Efficacy and safety of 1-step transnasal endoscopic nasobiliary drainage for the treatment of acute cholangitis in patients with previous endoscopic sphincterotomy (with videos)

Takao Itoi, MD, Takashi Kawai, MD, Atsushi Sofuni, MD, Fumihide Itokawa, MD, Takayoshi Tsuchiya, MD, Toshio Kurihara, MD, Chika Kusano, MD, Yutaka Saito, MD, Takuji Gotoda, MD

Tokyo, Japan

Background: Endoscopic nasobiliary drainage (NBD) for the treatment of acute cholangitis is an accepted method. A recently developed ultrathin transnasal videoendoscope is minimally invasive, even for patients who are critically ill.

Objective: To evaluate the clinical efficacy and safety of 1-step NBD by transnasal videoendoscopy (TNE).

Design: Prospective case study.

Setting: This study was performed at Tokyo Medical University Hospital.

Patients: Twenty patients with acute cholangitis who had previously undergone an endoscopic sphincterotomy (ES); including 10 with bile-duct stones, 8 with pancreatic cancers, 1 with chronic pancreatitis, and 1 with benign biliary stricture, were enrolled in this study. An indwelling self-expandable metallic stent (SEMS) was placed in all patients with pancreatic cancers.

Intervention: All patients underwent NBD via front-viewing TNE. A 5F NBD catheter was placed into the bile duct.

Main Outcome Measurement: The efficacy and safety of this technique.

Results: The transnasal insertion of TNE was feasible in all patients, and none had epistaxis. Abdominal pain, fever, and jaundice were improved at 24 hours after the procedure in the majority of patients. The mean procedural time was 18.1 minutes. One patient pulled out the NBD catheter. None of the patients died. TNE-NBD was achieved in 19 patients (95%).

Limitations: Maneuverability of the TNE, limited to patients with a previous ES or the placement of an SEMS.

Conclusions: NBD that uses TNE may be a useful and novel technique for the treatment of acute cholangitis in patients with previous ES. (Gastrointest Endosc 2008;68:84-90.)

At the present time, endoscopic drainage should be considered the drainage technique of first choice for acute cholangitis.[1-5] Endoscopic nasobiliary drainage (NBD) for treatment of acute cholangitis is an accepted method.[4,6,7] Recently, ultrathin transnasal videoendoscopy (TNE) was developed for various GI conditions.[8,9] TNE is less invasive for patients who are critically ill, it is less stressful to patients, and also has limited hemodynamic effects compared with the transoral videoendoscope.[10] Apart from its main purpose, some endoscopists describe unique reports about another indication of TNE for nasoenteral feeding tubes or the conversion from an orobiliary to a nasobiliary tube.[11,12] In this study, we evaluated the efficacy and safety of 1-step TNE-NBD for the treatment of acute cholangitis in patients who had previously undergone an endoscopic sphincterotomy (ES). This is the first report, to our knowledge, on NBD with TNE for the treatment of acute cholangitis.

Abbreviations: ES, endoscopic sphincterotomy; NBD, nasobiliary drainage; SEMS, self-expandable metallic stent; TNE, transnasal videoendoscopy.

0016-5107/$32.00
doi:10.1016/j.gie.2007.11.050

PATIENTS AND METHODS

Patients

Between January 2006 and February 2007, at Tokyo Medical University Hospital, 20 patients who had previously

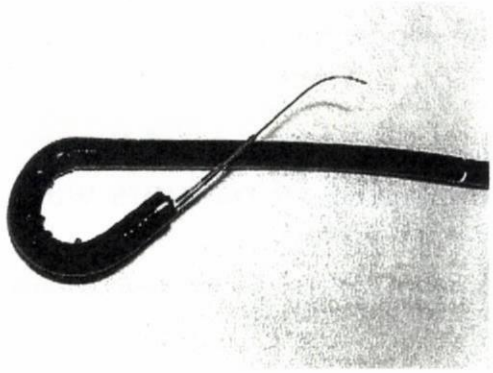

Figure 1. The complete TNE instrument, with the catheter and guidewire.

Capsule Summary

What is already known on this topic

- Endoscopic nasobiliary drainage (NBD) is an accepted treatment of acute cholangitis.
- Transnasal videoendoscopy (TNE) is less invasive, less stressful, and has limited hemodynamic effects compared with transoral videoendoscopy.

What this study adds to our knowledge

- In 20 patients with acute cholangitis and a previous endoscopic sphincterotomy, endoscopic NBD via TNE improved pain, fever, and jaundice within 24 hours for most patients.

undergone an ES and who were being seen for acute cholangitis that required endoscopic biliary drainage were enrolled in this study. The diagnosis of acute cholangitis was based on the presence of clinical (fever, leukocytosis, and abdominal pain) and radiographic (dilated bile duct by biliary obstruction) findings. Emergency biliary drainage was performed if any of the following conditions were present in addition to suspected cholangitis: (1) fever (temperature >39°C), (2) septic shock (systolic blood pressure <90 mm Hg), (3) increasing abdominal pain with clinical evidence of peritoneal inflammation (right upper quadrant pain with guarding on palpation), and (4) an impaired level of consciousness on admission. In patients without these features, endoscopic biliary drainage was performed only if the patient did not improve within 24 hours of conservative management (fever and leukocytosis). All patients were treated with intravenous antibiotics. Exclusion criteria were intact major duodenal papilla; a prior Roux-en-Y or Billroth II gastrojejunostomy; or ear, nose, and throat surgery. Written informed consent for the procedures and treatment were obtained from all patients or, in the case of impaired consciousness, their family. This study was approved by the institutional review board of our institution.

TNE-NBD procedure

ERCP was performed with a commercially available transnasal endoscope (front viewing, working length 1.100 mm; field of view 120°; outer diameter 5.9 mm; working channel 2.0 mm, tip deflection 210° up, 90° down, and 100° left and right) (FF-470N5; Fujinon Toshiba ES Systems Co, Ltd, Tokyo, Japan) (Fig. 1). The TNE-NBD procedure was performed by an experienced endoscopist (T.I.) with experience with TNE and ERCP. Before the TNE, each nasal cavity is sprayed with 0.05% naphazoline nitrate for vasoconstriction and then sprayed with 4% lidocaine solution, and the oropharynx is sprayed with 8% lidocaine solution as a topical anesthesia. Endoscopic procedures took place with the patient under sedation with flunitrazepam, if available. The patient was placed in a prone position. The TNE endoscope was inserted under direct vision through the most patent nostril to the pharynx. If insertion was not possible, then the other nostril was tried. The endoscope was advanced into the first and second portions of the duodenum. After confirming the major duodenal papilla, the tip of the endoscope was pressed against the orifice of the bile duct at a raised angle of the endoscope to insert a thin cannula (PR-110Q; Olympus Medical Systems, Tokyo, Japan) to perform a cholangiography. The catheter was expected to come out at the 6-o'clock position on the video display. After deep cannulation of the catheter into the common duct, a 0.018-inch stiff-type guidewire (Pathfinder; Boston Scientific Japan, Tokyo, Japan) was advanced into the right or left intrahepatic bile duct. When deep cannulation was difficult, a 0.025-inch Radifocus guidewire (Terumo Co, Ltd, Tokyo, Japan) was used. For patients with an indwelling self-expandable metallic stent (SEMS), insertion of the tip of the endoscope into the SEMS was attempted. When the orifice of the bile duct could not be confirmed by the standard method, the endoscope was advanced to the third portion of the duodenum, the tip of the endoscope was then rotated in a retroflexed position, and the papilla was confirmed while pulling back the tip, and then the catheter was inserted. When more than 30 minutes was needed for cannulation into the bile duct after endoscope insertion, the TNE-NBD procedure was discontinued, and ERCP with a side-viewing duodenoscope in a standard manner was performed. If bile was sufficiently aspirated, then injection of contrast medium was avoided to prevent further contamination of the biliary tree. A 5F straight-tip NBD catheter (ENBD-5-NAG; Cook Endoscopy Inc, Winston-Salem, NC) was then placed after the guidewire. Immediately after NBD catheter placement, in the ERCP room, bile was first aspirated, without irrigating with saline solution. After biliary drainage, the amount and characteristics of discharge from the NBD catheter were carefully observed every 8 hours. If a blockage of the NBD catheter was suspected, then a chief physician attempted to aspirate bile first, before irrigating with saline solution.

TABLE 1. Characteristics of patients who were undergoing an emergency TNE-NBD

Sex (M/F)	9/11
Mean ±SD age (y) (range)	67.2 ± 11.0 (43-87)
Laboratory values, mean (range)	
WBC ($\times 10^3/\mu L$)	11.2 (5.8-19.8)
Alanine transaminase (U/L)	278 (98-963)
Aspartate transaminase (U/L)	232 (81-1472)
Alkaline phosphatase (U/L)	795 (416-2153)
Gamma glutamyl transpeptidase (U/L)	538 (191-1843)
Bilirubin (mg/L)	5.64 (4.88-12.93)
Clinical presentation (no. [%])	
RUQ or epigastric pain	19 (95)
Fever	16 (80)
Jaundice	15 (75)
Hypotension	3 (15)
Peritonism	2 (10)
Etiology	
Common bile duct stones	10
Pancreatic carcinoma	8
Chronic pancreatitis	1
Postoperative biliary stricture	1
Previous gastrectomy: Billroth I reconstruction	1
Previous SEMS placement, no. (%)	8 (40)

WBC, White blood cell count; *RUQ*, right upper quadrant.

TABLE 2. Results of an emergency TNE-NBD

Success rate, no. patients (%)	19/20 (95)
Mode of sedation	
Conscious sedation	14
No sedation	6
Mean procedure time (min)	18.1 (range 9.5-31.2)
Clinical progress 24 h after TNE-NBD, no. patients (%)	
Pain improved	19/19 (100)
Fever improved	15/16 (94.7)
Jaundice improved	12/15 (80.0)
Complications after TNE-NBD, no. patients	1*
Blood culture, no. patients (%)	
Positive	8 (40)
Negative	12 (60)
Color of bile, no. patients (%)	
Purulent	9 (45)
Turbid	11 (55)

*The patient pulled out the catheter.

The patients were closely observed for evidence of procedure-related complications. Clinical improvement was defined as the normalization of fever, leukocytosis, hypotension, peritonitis, and altered sensorium and renal functions. Peripheral blood and biochemical tests were performed before the ERCP and then on days 1, 3, and 7 after the ERCP, or more often if indicated. After clinical improvement, a second ERCP in a standard manner was performed. Primary outcome measures included complications related to the ERCP and the clinical outcome.

RESULTS

The characteristics of the patients who were undergoing an emergency TNE-NBD are summarized in Table 1. A TNE was feasible in all patients, and none had epistaxis. Conscious sedation was not used in 6 patients (30%) for a number of reasons (eg, refusing administration of flurnitorazepam or a history of an adverse reaction to flunitrazepam) in 4 patients and 2 patients who were critically ill, respectively. Among the 6 unsedated patients, there was slight nasal pain in 2, but no vasovagal reaction occurred in any patient. All patients agreed that they would undergo all procedures from transnasal insertion of TNE endoscope to placement of the NBD catheter again if necessary.

TNE-NBD was achieved in 19 patients (95%) (Table 2). The mean procedural time was 18.1 minutes. In one patient, in whom an SEMS had previously been placed, TNE-NBD failed, because cannulation was difficult because of the duodenal stump protruding by 2 cm. This patient immediately underwent NBD by using a conventional duodenoscope. Abdominal pain, fever, and jaundice were improved at 24 hours after the ERCP in the majority of patients (Table 2). One patient pulled the NBD catheter out on the second day after TNE-NBD. This patient underwent a second ERCP by using conventional duodenoscopy to treat the cholangitis. The mean (±SD) duration of drainage was 6.3 ± 2.8 days (range 2-14 days). There were no fatalities.

