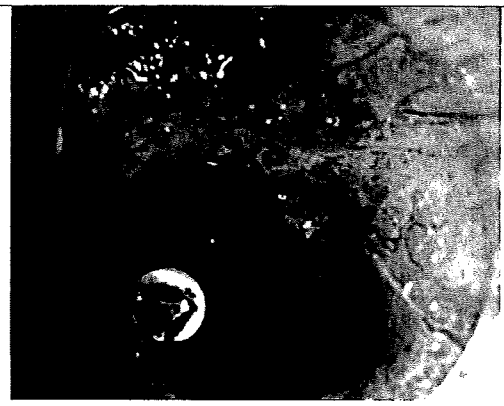
症例で身につける
消化器内視鏡シリーズ

食道・胃ESD

ITナイフによるESDの実際



Knack and pitfall of
gastrointestinal endoscopy in

Esophageal and gastric ESD with IT knife based on case study

小野裕之 編

羊土社
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第1章　治療法選択のための術前内視鏡診断
③ 画像強調（NBI）・拡大内視鏡診断

1. 食道

森田周子，武藤　学

食道表在癌の拾い上げと質的診断は，narrow band imaging（NBI）の登場により，より診断しやすくなった．食道表在癌はNBIでは，brownish areaとして視認でき，拡大内視鏡の併用により異型血管の増生を確認することで白色光観察より，より高精度に診断できる．また，拡大観察による血管パターンの鑑別により深達度診断も可能である．

食道表在癌はNBI（基礎編－第1章－③－2参照）の登場により白色光による観察に比較して検出しやすくなった．また，拡大機能と併用することで，微小血管構造の変化が明瞭に観察でき，より正確な質的診断そして深達度診断もできるようになってきた．ここではNBIによる病変の拾い上げと拡大併用NBIによる詳細観察について解説する．

拾い上げるべきNBI所見

NBIによる観察では白色光に比較して光量が少なくなるため視野がやや暗くなる．そこで送気をして管腔が開いた状態でやや近接しつつ観察する必要がある．また，NBIはヘモグロビン吸収波長に狭帯域を設定しているため，出血すると視野が茶褐色になり視野が不良になるので，出血させないように注意する必要がある．

拾い上げるべき食道表在癌のNBI所見は，

- 褐色の領域（brownish area）

である．食道表在癌は程度の差はあれ発赤した病変が多く，その理由として異常血管の増生があげられる．発赤はNBI観察では褐色になることから，癌部はやや白みがかった緑色の非腫瘍粘膜を背景にしたbrownish areaとして認識できる（図1 A～D）．brownish areaを見つければ，次は拡大観察にて質的診断と深達度診断を行う．

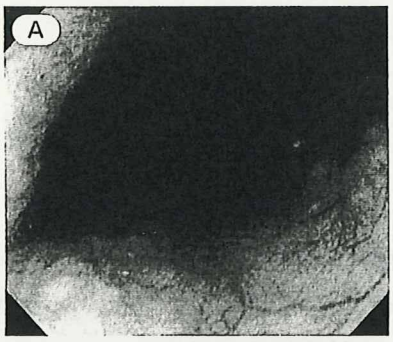
詳細観察のポイント

食道は管腔臓器であり，病変が接線方向になるため正面視しづらい．送気量を変えたり，内視鏡軸を回していろいろな角度から見てみたりして，できるだけ正面視しやすい方向を探す．また出血しないように注意しながら，先端アタッチメントを装着して食道粘膜をアタッチメントで押さえて観察することで容易に病変を正面視して拡大観察できる．

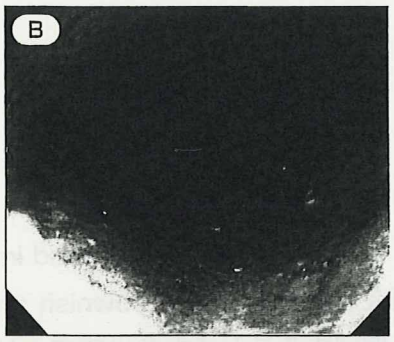
病変の存在を疑えば，拡大して病変内の異型血管を観察する．井上らはこの異型血管を上皮乳頭内ループ状毛細血管（intra-epithelial papillary capillary loop：IPCL）と呼んでいる．拡大観察を用いて詳細に観察する点は，

- 異型血管の形態パターン
- 境界が明瞭であるか

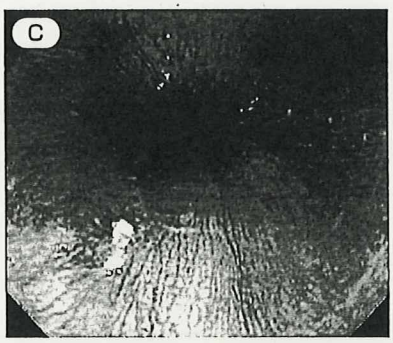
である．癌では“拡張，蛇行，口径不同，形状不均一”を特徴とする異常な異型血管をbrownish area内に認め，非癌部との間には明瞭な境界がある（図1 E）．周囲粘膜と境界を有



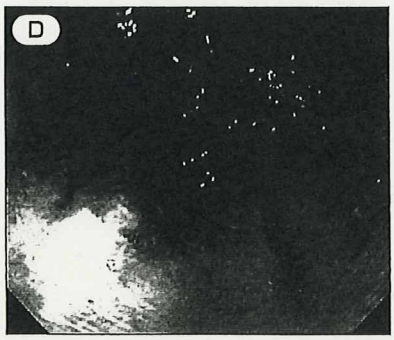
後壁に正常血管影の消失した平坦発赤部を認めるが，所見が乏しく認識にくい



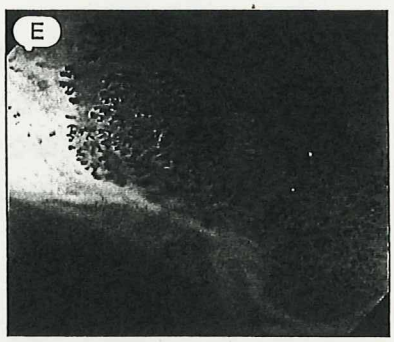
NBI を併用することで，緑色の非腫瘍を背景にした brownish area として認識しやすくなる



