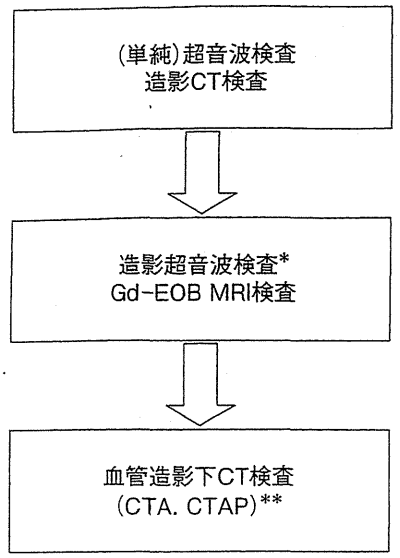


図 4　転移性肝腫瘍診断のフローチャート
*Levovist®を用いた造影超音波検査，SPIO MRI 検査は現在行っていない
**CTA：CT arteriography, CTAP：CT arterial portography

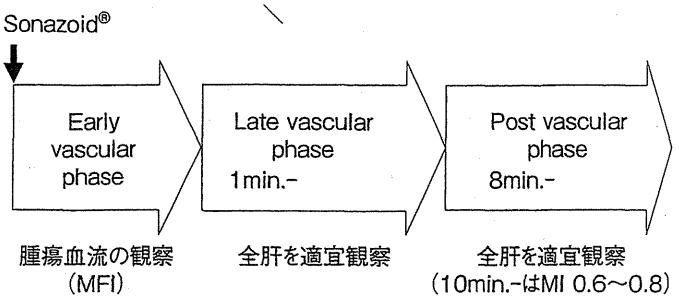


図 5　造影超音波検査プロトコル

0.0075 m*l*/ kg の Sonazoid®を 10 m*l* の生理食塩水で 1 m*l*/ sec にてフラッシュ注入し，造影超音波検査を行っている。Sonazoid®投与量は推奨投与量 0.015 m*l*/ kg の 1/ 4～1/ 2 量とかなり少なくしている。これは推奨投与量を用いた場合，vascular phase における血流信号強度が強くなりすぎるため，関心領域―腫瘍およびその周囲肝―の詳細な血流の検討がかえって難しくなることが当初経験されためである。Sonazoid®の投与量については使用装置および使用目的，撮像パラメータなどにより異なる報告がなされているが，転移性肝腫瘍検索においては推奨投与量～1/ 2 量とする報告が多い。Sonazoid®は懸濁液作成後，2 時間以内に使用している。

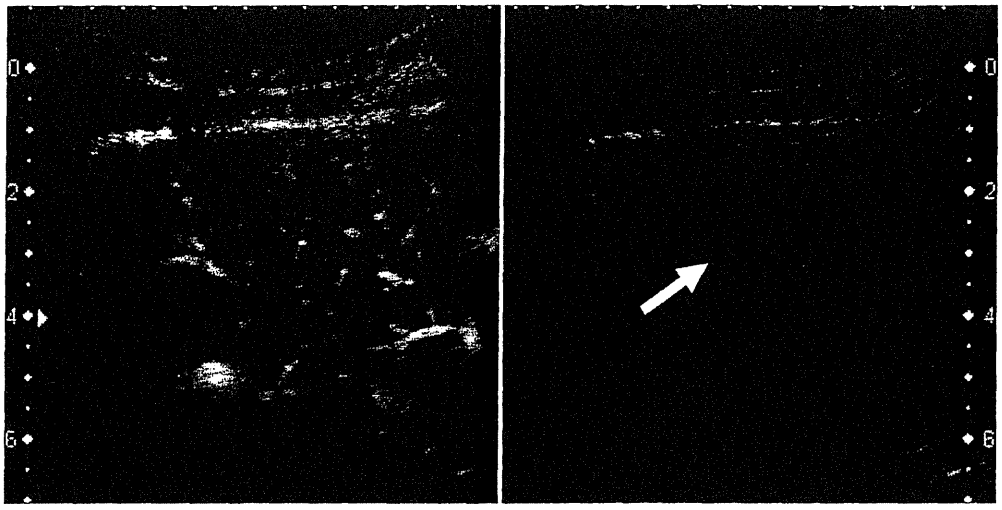
造影超音波検査のプロトコルを図 5 に示す。検査時の観察ポイントは以下の 5 点である。単純超音波検査にて肝腫瘍が認められる場合は主たる腫瘍に対し，①造影剤投与開始後 30 秒位まで Mechanical index (MI) 値 0.20～0.25 の低音圧にて腫瘍の動脈血流の連続観察（動脈濃染所見の観察，図 2)。②その後 1 分位までの間に高音圧を数フレーム送信して観察範囲の micro bubble を破壊・消失させ，その直後から観察範囲に再潅流する micro bubble 信号を加算表示する micro flow imaging (MFI) 法による腫瘍およびその周囲の微細な血管構築の観察(flash replenishment 法，図 6) を適宜行う。③1～8 分の Late vascular phase は MI 値 0.20～0.25 の低音圧にて全肝を適宜観察し，肝転移巣検索を施行。その際，腫瘍が認められた場合には血行動態の観察を行う。肝実質が優位に造影される 8 分以降の Post vascular phase は，④はじめは MI 値 0.20～0.25 の低音圧で，⑤10 分以降は MI 値 0.6～0.8 の中音圧で全肝を適宜観察し，肝転移巣検索を行う。

肝血管腫の半数以上は Post vascular phase で完全または不完全な造影欠損として描出される[3]。したがって Post vascular phase のみの肝転移巣検索は肝血管腫を肝転移と誤診する可能性があり推奨できない。肝転移巣検索においては，少なくとも Late vascular phase, Post vascular phase の観察は必要と考えている。

Ⅳ．手技上の注意

MI 値 0.20～0.25 の低音圧による観察では 7～8 cm 以深の肝の信号は弱く，その描出は不良となることが多い。これを補うべく MI 値を高くすると，肝表の micro bubble は破壊されるが音波はより深部へ届くようになる。10 分以降に MI 値を 0.6～0.8 の中音圧としているのは 7～8 cm 以深の肝描出能が多少改善されるのを期待するためである。MI 値を上げすぎるとより深部まで micro bubble が破壊されてしまうので，注意深く MI 値を上げる必要がある。また MI 値 0.20～0.25 の低音圧であっても同じ部位の観察をしばらく行うと，肝表の micro bubble は破壊され，肝表に位置する肝転移を見落としてしまう危険性がある。肝表の micro bubble の破壊の程度を気にしながらの観察を行うことが肝要である。

転移性肝腫瘍の中には高エコーを呈するものがあり，特に大腸癌の肝転移では石灰化を伴うものがある (図7)。このような高エコー腫瘤は背景エコーと micro bubble とが重なり腫瘍内血流評価（＝腫瘍の viability 評価）の難しい症例がしばしば経験される。このよう



a|b

図 6 micro flow imaging（MFI）
75 歳男性，C 型肝炎。左が MFI 画像，右は low MI の参照 B モード画像。
肝 S4 φ18 mm の高エコー域（→）およびその周囲の微細な血管構築ができる。

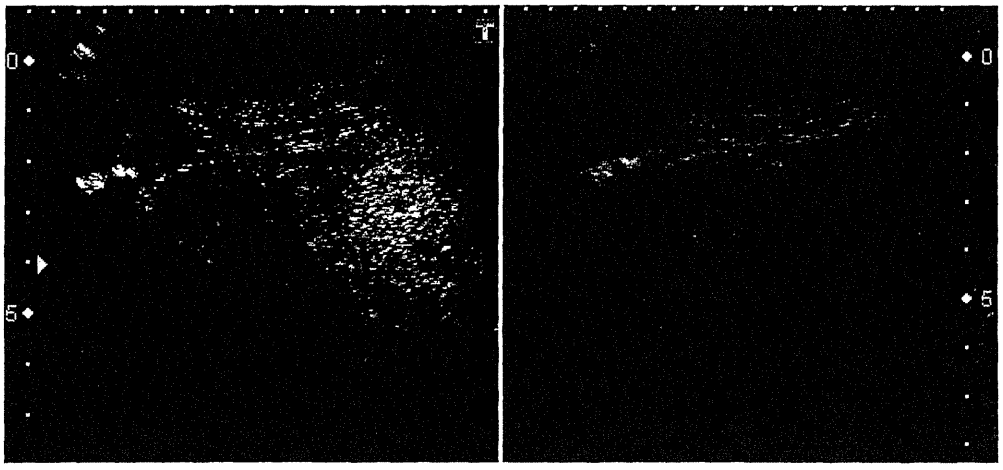


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図 7 石灰化を有する転移性肝腫瘍
高エコーを呈する腫瘤は背景エコーと micro bubble とが重なり腫瘍内血流評価が難しい。Gain をできるだけ下げて観察することが必要となるが，造影モード画像のみではどこ（何）を見ているのか分からなくなってしまう。B mode 画像を参照できる monitor mode での観察が望ましい。左が造影モード，右は low MI の参照 B モード画像。