The direct papillary approach by using the bend of the endoscope in the second portion was possible in 6 of 8 and 9 of 12 patients with and without an indwelling SEMS, respectively. In 4 patients without an indwelling SEMS, the orifice of the bile duct after an ES could be clearly observed

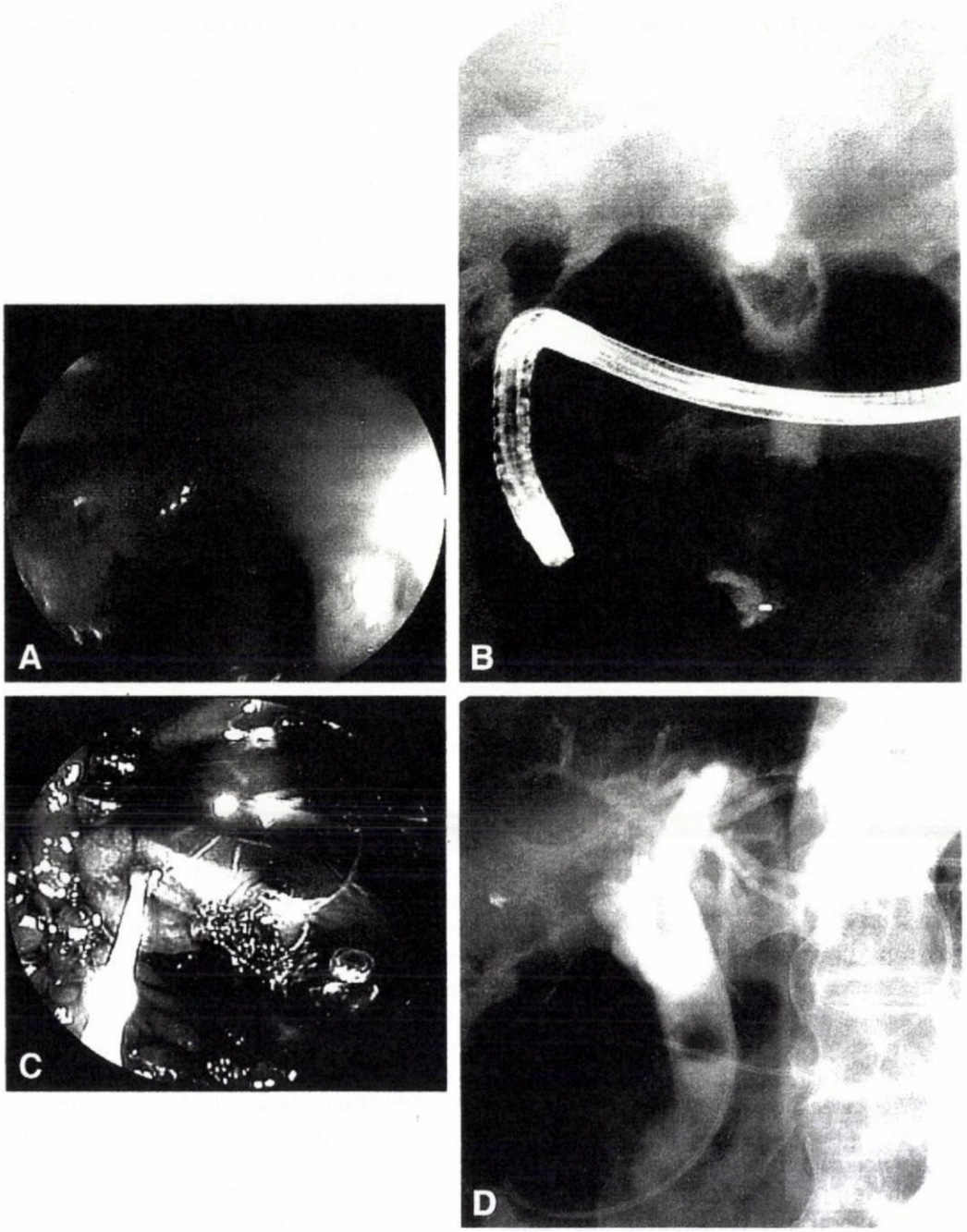

Figure 2. A, Thin catheter was inserted into the bile duct. **B,** Cholangiogram showed bile-duct stones. **C,** Infectious dirty bile flows after insertion of guidewire into the bile duct. **D,** 5F nasobiliary drainage tube was placed into the bile duct. (**A-D** are all from the same case.)

(Video 1, available online at www.giejournal.org), and cannulation was possible under direct observation (Fig. 2A). In the other 4 patients, the orifice could not be clearly observed, but cholangiography was possible by pressing the catheter tip against the orifice, and deep cannulation was subsequently performed by using the Radiofocus guidewire. In the 6 patients with a SEMS, the tip of the endoscope was directly inserted into the distal side of the SEMS (Fig. 3) (Video 2, available online at www.giejournal.org). For the 4 patients in whom direct cannulation into the bile-duct orifice in the second portion was not possible, the endoscope was rotated in a retroflexed position in the transverse part, and cannulation was performed (Fig. 4). The insertion of a 5F NBD catheter into the bile duct was possible in all 19 patients in whom duodenal cannulation was achieved (Fig. 2B to D). The endoscope could be removed without complications in all patients. Bile

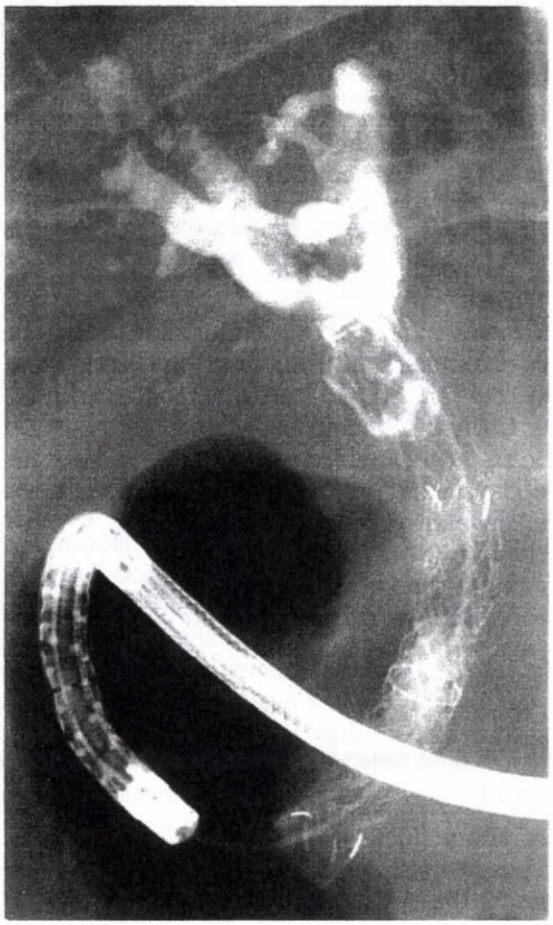

Figure 3. A cholangiogram, showing obstruction of the stent.

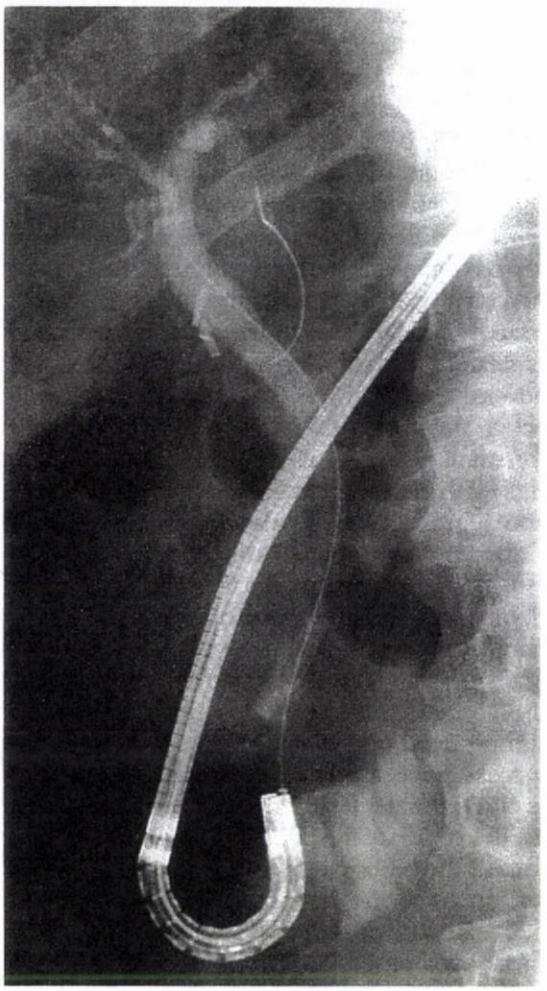

Figure 4. The catheter was inserted by rotating the endoscope tip.

aspirated immediately after NBD catheter fixation was purulent in 9 and turbid (Fig. 2C) in 11 patients (Table 2). A bile culture was positive in 8 patients.

The primary disease was treated by an elective ERCP after the remission of cholangitis in all patients. Stones were cleared from the bile duct in 10 patients (100%). In 8 patients with an SEMS obstruction from food impaction or debris, the SEMS was removed and replaced with a new one in 2 patients, and the stent was cleaned by using a basket or balloon catheter in the other 6 patients. In one patient with chronic pancreatitis and postoperative bile-duct stenosis, a 10F plastic stent was placed, and the patient was discharged.

DISCUSSION

In this preliminary study that used TNE for the placement of the NBD catheter, we demonstrated that TNE-BD was safe and feasible in patients with acute cholangitis who had a history of a prior ES or a SEMS placement, although all but 2 patients were not critically ill and could have undergone a regular ERCP. We think that TNE for an ERCP showed certain advantages: patients, especially patients who were critically ill, did not require sedation, although the ERCP procedure without sedation is not necessarily applicable in North America, where sedation is normal, and TNE is not particularly popular. It may be cumbersome to convert from an orobiliary to a nasobiliary tube after the endoscope is withdrawn. Furthermore, the endoscopist may be at risk of infectious diseases because of penetration of the skin from biting; the patients may suffer complications that result from the blind passage of a finger or a forceps into the posterior pharynx.[12] To avoid these unnecessary risks, a 1-step method that uses TNE-NBD has advantages. Moreover, although the patients were placed in the prone position in this study, one of the possible advantages of this technique would be the ability to do NBD at the bedside, with little or no manipulation of the patient and as little sedation as possible. It is possible to perform the technique with the patients supine and unsedated.

TNE has some disadvantages. Adverse effects of TNE are rare; the incidences of adverse effects range from 1.5% to 22.6%.[8-10] The most common adverse effect is a difficult

nasal insertion. Dumortier et al[9] reported that failures with TNE were more likely to occur in young women who had a TNE with instruments larger than 5.9 mm. In our study, a TNE was successful in all patients, but no inference could be made because of the small sample size. With regard to adverse effects, slight nasal pain was noted in 33% of the unsedated patients, but no epistaxis or vasovagal reaction occurred in any patient. Furthermore, all unsedated patients tolerated the TNE-NBD procedure. Further investigation with a large number of patients is necessary, and the development, in the near future, of more flexible and smaller endoscopes may overcome the adverse effects of transnasal insertion. However, the projected population that this technique would benefit is very small. Theoretically, it would be appropriate for patients who have cholangitis with a prior ES and who are too ill to consider conscious sedation. Otherwise, conventional endoscopic treatment would be preferable. This study should perhaps be followed by another study that looks specifically at this population.

Cannulation succeeded in 19 of the 20 patients, even though the TNE endoscope was front viewing, for which 2 reasons are considered. One reason is that the short and strong bend of TNE enabled us to increase not only the success rate of cannulation but also the insertion force of the NBD catheter by tightly pressing the endoscope tip against the orifice of the papilla. The second reason is that we limited the participants to the patients without intact papilla, such as the patients who received an ES or SEMS, because cannulation into the intact papilla by using commercially available TNE is still expected to be difficult and may increase the risk of pancreatitis. Interestingly, in addition to cannulation, observation of the orifice of the bile duct was possible in some cases after an ES. Furthermore, because the insertion of the endoscope tip into the distal side of SEMS is easy in cases of SEMS, TNE-NBD can be performed comparatively easily. However, it should be kept in mind that cannulation may not be possible when the duodenal stump of the SEMS is long, even though the bend of the endoscope tip is maximum and is performed by endoscopists skilled in the procedure.