食道・胃接合部口側の左壁に正常血管影の消失した発赤平坦部を認めるが，所見が乏しく認識しづらい



NBI を併用することで brownish area として認識しやすくなる



異型血管を有する brownish area が境界明瞭に全周を追うことができる

◆ 図 1 拾い上げ～詳細観察

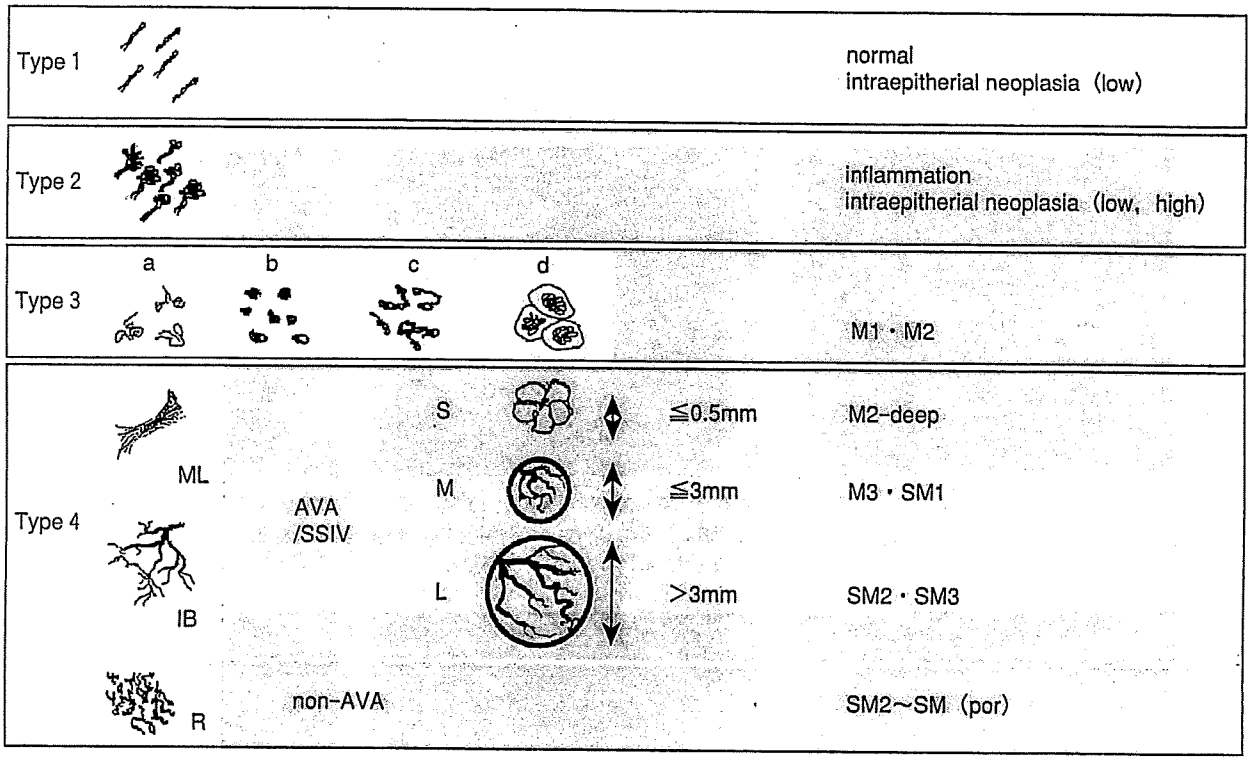
する brownish area と，内部に “拡張，蛇行，口径不同，形状不均一” を示す異型血管が観察できれば，癌の質的診断は容易である．

さらに，有馬ら，井上らは，その血管パターン診断が食道表在扁平上皮癌の診断および深達度診断に有用であることを明らかにした[1) 2)]．図 2，3 に示す両分類は名前が統一されていないが，いずれも深達度診断には有効であり，通常内視鏡診断に血管パターン診断を加えることでより正確に癌の深達度を診断することができる．

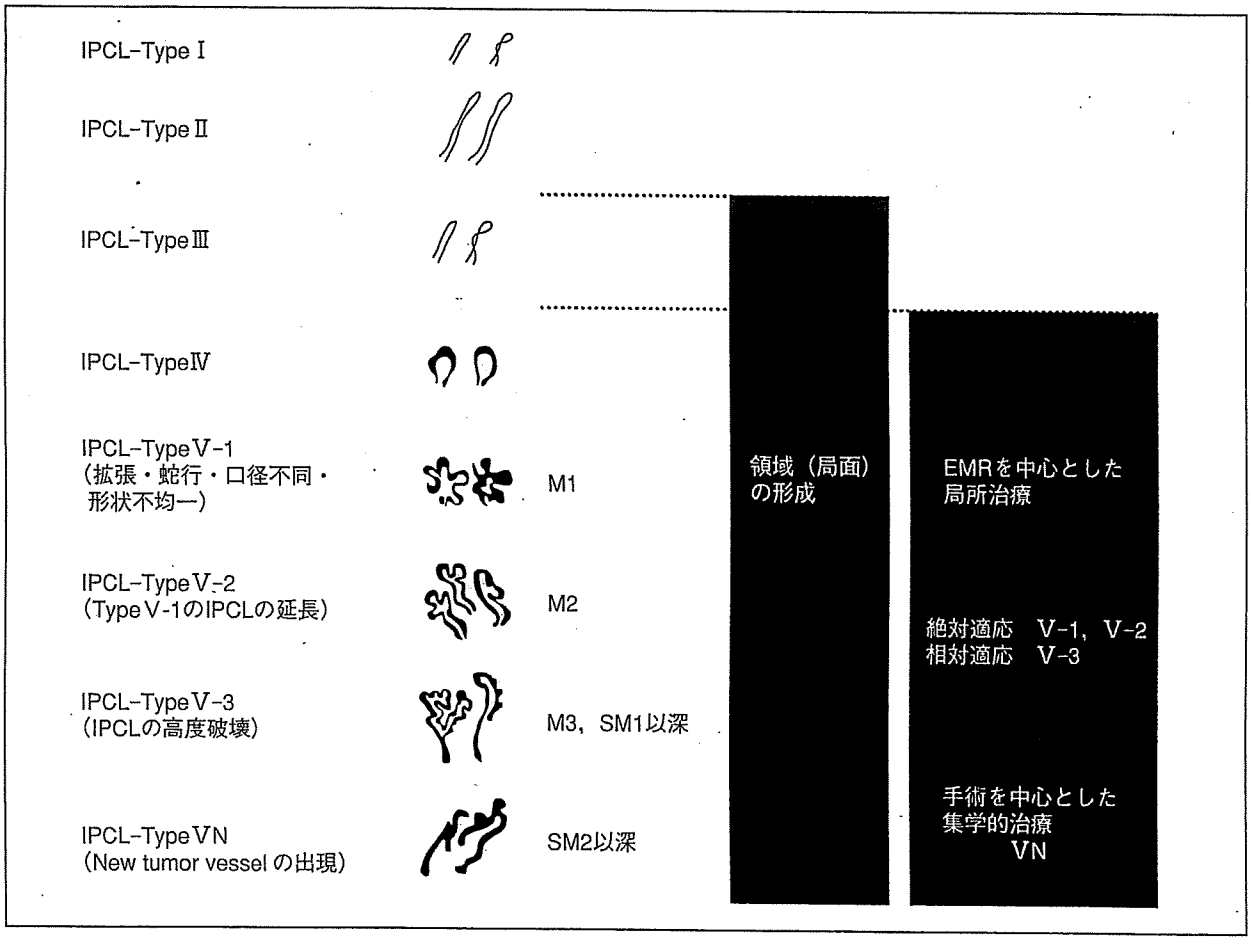
有馬分類・井上分類について図 2，3 に示す．それぞれの分類と深達度診断の参考にしていただきたい．