な場合は Gain をできるだけ下げて背景画像を消し，B mode 画像を参照できる monitor mode での観察が望ましい。

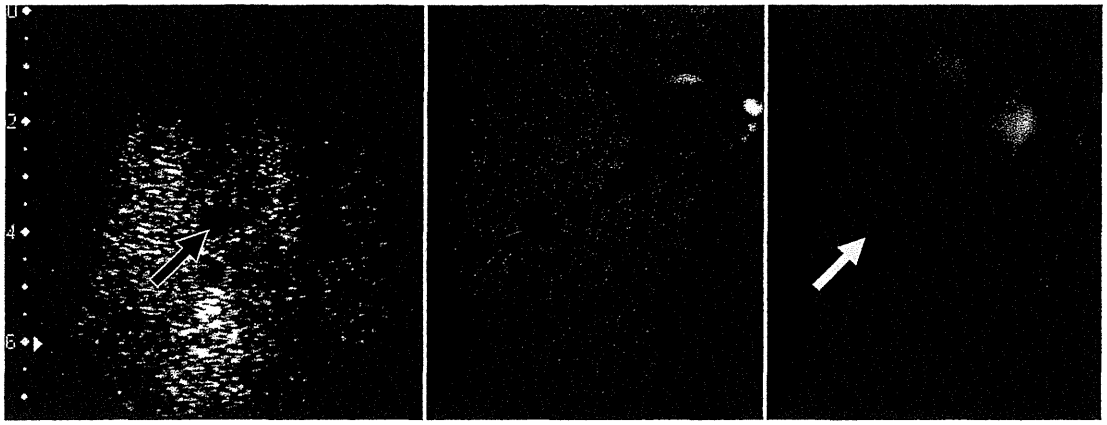
V．転移性肝腫瘍の検出能

当院にて転移性肝腫瘍検索および化学療法効果判定目的に，造影超音波検査の施行された原発性肝癌を除く 181 例のまとめを表 1 に示す。平均年齢は 64.3±12.0 歳，男性 119 名，女性 62 名である。対象には化学療法効果判定目的症例が多く含まれていたため，単純または造影超音波検査にて肝転移を認めた症例は 136 例と全体の 75.1％を占めた。そのうち造影超音波検査にて新たに腫瘍の検出された症例は 63 例（63/136＝46.3％）と約半数を占めており，造影超音波検査の有用性が示された。これを原発巣別にみると，大腸では 26 例（26/72＝36.1％），胃では 11 例（11/20＝55.0％），膵では 23 例（23/29＝79.3％）であり，膵癌および胃癌における肝転移巣検索に特に有用性が高いことが示唆された（図 1, 2）。膵癌は早期に肝転移を起こすことが知られており，また術後再発も肝転移の多いことから，膵癌病期診断における造影超音波検査の意義は非常に高いと思われる。また検出された腫瘍の大きさをみると，造影前に検出された腫瘍に比べ造影後に検出された腫瘍は小さい傾向にあった。

表 1　造影に伴う転移性肝腫瘍検出能の向上

原発巣	症例数	肝転移数別症例数（造影後新病変検出数）				
		0	1	2～5	5<	0<
大腸	85	13	29 (3)	29 (12)	14 (11)	72 (26＝36.1%)
胃	21	1	3 (0)	10 (7)	7 (4)	20 (11＝55.0%)
膵	48	19	3 (1)	9 (6)	17 (16)	29 (23＝79.3%)
その他	27	12	5 (0)	7 (2)	3 (1)	15 (3＝20.0%)
	181	45	136 (63＝46.3%)			

その他：GIST 6例，胆管6例，胆嚢3例，食道2例，扁桃・十二指腸乳頭・卵巣・乳房・後腹膜・多発性骨髄腫・原発不明各1例



a|b|c

図 8　Gd-EOB MRI と造影超音波

59歳女性。直腸癌肝転移。造影超音波検査では肝S6にϕ7 mmの内部血流を伴うSOL（→）を認め転移と診断（a）。Gd-EOB MRI検査の肝細胞相（b）では同部に低信号域（→）をみるが，拡散強調画像（c）では淡い高信号域（→）として描出され転移疑いと診断した。

VI. 腫瘍内血流の描出

腫瘍内血流の検討は肝転移を認めた136例全例において主腫瘍内を移動するmicro bubbleを観察することが可能であった（図3）。8分以降のPost vascular phaseでも腫瘍内を移動するmicro bubble観察は可能であったが，腫瘍内に流入・流出するmicro bubbleは時間の経過と共に減少傾向がみられ，腫瘍内血流評価は8分までのVascular phaseでの観察の方が容易であり望ましい。腫瘍内血流の評価が難しく，造影剤を初回量と同量再投与し腫瘍内血流の評価を行った（Defect re-perfusion imaging[4]）症例は8例である。造影超音波検査は腫瘍縮小効果に加え，腫瘍内血流などの機能評価の指標としての応用が今後期待される。

おわりに

肝転移巣検索における診断モダリティの精度については，諸家により報告がなされてはいるが[5~8]，その選択にあたっては検査の侵襲性，特異度，各施設の整備診断機器状況などに大きく依存しているのが実情である。当院では肝転移巣検索の精査においては，肝細胞特異性造影剤EOB・Primovist®を用い，拡散強調画像を併用したGd-EOB MRIと造影超音波検査とを相補的に用い診断している（図8）。

超音波検査の質は術者の力量，超音波の死角，患者の体格などに影響されるという欠点を有してはいるが，造影超音波検査は安定したPost vascular imagingが得られ，明瞭な肝―腫瘍コントラストを提供する。肝臓の観察が十分できる術者であればGd-EOB MRIと同等またはそれ以上の肝腫瘍検出力が期待できる。また超音波造影剤Sonazoid®はCTやMRIの造影剤に較べ遙かに安全で簡便に使用することができる。医療安全性および医療経済性なども考慮すると，現在広く普及し機動力のあるMDCTと造影超音波検査との組み合わせが広く一般に普及し，肝転移巣検出の精度向上に大いに貢献していくものと思われる。

現在，画像による化学療法の腫瘍効果判定は腫瘍径によりなされているが，Sonazoid®は腫瘍内血流の多寡を評価することができることから，腫瘍縮小効果に加え，腫瘍内血流量などの機能面を指標とした効果判定や，血管新生阻害剤などの適応判定への応用も今後期待したい。

謝　辞

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悪性リンパ腫、脾病変のSonazoid造影超音波所見

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はじめに

悪性リンパ腫の肝病変および脾病変は通常の超音波検査ではとらえられず、生検にてはじめて診断されることがしばしば経験される。Sonazoidのmicrobubbleは脾網内系に貪食されることにより、肝実質ばかりでなく脾実質の造影効果の持続を示すことが知られており、Sonazoid造影超音波検査の悪性リンパ腫脾病変の検出ならびに治療効果判定への有効性が期待される。今回、悪性リンパ腫脾病変4例のSonazoid造影超音波所見について検討したので報告する。

対象・方法

対象は2007年6月11日から11月14日までの期間に、当院にて悪性リンパ腫の肝浸潤巣精査目的にSonazoid造影超音波検査の施行された10例のうち、脾病変を認めた4例である。平均年齢は63歳(38～73歳)、男女比は3：1である。用いた超音波装置は東芝社製Aplio XG。造影超音波検査は通常の超音波検査に引き続いて施行した。前腕に留置した22Gの留置針より自動注入器Medrad Pulserを用い、0.0067mL/kgのSonazoidを生理食塩水10mLで1mL/secにてフラッシュ注入し、造影超音波検査を行った。Sonazoid平均投与量は0.39±0.04mLである。観察はpulse subtraction modeを用い、MI値0.2～0.3の低音圧にて10分まで行った。本研究は当院の倫理審査委員会の承認を受けており、全例検査に先立ち十分な説明を行い、文書による同意を得ている。

表1　悪性リンパ腫脾病変の超音波所見

症例		B mode(造影前)	Sonazoid造影		参考所見
			動脈相	実質相	
1	72/M	低(等)	等－低	低	LN
2	38/M	低(等)	等－低	低	LN
3	67/F	低(等)	等－低	低	liver SOL
4	73/M	低(等)	等－低	低	

✓ 脾臓は肝と同様に、実質の造影効果持続を認めた
✓ 全例造影後に新たにSOLの出現を認めた

結果

表1に4例の超音波所見を示す。全例複数の脾病変を有し、その最大径は3例で2cm以下、1例で4cm以下であった。脾病変はB-mode造影前には境界不明瞭な低エコー域または等エコー域を呈し、造影前には指摘できない病変も数多く認められた(図1)。造影剤投与直後より、脾病変は背景脾とほぼ同様に全体または外側部分がリング状に染まり、脾病変の不明瞭化が見られた(図2)。この脾病変の不明瞭化は造影剤投与後約4分まで持続した。造影剤投与後4分以降は、血管内microbubbleの減少とともに脾病変の造影効果減弱が見られ、時間の経過とともに脾病変およびその境界がより明瞭化することが観察された(図3)。

考察

悪性リンパ腫の転移リンパ節や肝病変、脾病変は、造影早期に濃染することが知

られている。脾病変は背景の脾実質と同じタイミングで造影されるため、造影早期には病変と背景の脾実質とのコントラストがつかなくなり、不明瞭となるものと思われた。また、網内系の貪食により実質の造影効果の持続する肝臓や脾臓における多血性病変は、blood pool内にSonazoid microbubbleがある程度存在している場合、多血性病変と背景実質とのコントラストがつかなくなり、病変およびその境界の不明瞭化が見られるものと推測され、悪性リンパ腫の脾病変における造影所見の特長と考えられる。類似した現象は肝細胞癌における肝臓において観察されており、造影CTにおける造影パターンをそのまま造影超音波のそれに適合してはならないと判断された。