If the major papilla is looked up at from below with a short endoscope, then, theoretically, deep cannulation to the bile duct with the catheter is easier than looking down on it with a long endoscope. However, even with a maximum up angulation, the tip of the endoscope usually cannot be turned up in the duodenal lumen, because the curve angle of the TNE is too large. Therefore, at full angulation, the endoscope should be rotated along its axis into the third portion of the duodenum and then returned to the original position (Fig. 4). This avoids the endoscope catching on the inferior duodenum angle, and when the inferior duodenum angle is overcome, then the papilla must be located. Naturally, this operation is slightly complicated. There may be a strong insertion resistance to propel the 5F NBD catheter through the working channel, because the tip of the endoscope is angulated so steeply. However, the merit of the long endoscope is not needing much power to advance the NBD catheter by tightly pressing the endoscope tip against the orifice of the papilla. The demerit is that there is some trouble in performing deep cannulation with a guidewire into the bile duct. Therefore, we think that the long endoscope position is better than the short endoscope for the TNE-NBD procedure.

Essentially, there are 2 endoscopic techniques for biliary decompression: NBD or an indwelling stent. Two prospective randomized studies demonstrated that endoscopic biliary decompression, whether by the NBD catheter or an indwelling stent, is an effective treatment for acute cholangitis.[6,7] Although NBD catheters are at risk of kinking and of being pulled out by the patients, the advantages of NBD are that it facilitates follow-up cholangiography, it can be used for the chemical dissolution of gallstones and for the sampling of bile for bacterial culture, and its patency can be maintained via lavage. In several studies on NBD for patients with acute cholangitis, stent diameters used were more than 6.5F. In the present study, because the diameter of the working channel was 2 mm, we could only use the 5F NBD catheter. Although it cannot be denied that this study included patients in whom biliary ductal clearance and drainage may have been possible with 1 session when using the conventional approach, the 5F NBD catheter was effective for the treatment of acute cholangitis because of our thorough attention to drainage. However, we think that a 5F small catheter may not consistently provide adequate drainage, especially in the presence of purulent bile. Therefore, TNE-NBD is not a primary method of choice but is an alternative in severe cholangitis when conventional ERCP may not be possible in patients considered at high risk for sedation. Moreover, in the present study, because we used concomitant antibiotic drugs, we cannot determine exactly the extent to which clinical improvement depended on TNE-NBD or antibiotics. Nevertheless, we believe that TNE-NBD contributes to the clinical improvement, if drainage is sufficiently maintained.

In conclusion, although further cases should be accumulated and the cases in which TNE-NBD is indicated are limited, NBD with TNE may be a useful and novel technique for the treatment of acute cholangitis in patients who have undergone ES.

ACKNOWLEDGMENTS

The authors thank Fuminori Moriyasu, Shujiro Tsuji, Kentaro Ishii, and Nobuhito Ikeuchi for their valuable help. The authors also thank J. Patrick Barron of the International Medical Communications Center of Tokyo Medical University for his review of this article.

DISCLOSURE

The authors report that there are no disclosures relevant to this publication.

REFERENCES

1. Leung JWC, Chung SCS, Sung JJY, et al. Urgent endoscopic drainage for acute suppurative cholangitis. Lancet 1989;10:1307-9.
2. Cotton PB. Endoscopic drainage for suppurative cholangitis. Lancet 1989;II:213.
3. Ikeda S, Tanaka M, Yoshimoto H, et al. Endoscopic biliary drainage for acute obstructive cholangitis: analysis of 100 consecutive patients. Dig Endosc 1990;2:214-7.
4. Lai ESC, Paterson IA, Tam PC, et al. Severe acute cholangitis: the role of emergency nasobiliary drainage. Surgery 1990;107:268-72.
5. Lai EC, Mok FP, Tan ES, et al. Endoscopic biliary drainage for severe acute cholangitis. N Engl J Med 1992;326:1582-6.
6. Lee DWH, Chan ACW, Lam YH, et al. Biliary decompression by nasobiliary catheter or biliary stent in acute suppurative cholangitis: a prospective randomized trial. Gastrointest Endosc 2002;56:361-5.
7. Sharm BC, Kumar R, Agarwal N, et al. Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis. Endoscopy 2005;37:439-43.
8. Abraham N, Barkun A, LaRocque M, et al. Predicting which patients can undergo upper endoscopy comfortably without conscious sedation. Gastrointest Endosc 2002;56:180-9.
9. Dumortier J, Napoleon B, Hedelius F, et al. Unsedated transnasal EGD in daily practice: results with 1100 consecutive patients. Gastrointest Endosc 2003;57:198-204.
10. Kawai T, Miyazaki I, Yagi K, et al. Comparison of the effects on cardiopulmonary function of ultrathin transnasal versus normal diameter transoral esophagogastroduodenoscopy in Japan. Hepatogastroenterology 2007;54:770-4.
11. Külling D, Bauerfeind P, Fried M. Transnasal versus transoral endoscopy for the placement of nasoenteral feeding tubes in critically ill patients. Gastrointest Endosc 2000;52:506-10.
12. Shah SMA, Barkin JS. Conversion from an orobiliary to a nasobiliary tube: a hands-off method. Gastrointest Endosc 2007;65:355-6.

Received July 2, 2007. Accepted November 24, 2007.

Current affiliations: Department Gastroenterology and Hepatology (T.I., T. Kawai, A.S., F.I., T.T., T. Kurihara), Tokyo Medical University, Endoscopic Center (C.K., Y.S., T.G.), National Cancer Center, Tokyo, Japan.

Reprint requests: Takao Itoi, MD, Department of Gastroenterology and Hepatology, Tokyo Medical University, Shinjuku-ku, Nishishinjuku 6-7-1, Tokyo, Japan.

Endoscopic diagnosis of pharyngeal carcinoma by NBI

Authors S. Nonaka, Y. Saito

Institution Division of Endoscopy, National Cancer Center Hospital, Tokyo, Japan

Bibliography
DOI 10.1055/s-2007-995433
Published online
11 February 2008
Endoscopy 2007; 39:
347–351 © Georg Thieme
Verlag KG Stuttgart · New York
ISSN 0013-726X

Corresponding author
Y. Saito, MD, PhD
Division of Endoscopy
National Cancer Center Hospital
5-1-1 Tsukiji
Chuo-ku
Tokyo, 104-0045
Japan
Fax: +81-3-35423815
ytsaito@ncc.go.jp

Head and neck cancer, especially pharyngeal cancer, frequently co-exist with esophageal cancer, but pharyngeal cancer has proven difficult to detect in such cases before its progression to an advanced stage. Several recent reports have indicated that narrow-band imaging (NBI) endoscopy with magnification is able to improve the detection of superficial pharyngeal cancer. NBI is a relatively new optical technology based on limiting the depth of light penetration into the mucosa. The recognition of these lesions is dramatically improved and the microvascular structure of the mucosal surface is significantly enhanced by NBI. As a result, NBI enables more accurate diagnosis and increases the detection rate of superficial pharyngeal cancer. This particular field has only been developed in recent years, however, and there are still a number of problems that need to be addressed in the future. It will be necessary to accumulate and evaluate resected specimens and follow up patients in order to establish the appropriate criteria for curative endoscopic treatment in these patients. The ease in using NBI in combination with this new diagnostic concept based on microvascular changes makes NBI suitable for worldwide use in the future.

Clinical background

According to the "field cancerization" concept [1], head and neck cancer, especially pharyngeal cancer, frequently co-exist with esophageal cancer [2–4], but pharyngeal cancer has proven difficult to detect in such cases before its progression to an advanced stage [5]. Possible reasons for the difficulty in detection include the following: it was previously considered important that the endoscope should pass through the pharynx area quickly without detailed observation in order to reduce patient discomfort during routine examinations; endoscopists in the past generally did not regard the pharynx as an examination subject; superficial pharyngeal lesions are generally asymptomatic and are difficult to detect endoscopically; endoscopists were unable to use Lugol solution because of the risk of aspiration into the patient's airway; and laryngoscopes used in otolaryngology provided poor definition images.

Consequently, most cases of pharyngeal cancer are detected at an advanced stage resulting in an overall poor prognosis [6–10]. In addition, surgical resection of advanced lesions requires extensive and often mutilating resections and is usually associated with a loss of function of swallowing and/or speaking. Early detection is thus important for both improved prognosis and less invasive treatment [11–16].

Recently, several reports have indicated the possibility of narrow-band imaging (NBI) endoscopy with magnification improving the detection of superficial pharyngeal cancer [17,18]. Compared with conventional endoscopy, the recognition of these lesions is dramatically improved and the microvascular structure of the mucosal surface is significantly enhanced by NBI.

Technical background

NBI is a relatively new optical technology that more clearly visualizes microvascular structures of the epithelium by limiting the depth of light penetration into the mucosa. The penetration depth depends on the wavelength of the light. The conventional video endoscope system uses three broadband optical filters (red, green, and blue) covering all wavelengths of the visible spectrum. In the NBI system, the band pass ranges of the blue and green optical filters have been shifted to shorter wavelengths (central

wavelengths of 415 nm and 540 nm, respectively) and narrowed to 30 nm. In addition, the red light is completely excluded when illuminating in the NBI mode [19,20]. The processor subsequently reconstructs a real-time image using the information from the two bandwidths of illumination. The blue light illumination provides most of the information on capillary structure of the mucosa, as it encompasses the peak absorption wavelength of hemoglobin. The NBI view and conventional endoscopy mode can be switched within a second by pushing a single button on the control handle of the endoscope.

Endoscopic procedures

Instruments

The instruments used are a magnifying endoscope with ×80 magnification (GIF-Q240Z/GIF-Q260Z; Olympus Optical Co., Tokyo, Japan), a standard video endoscope system (EVIS LUCERA; Olympus), and an NBI system (Olympus).

Endoscopic features of superficial pharyngeal cancer

The endoscopic features of superficial pharyngeal cancer by NBI endoscopy with magnification are a demarcated brownish area and increased intraepithelial papillary capillary loops (IPCL) with irregularity or microvascular proliferation (MVP) pattern (○ Fig. 1–4) [17,21]. The concept of using the appearance of the IPCL for the differential diagnosis and assessment of the depth of infiltration of superficial esophageal squamous cell carcinoma (SCC) was first described by Inoue et al. [22,23]. IPCLs normally appear on the mucosal surface of the esophagus, but cannot be observed during conventional examinations without magnification. When lesions such as carcinomas occur, changes in the number and appearance of the IPCLs can be seen by magnified observation including dilatation, tortuosity, caliber change in one IPCL, and various shapes in multiple IPCLs.

Classifications based on these IPCL findings have demonstrated an accuracy rate of 85% [21]. Lesions showing all four features are classified as Type V based on IPCL findings in lesions previously diagnosed as mucosal carcinomas. In addition, it has been proposed that Type V lesions can be further subdivided depending on whether: the IPCLs show all four features (Type V-1); the IPCLs are more elongated (Type V-2); there exists a more destructive form of the IPCL features (Type V-3); or new tumor vessels have appeared with the disappearance of IPCLs due to submucosal invasion (Type V_N) [24]. These findings probably apply to the pharyngeal lesions as well, because the pharynx and the esophagus are both lined with squamous epithelium and cancers in these areas are usually revealed to be SCC. Muto et al. also reported MVP pattern, and NBI endoscopy with magnification allows the detection of such abnormal capillary changes within pharyngeal malignant lesions [17].

