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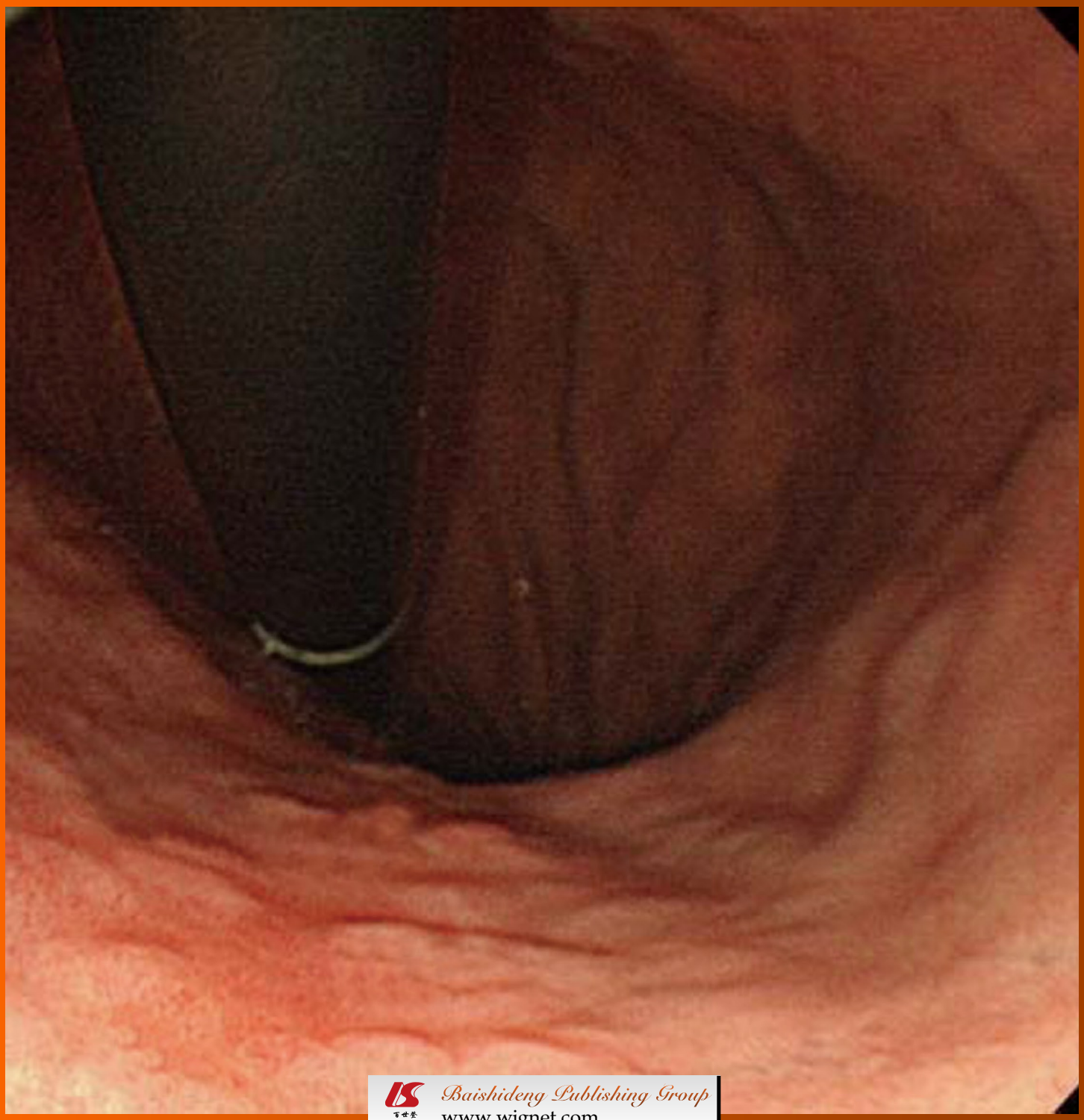

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TOPIC HIGHLIGHT

Peter Schemmer, MBA, Professor, *Series Editor*

Diagnosis and management of Barrett's metaplasia: What's new?

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Abstract

Barrett's esophagus (BE) is a complication of gastroesophageal reflux disease, and a premalignant lesion for esophageal adenocarcinoma (EAC). Observational studies suggest that endoscopic surveillance is associated with the detection of dysplasia and EAC at an early stage along with improved survival, but controversies still remain. The management of patients with BE involves endoscopic surveillance, preventive and clinical measures for cancer, and endoscopic and surgical approaches to treatment. Deciding upon the most appropriate treatment is a challenge. This study presents the results and the effectiveness of these practices.

Key words: Barrett's esophagus; Intestinal metaplasia; Metaplastic columnar mucosa; Esophageal premalignancy; Esophageal adenocarcinoma

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INTRODUCTION

Barrett's esophagus (BE) is a sequel of longstanding gastroesophageal reflux disease (GERD) and a premalignant lesion of esophageal adenocarcinoma (EAC), a cancer type whose incidence has been rapidly increasing in the Western world[1]. Interpretation of the exploding body of knowledge about BE is impaired by the use of several conflicting definitions[2]. The challenge is to achieve a definition which can be accepted world-wide. The initial informal consensus definition of BE is the partial replacement of normal squamous mucosa that lines the distal esophagus with metaplastic columnar mucosa[3].

BE is judged to develop through the process of metaplasia in which one adult cell type replaces another. The diagnosis of columnar-lined esophagus is typically established at endoscopy, but the final "definitive" diagnosis is confirmed by histological examination of biopsy tissue[4].

Over the last 20 years, particularly in the United States and Germany, many clinical researchers have applied a restrictive definition of BE including only individuals in whom intestinal-type metaplasia has been found[2], because this is the only type of esophageal columnar epithelium that clearly predisposes to malignancy. The Montreal Workshop agreed that the label "Barrett's esophagus" should be used when any type of esophageal columnar metaplasia is histologically confirmed, with the qualifier of the existence or absence of intestinal type-metaplasia[3].

Unfortunately, this simple conceptual definition does not translate readily into clinically useful diagnostic cri-

teria, because there are no universally accepted precise and validated landmarks delineating the distal extent of the esophagus. Moreover, there is no method for checking whether gastric-type columnar epithelia found in the distal esophagus are metaplastic[4]. The epithelial type required for BE diagnosis is currently unknown. The divergence between the United States and the British Society guidance is related to intestinalization and the presence of goblet cells[1].

Intestinal-type epithelium can be readily identified by the pathologist and, unlike the gastric-type epithelium, it is clearly abnormal when located in the esophagus[5]. However, there are data suggesting that cardia-type epithelium may not be normal, but rather a metaplastic lining that develops as a consequence of GERD[6]. Recent data suggest that cardia-type epithelium has histochemical and genetic abnormalities similar to those found in specialized intestinal metaplasia (SIM), which may predispose to malignancy, although the magnitude of that risk is not yet clearly defined[7].

Correct interpretation of biopsies at and around the gastroesophageal junction currently depends entirely on the accuracy of the endoscopist in locating biopsies. Some authors agree that the restricted definition of BE must be abandoned and that the importance of finding goblet cells in esophageal columnar metaplasia has been overestimated[2]. In addition, they recognize the malignant potential of "negative for intestinal-type metaplasia" BE biologically plausible. Since any histological type of esophageal columnar metaplasia carries risk for EAC, the diagnosis of BE should no longer require demonstration of intestinal-type metaplasia[2,7].

NATURAL HISTORY

In the 1960s, EAC was so rare that authorities questioned its existence. Over the recent decades, a marked change in the epidemiology of esophageal malignancy in North America and Europe has been reported, with an increasing incidence of EAC[8,9]. The reasons for this change are largely unknown, but several lifestyle and dietary risk factors have been proposed, like obesity, smoking and alcohol consumption. To date, relatively few studies have evaluated obesity and other lifestyle risk factors associated with esophageal premalignancy or potential biologic mechanisms underlying these epidemiologic observations[10].

GERD is a key factor for BE development, but other factors may underlie its development, since it only occurs in a minority (10%-15%) of patients with GERD. The key drivers of the development of dysplasia and EAC are still unknown[2,10,11].

MANAGEMENT OF BE

The management of patients with BE involves four major components: treatment of the associated GERD, measures to prevent cancer, endoscopic surveillance to detect dysplasia, and treatment of dysplasia.

The primary goal of antireflux therapy with proton pump inhibitors (PPI) for patients with BE is to control reflux symptoms. In addition, the goal of therapy is to prevent cancer development. Available data suggest, but do not prove, that aggressive antireflux therapy might also prevent cancer in these patients[12].

Observational clinical trials suggest that PPIs can protect patients from developing neoplasia[12,13]. Some prospective clinical studies have shown that PPI therapy is associated with a decrease in proliferation markers, a potentially cancer-protective effect, in biopsy specimens of Barrett's metaplasia[14,15]. However, prospective clinical studies have yet to prove that PPI therapy can prevent the development of dysplasia and its progression to BE[4].

Most available reports suggest that aspirin and other non-steroidal anti-inflammatory drugs can protect against cancer development in BE, although definitive studies are lacking. A recent technical review by The American Gastroenterology Association has concluded that it is appropriate to consider the prescription of low-dose aspirin for patients with BE who also have risk factors for cardiovascular disease[4].

Antireflux surgery (fundoplication) is another option for controlling GERD in patients with BE, although this does not appear to be more effective at preventing EAC than medical therapy[16].

Risk factors

There is a need to identify factors that are able to predict which patients with BE have an increased risk of developing high-grade dysplasia (HGD) and EAC. The risk is predominantly determined by the presence of low-grade dysplasia (LGD), a known duration of BE > 10 years, greater length of BE, and presence of esophagitis[17].

The study of molecular biomarkers of cancer progression could not only allow us to identify the group at high risk of progression of BE to cancer but also potentially to predict the response to endoscopic therapies[18].

Endoscopic surveillance

The transition of BE to adenocarcinoma is believed to progress through LGD and HGD, thus justifying endoscopic surveillance for these pre-malignant stages[19].

In the absence of any preventive strategy, regular surveillance to identify early neoplasia is the most pragmatic approach; thus, most international gastroenterological societies advise surveillance programs in patients with BE[18,20]. Intervals of 3-5 years have been suggested for patients who have no dysplasia, 6-12 mo for those who present LGD, and every 3 mo for patients with HGD who receive no invasive therapy[20]. Endoscopic surveillance can detect curable early neoplasia, and asymptomatic cancers discovered during surveillance are less advanced than those found in patients who present with cancer symptoms, such as dysphagia and weight loss[19].

In the absence of mucosal abnormalities, random four quadrant biopsies every 1-2 cm is the standard prac-

tice (Seattle Protocol). Unfortunately, this "blind biopsy protocol" renders visual recognition of areas of dysplasia or early EAC impossible[21,22]. Moreover, dysplasia is an imperfect marker for disease progression of BE to EAC. There are significant variations in interobserver agreement among pathologists, significant sampling errors in obtaining specimens, and the natural history of dysplasia is not linear and predictable for invasive potential[23,24]. The dilemma is identifying BE before the appearance of adenocarcinoma.

On the other hand, the relevance of surveillance programs has been questioned because they have never been shown to have any effect on survival and so are not cost-effective[23].

In a recent large population-based study, the absolute risk of EAC after a diagnosis of BE was several times lower than the risk reported in previous studies, and this forms the basis for current surveillance guidelines. This study is one the largest follow-up studies to date on the risk of adenocarcinoma in patients with BE[25].

As compared with the risk in the general population, the relative risk of adenocarcinoma was 11.3 and the absolute annual risk was 0.12%. This is much lower than the assumed risk of 0.5%, the basis of surveillance guidelines, which involved only a few hundred patients, thus increasing the risk of publication bias[25].

There is a solid evidence that EAC will develop in very few patients with BE[23]. Detection of LGD in the initial endoscopy was associated with a incidence rate of adenocarcinoma of 5.1 cases per 1000 person-year. Risk estimates for patients with HGD were slightly higher[25]. In contrast, the incidence rate among patients without dysplasia was 1.0 case per 1000 person-year[25].

The results of this study[25], together with another recent study[26] as well as studies of cost-effectiveness and patient quality of life[27,28], suggest that the risk of EAC among patients with BE is so minor that in the absence of dysplasia, routine surveillance of such patients is of doubtful value[25,29].

Intestinal metaplasia of the gastroesophageal junction is common in the population, but the natural history of this condition remains unclear. Subjects with intestinal metaplasia of the cardia who have distinct demographic and clinical characteristics from BE subjects, do not progress to adenocarcinoma, and may not require surveillance[28].

Advanced endoscopic imaging techniques

Wide-field technologies, high resolution and magnification endoscopy, multiple wide-field technologies including narrow-band imaging (NBI) and the Fujinon Intelligent Color Enhancement system, have been developed with the goal of highlighting suspicious gastrointestinal (GI) mucosa[30].

Better imaging modalities have the potential to improve detection of BE and surveillance for dysplasia and cancer. Many new endoscopic techniques continue to be developed, including magnification endoscopy, chromoendoscopy, and NBI. These techniques aim to achieve the best possible results with visually guided biopsies, to identify LGD and HGD and high risk patients for EAC and to reduce the number of random biopsies[31,32]. However, but none of these techniques is currently routinely used in clinical practice.

The diagnosis of BE with regular endoscopy may not always be accurate, because biopsy of specimens from short segment BE has been shown to identify metaplasia in only 40%-60% of patients. Furthermore, because the distribution of dysplasia and early EAC is uneven and focal, the accurate detection of these conditions using standard biopsy technique is low[33].

Chromoendoscopy involves the application of chemical agents that highlight various features of the esophageal mucosa in an attempt to improve the detection of abnormalities. Reports on the use of methylene blue, which is absorbed by non-dysplastic intestinal-type epithelium, have reported variable results[34]. A recent meta-analysis compared the detection rates for neoplasia in BE between methylene blue staining and four-quadrant, random biopsies of Barrett's metaplasia. No significantly higher yield was found for methylene blue over random biopsies in detecting HGD and early cancer[35]. In addition, another report has raised the issue of DNA damage resulting from methylene blue staining and white light illumination[36]. These concerns, along with safety issues, increased cost and procedure time, have prevented the widespread use of vital dye staining chromoendoscopy techniques.

Magnifying endoscopy with indigo carmine and acetic acid instillation has been reported to correctly identify SIM and HGD[37]. Various mucosal pit patterns, such as ridged/villous, circular and irregular/distorted patterns were identified by Sharma *et al*[37,38]. Ridged or villous patterns were associated with intestinal metaplasia, while the irregular or distorted pattern was noted with Barrett's HGD or superficial adenocarcinoma.

Guelrud *et al*[39] described four pit patterns using acetic acid and magnification endoscopy (round, reticular, villous and ridged) and found ridged and villous patterns to be associated with intestinal metaplasia. Overall, however, the pit pattern categorization systems have yet to be standardized, and there is high inter-observer variability.

NBI is a new endoscopic diagnostic technique capable of providing virtual chromoendoscopic images using only a single button touch. The technique consists of an electronic endoscope system and a source of light equipped with a narrow band filter, yielding very clear images of microvessels on mucosal surfaces. NBI with magnification could help in assessing the microstructural (pit) and vascular patterns of any suspicious areas detected in BE. Several studies have identified pit patterns and capillary patterns in BE[40-42]. Regular pit patterns include round, linear, tubular/ridged, and villous types. Irregular patterns and absent pit patterns are also reported. Microvascular patterns are classified as either regular or irregular. The sensitivity and specificity of the irregular microvascular and pit patterns for predicting HGD was

as high as 90% and 100% in an observational study[40]. Similarly, the villous, ridged, and absent pit patterns were considered highly suggestive of SIM, while round patterns were associated with columnar lined epithelium.

In a subsequent study by the same research team, a simplified classification system was proposed consisting of four different types of patterns: (1) round pits with regular microvasculature; (2) villous/ridged pits with regular microvasculature; (3) absent pits with regular microvasculature; and (4) distorted pits with irregular microvasculature. Pattern A had positive predictive value (PPV) and negative predictive value (NPV) of 100% and 97%, respectively, for columnar mucosa without intestinal metaplasia. Patterns B and C had a PPV and NPV of 88% and 91%, respectively, for SIM. Pattern D had a PPV and NPV of 81% and 99%, respectively, for HGD[42].

A prospective controlled trial comparing NBI with standard endoscopy found that NBI detected significantly more patients with dysplasia and higher grades of dysplasia with fewer biopsy samples[32]. A recent meta-analysis confirmed a high diagnostic accuracy of NBI with magnification in diagnosing SIM and dysplasia[43]. However, Kara *et al*[41] compared high resolution endoscopy using indigo carmine chromoendoscopy with NBI in 14 patients with Barrett's HGD and found the same efficacy in both techniques. Similar results were found by Curvers *et al*[44]. Moreover, poor inter-observer agreements have been reported in some reports[44-46].

In a recent study, Silva *et al*[47] evaluated the accuracy and inter-observer agreement of different classification systems grading BE using magnification endoscopy and narrow band imaging. They found all systems to have limitations in terms of accuracy for the detection of SIM, identification of dysplastic BE, and inter-observer agreement, regardless of the endoscopist's expertise[47]. Thus, even when these techniques are used and current classification systems are followed, they cannot as yet replace random biopsies and targeted biopsies of visible lesions.

In conclusion, the main limitations of the NBI system include the learning curve associated with the new technology, the lack of sufficiently validated and standardized classification schemes for the NBI patterns observed in various conditions, and the limited number of randomized controlled trials comparing NBI with conventional white light endoscopy. Thus, additional studies are needed before the system can be incorporated into routine clinical practice. Although initial studies are promising, none of these techniques has yet been shown to provide sufficient additional clinical information (beyond that of high resolution white light endoscopy) to justify its routine application for surveillance purposes. A thorough examination using high resolution white light endoscopy after clearing the mucosa with mucolytics should be the minimum standard to improve detection during Barrett's surveillance[2,44-47].

There is convincing evidence that biopsy guided by mucosal appearance, observing surface details, using high resolution endoscopes, is now substantially more sensitive for dysplasia and EAC detection than biopsies taken according to the Seattle Protocol[2].

Finally, maximization of the quality of endoscopic surveillance in BE requires more than enhancements of endoscopic equipment. Unfortunately, general endoscopists are rarely exposed to patients with dysplasia and EAC in training and routine clinical practice[31].

Overview of new technologies

The last several years have been marked by the emergence of several innovative "optical biopsy" technologies that provide real-time subcellular imaging of GI tract. Although many endoscopic techniques have initially shown high accuracy rates, these technologies are still evolving[30].

Optical coherence tomography[30,48]: Optical coherence tomography (OCT) is an endoscopic technique using light waves to generate images. It is an optical signal acquisition and processing method that can capture high resolution, three dimensional images within any optical scattering media, such as a biological tissue.

OCT is usually performed by introducing a linear or radial catheter into the accessory channel of a standard endoscope. An increased resolution allows for visualization of microscopic mucosal features such as villi, crypts and glands, but the sampling depth of OCT is limited to 1-2 mm by the scattering of light by tissue and the resolution is not sufficient to visualize some abnormalities[30].

Adler *et al*[48] reported the findings of three-dimensional OCT in BE and in a follow-up after radiofrequency ablation (RFA) looking for residual BE from incomplete ablation and buried BE glands beneath regenerative neosquamous epithelium.

Endocytoscopy: Endocytoscopy is based on the principle of light contact microscopy that allows real-time visualization of the cellular structures of the superficial epithelial layer in a plane parallel to the mucosal surface. Often, the mucosa is treated with a mucolytic such as N-acetylcysteine prior to staining with an absorptive contrast agent such methylene blue, cresyl violet or toluidine blue[30].

Confocal laser endomicroscopy[30,49]: Confocal laser endomicroscopy integrates a confocal laser microscope either in the tip of an endoscope or as a probe that can be passed through the channel of any endoscope. It offers the ability to make a real-time, *in vivo* histological assessment of GI mucosa[30].

In order to obtain images, the patient must be given a fluorescent contrast agent, like fluorescein, which appropriately highlights the vasculature, lamina propria and intracellular spaces, allowing visualization of vessel patterns and cellular architecture[30].

Sharma *et al*[49], in a recent, international multicenter, prospective, randomized, controlled trial demonstrated significantly improved sensitivity in the detection of

HGD and early carcinoma in BE with probe-based confocal laser endomicroscopy than with high-definition white-light endoscopy.

The ability to make a real-time histopathological diagnosis is potentially invaluable in enhancing the detection of early neoplasia and facilitating endoscopic invasive therapies. However, widespread application of these technologies is still limited by their high cost and the learning curve associated with the interpretation of the images[30].

ENDOSCOPIC ERADICATION THERAPY

Non-dysplastic Barrett esophagus and LGD

Several reports have established that endoscopic ablative therapies can eradicate non-dysplastic and low grade dysplastic Barrett's epithelium in the short-term for the majority of patients. It is not clear whether the potential benefit of ablation in reducing the small risk of cancer in this group warrants the risks and substantial expense of the ablative procedures[4]. A recent meta-analysis demonstrated that ablation significantly reduces the risk for cancer in patients with non-dysplastic BE and LGD[50].

Fleischer *et al*[51] proposed RFA as a safe, efficient and cost-effective method that should be considered in the management of patients with non-dysplastic or low-grade dysplastic BE, because it achieves complete response in all patients, eliminates all risk of developing cancer, with rare advent effects and less expense than surveillance in terms of absolute costs[51]. These authors reported complete response by intestinal metaplasia in 92% at 5-year follow-up. Biopsy depth was adequate to detect recurrence, and all failures (4/4, 100%) were converted to complete response with single session focal RFA[52].

However, in a recent Editorial, Spechler suggested that routine ablation of BE would not be an appropriate choice at this time and recommend a randomized, controlled trial to establish the cost, the risks and benefits of RFA for patients with BE[53].

An ideal management paradigm for a non-dysplatic population in the future might be to risk stratify patients by assaying for a genotype associated with propensity for neoplastic progression, and then eradicate the non-dysplasic BE in those patients at highest risk, with surveillance or no action in those patients at lower or zero risk.

HGD

Deciding upon the most appropriate treatment in a patient with BE and HGD is currently more difficult than in any time in the history of the disease. Until recently, surgical resection was the undisputed treatment of choice for localized esophageal cancer with or without regional lymph node metastases. This paradigm is currently challenged by interventional endoscopy (in the treatment of early cancer) and combined radiotherapy/chemotherapy (in treatment of regional and more advanced esophageal cancer)[54].

Endoscopic eradication therapy for BE includes endoscopic mucosal resection (EMR) and/or the endoscopic ablative techniques, which use thermal, photochemical, or radiofrequency energy to destroy the Barrett's epithelium without providing a tissue specimen. Results from a large multicenter cohort study highlight the low annual incidence rates of dysplasia and early EAC in patients with BE (EAC, 0.27%; HGD, 0.48%; and HGD/EAC 0.63%)[55].

For patients with verified HGD or early cancer in BE, there are generally four proposed management options: esophagectomy, endoscopic therapies that ablate the neoplastic tissues, EMR and intensive endoscopic surveillance in which invasive therapies are withheld until biopsy specimens reveal adenocarcinoma[4].

An emerging concept in the endoscopic management of neoplasia in BE is that endoscopic eradication may be best achieved by first removing visible abnormalities with EMR, a process which provides invaluable staging information as well as therapy, followed by the ablation of all remaining Barrett's metaplasia[4].

The largest reported experience with EMR as the primary technique to eradicate HGD and early cancer in BE involved 349 patients followed up for a mean of 63.6 mo. The early complete eradication rate for neoplasia was 97%, but metachronous neoplasms subsequently developed in 21.5% of patients; 85% of those received further endoscopic eradication therapy and achieved a second complete remission. Risk factors for metachronous neoplasm included piecemeal resection of the lesion, long-segment BE, no use of mucosal ablative therapies after EMR, time for complete remission over 10 mo, and multifocal neoplasia[55].

This fact highlights the importance of total eradication of intestinal metaplasia and not only areas of HGD/EAC. Recently the role of complete BE removal in patients with HGD/early EAC by using EMR has been explored. It involves the endoscopic resection of the entire BE, including the neoplastic lesion. In a recent study, Peters *et al*[56] evaluated the efficacy of this technique in 39 BE patients with early neoplasia (25 HGD, 14 EAC). Complete eradication of early neoplasia was achieved in all patients (mean number of 3 sessions), and complete removal of BE in 89% of patients. During a mean follow-up of 11 mo, none of the patients had a recurrence of intestinal metaplasia or dysplasia.

Among all the endoscopic techniques, photodynamic therapy (PDT) clearly has been most extensively used and reported in a randomized, controlled trial. Overholt *et al*[57] were the first to provide long-term results of a randomized, controlled trial that compared treatment alternatives in HGD patients. In this study, 208 patients with HGD were randomized 2:1 to receive either omeprazole alone or omeprazole with sodium porfimer PDT. In the initial report of this study, with a 2-year follow up, the primary goal of complete eradication of HGD was achieved in 77% of patients in the PDT group and 39% of patients in the control group ($P < 0.0001$). In a subsequent follow up study with these patients 5 years later, intention-to-treat analyses showed that PDT was significantly more ef-

fective than omeprazole alone for eradicating HGD [77% (106/138) *vs* 39% (27/70), $P < 0.0001$] and that PDT-treated patients were less likely to progress to cancer (15% *vs* 29%, $P = 0.027$), although the trial was not designed specifically to test this outcome[58].