まとめ

悪性リンパ腫脾病変の検出にはSonazoid造影超音波検査のpost vascular phaseが有用であり、質的診断にはその経時的変化の把握が有効である。

謝辞

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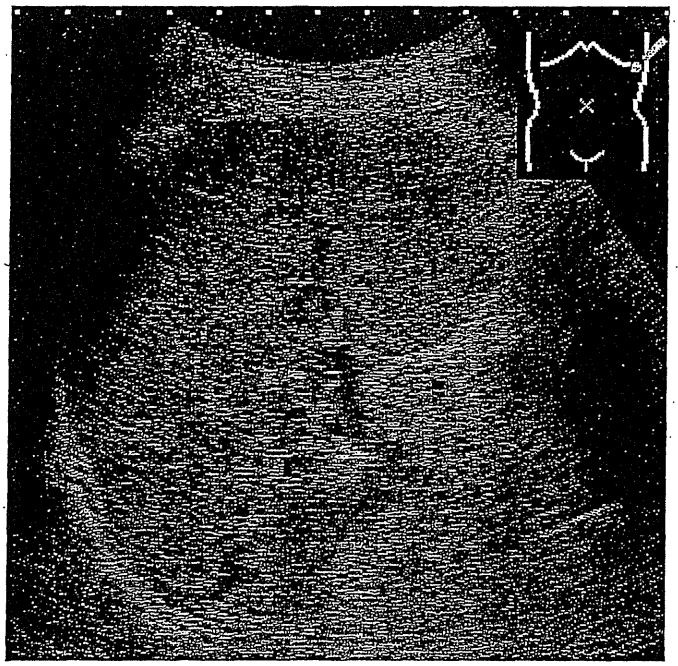

図1　B mode画像(造影前)

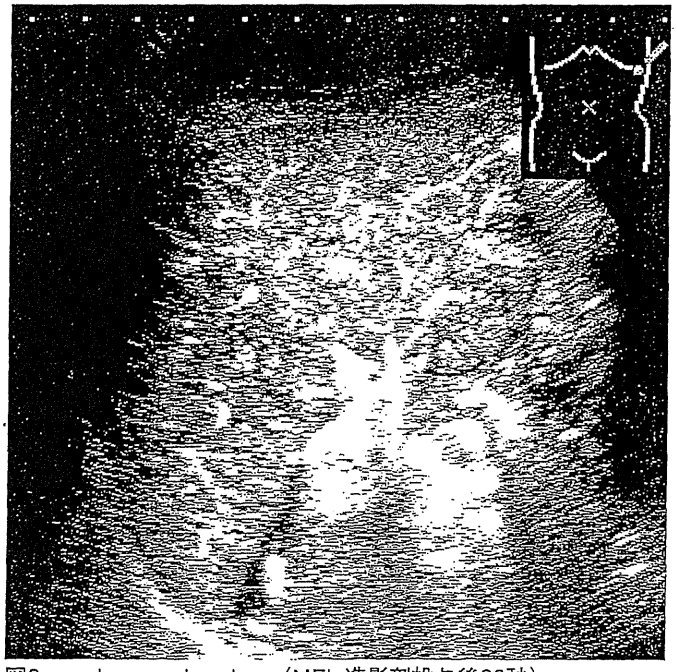

図2　early vascular phase(MFI、造影剤投与後20秒)

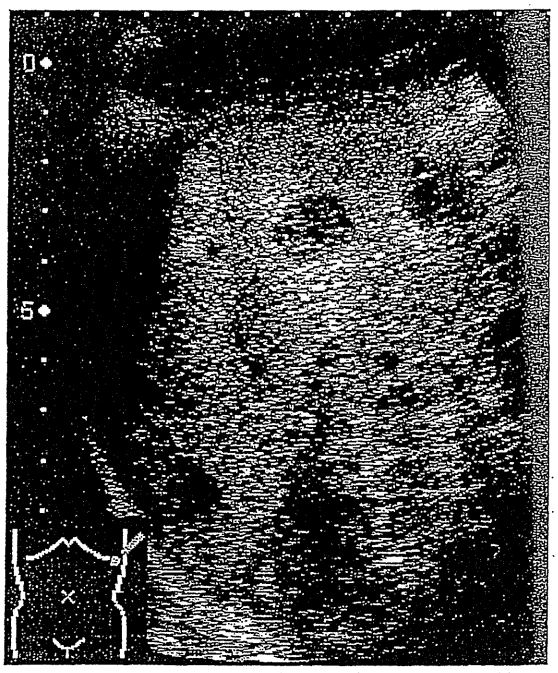

図3　post vascular phase(造影剤投与後6分50秒)

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Narrow band imaging for detecting superficial squamous cell carcinoma of the head and neck in patients with esophageal squamous cell carcinoma

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Background and study aims: Narrow band imaging combined with magnifying endoscopy (NBI-ME) is useful for the detection of superficial squamous cell carcinoma (SCC) within the oropharynx, hypopharynx, and oral cavity. The risk of a second primary SCC of the head and neck is very high in patients with esophageal SCC. This prospective study evaluated the detection rate of superficial SCC within the head and neck region (superficial SCCHN) with NBI-ME in patients with esophageal SCC.

Patients and methods: Between March 2006 and February 2008, 112 patients with a current or previous diagnosis of esophageal SCC were enrolled. All patients underwent endoscopic screening of the head and neck by NBI-ME. The primary end point was the detection rate for superficial SCCHN. Secondary end points were to compare demographic characteristics between patients with and without superficial SCCHN and to assess the clinical course of patients with superficial SCCHN.

Results: The detection rate for superficial SCCHN was 13% (15/112). The prevalence of multiple Lugol-voiding lesions, observed endoscopically throughout the esophageal mucosa after application of Lugol dye solution, was significantly higher in patients with superficial SCCHN than in those without (100% vs. 24%, $P < 0.0001$). Minimally invasive curative treatment with organ preservation was feasible without severe complications in patients with superficial SCCHN after curative treatment of esophageal SCC.

Conclusions: In patients with esophageal SCC, NBI-ME is useful for detecting superficial SCCHN, thereby facilitating minimally invasive treatment.

Introduction

Gastrointestinal endoscopy is an essential technique for the diagnosis of esophageal and gastrointestinal lesions. Narrow band imaging (NBI) is a novel optical technique that enhances the diagnostic capability of gastrointestinal endoscopy by highlighting the intraepithelial papillary capillary loops of the squamous cell mucosa by means of light passed through filters that narrow the spectral bandwidths, incorporated into a red–green–blue sequential illumination system [1]. It has previously been reported that NBI combined with magnifying endoscopy (NBI-ME) could detect superficial squamous cell carcinoma (superficial SCC) within the oropharynx, hypopharynx, and oral cavity [2–5]. Muto et al. reported that NBI-ME had higher rates for both detection and diagnostic accuracy for superficial SCC within the head and neck region (superficial SCCHN) than did conventional white light observation with magnifying endoscopy on back-to-back endoscopic examination [6].

Since in patients with esophageal cancer the most common site for synchronous and metachronous second primary malignancies is the head and neck [7–9], we prospectively studied the ability of NBI-ME to detect superficial SCCHN in patients with a current or previous diagnosis of esophageal SCC.

Patients and methods

Between March 2006 and February 2008, 112 patients were enrolled who met the following criteria: (i) a current or previous diagnosis of esophageal SCC; (ii) age of at least 20 years; (iii) no history of head and neck cancer; (iv) no symptoms of the head and neck; (v) no previous surgical treatment or radiotherapy of the head and neck; and (vi) no previous endoscopic screening of the head and neck by NBI-ME. The study protocol and informed consent form were approved by our institutional review board in February 2006.

Written informed consent was obtained from all patients.

The patients underwent endoscopic screening of the head and neck by NBI-ME. In this study, we performed NBI using a high definition video endoscopy system (CV-260SL, processor, CLV-260SL light source; Olympus Optical Co., Tokyo, Japan) and an optical magnifying endoscope with a system that could magnify objects up to 80 times (GIF Q240Z video endoscope; Olympus). The diameter of the GIF Q240Z video endoscope was 10.2 mm, and the flexibility was similar to that of a conventional gastrointestinal endoscope. Screening was done in the following order: (i) observation with shifting of the tongue to create sufficient space for screening the oral cavity without mouth gear, and (ii) observation with vocal exercise to create sufficient space for screening the oropharyngeal, hypopharyngeal, and laryngeal regions with mouth gear.

The primary end point was the detection rate of superficial SCCHN by endoscopic screening using NBI-ME in patients with a current or previous diagnosis of esophageal SCC. Secondary end points were: (i) to compare demographic characteristics between patients with and those without superficial SCCHN, and (ii) to assess the clinical course of patients with superficial SCCHN.

Because prospective studies assessing the ability of NBI to detect early, superficial SCCHN have not been reported previously, it was difficult to estimate the required sample size. We therefore set the study period at 2 years, during which we estimated that at least 100 patients could be enrolled.

Only superficial cancers, that is, microinvasive SCC and high grade intraepithelial neoplasia as defined by the World Health Organization classification of tumors, were studied [10]. An NBI diagnosis of superficial SCC required the presence of both (i) a well-demarcated brownish area, and (ii) an irregular microvascular pattern [2–4]. Examples of superficial SCC in the left piriform sinus, the left superior wall of the oropharynx, and the left side of the tongue are shown in **Figs. 1–3**. Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (**Figs. 1a**, **2a**, and **3a**). NBI showed a well-demarcated brownish area (**Figs. 1b**, **2b**, and **3b**). NBI combined with maximum magnification (×80) showed an irregular microvascular pattern (**Figs. 1c**, **2c**, and **3c**).

Biopsy specimens were taken after the completion of screening for all superficial cancers in the head and neck region. Before biopsy in the laryngeal region, 4% lidocaine solution was sprayed through the endoscope to attenuate the gag reflex. Resected specimens, biopsy specimens, or both, were evaluated histopathologically. The histological characteristics of neoplasms were classified according to the World Health Organization criteria for esophageal tumors [10]. We used the histological diagnosis as the gold standard diagnosis. Although the results of endoscopy were not blinded, the histological diagnosis was confirmed by two gastrointestinal pathologists.