Pharyngeal cancers can be recognized as demarcated brownish areas compared with surrounding mucosa even without magnified observation, which allows for their detection in overview during the initial phase of examinations [17]. There are two types of brownish areas: those that are demarcated and those with an unclear margin. Brownish areas with unclear margins compared with the surrounding mucosa are likely to be diagnosed as benign lesions such as inflammation. Although IPCL findings in inflammation also demonstrate some change, it is possible to distinguish inflammation from neoplastic lesions because irregularity of the IPCLs is unclear and their density is relatively low in brownish areas with unclear margins. We consider, therefore, that these findings of demarcated brownish areas and increased IPCLs with irregularity or MVP pattern are the endoscopic features of superficial pharyngeal cancer. If this is the only finding, however, it is difficult to make an exact diagnosis of a neoplastic lesion. This is in contrast to features of pharyngeal cancer using conventional endoscopy where a reddish or discolored elevation, white deposits, erosions, bleeding, and disappearance of the microvascular structure are required to detect the lesion using the conventional view. It is extremely difficult, however, to detect lesions except in those cases that present a remarkable visual change, so most superficial lesions remain undetected by conventional endoscopy.

Definition of superficial pharyngeal lesion

The pharynx consists of stratified layers of squamous epithelium, lamina propria mucosae, submucosa, muscle, and adventitia. The elastic fiber layer of submucosa is recognized as being equivalent to muscularis mucosae, which is absent in the pharynx. According to the Japan Society for Head and Neck Cancer [5], a superficial pharyngeal lesion is defined as one in which vertical invasion is comparatively shallow and visual changes do not indicate an advanced cancer. This rather vague definition suggests that vertical invasion is limited to the epithelium or just beneath the epithelium, but does not extend to the muscle layer. The Japan Society for Head and Neck Cancer has also determined that the macroscopic classification of superficial lesions is to follow the guidelines of The Japan Esophageal Society [25]. This means that if a lesion is equivalent to a 0–II type esophageal superficial cancer (i.e. flat type lesion), it is considered that invasion does not extend to the muscle layer.

Endoscopic examinations

Before the examinations, scopolamine butylbromide (20 mg) and midazolam (2–5 mg) or pethidine (15–30 mg) are administered intravenously if there are no contraindications to prevent sialorrhea and gag reflex, respectively. In addition, patients also receive pharyngeal anesthesia using xylocaine, either in spray or viscous form.

At the beginning of each examination, we initially perform NBI endoscopy without magnification in order to carefully inspect the oropharyngeal and hypopharyngeal mucosal sites for brownish areas that may indicate an SCC. In particular, the piriform sinus, which is the most common site for hypopharyngeal cancer [5], is examined closely by having patients hold their breath because the piriform sinus expands when the glottis is closed. If a demarcated brownish area is observed during the examination, we then add magnification to obtain a more accurate diagnosis by evaluating the IPCL or MVP findings. Lesions are then biopsied in a standard manner.

During the examination procedure, it is very important to avoid inducing the gag reflex. If an endoscope inadvertently touches the aryepiglottic fold near the airway, a gag reflex with heavy coughing is likely to occur and continue for some time. The aryepiglottic fold is adjacent to the piriform sinus in the hypopharynx, where superficial SCC most frequently occurs, so observation must be performed with great care to prevent a gag reflex and to allow optimal inspection of this area.

These procedures are performed before inserting the endoscope into the esophagus. Chromoendoscopy using Lugol solution should not be performed in the pharynx during routine examinations because of the risk of aspiration and severe mucosal irri-

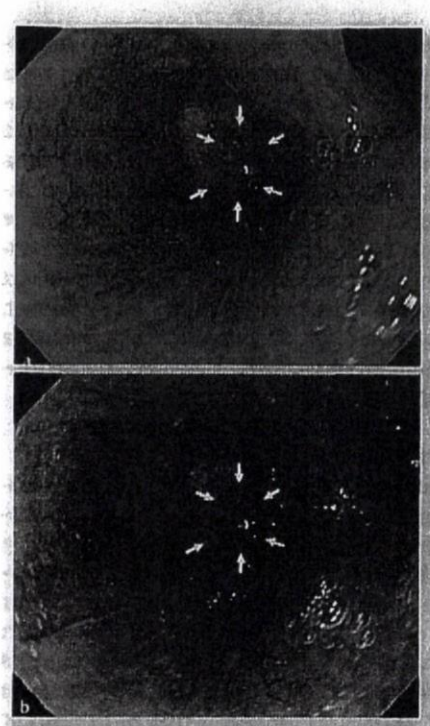

Fig. 1 a It was virtually impossible to detect this lesion using conventional endoscopy due to the lack of contrast between the lesion and the surrounding normal mucosa (arrows). b Narrow-band imaging endoscopy detected a small brownish area (arrows).

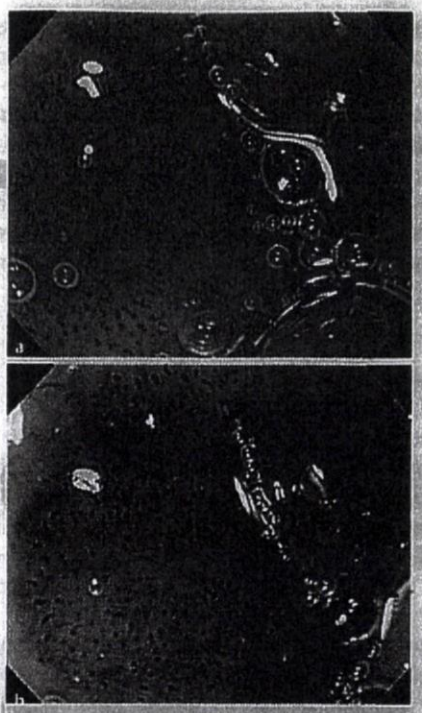

Fig. 3 a Conventional endoscopy with magnification demonstrated increased intraepithelial papillary capillary loops (IPCLs) with irregularity that showed four features as superficial pharyngeal cancer. b Narrow-band imaging endoscopy with magnification more clearly demonstrated IPCL findings that showed four features as superficial pharyngeal cancer in the demarcated brownish area.

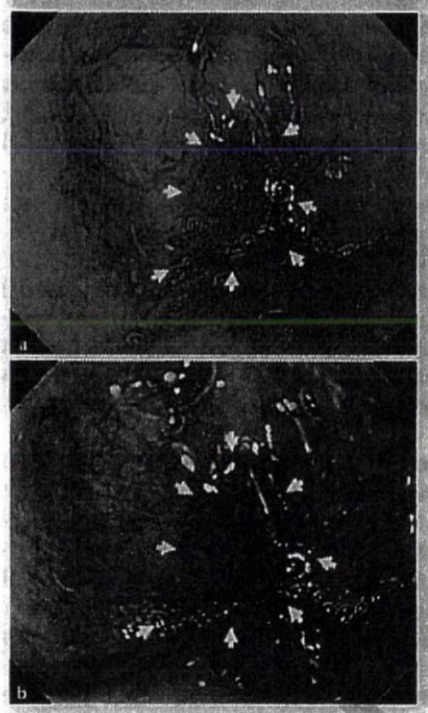

Fig. 2 a Conventional endoscopy close-up view showed a slightly reddish area with unclear margin and disappearance of normal microvascular structure (arrows). b Narrow-band imaging endoscopy close-up view identified a clearly demarcated brownish area (arrows).

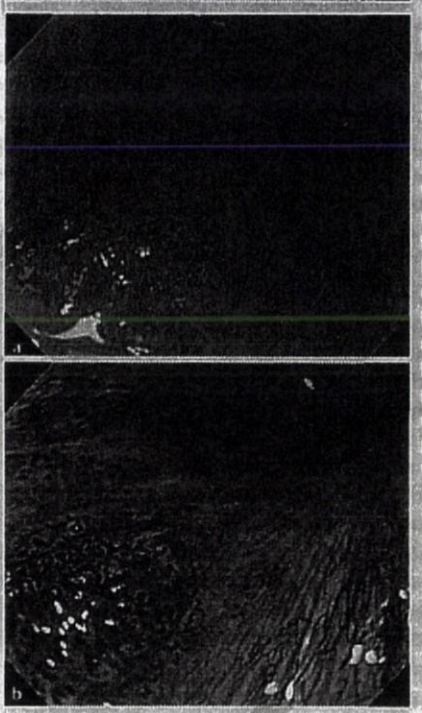

Fig. 4 a Conventional endoscopy with magnification demonstrated only elevated component of distal lesion margin with limited intraepithelial papillary capillary loop (IPCLs) findings observed. b Narrow-band imaging endoscopy with magnification more clearly demonstrated IPCL findings and distal lesion margin surrounded by mucosa that showed normal microvascular structure.

Fig. 1–4 Superficial hypopharyngeal cancer identified as a slightly elevated lesion (0-IIa, 10 mm) in the left piriform sinus was revealed to be squamous cell carcinoma.

tation. Instead, Lugol solution should only be used for procedures that are performed under general anesthesia.

Experience in detecting pharyngeal cancer

We screened for second primary pharyngeal cancer using NBI endoscopy with magnification between April and October 2005 in 91 patients with esophageal SCC who had undergone surgery and/or chemoradiotherapy at the National Cancer Center Hospital in Tokyo. The detection rate was 10% for superficial pharyngeal cancer with an average lesion size of approximately 15 mm in diameter [26]. Although only patients who had received previous treatment for esophageal SCC were included in this study, these results are similar to research data obtained from esophageal SCC patients before treatment [27]. Otolaryngologists specializing in laryngoscopy have also reported on the use of NBI for inspection of oropharyngeal and hypopharyngeal sites by NBI. A total of six superficial lesions in six of 217 patients with esophageal cancer were identified by laryngoscopy with NBI,

with four of these six lesions having a diameter of 5 mm or less [18].

There have been numerous reports on the relationship between esophageal SCC and head and neck cancer [11–15,28,29]. Based on our results and previous reports, we believe that the incidence of pharyngeal cancer in esophageal SCC patients may be as high as 10%. This is important to know beforehand in order to make suitable preparations before examinations.

Problems to be solved

Treatments and pathological criteria

This particular field has only been developed in recent years and there are still a number of problems that need to be resolved in the future. Previously, the only treatment choices for pharyngeal cancer patients were surgery or chemoradiotherapy. More recently, however, local resections such as endoscopic mucosal resection (EMR) have become possible because of an increased ability to detect superficial pharyngeal lesions. EMR, EMR using a cap-fitted panendoscope, endoscopic submucosal dissection, coagulation and less invasive operations such as transoral surgery, are currently being performed under general anesthesia as part of clinical studies at advanced institutions [30–32]. It is still unknown which treatment method is the most effective because criteria for a curative resection are still uncertain due to the absence of muscularis mucosae in the pharynx, unlike in the gastrointestinal tract. The frequency of lymph-node metastasis also differs with each organ in the gastrointestinal tract. At this point, however, the effect that lesion invasion depth has on the risk of lymph-node metastasis is unknown (unlike for most areas in the gastrointestinal tract), as there have been few reported cases of superficial pharyngeal lesions. Although we currently believe that local resections are advisable, it is necessary to solve these problems by accumulating and evaluating resected specimens and through continued long-term follow-up of patients who have been treated endoscopically.

Micro lesions

The availability of NBI for routine upper endoscopy now allows for the detection of minute pharyngeal lesions that are impossible to identify by conventional endoscopy. The fact is that we have no knowledge as to the natural history of micro lesions that measure only a few millimeters in size. Can these disappear spontaneously or do they always progress into an advanced cancer and if so, how much time is necessary for such development?

Discussion

We believe NBI endoscopy with magnification increases the detection rate of superficial pharyngeal cancers that are often difficult to detect with standard endoscopy. Although we are able to recognize lesions in overview as an abnormal area with a brownish coloration, it may be difficult to make an exact diagnosis without magnification, as not enough information can be obtained regarding microvascular changes to determine whether the lesion is malignant or not. There is also an additional benefit associated with inspection using magnification because biopsies, which are difficult to obtain in the pharynx, are not required before endoscopic treatment because an accurate diagnosis can be made using NBI with magnification.