1 有馬分類（図 2）

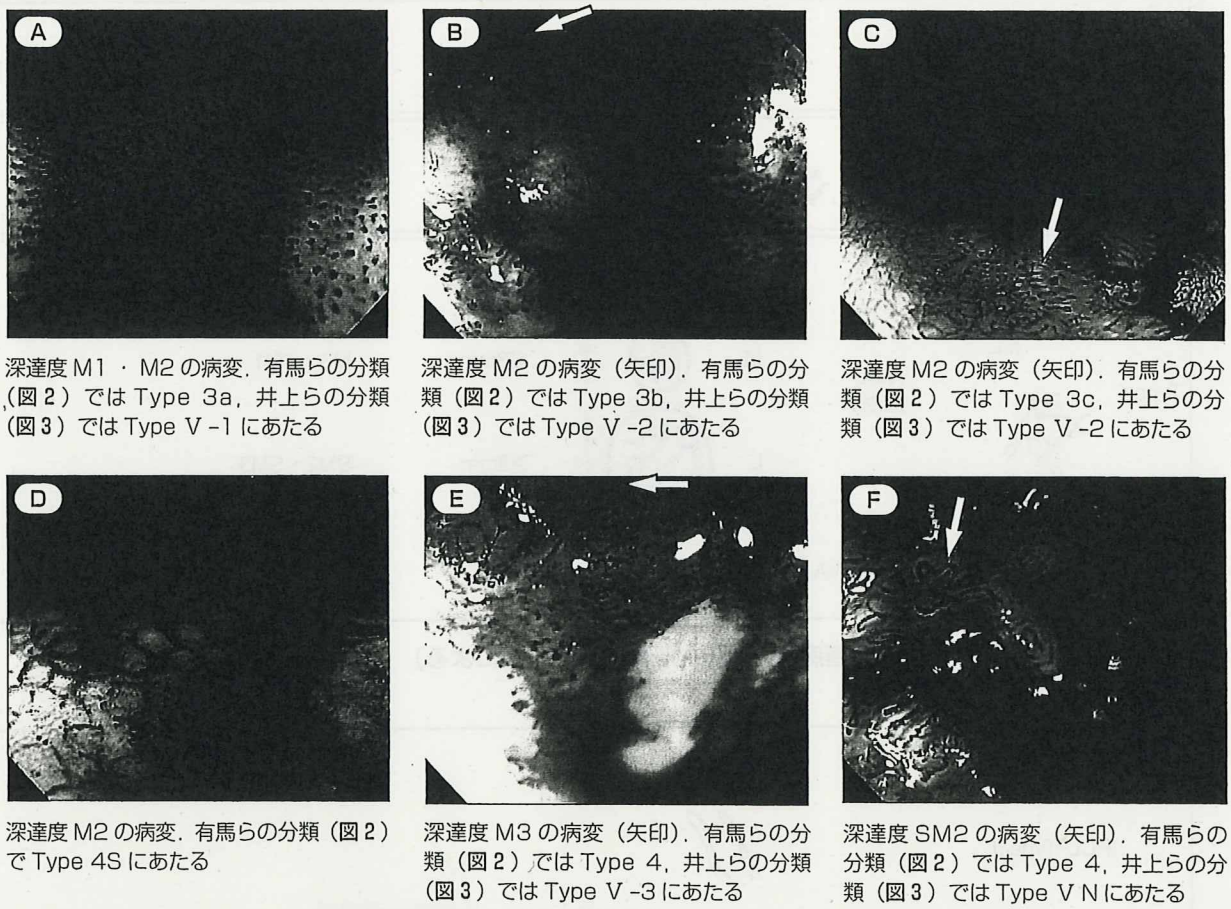
- Type 1：細く直線的な乳頭内血管が観察されるか，ほとんど乳頭内血管が観察されないもの
- Type 2：血管の伸張や血管径の拡張，分岐や螺旋状腫大，血管数の増加はあるが，乳頭内血管構造が保たれ，配列の規則性が比較的保たれるもの
- Type 3：乳頭内血管構造の破壊と口径不同を伴う糸くず状・潰れた赤丸状・らせん状血管で，配列が不揃いなものである．Type 3 には 4 つの subtype がある
  - 3a：壊れた糸くず状血管（図 4 A）
  - 3b：潰れた赤丸状血管（図 4 B）
  - 3c：3b が伸張したり癒合がみられるもの（図 4 C）
  - 3d：イクラ状の形態のもの
- Type 4：乳頭から逸脱した血管で，多重状（multi-layered：ML），不整樹枝状（irregu-



◆ 図2 拡大観察による表在食道病変の微細血管分類（有馬らによる）



◆ 図3 IPCL パターン分類（井上らによる）



深達度M1・M2の病変．有馬らの分類（図2）ではType 3a，井上らの分類（図3）ではType V-1にあたる

深達度M2の病変（矢印）．有馬らの分類（図2）ではType 3b，井上らの分類（図3）ではType V-2にあたる

深達度M2の病変（矢印）．有馬らの分類（図2）ではType 3c，井上らの分類（図3）ではType V-2にあたる

深達度M2の病変．有馬らの分類（図2）でType 4Sにあたる

深達度M3の病変（矢印）．有馬らの分類（図2）ではType 4，井上らの分類（図3）ではType V-3にあたる

深達度SM2の病変（矢印）．有馬らの分類（図2）ではType 4，井上らの分類（図3）ではType V Nにあたる

◆ 図4 深達度診断

larly-branched：IB），網状（reticular：R）の3つに分類される．Type 4血管が，血管に乏しい領域（avascular area：AVA）を取り囲む変化が出現する．このAVAの長径と深達度には関係があるので，4S：0.5mm以下（図4 D），4M：3mm以下，4L：3mm以上と分類している（図4 E，F）

2 井上分類（図3）

- Type V-1：“拡張，蛇行，口径不同，形状不均一”の所見を認めるIPCL（図4 A）
- Type V-2：Type V-1の所見が深部に向かって延長を始めるもの（図4 C）
- Type V-3：Type V-2の変化がさらに構造の破壊が進んだもの（図4 E）
- Type VN：腫瘍内を無秩序に走行する太い腫瘍血管（図4 F）

通常観察での深達度診断にこれらの拡大内視鏡所見を加味して深達度を診断する．

MEMO

NBIとは基本的な技術は異なるが，分光特性を応用したFICE（FUJI intelligent color enhancement）でも拡大観察により異常血管パターンが観察可能であり，食道表在癌の深達度を正確に診断できる[1]．最近では，従来の色素法に加え，これら光学的または機械的に色調を変化させて観察したい病変を強調する技術をimage enhanced endoscopy（IEE）と総称することが提唱されている．

注意

食道癌は他臓器重複癌が多い．堅田らは他臓器重複癌の頻度は 47 %で，特に頭頸部重複癌が 36 %と多かったと報告している[3]．食道癌症例では頭頸部癌のリスクが高いことを考慮して，内視鏡挿入時から NBI を併用して咽頭・喉頭の観察が必要である．頭頸部癌の内視鏡所見も食道癌と同様に，境界の明瞭な brownish area と，拡大内視鏡観察の併用による拡張，蛇行，口径不同，形状不均一の所見をもつ異常血管の指摘である．しかし深達度の診断はまだ確立されていない．

ポイント☞

- 拾い上げるべき食道表在癌の NBI 所見は brownish area である
- 拡大観察を用いて詳細に観察する点は異型血管の形態変化である

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3）堅田親利, 武藤 学：背景因子からみた異時性多発食道癌の長期経過. 胃と腸, 42 : 1355-1363, 2007

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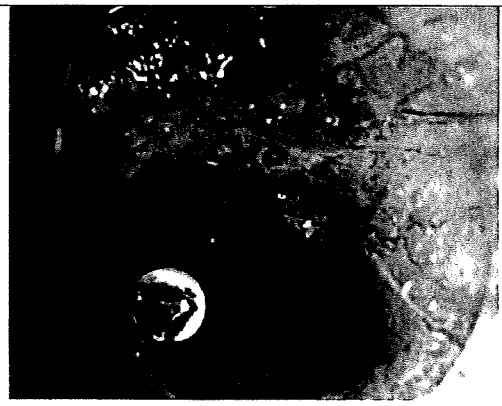

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第1章 治療法選択のための術前内視鏡診断
② 病変部の通常・色素内視鏡診断

1. 食道

森田周子，武藤 学

内視鏡治療の対象になる食道表在癌は内視鏡所見が乏しいことが多く，注意深く観察することが望ましい．粘液や残渣が多い場合には，丹念にガスコン水で洗浄し粘液を十分に除去した状態で観察する必要がある．ヨード色素内視鏡の際にも，粘液付着はヨードの染色性を低下させ診断の妨げになるため，粘液や残渣などの付着物は十分に洗い流しておく必要がある．

通常観察による病変の拾い上げ

食道表在癌は内視鏡所見に乏しいため白色光による通常観察では発見が難しい場合が多い．ヨード色素内視鏡による病変の拾い上げの有効性は広く認識されているが[1]，刺激性が強いためすべての被験者に行うには決して楽で安全な検査とは言いがたい．そこで，いかに病変の最初の拾い上げを通常観察で行うかが重要になってくる．