Lugol chromoendoscopy of the esophageal mucosa was carried out in all patients, using the Lugol dye staining method [11]. A 1.5% solution of Lugol dye was used in this study. Multiple Lugol-voiding lesions (LVLs) were defined to be numerous, well-defined, irregularly shaped lesions that appeared throughout the entire esophageal mucosa after the application of Lugol dye solution [12, 13].

Because the oral cavity and superior wall of the oropharynx could easily be accessed by a surgical device, transoral surgical mucosectomy (TSM) of lesions in such regions was done by a head and neck surgeon, with the patient under general anesthesia. Lesions were removed using an electric surgical knife or carbon dioxide laser, without injecting saline beneath the epithelium to lift the lesion above the surrounding mucosa [4]. If a transoral direct surgical approach was difficult, endoscopic mucosal resection (EMR) was performed by a gastrointestinal endoscopist with the patient under general anesthesia; lesions were removed using a transparent, soft plastic cap [2, 14]. We used an orotracheal route for intubation at the time of EMR. However, in patients who underwent TSM because a transoral direct surgical approach was possible, a nasotracheal route was used for intubation to secure a good operative field.

In patients with superficial SCCHN treated with curative intent, follow-up examinations by NBI-ME and computed tomography (CT) examination were repeated at least every 6 months after treatment. The duration of follow-up was longer than 1 year in this study.

All statistical analyses were carried out using the StatView software package for Macintosh (Version 5; Abacus Concepts, Inc., Berkeley, California, USA). The significance of differences was assessed with Fisher's exact test. P values of < 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Patient characteristics are shown in **Table 1**. The study group comprised 100 men (89%) and 12 women (11%), with a mean age (± SD) of 67 ± 7.5 years. The clinical stage of esophageal cancer was stage I in 42 patients (38%), stage II in 26 (23%), stage III in 32 (29%), and stage IV in 12 (11%).

Of the patients, 80 (71%) had a current diagnosis of esophageal SCC and it had been previously diagnosed in 32 (29%). There was a history of cancer in other organs in 12 patients (11%): gastric cancer in 7 (6%), lung cancer in 2 (2%), liver cancer in 1 (1%), bladder cancer in 1 (1%), and leukemia in 1 (1%). The remaining 100 patients (89%) had no history of cancer in other organs.

Habitual alcohol use was reported by 101 patients (90%), and 98 (88%) were smokers. Multiple LVLs of esophageal mucosa were found in 38 patients (34%).

Detection of superficial SCCHN

The detection rate for superficial SCCHN was 13% (15/112), with 16 lesions detected in 15 patients. One patient had two lesions, 1 each in oropharyngeal and hypopharyngeal mucosal sites. No advanced cancer was detected. The 16 lesions comprised 3 (19%) detected in the oral cavity, 4 (25%) in the oropharynx, and 9 (56%) in the hypopharynx (**Table 2**); no laryngeal cancer was detected. For 8 of the 16 lesions, biopsy specimen and resection specimens were available for histological evaluation; for the remaining 8 lesions, only biopsy specimens were available since these patients were treated with techniques other than surgical or endoscopic resection. All 16 superficial SCCHNs were diagnosed endoscopically and confirmed histopathologically.

The characteristics of patients with and without superficial SCCHN are compared in **Table 3**. The prevalence of multiple LVLs of the background esophageal mucosa was significantly higher in patients with superficial SCCHN (100% vs. 24%, $P < 0.0001$). Other characteristics did not differ significantly between the groups.

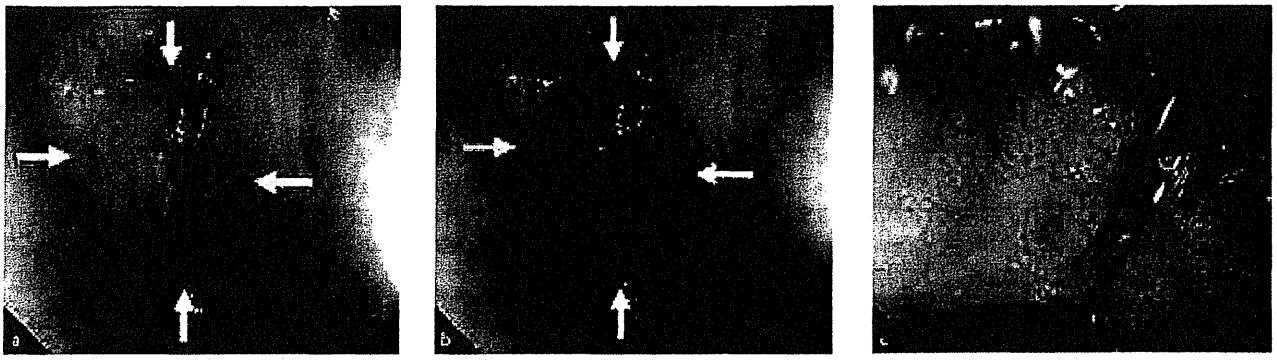

Fig. 1 Superficial squamous cell carcinoma in the left piriform sinus of the hypopharynx. **a** Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (arrows). **b** Narrow band imaging (NBI) showed a well-demarcated brownish area (arrows). **c** NBI combined with maximum magnification (×80) showed an irregular microvascular pattern.

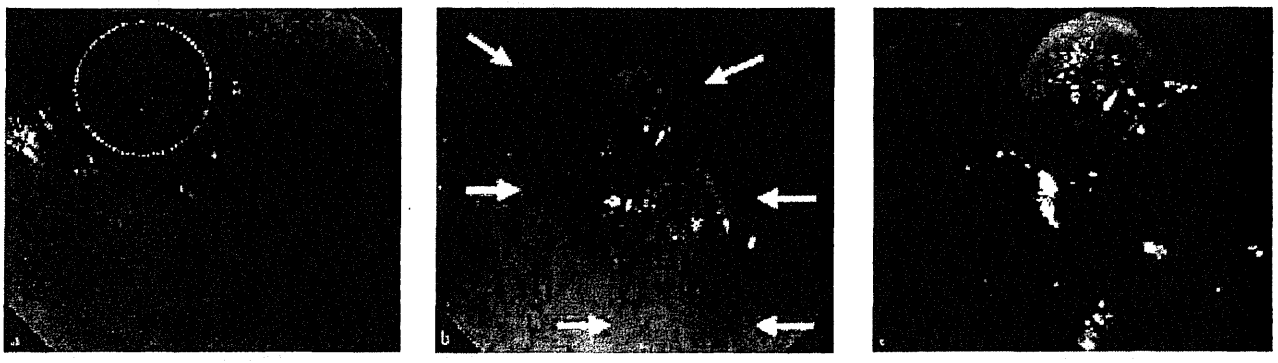

Fig. 2 Superficial squamous cell carcinoma in the left superior wall of the oropharynx. **a** Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (dotted line). **b** Narrow band imaging (NBI) showed a well-demarcated brownish area (arrows). **c** NBI combined with maximum magnification (×80) showed an irregular microvascular pattern.

Fig. 3 Superficial squamous cell carcinoma in the left side of the tongue. **a** Conventional white light observation showed a slightly reddish area with mild mucosal irregularity (arrows). Frenulum labii inferior. **b** Narrow band imaging (NBI) showed a well-demarcated brownish area (arrows). **c** NBI combined with maximum magnification (× 80) showed an irregular microvascular pattern.

Treatment and course

In the 15 patients with superficial SCCHN, their esophageal cancer had been previously diagnosed in 3 and had been currently (at the time of the present study) diagnosed in 12. Because 10 patients were transiently disease-free after treatment for esophageal cancer, their superficial SCCHNs were treated with curative intent.

Fig. 4 summarizes the clinical courses of the ten patients in whom 11 superficial SCCHNs were treated with curative intent. Of the 11 lesions, 8 were resected (TSM 4, EMR 4; see below for further details); 2 lesions arising in the piriform sinus were treated by chemoradiotherapy [15]; and another 1 lesion in the piriform sinus by radiotherapy. The patient receiving radiotherapy for this hypopharyngeal SCCHN had two lesions and underwent TSM for an oropharyngeal lesion.

All of these patients were followed up every 6 months for at least 1 year. The average follow-up period (± SD) was 25 ± 6.3 months (range 14–33), and the average number of examinations per patient (± SD) was 4.8 ± 1 (range 3–6). No recurrent or newly diagnosed superficial SCCHN was detected during follow up.

One patient had synchronous advanced esophageal cancer and superficial SCC of the oral cavity, which were treated by chemoradiotherapy and TSM, respectively. However, this patient died because of recurrence of the esophageal cancer. The superficial SCC of the oral cavity was unrelated to the cause of death. With a median follow-up period of 29 months (range 14–33), all of

Table 1 Characteristics of patients (n = 112) and lesions.

Men, n (%)	100 (89 %)
Age, mean ± SD, years	67 ± 7.5
Clinical stage of esophageal cancer, n (%)	
I	42 (38 %)
II	26 (23 %)
III	32 (29 %)
IV	12 (11 %)
Esophageal cancer	
Current	80 (71 %)
Previous	32 (29 %)
History of cancer in other organs, n (%)	
None	100 (89 %)
Stomach	7 (6 %)
Lung	2 (2 %)
Liver	1 (1 %)
Bladder	1 (1 %)
Leukemia	1 (1 %)
Habitual alcohol use, n (%)	
Yes	101 (90 %)
No	11 (10 %)
Smoking, n (%)	
Yes	98 (88 %)
No	14 (13 %)
Multiple Lugol-voiding lesions, n (%)	
Yes	38 (34 %)
No	74 (66 %)

the other patients have remained disease-free without severe complications.