The estimated age-standardized rate of mouth and pharynx cancer incidence per 100 000 is < 5 in Japan and is only about 12 throughout the world. It is therefore necessary to define high-risk populations because screening for these cancers in all patients is virtually impossible as well as unnecessary [33]. Careful examination of the pharynx needs to be considered in high-risk populations. These high-risk populations include patients with esophageal cancer or multiple Lugol-voiding lesions in their background esophageal mucosa, heavy drinkers, smokers, males over 50 years of age [28,34–38], and individuals with high mean corpuscular volume (MCV) levels which have been closely associated with esophageal cancer [39]. The clinical effectiveness of NBI endoscopy with magnification has been increasingly reported, not only in the head and neck region and esophagus including Barrett's esophagus [17,18,21,40–42], but also in the bronchial tree, stomach, and colon [43–50].

As we have already indicated, one of the reported reasons that NBI has been so effective recently is that it is easy to use. In the stomach and colon regions, insufficient illumination sometimes makes observation with NBI more difficult, but the pharynx and esophagus are considered to be more suitable areas for obtaining high-quality NBI images due to the narrowness of the lumen. NBI does not require a special endoscope or any particular preparation and it allows switching back and forth with conventional endoscopy at any time at the press of a single button. Such ease of use combined with the new diagnostic concept based on microvascular changes makes NBI suitable for worldwide use in the future.

In conclusion, we believe that NBI endoscopy with magnification is superior to conventional endoscopy in the detection, visual recognition, and assessment of infiltration depth of lesions, and that it will become part of standard endoscopy in the pharynx and esophagus. At the same time, however, it will be necessary to accumulate and evaluate resected specimens and follow up patients in order to establish the appropriate criteria for curative endoscopic treatment in these patients.

Competing Interests: None

References

1 *Slaughter DP, Southwick HW, Smejkal W.* Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953; 6: 963–968
2 *Shibuya H, Wakita T, Nakagawa T et al.* The relation between an esophageal cancer and associated cancers in adjacent organs. Cancer 1995; 76: 101–105
3 *Begg CB, Zhang ZF, Sun M et al.* Methodology for evaluating the incidence of second primary cancers with application to smoking-related cancers from the Surveillance, Epidemiology, and End Results (SEER) program. Am J Epidemiol 1995; 142: 653–665
4 *Petit T, Georges C, Jung GM et al.* Systematic esophageal endoscopy screening in patients previously treated for head and neck squamous-cell carcinoma. Ann Oncol 2001; 12: 643–646
5 *Japan Society for Head and Neck Cancer.* General rules for clinical studies on head and neck cancer. Tokyo: Kanehara Syuppan, 2005
6 *Erkal HS, Mendenhall WM, Amdur RJ et al.* Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. J Clin Oncol 2001; 19: 1358–1362
7 *Kraus DH, Zelefsky MJ, Brock HA et al.* Combined surgery and radiation therapy for squamous cell carcinoma of the hypopharynx. Otolaryngol Head Neck Surg 1997; 116: 637–641
8 *Johansen LV, Grau C, Overgaard J.* Hypopharyngeal squamous cell carcinoma – treatment results in 138 consecutively admitted patients. Acta Oncol 2000; 39: 529–536

9 *Eckel HE, Staar S, Volling P et al.* Surgical treatment for hypopharynx carcinoma: feasibility, mortality, and results. Otolaryngol Head Neck Surg 2001; 124: 561–569

10 *Wahlberg PC, Andersson KE, Biorklund AT et al.* Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. Head Neck 1998; 20: 714–719

11 *Kumagai Y, Kawano T, Nakajima Y et al.* Multiple primary cancers associated with esophageal carcinoma. Surg Today 2001; 31: 872–876

12 *Natsugoe S, Matsumoto M, Okumura H et al.* Multiple primary carcinomas with esophageal squamous cell cancer: clinicopathologic outcome. World J Surg 2005; 29: 46–49

13 *Noguchi T, Kato T, Takeno S et al.* Necessity of screening for multiple primary cancers in patients with esophageal cancer. Ann Thorac Cardiovasc Surg 2002; 8: 336–342

14 *Nagasawa S, Onda M, Sasajima K et al.* Multiple primary malignant neoplasms in patients with esophageal cancer. Dis Esophagus 2000; 13: 226–230

15 *Shimizu Y, Tsukagoshi H, Fujita M et al.* Head and neck cancer arising after endoscopic mucosal resection for squamous cell carcinoma of the esophagus. Endoscopy 2003; 35: 322–326

16 *Watanabe A, Hosokawa M, Taniguchi M et al.* Periodic pharyngolaryngoscopy detects early head and neck cancer and improves survival in esophageal cancer. Ann Thorac Surg 2003; 76: 1699–1705

17 *Muto M, Nakane M, Katada C et al.* Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites. Cancer 2004; 101: 1375–1381

18 *Watanabe A, Tsujie H, Taniguchi M et al.* Laryngoscopic detection of pharyngeal carcinoma in situ with narrowband imaging. Laryngoscope 2006; 116: 650–654

19 *Gono K, Yamazaki K, Doguchi N et al.* Endoscopic observation of tissue by narrowband illumination. Opt Rev 2003; 10: 211–215

20 *Gono K, Obi T, Yamaguchi M et al.* Appearance of enhanced tissue features in narrow-band endoscopic imaging. J Biomed Opt 2004; 9: 568–577

21 *Yoshida T, Inoue H, Usui S et al.* Narrow-band imaging system with magnifying endoscopy for superficial esophageal lesions. Gastrointest Endosc 2004; 59: 288–295

22 *Kumagai Y, Inoue H, Nagai K et al.* Magnifying endoscopy, stereoscopic microscopy, and the microvascular architecture of superficial esophageal carcinoma. Endoscopy 2002; 34: 369–375

23 *Inoue H, Honda T, Nagai K et al.* Ultra-high magnification endoscopic observation of carcinoma in situ of the esophagus. Dig Endosc 1997; 9: 16–18

24 *Inoue H.* Magnification endoscopy in the esophagus and stomach. Dig Endosc 2001; 13: 40–41

25 *The Japan Esophageal Society.* Guide lines for the clinical and pathologic studies on carcinoma of the esophagus. Tokyo: Kanehara Syuppan, 2007

26 *Nonaka S, Saito Y, Gotoda T et al.* Narrow band imaging (NBI) system is promising device to detect superficial pharyngeal cancer at an early stage in patients with esophageal squamous cell carcinoma (SCC). Gastrointest Endosc 2006; 63: AB250

27 *Nonaka S, Saito Y, Kozu T et al.* Effectiveness of narrow-band imaging (NBI) in early detection of synchronous superficial pharyngeal cancer in patients with squamous cell carcinoma (SCC) before treatment – Can NBI observation exceed endoscopic experience? Gastrointest Endosc 2007; 65: AB339

28 *Matsubara T, Yamada K, Nakagawa A.* Risk of second primary malignancy after esophagectomy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 2003; 21: 4336–4341

29 *Muto M, Katada C, Sano Y et al.* Narrow band imaging: a new diagnostic approach to visualize angiogenesis in superficial neoplasia. Clin Gastroenterol Hepatol 2005; 3: S16–20

30 *Inoue H, Endo M, Takeshita K et al.* A new simplified technique of endoscopic esophageal mucosal resection using a cap-fitted panendoscope (EMRC). Surg Endosc 1992; 6: 264–265

31 *Shimizu Y, Yamamoto J, Kato M et al.* Endoscopic submucosal dissection for treatment of early stage hypopharyngeal carcinoma. Gastrointest Endosc 2006; 64: 255–259

32 *Satou Y, Omori T, Yokoyama A et al.* Treatment of superficial carcinoma in the pharynx and the larynx [in Japanese with English abstract]. Endosc Dig 2006; 18: 1407–1416

33 *Parkin DM, Pisani P, Ferlay J.* Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999; 80: 827–841

34 *Muto M, Hironaka S, Nakane M et al.* Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. Gastrointest Endosc 2002; 56: 517–521

35 *Muto M, Takahashi M, Ohtsu A et al.* Risk of multiple squamous cell carcinomas both in the esophagus and the head and neck region. Carcinogenesis 2005; 26: 1008–1012

36 *Takezaki T, Shinoda M, Hatooka S et al.* Subsite-specific risk factors for hypopharyngeal and esophageal cancer (Japan). Cancer Causes Control 2000; 11: 597–608

37 *Zeka A, Gore R, Kriebel D.* Effects of alcohol and tobacco on aerodigestive cancer risks: a meta-regression analysis. Cancer Causes Control 2003; 14: 897–906

38 *Yokoyama A, Omori T.* Genetic polymorphisms of alcohol and aldehyde dehydrogenases and risk for esophageal and head and neck cancers. Jpn J Clin Oncol 2003; 33: 111–121

39 *Yokoyama A, Yokoyama T, Kumagai Y et al.* Mean corpuscular volume, alcohol flushing, and the predicted risk of squamous cell carcinoma of the esophagus in cancer-free Japanese men. Alcohol Clin Exp Res 2005; 29: 1877–1883

40 *Hamamoto Y, Endo T, Nosho K et al.* Usefulness of narrow-band imaging endoscopy for diagnosis of Barrett's esophagus. J Gastroenterol 2004; 39: 14–20

41 *Goda K, Tajiri H, Ikegami M et al.* Usefulness of magnifying endoscopy with narrow band imaging for the detection of specialized intestinal metaplasia in columnar-lined esophagus and Barrett's adenocarcinoma. Gastrointest Endosc 2007; 65: 36–46

42 *Kara MA, Ennahachi M, Fockens P et al.* Detection and classification of the mucosal and vascular patterns (mucosal morphology) in Barrett's esophagus by using narrow band imaging. Gastrointest Endosc 2006; 64: 155–166

43 *Nakayoshi T, Tajiri H, Matsuda K et al.* Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology. Endoscopy 2004; 36: 1080–1084

44 *Sumiyama K, Kaise M, Nakayoshi T et al.* Combined use of a magnifying endoscope with a narrow band imaging system and a multibending endoscope for en bloc EMR of early stage gastric cancer. Gastrointest Endosc 2004; 60: 79–84

45 *Machida H, Sano Y, Hamamoto Y et al.* Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. Endoscopy 2004; 36: 1094–1098

46 *Shibuya K, Hoshino H, Chiyo M et al.* High magnification bronchovideoscopy combined with narrow band imaging could detect capillary loops of angiogenic squamous dysplasia in heavy smokers at high risk for lung cancer. Thorax 2003; 58: 989–995

47 *Vincent BD, Praig M, Silvestri GA.* A pilot study of narrow-band imaging compared to white light bronchoscopy for evaluation of normal airways and premalignant and malignant airways disease. Chest 2007; 131: 1794–1799

48 *Hirata M, Tanaka S, Oka S et al.* Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. Gastrointest Endosc 2007; 65: 988–995

49 *Chiu HM, Chang CY, Chen CC et al.* A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007; 56: 373–379

50 *Uedo N, Ishihara R, Iishi H et al.* A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. Endoscopy 2006; 38: 819–824

American Journal of Gastroenterology
© 2008 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2008.01931.x

Does Autofluorescence Imaging Videoendoscopy System Improve the Colonoscopic Polyp Detection Rate?—A Pilot Study

Takahisa Matsuda, M.D.,[1] Yutaka Saito, M.D., Ph.D.,[1] Kuang-I Fu, M.D., Ph.D.,[2] Toshio Uraoka, M.D., Ph.D.,[1] Nozomu Kobayashi, M.D.,[1] Takeshi Nakajima, M.D.,[1] Hisatomo Ikehara, M.D.,[1] Yumi Mashimo, M.D., Ph.D.,[1] Tadakazu Shimoda, M.D., Ph.D.,[3] Yoshitaka Murakami, M.D., Ph.D.,[4] Adolfo Parra-Blanco, M.D., Ph.D.,[5] Takahiro Fujimori, M.D., Ph.D.,[2] and Daizo Saito, M.D., Ph.D.[1]

[1]*Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan;* [2]*Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine, Shimotsuga, Tochigi, Japan;* [3]*Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan;* [4]*Department of Health Science, Shiga University of Medical Science, Shiga, Japan; and* [5]*Department of Gastroenterology, Hospital Universitario de Canarias, Tenerife, Spain*