RFA is the only technique besides PDT that has been evaluated in a multicenter, prospective, sham-controlled, randomized trial in BE patients with dysplasia, including 63 patients with HGD (42 RFA, 21 sham). Complete eradication of dysplasia was achieved in 81% in the RFA arm compared with 19% in the sham group ($P < 0.001$), and complete eradication of intestinal metaplasia was achieved in 74% *vs* 0% ($P < 0.0001$) with no progression to cancer in patients in the RFA arm[59].

The use of RFA for complete eradication of BE has shown promise in trials conducted predominantly at tertiary academic centers, however less is known regarding outcomes in the community. Recently a multicenter study conducted at four community-based practices observed that safety and efficacy outcomes associated with RFA for BE are comparable to those reported in multicenter trial predominantly from tertiary academic centers. In addition, RFA was associated with improvement in disease-specific health-related quality of life[60]. RFA use in patients in whom ablative therapy has previously failed was described by Dunn *et al*[61] in 14 patients with residual HGD following PDT. An overall complete reversal of dysplasia was achieved in 86% with a combination of RFA and rescue EMR. The median total follow-up was 19 mo. The rate of strictures was 7% (1/14) and there was a low rate of buried glands (0.5% follow-up biopsies). This study is limited by its relatively small sample size and non-randomized design.

After endoscopic RFA of dysplastic BE, endoscopic biopsy samples are obtained to assess response to therapy. Whether these biopsies are of adequate depth to assess efficacy is unknown. Shaheen *et al*[62] analyzed 5648 biopsy fragments from 113 subjects (78 RFA, 35 sham; mean 50.0 fragments per subject). Squamous biopsy samples from RFA and sham subjects demonstrated subepithelium at similar rates (78.4% *vs* 79.1%, respectively). Columnar biopsy samples from RFA and sham subjects also included subepithelium at similar rates (99% *vs* 98.8%, respectively). Almost 80% of all biopsy samples were adequate to evaluate for subsquamous intestinal metaplasia.

If an ablation procedure does not destroy all of the metaplastic epithelium, then the partially ablated mucosa may heal with an overlying layer of neosquamous epithelium that buries metaplastic glands in the lamina propria, hiding them from the endoscopist's view. This "buried metaplasia" may have malignant potential[63]. A recent systematic review found in 22 reports on PDT for 953 patients, with buried metaplasia in 135 (14.2%). In 18 reports on RFA for 1004 patients, buried metaplasia was found in only 9 (0.9%). A major problem limiting the conclusions that can drawn from these reports is that they do not describe specifically how frequently biopsy specimens contained sufficient subepithelial lamina propria to be informative for buried metaplasia[63]. A different result was found by Vaccaro *et al*[64] who performed a retrospective analysis of patients with BE who underwent RFA. The cumulative incidence of newly detected intestinal metaplasia at 1 year was 25.9%. Pouw *et al*[65] evaluated the post-RFA neosquamous epithelium for genetic abnormalities and buried glandular mucosa and found neither persistent genetic abnormalities nor buried glandular mucosa. Therefore, the frequency and importance of buried metaplasia after endoscopic ablation remain unclear.

In conclusion, prospective, randomized trials have established that endoscopic ablation therapy with PDT and RFA is superior to treatment with PPIs alone for preventing the progression from HGD to cancer in BE. RFA has a similar efficacy to PDT, but gives less patient inconvenience and fewer side effects[46].

It is important to note that recurrence of intestinal metaplasia following endoscopic eradication therapy and the risk of squamous glands are associated with all ablative therapies and routine surveillance of these patients is required[17].

Unfortunately, the follow up duration of most reported studies on treatments for HGD and early cancer in BE is considerably less than 5 years, which severely limits the conclusions that can be drawn regarding the efficacy of therapy. In addition, most studies on this issue are not randomized or controlled and involve relatively small numbers of patients. Also, it remains unclear whether the excellent results for endoscopic eradication therapy reported by the few expert centers that have studied those techniques can be reproduced in the community[4].

Presently, the choice between surgical or endoscopic therapy for early Barrett's esophageal cancer is, in most institutions, still primarily based on the available expertise with one or other treatment modality and the patient's operation risk, and both treatments have limitations[54,66].

CONCLUSION

In the 1950s, Norman Barrett and other colleagues published a study on the association between EAC and esophageal columnar metaplasia. Ever since then, we have been looking forward to achieving a world-wide definition of BE, the best screening, surveillance and treatment modality.

Aggressive antireflux therapy with PPI can protect against but cannot prevent the development of dysplasia and its progression to adenocarcinoma. Both endoscopic and surgical treatments still have important limitations. It should be remembered that the best evidence will come from direct comparison in the form of a prospective trial, and this has not yet been carried out.

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TOPIC HIGHLIGHT

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Role of narrow band imaging in endoscopic submucosal dissection

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Abstract

Narrow band imaging (NBI) is a new image enhancement system employing optic digital methods to enhance images of blood vessels on mucosal surfaces, allowing improved visualization of mucosal surface structures. Studies have progressed over the last several years, and the clinical usefulness has been demonstrated. NBI has become frequently applied for preoperative diagnosis before endoscopic submucosal dissection (ESD) of digestive tract cancers, as well as for assessment of the range of ESD for *en-bloc* resection of large lesions. Consensus has been reached with regard to the usefulness of NBI for detecting micro-lesions of esophageal squamous cell carcinoma indicated for ESD, for the diagnosis of the range and depth. NBI has also been attracting attention for diagnosing gastric cancer based on the observation of micro blood vessels on the mucosal surface and mucosal surface microstructures. The usefulness of NBI has been reported in relation to various aspects of colon cancer, including diagnoses of the presence, quality, range, and depth of lesions. However, as NBI has not surpassed diagnostic methods based on magnifying observation combined with the established and widely employed dye method, its role in ESD is limited at present. Although NBI is very useful for the diagnosis of digestive tract cancers, comprehensive endoscopic diagnosis employing the combination of conventional endoscopy including dye spraying, EUS, and NBI may be important and essential for ESD.

Key words: Endoscopic submucosal dissection; Narrow band imaging; Digestive tract cancer

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INTRODUCTION

Endoscopic submucosal dissection (ESD) was first reported in the late 1990s in Japan as a treatment for early-stage gastric cancer, and it has rapidly spread, surpassing conventional endoscopic mucosal resection (EMR)[1-4]. The advantage of ESD it that *en-bloc* resection employing ESD is possible even if the lesion is large and pathological evaluation of *en-bloc* resected specimen is accurate. Therefore, the preoperative diagnosis of not only cancer but also its range is very important before ESD.

Recently, diagnoses based on the observation of micro blood vessels on the mucosal surface and mucosal microstructures by narrow band imaging (NBI) have rapidly become common. Previous studies reported that this pro-

cedure was useful for the diagnosis of tumors of the digestive tract, suggesting its usefulness in screening, the differentiation between epithelial and non-epithelial tumors, differentiation between benign and malignant tumors, and evaluation of the infiltration of digestive tract cancer[5-10].

The role of NBI in ESD has become increasingly important, and NBI has been employed for not only detecting early neoplastic lesions indicated for treatment and the differentiation of benign and malignant lesions, but also for diagnosis of the range of lesions.

In this report, the usefulness of NBI for ESD and current problems are described by digestive organ (esophagus, stomach, and colon).

PRINCIPLE OF NARROW BAND IMAGING

In vivo, pigments absorb a specific wavelength of visible light. Under an endoscope, a pigmental protein contained in blood, hemoglobin, can be observed. Figure 1 shows the absorption characteristics of hemoglobin. Strong peaks are noted at approximately 415 and 540 nm, suggesting that red light with a long wavelength is not absorbed. Therefore, to display capillaries in the superficial mucosal layer at a high contrast, blue and green light at 415 and 540 nm respectively, should be employed for illumination.

NBI is an image enhancement technology using the optical digital method developed by Olympus Co. Light is employed with central wavelengths of 415 and 540 nm, the same as those strongly absorbed by blood and strongly reflected and scattered by the mucosa. The spectrum widths are changed to narrow bands, through which images of micro blood vessels on the mucosal surface and mucosal micro patterns are enhanced at a higher contrast than those observed under white light[11].

Typical images are shown in Figure 2. On standard endoscopy, fine blood vessels in the superficial layer and thick blood vessels in the deep layer are visualized as red areas. In addition, NBI facilitates the observation of capillaries in the superficial layer, which cannot be observed on standard endoscopy. Furthermore, it is possible to identify blood vessels at different depths by differences in the color tone. As a result, NBI may improve the visualization of capillaries in the superficial mucosal layer, which is important for the early diagnosis of cancer. In addition, the absorption/diffraction of narrow band light with a central wavelength of 415 nm in the stomach and colon, as well as the visualization of fine structures on the mucosal surface as a white pattern in contrast to enhanced capillaries, are important. Microvascular features may be a useful independent factor in cancer diagnosis.

Esophagus

In the treatment of esophageal squamous cell carcinomas (ESCCs), early detection in the phase where endoscopic treatment, less invasive than surgery, is possible, is essential to improving the prognosis.

Noninvasive carcinoma (carcinoma *in situ*, m1; EP) and intramucosal invasive carcinoma limited to the lamina propria mucosae (m2; LPM) without vessel infiltration, have proved to have no lymph node or distant metastases. This has been shown by a large number of retrospective histopathological analyses of surgically resected esophageal squamous cell neoplasms (SCNs) and, as a result, endoscopic therapy may be considered as a treatment option for these lesions. EMR and ESD have been accepted widely for localized SCNs as an alternative to surgical therapy, especially in Japan, because of the considerable rates of surgical mortality and postsurgical complications related to esophagectomy (range 2.1% to 13.7%) that result in poor patient quality-of-life[11-13].

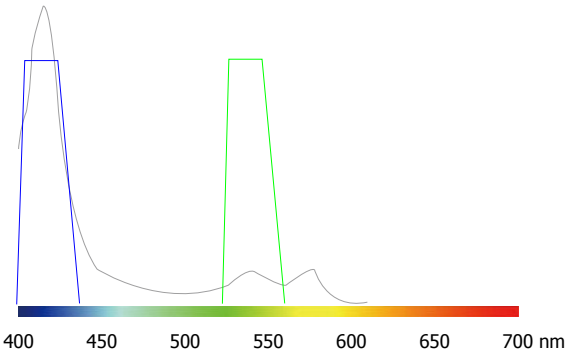

Figure 1 Light wavelength-related differences in hemoglobin absorption (hemoglobin absorption curve). The transverse axis indicates the wavelength of visible light. The longitudinal axis indicates the absorption coefficient. The curve represents the relationship between the wavelength and hemoglobin absorption coefficient (provided from Olympus).

There is a considerable increase in the number of esophageal SCNs indicated for local treatment thanks to recent developments in endoscopy, including magnifying endoscopy by using NBI.

The superficial esophageal vascular network consists of thick blood vessels in the submucosal layer, a branch-like vascular network existing immediately above the mucosal myotome, and the intra-epithelial papillary capillary loop (IPCL) vertical to the branch-like vascular network. On standard endoscopy, branch-like or larger blood vessels can be observed. When performing magnifying observation using NBI, which facilitates the visualization of hemoglobin, i.e., blood vessels, the IPCL may be visualized, as shown in Figure 2. Inoue *et al*[14] reported that changes in the IPCL pattern were very useful for the qualitative diagnosis of cancer/non-cancerous lesions and evaluation of the degree of infiltration. NBI is advantageous for IPCL-pattern recognition (Figure 3).

A basic diagnostic method for ESCCs is to observe the mucosa under a standard endoscope and find flare points/surfaces. When finding them, this method should be switched to NBI observation by pressing a switch, facilitating the visualization of the lesion site as a brownish area. Under magnifying observation, the qualitative diagnosis of cancer/non-cancerous lesions and evaluation of the degree of infiltration are performed based on the IPCL pattern. Currently, microcarcinoma can be relatively readily detected by making a diagnosis in this way (Figure 3).

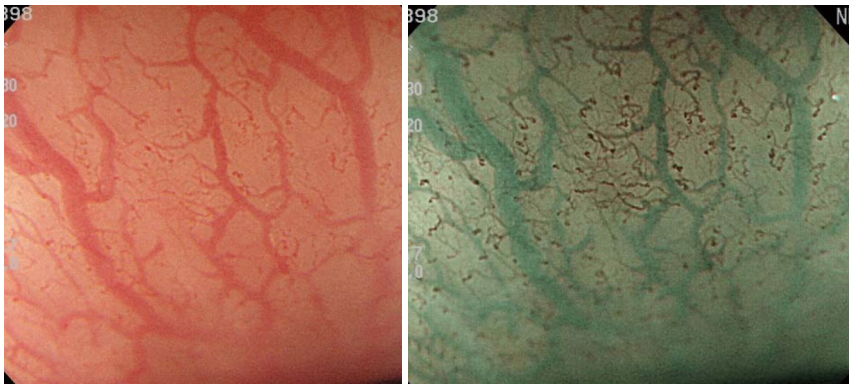

Figure 2 Basic effects of narrow band imaging (white light and narrow band imaging).

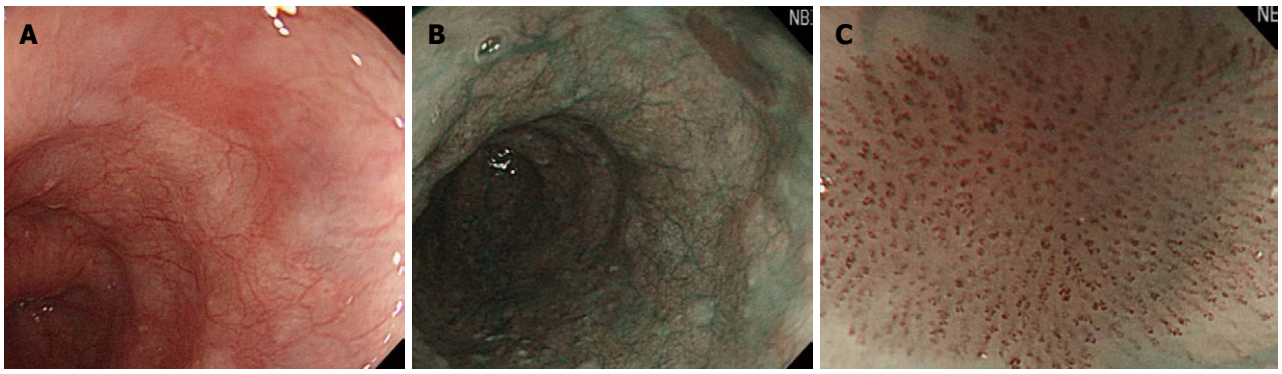

Figure 3 Diagnosis of an esophageal micro-lesion. A: In the upper esophagus, a flare lesion measuring 4 mm was noted; B: When switching standard endoscopy to narrow band imaging-combined magnifying endoscopy, the lesion could be recognized as a clear brownish area; C: On magnifying endoscopy, a tumorous intra-epithelial papillary capillary loop pattern was visualized.

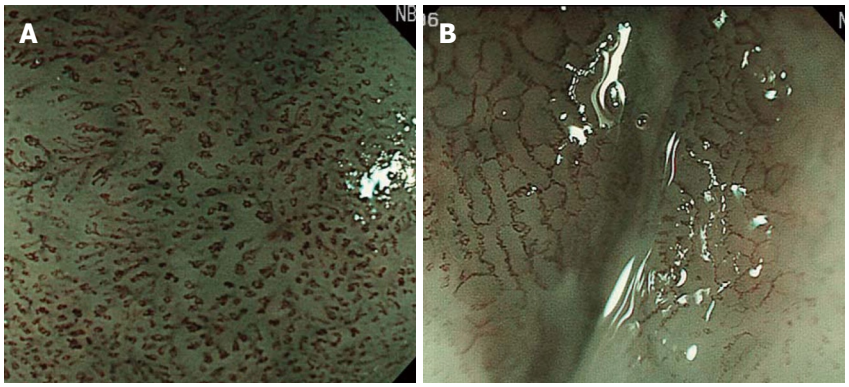

Figure 4 The development of narrow band imaging facilitated the visual observation of intra-epithelial papillary capillary loop, revolutionizing the diagnosis of the depth. A: Findings of narrow band imaging-combined magnifying observation of a lesion diagnosed as M2 after endoscopic submucosal dissection (ESD). Dilated and curving intra-epithelial papillary capillary loop (IPCL) with an irregular width extending in a transverse direction; B: Findings of narrow band imaging-combined magnifying observation of a lesion diagnosed as M3 after ESD. IPCL was severely damaged , and a connection with the adjacent IPCL was also observed.

Muto *et al*[5] compared conventional endoscopic white light imaging (WLI) with NBI in high-risk patients in a prospective, randomized study of the capacity to diagnose ESCCs, and reported that NBI was more useful for the early detection of superficial esophageal cancer.

Before the development of NBI, the preoperative depth of lesions indicated for ESD, i.e., lesions without lymph node metastasis at a depth up to that of intramucosal invasive carcinoma limited to the lamina propria mucosae (m2; LPM), was comprehensively diagnosed based on conventional observation under white light, EUS, and X-ray. However, it was difficult to reliably diagnose M2 and M3 prior to ESD. The development of NBI facilitated the visual observation of IPCL, revolutionizing the diagnosis of depth (Figure 4). However, it is necessary to demonstrate improved diagnosis of depth by add-

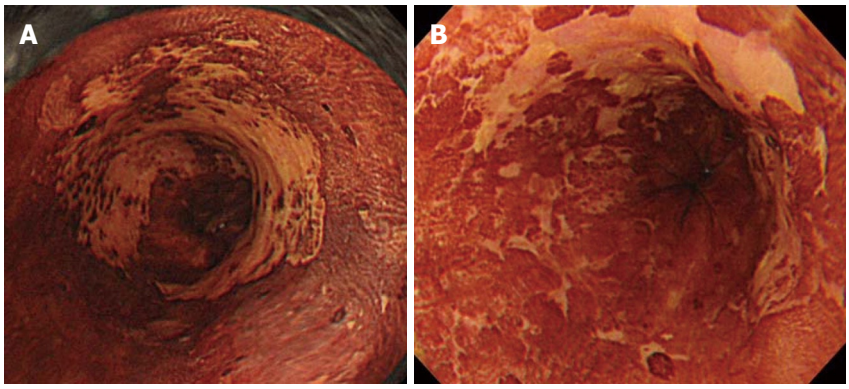

Figure 5 Lugol spray-induced morphological changes in lesions. A: A 4/5 circumferential zone unstained with Lugol was observed on the left side of the middle thoracic esophagus; B: The lesion shown in A, 2 wk after Lugol spraying. The morphology and size of the unstained zone changed.

ing NBI to the current diagnostic tools, and the further accumulation and investigation of cases is expected.

For ESD, the range of superficial esophageal SCNs is diagnosed by Lugol spraying, and its usefulness remains unchanged. However, this method causes unpleasant adverse effects such as severe chest pain and discomfort, and attention must be paid to possible patient allergy to iodine. Moreover, not only normal but also cancerous epithelium is partially desquamated by Lugol spraying because of its strong irritability. When Lugol is sprayed immediately before treatment, the size and morphology of regions not stained on the previous examination may be markedly changed and it should, therefore, be applied carefully (Figure 5). We require at least a 4-wk interval after the final Lugol spraying before ESD. When diagnosis of range is necessary immediately before ESD, we confirm the brownish area in NBI as the lesion. NBI can be introduced by pressing a switch, and it is very advantageous that this procedure is non-invasive.

NBI for esophageal superficial squamous cell carcinoma is the most advanced field, and consensus concerning the usefulness of NBI has been reached with regard to the detection of lesions and diagnoses of the quality, range, and depth.

Barrett's esophageal adenocarcinoma, which is frequent in Europe and the United States, is a type of adenocarcinoma. Therefore, the diagnostic method for this carcinoma differs from that for squamous cell carcinoma of the esophagus. On NBI, there are no characteristic findings. A diagnosis of Barrett's esophagus and Barrett's esophageal adenocarcinoma is made based on the fine mucosal structure and microvascular features, as described below in relation to the stomach. In patients with Barrett's esophagus, the risk of adenocarcinoma is 30 to 125 times higher than in the general population[15,16]. Therefore, close follow-up is needed. However, a recent meta-analysis showed that chromoendoscopy was less useful than random biopsy[17]. For the regular surveillance of Barrett's esophagus, a large number of random biopsies are still always performed.

In 2010, Mannath reporting the results of a meta-analysis[18], found that the sensitivity and specificity of NBI for the diagnosis of high-grade dysplasia were high in patients with Barrett's esophagus, suggesting its usefulness. In future, spot biopsy with NBI-combined magnifying observation at sites where high-grade dysplasia is suspected may decrease the number of unnecessary biopsies. This procedure may also be useful for diagnosis on endoscopic treatment for early neoplastic lesions.

Stomach

In contrast to the esophagus and colon, NBI is not ideal for screening in the stomach due to the presence of mucus/regurgitated bile and wide cavity-related light volume insufficiency. Even when examining normal mucosa, NBI findings differ between sites. In addition, chronic food-associated stimuli and *H. pylori*-related gastritis further complicate the understanding of magnifying NBI findings and diagnosis. However, with recent advances in research on magnifying NBI of the stomach, many studies have reported that NBI-combined magnifying observation is useful for differentiating malignant from benign epithelial tumors, evaluating the extent of gastric cancer, and predicting the histological type of gastric cancer[9,19-21]. NBI-combined magnifying endoscopy of the gastric mucosa facilitates the visualization of various microvessels below the mucosal epithelium and fine structures on the mucosal surface. For magnifying NBI-guided assessment of the stomach, it is necessary to analyze microvascular features and fine mucosal structures separately and make a diagnosis based on these findings.

Initially, we will explain the microsurface pattern. On NBI-combined magnifying endoscopy, the marginal crypt epithelium (MCE) is visualized as a white line, as shown in Figure 6. When the morphology of the white line is similar to that of the peripheral mucosa, the microsurface pattern is regarded as "regular". When the morphology, width, and arrangement are irregular in comparison with the peripheral mucosa, the microsurface pattern is regarded as "irregular". When the white line shows a tendency toward disappearance or completely disappears, the microsurface pattern is regarded as showing "disappearance tendency or disappearance". Many patients with an irregular pattern have cancer. However, it is often

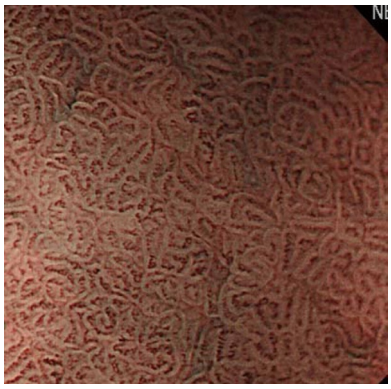

Figure 6 Marginal crypt epithelium. Coil-like subepithelial capillaries were visualized as brown areas, and the peripheral, multi-angle marginal crypt epithelium as a white area.

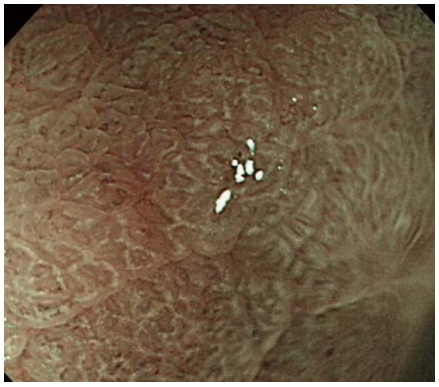

Figure 7 White opaque substance. Magnifying endoscopy findings with narrow band imaging within an adenoma of the superficial elevated type. The subepithelial microvessels cannot be visualized because a dense white opaque substance obscuring the subepithelial microvessels.

difficult to differentiate cancer from gastritis. In those with "disappearance tendency or disappearance", undifferentiated carcinoma involving the glandular cervical region and atrophic gastritis with mucosal atrophy must be considered. Therefore, it is important to make a diagnosis based on comprehensive findings including microvascular features.