Resections. Regarding the 8 resected superficial SCCHNs, 2 lesions arose in the oral cavity, and 2 in the oropharynx, and these were removed by TSM; the remaining 4, in the hypopharynx, were all removed by EMR.

The average resected tumor size (± SD) was 18 ± 5 mm (range 10–25). No lesion was < 10 mm in diameter, 3 were ≥ 10 to < 20 mm in diameter, and 5 were ≥ 20 to < 30 mm in diameter.

Histologically, 4 of these lesions were high grade intraepithelial neoplasia, and 4 were microinvasive SCC. Two of the microinvasive SCCs were treated by EMR, and the deep resection margins in both patients were free of tumor. Lymphatic or vessel invasion was not found in any resected specimen.

In two patients with hypopharyngeal lesions, laryngeal edema developed during the EMR procedure. This complication was treated by temporary tracheotomy. No patient had bleeding, stenosis, or perforation as a complication of resection. The median follow-up period was 27 months (range, 14–33 months), and, as noted above, 1 of the 8 patients died of recurrent esophageal cancer.

Table 2 Detection rate and location of superficial squamous cell carcinomas in the head and neck region (superficial SCCHN) in 112 patients with a previous or current diagnosis of esophageal cancer.

Detection rate per-patient, % (n/n)	13 % (15/112)
Detected lesions, n	16
Tumor location	
Oral cavity	3 (19 %)
Tongue	2 (13 %)
Hard palate	1 (6 %)
Oropharynx	4 (25 %)
Superior wall	3 (19 %)
Posterior wall	1 (6 %)
Hypopharynx	9 (56 %)
Piriform sinus	5 (31 %)
Postcricoid area	4 (25 %)
Larynx	0 (0 %)

Discussion

Annually, about 50 000 cases of SCCHN are newly diagnosed worldwide annually. Tumors of the hypopharynx are particularly problematic because they are usually are diagnosed at an advanced stage and carry a poor prognosis [16–19]. Recent studies have reported that NBI-ME is useful for the detection of superficial SCCHN [2–5]. In patients with esophageal cancer, synchronous and metachronous second primary malignancies most commonly arise in the upper aerodigestive organs, including the head and neck, stomach, and lung [7–9,20–22]. An exceptionally strong association of esophageal cancer with head and neck cancer has been reported [7–9,23,24]. Matsubara et al. reported that the risk of head and neck cancer markedly increases after esophagectomy (relative risk 34.9; 95 %CI 24.3–48.6). The 5-year cumulative risk of developing head and neck cancer was estimated to be 7 % [9]. Consistent with these results, the detection rate of a second head and neck cancer in patients who had previously had esophageal cancer was 9 % (3/32) in our study. These findings suggest that endoscopic screening of the head and neck region by NBI-ME may substantially contribute to the early detection of head and neck cancer in patients with esophageal SCC. In the future, large prospective follow-up studies are needed to establish the optimal interval for surveillance by NBI-ME after treatment for esophageal SCC.

In the esophagus and head and neck region, the development of multiple primary SCCs and widespread epithelial oncogenic alterations, including carcinoma in situ, dysplasia, and hyperkeratosis, have long been a recognized phenomenon [25]. Clinically, Lugol chromoendoscopy can be used to visualize epithelial changes such as multiple LVLs, since dysplastic or hyperkeratotic epithelium does not stain with Lugol iodine solution and appears white or pink, whereas normal epithelium is stained brown

	With superficial SCCHN n = 15	Without superficial SCCHN n = 97	P value
Males	15 (100 %)	85 (88 %)	0.36
Older (≥ 70 years)	3 (20 %)	35 (36 %)	0.26
Current esophageal cancer	12 (80 %)	68 (70 %)	0.55
History of cancer in other organs	3 (20 %)	9 (9 %)	0.2
Habitual alcohol use	15 (100 %)	86 (89 %)	0.35
Smoking	15 (100 %)	83 (86 %)	0.21
Habitual alcohol use with smoking	15 (100 %)	83 (86 %)	0.21
Multiple Lugol-voiding lesions (LVLs)	15 (100 %)	23 (24 %)	< 0.0001

* P values were calculated using Fisher's exact test.

Table 3 Comparison of demographic characteristics between those with and those without superficial squamous cell carcinomas in the head and neck region (superficial SCCHN), in 112 patients with a previous or current diagnosis of esophageal cancer.

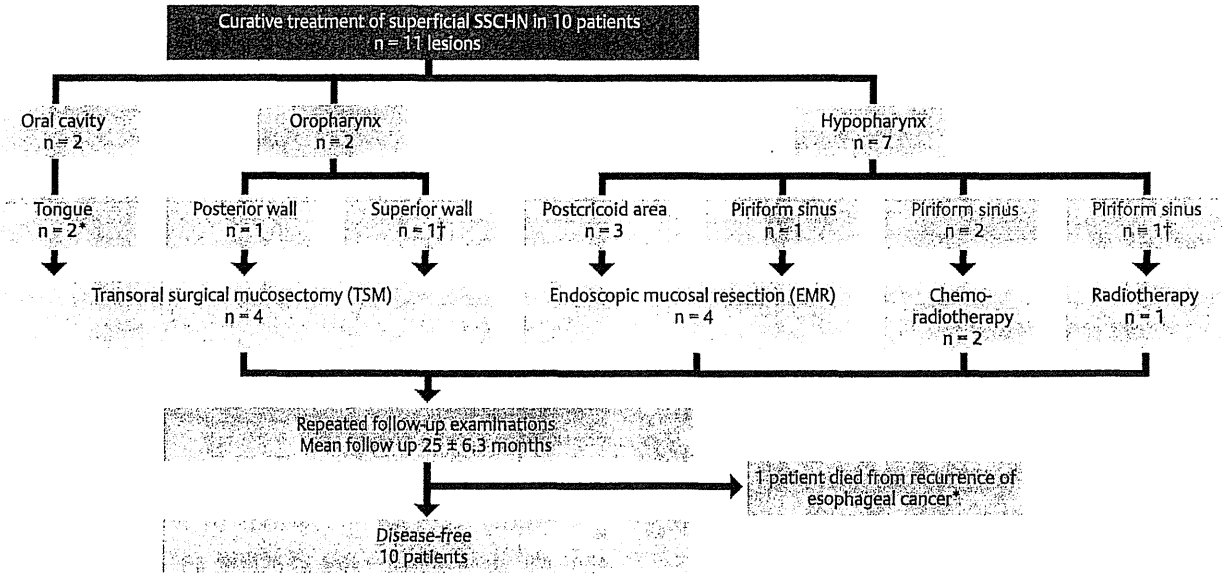

Fig. 4 Clinical course of curative treatment of 11 lesions in 10 patients with superficial squamous cell carcinoma within the head and neck region (superficial SCCHN). * One patient died of recurrent esophageal cancer; † one patient had 2 lesions, 1 each in oropharyngeal and hypopharyngeal mucosal sites.

[11,12]. Multiple LVLs of esophageal mucosa are considered precursors for a second primary esophageal cancer in patients with head and neck cancer [12], and have also been associated with a very high risk of multiple cancers in the esophagus, as well as the head and neck [13,26,27]. In our study, the prevalence of multiple LVLs of esophageal mucosa was significantly increased in patients with superficial SCCHN. The presence of multiple LVLs of esophageal mucosa may therefore be a powerful biomarker for detecting a second primary superficial SCCHN. The Lugol dye staining method cannot be used in the head and neck region because it causes severe mucosal irritation, leading to pain and discomfort; the dye solution may even be aspirated into the airway. Therefore, patients with esophageal cancer who have multiple LVLs of the esophageal mucosa should undergo careful endoscopic screening of the head and neck by NBI-ME.

Effective treatment of superficial SCCHN is considered essential for cure in patients with esophageal SCC, but definitive studies are lacking. The safety and efficacy of follow-up treatment for superficial SCC thus remains unclear. In our series, curative treatment of superficial SCCHN was possible without severe complications in all patients in whom the esophageal SCC was successfully treated. Although 2 of 4 patients (50%) had laryngeal edema during the EMR procedure, which was treated by temporary tracheotomy, the incidence of laryngeal edema can be lowered by minimizing mechanical stimulation caused by contact with surgical devices and chemical stimulation caused by Lugol dye solution on the laryngeal and hypopharyngeal regions at the time of treatment. All patients who underwent curative treatment remained disease-free and retained their larynx. Our results suggest that minimally invasive curative treatment with organ preservation is possible in patients with superficial SCCHN. Since EMR or TSM of head and neck region is less invasive than chemoradiotherapy or radiotherapy, expected benefits should be weighed against potential risks when selecting the treatment strategy. If superficial SCCHN is detected in patients with esophageal SCC, our results may suggest important clues for disease management. In the future, more definitive studies are needed to clarify the safety and efficacy of follow-up treatment for superficial SCCHN.

In conclusion, our results suggest that endoscopic screening by NBI-ME is useful for the detection of superficial SCCHN in patients with esophageal SCC. In particular, patients with multiple LVLs of the esophageal mucosa should be closely monitored to facilitate early detection of superficial SCCHN and permit minimally invasive curative treatment with organ preservation.