まず，観察しやすい環境作りが大切である．食道の粘液や残渣を十分に除去してわずかな変化を観察しやすくするために，咽頭麻酔前にガスコン® ドロップとプロナーゼ® を溶かした微温湯（2％ガスコン® ドロップ 20mL，プロナーゼ® 1/900g，炭酸水素ナトリウム 2/900g，蒸留水 10mL）を服用してもらい，食道に内視鏡を挿入した後も，ガスコン水にて食道壁を十分に洗浄する．

次に，粘液のない状態で食道を観察して，粘膜面の発赤，白苔付着の有無，凹凸不整，光沢の消失，正常血管網の消失を探す（図1 A，B）．食道表在癌の凹凸はごく浅い陥凹や低い隆起であり，送気量が多いと病変が平坦になって認識しづらくなる（図1 D）．そこで食道の観察時には軽度脱気するなど，送気量を変えながら観察したほうが病変を拾い上げやすい場合がある（図1 E）．

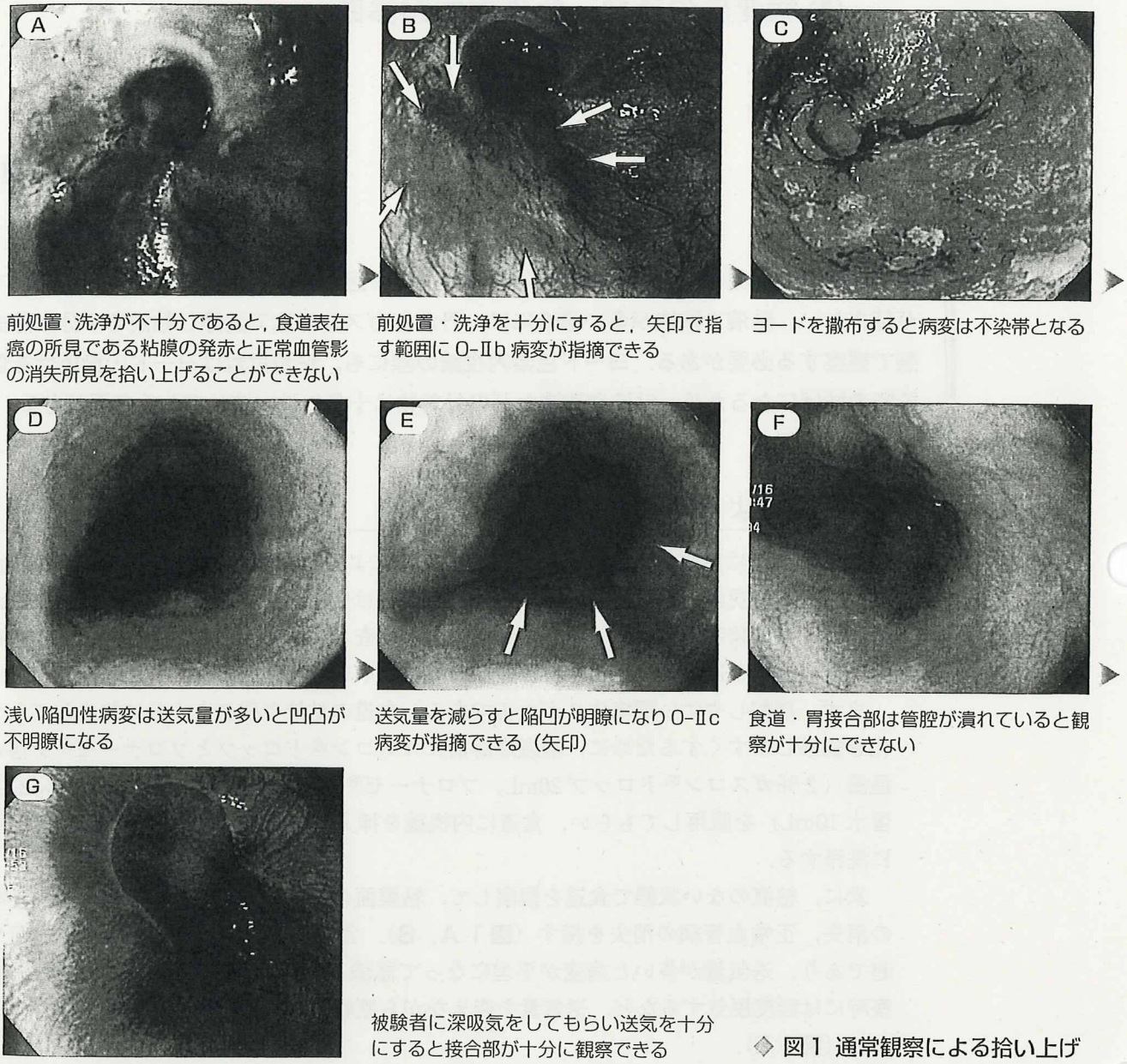
管腔を十分拡張させて観察することが難しい食道入口部と食道胃接合部では，呼吸を取り入れて観察する．食道入口部は，内視鏡を抜きながら観察し息を吐かせた状態にすると内腔が広がる瞬間があるのでそのタイミングを逃さず観察する．食道胃接合部では被験者に深吸気をしてもらうことで，食道粘膜と胃粘膜の連続性が観察しやすくなる（図1 F，G）．

頭頸部・食道癌の既往歴がある，アルコール多飲者であるといった高リスクの症例ではヨード染色を行う（図1 C）．

ヨード染色による詳細観察

病変の存在を疑う所見を認めた場合，癌かどうかの質的診断と，病変の範囲および深達度を診断するために詳細な観察をする必要がある．質的診断にはヨード染色法と基礎編-第1章-③-1で述べる narrow band imaging（NBI）が有用であるが，ここではヨード染色法について記載する．

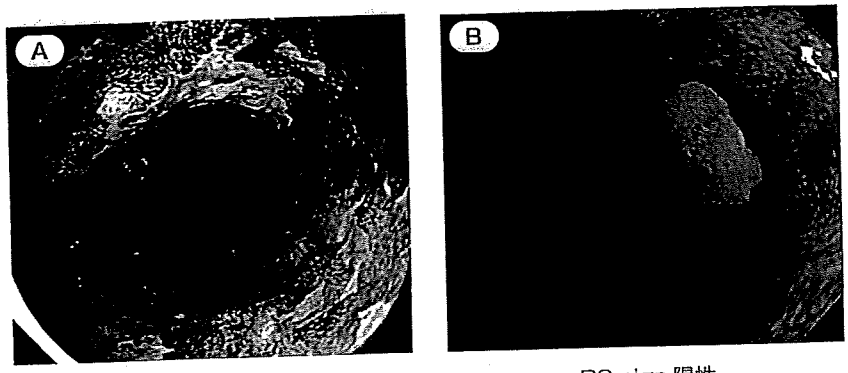
粘液を十分に除去した後，1.5％ヨードを食道全体または部分的に撒布する（図1 C）．食道全体に撒布する理由は，多発癌の頻度が多いことがあげられる．また，ヨード液を撒布する際の注意点として，被検者の苦痛や誤嚥などのリスクを軽減するために過剰な量を撒布しないこ



◇ 図 1　通常観察による拾い上げ

と，染色後は速やかに観察することがあげられる．われわれは，内視鏡を切歯 17 ～ 18cm まで引き抜いた後に，撒布チューブを鉗子口から肛門側に約 10 ～ 15cm 出してヨードを撒布しながら撒布チューブを鉗子口に引き戻す方法を推奨している．この場合，ヨード液は重力によって前壁側（9 時の方向）にたまりやすくなるので，**後壁側（3 時の方向）に向けて撒布するのがまんべんなく染色するコツである．**いったん目的の食道壁が染色されたら，引き続いて内視鏡を非染色部まで挿入し同じ作業を繰り返す．この行程により，2 ～ 3 回の撒布で食道全体が染色され，使用するヨード液も約 10mL 程度に抑えられる．逆に，撒布チューブを用いる場合でも胃食道接合部から撒布を始めると 20mL 以上の撒布量になることが多い．また，20 ～ 30mL のシリンジでヨード液を大胆に撒布し，不足した場合に追加撒布すると数 10mL の撒布量になるので，被検者へ与える苦痛は大きくなる．余分なヨード液は随時吸引して，観察の妨げにならないようにする．