In addition, a white opaque substance (WOS) and light blue crest (LBC) were reported by Yao *et al*[9] and Uedo *et al*[22], respectively, as indices of fine mucosal structures. WOS (Figure 7) is a white substance existing in the superficial mucosal layer. Its presence reduces mucosal permeability, making the visualization of microvessels immediately below the epithelium difficult. The characteristics of this substance remain to be clarified. WOS appears in the presence of gastric adenoma or cancer, in most cases. In particular, its appearance is more frequent in patients with gastric adenoma and previous studies suggested its usefulness for the diagnosis of this condition[9,23]. WOS is visualized on white light or NBI-combined magnifying observation. However, it is more clearly visualized on NBI-combined magnifying observation. LBC (Figure 8) is a specific phenomenon visualized

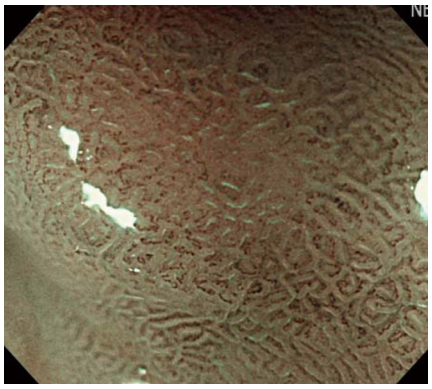

Figure 8 Light blue crest. A light blue crest was observed along the marginal crypt epithelium surface.

only on NBI. When performing NBI-combined magnifying endoscopy of the gastric mucosa in patients with *Helicobacter pylori*-related chronic gastritis, light blue, linear reflex light is sometimes observed at the epithelial margin. This is termed LBC and is reportedly useful for the objective, endoscopic diagnosis of intestinal metaplasia of the gastric mucosa[22].

Next, we will explain the microvascular pattern. When conducting NBI-combined magnifying endoscopy of the gastric mucosa in a physiological state, microvessels such as subepithelial capillaries and collecting venules can be observed. In a morbid state, blood vessels appearing in the healing process of inflammations such as ulcers, as well as tumor microvessels, can be observed. In particular, it is necessary to recognize, by NBI-combined magnifying observation, the presence or absence of abnormal blood vessels appearing in tumors and make a diagnosis based on comprehensive findings including fine mucosal structures. However, the absence of visualized microvascular features must also be regarded as a significant finding.

Next, we will describe abnormal microvessels. Nakayoshi *et al*[21] reported that, on NBI-combined magnifying endoscopy in gastric cancer patients, microvessels could be classified into 2 patterns: fine network and corkscrew patterns (Figure 9). They indicated that 68.4% of differentiated adenocarcinoma patients showed the fine network pattern, whereas 85.3% of undifferentiated carcinoma patients showed the corkscrew pattern. Based on this, it became possible to predict the histological type of gastric cancer to some extent by employing NBI-combined magnifying endoscopy in the absence of biopsy. Currently, although this procedure is utilized in clinical practice, it is an auxiliary diagnostic method and biopsy is still the gold standard.

In Japan, ESD for gastric cancer is generally indicated for differentiated adenocarcinoma lesions in the mucosa, and caution is necessary when deciding a therapeutic policy when it is applied for the undifferentiated type. At present, for the undifferentiated type of cancer, ESD is performed for 2-cm or smaller undifferentiated intramucosal carcinoma without lymph node metastasis and

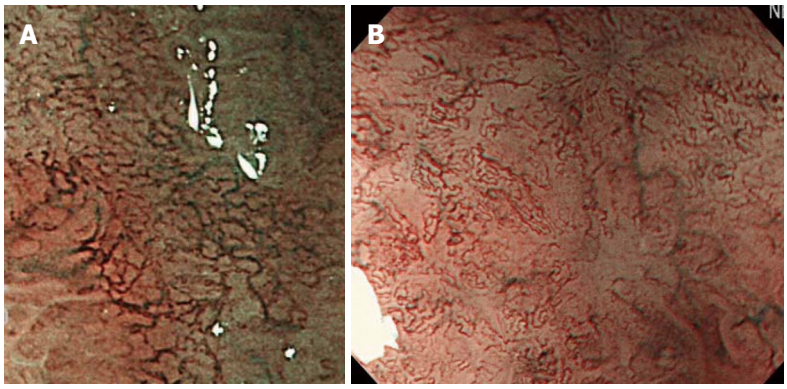

Figure 9 A fine network pattern, a corkscrew pattern. A: Fine network pattern: microvessels comprising a mesh-like network; B: Corkscrew pattern: isolated, disordered microvessels.

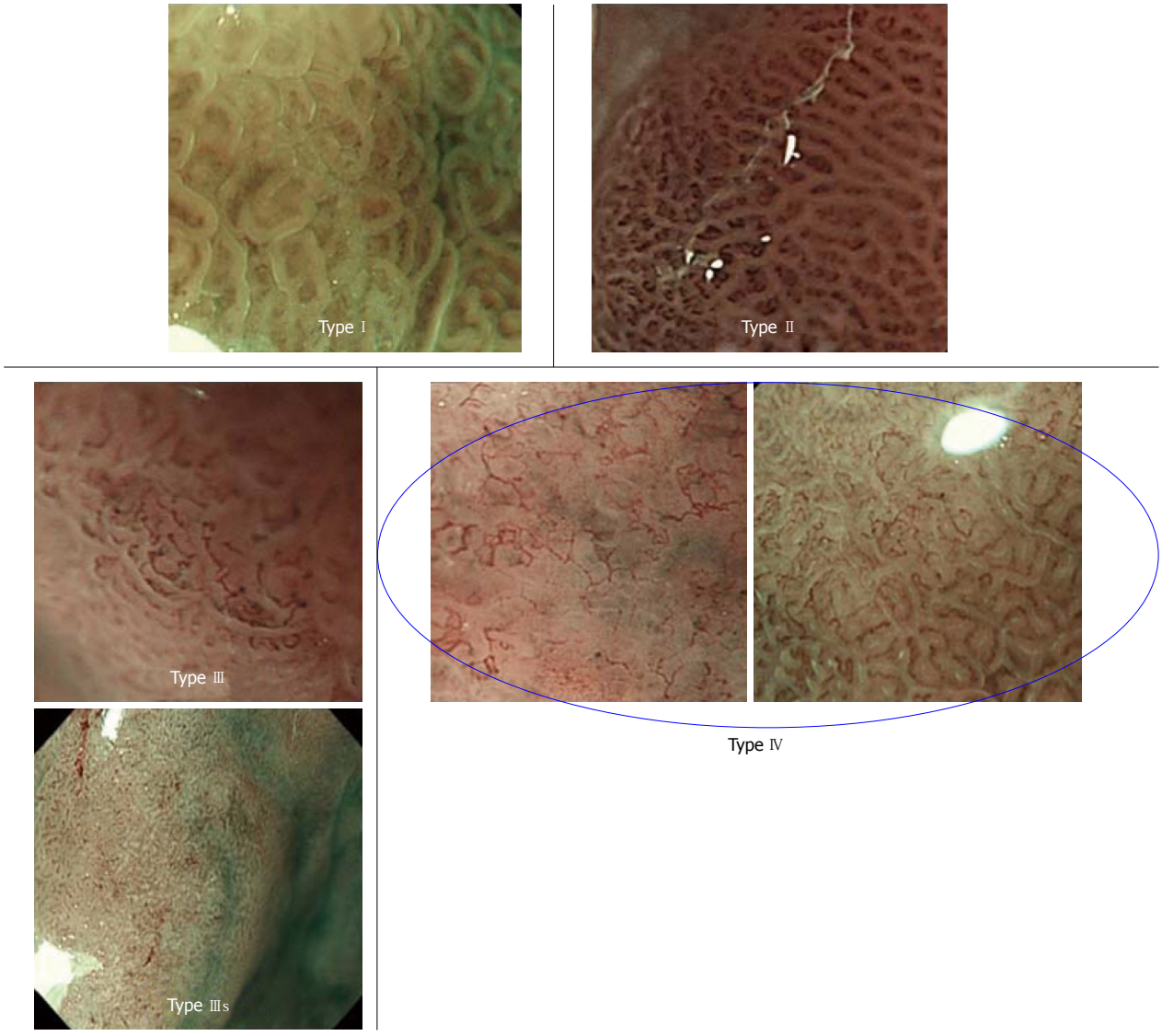

Figure 10 Narrow band imaging typing. Type Ⅰ: "Clear" mucosal microstructure and "unclear" microvessel image; Type Ⅱ: "Clear" mucosal microstructure and "clear" microvessel image; Type Ⅲ: "Clear" mucosal microstructure and "abnormal" microvessel image; Type Ⅲs: Very dense arrangement of small glands and "dots" or "unclear" microvessel image; Type Ⅳ: "Obscured" mucosal microstructure and "abnormal" microvessel image.

ulcerative changes as an extended indication at a limited number of facilities for patients who give consent. For lesions suspected to be a mixture of differentiated and undifferentiated types, it is necessary to perform NBI-

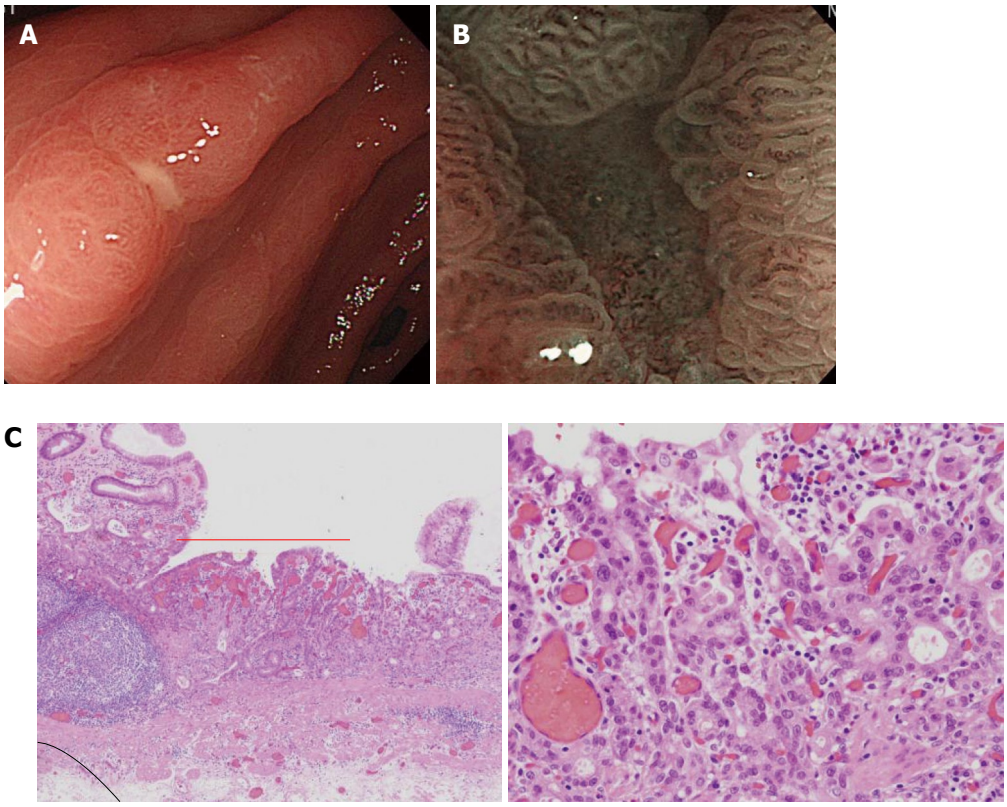

Figure 11 Differentiation of benignity and malignancy of a small depressed lesion. A: A solitary erosion was present in the antrum on the small curvature side. Differentiation of benignity and malignancy by conventional observation was difficult; B: The gland structure on the erosion surface was apparently different from the surrounding region, and a few abnormal micro blood vessels with an abnormal distribution and irregular width were present in this region; C: The lesion was an intramucosal moderately differentiated adenocarcinoma on pathological examination after endoscopic submucosal dissection. HE, original magnification, × 100 (left), original magnification, × 400 (right).

combined magnifying observation, biopsy of both types of lesions, and thereafter decide on a therapeutic policy based on the findings.

We will briefly explain microsurface and microvascular pattern-based diagnosis. We performed NBI-combined magnifying endoscopy on protruding lesions in which differentiation between gastric adenoma and differentiated adenocarcinoma was necessary, and reported that the two lesions could be simply and accurately differentiated by classifying them into 4 types, as shown in Figure 10. According to our classification, 79% of type Ⅰ/Ⅱ patients had gastric adenoma, and 93% of type Ⅲ/Ⅳ patients had differentiated adenocarcinoma[23]. Gastric adenoma is a benign tumor, and the selection of course observation is not problematic in most cases. When no changes are observed in the morphology or size on periodic endoscopy of the upper digestive tract, and adenoma is diagnosed by biopsy, course observation may normally be acceptable. However, high-risk cases, such as patients who are under oral anticoagulant treatment and require heparin substitution only for biopsy, have been increasing in the currently aging society. If gastric adenoma and differentiated adenocarcinoma can be distinguished by endoscopy alone without biopsy, this may be very useful as a diagnostic system. Considering that the diagnostic accuracy of gastric adenoma by biopsy is only about 50%-70%[24], our classification by NBI may be equally or more useful than biopsy.

Another study also indicated that a definitive diagnosis of cancer could be made at a high probability on the basis of microsurface and microvascular patterns, as described in our study[9,19]. Ezoe *et al*[10] conducted a prospective study, and reported that the accurate diagnosis rate for the combination of WLI and NBI was higher than that for WLI alone in small, depressive gastric lesions, including gastritis and cancerous lesions.

Here, we present one case for which NBI-combined magnifying observation was useful for the differentiation of benignity and malignancy of a small depressed lesion (erosion) (Figure 11). Solitary erosion was present in the antrum on the small curvature side. Diagnosis by conventional observation was limited, but when close NBI magnifying observation was applied, the glandular structure of the erosion surface was clearly different from that of the surrounding region, and a few abnormal micro blood vessels with an abnormal distribution and irregular width were observed. After ESD, moderately differentiated adenocarcinoma (tub2) was diagnosed.

Recently, the widespread application of ESD has contributed to marked advances in the treatment of early gastric cancer. In the stomach, it has become possible to perform ESD regardless of the lesion size. However, border diagnosis becomes more important with increasing lesion size. In differentiated adenocarcinoma lesions, the border can usually be recognized employing standard

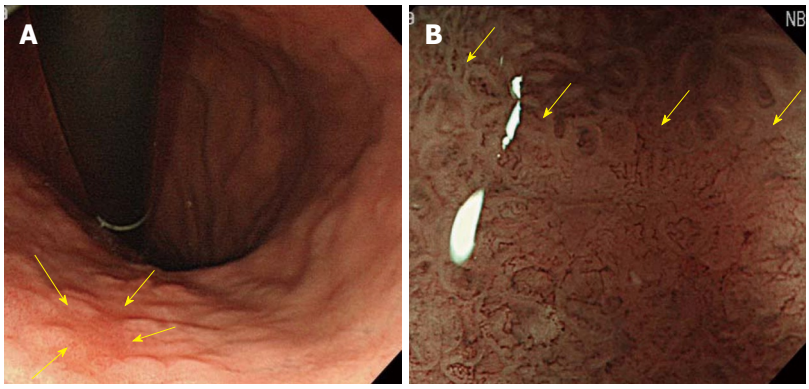

Figure 12 A case of small flat-type differentiated early-stage gastric cancer with an unclear boundary. A: A small flat-type differentiated early-stage gastric cancer of about 6 mm with an unclear boundary was present in the small curvature of the lower body of the stomach (arrows), but visualization of the lesion by conventional observation was difficult; B: Findings on narrow band imaging-combined magnifying observation: The border between the tumor and non-tumorous region was clearly observed, and apparently abnormal blood vessels were present inside the demarcation line (arrows).

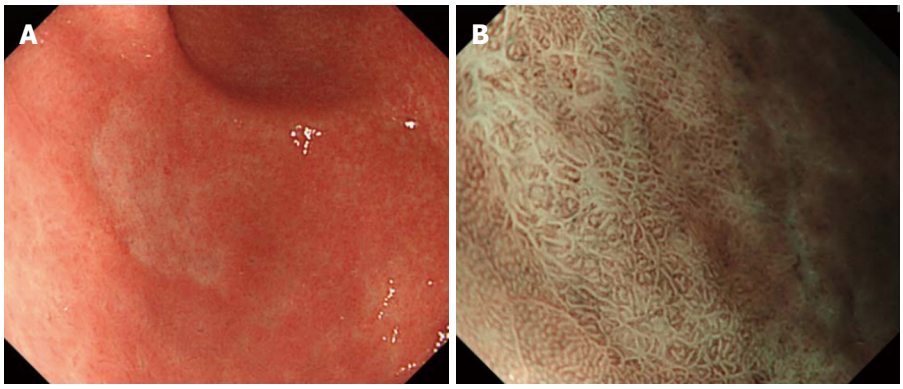

Figure 13 A case of gastric undifferentiated adenocarcinoma. A: A pale concave lesion was noted in the antrum on the anterior wall side of the greater curvature (undifferentiated cancer was diagnosed by biopsy); B: Findings on narrow band imaging-combined magnifying observation of A: Only swollen intervening parts and increased intervals between the white lines were observed, and there were no abnormal blood vessels. The gland structures in the surrounding normal mucosa appeared different from those of the concave surface.

endoscopy and the chromoendoscopy. However, there are many superficial-type lesions whose borders are difficult to recognize. In this case, NBI-combined magnifying endoscopy is very useful and the demarcation line (DL), recognized on the basis of differences in the microsurface or microvascular patterns between the gastric cancer lesion and non-lesion site, is very useful for evaluating the extent of gastric cancer.

As shown in Figure 12, a small flat-type differentiated early-stage gastric cancer of about 6-mm with an unclear boundary was present in the small curvature of the lower gastric body. The lesion was undetectable by conventional observation, giving considerably difficulty in diagnosing the range. Employing NBI magnifying endoscopy, the observation of tumor blood vessels and an apparent tumor/non-tumor boundary is possible.

On the other hand, caution is needed for border diagnosis in undifferentiated carcinoma lesions. Undifferentiated carcinoma transversely infiltrates the deep mucosal and submucosal layers; cancer does not appear on the surface in many cases.

As described above, on NBI magnifying endoscopy of undifferentiated cancer, abnormal blood vessels showing a cork screw pattern are observed in some cases, whereas only an increased interval between white lines due to swelling of the intervening part of glands without abnormal blood vessels is observed in others, as shown in Figure 13. These findings may serve as a clue to decide on the range of undifferentiated cancer although only micro blood vessels directly below the microstructure of the mucosal surface are visually observed by NBI magnifying endoscopy. Therefore, the boundary of undifferentiated cancer advancing in the deep mucosal or submucosal layer should not be diagnosed by NBI.

In undifferentiated carcinoma lesions, ESD and surgical resection lines should be established by verifying cancer-negative reactions using biopsy specimens.

Finally, we describe findings on NBI-combined magnifying observation of non-epithelial tumors, such as MALT lymphoma, which may require differentiation from early-stage gastric cancer. We previously reported that, when performing NBI-combined magnifying endoscopy of non-epithelial tumors such as mucosa-associated lymphoid tissue lymphomas and Mantle lymphomas of the stomach, some patients showed a tree-like appearance, as presented in Figure 14[7,8]. Since collecting ve-

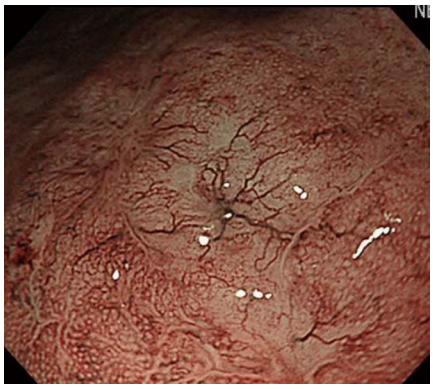

Figure 14 Tree Like appearance. Images of abnormal blood vessels resembling branches from the trunk of a tree in the shiny mucosa, in which the glandular structure tends to be lost.

nules are present in the mucosa of an *H. pylori*-negative normal stomach body as a branching vascular network, differentiation from abnormal blood vessels branching like trees in MALT lymphoma is necessary, and these can be distinguished based on the microstructure of the background mucosa of abnormal branching blood vessels. In MALT lymphoma, the gland structure is destroyed by lymphoma cells infiltrating the proper lamina and the mucosal microstructure is lost, giving the mucosa a glossy appearance. In contrast, the background mucosal microstructure shows a normal regular pattern of collecting venules. In addition, the collecting venules are seen as a greenish-blue color on NBI because venules are present in a slightly deeper region of the mucosa, another point of differentiation.

Furthermore, this procedure may be useful for differentiating non-epithelial tumors from gastric cancer and gastritis when standard endoscopic findings are similar. In the future, this should be further investigated in a larger number of patients.

Colon

ESD for the colon has not surpassed EMR and it is performed by only a limited number of facilities because of its technical difficulty and a high complication rate[25-29]. Moreover, the role of NBI in the colon ESD is very limited. In the diagnosis of the range for ESD, the mucosal thickness of colorectal tumor lesions is different from that of the normal mucosa. Therefore, the boundary is clear on conventional observation (including dye spraying) even after local injection. Accordingly, diagnosis of the boundary is not problematic, unlike in esophageal and gastric ESD, and no mark is applied around lesions for ESD, as is characteristic of colon ESD. NBI-combined magnifying observation before ESD is useful for the diagnosis of lesion depth because it can be simply applied by pressing a button. However, it has not yet surpassed the dye sprayed magnifying endoscopic diagnosis (pit pattern diagnostics) established by Kudo *et al*[30].

Kudo *et al*[30,31] reported that, in the diagnosis of colon polyps, magnifying chromoendoscopy of pit appearance

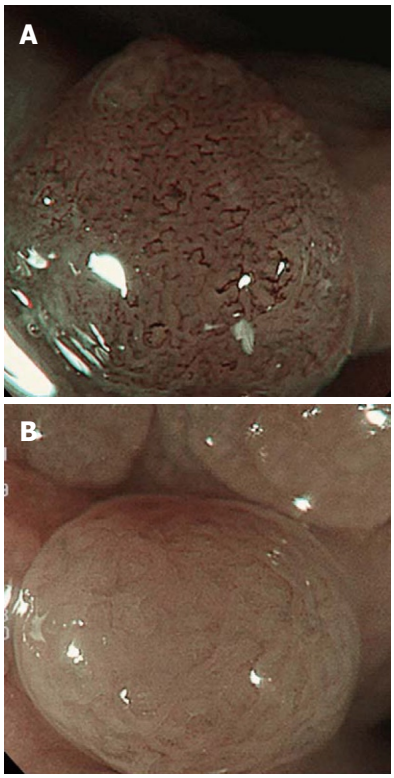

Figure 15 Hyperplastic polyp and adenoma. A: Hyperplastic polyp: meshed capillary vessels (-); B: Adenoma: meshed capillary vessels (+), capillary vessel surrounding mucosal glands.

on the polyp surface was useful for differentiating tumors from non-tumorous lesions and evaluating the degree of infiltration. Currently, their pit-pattern classification is employed throughout the world. Two NBI-based diagnostic methods for colon lesions have been proposed: one is to examine microvascular features on the mucosal surface[6], and the other is to make a diagnosis based on fine mucosal structure and microvascular features[32], as reported for the stomach. According to East *et al*[33], a fine mucosal structure observed on NBI-combined magnifying endoscopy, of pit-like appearance, may differ from a pit pattern observed on magnifying chromoendoscopy. This may be because microvessels in which hemoglobin is present are emphasized on NBI-combined endoscopy, and the visualization of a fine mucosal structure as a secondary finding, whereas the pit pattern is a direct observation in chromoendoscopy.

The clinical significance of NBI-combined magnifying endoscopy in tumorous lesions of the colon is its ability to pick up lesions. However, a consensus has not yet been reached on this[6,34,35]. On the other hand, an international consensus regarding the usefulness of this procedure for the differential diagnosis of tumors from non-tumorous lesions has been reached[36,37]. Sano *et al*[6] reported that NBI-combined magnifying endoscopy involving the observation of meshed capillary vessels on the polyp surface was useful for differentiating tumorous from non-tumorous colon polyps (Figure 15).

Furthermore, this procedure provides a simple meth-

od for the indirect evaluation of a pit-like appearance without dye spray. Tanaka *et al*[38] reported that the degree of infiltration of early colorectal cancer could be assessed by comprehensively evaluating the microvascular structure and surface pattern (pit-like appearance). According to their classification, lesions are classified into 3 types: A, B, and C. In addition, type C lesions are divided into 3 subtypes: C1 to C3. They observed that 94% of C3 lesions showed massive SM infiltration ($P < 0.01$[32]).

Although the role of NBI in the colon ESD is limited, the simplicity of its application makes it useful for the differentiation between tumors and non-tumors and diagnosis of the depth of early-stage colorectal cancer, as described above. The addition of evaluation of microvascular construction by NIB-combined magnifying observation to pit pattern diagnostics may further increase the accuracy of colonoscopic diagnosis.

CONCLUSION

The use of ESD has markedly spread over the last several years with the development of devices, and is becoming established as a minimally-invasive treatment for tumors. In parallel with this, clinical studies on NBI have markedly progressed and spread over the last several years, demonstrating its usefulness and increasing its role in ESD.

However, not all problems have been completely resolved, and because only the mucosal surface is observed and diagnosed on NBI this limits its value in the diagnoses of the range of undifferentiated gastric cancer and depth of gastric cancer. In the colon, NBI has not surpassed pit pattern diagnostics by magnifying observation employing dye spraying. In the esophagus, the use NBI magnifying observation of Barett's esophageal adenocarcinoma in Barett's esophagus, frequently observed in Western countries, is still under development.