Competing interests: None

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Detection of Superficial Squamous Cell Carcinoma in the Head and Neck Region and Esophagus by Narrow Band Imaging: A Multicenter Randomized Controlled Trial

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ABSTRACT

Purpose
Most of the esophageal squamous cell carcinomas (ESCCs) and cancers of the head and neck (H&N) region are diagnosed at later stages. To achieve better survival, early detection is necessary. We compared the real-time diagnostic yield of superficial cancer in these regions between conventional white light imaging (WLI) and narrow band imaging (NBI) in high-risk patients.

Patients and Methods
In a multicenter, prospective, randomized controlled trial, 320 patients with ESCC were randomly assigned to primary WLI followed by NBI (n = 162) or primary NBI followed by WLI (n = 158) in a back-to-back fashion. The primary aim was to compare the real-time detection rates of superficial cancer in the H&N region and the esophagus between WLI and NBI. The secondary aim was to evaluate the diagnostic accuracy of these techniques.

Results
NBI detected superficial cancer more frequently than did WLI in both the H&N region and the esophagus (100% *v* 8%, $P < .001$; 97% *v* 55%, $P < .001$, respectively). The sensitivity of NBI for diagnosis of superficial cancer was 100% and 97.2% in the H&N region and the esophagus, respectively. The accuracy of NBI for diagnosis of superficial cancer was 86.7% and 88.9% in these regions, respectively. The sensitivity and accuracy were significantly higher using NBI than WLI in both regions ($P < .001$ and $P = .02$ for the H&N region; $P < .001$ for both measures for the esophagus, respectively).

Conclusion
NBI could be the standard examination for the early detection of superficial cancer in the H&N region and the esophagus.

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INTRODUCTION

Esophageal cancer is the eighth most common cancer worldwide, accounting for 462,000 new cases in 2002, and is the sixth most common cause of cancer-related death (386,000 deaths).[1] Squamous cell carcinoma (SCC) is the most common histologic type worldwide.[1] Head and neck (H&N) cancer accounted for 607,000 new cases and 261,000 deaths in 2002.[1] The most common histologic type of H&N cancer is also SCC.

The early detection of cancer offers the best prognosis. Currently, however, esophageal SCC (ESCC) and H&N SCC (HNSCC) are detected at a late stage and then have poor prognoses.[1] Early detection of these cancers is difficult by conventional endoscopic white light imaging (WLI). Lugol chromoendoscopy can be used to detect superficial ESCC, but it causes unpleasant adverse effects such as severe chest pain and chest discomfort,[2-4] and it cannot be used for HNSCC screening because of the risk of aspiration.

The narrow band imaging (NBI) system is an innovative optical image-enhanced technology that uses narrow bandwidth NBI filters.[5,6] The central wavelengths of the NBI filters are 415 and 540 nm and each has a bandwidth of 30 nm. This system is easily activated by pushing a button on the endoscope. NBI combined with magnifying endoscopy can clearly visualize the microvascular structure of the organ surface,[6,7] because the 415-nm light is well absorbed by hemoglobin. Surface microvascular irregularities provide useful landmarks for identifying an early neoplasm in the H&N region, bronchus,

and the GI tract.[7-15] We previously reported that NBI was useful for identifying HNSCC at an early stage.[8] Watanabe et al[16,17] also reported the usefulness of NBI rhinolaryngovideoscopy for the diagnosis of HNSCC. Yoshida et al[18] reported that NBI improves the accuracy of magnifying WLI in the assessment of ESCC.

However, the diagnostic yield of NBI in the early detection of superficial SCC has not been investigated. We conducted a prospective randomized study to directly compare WLI and NBI in the early diagnosis of SCC in the H&N region and the esophagus among high-risk patients.

PATIENTS AND METHODS

Study Rationale

Because ESCC patients frequently develop multiple intraesophageal SCC and second primary HNSCC synchronously and metachronously,[4,19-22] they provide a good cancer screening model. Whereas massively invasive SCC is easy to detect by endoscope, superficial cancer has been difficult. Furthermore, detection of high-grade intraepithelial neoplasia (HGIN) is clinically important because HGINs have the potential to become malignant invasive cancers.[23,24] Therefore, in this study, we targeted only macroscopic superficial cancer including HGIN that appeared as slightly elevated lesions lower than 5 mm, flat lesions, and lesions with a shallow depression. Lesions with an apparent elevation greater than 5 mm or those with apparent deeper ulceration were not evaluated.

The primary analysis of this study was a comparison of the detection rates of superficial cancer (HGIN, carcinoma in situ, and microinvasive SCC) using WLI and NBI. The secondary analysis was a comparison of the diagnostic accuracy (sensitivity and specificity) of the two imaging methods, size of the lesion detected, and the examination time. To evaluate diagnostic accuracy, we used the histologic diagnosis from a biopsy specimen as the gold standard diagnosis.

Study Populations

The protocol and consent form for this study were approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients. The inclusion criteria were histologically confirmed present or previous ESCC and an age of 20 years or older. Although this study included patients with advanced ESCC, we evaluated only concomitant superficial cancer but not primary advanced cancer. Patients who had been previously treated for ESCC by endoscopic mucosal resection were included, because their esophagus was preserved with minimal damage. Patients with prior chemotherapy, radiotherapy, chemoradiotherapy, or surgical resection for ESCC or HNSCC were excluded, because their esophagus or pharynx was removed or too damaged to evaluate. Patients referred from another hospital with newly diagnosed ESCC were also included because they required more detailed examination (Fig 1) . The endoscopists were blinded to the endoscopic information. Patients with esophageal stricture, esophageal varices, or allergy to lugol dye solution were excluded.

Study Design

Patients were randomly assigned to receive primary WLI or primary NBI. To investigate whether a lesion detected by primary imaging could be identified subsequently by the other type of imaging, or whether a lesion missed by primary imaging could be identified subsequently by the other type of imaging, we performed both imaging methods in a back-to-back fashion so that primary WLI was followed by NBI and primary NBI was followed by WLI. To avoid affecting the first imaging results, the report of the first examination was completed before the second imaging was started.

To improve the quality of the reporting in the diagnostic accuracy study, we complied with the Standards for Reporting of Diagnostic Accuracy (STARD) initiative.[25] We set WLI as reference standard and NBI as index test.

Random assignment was performed in each case by an investigator using a computer-aided system on Medical Research Support Web site (Kyoto, Japan). This Web site was available only to the study participants. Using a minimization algorithm, the selection of the primary examination was balanced with respect to five stratification variables: institution, age (< 60 and ≥ 60 years), sex, alcohol consumption, and smoking habit.

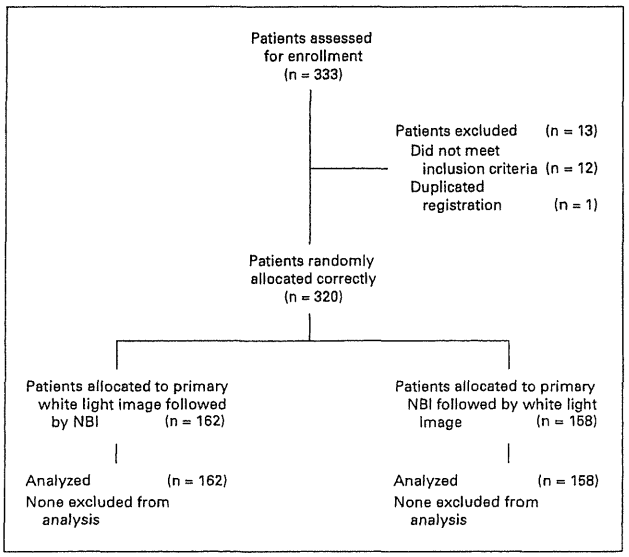

Fig 1. CONSORT diagram; overview of the study design. NBI, narrow band imaging.

Calculation of the Sample Size

For the purposes of this study, we set the probability for error (α) to .05 with a power of 0.80 (reflecting a β error of .2). Because there are no published comparative studies of NBI in ESCC patients, we estimated that the NBI system would increase the detection yield for superficial cancer by at least threefold compared with conventional WLI. This resulted in a calculated sample size of 250 patients (125 per group). Finally, we recruited an additional 50 patients in anticipation of instances of ineligibility or withdrawal during the examination because of discomfort (25 per group).

Endoscopic Examination

We used the same magnifying endoscope, with the capability for 80 times optical magnification (GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) for both WLI and NBI. The two imaging methods can be performed in a same video-endoscopy system (EVIS LUCERA system, Olympus Medical Systems, Tokyo, Japan). The details of the NBI system have been published elsewhere.[1,2,26,27] To maintain the quality of the endoscopic images, we used the same liquid-crystal color display for both imaging methods. Before the study started, all the participating endoscopists were trained using a central review of demonstrable NBI images of superficial squamous lesions (13 neoplasias and seven non-neoplastic lesions).

All endoscopic observations were made according to the protocol. During the first imaging, all parts of the oropharynx and hypopharynx were evaluated. The nasopharynx was not included the examination. After the first imaging was completed, an assistant physician immediately recorded the results on the case record form (CRF). After completion of the first imaging CRF, the second imaging of the oropharynx and hypopharynx was performed and the results were recorded on the CRF.

Next, all parts of the esophagus were evaluated using the same imaging as used for the H&N region. The endoscope was inserted to gain a view from the cervical esophagus to the esophagogastric junction, and the results were recorded on the CRF. The second imaging was performed on withdrawal of the endoscope, and the results were recorded on the CRF. During the procedure, we measured the examination time from start to finish of each imaging at each site. These procedure times included the evaluation of the lesion but not the biopsy procedure. The findings obtained by lugol chromoendoscopy are not included in this study.