ヨード撒布直後には正常上皮部ではヨードが茶色に発色してくるので，癌を示す境界明瞭なヨード不染の有無を観察する．また撒布から 3 ～ 4 分経過すると，癌部はピンク色に変化する pink color sign（PC sign）を呈するため，質的診断が容易になる[2]．この PC sign は感度・特



ヨード撒布から3～4分経過するとヨードがやや褪色しかけて，癌によるヨード不染帯はピンク色に変化する pink color sign（PC sign）が陽性となる

PC sign 陽性

◆図2 PC sign

異度が90％を超えるため質的診断にはきわめて有用である（**図2**）．

MEMO

多発ヨード不染を伴う場合は，不染の大きさや形態や境界の明瞭さ，不染なのか淡染なのか，PC sign の有無などを総合して，治療が必要な不染，生検すべき不染，経過観察が必要な不染かどうかを判断する．

注意 **食道表在癌にヨードを撒布すると，表層部のみが脱落して非腫瘍性上皮が再生するため基底層型癌になることがある[3]．基底層型癌はヨードで染色されるため，病変範囲を誤る可能性がある．そこで確実な内視鏡切除を行うためには，初回のヨード染色像を参考にして切除範囲を決める方がよい．**

深達度診断

内視鏡治療の適応になりうる壁深達度 SM1 までを深達度別に解説する（基礎編－第2章－1 **図1**参照）．

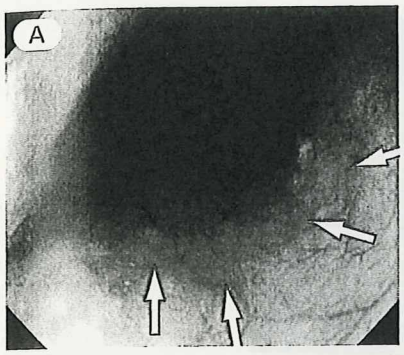
1 EP・LPM

EP（粘膜上皮）・LPM（粘膜固有層）の病変は平坦な 0-Ⅱb 病変（**図3 A**）と，ごく浅い陥凹性病変（0-Ⅱc：**図3 B**）と，高さが 1mm までの低い白色調の隆起性病変（0-Ⅱa）が含まれる（**図3 C**）．EP の大部分は 0-Ⅱb 病変である．0-Ⅱc 病変では辺縁隆起を伴っておらず，いずれも病変内は平坦であるか細顆粒状である．ヨードを撒布すると境界が明瞭な不染帯となり，不染帯は時間とともにピンク色になる PC sign が陽性になる．不染帯内部にはヨードに染まる非腫瘍扁平上皮が散在することが多い．また EP，LPM の病変では，送気量を調節すると畳み目ひだと呼ばれる粘膜筋板の収縮である横ひだが病変内部に観察できる（**図3 D**）．

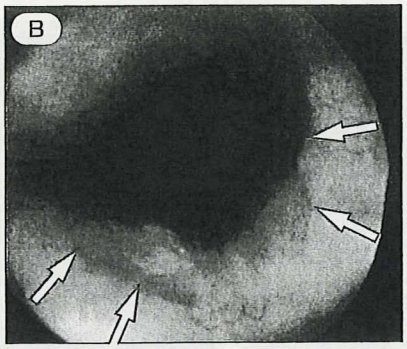
2 MM・SM1

深達度 SM1 とは，粘膜下層（SM）を3等分し，上 1/3 にとどまる病変であり，これは内視鏡的に切除された標本では粘膜筋板（MM）から 200 μm 以内の粘膜下層にとどまる病変と定義している[4]．

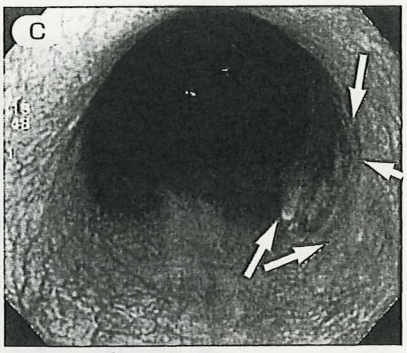
MM・SM1 の 0-Ⅱa 病変は，高さが 2mm くらいのやや高い隆起で，隆起の立ち上がりは比較的なだらかである．0-Ⅱc 病変は極軽度の辺縁隆起を伴う浅い陥凹で，陥凹内部には顆粒状の変化を伴う（**図3 E**）．ヨードを撒布すると境界が明瞭な不染帯となり，PC sign が陽性になる．MM，SM1 の病変では畳み目ひだが消失し（**図3 F**），輪状筋の収縮によって出現する縦ひだに太まりが出現する（**図3 G**）．



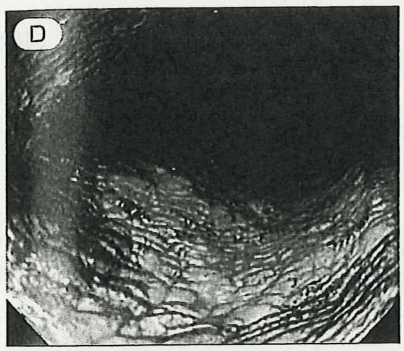
深達度 M1 ・ M2 の 0-Ⅱb 病変（矢印）



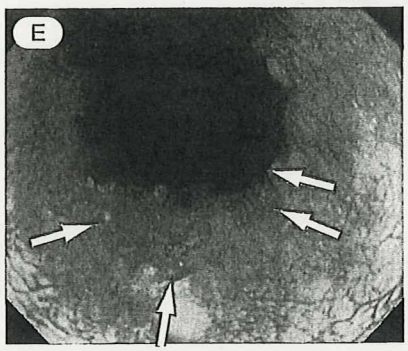
深達度 M1 ・ M2 の 0-Ⅱc 病変（矢印）



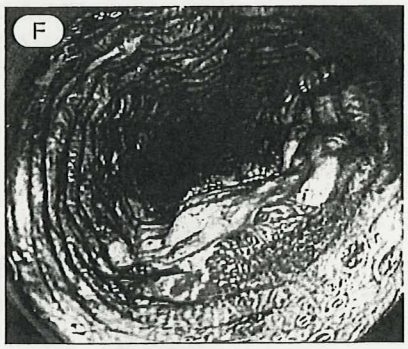
深達度 M1 ・ M2 の白色調の 0-Ⅱa 病変（矢印）



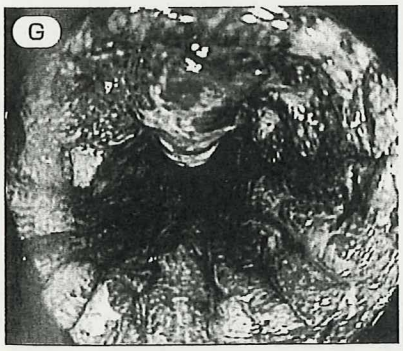
ヨード染色像．M1，M2 の病変では，送気量を調節すると畳み目ひだと呼ばれる粘膜筋板の収縮である横襞が病変内部に観察できる



深達度 M3 ・ SM1 の 0-Ⅱc 病変は極軽度の辺縁隆起を伴う浅い陥凹である（矢印）



ヨード染色像．深達度 M3，SM1 の病変では畳み目ひだが消失する



ヨード染色像．深達度 M3，SM1 の病変では輪状筋の収縮によって出現する縦ひだに太まりが出現する

◆ 図 3 深達度診断

ポイント☞

- 食道内の洗浄をしっかり行って，観察しやすくする
- 食道表在癌の所見である粘膜面の発赤，凹凸，光沢の消失，正常血管影の消失を探す
- ヨード染色法も併用して，範囲と深達度を正確に診断して内視鏡治療の適応を決定する

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GASTROENTEROLOGY

Narrow-band imaging endoscopy with magnification is useful for detecting metachronous superficial pharyngeal cancer in patients with esophageal squamous cell carcinoma

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Key words
esophageal squamous cell carcinoma, head and neck cancer, magnification, narrow-band imaging, pharyngeal cancer.