For the endoscopic diagnosis of ESD, NBI-combined comprehensive diagnosis by conventional endoscopy including dye spraying and EUS is important and essential.

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ORIGINAL ARTICLE

Comparison between needle-knife fistulotomy and standard cannulation in ERCP

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Author contributions: Ayoubi M performed all the Endoscopic procedures and contributed to the writing of article; Sansoè G contributed to the writing of the article and statistical analysis; Castellino F and Leone N followed patients in the days after ERCP to record any post ERCP complication.

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Abstract

AIM: To compare the rates of success and complications of two different methods of access into the common bile duct (CBD).

METHODS: Between October 2007 and November 2008, 173 consecutive patients (71 men, 102 women, mean age 68.6 years) requiring endoscopic retrograde cannulation of the papilla and endoscopic treatment were studied. In the first 88 patients CBD cannulation was performed through supra-papillary fistulotomy (group F); in the following 85 patients standard cannulation was performed through the Oddi sphincter (group S). Indications for the procedure were: choledocholithiasis, biliary obstruction, postoperative leak, sclerosing cholangitis, and Mirizzi's syndrome.

RESULTS: Deep CBD cannulation was successful in 85/88 patients (96.5%) in group F *vs* 60/85 patients (70.6%) in group S ($P < 0.0001$). The remaining 25 group S patients in whom cannulation failed were shifted to fistulotomy. Fistulotomy was successful in 21/25 patients (84%). As for complications, hyperamilasemia occurred in 7 (7.9%) group F patients *vs* 7 (8.2%) group S patients (P = NS); mild pancreatitis in 1 (1.1%) group F patient *vs* 5 (5.8%) group S patients (P = NS); bleeding in 3 (3.4%) group F patients *vs* 3 (3.5%) group S patients (P = NS).

CONCLUSION: Needle-knife fistulotomy should represent either the first approach to therapeutic cannulation or rescue therapy after unsuccessful standard cannulation.

Key words: Common bile duct; Fistulotomy; Papillotomy; Biliary stones; Pancreatitis

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INTRODUCTION

Endoscopic retrograde cannulation of the papilla of Vater (ERCP) has become the procedure of choice for the treatment of pancreatic and biliary obstructive disorders. Transpapillary biliary cannulation is the preferred technique to enter the common bile duct (CBD), but access from the sphincter of Oddi to the biliary tract during ERCP is not always possible using standard cannulation techniques. The success rate for deep cannulation of the biliary tree during ERCP ranges between 80% and 95% in the hands of experienced endoscopists[1,2].

When standard cannulation is not possible, alternative techniques may be used: transpancreatic pre-cut, needle-

knife pre-cut, needle-knife fistulotomy, and needle-knife pre-cut over pancreatic stent[3]. The rate of complications with these techniques varies widely, some authors report no increased risk while others find rates significantly increased. This discrepancy probably relates to the endoscopist's level of expertise and the number of failed attempts at cannulation before attempting pre-cut. In experienced hands and in an appropriate clinical setting, pre-cut sphincterotomy appears to be an acceptable method of access into the bile duct[2,4-6].

The study aims to evaluate post-ERCP success and complication rates in two different patient groups: patients submitted to CBD cannulation directly through suprapapillary fistulotomy and patients submitted to the same manoeuvre after unsuccessful standard cannulation of CBD.

MATERIALS AND METHODS

In our digestive endoscopy unit, we have been performing ERCPs for 20 years now, with roughly 420 procedures each year (performed by not more than two endoscopists). Where standard cannulation fails, we have usually tried an alternative technique such as needle-knife pre-cut, transpancreatic pre-cut, needle-knife fistulotomy, *etc*. However in recent years, we have focused on needle-knife fistulotomy as the alternative technique. Between October 2007 and November 2008, 173 consecutive patients (71 men, 102 women, mean age 68 years, range 32-97 years) required an operative ERCP (performed by one of two endoscopists). All patients provided informed written consent.

Patients with a previous history of failed ERCP, of acute or chronic pancreatitis, those requiring a pancreatogram, those with severe coagulopathy or previous gastric surgery with Roux-en-Y gastro-jejunostomy were excluded from this retrospective analysis. Patients with previous gastric resection according to the Billroth Ⅱ technique were included in the study (Figure 1).

Out of the above group of patients, eighty-eight underwent CBD cannulation through supra-papillary fistulotomy with needle knife (group F); the other 85 patients received standard cannulation through the Oddi sphincter with a wire-guided sphincterotome (group S) (Table 1). The initial diagnosis was defined using clinical, laboratory, and radiologic data,; the final diagnosis comprised the categories: choledocholithiasis (113 patients), biliary obstruction (55 pts) postoperative leak (3 pts), sclerosing cholangitis (1 pt), and Mirizzi's syndrome (1 pt). All the procedures were performed by a single endoscopist (MA) with experience of over 5000 ERCP's.

With the supra-papillary needle-knife fistulotomy technique (group F), a small incision was made by means of a 4 mm Huibregtse-Wilson Cook needle-knife or an Olympus modified sphincterotome a few millimeters above the papillary orifice to avoid injuring the pancreatic duct and to minimize the rate of post-ERCP pancreatitis, which is the most serious complication of such procedures.

Table 1 Characteristics of patients

	Group F	Group S	*P* value
No. of patients	88	85	
Sex (male/female)	48/40	47/38	NS
Mean age (yr)	68 (36–93)	70 (32–96)	NS[1]
Diagnosis			
Choledocholithiasis	58	59	
Malignant stenosis	20	17	
Benign stenosis	6	8	
Postoperative leak	2	1	
Scleroses cholangitis	1	0	
Mirizzi's syndrome	1	0	

[1]Evaluation of statistical significance according to Student *t* test for unpaired data. Evaluation of statistical significance according to χ^2 test. NS: Not significant.

The starting point of the fistulotomy on the papilla (distal third, midportion or proximal third) and the length of the incision varied depending on the disorder being treated (bile duct stones, strictures, *etc*.) and on the size of the papilla (Figure 2).

For the insertion of a 10 Fr plastic stent just a small incision in the proximal third was required; however, removal of a large stone or the placement of a 10 mm metallic stent, needed the incision of the distal third or midportion (Figures 3 and 4).

If cannulation of the CBD through this opening was not possible, one or two additional small but deeper incisions were performed. After fistulotomy, the CBD was cannulated through the incision with a wire-guided sphincterotome (Ultratome XL Microvasive with 0.89 mm straight Terumo). After deep cannulation, the correct position of the guidewire in the CBD was checked, dye was injected to obtain a cholangiogram, and finally, a complete papillotomy could be carried out (Figure 5). In these patients (group F) the sphincter of Oddi remained untouched.

In group S, selective cannulation of the CBD was attempted through the Oddi sphincter with a wire-guided sphincterotome (Ultratome XL Microvasive with 0.89 mm straight Terumo) using no more than 4 attempts, each one lasting less than 5 min. If the CBD cannulation was not achieved within 4 attempts, the patients were switched to the fistulotomy approach.

Patients remained hospitalized for at least 48 h after ERCP and their further course was followed by means of telephone interviews for a week to record any post-ERCP complications. Post-ERCP complications were defined according to consensus criteria[7]: (1) hyperamylasemia**:** any two-fold increase (or more) in serum amylase levels above the upper limit of normal but without abdominal symptoms; (2) mild pancreatitis: clinical symptoms (abdominal pain, nausea, and/or vomiting), serum amylase level increased at least three times the upper limit of normal for 24 h after ERCP, and illness requiring admission or prolongation of a planned admission to the hospital by 2 to 3 d; (3) moderate pancreatitis: as above but with duration of hospitalization between 4 and 10 d; (4) severe pancreatitis: acute pancreatitis needing more

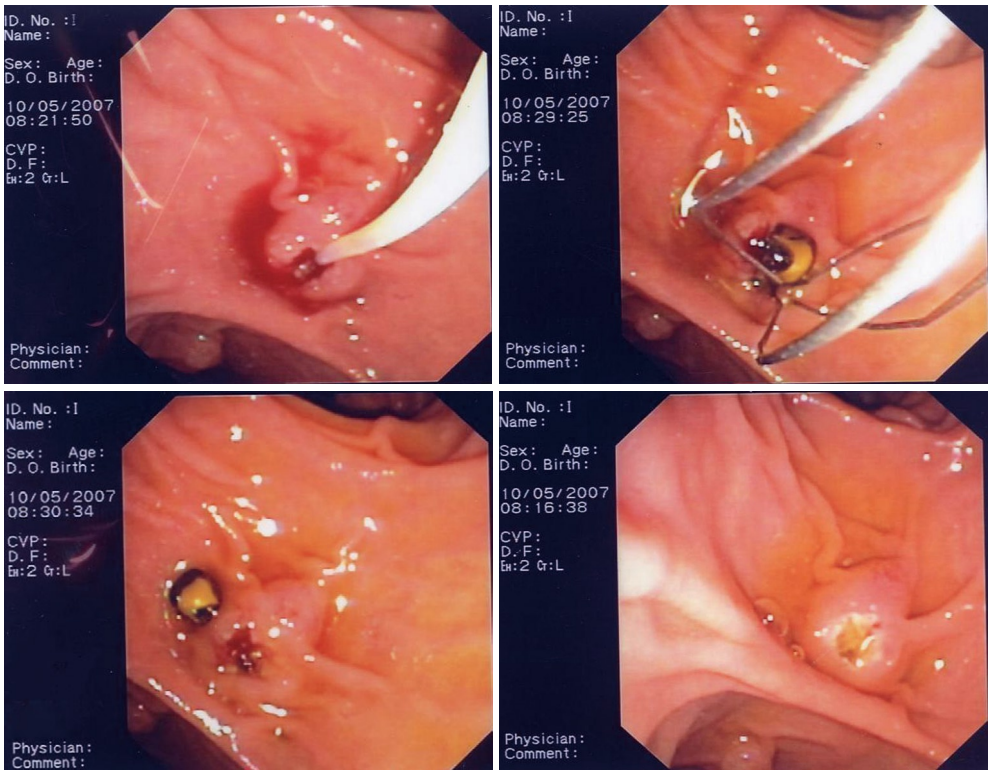

Figure 1 Needle-knife fistulotomy in Billroth II and removal of stone.

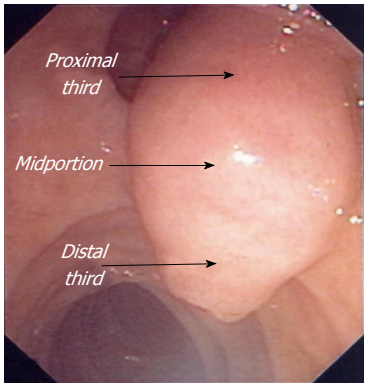

Figure 2 The starting point of the fistulotomy on the papilla.

than 10 d hospitalization or haemorrhagic pancreatitis, pancreatic phlegmon, pancreatic pseudocyst, or requirement of surgical or radiologic interventional therapy; (5) retroperitoneal perforation: retroperitoneal air or leakage of contrast medium into the retroperitoneum during injection of contrast through a false track created by the sphincterotomy (or pre-cut or fistulotomia, *etc.*); (6) minor bleeding: bleeding controlled by endoscopic hemostasis, without changes in hemodynamics or fall in hemoglobin levels; and (7) major bleeding: occurrence of hematemesis, melena, decrease in hemoglobin levels to less than 80 g/L, and need for transfusion.

Statistical analysis

Statistical significance was evaluated according to χ^2 test or Student t test for unpaired data, as stated following each table.

Table 2 Complication rate *n* (%)

Adverse effect	Group F 12/88 (13.6)	Group S 15/85 (17.6)	*P* value
Hyperamilasemia	7 (7.9)	7 (8.2)	NS
Mild pancreatitis	1 (1.1)	5 (5.8)	NS
Minor bleeding	2 (2.27)	2 (2.35)	NS
Major bleeding	1 (1.13)	1 (1.17)	NS
Death	0	1 (1.17)	NS

Evaluation of statistical significance according to χ^2 test. NS: Not significant.

RESULTS

Complication rate

Complications (Table 2), as defined above, occurred in 11/88 (12.5%) of the patients in group F and in 15/85 (17.6%) of the patients in group S (*P* = NS). Hyperamilasemia occurred in 7 patients in each of the two groups, but these 14 patients needed no treatment since serum amylase levels returned to normal within 24 to 36 h after ERCP. Mild pancreatitis occurred in 1 (1.1%) group F patient *vs* 5 (5.8%) group S patients (*P* = NS); bleeding occurred in 3 (3.4%) group F patients *vs* 3 (3.5%) group S patients. Among the 6 cases of bleeding (5 patients with choledocholitiasis and 1 patient with malignant stenosis), 4 were classified as mild and 2 as major (one in

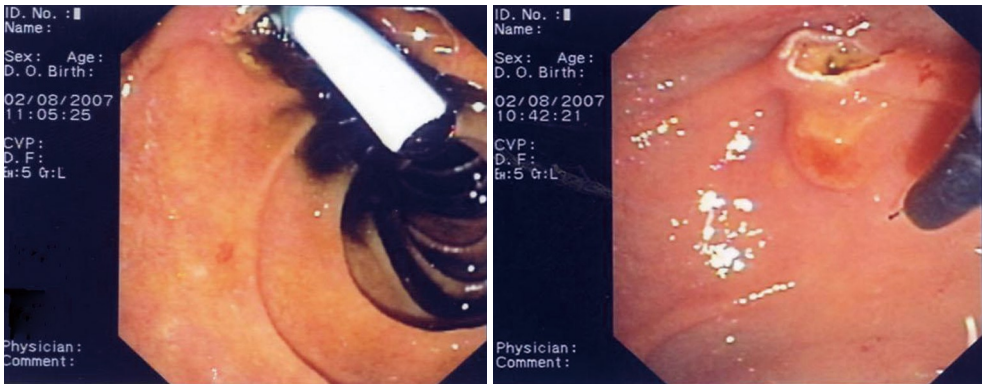

Figure 3 Needle-knife fistulotomy and placement of 10 Fr plastic stent.

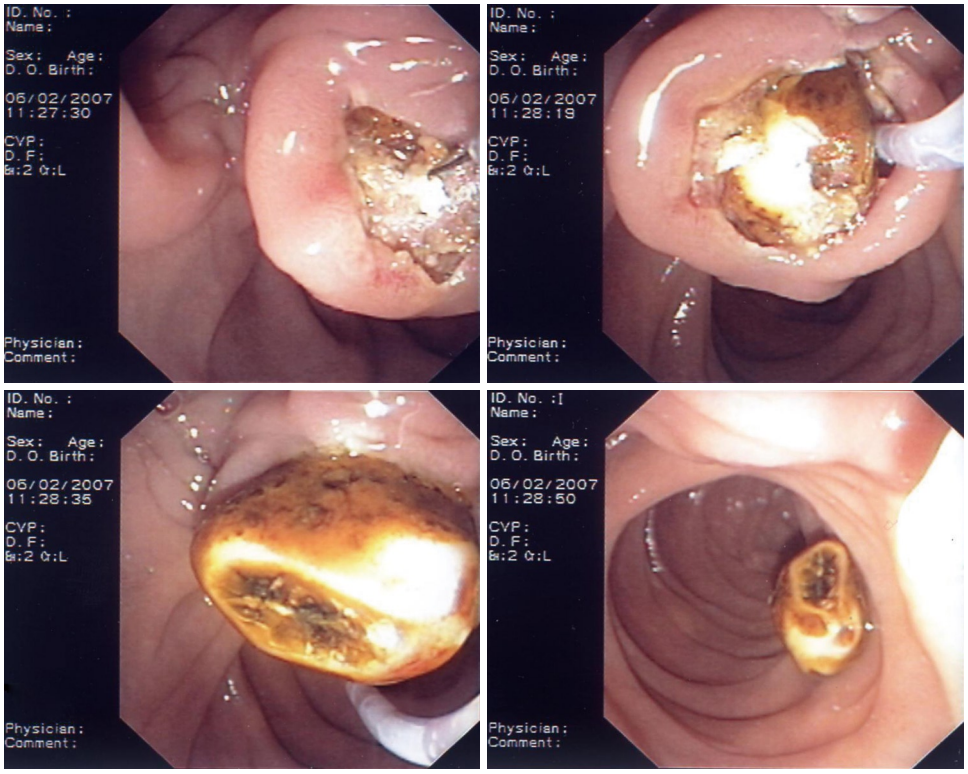

Figure 4 Needle-knife fistulotomy and removal of large stone.

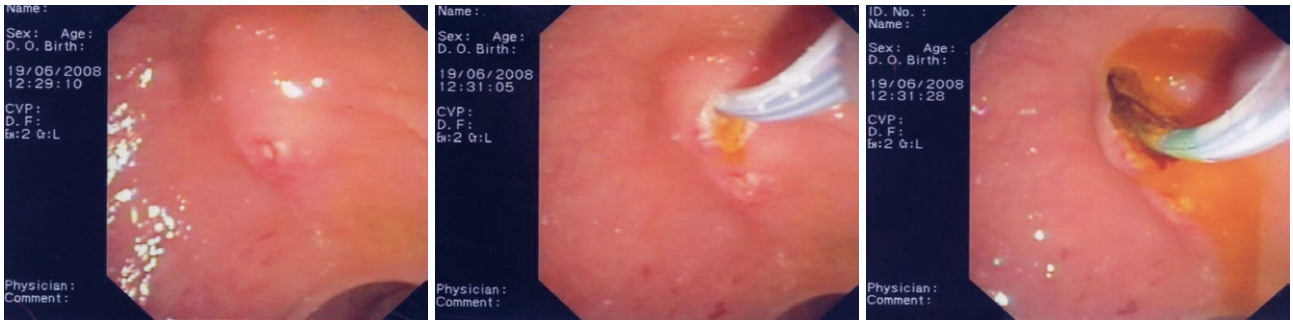

Figure 5 Papilla, needle-knife fistulotomy, deep cannulation and papillotomy.

each group). In both patients with major bleeding a repeat endoscopy was performed and followed by injection therapy with 1:10 000 epinephrine solution (5-10 mL). One of these patients needed no further treatment while

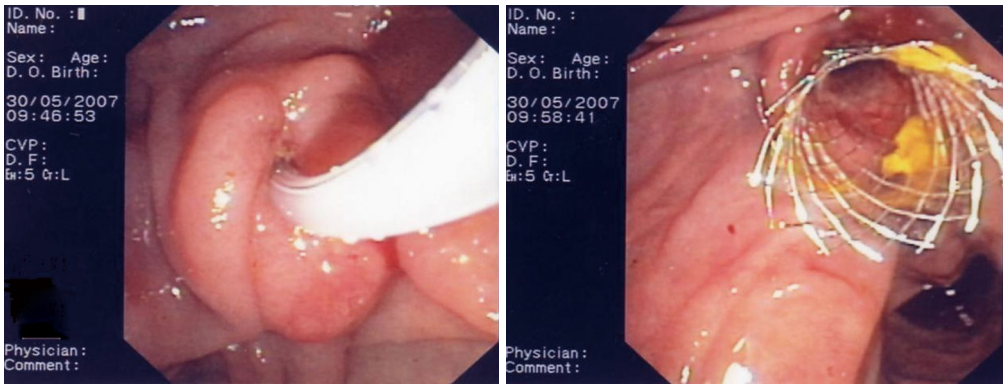

Figure 6 Needle-knife fistulotomy and placement of metallic stent.

Table 3 Deep biliary cannulation success rate

	Group F	Group S	*P* value
During the first ERCP	85/88 (96.5%)	60/85 (70.6%) (within 4 attempts of no more than 5 min) Patients shifted to fistulotomy 21/24 (84%)	< 0.0001
During the second ERCP after 7 d	0	4 (4.7%)	
Overall success rate	96.5%	98.8%	

Evaluation of statistical significance according to χ^2 test. ERCP: Endoscopic retrograde cannulation of the papilla; NS: Not significant.

the other (aged 92 years, belonging to group S) received no benefit from endoscopic treatment and underwent surgery. He died 3 d after the operation.

Final diagnoses

Patients in group F were finally diagnosed as being affected by choledocholithiasis (n = 55), malignant bile duct stenosis (n = 20), benign bile duct stenosis (n = 6), postoperative leak (n = 2), sclerosing cholangitis (n = 1), Mirizzi's syndrome (n = 1). In group S, we documented choledocholithiasis (58 patients), malignant bile duct stenosis (n = 17), benign bile duct stenosis (n = 8), postoperative leak (n = 1). The 24 group S, patients who were shifted to fistulotomy had the following final diagnosis: choledocholithiasis (n = 15), malignant bile duct stenosis (n = 7), benign bile duct stenosis (n = 2).

Success rate

Deep cannulation was successful at the first attempt in 85/88 pts (96.5%) in group F *vs* 60/85 pts (70.6%) in group S (P < 0.0001) (Table 3). The remaining 25 group S patients, in whom cannulation failed despite 4 attempts, were shifted to fistulotomy, which was successful in 21/25 pts (84%). The remaining 4 patients underwent a second ERCP 7 d after the first one. During the second ERCP successful cannulation through the incision of fistulotomy was achieved in 3 additional patients. So the overall success rate in the S group was 84/85 pts (98.8%).

Stone extraction with Dormia basket was achieved in 52 of 55 (94.5%) group F patients and in 56 of 58 (96.5%) group S patients (P = NS). In 4 elderly patients with poor clinical conditions a 10 Fr plastic stent was placed to treat their large and multiple CBD stones. In 1 of 55 (1.8%) patients in the F group stone extraction was performed with a mechanical lithotriptor. Malignant bile duct stenosis was relieved with single 10 Fr plastic stents in 19 out of 20 (95%) patients in group F and in 17 out of 17 patients in the group S (P = NS). In one patient of F group a metallic stent was placed (Figure 6). All patients with a benign bile duct stenosis were treated with two 10 Fr plastic stents.

DISCUSSION

Endoscopists performing ERCP usually aim for the highest rate of successful CBD cannulation with the lowest rate of complications. Achieving deep cannulation of CBD remains a substantial challenge in ERCP for novices and experts alike. Transpapillary biliary cannulation is the preferred technique; however, 5%-15% of the most experienced endoscopists fail to cannulate the CBD. Precutting (transpancreatic pre-cut, needle-knife pre-cut, needle-knife fistulotomy, and needle-knife pre-cut over pancreatic stent) is the most popular technique when standard cannulation fails. In the search for an alternative technique when standard cannulation fails, fistulotomy above the papillary orifice has been considered in some studies[1-3,8-10].

In our study, we demonstrated that the starting point of the fistulotomy on the papilla (distal third, midportion or proximal third) and the length of the incision varied depending on the disorder being treated (bile duct stones, strictures, *etc.*) and on the size of the papilla.

For the insertion of a 10 Fr plastic stent just a small incision in the proximal third was required. Conversely, removal of a large stone or placement of a 10 mm metallic stent, required incision of the distal third or midportion. If cannulation of the CBD through this opening was not possible, one or two additional small but deeper incisions were performed.

ERCP can be associated with serious complications including pancreatitis, bleeding, cholangitis, cholecystitis, and perforation. Of these complications, post-ERCP

pancreatitis is the most frequent though often mild or moderate, although in about 10% of cases it is severe and potentially fatal.

Since the CBD and the duct of Wirsung share frequently a final common pathway, it is easy to injure the Wirsung duct during cannulation when multiple attempts are needed. Difficulty in CBD cannulation is one of the main factors increasing the risk of post-ERCP pancreatitis[5,11-13]. During ERCP the possible causes of pancreatitis are mechanical injury to the ampulla and pancreatic sphincter from repeated attempts to cannulate the bile duct, hydrostatic and chemical injury from multiple injections of contrast into the pancreatic duct, or thermal injury from endoscopic sphincterotomy[7,14,15]. Moreover, strong evidence indicates that multiple attempts at cannulation increase the risk of post-ERCP pancreatitis and no pharmacological prophylaxis has yet been reported to reduce significantly the incidence of post-ERCP pancreatitis[16,17].

One study[18] reported no cases of pancreatitis when the CBD was cannulated from the suprapapillary portion (i.e., at a defined distance from the Oddi sphincter). A randomized comparative study of "fistulotomy" above the orifice *vs* conventional needle knifing at the orifice found a significantly lower rate of pancreatits in the fistulotomy subset (0% *vs* 8%) of 153 patients with suspected choledocholithiasis[19].

In our study, group F showed only one case of mild pancreatitis; in group S there were only mild cases of pancreatitis (5.8% of patients). In group S, CBD cannulation was achieved within 4 attempts in 60/85 pts (70.5%), a figure that is comparable with previously reported data[8,20,21]. In agreement with current literature, in our study fistulotomy after failure of standard cannulation increased the overall success rate[6,17,22-24].

We conclude that in experienced hands, needle-knife fistulotomy is as safe as standard Oddi sphincter cannulation. Since it decreases the frequency of post-ERCP pancreatitis, it may be regarded both as an approach to therapeutic cannulation, and as a rescue procedure after unsuccessful cannulation of the sphincter of Oddi.