Endoscopic Evaluation of Superficial Cancers

In this study, the real-time on-site diagnosis was evaluated because making an accurate diagnosis during an examination is clinically more important than a retrospective evaluation using a stored database. On WLI, if the lesion showed both a reddish color with uneven surface and disappearance of the vascular network pattern (Fig 2A), we diagnosed it as endoscopically suspected "superficial cancer." On NBI, if the lesion exhibited a well-demarcated brownish area as well as irregular microvascular patterns (Fig 2B), we diagnosed it as endoscopically suspected "superficial cancer." Details of these findings have been described previously.[7,8] If the lesion did not show these characteristics, the lesion was diagnosed as "non-cancer." Mucosal abnormalities were recorded with regard to endoscopic diagnosis, location, and size of the lesion.

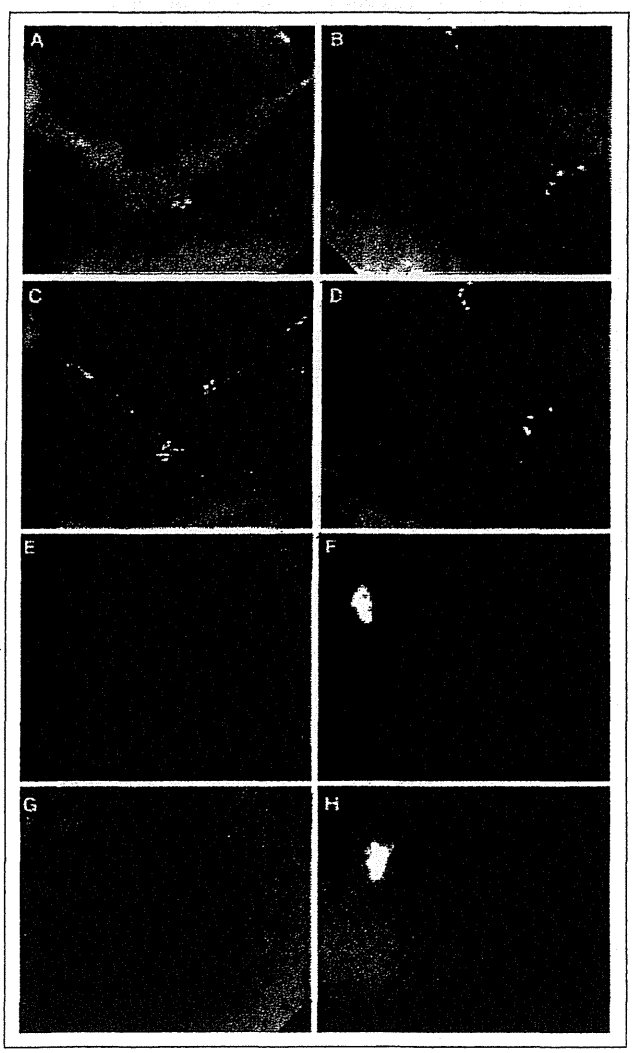

Fig 2. Superficial cancer in the head and neck region and esophagus. (A) White light imaging (WLI) shows a small reddish area (arrows) in the posterior wall of the hypopharynx. (B) Magnifying WLI shows a slightly reddish area with tiny microdots. (C) Narrow band imaging (NBI) shows a well-demarcated brownish area (arrows) in the posterior wall of the hypopharynx. (D) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as squamous cell carcinoma in situ. (E) WLI shows a slightly reddish and depressed lesion (arrows) in the esophagus, although it is difficult to detect by WLI alone. (F) Magnifying WLI shows a slightly reddish area with an irregular microvascular pattern. (G) NBI shows a well-demarcated brownish area (arrows). (H) Magnifying NBI shows many tiny dots in the brownish area. This lesion was diagnosed histologically as high-grade intraepithelial cancer.

Pathologic Evaluation

Biopsy specimens were taken from each lesion after the completion of both types of imaging. Histologic evaluation was performed by central review by four experienced pathologists (H.S., A.O., T.S., and H.W.) who were blinded to the recorded endoscopic assessment. Histologic diagnoses were made according to WHO criteria[23] and were classified into two groups. One group included superficial cancers and the other group included non-cancers such as parakeratosis and inflammation. Microinvasion was estimated by the subepithelial invasion. The final pathologic diagnosis was made by the agreement of three of the four pathologists.

Statistical Analysis

The absolute and relative frequencies for qualitative variables were calculated for each group. Statistical analysis was performed using SPSS version

Table 1. Characteristics of Patients

Characteristic	Primary WLI (n = 162) No.	%	Primary NBI (n = 158) No.	%	P
Age, years					
Median	64		64		
Range	39-84		46-84		.99
Male sex	143	88	141	89	.86
Alcohol habit					
Drinking duration, years	157	97	148	94	.19
Median	41		40		.17
Range	10-63		5-60		
Favorite beverage					
Beer	61	38	59	37	1.00
Shochu	66	41	55	35	.30
Sake	43	27	48	30	.71
Whisky	22	14	24	15	.75
Wine	8	5	7	4	1.00
Others	1	0.6	0	0	1.00
Hot flashes					
Formerly had hot flashes	117	72	109	69	.62
Currently has hot flashes	75	46	70	44	.91
Smoking habit					
No. of smokers	145	90	142	90	1.00
Smoking duration, years					
Median	37		40		
Range	1-61		5-61		.41
No. of packs per day					
Median	1		1		
Range	0.05-4		0.125-4		.64
No. of packs per year					
Median	41		42		
Range	0.5-180		1.3-160		.89
Esophageal cancer					
No. of patients newly diagnosed	110	68	115	73	.39
Previously treated EMR	52	32	43	27	.39
Duration from previous EMR, years					
> 1	17	10	20	13	.60
1	45	28	33	21	.16
Depth of invasion					
Tis-T1a	74	46	67	42	.57
T1b	25	15	20	13	.27
T2	12	7	22	14	.07
T3	49	30	46	29	.90
T4	2	1	3	2	.68

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; EMR, endoscopic mucosal resection.

17 software (SPSS, Chicago, IL). The continuous variables are expressed as medians and ranges. Continuous data were compared using the Mann-Whitney U test. Pearson's χ^2 test or Fisher's exact test was used to analyze categoric data to compare proportions. All P values were two-tailed, and a P value of $< .05$ was considered significant.

RESULTS

Between March 2005 and December 2005, 333 patients were enrolled onto this study (Fig 1). Twelve patients did not meet the inclusion criteria, and one was registered twice, so the remaining 320 patients were randomly assigned correctly into two groups: (1) 162 patients who underwent primary WLI followed by NBI, and (2) 158 patients who were examined by primary NBI followed by WLI.

The characteristics of the two groups are listed in Table 1. The two groups did not differ significantly in age, sex, alcohol consumption, smoking habits, or history of esophageal cancer treatment. In both groups, approximately 70% of the patients had newly diagnosed ESCC. Sixty-three (39%) patients in the primary WLI group and 71 (45%) patients in the primary NBI group had advanced ESCC deeper than the submucosal layer.

Table 2 provides the distribution of histologically confirmed superficial cancers. The total numbers of superficial cancer in the H&N region and the esophagus were 28 and 212, respectively. Total numbers of histologically confirmed non-cancer were 36 and 38 in each region. In all patients, superficial cancers were detected in 8% (26 of 320) in the H&N region and in 38% (121 of 320) in the esophagus. Multiple cancers were found in 0.6% of the patients in the H&N region and in 12% in the esophagus. The number of patients with superficial cancer, total number of superficial cancers, and their sizes and distribution did not differ between the two groups.

The diagnostic yields for superficial cancer using primary WLI and primary NBI detection are summarized in Table 3. The total numbers of superficial cancers detected by primary imaging differed between the two groups. In the H&N region, primary NBI detected all (100%; 15 of 15) of the superficial cancers, but primary WLI detected only one lesion (8%; 1 of 13). In the esophagus, only 58 (55%) lesions were detected by primary WLI, whereas 104 (97%) lesions were detected by primary NBI. All these differences were statistically significant ($P < .001$). The detection rate was significantly higher with primary NBI than with primary WLI, even for small lesions (< 10 mm in diameter) in both the H&N region ($P < .001$) and the esophagus ($P = .03$).

In the back-to-back analysis, secondary NBI after primary WLI significantly increased the detection rate in both the H&N region (8% v 77%; $P < .001$) and esophagus (55% v 95%; $P < .001$; Appendix Table A1, online only). In contrast, secondary WLI after NBI significantly decreased the detection rate (Appendix Table A1). Moreover, 16 (57%) superficial cancers in the H&N region and 48 (23%) superficial cancers in the esophagus were detected only by NBI (Appendix Table A2, online only). In contrast, no lesion was detected only

Table 2. Distribution of Histologically Confirmed Superficial Cancer According to Lesion in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of patients	12	7	3.3 to 11.4	14	9	4.4 to 13.3	.66
No. of lesions per patient							
1	12	7	3.3 to 11.4	14	9	4.4 to 13.3	> .999
≥ 2	1	0.6	−0.6 to 1.8	1	0.6	−0.5 to 1.9	
Total No. of superficial neoplasias	13			15			
Size threshold, mm							
< 10	7			10			.50
11-20	5			5			
≥ 21	1			0			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	10			15			.09
Microinvasive cancer	3			0			
Esophagus							
No. of patients	58	36	28.4 to 43.2	63	40	32.2 to 47.6	.49
No. of lesions per patient							
1	39	24	17.4 to 30.7	43	27	20.3 to 34.2	> .999
≥ 2	19	12	6.7 to 16.7	20	13	7.4 to 17.9	
Total No. of superficial cancers	105			107			
Size threshold, mm							
< 10	18			18			.91
11-20	21			19			
≥ 21	66			70			
Histologic diagnosis							
High-grade intraepithelial neoplasia or carcinoma in situ	73			84			.16
Microinvasive cancer	32			23			

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

Table 3. Diagnostic Yield of Primary WLI and Primary NBI for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI (n = 162)			Primary NBI (n = 158)			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck region							
No. of superficial cancers	1/13	8	0.2 to 36.0	15/15	100	78.2 to 100	< .001
Size of superficial cancer, mm							
< 10	0/7	0	0 to 41.0	10/10	100	69.2 to 100	< .001
11-20	1/5	20	0.5 to 71.6	5/5	100	48.7 to 100	.12
≥ 21	0/1	0	0.0 to 0.0	to			—
Esophagus							
No. of superficial cancers	58/105	55	45.2 to 65.0	104/107	97	92.0 to 99.4	< .001
Size of superficial cancer, mm							
< 10	7/18	39	17.3 to 64.3	17/18	94	72.7 to 99.9	.03
11-20	7/21	33	14.6 to 57.0	18/19	95	74.0 to 99.9	.02
≥ 21	44/66	67	54.0 to 77.8	69/70	99	92.3 to 100	< .005

Abbreviations: WLI, white light imaging; NBI, narrow band imaging.

by WLI, except one lesion of > 20 mm in the esophagus. No lesions were undetected by both WLI and NBI in either region.