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Abstract

Background and Aims: Head and neck cancers, especially pharyngeal cancers, as well as esophageal cancers frequently coexist either synchronously or metachronously, but most cases of pharyngeal cancer are detected at an advanced stage resulting in poor prognosis. The aim of this study is to evaluate the effectiveness of using narrow-band imaging (NBI) endoscopy with magnification for early detection of pharyngeal cancer on patients following their treatment for esophageal squamous cell carcinoma (SCC).

Methods: This case series was conducted at the National Cancer Center Hospital in Tokyo between April and October 2005 and included 424 consecutive patients for surveillance endoscopy who had previously undergone chemoradiotherapy (CRT) and/or surgery for esophageal SCC. Observation of the pharyngeal region was randomly conducted on 91 patients using NBI endoscopy with magnification (NBI group) and 333 patients using conventional white light endoscopy (control group).

Results: The detection rate for pharyngeal cancer was significantly higher using NBI endoscopy with magnification (10.9%; 10/91) compared with conventional endoscopy (1.2%; 4/333) ($P < 0.0001$). In particular, the detection rate in CRT patients was significantly higher in the NBI group (12.9%; 7/54) than the control group (0.5%; 1/191) ($P < 0.0001$). In addition, diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value for the NBI group were 100% (10/10), 97.5% (79/81), 97.8% (89/91), 83.3% (10/12) and 100% (79/79), respectively.

Conclusion: NBI endoscopy with magnification is a promising technique for detecting superficial pharyngeal cancer at an early stage in patients previously treated for esophageal SCC.

Introduction

According to the 'field cancerization' concept,[1] head and neck cancers, especially pharyngeal cancers, as well as esophageal cancers occurring from the same region of squamous epithelium, frequently coexist either synchronously or metachronously.[2–4] Because it is difficult to detect pharyngeal cancer at an early stage, however, most cases are detected at an advanced stage resulting in poor prognosis.[5] Patients surviving esophageal cancer undergo regular endoscopic examinations following surgery and/or chemoradiotherapy (CRT), but we continue to be confronted by detection of pharyngeal cancer at an advanced stage. Because prognosis is extremely poor with advanced hypopharyngeal cancer, early detection is vitally important.[6–10]

Esophageal cancer also is difficult to detect as a small or flat lesion, but early detection is possible by using Lugol solution that reveals the cancer as a Lugol-voiding lesion (LVL) white or pink in color.[11–14] This method causes severe mucosal irritation, however, leading to patient pain and discomfort. In addition, we cannot use Lugol solution to detect pharyngeal cancer because of possible aspiration to the patient's airway.

Given the problems associated with Lugol chromoendoscopy, new alternative methods of endoscopic diagnosis need to be developed and one of them, the narrow-band imaging (NBI) system, is attracting considerable attention. The usefulness of NBI in the gastrointestinal region has been reported[15–19] and some studies suggest its possible application in the diagnosis of esophageal and pharyngeal cancers.[20–23] Because oropharyngeal and hypopharyngeal mucosal sites also are squamous epithelium and cancers located there are usually squamous cell carcinoma (SCC), similar findings are likely regarding early cancer detection in those regions.[24,25]

Therefore, we performed NBI endoscopy with magnification on patients following their treatment for esophageal SCC to evaluate

Journal of Gastroenterology and Hepatology 25 (2010) 264–269

the effectiveness of the NBI system in the early detection of pharyngeal cancer possibly leading to an improved quality of life for such patients.

Methods

NBI system

The conventional video-endoscope system uses three broad-band optical filters covering all visible spectrum wavelengths. The NBI system narrows the bandwidth of spectral transmittance so the central wavelengths of the dedicated trichromatic optical filters are shifted to shorter wavelengths of 415 nm and 540 nm, respectively, with a bandwidth of 30 nm.[26,27] Mucosal surface structure is enhanced using NBI, thereby revealing more precise lesion information.

Patients

We screened for second primary pharyngeal cancer using either NBI endoscopy with magnification or conventional white light endoscopy between April and October 2005 in patients with esophageal SCC who had previously undergone surgery and/or CRT at the National Cancer Center Hospital (NCCH) in Tokyo. We examined a total of 424 consecutive patients which was the total number of patients receiving surveillance endoscopy during that period. Those patients had been followed up regularly at our institution after receiving earlier treatment. Patients who were of clinical or pathological stage IV and/or had a past history or record of treatment for head and neck cancer were excluded. If surveillance endoscopy was repeated in that period, we included only the initial one in this study. Endoscopies were performed using NBI with magnification on 91 patients as the NBI group while a control group of 333 patients received conventional endoscopies. The four NBI group endoscopists had a mean of 9.5 years of experience (range 5–15 years) while the eight control group endoscopists had a mean of 12.1 years of experience (range 5–25 years). The discrepancy in the size of the two groups was strictly the result of only one out of six endoscopic examination rooms at NCCH at that time being equipped with the NBI system. All room assignments for patients in both groups were randomly determined by the scheduling staff without any selection bias or input whatsoever from the endoscopists involved in this study. The detection rate for oropharyngeal and hypopharyngeal cancer was then evaluated in this study.

The instruments used were a magnifying endoscope with × 80 magnification (GIF-Q240Z; Olympus Optical, Tokyo, Japan) in the NBI group and conventional endoscope (GIF-Q240, H260; Olympus Optical) in the control group, a standard video-endoscope system (EVIS LUCERA; Olympus Optical) and an NBI system (Olympus Optical).

Examinations

None of the NBI group patients exhibited any symptoms in the pharynx and all of them underwent an NBI endoscopy as part of their regular examinations. Before the NBI, scopolamine butylbromide (20 mg) was administered i.v. if there were no contraindications to prevent sialorrhea. If a lesion was found during the NBI endoscopy, midazolam (2–5 mg) or pethidine (17.5–35 mg) was also administered i.v. to prevent gag reflex because of the lengthened procedure time.

Narrow-band imaging endoscopy without magnification was initially performed on the oropharyngeal and hypopharyngeal mucosal sites of the NBI group patients. We then added magnification if an abnormal mucosal area was identified during the examination. A brownish area and increased intraepithelial papillary capillary loops (IPCL) with irregularity were evaluated as endoscopic features of superficial pharyngeal cancer (Figs a–f).[21,24,28–30] Once a lesion was identified by NBI, we changed to the conventional view to determine if the lesion could be detected for comparative purposes. Lesions were then biopsied in the standard manner using NBI.

All the control group patients underwent a conventional endoscopic procedure without magnification or NBI with only scopolamine butylbromide being administered i.v. in accordance with our standard procedure. If a lesion was found during conventional endoscopy, midazolam or pethidine was administered similar to the NBI group.

Statistical analysis

All variables in this study were described in terms of mean, standard deviation (SD), median and range. In comparing baseline characteristics between the two groups, we used a Student's *t*-test for continuous variables and a χ^2-test for dichotomous variables. All statistical analyses were performed using SAS ver. 8.0 (SAS Institute, Cary, NC, USA). The *P*-values were two-sided and $P < 0.05$ was used to determine statistical significance.

Ethics

The NCCH ethics committee approved the study protocol and informed consent was obtained from all patients in the NBI group before they entered the study.