OBJECTIVES: **Colonoscopy is considered the gold standard for the detection of colorectal polyps; however, polyps can be missed with conventional white light (WL) colonoscopy. The aim of this pilot study was to evaluate whether a newly developed autofluorescence imaging (AFI) system can detect more colorectal polyps than WL.**

METHODS: **A modified back-to-back colonoscopy using AFI and WL was conducted for 167 patients in the right-sided colon including cecum, ascending and transverse colon by a single experienced colonoscopist. The patient was randomized to undergo the first colonoscopy with either AFI or WL (group A: AFI-WL, group B: WL-AFI). The time needed for both insertion and examination for withdrawal and all lesions detected in the right-sided colon were recorded.**

RESULTS: **Eighty-three patients were randomized to group A and 84 to group B. The total number of polyps detected by AFI and WL colonoscopy was 100 and 73, respectively. The miss rate for all polyps with AFI (30%) was significantly less than that with WL (49%) ($P = 0.01$).**

CONCLUSIONS: **AFI detects more polyps in the right-sided colon compared to WL colonoscopy.**

(Am J Gastroenterol 2008;103:1926–1932)

INTRODUCTION

Colorectal cancer is one of the most common cancers in the world. Early detection and removal of colorectal adenomas have been shown to be the most effective way of colorectal cancer prevention (1, 2). Colonoscopy is considered the gold standard for detection and treatment of colorectal polyps, however, some polyps can be missed during routine colonoscopies. According to the results of back-to-back colonoscopies by Rex *et al.*, the miss rate for adenomas $\geq$1 cm was 6%, for adenomas 6–9 mm was 13%, and for adenomas $\leq$5 mm was 27%, respectively (3). Furthermore, there was a trend toward right-sided colorectal adenomas being missed more often than left-sided ones (27% *vs* 21%). As missing adenomas or cancers during colonoscopy would result in increasing the need of surgery and death from colorectal cancers, attempts to reduce this kind of miss rate include pan-colonic dye spraying (4, 5), wide angle colonoscopy (6, 7) or cap-fitted colonoscopy (8).

On the other hand, a new prototype of endoscopic autofluorescence imaging (AFI) system has been developed (9). AFI produces real-time pseudo-color images to identify gastrointestinal malignancies (10–13) as well as malignancies of larynx, cervix, lung, and bladder. During AFI colonoscopy, non-neoplastic lesion appears green, while neoplastic lesion has a magenta (reddish purple) image (14, 15). The usefulness of AFI for differential diagnosis between neoplastic and non-neoplastic lesions has been reported (16–21); however, its effectiveness, measured as frequency of detection of colorectal polyps in comparison to conventional white light colonoscopy (WL), has not been investigated enough (22). We therefore conducted this pilot study to evaluate whether AFI can detect more colorectal polyps than WL.

METHODS

Patients

Between June and October 2006, consecutive patients who underwent total colonoscopy using a colonoscope with AFI function were considered eligible for inclusion in the study. This study was conducted prospectively, and our institutional review board approved the study protocol. Written informed consent for examination and treatment were obtained from all of the studied patients prior to the procedures. Patients with previously detected polyps or with a history of surgical resection of the proximal colon (cecum, ascending colon and transverse colon) were excluded from this study. Patients with inflammatory bowel disease (IBD), familial adenomatous polyposis (FAP), or hereditary nonpolyposis colorectal cancer (HNPCC) were also considered ineligible for the study.

Autofluorescence Imaging System (AFI)

The prototype autofluorescence imaging system used in this study (AFI; Olympus Medical Systems Corp., Tokyo, Japan) has a sequential light source (XCLV-260HP) and a high-resolution videoendoscope (XCF-H240FZI) and XCV-260HP video system. AFI equipped two CCDs: One for high-resolution white-light observation and another for autofluorescence observation on the tip of the scope, and they could be easily switched by pushing a button on the scope handle. As shown in Figure 1, AFI composes real-time images from pseudo-colors of autofluorescence (excitation: 390–470 nm, detection: 500–630 nm) and green reflection (G': 540–560 nm) by sequential method in order to represent clear image profiles and to distinguish reduction of autofluorescence by tumor from that by hemoglobin. Furthermore, this AFI videoendoscope is equipped with an accessory channel with an internal diameter of 3.2 mm. The outer diameter of the distal tip of this AFI videoscope is 14.8 mm and also has the function of variable stiffness and magnification (up to ×75 under the WL image).

Endoscopic Procedure

All patients were prepared for colonoscopy by ingesting 2–3 liters of polyethylene glycol-electrolyte solution on the same-day morning. Scopolamine butylbromide (10 mg) was administered intravenously to avoid bowel movement prior to examination for the patients with no contraindication to the use of this agent. Quality of bowel preparation was assessed by the examiner as follows: (a) excellent (near 100% mucosal visualization following suction of fluid residue), (b) good (near 90% mucosal visualization), (c) fair (less than 90% mucosal visualization). Colonoscopic examinations were performed in a modified back-to-back fashion, using WL and AFI in the right-sided colon including cecum, ascending colon, and transverse colon by a single experienced colonoscopist having performed more than 10,000 colonoscopies. Each patient was randomized in one of the following two groups with a computer-generated random number list; group A: after cecal insertion by WL, the colonoscope was withdrawn from the cecum to the splenic flexure with AFI mode, and then re-withdrawing the colonoscope with WL from the cecum to the splenic flexure after reinsertion of the scope to the cecum by WL (AFI-WL); group B: withdrawing the colonoscope in the inverse order of group A (first WL and then AFI; WL-AFI).

All lesions detected during either examination of AFI or WL were removed endoscopically and sent for histological evaluation without exception. All lesions identified on the second examination were considered as lesions missed by the first examination. The location of each lesion was defined according to landmarks including hepatic flexure and splenic flexure. The size of the lesions was estimated using open endoscopic biopsy forceps.

Histopathological Evaluation

Resected specimens were immediately fixed in 10% buffered formalin solution and subsequently stained with hematoxylin-eosin. Experienced gastrointestinal pathologists who were completely blinded to each endoscopic diagnosis evaluated all pathological specimens. Histological diagnoses were determined according to the World Health Organization (WHO) criteria (23).

Statistical Analysis

This study was mainly designed to demonstrate that the colonoscope with AFI has a different reliability than with WL for polyp detection. The design of the study included

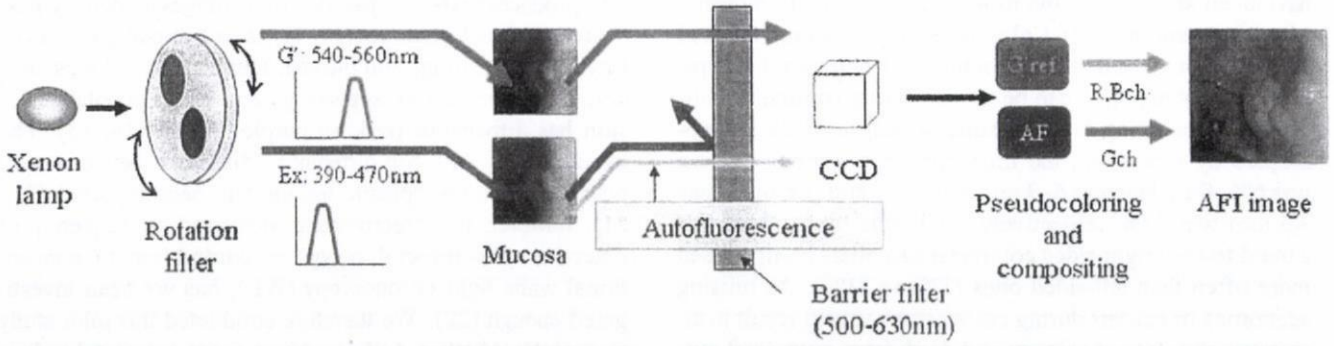

Figure 1. Autofluorescence Imaging (AFI) System.

two independent groups; group A underwent colonoscopy with WL after colonoscopy with AFI, and group B underwent colonoscopy with AFI after colonoscopy with WL.

Nominal and ordinal variables are expressed with frequencies and percentages. Continuous variables are expressed with means and standard deviations. The comparisons of proportions of detected polyps between both groups A (AFI-WL) and B (WL-AFI) in the second exam was carried out with the Kruskal–Wallis test for singly ordered 2 × 2 table (based on χ^2 distribution with 1 degree of freedom). Proportions between groups on sex, indication for colonoscopy, bowel preparation, location and macroscopic type, size of the lesion, and histopathology were compared with χ^2 test or Fisher's exact test as appropriate. Statistical analysis was conducted with SPSS V. (Chicago, IL), StatXact v. 5.0.3 (Cytel Co., MA), and Statistica v. 5.5 (Tulsa, OK). All statistical tests were 2-sided and significance was defined as $P < 0.05$.

RESULTS

Patient Characteristics and Bowel Preparation

A total of 167 patients were enrolled in this study. The 167 patients included 107 (64%) men, and the mean age was 62.2 ± 9.8 yr. The indications for colonoscopy were polyp surveillance (N = 78), screening (N = 76), abdominal pain/constipation (N = 7), and fecal occult blood test positive (N = 6). The bowel preparation was described as excellent or good in 139 cases (83%) and fair in 28 (17%) (Table 1).

Detected Lesions

Total number of detected and removed lesions by AFI and WL colonoscopy was 100 and 73, respectively. The miss proportion for all polyps with AFI (30%) was significantly less than the miss proportion with WL (49%) ($P = 0.01$). Among all detected polyps, the number of neoplastic lesions detected by AFI and WL colonoscopy was 92 and 69, respectively. Among 66 neoplastic lesions, which were diagnosed in group A, 47 (71%) lesions were detected at the first AFI withdrawal technique (Fig. 2). In contrast, in group B (among 95 neoplastic lesions), only 50 (53%) lesions were recognized at the first WL withdrawal technique, and 45 (47%) lesions were detected by the second AFI examination. Significantly more neoplastic lesions were missed by WL compared with AFI system ($P = 0.02$) (Tables 2 and 3).

Table 1. Patient Characteristics and Indications for Colonoscopy

	Group A (AFI-WL) (N = 83)	Group B (WL-AFI) (N = 84)
Male sex no. (%)	58 (70)	49 (58)
Age* (yr)	62.2 ± 10.2	62.2 ± 9.5
Indication for colonoscopy no. (%)		
Polyps surveillance	42 (51)	36 (43)
Screening	35 (42)	41 (49)
Abdominal pain/constipation	2 (2)	5 (6)
FOBT† (+)	4 (5)	2 (2)
Bowel preparation no. (%)		
Excellent	18 (22)	23 (27)
Good	49 (59)	49 (58)
Fair	16 (19)	12 (14)

*Data presented with mean ± SD.
†Fecal occult blood test.

Characteristics of the Missed Lesions

Characteristics of the missed neoplastic lesions by AFI and WL colonoscopy were flat elevated: 14 (74%) and 39 (87%), small (≤5 mm): 18 (95%) and 41 (91%) and low-grade dysplasia (LGD): 19 (100%) and 45 (100%), respectively (Table 4).

DISCUSSION

In this pilot study, we investigated the utility of a prototype Olympus AFI videoendoscopy system on miss rates during colonoscopy and the efficiency of colonoscopic withdrawal. Based on the results of our study, AFI videoendoscopy system is useful for the detection of colorectal adenomas in the right-sided colon compared to WL conventional colonoscopy. The largest advantage of this system may prove to be the ability to perform faster and more efficient examination without the need for additional attachments to the endoscope and without the time and cost required for dye spraying or infusion. Even though this system is not available in the United States yet, we think it will be available in the near future.

According to the National Polyp Study (NPS), the incidence of colorectal cancer was decreased by endoscopic intervention. In brief, polypectomy during routine colonoscopy has been shown to prevent the development of colorectal cancer, compared with the incidence of it in reference groups. Therefore, colonoscopy is considered as a gold standard for detection and treatment of colorectal adenomas, however, the conventional colonoscopic technique during withdrawal, even if very careful, cannot detect all lesions, especially flat and small depressed ones.