COMMENTS

Background

When pancreatic and biliary obstructive disorders are to be treated, access from the sphincter of Oddi to the biliary tract during endoscopic retrograde cannulation of the papilla (ERCP) is not always possible using standard cannulation techniques. Alternative techniques may be used. In appropriate clinical settings, precut sphincterotomy appears to be an acceptable method of access into the bile duct. Therefore, the authors evaluated post-ERCP success and complication rates in two different patients' groups: patients submitted to common bile duct (CBD) cannulation directly through suprapapillary fistulotomy and patients submitted to the same manoeuvre after unsuccessful standard cannulation of CBD.

Research frontiers

Transpancreatic pre-cut, needle-knife pre-cut, needle-knife fistulotomy, and needle-knife pre-cut over pancreatic stent are currently used to access CBD when the sphincter of Oddi cannot be cannulated.

Innovations and breakthroughs

The authors demonstrate that needle-knife fistulotomy is as safe as standard Oddi sphincter cannulation.

Applications

Since needle-knife fistulotomy also decreases the frequency of post-ERCP pancreatitis, it may be regarded both as an approach to therapeutic cannulation, and as a rescue procedure after unsuccessful cannulation of the sphincter of Oddi.

Peer review

It is good work to be accepted with minor revision.

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BRIEF ARTICLE

Fully covered self-expandable metal stents for treatment of malignant and benign biliary strictures

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Abstract

AIM: To present a series of covered self-expandable metal stents (CSEMS) placed for different indications and to evaluate the effectiveness, complications and extractability of these devices.

METHODS: We therefore retrospectively reviewed the courses of patients who received CSEMS due to malignant as well as benign biliary strictures and post-sphincterotomy bleeding in our endoscopic unit between January 2010 and October 2011.

RESULTS: Twenty-six patients received 28 stents due to different indications (20 stents due to malignant biliary strictures, six stents due to benign biliary strictures and two stents due to post-sphincterotomy bleeding). Biliary obstruction was relieved in all cases, regardless of the underlying cause. Hemostasis could be achieved in the two patients who received the stents for this purpose. Complications occurred in five patients (18%). Two patients (7%) developed cholecystitis, stents dislocated/migrated in other two patients (7%), and in one patient (3.6%) stent occlusion was documented during the study period. Seven stents were extracted endoscopically. Removal of stents was easily possible in all cases in which it was desired using standard forceps. Twelve patients underwent surgery with pylorus preserving duodenopancreatectomy. In all patients stents could be removed during the operation without difficulties.

CONCLUSION: Despite the higher costs of these devices, fully covered self-expanding metal stents may be suitable to relief biliary obstruction due to bile duct stenosis, regardless of the underlying cause. CSEMS may also represent an effective treatment strategy of severe post-sphincterotomy bleeding, not controlled by other measures.

Key words: Completely covered self-expandable metal stents; Pancreatic carcinoma; Biliary stenosis

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INTRODUCTION

Recently, fully covered self-expandable metal stents

(CSEMS) have been lately used for the management of various malignant as well as non malignant biliary conditions, including strictures of the distal bile duct, anastomotic stenosis after orthotopic liver transplantation and post-sphincterotomy bleeding. We here report our experience using fully-CSEMS for these patients.

MATERIALS AND METHODS

Between January 2010 and October 2011, 26 patients received 28 fully covered self-expanding metal stents (WallFlex RX, Boston Scientific) for various reasons. There were 20 patients with carcinoma of the pancreatic head, three patients with stenosis of the distal bile duct because of chronic pancreatitis (four stents), one patient with stenosis of the bile duct anastomosis following orthotopic liver transplantation (two stents) and two patients with severe bleeding following endoscopic sphincterotomy. The mean length of strictures was 20 mm. Depending on the type of stenosis a length of either 40 mm with 10 mm diameter (22 stents) or a length of 60 mm with 8 mm diameter (6 stents) was chosen. All stents were placed transpapillary by endoscopic retrograde cholangiography (ERC) following sphincterotomy and dilation of the stenosis with an 8.5 French rigid dilator (except for the patients with bleeding after sphincterotomy). Antibiotics were only administered if cholangitis was suspected. For sufficient bile flow, all patients were hydrated by administrating 1000 mL of Ringer, lactate solution daily for 2 d peri-interventionally. All endoscopic procedures were performed by four interventional gastroenterologists.

RESULTS

Twenty-six patients (8 male and 18 Female) received 28 fully covered self-expanding metal stents. The mean age of the patients was 58.5 years. In patients with pancreatic carcinoma, the procedure was performed within 2 d after admission if abdominal ultrasound or computed tomography showed biliary obstruction and/or laboratory tests indicated cholestasis. ERC and sphincterotomy and stent placement were successful at first attempt in all cases of pancreatic carcinoma. In the other six patients who received stents due to benign indications sphincterotomy had already been performed previously, and stent placement was technically feasible in all patients at first attempt. Drainage was achieved as monitored by a rapid decrease or normalization of bilirubin. In two patients, the stent was inserted because of severe bleeding following endoscopic sphincterotomy. This procedure led to an immediate pressure onto the bleeding area and made control of bleeding by injection of saline/epinephrine easy and safe.

No re-stenosis occurred during a follow-up period of 6 mo in two patients with distal bile duct stenosis due to chronic pancreatitis. The third patient underwent surgery as malignancy could not be excluded.

Complications

In our series, five from 26 patients with 28 implanted stents (18%) developed complications.

Two patients developed cholecystitis (7%). In one of these patients the stent had to be removed as it blocked the cystic duct, in the second patient this complication could be managed by administration of antibiotics. In two patients (7%) in whom stents were implanted due to benign indications stent dislocation occurred. In one patient (anastomosis stenosis after orthotopic liver transplantation) the stent migrated distally, leading to cholestasis again. The stent was extracted and replaced by a longer one (6 cm). In another patient with distal bile duct stenosis due to chronic pancreatitis spontaneous dislocation of the stent occurred, which was not found on scheduled ERC done 6 mo after stent implantation. Stent occlusion occurred only in one patient (3.6%) with pancreatic carcinoma due to a bile duct stone previously not diagnosed.

Removal of stents

Seven stents were removed endoscopically. Removal of stents was easily possible in all cases using standard forceps. The stents were removed after a mean time of 50 d (3-168 d).

The two patients with bleeding after sphincterotomy had their stents removed after 14 d. In the liver transplant patient with stenosis of the bile duct anastomosis, the first stent was found dislocated distally when scheduled ERC was preformed 6 wk after stent placement. The stent was removed from the distal bile duct and replaced with another stent, which was extracted 30 d later. No re-stenosis occurred since. In two patients with chronic pancreatitis the stents were removed after 82 d and 168 d respectively, there was no significant stenosis after removal of the stents and a wait and see policy was suggested. The third patient underwent resection of the pancreatic head as malignancy could not be excluded preoperatively, and the stent was removed during this procedure. In one patient with pancreatic carcinoma who developed acute cholecystitis after stent insertion, the stent was removed after 3 d.

Twelve patients with stenosis of the distal bile duct because of malignancy underwent surgery with pylorus preserving duodenopancreatectomy after a mean duration of 8 d following biliary drainage and complete staging of the tumor with computed tomography and sonography in all cases. In all patients stents could be removed during the operation without difficulties. Leakage of the biliodigestive anastomosis occurred in one patient (8.5%). This patient died due to a cause not related to the procedure (liver failure). Otherwise, no increased rate of complications or difficulties in creating an anastomosis with the remaining bile duct was reported by our surgeons. The median postoperative duration of hospitalization was 20 d. The eight patients with malignant stenosis of the bile duct who did not undergo an operation because of

far advanced disease were monitored on follow-up for a mean time of 64 d (30-75 d). Except for one patient with stent occlusion due to a bile duct stone previously not diagnosed no complications were documented.

DISCUSSION

Our report shows that biliary drainage can be achieved using fully covered self-expanding metal stents regardless of the underlying disease, be it benign or malignant. Recent and our data suggest that CSEMS were not associated with a higher rate of complication compared to uncovered self-expanding metal stents or plastic stents. In contrast to the latter a much lower rate of occlusion and subsequent cholangitis was observed. This is in accordance with another recent report, in which the authors recommend fully covered self-expanding stents as the initial intervention for biliary obstruction even if the surgical respectability status is uncertain[1]. The internal diameter of 8 mm to 10 mm of these stents ascertains sufficient bile flow, if bile is very viscous because of previous biliary obstruction. We chose the length of the stent as short as possible to avoid any alteration of the proximal common bile duct. If surgery for the underlying disease was possible, no biliary leaks or complications of the biliary anastomosis were observed. In the patients in whom resection was not intended or could not be performed because of widespread or metastatic disease, stents remained in place on follow-up.

CSEMS intended initially to palliate malignant biliary obstruction, have been used recently in management of various benign biliary conditions and iatrogenic complications, as in post-sphincterotomy bleeding. In a case series including five patients, the use of CSEMS was effective to achieve hemostasis in all patients. However, migration of the stents occurred in two patients[2]. In the two patients described in our paper temporary placement of fully CSEMS was effective in controlling severe bleeding following endoscopic sphincterotomy, which could not be managed by other means. No stent dislocation occurred, as we removed the stents 2 wk after implantation. New development, like anchoring flap at the proximal end of the stent may be an option as well to prevent stent migration[3].

So far, only plastic stents could be removed safely endoscopically if necessary. The disadvantage of these stents, however, is the small internal diameter which predisposes to occlusion by biliary sludge. On the other hand, self-expanding metal stents resulted in efficient drainage of biliary obstruction with good bile flow due to the large diameter in contrast to plastic stents. The big drawback of self-expanding metal stents, nevertheless, was that they could not be extracted easily, if at all. With the availability of fully covered self-expanding stents this short coming has been overcome.

In a multicenter study, including 37 patients removal attempts of the CSEMS were successful in all cases[4]. The endoscopic feasibility and safety of stent removal were also documented by other authors[5]. In our series endoscopic removal of the stents was feasible and safe in all patients, in whom stent explanation was desired.

We observed cholecystitis in two patients. In both patients, the outlet of the cystic duct into the common bile duct was blocked by the stent. Although the numbers are small, we suggest that this complication should be avoided by using a stent length with the upper end distal to the cystic duct outlet. In one study, this complication occurred in 20% of cases if the CSEMS covered the cystic duct. A gallbladder stent (seven French transpapillary pigtail gallbladder stent) was effective in reducing the risk of developing cholecystitis after CSEMS placement[6].

Despite the higher costs of these devices, fully CSEMS may suitable to relief biliary obstruction due to bile duct stenosis, regardless of the underlying cause. They can easily be extracted and do not increase complications following bile duct anastomosis in surgical tumor resection. CSEMS may be also an effective treatment option in severe post-sphincterotomy bleeding, not controlled by other measures.

COMMENTS

Background

Transpapillary stents are used to treat biliary strictures, whether benign or malignant. However, there are different stent types and data are controversial. Recently, completely covered self-expandable metal stents (CSEMS) have become available.

Research frontiers

The aim of this study is to present a series of CSEMS placed for different indications and to evaluate the effectiveness, complications and extractability of these devices.

Innovations and breakthroughs

CSEMS intended initially to palliate malignant biliary obstruction, have been used recently in management of various benign biliary conditions and iatrogenic complications. The internal diameter of 8 to 10 mm of these stents ascertains sufficient bile flow, if bile is very viscous because of previous biliary obstruction. So far, only plastic stents could be removed safely endoscopically if necessary. The disadvantage of these stents, however, is the small internal diameter which predisposes to occlusion by biliary sludge. CSEMS can be easily removed endoscopically in almost all patients, in whom stent explanation is desired.

Applications

Fully CSEMS may suitable to relief biliary obstruction due to bile duct stenosis, regardless of the underlying cause.

Terminology

CSEMS: completely covered self-expandable metal stent is a metallic tube used to hold open the biliary passages. The most common indication of this device is to alleviate symptoms caused by biliary tract obstruction due to various benign and malignant conditions. The stent is inserted under fluoroscopic and endoscopic control.

Peer review

This paper adds to a growing literature demonstrating the feasibility, ease, and safety of CSEMS for malignant and benign strictures.

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BRIEF ARTICLE

Impact of antiplatelet treatment on colorectal cancer staging characteristics

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Abstract

AIM: To evaluate whether antiplatelet medication leads to an earlier stage colorectal cancer (CRC) diagnosis.

METHODS: From January 2002 until March 2010, patients that presented to our institution with the initial diagnosis of CRC and were submitted to an open curative CRC resection or a palliative procedure were retrospectively reviewed. Exclusion criteria were the use of antithrombotic medication, i.e., coumarins, and appendiceal malignancies. Data acquired from medical files included age, gender, past medical history, antithrombotic treatment received prior to endoscopic diagnosis, preoperative imaging staging, location of the tumor, surgical and final histopathological report. Patients that did not receive any antithrombotic medication prior to the endoscopic diagnosis comprised the control group of the study, while patients that were on antiplatelet medication comprised the antiplatelet group. Primary end point was a comparison of CRC stage in the two groups of the study. CRC presenting symptoms and the incidence of each cancer stage in the two groups were also evaluated.

RESULTS: A total of 387 patients with the diagnosis of CRC were submitted to our department for further surgical treatment. Ninety-eight patients (25.32%), with a median age of 71 years (range 52-91 years), were included in the antiplatelet group, while 289 (74.67%) patients, with a median age of 67 years (range 41-90 years), were not in any thrombosis prophylaxis medication (control group). Thirty-one patients were treated with some kind of palliative procedure, either endoscopic, such as endoscopic stent placement, or surgical, such as de-compressive colostomy or deviation. Coronary disease (77.55% - 76 patients), stroke recurrence prevention (14.28% - 14 patients) and peripheral arterial disease (8.16% - 8 patients) were the indications for the administration of antiplatelet treatment (aspirin, clopidogrel, ticlopidine or dipyridamole) in the antiplatelet group. All patients on aspirin treatment received a dosage of 100 mg/d, while the minimum prophylactic dosages were also used for the rest of the antiplatelet drugs. Investigation of an iron deficiency anemia (147 patients), per rectum blood loss (84 patients), bowel obstruction and/or perforation (81 patients), bowel habits alterations (32 patients), non-specific symptoms, such as weight loss, intermittent abdominal pain and fatigue, (22 patients) or population screening (21 patients) were the indications for the endoscopic investigation in both groups. Bleeding, either chronic presenting as anemia or acute was significantly higher (P = 0.002) for the antiplatelet arm of the study (71 patients - 72.4% of the antiplatelet group *vs* 160 patients - 55.3% of the control group). The mean tumor, node and metastasis stage was 2.57 ± 0.96 for the control group, 2.27 ± 0.93 for the antiplatelet group (P = 0.007) and 2.19 ± 0.92 for the subgroup of patients taking aspirin (P = 0.003). The incidence of advanced disease (stage Ⅳ) was lower for the antiplatelet group of the study (P = 0.033).

CONCLUSION: The adverse effect of bleeding that is justifiably attached to this drug category seems to have a favorable impact on the staging characteristics of CRC.

Key words: Colorectal cancer; Antiplatelets; Cancer stage; Abdominal surgery; Colonoscopy

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INTRODUCTION

Antiplatelet drugs, such as aspirin, dipyridamole, clopidogrel and ticlopidine, are increasingly used in order to prevent cardiovascular events[1]. Generally, aspirin and the other antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation, especially in the arterial circulation. In high risk patients, even dual antithrombotic therapy is warranted. Prevention of recurrent cardiac ischemia after coronary intervention or by-pass surgery for peripheral arterial disease represents indications where the concurrent administration of two antiplatelet agents increase the prophylactic benefits for the patient[2]. However, one common side effect of this drug category is the susceptibility to bleeding[3].

On the other hand, lower gastrointestinal bleeding, either chronic or acute, may be the presenting symptom of colorectal cancer (CRC) that usually dictates the endoscopic work-up. In this retrospective study, we aimed to evaluate whether antiplatelet treatment, a popular medication among elderly patients with concomitant coronary or peripheral arterial disease, leads to an earlier stage diagnosis of CRC. Mean CRC stage in patients receiving antiplatelet medication (antiplatelet group) was compared with CRC stage in their counterparts that were not on any thrombosis prophylaxis medication (control group). CRC presenting symptoms that led to the endoscopic diagnosis and the incidence of each cancer stage in the two groups of the study were also evaluated.

MATERIALS AND METHODS

Internal board approval and ethics committee permission were obtained for the initiation of this study. From January 2002 until March 2010, patients that presented to our institution with the initial diagnosis of CRC and were submitted to an open curative CRC resection or to a palliative procedure were retrospectively reviewed. Exclusion criteria were: (1) the use of antithrombotic medication, i.e., coumarins; and (2) appendiceal malignancies. Data acquired from the medical files included age, gender, past medical history, antithrombotic treatment received prior to endoscopic diagnosis, preoperative imaging staging, location of the tumor, surgical and final histopathological report.

All patients were staged using the tumor, node and metastasis (TNM) staging system of the American Joint Committee on Cancer. Each TNM cancer stage (Ⅰ, Ⅱ, Ⅲ, Ⅳ stage) was signed with a consecutive number (1, 2, 3 and 4 respectively) for comparison purposes. Patients were divided into two groups. Those patients that did not receive any antithrombotic medication (including antiplatelets and coumarins) prior to the endoscopic diagnosis comprised the control group of the study while CRC patients that were on antiplatelet medication comprised the antiplatelet group.

Statistical analysis

The statistical analysis was made using the Statistical Package for Social Sciences version 15 statistical analysis software. In each group, we calculated the TNM cancer stage mean ± SD. We also assessed the distribution of CRC presenting symptoms and the incidence of each cancer stage in the two groups. The unpaired *t* test was used to compare the mean cancer stage (mean ± SD) between the two groups while the Fisher's exact test was used to compare the differences in the presenting symptoms and cancer stage incidence.

RESULTS

A total of 387 patients with the diagnosis of CRC were submitted to our department for further surgical treatment. Ninety-eight patients (25.32%), with a median age of 71 years (range 52-91 years), were included in the antiplatelet group, while 289 patients (74.67%), with a median age of 67 years (range 41-90 years), were not on any thrombosis prophylaxis medication (control group). Thirty-one patients (eight patients from the antiplatelet group and twenty-three patients from the control group) were treated with some sort of palliative procedure, either endoscopic (seven patients), such as endoscopic stent placement, or surgical (twenty-four patients), such as de-compressive colostomy or deviation. Advanced loco-regional or metastatic disease and diminished cardiopulmonary resources mandated the utilization of minimally invasive procedures in these patients. We used available data from the preoperative imaging studies and the surgical reports in order to stage these patients.

Coronary disease (77.55% - 76 patients), stroke recurrence prevention (14.28% - 14 patients) and peripheral arterial disease (8.16% - 8 patients) were the indications for the antiplatelet treatment in the antiplatelet group. Aspirin, clopidogrel, ticlopidid and dipyridamole

Table 1 Number of patients in each group of the study (control - antiplatelet group), the type of therapy, tumor, nodes and metastasis stage (1-4) in each group *n* (%)

	No. of patients	TNM stage (mean ± SD)
Total	387	
Control group	289 (74.6)	2.57 ± 0.96
Antiplatelet group	98 (25.4)	2.27 ± 0.93
Aspirin	65	2.19 ± 0.92
Clopidogrel	17	
Ticlopidid	6	
Dipyridamole	4	
Dual therapy	6	

TNM: Tumor, nodes and metastasis staging system of the American Joint Committee on Cancer.

Table 2 Incidence of colorectal cancer presenting symptoms and the distribution of cancer in the two groups of the study *n* (%)

	Antiplatelet group (*n* = 98)	Control group (*n* = 289)
Symptoms		
Anemia	43 (43.8)	104 (35.9)
Blood loss per rectum	28 (28.5)	56 (19.3)
Obstruction/perforation	15 (15.3)	66 (22.8)
Altered bowel habits	3 (3)	29 (10)
Non-specific symptoms	4 (4)	18 (6.2)
Screening	5 (5.1)	16 (5.5)
Distribution		
Right	42 (42.8)	116 (40.1)
Left	33 (33.6)	104 (35.9)
Rectum	23 (23.4)	69 (23.8)

were the antiplatelet agents administered in this patient group (Table 1). All patients on aspirin treatment, mean duration of administration 15.3 ± 6.51 years, received a dosage of 100 mg/d, while the minimum prophylactic dosages were also used for the rest of the antiplatelet drugs, mean duration of administration 5.85 ± 3.46 years (Ticlopidid 250 mg twice daily; clopidogrel 75 mg/d; and dipyridamole 200 mg twice daily). Generally, the overwhelming majority of patients reported absolute compliance to the prescribed antiplatelet medication. Only three patients admitted inattentiveness to medication. Regarding dual therapies, four patients were on concurrent aspirin and clopidogrel medication, while in two patients, aspirin was combined with ticlopidid. In addition, twenty-one female patients (six from the antiplatelet group and fifteen from the control group) routinely received calcium supplementation orally. None of the patients in the study received folic acid on a regular basis.

Investigation of an iron deficiency anemia (37.9% - 147 patients), per rectum blood loss (21.7% - 84 patients), bowel obstruction and/or perforation (20.9% - 81 patients), bowel habits alterations (8.2% - 32 patients), non-specific symptoms, such as weight loss, intermittent abdominal pain and fatigue, (5.6% - 22 patients) or population screening (5.4% - 21 patients) were the indications for the endoscopic investigation in both groups (Table 2). Although some patients reported more than one symptom, we included the primary indication for the endoscopy in the analysis as it was noted in the colonoscopy report. In cases where the indications overlapped, such as anemia and blood loss per rectum, the initial symptom was only scored. The distribution of CRC (right colon, left colon, rectum) in the two groups is shown in Table 2.

Table 3 The incidence of each stage in each group (Antiplatelet and control group) and the comparison between the two groups *n* (%)

	Antiplatelet group (*n* = 98)	Control group (*n* = 289)	*P* value
Stage Ⅰ (1)	24 (24.4)	47 (16.2)	0.0721
Stage Ⅱ (2)	32 (32.6)	79 (27.3)	0.3656
Stage Ⅲ (3)	34 (34.6)	114 (39.3)	0.4707
Stage Ⅳ (4)	8 (8.1)	49 (16.9)	0.033

Bleeding, either chronic presenting as anemia or acute, was significantly higher (P = 0.002) for the antiplatelet arm of the study (71 patients - 72.4% of the antiplatelet group *vs* 160 patients - 55.3% of the control group) (Table 2). The mean TNM stage was 2.57 ± 0.96 for the control group, 2.27 ± 0.93 for the antiplatelet group (P = 0.007) and 2.19 ± 0.92 for the subgroup of patients taking aspirin (P = 0.003) (Table 1). Cancer stage incidence in the two groups of the study and the subsequent statistical comparison are shown in Table 3. The incidence of advanced disease (stage Ⅳ) was lower for the antiplatelet group of the study (P = 0.033).

DISCUSSION

Aspirin, also called acetylsalicylic acid, has become a very popular medication, especially among the elderly. As a platelet aggregation inhibitor, it is used for a variety of medical conditions[4]. Besides aspirin, newly introduced antiplatelet agents, such as clopidogrel, are also used in order to reduce the risk of thrombosis recurrence in patients with prior myocardial infarction, stroke or peripheral arterial disease[2,5]. In addition, the beneficial role of non-steroid anti-inflammatory drugs (NSAIDs) seems to also be expanded in the field of primary prevention of CRC. It is suggested that the cyclooxygenase-2 inhibitors and the NSAIDs generally can reduce the risk of colonic adenomas and subsequently the incidence of CRC[6-9].

However, there is a scarcity of data in the literature regarding the possible favorable effects of antiplatelet treatment on unmasking an existent CRC, leading to an early diagnosis. A study that tried to investigate the characteristics of colon cancer diagnosed in patients taking aspirin or warfarin concluded that bleeding related to aspirin or warfarin use has no effect on an earlier diagnosis of CRC[10]. In an attempt to throw some additional light on this, we conducted our survey, taking into account, not only aspirin, but also the most recently used antiplatelet agents. However, we avoided including coumarins in

our analysis as the final antithrombotic effect in this drug category is determined by the international normalized ratio levels. Therefore, dosages (the only available data) alone are not an objective parameter in order to assess the antithrombotic effects of these drugs.

Patients receiving different antiplatelet agents comprised the second group of the study. As aspirin was notably the most popular medication, a partial analysis was conducted selectively only for aspirin patients. However, we consider this rather obligatory, taking into account the limited number of patients in the other antiplatelet subgroups. A distinctive approach in a study with increased number of patients in each subgroup could more accurately delineate the true role of each agent. Regarding cancer staging, we chose to use only the main TNM cancer stages, i.e., stage Ⅰ, Ⅱ, Ⅲ, Ⅳ in the study design in order to reach the study end points, at the cost, however, of the reduced prognostic correspondence.

As the higher intake of calcium and vitamin D has been associated with a reduced risk of CRC in epidemiological studies and polyp recurrence in polyp-prevention trials, data regarding oral calcium supplementation in the patients included in the study were provided[11]. Generally, the administration of oral calcium and folic acid, another possible chemopreventive agent[12], supplements in both groups of the study was equally low. The elimination of possible bias emanating from the possible chemopreventive action of calcium or other agents on CRC stage that could possibly interfere with the results of the study was the main argument for this approach.

