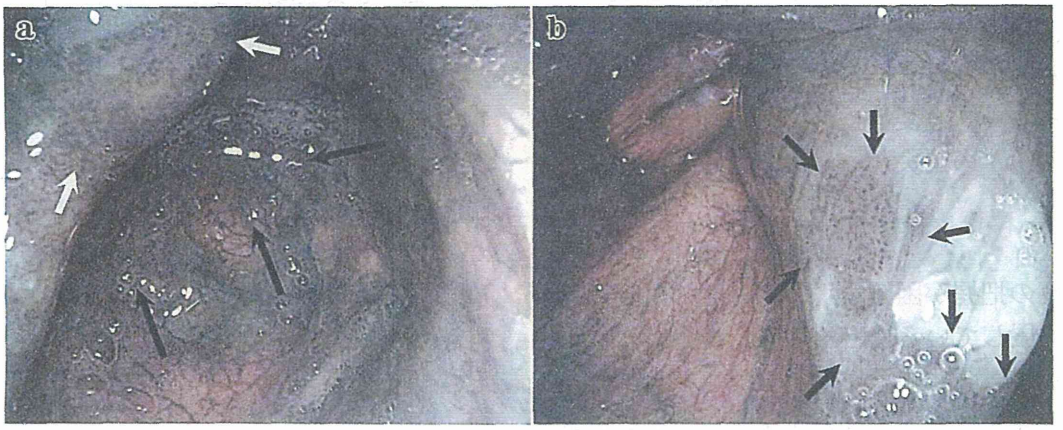

図 4　症例 2 の NBI 画像
a：腫瘍は左下咽頭梨状陥凹（黒矢印）から披裂部に伸展している（白矢印）。
b：喉頭内の伸展範囲が確認された。（黒矢印）。

〔症例 2〕　72 歳，男性。

主　訴：胃癌術後の内視鏡検査で下咽頭病変を指摘された。

経　過：上部消化管内視鏡検査で下咽頭左梨状陥凹に腫瘍を指摘され，当科を受診した。NBI ビデオスコープを用いた内視鏡検査では左梨状陥凹から披裂喉頭蓋ヒダを越え，喉頭内にまで伸展する表在癌を認めた。喉頭内伸展は NBI ビデオスコープで確認できたことより，経口手術可能と判断した（図 4）。

手術は全身麻酔下に ELPS を行った。切除範囲の決定は下咽頭ではヨード染色後にヨード不染帯から 2 mm 離しマーキングし，その周囲で切除することとした。喉頭内はヨード染色性が悪いために NBI 画像で茶褐色の領域から 2 mm 離しマーキングを行いその周囲で切除することとした。一塊切除可能であった（図 5）。また，挿管チューブを翌日に抜管することで気管切開を必要としなかった。切除標本は咽頭側も喉頭側も切除断端陰性，さらに深部断端も陰性で完全切除できていた。

症例の問題点の解説

中下咽頭領域にも表在癌が多く診断されるようになった[1]。これら表在癌は完全切除することで良好な予後が得られることより，患者さんに低侵襲な治療として経口手術が多く行われるようなった[2]。経口手術は文字のごとく口の中からさまざまな器械を用いて切除するが解剖学的に操作に制限がでてくるため，切除容易な部位と困難な部位が認められる。下咽頭の亜部位の中では輪状後部

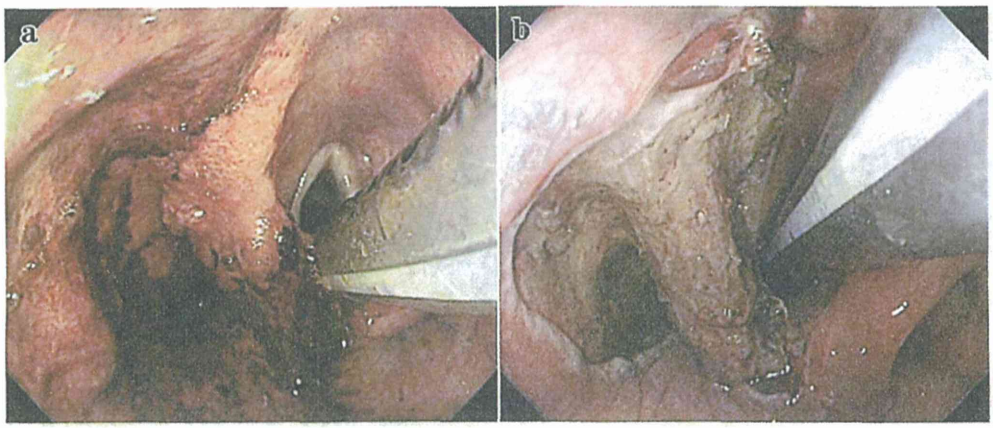

図 5　症例の NBI 画像（ELPS 時）
a：ヨード染色後，腫瘍は不染帯として認められた。b：切除後。

は経口的にアプローチすることが困難な部位の一つであり，治療前に伸展範囲を把握することも比較的困難な部位である。また，下咽頭から隣接部位に広がっている病変等にも通常切除では対応が難しく，何らかの工夫が必要なことがある。

解決策

伸展範囲の把握が困難な場合，さらに隣接部位等に広く伸展している場合などは，全身麻酔下に生検を兼ねて彎曲喉頭鏡による展開を行い腫瘍伸展範囲が全周性に確認できるかを行う方法もあると思われる。さらに症例1のようにバルサルバ法，modified Killian 法[3]など下咽頭を広く伸展できる診察方法を行うことで外来診察でも腫瘍の伸展範囲が確認でき，手術可能かどうかの判断をすることが可能である。

次に喉頭内伸展例の場合には下咽頭で行っているヨード染色による腫瘍伸展範囲決定が困難であり，NBI 内視鏡等の特殊光を用いた切除範囲決定が必要となってくる。手術時に通常白色光以外に NBI 等の特殊光機能を有した内視鏡を準備することで確実な安全域をもった切除が可能となる。

このような切除範囲を把握することが困難な症例では完全切除するのに長時間を必要とすることも少なくない。その際，長時間手術の術後に喉頭浮腫等を起こし，呼吸困難を呈することがある。「経口手術が可能かどうかわからない！」の最期に，長時間手術や喉頭への侵襲が大きいと判断し，術後に喉頭浮腫が予測される場合には気管切開行うことが解決策の1つになることを書き加えたい。

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