Endoscopic imaging techniques aimed at early detection of colorectal cancer and its precursors have been developed over the last decade. Techniques that improve the detection of mucosal irregularities, such as pancolonic chromoendoscopy, narrow band imaging (NBI), high-resolution imaging, and AFI, have been applied in a variety of clinical situations to enhance the detection of flat and depressed lesions or to enable histopathological diagnosis.

Many authors have reported that chromoendoscopy is helpful for the detection and detailed morphological assessment of flat and depressed colorectal lesions (24–31). Pancolonic chromoscopy using an indigo carmine (IC) diffusion during withdrawal from the cecum, which highlighted subtle mucosal irregularities, has been reported to significantly increase the detection of diminutive, flat neoplastic lesions in the right colon. However, the withdrawal time for the IC

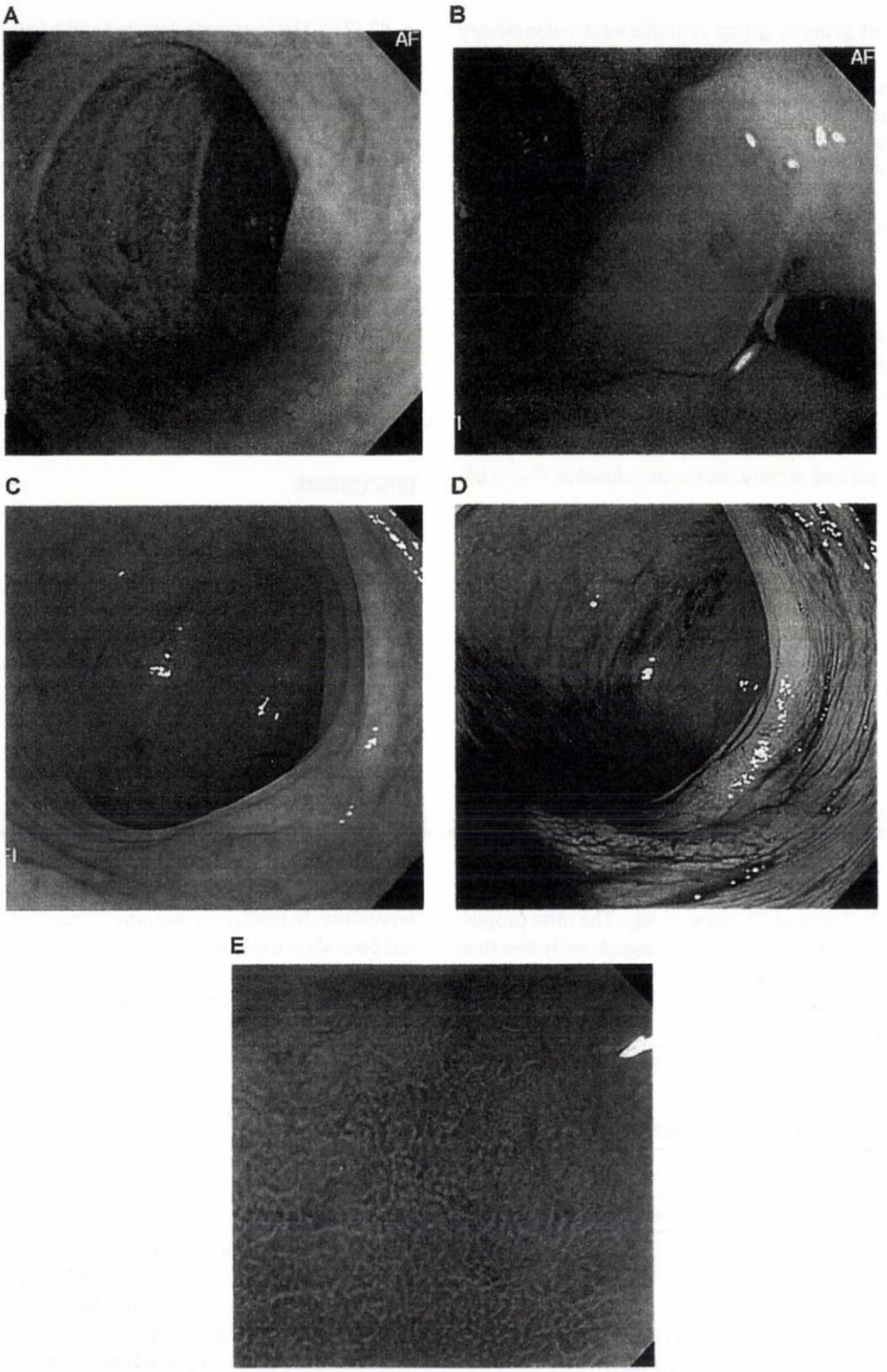

Figure 2. (*A*) A 64-year-old man who enrolled in this study and classified into Group A was referred with positive fecal occult blood test. The lesion was detected in the transverse colon at first AFI examination. (*B*) AFI image revealed a magenta-colored flat elevated lesion, which was macroscopically diagnosed as laterally spreading tumor, non-granular type (LST-NG). The size of the lesion was 20 mm in diameter. (*C*) Conventional (WL) image. (*D*) Chromoendoscopy image (indigo carmine). (*E*) Magnifying view (crystal-violet); Non-invasive (Kudo's type IIIs and IIIL pit) pattern. The final endoscopic diagnosis was HGD without submucosal invasion. We performed endoscopic submucosal dissection (ESD) using B-knife. The final histopathological diagnosis was HGD (intramucosal carcinoma).

Table 2. Detected Lesions in Each Group

		Group A (AFI-WL) (N = 83)		Group B (WL-AFI) (N = 84)	*P*
Total number of lesions (%)					
First exam	AFI	50 (70)	WL	52 (51)	0.01
Second exam	WL	21 (30)	AFI	50 (49)	
Neoplastic lesions (%)					
First exam	AFI	47 (71)	WL	50 (53)	0.02
Second exam	WL	19 (29)	AFI	45 (47)	
Non-neoplastic lesions no. (%)					
First exam	AFI	3 (60)	WL	2 (29)	0.28
Second exam	WL	2 (40)	AFI	5 (71)	

dye spray group was almost twice as long as for the control group (4).

Another technology recently demonstrated to be effective for detecting neoplastic lesions is NBI. The NBI system has been shown to be helpful in visualizing such lesions by improving contrast and is considered to be a new type of optical/digital chromoendoscopy (32, 33). In particular, magnification using NBI colonoscopy for the observation of the presence of "meshed brown capillary vessels" is extremely useful for distinguishing between neoplastic and non-neoplastic lesions without any dye solution. Regarding polyp detection, however, it is controversial at this moment (34). Furthermore, during NBI colonoscopy examinations, intestinal fluid was seen as being reddish in color similar to blood. Therefore, proper bowel preparation is one of the limitations when using this system.

Meanwhile, the feasibility of AFI system use for gastrointestinal (GI) screening and surveillance has not been clarified previously. In 2005, Nakaniwa *et al.* (14) developed and reported a new AFI videoscope system. Images acquired by this new AFI system provided better brightness than old fiberscopic images. From this report, the sensitivity and specificity of differentiating adenomatous and hyperplastic polyps were

Table 3. Clinicopathologic Characteristics of Lesions Detected by AFI and WL Colonoscopy

	AFI	WL	*P*
No. of lesions	100	73	
Location no. (%)			
Cecum	9 (9)	8 (11)	0.31
Ascending	37 (37)	19 (26)	
Transverse	54 (54)	46 (63)	
Macroscopic type no. (%)			
Polypoid	23 (23)	26 (36)	0.07
Flat elevated	77 (77)	47 (64)	
Size no. (%)			
0–5 mm	84 (84)	53 (73)	0.19
6–10 mm	10 (10)	12 (16)	
> 11 mm	6 (6)	8 (11)	
Histopathology no. (%)			
Neoplastic LGD	85 (85)	63 (86)	0.92
HGD	6 (6)	5 (7)	
Inv.ca	1 (1)	1 (1)	
Non-neoplastic	8 (8)	4 (5)	

Table 4. Characteristics of the Missed Neoplastic Lesions by AFI and WL Colonoscopy

	AFI	WL	*P*
No. of lesions	19	45	
Location no. (%)			
Cecum	3 (16)	2 (4)	0.13
Ascending	4 (21)	19 (42)	
Transverse	12 (63)	24 (54)	
Macroscopic type no. (%)			
Polypoid	5 (26)	6 (13)	0.21
Flat elevated	14 (74)	39 (87)	
Size no. (%)			
0–5 mm	18 (95)	41 (91)	0.62
6–10 mm	1 (5)	4 (9)	
Histopathology no. (%)			
LGD	19 (100)	45 (100)	

89% and 81%, respectively. However, there are few prospective studies that have attempted to clarify the usefulness of the adenoma detection rate using AFI system.

In this study, a total of 173 lesions from 167 patients were detected and removed endoscopically. Among these lesions, the number of neoplastic lesion detected by AFI and WL was 92 (92%) and 69 (95%), respectively. In contrast, the number of non-neoplastic lesions recognized as a polyp and removed by AFI and WL colonoscopy was only 8 (8%) and 4 (5%), respectively. The lesions we diagnosed and resected in this study with AFI and WL systems were mostly neoplastic ones. Consequently, our results evaluate the diagnostic yield of adenomatous polyp detection. However, we consider further investigation is necessary to evaluate the efficiency for differential diagnosis with AFI system.

Diminutive flat elevated lesions are thought to be of little clinical significance because such lesions, especially less than 5 mm polyps, are low-grade dysplasia (LGD) in most cases. Meanwhile, depressed lesions are considered to have a high malignant potential compared to polypoid ones in similar size (35–38). In this present study, all detected lesions' macroscopic type was flat elevated or polypoid. Because of low incidence, there were no depressed lesions in this study. However, significantly more small and/or flat neoplastic lesions were detected by AFI compared with WL colonoscopy. Therefore, AFI colonoscopy is considered to be a promising modality to detect small depressed lesions.

There are several limitations in our study. First, we conducted this study using a single experienced colonoscopist. True, our data are precise, but it is uncertain whether it would be available for all examiners. Therefore, additional multicenter studies are necessary to clarify the usefulness of AFI system for all colonoscopists. Another point worth mentioning is that our study was conducted within the limits of the right colon. The higher prevalence of flat and diminutive lesions diagnosed in the right colon may be consistent with Woolfson (39) and Hofstad's (40) description. Furthermore, a higher miss rate of detection has been reported in the right colon compared to the left colon (3). Complete back-to-back colonoscopy may be painful for patients under no sedation.

Therefore, we defined from the cecum to the splenic flexure as the target area in our prospective study. In addition, it is suggested that proper bowel preparation is indispensable to achieve success to detect small colorectal lesions. In this study, the bowel preparation was described as excellent or good in 83% and adequate but imperfect in 17%.

In conclusion, AFI videoendoscopy system is useful for the detection of right-sided colonic polyps, especially flat and/or diminutive adenomatous lesions compared to conventional (WL) colonoscopy. In the near future, multicenter trials should be performed to validate the usefulness of this system.

ACKNOWLEDGMENTS

We would like to express our appreciation to Dr. Alejandro Jimenez (Hospital Universitario de Canarias, Tenerife, Spain) for his help in the statistical analysis of this manuscript. This study was presented at the ASGE, Digestive Disease Week (DDW), Washington DC, USA, 2007.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Polyps can be missed with conventional white light (WL) colonoscopy.
- Efficacy of autofluorescence imaging (AFI) system is unclear.

What Is New Here

- AFI detects more polyps, especially flat and diminutive lesions, in the right-sided colon than conventional (WL) colonoscopy.
- Prospective multicenter studies are necessary to validate the usefulness of this system.

Reprint requests and correspondence: Takahisa Matsuda, M.D., National Cancer Center Hospital, Endoscopy Division, 5-1-1, Tsukiji, Chuo-ku, Tokyo, Japan.

Received September 2, 2007; accepted February 26, 2008.