According to our data, tumor related bleeding, either chronic manifested as anemia or acute per rectum blood loss that dictated the endoscopic assessment, was more frequent in the antithrombotic arm of the study (P = 0.002). This susceptibility to hemorrhage that patients receiving antiplatelet medication exhibit as an adverse side effect seems beneficial in unmasking an existent CRC at an earlier stage (P = 0.007). The partial analysis, only for aspirin patients, yielded respective results (P = 0.003) resolving initial fears for bias from the approach to group all antiplatelet agents together in the analysis.

Differences in the incidence of each cancer stage in the two groups were also observed. The incidence of advanced stage Ⅳ disease was lower in the antiplatelet group of the study (P = 0.033). Generally, in the given patient sample, patients on antiplatelet medication tended to have a lower mean CRC stage. However, this finding can be underlined with statistical power only for stage Ⅳ patients. The increased incidence of early stage disease (stage Ⅰ, Ⅱ) in the antiplatelet group, although not statistically significant, could possibly suggest the favorable impact of antiplatelet medication on the earlier CRC diagnosis.

However, a few things should be kept in mind before interpreting the results of the present study and seeking for correspondence in clinical practice. The issues raised in this paper could be only half of the story in CRC patients taking antiplatelets. The retrospective nature of the study and the selection bias represent limitations. The inclusion criteria for the study were the diagnosis of CRC, either through a selective endoscopy and biopsy or through an emergency investigation due to a tumor related complication. Consequently, patients finally included in the study are a selective population submitted to one surgical unit, rendering the given patient sample not accurately representative of all CRC patients. Additionally, we assume that patients with co-morbidities requiring chronic medications, such as antiplatelets, are generally managed by their physicians more attentively than their control counterparts. In this patient group, the threshold for diagnostic evaluation of cancer related symptoms is logically lowered. This at least theoretical inequality represents another possible limitation. However, differences between the two groups in cancer diagnosis through a screening colonoscopy were not encountered. We had inadequate data regarding patients with benign and/or dysplastic polyps submitted to endoscopic polypectomy alone and consequently these patients were not included in the study. Possibly, the incorporation in the final analysis of patients that the malignant transformation was terminated in the dysplastic polyp stage due to polypectomy would provide more objective results.

Initially, the results of the present study appear to be more an observation with limited clinical significance and usefulness. However, clinical decisions regarding CRC patients can be affected beneficially, based on the results of this study. Third age patients with multiple co-morbidities receiving antiplatelet medication are the most common scenario in clinical practice. In these patients, notable hesitation and increased amount of subjectivity characterize the therapeutic decisions from the surgeon's viewpoint. On the other hand, the diagnosis of an existent CRC at an earlier stage is theoretically associated with an increased likelihood of a feasible surgical resection from the technical and oncological viewpoints. Of course, correlations with the prognosis would be inappropriate, taking into account the co-morbidities present in these patients and the actual cancer stage. The results of the present study can, however, give surgeons the impetus in order to more readily provide this patient group with the opportunity of a surgical procedure with curative intent.

In conclusion, antiplatelet medication seems to be a blessing in disguise for CRC patients. Generally, the adverse effect of bleeding that is justifiably attached to this drug category seems to have a favorable impact on the staging characteristics of an existent CRC.

COMMENTS

Background

Aspirin, also called acetylsalicylic acid, has become a very popular medication, especially among the elderly. As a platelet aggregation inhibitor, it is used in a variety of medical conditions. Besides aspirin, newly introduced antiplatelet agents, such as clopidogrel, are also used in order to reduce the risk of thrombosis recurrence in patients with prior myocardial infarction, stroke or peripheral arterial disease.

Research frontiers

The antithrombotic indications of antiplatelet treatment are well established.

However, there is a scarcity of data regarding the possible favorable effects of antiplatelet treatment on colorectal cancer (CRC) staging characteristics.

Innovations and breakthroughs

In the present study, the authors aimed to evaluate whether antiplatelet treatment leads to the diagnosis of an existent CRC at an earlier stage. According to the data, tumor related bleeding, either chronic manifested as anemia or acute per rectum blood loss that dictated the endoscopic assessment, was more frequent in patients receiving antiplatelet medication. This susceptibility to hemorrhage that patients receiving antiplatelet medication exhibit as an adverse side effect appeared beneficial in unmasking an existent CRC at an earlier stage. The incidence of advanced disease was also lower in patients receiving antiplatelet medication.

Applications

Initially, the results of the present study appear to be more an observation with limited clinical significance and usefulness. However, clinical decisions regarding CRC patients can be affected beneficially, based on the results of this study. Third age patients with multiple co-morbidities receiving antiplatelet medication are the most common scenario in clinical practice. In these patients, notable hesitation and increased amount of subjectivity characterize the therapeutic decisions from the surgeon's viewpoint. On the other hand, the diagnosis of an existent CRC at an earlier stage is theoretically associated with an increased likelihood of a feasible surgical resection from the technical and oncological viewpoints. Of course, correlations with the prognosis would be inappropriate, taking into account the co-morbidities present in these patients and the actual cancer stage. The results of the present study can, however, give surgeons the impetus in order to more readily provide this patient group with the opportunity of a surgical procedure with curative intent.

Terminology

Antiplatelet drugs, such as aspirin, decrease platelet aggregation and inhibit thrombus formation, especially in the arterial circulation, and are commonly administered in high risk patients in order to prevent recurrent cardiac ischemia and cardiovascular events generally. On the other hand, cancer of the colon or rectum, i.e., CRC, is a common adult malignancy. The tumor, nodes and metastasis staging system is the most widely used cancer staging system worldwide.

Peer review

Although this paper is a retrospective study, the authors show an interesting result that the incidence of stage Ⅳ disease is lower in patients taking antiplatelet agents compared to the control group.

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BRIEF ARTICLE

Diagnostic accuracy of confocal laser endomicroscopy in diagnosing dysplasia in patients affected by long-standing ulcerative colitis

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Abstract

AIM: To evaluate the diagnostic accuracy of confocal laser endomicroscopy (CLE) for the detection of dysplasia in long-standing ulcerative colitis (UC).

METHODS: We prospectively performed a surveillance colonoscopy in 51 patients affected by long-standing UC. Also, in the presence of macroscopic areas with suspected dysplasia, both targeted contrasted indigo carmine endoscopic assessment and probe-based CLE were performed. Colic mucosal biopsies and histology, utilised as the gold standard, were assessed randomly and on visible lesions, in accordance with current guidelines.

RESULTS: Fourteen of the 51 patients (27%) showed macroscopic mucosal alterations with the suspected presence of dysplasia, needing chromoendoscopic and CLE evaluation. In 5 macroscopically suspected cases, the presence of dysplasia was confirmed by histology (3 flat dysplasia; 2 DALMs). No dysplasia/cancer was found on any of the outstanding random biopsies. The diagnostic accuracy of CLE for the detection of dysplasia compared to standard histology was sensitivity 100%, specificity 90%, positive predictive value 83% and negative predictive value 100%.

CONCLUSION: CLE is an accurate tool for the detection of dysplasia in long-standing UC and shows optimal values of sensitivity and negative predictivity. The scheduled combined application of chromoendoscopy and CLE could maximize the endoscopic diagnostic accuracy for diagnosis of dysplasia in UC patients, thus limiting the need for biopsies.

Key words: Ulcerative colitis; Cancer; Confocal; Surveillance

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INTRODUCTION

The risk of colorectal cancer (CRC) is increased in patients affected by inflammatory bowel disease (IBD), even if the exact magnitude of the risk is difficult to quantify because of several biases and methodological shortcomings[1,2]. According to the well-known meta-analysis by Eaden *et al*[3], the overall prevalence of CRC in patients with ulcerative colitis (UC) is approximately 3.7% and 5.4% for those with pancolitis, with a pooled estimate of cumulative CRC incidence of 2% at 10 years, 8% at 20 years, and 18% after 30 years of disease[3,4].

On the basis of these assumptions, patients affected by long-standing UC (and colic Crohn's disease) are candidates for surveillance colonoscopy/histology and this issue has been clearly underlined in a variety of clinical and endoscopic practice guidelines[5-7].

In particular, UC patients should undergo a screening colonoscopy 8 years after the onset of symptoms and every other year after that (every 5 years for distal colitis)[6]. At present, the main goal of the surveillance program remains the recognition of flat dysplasia, usually detected microscopically in random biopsies from unremarkable mucosa. It has been calculated that when random biopsies are performed, 33 biopsy specimens are needed in order to exclude dysplasia with a sensitivity of 90%[8,9]. However, this diagnostic approach is considered time-consuming and of doubtful utility in terms of cost-efficacy[10].

More recently, chromoendoscopy has successfully been applied in this diagnostic field. Indeed, since the first study by Kiesslich *et al*[11], many reports have shown a clear diagnostic gain using the dye spray enhancement with indigo carmine (and methylene blue), with a 3 to 5-fold increased probability of detection of dysplasia in this context[11-14]. In accordance with these results, the European Crohn's and Colitis Organisation (ECCO) guidelines define chromoendoscopy as an alternative procedure to random biopsies for appropriately trained endoscopists due to its superiority in the detection rate of neoplastic lesions[6].

In the last 5 years, confocal laser endomicroscopy (CLE) has been widely used for the diagnosis of superficial and early colorectal neoplasia, in view of its high agreement with the histopathology[15-17]. In addition, a small number of studies have recently suggested a possible role for this procedure in the diagnostic work-up of IBD[18,19]. In particular, a pilot study by Kiesslich *et al*[20] has shown the excellent diagnostic accuracy of CLE (sensitivity 95%; specificity 98%) in detecting dysplasia/neoplasia in UC patients.

On the basis of these considerations, we aimed to evaluate the diagnostic accuracy of CLE for the diagnosis of dysplasia in a group of patients affected by long-standing UC.

MATERIALS AND METHODS

From March 2009 to March 2011, we prospectively performed a surveillance colonoscopy in patients affected by long-standing UC who were consecutively examined at our IBD Unit. The indication for the endoscopic examination was based on the ECCO guidelines[6]. Also, in the presence of macroscopic areas suspected for dysplasia (on flat mucosa or mass), both targeted contrasted indigo carmine endoscopic assessment and probe-based CLE (pCLE) were performed. Colic mucosal biopsies and histology, utilised as the gold standard, were carried out randomly, as well as on visible lesions.

Patients

Consecutive patients with clinically inactive, longstanding UC (minimum duration 8 years) were recruited from the outpatient clinic of our IBD Unit. Potential participants were identified using the previously reported inclusion and exclusion criteria[20]. In addition, the presence of diffuse pseudo-polyps was added as an exclusion criterion.

The potential participants were thus identified, their primary care physicians were invited to participate in the study and informed consent was obtained from all participants. The study was approved by the local ethical committee (prot.653/08).

CLE equipment

CLE was performed using the Cellvizio® Endomicroscopy System (Mauna Kea Technologies, Paris, France) using a Coloflex UHD-type probe (1 μm lateral resolution; 12 frames/s).

This system uses a 2.5mm catheter probe (Coloflex UHD-type probe) that is inserted through the endoscope working channel to obtain dynamic imaging of the mucosa. This probe has a field of view of 240 μm × 200 μm, with a lateral resolution of 1 μm. pCLE imaging data were collected at a scan rate of 12 frames/s with a scanning field of 30 000 pixels. Single video frames were reconstructed into a single larger static image (4 mm × 2 mm) by a special computer software ("mosaicing" Mauna Kea Technologies). Five-ten millilitres of 10% sodium fluorescein were injected intravenously as a contrasting agent before CLE image acquisition.

Procedure

An experienced endoscopist, who had performed over 100 CLE procedures before index patient recruitment, performed all examinations. Twenty-four hours prior to the procedure, participating patients underwent colon preparation with 4 L of hypertonic polyethylene glycol solution. Conscious sedation with midazolam (5-10 mg iv) was administered at the patient's request. Lesions and suspected areas were identified using white-light endoscopy (colonscope Olympus CF-Q145I), followed by targeted

Table 1 Features of ulcerative colitis patients

Variable	UC
Number	51
Age (yr)	52 (24-66)
Gender (M/F)	28/23
Extension (E1-E2-E3)	0-23-28
Length of disease (yr)	18 (10-29)
Primary sclerosing cholangitis	1
Drugs	
5-ASA	37
Immunosuppressors	9
Anti-TNF	2

E1: Proctitis; E2: Distal colitis; E3: Extensive colitis; UC: Ulcerative colitis; TNF: Tumor necrosis factor.

chromoendoscopic enhancement with indigo carmine 0.1% according to the SURFACE guidelines[21]. The mucosal areas with the suspected presence of dysplasia were studied by CLE. After localization of each lesion/area, a 10-20 mg intravenous bolus of Buscopan (hyoscine-N-butyl-bromide) was administered in order to limit peristaltic artifacts; 10 mL of 10% sodium fluorescein were also administered for CLE image acquisition. CLE image acquisition was performed by placing the tip of the probe in direct contact with the target tissue site using an endoscopic cap to stabilize the mucosa. CLE images of each observed lesion were stored digitally in specific folders in a database. CLE images were defined diagnostic for neoplastic tissue in presence of "dark" cells, with mucin depletion and goblet cell/crypt density attenuation, with irregular architectural pattern and epithelial thickness, villiform structures and "dark" epithelial border[15].

Endoscopically resected lesions and/or target biopsy specimens were evaluated by an experienced pathologist (SS) in a blinded fashion and graded in accordance with the Vienna modified classification of gastrointestinal epithelial neoplasia[22].

Statistical analysis

The diagnostic accuracy of CLE for the prediction of dysplasia when compared to standard histology was assessed by using Stats Direct statistical software.

RESULTS

By the end of the study, 55 patients affected by longstanding UC had been enrolled. Four patients were excluded from the investigation due to the presence of diffuse pseudo-polyposis and therefore the final analysis comprised of 51 patients (Table 1).

Fourteen of the 51 patients (27%) showed macroscopic mucosal alterations with the suspected presence of dysplasia, requiring targeted chromoendoscopic and CLE evaluation.

In 5 of these 14 macroscopically suspected cases (35%), the presence of dysplasia was confirmed by both histology and CLE examination. In 3 cases, the diagnosis of flat dysplasia (1 low-grade; 2 high-grade) was made (Figure 1), while the other 2 cases were diagnosed as dysplasia associated with lesion/mass (DALM) (Figure 2). All the cases of dysplasia were confirmed at subsequent surgery.

Table 2 Diagnostic accuracy of confocal laser endomicroscopy compared to standard histology

	%	95% CI
Sensitivity	100	70-100
Specificity	90	65-98
Positive predictive value	83	43-96
Negative predictive value	100	70-100

All five cases with dysplasia had an UC lasting at least 10 years. All patients were in maintenance treatment with 5-ASA derivates. Four of these 5 patients had a history of steroid-dependency. In the dysplastic group, 3 UC patients were affected by an extensive colitis, while the remaining two subjects suffered from a distal colitis. The two DALMs were both located at the sigmoid colon, while the other 3 cases of dysplasia were sited at the ascending colon, transverse colon and sigmoid colon, respectively.

When compared with standard histology, the targeted chromoendoscopy/CLE combination enabled the detection of dysplasia in 5 patients (true positive: 5; false positive: 1) and the ruling out of neoplastic complications in 9 subjects (true negative: 9; false negative: 0).

Finally, the diagnostic accuracy of CLE for the detection of dysplasia compared to standard histology was sensitivity 100%, specificity 90%, positive predictive value 83% and negative predictive value 100% (Table 2).

In three cases, we detected the presence of an isolated and irregular polypoid lesion which we then proceeded to resect (performing multiple biopsies around the base of the polyp). In one of these three cases, the diagnosis of DALM was made, while the other two cases were diagnosed as inflammatory pseudo-polyps. In all these circumstances, the CLE evaluation correctly predicted the histological outcome that followed (Figures 2 and 3).

With regards to the routine histological sampling, no dysplasia/cancer was found on any of the outstanding random biopsies.

DISCUSSION

Patients affected by long-standing UC have high relative risk of CRC and are candidates for endoscopic surveillance[1-4]. In the present study, the combined use of chromoendoscopy and pCLE led to the diagnosis of dysplasia in 5 of 51 patients affected by UC (3 cases of flat dysplasia, 2 of DALMs). The high percentage of dysplasia/cancer (9%) in our population is probably related to the presence of important risk factors for neoplastic complication (all cases of dysplasia in pancolitis; mean UC duration: 18 years; 1 case in PSC; UC patients afferent to a third-level IBD Unit). At present, the main aim of this surveillance scheme is the early diagnosis of dysplasia, which in many cases represents the indication for proctocolectomy[6]. However, the endoscopic and histological

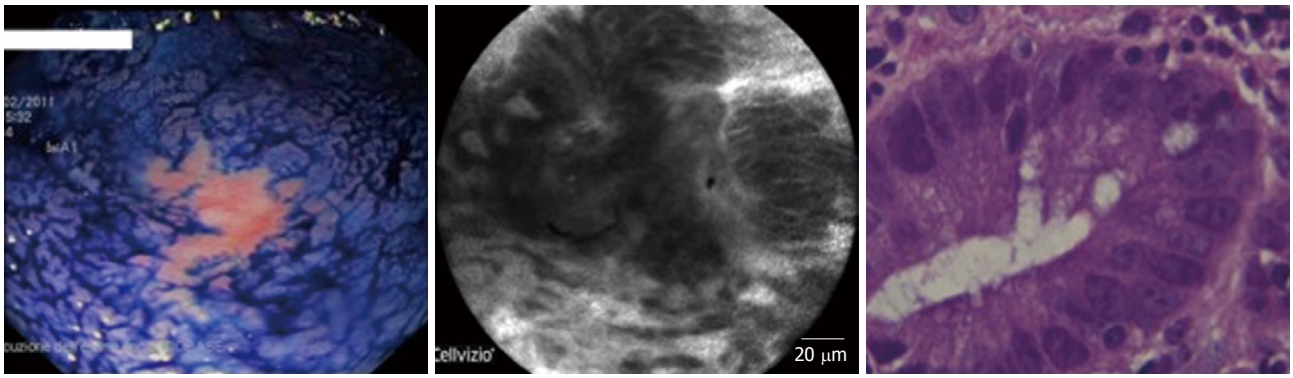

Figure 1 Low-grade dysplasia on flat mucosa after chromoendoscopy and confocal laser endomicroscopy.

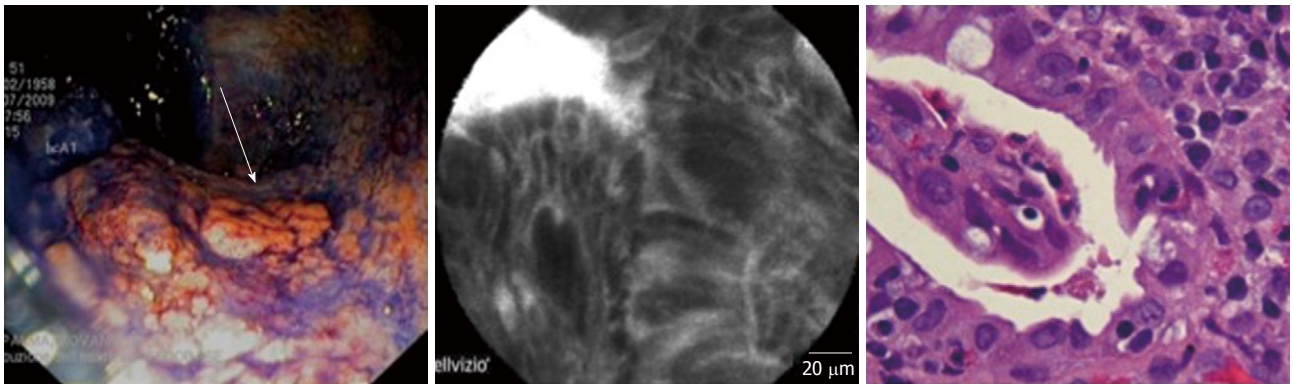

Figure 2 Dysplasia associated with a lesion/mass. Better detection of the lesion after chromoendoscopy (arrow) and confocal laser endomicroscopy evaluation

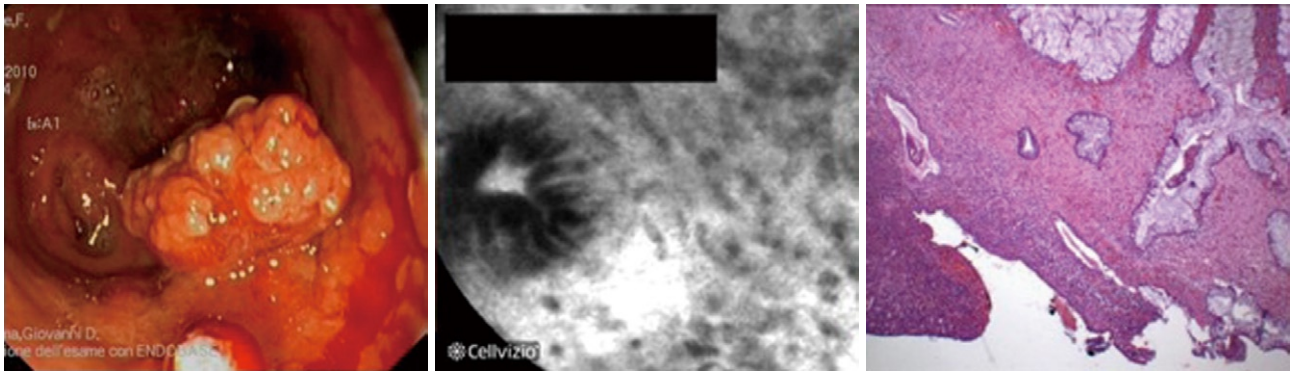

Figure 3 Inflammatory pseudo-polyp. The confocal laser endomicroscopy evaluation was negative for dysplasia/neoplasia.

surveillance of UC patients is difficult, time-consuming and is considered of doubtful clinical significance[23] due to its inadequate profile of cost-efficacy. Hence, there is a need for more accurate and practical approaches.

One of the most important diagnostic goals in the management of patients with UC, especially of those who present risk factors for cancer development, should be the "real-time" endoscopic identification and diagnosis of dysplasia/neoplasia, as this would reduce the number of unnecessary biopsies with their associated time and costs. In view of this, recent studies on the use of dye spray chromoendoscopy have underlined the efficacy of this procedure in diagnosing dysplasia in UC patients, with a 4-5 fold diagnostic gain when compared with the standard procedure[24]. Furthermore, Kiesslich *et al*[20] have shown for the first time that the diagnosis of dysplasia/neoplasia in UC could be maximized by using both chromoendoscopy and CLE, with high values of diagnostic accuracy (sensitivity 94%, specificity 98%). This result has been recently confirmed, although with less remarkable diagnostic values, by van den Broek *et al*[25], who reported a diagnostic accuracy of 81% when comparing CLE with narrow-band imaging (NBI) plus high-definition endoscopy (HDE) (diagnostic accuracy 92%).

Our study mainly focused on the combined application of chromoendoscopy and CLE, confirming the high

diagnostic potential of these procedures (sensitivity and negative predictive values of 100%). The striking diagnostic performance of pCLE in our hands compared to that observed in other studies is probably related to the experience of our first operator. Indeed, as shown in previous papers, the operator's endoscopic expertise and learning curve represent the crucial issues and main limitation for the routine application of this endoscopic technique[15-17]. However, a recent report has highlighted that the ability to accurately interpret CLE images for predicting neoplastic lesions can be learned rapidly by a range of GI specialists[26]; similarly, the ability to acquire high-quality CLE images can also be learned quickly[26].

Some studies have investigated the utility of using NBI in endoscopic follow-up of UC. The majority of these reports have shown conflicting outcomes, most likely as the result of the confounding effect of baseline inflammation[27]. On the basis of this evidence, we decided to exclude NBI evaluation from our protocol.

The introduction of magnified HDE, and therefore the possibility to accurately analyze the "pit-pattern" of the colic glands, has significantly improved the diagnostic and prognostic accuracy of endoscopy in the study of sporadic polyps and colic neoplasms. However, data about the use of this method in the context of IBD are still lacking and it is not clear whether the pit-pattern evaluation will prove to be of the same significance in the presence of diffuse mucosal inflammation. In this field of research, a recent study has highlighted a possible role for this procedure, showing that HDE was highly accurate in the diagnosis of dysplasia in cases of UC (sensitivity 100%, specificity 82%)[25]. However, we decided not to routinely perform the high definition endoscopic examination (with magnification) in our patients in order to avoid introducing further diagnostic variables and therefore to simplify, as far as possible, the data on the combined use of CLE and chromoendoscopy. Nevertheless, one of the most significant aims of future studies should be the evaluation of the diagnostic efficacy of CLE in comparison with HDE with magnification, with a view to accurately define the value of new endoscopic technologies in this field of research.