Results

There were no differences in patient characteristics between the two groups except for the number (Table 1). We identified a total of 18 superficial lesions in 14 of 424 patients (3.3%). All 14 patients were male. Fourteen lesions were detected in 10 of 91 patients (10.9%) in the NBI group and four lesions in four of 333 patients (1.2%) in the control group. The detection rate for pharyngeal cancer was significantly higher using NBI endoscopy with magnification (10.9%; 10/91) compared with conventional endoscopy (1.2%; 4/333) in esophageal SCC patients following treatment ($P < 0.0001$). The detection rate was also significantly higher among CRT patients in the NBI group (12.9%; 7/54) than in the control group (0.5%; 1/191) ($P < 0.0001$) (Table 2). In addition, diagnostic sensitivity, specificity, accuracy, positive predictive value and negative predictive value for the NBI group were 100% (10/10), 97.5% (79/81), 97.8% (89/91), 83.3% (10/12) and 100% (79/79), respectively. All lesions in both groups were determined to be SCC histologically.

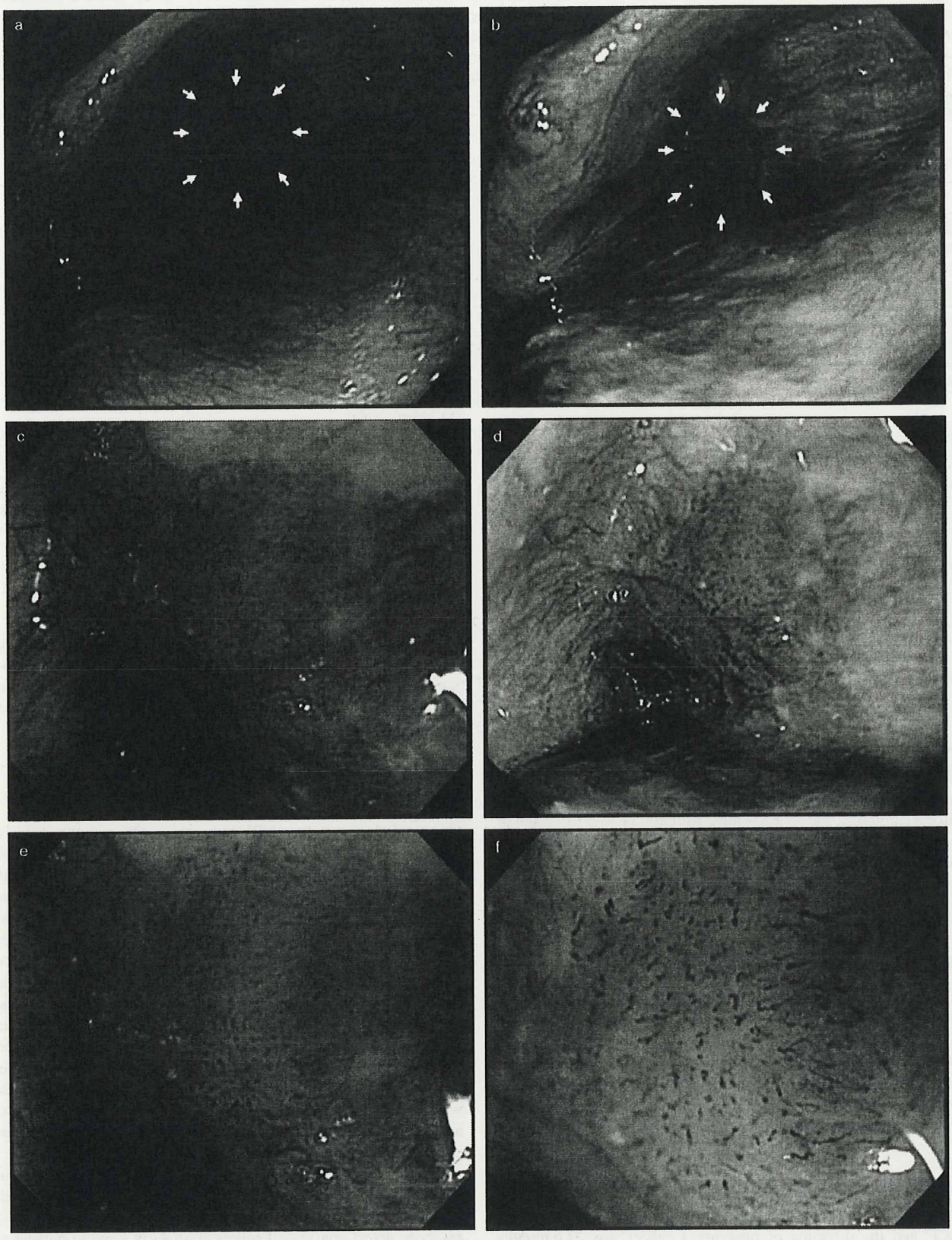

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Figure 1 Squamous cell carcinoma *in situ* in the right pyriform sinus of the hypopharynx (0-IIb; tumor diameter 10 mm). (a) Conventional endoscopy shows a slightly reddish area indicated by the arrows. (b) Narrow-band imaging endoscopy identifies a clearly demarcated brownish area indicated by the arrows. (c) Conventional endoscopy showing a close-up and slightly magnified view. (d) Narrow-band imaging endoscopy showing a close-up and slightly magnified view. The brownish area is clearly demonstrated compared with the surrounding mucosa. (e) Conventional endoscopy with magnification showing abnormal microvascular structures of the mucosa. (f) Narrow-band imaging endoscopy with magnification clearly demonstrates increased intraepithelial papillary capillary loops with irregularity on the surface of the lesion.

Table 1 Patients characteristics

	NBI	Control	*P*-value
No. of patients	91	333	–
Age (years; mean ± SD)	64.9 ± 7.9	66.1 ± 8.4	NS
Male : female	4.1:1	6.7:1	NS
CRT†/surgery (%)	59/41	57/43	NS

†Chemoradiotherapy includes three patients in the NBI group and five patients in the control group who received Radiotherapy only. CRT, chemoradiotherapy; NBI, narrow-band imaging endoscopy; NS, not significant; SD, standard deviation.

Table 2 Detection rate for pharyngeal cancer

	NBI	Control	*P*-value
Prior treatment†			
CRT	12.9% (7/54)	0.5% (1/191)	< 0.0001
Surgery	8.1% (3/37)	2.1% (3/142)	NS
Sex			
Male	13.7% (10/73)	1.4% (4/290)	< 0.0001
Female	0.0% (0/18)	0.0% (0/43)	–
Total	10.9% (10/91)	1.2% (4/333)	< 0.0001

†Initial treatment for primary esophageal cancer. CRT, chemoradiotherapy; NBI, narrow-band imaging endoscopy; NS, not significant.

Location

With the exception of five oropharynx lesions in the NBI group, all lesions in both groups were located in the hypopharynx and multifocal carcinoma was found in three patients (21%; 3/14). Eight of 14 (57%) lesions in the NBI group and two of four (50%) lesions in the control group were located on the right side (Table 3). The pyriform sinus was the most common primary site in both groups (12/18; 66%).

Macroscopic type and size

Using the esophageal cancer macroscopic classification,[31] six tumors were classified primarily as 0-IIa (43%; 6/14), five as 0-IIb (36%; 5/14), two as 0-IIc (14%; 2/14) and one as 0-I (7%; 1//14) in the NBI group and two as 0-IIc (50%; 2/4), one as 0-IIb (25%; 1/4) and one as 0-I (25%; 1/4) in the control group. The lesion size was 15.7 ± 6.8 mm (mean ± SD) in the NBI group and 17.5 ± 2.5 mm in the control group (Table 3).

Detection periods and number of examinations

The median period between the end of treatment for esophageal SCC and the detection of pharyngeal cancer was 27.6 months (range 7.1–143.5) in the NBI group and 101.0 months (range 11.0–134.5) in the control group. The median number of endoscopic examinations between initial examination and detection was 9.0 (range 2–31) in the NBI group and 8.5 (range 7–14) in the control group (Table 3).