Table 4 summarizes the diagnostic performance of primary WLI and primary NBI for detecting superficial cancer. The sensitivity of primary NBI was significantly higher than that of primary WLI in both the H&N region (100% *v* 7.7%; $P < .001$) and the esophagus (97.2% *v* 55.2%; $P < .001$). Accuracy was also significantly higher for primary NBI than for primary WLI in both regions (85.7% *v* 62.9%, $P = .02$ and 88.9% *v* 56.5%, $P < .001$, respectively). Specificity was not significantly different in the two regions ($P = .28$ and $P = .33$, respectively). The positive predictive value did not differ between the two imaging techniques, but the negative predictive value was significantly higher for primary NBI than for primary WLI in both the H&N region ($P = .02$) and the esophagus ($P < .002$).

The median procedure times of primary WLI and primary NBI for the H&N region were 120 seconds (range, 34 to 275 seconds) and 162 seconds (range, 30 to 525 seconds), respectively. Those for the esophagus were 95 seconds (range, 30 to 360 seconds) and 135 seconds (range, 30 to 616 seconds), respectively. These differences were statistically significant ($P < .001$). The procedure times in the secondary imaging in the back-to-back experiments also differed significantly between WLI and NBI in both regions (Appendix Table A3, online only). There were no serious adverse events related to examination with either procedure. All patients tolerated both procedures well.

DISCUSSION

This study clearly demonstrates that NBI is a more sensitive method for detecting and diagnosing superficial SCC in the H&N region and the esophagus. According to the concept of "field cancerization,"[28] patients with ESCC or HNSCC are at high risk for the development of multiple SCCs. In the clinical context, the early detection strategy for superficial SCC is the same between patients at high risk and those at risk because of heavy drinking, smoking, or aldehyde dehydrogenase 2 deficiency.[20-35] In addition, detection technique should not only be sensitive but should also be easily applicable. From this perspective, NBI is easily applied with a modicum of experience and will have a rapid learning curve compared with WLI. Thus, NBI is the ideal method for effectively detecting superficial SCC.

Table 4. Diagnostic Performance of Primary WLI and Primary NBI Observation for Detection of Superficial Cancer in the Head and Neck Region and the Esophagus

Variable	Primary WLI			Primary NBI			P
	No.	%	95% CI	No.	%	95% CI	
Head and neck							
Sensitivity	1/13	7.7	0.2 to 36.0	15/15	100	100	< .001
Specificity	21/22	95.5	77.2 to 99.9	11/14	78.6	54.6 to 98.1	.28
Accuracy	22/35	62.9	47.6 to 76.4	26/29	86.7	72.6 to 97.8	.02
PPV	1/2	50	1.3 to 98.7	15/18	83.3	58.6 to 96.4	.37
NPV	21/33	63.6	54.1 to 79.6	11/11	100	100	.02
Esophagus							
Sensitivity	58/105	55.2	45.2 to 65.0	104/107	97.2	92.0 to 99.4	< .001
Specificity	12/19	63.2	38.4 to 83.7	8/19	42.1	20.3 to 66.5	.33
Accuracy	70/124	56.5	47.3 to 65.3	112/126	88.9	82.1 to 93.8	< .001
PPV	58/65	89.2	79.1 to 95.6	104/115	90.4	85.3 to 95.1	.80
NPV	12/59	20.3	11.0 to 32.8	8/11	72.8	39 to 94	< .002

Abbreviations: WLI, white light imaging; NBI, narrow band imaging; PPV, positive predictive value; NPV, negative predictive value.

Detecting cancer at an early stage is an optimal strategy for preventing the development of advanced cancer and improving survival. Furthermore, early detection uses a minimally invasive treatment (eg, endoscopic resection) with curative intent.[8,36-38] In fact, in our study, 75% (21 of 28) of the superficial HNSCCs were completely removed by endoscopic resection or biopsy alone, while early detection of HNSCC had been quite difficult. These results provide us with new diagnostic and treatment strategies for ESCC patients, because the risk of development of HNSCC after esophagectomy is quite high.[21]

As the criteria for diagnosing superficial SCC by NBI, we used two endoscopic findings: a well-demarcated brownish area and an irregular microvascular pattern.[7-9] Using only these two findings, the sensitivity of primary NBI for the diagnosis of superficial SCC was 100% in the H&N region and 97.2% in the esophagus. The diagnostic accuracy was nearly 90%. These results indicate that these NBI findings are quite useful for the accurate diagnosis of superficial SCC.

Lugol chromoendoscopy is useful for the detection of superficial ESCC.[2-3] However, the administration of lugol solution is time-consuming, and accurate diagnosis by lugol chromoendoscopy is difficult[4] because the staining pattern shows wide variations.[2] This increases the incidence of false-positive lesions and leads to unnecessary biopsies. In contrast, NBI is easily manipulated and shows high sensitivity. Thus, NBI could reduce the number of unnecessary biopsies and shorten examination time. Furthermore, lugol chromoendoscopy is more invasive than both WLI and NBI, and WLI is still the gold standard for cancer screening. Therefore, we did not compare the diagnostic yield of NBI and lugol chromoendoscopy, and we used WLI as the standard reference to compared the diagnostic yield of WLI and NBI.

NBI required a significantly longer examination time than WLI. This might be related to the high detection rate and more frequent time spent in magnification during NBI, because if the lesions were not seen by WLI, no magnification was performed. The actual time difference between NBI and WLI was only 20 to 42 seconds. This is clinically acceptable, because the important time issue is not that NBI takes slightly longer than WLI, but rather that endoscopists spend more time in the careful observation of high-risk patients.

In this study, ESCC patients referred from another hospital were included. Even if the biopsies were previously done, the earlier biopsy sites were healed by the time of this study and were not generally detectable by either imaging method. Therefore, we thought that it was not a confounding factor.

The same endoscopists performed both imaging procedures in this study, whereas the endoscopists ideally should be separated and blinded to each imaging procedure. However, it was clinically impossible to change and blind the endoscopists during this series of examinations. Furthermore, the result produced with NBI first followed by WLI might underestimate the benefit of NBI because NBI is more sensitive than WLI. However, the detection and diagnosis of superficial SCC by NBI was significantly better than that using WLI in both the H&N region and the esophagus, regardless of whether NBI was primary or secondary. These results indicate that NBI should be the standard examination.

Significant detection results seen in this study were all achieved without the newest generation high-definition endoscope. If we use the newest high-definition endoscope with NBI, the rates of detection might increase compared with those found in this study. Furthermore, the endoscopy system used in this study and in most Asian countries was different from those used in North America and Europe.[26,27] However, we previously reported that even the nonmagnifying laryngoscope based on same system as that used in North America and Europe could dramatically improve the visualization of both the brownish area and irregular microvascular patterns.[39] Therefore, we believe that differences in the system are no longer as important as careful observation by NBI.

In conclusion, NBI combined with magnifying endoscopy significantly improved the detection rates for SCC with quite high sensitivity, and this new image-enhanced technology can be applied easily in clinical practice. Furthermore, early detection facilitates the potential of minimally invasive treatment, such as endoscopic resection or partial surgical resection.

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Appendix

Results

Among the 28 superficial head and neck squamous cell carcinomas (HNSCCs) detected, 16 lesions were treated with endoscopic resection, five lesions disappeared after only biopsy, and one lesion was treated with radiotherapy. The remaining six lesions were not treated, because the concomitant esophageal cancers had distant metastasis. Among 16 lesions removed by endoscopic resection, seven lesions were carcinoma in situ and the remaining nine lesions were microinvasive SCC. With a median follow-up of 33 months (range, 6 to 59 months), no patients developed lymph node metastasis from HNSCC.

Among the 212 superficial esophageal squamous cell carcinomas, those with accompanying advanced cancers and those with submucosal invasive cancers were treated with surgery or chemotherapy with or without radiotherapy. The remaining superficial cancers within the mucosal layer were removed by endoscopic resection.

Discussion

Most research on the endoscopic detection and diagnosis of GI disease has been performed by retrospectively reviewing static images in a database and selecting only the best of the stored images (Singh R: Endoscopy 40:457-463, 2008; Sharma P: Gastroenterology 133:454-464, 2007; Chiu HM: Gut 56:373-379, 2007). Evaluating selected stored images by retrospective review does not exclude the