Our results show that chromoscopy-guided pCLE is a procedure that could enable a rapid diagnosis of dysplasia in patients with long-standing UC, combining the advantages of both the above mentioned techniques. In our hands, CLE showed sensitivity and negative predictive values of 100%, with high specificity (90%). In particular, the combined use of the two procedures led to the diagnosis of dysplasia in 5 of 51 patients affected by UC (3 cases of flat dysplasia, 2 of DALMs), all confirmed by histology and subsequent surgery (proctocolectomy). In the future, the remarkable negative predictive value of this technique might enable us to avoid performing unnecessary biopsies and endoscopic resections in cases of CLE-negative suspected lesions/areas. We found 1 false positive case of dysplasia in the presence of high background inflammation; this issue should always be considered when performing CLE evaluation. In addition, this diagnostic approach proved effective in predicting histology after endoscopic resection of polypoid lesions. In all three cases of polypectomy, the pCLE evaluation (of the polyp and the surrounding mucosa) clearly predicted the diagnosis (1 case of DALM, 2 of inflammatory pseudopolyps; Figures 2 and 3). In view of this result, chromoendoscopy/CLE evaluation could probably be used to better differentiate "adenoma-like mass" (ALM) from DALM lesions, confirming our previously reported experience in *in vivo* characterization of DALM in UC[28].

Our study presents some limitations. Firstly, the number of patients with the final diagnosis of dysplasia is quite small. However, this is a "real life" study and reflects the number of UC patients with dysplasia well that a third-level IBD Unit can diagnose during a 2 years period; so this shows the usefulness of such a procedure, even in every day clinical practice. According to the small number of patients with dysplasia, the 95% confidence intervals of the sensitivity, specificity and predictive values of CLE are likely wide. Furthermore, our study was mainly aimed at defining the diagnostic accuracy of using chromoendoscopy/CLE in the context of UC and did not focus on issues of feasibility; hence, several technical variables which have already been investigated in depth by other authors (e.g., time of endoscopic/chromoendoscopic procedure; total time of CLE imaging required to produce a video; proportion of total imaging time in which crypts/vessels were visible on the CLE images; and CLE video quality) were not fully recorded. However, about these concerns, our results would be not significantly different from those previously reported by other groups with well-known expertise[20,26]. Another critical issue in the present study is the small number of cases of patients with "low-grade dysplasia" in our UC population. Undoubtedly, this is an important issue if we aim to establish useful criteria for the endoscopic/histological surveillance of these patients. In effect, in the presence of this type of dysplastic lesion, the overall diagnostic accuracy of CLE could be less remarkable, even if in the Kiesslich's experience this type of dysplastic lesions did not influence the diagnostic outcome of CLE[20,29]. However, starting from these considerations, our future aim will be a multicenter study able to significantly increase the number of this kind of lesions.

In conclusion, in view of its remarkable values of sensitivity and negative predictivity, confocal fluorescence microscopy could prove an accurate tool for the detection of dysplasia in cases of long-standing UC. The scheduled combined use of chromoendoscopy and CLE could maximize the endoscopic diagnostic accuracy for the diagnosis of dysplasia in UC patients. Further studies examining a wider population are needed to confirm our suggestion.

COMMENTS

Background

Patients affected by long-standing ulcerative colitis (UC) need a surveillance colonoscopy in view of the increased risk of colon cancer. Previous studies on

confocal laser endomicroscopy (CLE) have shown that detection of dysplasia is significantly increased in sporadic colon cancer with good agreement with standard histology. However, data about the use of CLE in detecting dysplasia in UC are still scarce.

Research frontiers

This study provides further results in favor of the use of high-tech endoscopy in detecting dysplasia in patients affected by UC.

Innovations and breakthroughs

The results of this study show that chromoscopy-guided probe-based confocal laser endomicroscopy (pCLE) is a procedure that could enable a rapid diagnosis of dysplasia in patients with long-standing UC. In our hands, CLE showed sensitivity and negative predictive values of 100%, with high specificity (90%). In the future, the remarkable negative predictive value of this technique might enable us to avoid performing unnecessary biopsies and endoscopic resections in cases of CLE-negative suspected lesions/areas.

Applications

Chromoscopy-guided pCLE can be utilized as an accurate tool for defining the presence of dysplasia in patients affected by UC.

Terminology

Chromoscopy-guided pCLE refers to CLE performed at the level of suspected areas after targeted application of colorant (indigo carmine) during the endoscopic procedure.

Peer review

This study evaluated the diagnostic accuracy of CLE for the detection of dysplasia in long-standing UC. The paper is of interest to readers of the journal and the comments are satisfactorily.

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BRIEF ARTICLE

Efficacy of computed image modification of capsule endoscopy in patients with obscure gastrointestinal bleeding

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Abstract

AIM: To investigate whether flexible spectral color enhancement (FICE) improves diagnostic yields of capsule endoscopy (CE) for obscure gastro-intestinal bleeding (OGIB).

METHODS: The study subjects consisted of 81 patients. Using FICE, there were three different sets with different wavelengths. Using randomly selected sets of FICE, images of CE were evaluated again by two individuals who were not shown the conventional CE reports and findings. The difference between FICE and conventional imaging was examined.

RESULTS: The overall diagnostic yields in FICE sets 1, 2, 3 and conventional imaging (48.1%) were 51.9%, 40.7%, 51.9% and 48.1%, respectively, which showed no statistical difference compared to conventional imaging. The total numbers of detected lesions per examination in FICE imaging and conventional imaging were 2.5 ± 2.1 and 1.8 ± 1.7, respectively, which showed a significant difference (P = 0.01).

CONCLUSION: The diagnostic yield for OGIB is not improved by FICE. However, FICE can detect significantly more small bowel lesions compared to conventional imaging.

Key words: Computed virtual chromoendoscopy; Flexible spectral color enhancement; Capsule endoscopy; Obscure gastro-intestinal bleeding; Diagnostic yield

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as recurrent or persistent bleeding with negative esophagogastroduodenoscopy (EGD), ileocolonoscopy and small bowel radiography[1]. Capsule endoscopy (CE) is the investigation of choice in OGIB, with a high diagnostic yield compared to other modalities. In a previous

study, the diagnostic yield of CE in OGIB was reported to range from 30% to 80%[2-9], a higher value than that obtained by push enteroscopy[10,11], small bowel radiography[12] and computed tomography (CT)[13]. Based on these findings, CE has been recognized as the examination of choice for patients with OGIB after negative EGD and colonoscopy. However, there are some cases in which the bleeding lesion cannot be determined.

Computed virtual chromoendoscopy, both flexible spectral color enhancement (FICE) and narrow-band imaging (NBI), recently was introduced into gastrointestinal endoscopy, with the expectation that it would replace dye staining for heightening contrast and highlighting lesions. Over the past years, a multitude of reports have shown that modified imaging with FICE and NBI at high-resolution endoscopy improves detection of lesions in the upper gastrointestinal tract and enhances differentiation between neoplastic and non-neoplastic tissue[14-18]. Very recently, FICE software was implemented within the workstation of a video capsule system. However, it has rarely been investigated whether the FICE system can improve the diagnostic yields of CE for OGIB.

The aim of this study was to assess whether FICE can improve diagnostic yields better than conventional CE imaging in the examination of OGIB.

MATERIALS AND METHODS

Study population

The study subjects consisted of 81 patients who underwent CE in Chiba University Hospital (Japan) for OGIB between September 2008 and June 2010. These patients had recently undergone at least two endoscopic examinations on the upper gastrointestinal tract and at least one colonoscopy, which showed negative findings. This study was reviewed and approved by the institutional review board of Chiba University School of Medicine. Informed consent was obtained from all patients.

CE

CE was performed with Pillcam SB or Pillcam SB2 (Given Imaging, Yoqneam, Israel). CE studies were performed according to our unit's protocol, which includes an overnight fast and bowel preparation (magnesium citrate 34 g). During a period from May 2010 until June 2010, patients were also administered 1 L of polyethylene glycol-electrolyte. A prokinetic agent (metoclopramide 10 mg) was added for patients with longstanding diabetes mellitus or a known slow transit was added.

FICE technique

FICE is a spectral estimation technology based on arithmetical processing of ordinary images. Application of FICE for CE does not require any re-engineering of the capsule device, only integration of FICE software in the computer workstation. The wavelength spectrum used for creation of optical images is influenced by several factors: the spectrum of the light source, the optical device and the spectral sensitivity of the sensing element. However, these factors differ between flexible endoscopy and CE; therefore different FICE estimation algorithms with different estimation coefficients are required to optimize imaging. The spectral specifications (wavelengths) of the FICE settings that are useful in CE are as follows: Set 1: red 595 nm, green 540 nm, blue 535 nm; Set 2: red 420 nm, green 520 nm, blue 530 nm; and Set 3: red 595 nm, green 570 nm, blue 415 nm (Figure 1). With integration of the FICE digital processing system into the RAPID 6.0 workstation (Given Imaging), it enables a switchover between a conventional imaging and a FICE imaging immediately by a simple push of a button at the workstation. The three different settings make it possible to select the most suitable wavelengths required for evaluation of the capsule video.

Diagnostic definition at CE

The results of CE were evaluated separately by two endoscopists with experience of CE with and without the FICE system. If discrepancies occurred, the findings were reviewed simultaneously by both examiners and a consensus was reached. Two endoscopists were not shown the conventional CE reports and findings. Each set of FICE images was used randomly, on condition that the positive studies of conventional imaging were assigned equally. The differences between FICE imaging and conventional imaging of CE were examined to assess the clinical utility of FICE for diagnosing the cause of OGIB.

The outcome of CE was determined according to the definition reported by Macdonald *et al*[19] with a slight modification. CE findings were classified according to standard practice as highly relevant lesions (P2) or less-relevant lesions (P1, P0). An abnormal finding was classified as a P2 lesion when it was considered to be the cause of or an explanation for OGIB, such as angiodysplasia, Dieulafoy's lesion, varix, arteriovenous malformation, tumor, polyp, ulceration, multiple (> 3) erosion, diverticulum or the presence of blood and/or blood clots in the lumen of the small bowel. When a definite abnormality was identified but was not thought to be the cause of or explanation for blood loss, it was assigned a P1 status. Minor mucosal changes or abnormalities that were not diagnostic were also categorized as P1 lesions and non-specific mucosal changes including isolated red spots, mucosal breaks and visible submucosal veins were regarded as of P1 status. A finding that definitely explained clinical symptoms was regarded as a "positive finding". In this study, examinations that demonstrated one or more P2 lesions were recorded as positive findings, whereas those with only P1 lesions or no abnormality (P0) were negative. Diagnostic yield was established and the difference between FICE imaging and conventional imaging of CE were examined. Additionally, total numbers of detected lesions per CE examination were counted. If more

Table 1 Clinical characteristics of patients with obscure gastro-intestinal bleeding

	Conventional CE imaging (n = 81)	FICE set 1 (n = 27)	FICE set 2 (n = 27)	FICE set 3 (n = 27)
Sex (male/female)	44/37	14/13	12/15	11/18
Age (yr, mean ± SD)	63.5 ± 16.5	67.4 ± 13.1	60.3 ± 20.6	62.9 ± 14.7
Type of OGIB				
Overt OGIB	57	18	18	21
Occult OGIB	24	9	9	6
Medication used				
Anti-coagulant	13	6	3	4
Anti-platelet drugs	21	9	4	8
NSAIDs (excluding low-dose aspirin)	14	3	4	7
Comorbidity				
Liver cirrhosis	5	1	2	2
Chronic renal failure	4	1	2	1
Heart disease	7	2	2	3

CE: Capsule endoscopy; FICE: Flexible spectral color enhancement; OGIB: Obscure gastro-intestinal bleeding; NSAIDs: Nonsteroidal anti-inflammatory drugs.

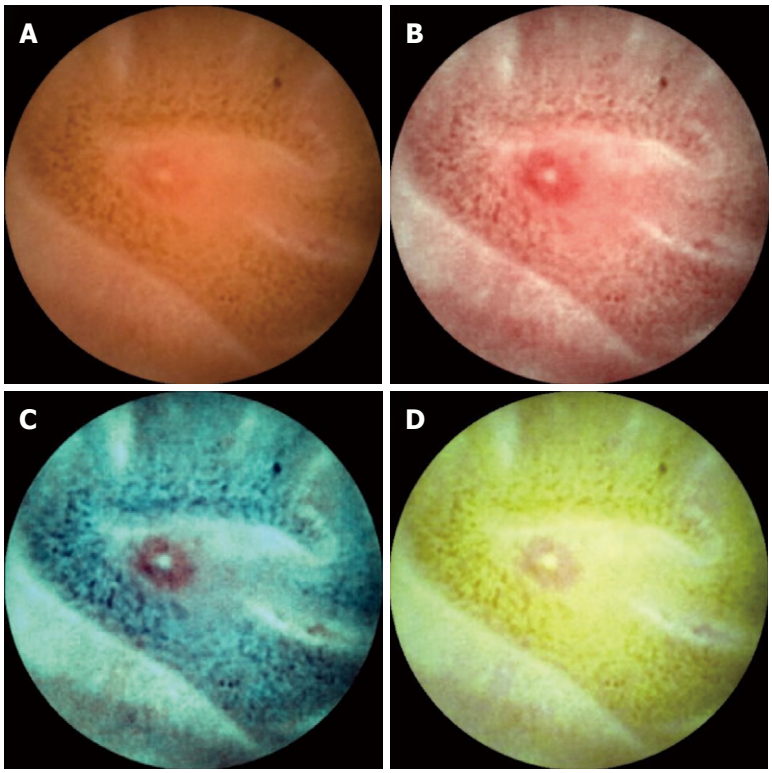

Figure 1 Effect of the spectral specification of flexible spectral color enhancement on the mucosal contrast of a small bowel erosion. A: Conventional capsule endoscopy image; B-D: Capsule endoscopy-flexible spectral color enhancement images derived from the 3 different wavelength settings [set 1 (B), set 2 (C), set 3 (D)].

than ten lesions were detected per examination, it was regarded as ten.

Statistical analysis

The baseline data are presented as mean ± SD. The differences in the values of clinical parameters between the three sets were analyzed by the χ^2 test. The difference of the diagnostic yields was analyzed by the *McNemar* test. The difference of the numbers of lesions was analyzed by the *Wilcoxon* test. All analyses were performed with the statistical program SPSS 16.0 (SPSS Inc., Chicago, IL, United States); a P value of less than 0.05 was considered statistically significant.

RESULTS

Demographic data

The clinical characteristics of patients with OGIB are shown in Table 1. The patient group comprised 44 males and 37 females with ages ranging from 17 to 89 years

Table 2 Total numbers of detected lesions per capsule endoscopy examination according to the type of lesions

Diagnosis	Conventional CE imaging	FICE imaging	*P* value
Total numbers of detected lesions (*n* = 45)	1.8 ± 1.7	2.5 ± 2.1	0.01[1]
Mucosal lesion (*n* = 24)	1.9 ± 1.9	2.9 ± 2.5	0.03[1]
Vascular lesion (*n* = 14)	2.0 ± 1.5	2.5 ± 1.6	NS[1]
Small bowel tumors (*n* = 7)	1	1	NS[1]

[1]*Wilcoxon* test; NS: Not significant; CE: Capsule endoscopy; FICE: Flexible spectral color enhancement.

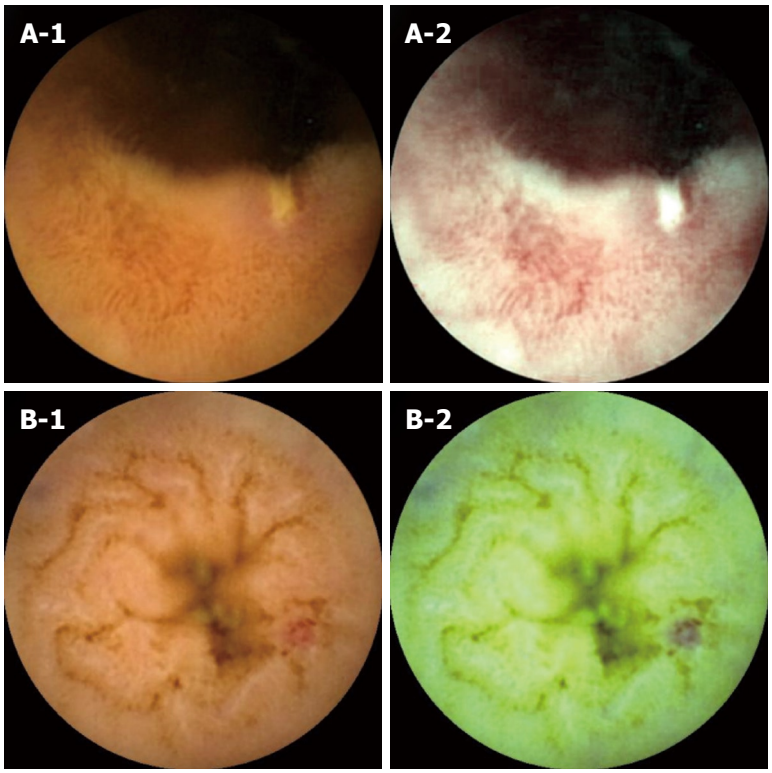

Figure 2 Two cases of flexible spectral color enhancement could effectively detect of a small bowel lesion that was missed on conventional capsule endoscopy imaging. A-1: Conventional capsule endoscopy (CE) image; A-2: Flexible spectral color enhancement (FICE) set 1. An ulcer was missed with conventional CE imaging and only detected with FICE imaging; B-1: Conventional CE image; B-2: FICE set 3. An angioectasia was missed with conventional CE imaging and only detected with FICE imaging.

(mean ± SD; 63.5 years ± 16.5 years). There was no statistical difference among each set of FICE imaging in the clinical characteristics.

CE findings

Positives of FICE imaging and the negatives of conventional CE imaging: There were two cases that FICE detected small bowel lesions that were missed with conventional CE imaging (Figure 2). In the first case (Figure 2A-1 and A-2), an ulcer was missed with conventional CE imaging and only detected with FICE imaging (set 1). With FICE imaging, it became easier to observe tissue characterization on surface parts compared with the conventional CE image. In the second case (Figure 2B-1 and B-2), an angioectasia was missed with conventional CE imaging and only detected with FICE imaging (set 3). With FICE imaging, angioectasia was clearly visualized when compared with conventional CE imaging.

Negatives of FICE imaging and the positives of conventional CE imaging: There were two cases that FICE could not detect small bowel lesions that were detected with conventional CE imaging (Figure 3). In the first case (Figure 3A-1 and A-2), an annular ulcer was missed with FICE imaging (set 2) and only detected with conventional CE imaging. In the second case (Figure 3B-1 and B-2), an ulcer was missed with FICE imaging (set 2) and only detected with conventional CE imaging.

Total numbers of detected lesions per CE examination

The total numbers of detected lesions per CE examination in FICE imaging and the conventional CE imaging were 2.5 ± 2.1 and 1.8 ± 1.7, respectively, which showed a significant difference (*Wilcoxon* test, $P = 0.01$, Table 2). Ulceration and erosion were defined as mucosal lesions. Angiodysplasia, Dieulafoy's lesion, varix and arteriovenous malformation were defined as vascular lesions.

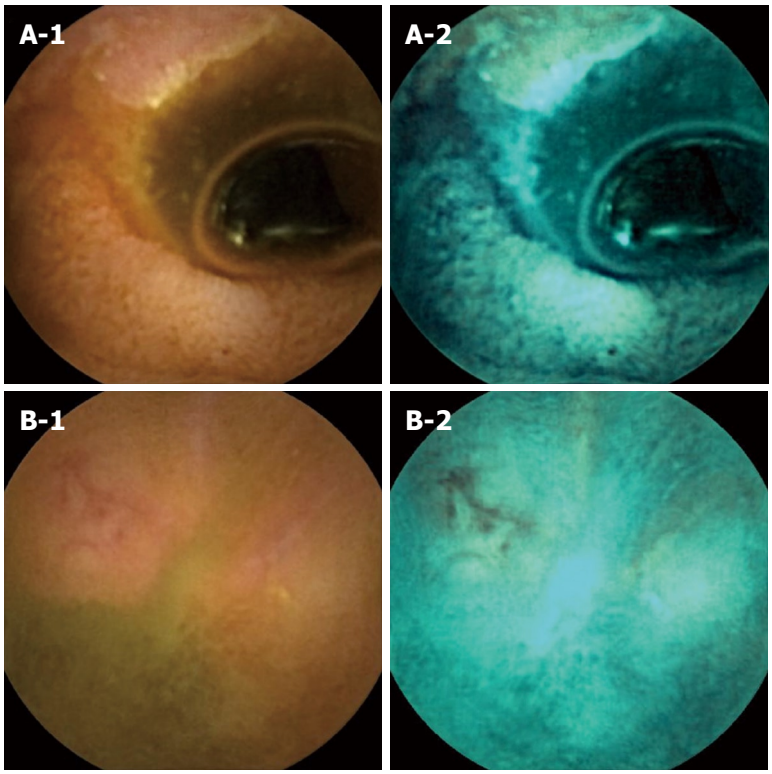

Figure 3 Two cases of small bowel lesions were missed with flexible spectral color enhancement imaging. A-1: Conventional capsule endoscopy (CE) image; A-2: FICE set 2. An ulcer was missed with flexible spectral color enhancement (FICE) imaging and only detected with conventional CE imaging; B-1: Conventional CE image; B-2: FICE set 2. An ulcer was missed with FICE imaging and only detected with conventional CE imaging.

Table 3 Total numbers of detected lesions per capsule endoscopy examination according to each set of flexible spectral color enhancement imaging

FICE set	Conventional CE imaging	FICE imaging	*P* value
FICE1, 2 and 3 (n = 45)	1.8 ± 1.7	2.5 ± 2.1	0.01[1]
FICE1 (n = 15)	2.3 ± 2.2	2.7 ± 2.1	0.068[1]
FICE2 (n = 13)	1.4 ± 1.5	2.7 ± 2.9	0.069[1]
FICE3 (n = 17)	1.9 ± 1.3	2.2 ± 1.6	0.35[1]

[1]*Wilcoxon* test. CE: Capsule endoscopy; FICE: Flexible spectral color enhancement.

Table 4 Total numbers of mucosal lesions per capsule endoscopy examination according to the each set of Flexible spectral color enhancement imaging

FICE set	Conventional CE imaging	FICE imaging	*P* value
FICE1, 2 and 3 (n = 24)	1.9 ± 1.9	2.9 ± 2.5	< 0.05[1]
FICE1 (n = 9)	2.7 ± 2.6	3.3 ± 2.3	0.08[1]
FICE2 (n = 8)	1.8 ± 1.8	3.6 ± 3.4	NS[1]
FICE3 (n = 7)	1.9 ± 0.9	1.9 ± 1.2	NS[1]

[1]*Wilcoxon* test; NS: Not significant; CE: Capsule endoscopy; FICE: Flexible spectral color enhancement.

Total numbers of detected lesions according to the type of lesions are shown in Table 2. The number of mucosal lesions differed significantly when comparing FICE imaging to conventional CE imaging (*Wilcoxon* test, P = 0.03). The total numbers of detected lesions according to the each set of FICE imaging are shown in Table 3. FICE sets 1 and 2 detected a lot more lesions but it was not a statistical difference (P = 0.068 and 0.069, respectively). FICE set 3 did not detect more compared to the conventional CE imaging (P = 0.35). The total numbers of mucosal lesions per CE examination according to the each set of FICE imaging are shown in Table 4. FICE set 1 detected more lesions but it was not a statistical difference (P = 0.08). The total numbers of vascular lesions per CE examination according to the each set of FICE imaging are shown in Table 5. There were no significant differences between each set using the FICE system.

Table 5 Total numbers of vascular lesions per capsule endoscopy examination according to the each set of flexible spectral color enhancement imaging

FICE set	Conventional CE imaging	FICE imaging	*P* value
FICE1, 2 and 3 (n = 14)	2.0 ± 1.5	2.5 ± 1.6	NS[1]
FICE1 (n = 5)	2.0 ± 1.4	2.0 ± 1.4	NS[1]
FICE2 (n = 4)	0.8 ± 0.5	1.3 ± 0.5	NS[1]
FICE3 (n = 5)	3.0 ± 1.9	4.0 ± 1.2	NS[1]

[1]*Wilcoxon* test; NS: Not significant; CE: Capsule endoscopy; FICE: Flexible spectral color enhancement.