REFERENCES

1. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N Engl J Med 1993;328:901–6.
2. Winawer SJ, Zauber AG, Ho MN, et al. The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med 1993;329:1977–81.
3. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. Gastroenterology 1997;112:24–8.
4. Brooker JC, Saunders BP, Shah SG, et al. Total colonic dye-spray increases the detection of diminutive adenomas during routine colonoscopy: A randomized controlled trial. Gastrointest Endosc 2002;56:333–8.
5. Hurlstone DP, Cross SS, Slater R, et al. Detecting diminutive colorectal lesions at colonoscopy: A randomized controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004;53:376–80.
6. Rex DK, Chadalawada V, Helper DJ. Wide angle colonoscopy with a prototype instrument: Impact on miss rates and efficiency as determined by back-to-back colonoscopies. Am J Gastroenterol 2003;98:2000–5.
7. Deenadayalu VP, Chadalawada V, Rex DK. 170 degrees wide-angle colonoscope: effect on efficiency and miss rates. Am J Gastroenterol 2004;99:2138–42.
8. Matsushita M, Hajiro K, Okazaki K, et al. Efficacy of total colonoscopy with a transparent cap in comparison with colonoscopy without the cap. Endoscopy 1998;30:444–7.
9. Takehana S, Kaneko M, Mizuno H. Endoscopic diagnostic system using autofluorescence. Diagn Ther Endosc 1999;5:59–63.
10. Panjehpour M, Overholt BF, Vo-Dinh T, et al. Endoscopic fluorescence detection of high-grade dysplasia in Barrett's esophagus. Gasrtoenterology 1996;111:93–101.
11. Mayinger B, Neidhardt S, Reh H, et al. Fluorescence induced with 5-aminolevulinic acid for the endoscopic detection and follow-up of esophageal lesions. Gastrointest Endosc 2001;54:572–8.
12. Kobayashi M, Tajiri H, Seike E, et al. Detection of early gastric cancer by a real-time autofluorescence imaging system. Cancer Lett 2001;165:155–9.
13. Ohkawa A, Miwa H, Namihisa A, et al. Diagnostic performance of light-induced fluorescence endoscopy for gastric neoplasms. Endoscopy 2004;36:515–21.
14. Nakaniwa N, Namihisa A, Ogihara T, et al. Newly developed autofluorescence imaging videoscope system for the detection of colonic neoplasms. Dig Endosc 2005;17:235–40.
15. Uedo N, Iishi H, Tatsuta M, et al. A novel videoendoscopy system by using autofluorescence and reflectance imaging for diagnosis of esophagogastric cancers. Gastrointest Endosc 2005;62:521–8.
16. Haringsma J, Tytgat GN. The value of fluorescence techniques in gastrointestinal endoscopy: Better than the endoscopist's eye? The European experience. Endoscopy 1998;30:416–8.
17. Haringsma J, Tytgat GN, Yano H, et al. Autofluorescence endoscopy: Feasibility of detection of GI neoplasms unapparent to white light endoscopy with an evolving technology. Gastrointest Endosc 2001;53:642–50.
18. Izuishi K, Tajiri H, Fujii T, et al. The histological basis on detection of adenoma and cancer in the colon by autofluorescence endoscopic imaging. Endoscopy 1999;31:511–6.
19. Schomacker KT, Frisoli JK, Compton CC, et al. Ultraviolet laser-induced fluorescence of colonic polyps. Gastroenterology 1992;102:1155–60.
20. Kapadia CR, Cutruzzola FW, O'Brien KM, et al. Laser-induced fluorescence spectroscopy of human colonic mucosa. Detection of adenomatous transformation. Gastroenterology 1990;99:150–7.
21. Cothren RM, Sivak MV Jr, Van Dam J, et al. Detection of dysplasia at colonoscopy using laser-induced fluorescence: A blinded study. Gastrointest Endosc 1996;44:168–76.
22. Uedo N, Higashino K, Ishihara R, et al. Diagnosis of colonic adenomas by new autofluorescence imaging system: A pilot study. Dig Endosc 2007;19:134–8.

23. Hamilton SR, Aaltonen LA, eds. World Health Organization classification of tumours: Pathology and genetics of tumours of the digestive system. Lyon, France: IARC Press, 2000;104–19.
24. Fujii T, Hasegawa RT, Saitoh Y, et al. Chromoscopy during colonoscopy. Endoscopy 2001;33:1036–41.
25. Kudo S, Tamura S, Nakajima T, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointest Endosc 1996;44:8–14.
26. Hurlstone DP, Cross SS, Adam I, et al. A prospective clinicopathological and endoscopic evaluation of flat and depressed colorectal lesions in the United Kingdom. Am J Gastroenterol 2003;98:2543–9.
27. Adachi M, Okinaga K, Muto T. Flat adenoma of the large bowel: Re-evaluation with special reference to central depression. Dis Colon Rectum 2000;43:782–7.
28. Tanaka S, Haruma K, Ito M, et al. Detailed colonoscopy for detecting early superficial carcinoma: Recent developments. J Gastroenterol 2000;35:121–5.
29. Kiesslich R, Von Bergh M, Hahn M, et al. Chromoendoscopy with indigo carmine improves the detection of adenomatous and nonadenomatous lesions in the colon. Endoscopy 2001;33:1001–6.
30. Lapalus MG, Helbert T, Napoleon B, et al. Does chromoendoscopy with structure enhancement improve the colonoscopic adenoma detection rate? Endoscopy 2006;38:444–8.
31. Rembacken BJ, Fujii T, Cairns A, et al. Flat and depressed colonic neoplasms; a prospective study of 1000 colonoscopies in the UK. Lancet 2000;355:1211–4.
32. Sano Y, Muto M, Tajiri H, et al. Optical/digital chromoendoscopy during colonoscopy using narrow-band image system. Dig Endosc 2005;17:43–8.
33. Chiu HM, Chang CY, Chen CC, et al. A prospective comparative study of narrow-band imaging, chromoendoscopy, and conventional colonoscopy in the diagnosis of colorectal neoplasia. Gut 2007;56:373–9.
34. Rex DK, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. Gastroenterology 2007;133:42–7.
35. Kudo S. Colonoscopic diagnosis and management of nonpolypoid early colorectal cancer. World J Surg 2000;24:1081–90.
36. Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. Gastroenterology 2001;120:1657–65.
37. Tsuda S, Veress B, Toth E, et al. Flat and depressed colorectal tumours in a southern Swedish population: A prospective chromoendoscopic and histopathological study. Gut 2002;51:550–5.
38. Soetikno R, Friedland S, Kaltenbach T, et al. Nonpolypoid (flat and depressed) colorectal neoplasms. Gasrtoenterology 2006;130:566–76.
39. Woolfson IK, Eckholdt GJ, Wetzel CR, et al. Usefulness of performing colonoscopy one year after endoscopic polypectomy. Dis Colon Rectum 1990;33:389–93.
40. Hofstad B, Vatn M, Larsen S, et al. Growth of colorectal polyps: Recovery and evaluation of unresected polyps of less than 10 mm, 1 year after detection. Scand J Gastroenterol 1994;29:640–5.

CONFLICT OF INTEREST

Even though the prototype autofluorescence imaging scope was provided by Olympus Medical Systems Corp., Tokyo, Japan, this is not a collaborative study. Thus, this study being an absolutely independent investigation, there is neither financial support nor interest from Olympus Corporation.

False-positive nonlifting sign

To the Editor:

We read with great interest the article by Han et al[1] describing the influence of biopsy on the nonlifting sign in submucosal invasive colorectal carcinoma (SICC).

We have previously performed similar research.[2] Two hundred seventy-one colorectal neoplastic lesions, including 38 SICCs, were evaluated prospectively, and the presence or absence of the nonlifting sign and endoscopic diagnosis of invasion depth were compared with histopathologic findings. The proportion of sm1 cancers was 31.6%, and 16 of the 38 SICCs (42.1%) showed the nonlifting sign.[3]

In comparison with our results, the incidence of the nonlifting sign reported by Han et al was low (19.7%), and the proportion of sm1 cancers was high (47.4%). This discrepancy may be explained by the fact that Han et al excluded 82 cases in which the nonlifting sign was not checked. Such lesions, judged as sm2 or 3 cancers only on the basis of endoscopic assessment, were highly suspected to show the nonlifting sign.

In addition, we believe that intramucosal lesions, not SICCs, should be evaluated to assess the influence of biopsy. Intramucosal lesions with no history of biopsy rarely show the nonlifting sign,[4] and therefore in this situation the nonlifting sign can be explained by the influence of biopsy. In our study, among the 31 intramucosal neoplastic lesions that were subjected to biopsy before EMR, 2 (6.5%) showed the nonlifting sign, whereas only 2 of 202 cases (1.0%) without a history of biopsy did so ($P = .03$, unpublished data). This significant difference confirmed the influence of biopsy on the nonlifting sign.

Another reason for the discrepancy between the results of the 2 series was the difference in certain aspects of the histopathologic diagnosis. First, Han et al used a different classification of sm depth depending on the method of resection. Their sm1 cancer in surgically resected specimens could have been judged as sm2 if EMR had been performed for it. Second, to assess the invasion depth of SICCs accurately, we believe that resected specimens should be stretched before fixing. The figures presented by Han et al suggest that their handling of the specimens was inappropriate for detailed histopathologic evaluation. Finally, the condition of the muscularis mucosae requires closer attention.[5] When the muscularis mucosae has been destroyed, invasion depth should be measured from the surface of the lesion. In the case shown by Han et al in their Figure 2, the muscularis mucosae in the center of the lesion was destroyed, and therefore we consider that the invasion depth was more than 1000 μm, necessitating classification as sm2.

The conclusion of our study was that the nonlifting sign cannot reliably predict deeper cancer invasion in comparison with endoscopic diagnosis. For successful endoscopic treatment, accurate endoscopic assessment without biopsy is necessary to avoid a "false-positive nonlifting sign."

Nozomu Kobayashi, MD
Division of Endoscopy
National Cancer Center Hospital
Tokyo, Japan
Department of Diagnostic Imaging
Tochigi Cancer Center
Tochigi, Japan
Yutaka Saito, MD, PhD
Takahisa Matsuda, MD
Division of Endoscopy
National Cancer Center Hospital
Tokyo, Japan
Kuang-I Fu, MD, PhD
Department of Endoscopy
National Cancer Center Hospital East
Chiba, Japan

REFERENCES

1. Han KS, Sohn DK, Choi DH, et al. Prolongation of the period between biopsy and EMR can influence the nonlifting sign in endoscopically resectable colorectal cancers. Gastrointest Endosc 2008;67:97-102.
2. Kobayashi N, Saito Y, Sano Y, et al. Determining the treatment strategy for colorectal neoplastic lesions: endoscopic assessment or the non-lifting sign for diagnosing invasion depth? Endoscopy 2007;39:701-5.
3. Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach and colon. Gastrointest Endosc 2003;58:S3-S43.
4. Uno Y, Munakata A. The non-lifting sign of invasive colon cancer. Gastrointest Endosc 1994;40:485-9.
5. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaborative study. J Gastroenterol 2004;39:534-43.

doi:10.1016/j.gie.2008.01.019

Response:

We read the letter from Kobayashi et al discussing false-positive nonlifting signs. We are pleased to receive their interesting comments, and we agree that accurate endoscopic assessment without biopsy is necessary to avoid false-positive nonlifting signs.

Our previous study showed that, among 76 patients with submucosal invasive colorectal carcinomas (SICCs), the incidence of nonlifting signs was 19.7% (15/76), and the proportion of sm1 cancers was 47.4% (36/76).[1] In contrast, Kobayashi et al[2] reported that among 38 patients with SICCs, the incidence of nonlifting signs was 42.1% (16/38) and the proportion of sm1 cancers was 31.6% (12/38). While the discrepancy between these sets of findings may have resulted from the limitations of our retrospective study, other researchers have reported results similar to ours. For example, Ishiguro et al[3] reported that the proportion of sm1 cancers was 51.7% (31/60) and the incidence of nonlifting signs