Table 3 Characteristics of patients with pharyngeal cancer

	NBI	Control
Male/female	10/0	4/0
CRT/surgery	7/3	1/3
No. of lesions	14	4
Location†		
Oropharynx/hypopharynx	5/11	0/4
Right/center/left	8/5/3	2/1/1
Size (mm; mean ± SD)	15.7 ± 6.8	17.5 ± 2.5
0-IIa/0-IIb/0-IIc/0-I‡	6/5/2/1	0/1/2/1
Times of endoscopy (median; range)	9.0 (2–31)	8.5 (7–14)
Median period in months to pharyngeal cancer detection (range)	27.6 (7.1–143.5)	101.0 (11.0–134.5)

†Locations overlapped. ‡Macroscopic type using the esophageal cancer classification. CRT, chemoradiotherapy; NBI, narrow-band imaging endoscopy; NS, not significant; SD, standard deviation.

Discussion

Our results suggest that NBI endoscopy with magnification is superior to conventional endoscopy for the early detection of pharyngeal cancer in patients following treatment for esophageal SCC. We strongly recommend careful observation particularly in male and CRT patients. The visual recognition of lesions was significantly improved by being able to identify brownish areas and increased IPCL with irregularity as malignant disease. It was difficult to precisely diagnose simply from the existence of a brownish area, however, when an abnormal mucosal area was identified using NBI without magnification. Minute observation of the microvascular structure of the squamous epithelium for increased IPCL with irregularity was required for an accurate diagnosis.[21,28,29] Because NBI can be utilized in all endoscopes with such a system by pushing a single button, it is very easy to use and capable of becoming a valuable tool for endoscopic diagnosis particularly in the esophagus and pharynx.

In terms of esophageal cancer, careful follow up of patients who are completely cured becomes even more important with increased improvement in recent treatment outcomes.[32–34] Because it is necessary to detect pharyngeal cancer at an early stage to prevent a

poor prognosis,[35–40] NBI endoscopy with magnification is considered to be a positive advancement for ensuring a good prognosis through early detection.

Those patients, who previously underwent CRT, generally received surveillance endoscopy every 3–6 months following their treatment while surgical patients received such examinations once a year at our institution. Although it is difficult to precisely determine a suitable frequency from our results, we believe that 6–12 months is generally an acceptable interval.

Disadvantages of conventional endoscopy

Conventional endoscopy does not provide clear and comprehensible IPCL images. In addition, abnormal findings seen as reddish areas are less visually distinct than the brownish areas shown by NBI. Because Lugol chromoendoscopy cannot be performed in the pharynx because of the risk of aspiration, early detection is even more difficult as a result.

Visual recognition

In considering lesion size, the NBI group had slightly smaller lesions than the control group. In addition, the mean size of four lesions (10 ± 7.1 mm) in the NBI group which were undetected during the subsequent conventional view was smaller than that of the 10 lesions (20 ± 7.0 mm) which could be detected by careful examination during the subsequent conventional view. This suggests that NBI is particularly useful for detecting smaller lesions with no remarkable visual change.

There were more lesions detected on the right side in the NBI group. If a lesion was located on the left side, the standard endoscopic pathway, it is likely that it would have been easier to detect. A lesion on the right side is generally more difficult to detect, but use of the NBI system may help address this problem.

High-risk group

Since the estimated age standardized rate of cancer incidence (per 100 000) in the mouth and pharynx is less than five in Japan,[41] it is advisable to establish high-risk populations because screening for such cancer in all patients is virtually impossible as well as unnecessary. Careful examination of the pharynx only needs to be performed in high-risk populations including patients with esophageal cancer or multiple LVL in their background esophageal mucosa, heavy drinkers, smokers and men over 50 years of age.[42–44]

Future vision

Narrow-band imaging endoscopy with magnification should become a standard endoscopic diagnostic technique in the esophagus and pharynx regions in the future with the realistic expectation of a corresponding increase in the number of lesions detected at an early stage. Accordingly, we will need to determine diagnosis of NBI endoscopy with magnification based on observation of brownish areas and increased IPCL with irregularity and also diagnosis of the depth of invasion in the absence of muscularis mucosae in the pharynx region. In addition, we will have to investigate what kind of endoscopic treatment procedures are most feasible.

Limitations

The difference in the number of patients in the NBI group (91) and the control group (333) and the fact that our research was not based on a randomized control trial, are limitations of this study.

Conclusion

NBI endoscopy with magnification is a promising technique for detecting superficial pharyngeal cancer at an early stage in patients previously treated for esophageal SCC.

Acknowledgments

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Effect of Orally Administered Bovine Lactoferrin on the Growth of Adenomatous Colorectal Polyps in a Randomized, Placebo-Controlled Clinical Trial

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Abstract Lactoferrin (LF), a secreted, iron binding glycoprotein originally discovered as a component of milk, is found in a variety of exocrine secretions and in the secondary granules of polymorphonuclear leukocytes. Animal experiments have shown that oral administration of bovine lactoferrin (bLF) exerts anticarcinogenesis effects in the colon and other organs of the rat. The aim of this study was to determine whether oral bLF could inhibit the growth of adenomatous colorectal polyps in human patients. A randomized, double-blind, controlled trial was conducted in 104 participants, ages 40 to 75 years, with polyps ≤5 mm in diameter and likely to be adenomas. Participants were assigned to receive placebo, 1.5-g bLF, or 3.0-g bLF daily for 12 months. Target adenomatous polyps were monitored by colonoscopy. Ingestion of 3.0-g bLF significantly retarded adenomatous polyp growth in participants 63 years old or younger. Removal of adenomatous colorectal polyps is done as a preventative measure against colorectal cancer; however, polyps can be overlooked, and when detected, polypectomy is not always 100% effective in eradicating a polyp. Our study suggests that daily intake of 3.0 g of bLF could be a clinically beneficial adjunct to colorectal polyp extraction.

Colorectal cancer is one of the most frequent causes of death from cancer (1–5). Most colorectal cancers arise from benign adenomas (6). Adenoma formation and colorectal cancer incidence have been reported to be influenced by food elements and nutrition (7–10), making diet and dietary supplements factors in colorectal cancer. Bovine lactoferrin (bLF) isolated from cow milk has been studied for inhibition of colorectal and other cancers (11–15). Specifically, supplementation of bLF to the diet of azoxymethane-treated rats decreased the incidence of both colorectal cancer and aberrant crypt foci (12, 14, 15). Importantly, bLF has been reported to be well tolerated in clinical research (16, 17).

In the present study, we conducted a randomized controlled trial to evaluate whether a 1-year oral intake of bLF-containing tablets (Morinaga Milk Industry Co. Ltd.) inhibits the growth of colorectal polyps <5 mm in diameter with pit pattern III. Because polyps with pit pattern III have been reported to be histologically adenomatous in ~90% of the cases (18–20) and polyps <5 mm in diameter show a tendency to grow in size (21), our target lesion is suitable for the current study and measurement of polyp diameter is a promising surrogate end point. We found a statistically significant retardation of polyp growth in participants 63 years old or younger ingesting 3.0-g bLF daily over the course of 12 months.

Ingestion of bLF inhibits colorectal carcinogenesis in animal studies (12, 14, 15). In addition, ingestion of bLF enhances immune function, both in animal studies (22, 23) and in human patients (24). Finally, numerous studies have revealed the crucial role of the immune system in inhibiting the neoplastic process (25). Therefore, immunologic parameters associated with bLF ingestion were measured: interleukin-18 and IFNγ, because ingestion of bLF enhances expression of interleukin-18 and IFNγ in the mouse small intestine (22); T-cell subpopulation numbers, because ingestion of bLF reconstitutes T-cell populations in immunosuppressed mice (26); natural killer (NK) cell number and activity, because ingestion of bLF enhances NK cell activity in rats (12); and neutrophil number, because

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