When studying small bowel tumors, we detected tumors in seven patients. In four of these patients, a double

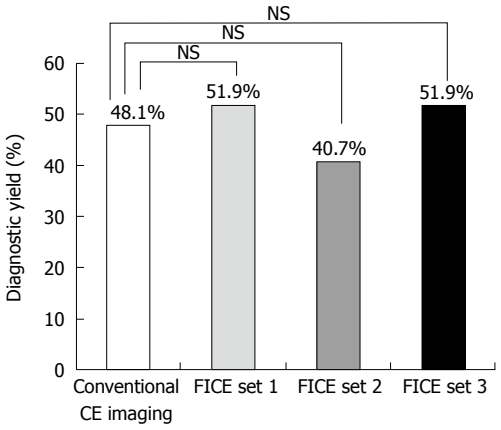

Figure 4 Diagnostic yields in conventional capsule endoscopy imaging and each set of flexible spectral color enhancement imaging. The overall diagnostic yields of capsule endoscopy (CE) in flexible spectral color enhancement sets 1, 2, 3 and the conventional CE imaging were 51.9%, 40.7%, 51.9% and 48.1%, respectively, which showed no statistical difference (P = 0.5, 0.23 and 0.5, respectively).

balloon enteroscopy was performed after CE. The final diagnoses were ileal adenocarcinoma, ileal inflammatory polyp, malignant lymphoma and follicular lymphoma in one, respectively. Another three patients did not undergo additional examination because it had been thought that the polyp was not a cause of bleeding or any malignant tumors. In these seven patients, all of the same tumors were detected by both conventional CE imaging and the FICE imaging. There were no significant differences between each set using the FICE system.

Diagnostic yields of CE

The overall diagnostic yields of CE in FICE sets 1, 2, 3 and the conventional CE imaging were 51.9%, 40.7%, 51.9% and 48.1%, respectively (Figure 4), which showed no statistical difference compared to conventional imaging (P = 0.5, 0.23 and 0.5, respectively, *McNemar* test). There were no significant differences between each set using the FICE system in terms of diagnostic yields (χ^2 test).

DISCUSSION

CE is used widely for detecting the cause of OGIB. However, there are some cases without an obvious bleeding lesion. In previous studies, some factors have been reported to be associated with diagnostic yield of CE in patients with OGIB; for example, the type of bleeding[2,4,10,11], the timing of performing CE[20-23], patient age[21], an obvious decrease in hemoglobin (Hb) value[24], the use of low-dose aspirin[9] and having another potential source of bleeding[25]. In CE, there are many reports about the diagnostic yield of OGIB. However, it is uncertain how much of a substantial miss rate exists and whether computed virtual chromoendoscopy can improve the diagnostic yield for OGIB. Recently, FICE software was implemented within the workstation of a video capsule system and there are some reports about the clinical usefulness of FICE in CE[26-28]. Imagawa *et al*[27] reported that FICE improves the visibility of angioectasia, erosion/ulceration and tumors in the small intestine and improves detectability of small bowel lesions[28]. In contrast, Gupta *et al*[29] reported that FICE was not better than conventional CE imaging for diagnosing and characterizing significant lesions on CE for OGIB. It was the first report of the diagnostic yields in CE for OGIB. However, they used only FICE set 1. In this study, we used FICE set 1, 2 and 3 and investigated the clinical utility of FICE, by dividing them by lesion type. In this study, the FICE system detected significantly more small bowel lesions when compared to the conventional CE imaging like the previous reports. However, diagnostic yields for OGIB were not improved by a computed virtual chromoendoscopy with the FICE system. It showed similar findings to the report from Gupta *et al*[29]. That is, even if the FICE system detected many lesions in the small bowel, it was uncertain whether these lesions coincided with the cause of OGIB. Therefore, the improvement of detectability did not always improve diagnostic yields. In addition, because two expert endoscopists with high ability in detection evaluated CE in this study, the FICE system might not be able to increase the diagnostic yields more. We need further analysis to clarify whether FICE can reduce the missing microlesions and improve diagnostic yield in beginners. In addition, this FICE technique may be possible to make the interpretation time short. Now in FICE, there were three different FICE sets in the Rapid 6.0 workstation and three different settings that make it possible to select the most suitable wavelengths required for evaluation of the capsule video. However, there are many situations of the capsule video per patient. For example, these situations include when there is or is not internal bleeding in the small bowel, food debris and bile acid. Therefore, it is troublesome to change settings to match these situations. So we investigated which set of wavelengths in FICE was the most suitable for determining the cause of OGIB. In this study, FICE sets 1 and 2 detected more lesions compared to the conventional CE imaging. However, there were no significant differences in terms of diagnostic yield. There were two cases that FICE set 2 could not detect ulcers which were detected with conventional CE imaging. This data might be caused by bad preparation and strong halation of the lesion from using the FICE system. However, it is uncertain whether these results could be avoided if we selected the most suitable wavelengths required for evaluation of the capsule video in these situations.

In conclusion, in CE, diagnostic yields for OGIB are not improved by computed virtual chromoendoscopy with the FICE system compared to conventional CE imaging. However, the FICE system can detect significantly more small bowel lesions when compared to conventional CE imaging.

COMMENTS

Background

Computed virtual chromoendoscopy with the flexible spectral color enhance-

ment (FICE) system has been reported to improve visualization of the lesions in the gastrointestinal tract. However, it has rarely been investigated whether the FICE system can improve the diagnostic yields of capsule endoscopy (CE) for obscure gastro-intestinal bleeding (OGIB).

Research frontiers

A recent study demonstrated that the FICE system improved visibility of small bowel lesions compared to conventional CE imaging. Thus, the authors thought that it was important to validate that FICE practically improves the diagnostic yield of small bowel lesions.

Innovations and breakthroughs

Diagnostic yields for OGIB are not improved by the FICE system in comparison with the conventional CE imaging in this study. However, the FICE system can detect significantly more small bowel lesions when compared to conventional CE imaging.

Applications

By understanding that FICE can detect significantly more small bowel lesions, this technique may make the interpretation time short and reduce the missing microlesions.

Terminology

OGIB is defined as recurrent or persistent digestive bleeding of unknown origin that persists or recurs after a negative endoscopy work-up. CE is a non-invasive method allowing a complete investigation of the small bowel. FICE is a new chromoendoscopic tool that has been designed for enhancing visibility of lesions compared to conventional imaging.

Peer review

This paper shows an influence of computed image modification for the patients with obscure GI bleeding in CE. The data are well analyzed and it could be informative and contribute to readers in the field of diagnostic endoscopy.

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CASE REPORT

Basketing a basket: A novel emergency rescue technique

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Abstract

Fracture of the central lead wire of an impacted basket during a mechanical lithotripsy for large common bile duct (CBD) stones poses a special challenge. Different maneuvers have been described to resolve this problem. Most techniques require equipment or facilities which may not be readily available in small community hospitals. We present here a similar situation in a patient with a large stone at the level of the cystic duct. Through the duodenoscope, a smaller Dormia basket was introduced into the CBD along the side of the impacted broken basket. The tip of the impacted basket was grasped and, by pulling downwards, the basket was disengaged from the stone. The two baskets were then removed successfully. We suggest this simple technique should be tried initially, before resorting to more advanced procedures.

Key words: Endoscopic retrograde cholangiopancreatography; Impacted Dormia basket; Mechanical lithotripsy; Fractured Dormia basket

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Khawaja FI, Ahmad MM. Basketing a basket: A novel emergency rescue technique. *World J Gastrointest Endosc* 2012; 4(9): 429-431 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i9/429.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i9.429

INTRODUCTION

Endoscopic management is now the standard of care for primary management of common bile duct (CBD) stones causing biliary obstruction. Stones are successfully removed with Endoscopic Retrograde Cholangiopancreatography (ERCP) using a Dormia basket or balloon catheters in 85% to 90% of cases[1]. ERCP is now available even in small community hospitals. The usual complications of ERCP are hyperamylasemia, acute pancreatitis, bleeding, perforation and infection. Difficulty during stone removal occurs when the stone is hard and large (> 1 cm) or when there is discrepancy between the stone size and diameter of the distal bile duct. The management of non-extractable CBD stones includes mechanical lithotripsy, electrohydraulic probe lithotripsy, extracorporeal shock wave lithotripsy, laser lithotripsy and stenting until definitive stone treatment[2]. Impaction of a biliary basket due to a hard stone is not an uncommon complication, reported in 0.8-5.9% of cases[3]. Mechanical lithotripsy usually solves the problem by crushing the stone. Rarely, fracture of the basket during lithotripsy occurs and poses a special management problem. While referral to a higher facility due to lack of equipment or expertise is well accepted by patients, emergency referral for procedural complications may not be acceptable and runs a risk of potential litigation. With this particular situation in the background, we describe here a maneuver to remove an impacted and fractured Dormia basket, which can easily convert an emergency situation to a more planned referral.

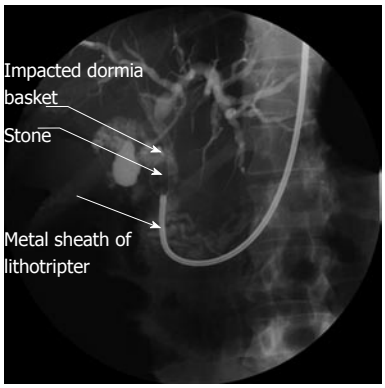

Figure 1 Impacted stone and the entrapped basket. A metal sheath of Soehendra type extra-endoscopic mechanical lithotripter was introduced to crush the stone.

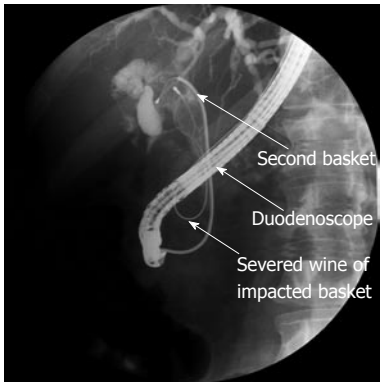

Figure 2 The second basket passed through the duodenoscope which was re-introduced, then advanced alongside the severed central wire of the first (entrapped) basket in order to catch the impacted one.

CASE REPORT

A 70-year-old Saudi male was admitted with a 1 wk history of colicky right upper quadrant pain and jaundice, associated with nausea and occasional vomiting. He had no past medical history. Physical examination revealed deep icterus, vitiligo on the forehead and tenderness in the right upper quadrant of the abdomen. Baseline investigations revealed high blood glucose (19.9 mmol/L) and raised total bilirubin (155 μmol/L) and alkaline phosphatase (310 U/L). Other parameters were normal. Ultrasound abdomen reported a stone in left hepatic duct, measuring 1.5 cm in diameter. He was subjected to ERCP. The common hepatic duct was dilated with a stone at the level of the cystic duct and CBD junction. Further injection of dye displaced the common duct medially, confirming Mirizzi's syndrome. A Dormia basket (FG-23Q-1; Olympus) was advanced for a trial to remove the stone, which would otherwise need surgery. Unfortunately, it was stuck and could not be disengaged. The duodenoscope (TJF; Olympus) was withdrawn. In order to crush the stone, a metal sheath of extra-endoscopic lithotriptor (MAJ-430; Olympus) was advanced over the basket wire after cutting away the handle and attached to Soehendra-type mechanical lithotriptor handle (BML-110A-1; Olympus) (Figure 1). However, upon cranking, the central wire of the Dormia basket severed at the proximal end just outside the oral cavity. The lithotriptor was withdrawn and the duodenoscope re-introduced. Another Dormia basket was introduced along the side of the severed central wire and caught the upper tip of impacted basket (Figure 2). It was then pushed in the cephalad direction and the trapped basket flipped down (Figure 3), in order to splay the wires of impacted basket sideways. Subsequently, the trapped and severed basket disengaged from the stone and was removed (Figures 4 and 5). A plastic

Figure 3 Tip of the impacted basket caught by the second basket.

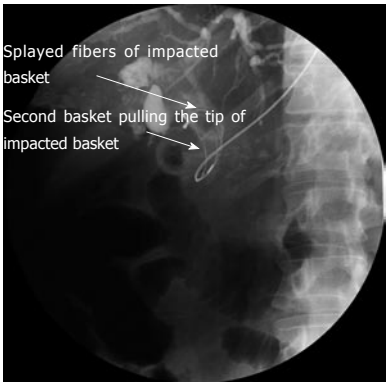

Figure 4 Splaying of impacted basket fibers during its disengagement from the stone.

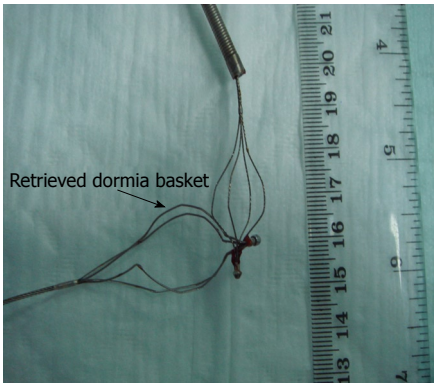

Figure 5 Still image of the retrieved Dormia basket.

stent (7 Fr) was inserted in the CBD to relieve obstruction and later the patient was subjected to surgical treatment.

DISCUSSION

Surgical treatment is the gold standard for Mirizzi's syndrome. However, an endoscopic attempt to remove the impacted stone will help in biliary drainage. Stone extraction using a Dormia basket and mechanical lithotripsy is a simple choice[4]. Other reported endoscopic approaches for Mirizzi's syndrome include electrohydraulic lithotripsy[5]. A junctional stone larger than the distal narrow CBD is at high risk of basket entrapment. However, the majority of these problems are resolved by mechanical lithotripsy. Although this might encourage the endoscopist to take a more aggressive approach, it is wise to avoid all temptation to use a basket unless reasonable facilities and expertise are available for advanced lithotripsy.

A fractured biliary basket is a rare but well known problem during ERCP for stone extraction and urological procedures. In the past, surgical intervention was the standard management. Non-surgical techniques to release the impacted stone and basket have been increasingly reported. If the stone is impacted at the papilla, extending the sphincterotomy might be enough. Spontaneous passage of the impacted basket and stone after successful biliary stent placement has also been reported[6]. Lithotripsy to break the impacted stone and release the basket has been the most common approach used with success. Extra-endoscopic mechanical lithotripsy, extracorporeal shock wave lithotripsy[7], endoscopic pulse-dye laser[8,9] and transhepatic choledochoscopic lithotripsy[10] have all been reported. Some of these techniques involve other specialties and may require shifting the patient to another facility on an emergency basis. In our case, we simply used another basket which is universally available. This technique is simple, cheap and does not need any special equipment or extra training. The endoscopic procedural complication was resolved immediately and without surgery. A similar case has been described before, where a second basket was used successfully to retrieve a severed basket with an impacted stone[11]. Recently, Ryozawa *et al*[12] used rat-tooth forceps to catch the basket fibers and disengage the trapped basket. Because ERCP is done under one dimensional fluoroscopy guidance, we feel that using forceps carries a higher risk of inadvertent injury to the bile duct compared to a basket. The main drawback of the technique we described is that, unlike other lithotripsy procedures, the stone still remains *in situ*. Nevertheless, the simplicity of the maneuver makes it a worthwhile first line salvage technique before referring the patient for more complicated and invasive procedures.

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CASE REPORT

Mucosal hyperplasia in an uncovered portion of partially covered metal stent

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Abstract

Covered self-expandable metal stents were developed to overcome tumor in-growth through the metal mesh. Stent migration is one of their malfunctions. Recently, the partially covered wallflex stent (PCWS) was developed with flared ends to prevent migration However, difficulty has been reported in its removal. We describe the removal of a PCWS embedded in mucosal hyperplasia at the uncovered proximal flared end, visualized by using SpyGlass cholangioscopy.

Key words: Self-expandable metal stent; Complication; Mucosal hyperplasia; Stent removal

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INTRODUCTION

A covered self-expandable metal stent (SEMS) was developed to overcome tumor-in growth through the metal mesh[1]. Stent migration is one of the malfunctions of covered SEMS[2]. Recently, the partially covered Wallflex stent (PCWS) (Boston Scientific, Natick, MA, United States) was developed with flared ends to prevent migration. However, this design had negative effect on stent removal[3]. We describe a patient in whom there was difficulty in removal of a PCWS embedded in mucosal hyperplasia at the uncovered proximal flared end, successfully visualized by using SpyGlass cholangioscopy (Boston Scientific, Natick, MA, United States).

CASE REPORT

A 70-year-old man presented to our institution with fever and jaundice. Two years earlier, he received a PCWS for malignant biliary obstruction due to pancreatic head cancer and underwent systematic chemotherapy. Endoscopic retrograde cholangiopancreatography revealed a distally migrated PCWS and a biliary sludge inside the PCWS but no tumor in growth. Removal of the PCWS was attempted with a snare, but failed (Figure 1). After mechanical cleaning by a balloon catheter, cholangiography showed a filling defect at the proximal end of the PCWS (Figure 2). The SpyGlass direct visualization system revealed reddened

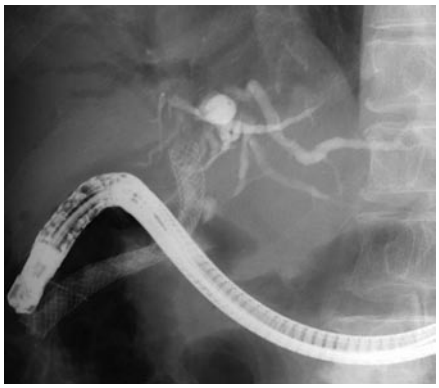

Figure 1 Fluoroscopic image a showing metal stent grasped with a snare. It was impossible to remove the stent.

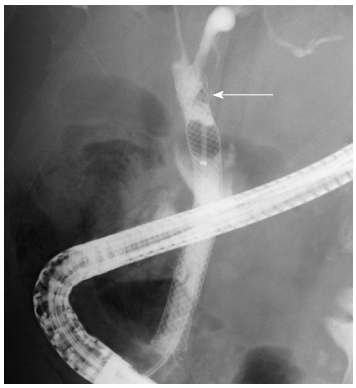

Figure 2 Fluoroscopic image showing a filling defect at the proximal end of a partially covered Wallflex stent (arrow).

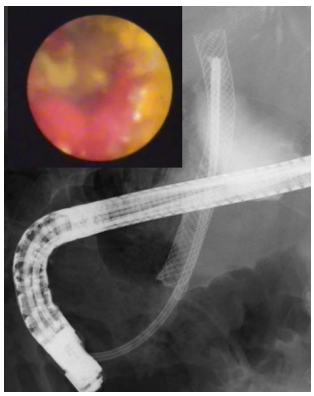

Figure 3 SpyGlass cholangioscopic image showing mucosal hyperplasia in an uncovered portion of a partially covered Wallflex stent.

mucosal hyperplasia in almost two thirds of the uncovered portion of the PCWS (Figure 3). The uncovered portion of the PCWS was totally embedded in the mucosal hyperplasia. Mucosal hyperplasia was not present at the covered portion of PCWS. We also performed biopsy of the mucosal hyperplasia under direct cholangioscopic visualization by using Spybite forceps (Boston Scientific, Natick, MA, United States) and confirmed the presence of inflammatory bile duct mucosa without malignancy

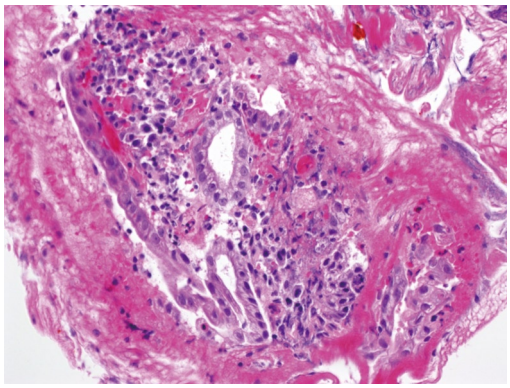

Figure 4 Biopsy specimen of mucosal hyperplasia showing inflammatory bile duct mucosa without malignancy.

(Figure 4). The cholangitis subsided with mechanical cleaning of biliary sludge inside the PCWS, and the patient was discharged on the second day after the procedure without further intervention.

DISCUSSION

In previous reports, covered a number of SEMS were safely and easily removed endoscopically using a snare or rat-tooth forceps[4,5]. A PCWS has uncovered flared ends to prevent migration, which ironically may cause tissue inflammation and mucosal hyperplasia at the proximal flared ends. In patients, the uncovered portion of the PCWS may become totally embedded into this mucosal hyperplasia, leading to difficulty in stent removal. A PCWS cannot always be removed endoscopically due to mucosal hyperplasia at the proximal flared end. In this case, the invagination method may be useful for the removal of an embedded PCWS[3], wherby the proximal end of PCWS is grasped, pulled off the bile duct and gradually invaginated by using a forceps.

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CASE REPORT

Submucosal hematoma is a highly suggestive finding for amyloid light-chain amyloidosis: Two case reports

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Abstract

The clinical and endoscopic features of amyloid light-chain (AL) amyloidosis are diverse and mimic various other diseases. Endoscopically, few reports on submucosal hematomas of the gastrointestinal (GI) tract are available in the literature. Here, we report two cases of AL amyloidosis presenting as submucosal hematomas in the absence of clinical disease elsewhere in the body. The 2 cases were referred to our hospital because of hematochezia. The endoscopic findings in both cases were similar in submucosal hematoma formation. However, the clinical courses differed. In the first case, there was no evidence of systemic amyloidosis and the disease was conservatively managed. In the second case, the disease progressed to systemic amyloidosis and the patient died within a short time. We conclude that the endoscopic detection of a submucosal hematoma in the setting of GI bleeding should raise suspicion of AL amyloidosis. Referral to a hematologist should be done immediately for treatment while the involvement is limited to the GI tract.

Key words: Amyloid light-chain amyloidosis; Submucosal hematoma; Gastrointestinal bleeding; Colonoscopy

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INTRODUCTION

Early diagnosis of amyloid light-chain (AL) amyloidosis is important because most cases are diagnosed late and have a grave prognosis. The clinical manifestations of

amyloidosis may mimic other diseases, such as inflammatory bowel disease, malignancy, ischemic colitis and collagenous colitis[1]. Endoscopically, the fine granular appearance is significantly found more often in AA amyloid cases, whereas multiple polypoid protrusions and thickening of the valvulae conniventes were observed solely in AL cases[2]. However, those results were mainly obtained from investigations of cases associated with the small intestine.

Previous case reports have identified submucosal hematomas associated with AL amyloidosis; however, these were single cases in which the endoscopic appearance was not completely characterized[3,4]. Here, we report two cases of AL amyloidosis presenting as submucosal hematomas during colonoscopy.

CASE REPORT

Case 1

A 48-year-old woman was referred because of hematochezia. She had no past history of tuberculosis, rheumatoid arthritis or collagen vascular disease. The results of routine laboratory tests were normal. Initial colonoscopy revealed reddish elevated lesions within plaque-like erythema in the sigmoid and transverse colon. The colon surface was covered by non-neoplastic mucosa (Figure 1A).

A biopsy was not performed in the initial colonoscopy because of the possibility of vascular lesions, such as blue rubber bleb nevus syndrome, and because it might induce bleeding. Repeat colonoscopy performed after approximately 1 mo revealed a healed scar and discoid discoloration where the submucosal hematoma was located; this suggested that the lesion had healed without intervention (Figure 1B). However, another distally developed submucosal hematoma was found (not shown). It was similar to the lesion in the initial colonoscopy. Endoscopic biopsies were performed for the submucosal hematomas and discoid discoloration. There were active bleedings from both after biopsy but hemostasis was achieved by the hemoclip method.

Histological examination of a biopsy specimen from one of the submucosal hematomas revealed mucosal hemorrhages (Figure 1C) and that from the submucosal hematomas and discoid discoloration revealed deposition of amorphous material in the lamina propria and in the vessel walls of the submucosa (hematoxylin-eosin stain and Congo red stain) (Figure 1D and E). On examining the same specimen under polarized light with Congo red stain, an apple-green birefringence, which is characteristic of amyloid, was observed (Figure 1F). Staining with amyloid A, κ and λ was negative. AL amyloidosis was strongly considered in this case because a significant proportion of AL amyloid deposits could not be stained while AA amyloid could be diagnosed in all cases. Biopsies of the stomach and duodenum and immunoelectrophoresis results of the serum and urine were negative. An echocardiogram showed no evidence of amyloid infiltration. This was believed to be a case of localized AL amyloidosis of the colon. During a follow-up of approximately 2 years, the patient has been conservatively managed and remains healthy.

Case 2

A 50-year-old woman was referred because of hematochezia and abdominal pain. Her past history solely revealed bronchial asthma. Colonoscopy revealed submucosal hematomas that resembled case 1, from the ascending colon to the rectum (Figure 2A). Endoscopic biopsies were performed for the submucosal hematomas. There was active bleeding after biopsy but hemostasis was achieved by the hemoclip method.

Histological examination revealed amyloid deposition in the lamina propria and in the vessel walls of the submucosa (hematoxylin-eosin stain and direct fast scarlet stain) (Figure 2B and C). Direct fast scarlet stain produced birefringence under polarized light. Staining with κ was positive (Figure 2D). Subcutaneous biopsy of the auricle produced the same result. A 24 h urine specimen contained more than 5 g of protein and an echocardiogram revealed thickening of the left ventricle wall. Systemic AL amyloidosis was diagnosed. We referred the patient to a hematologist and high-dose chemotherapy with hematopoietic stem cell transplantation was planned. However, the cardiac amyloidosis deteriorated and she died 2 mo later.

DISCUSSION

The clinical and endoscopic features of AL amyloidosis are diverse and mimic various other diseases[1]. Endoscopically, few reports are available in the literature on submucosal hematomas of the gastrointestinal (GI) tract[3,4]. Early diagnosis of AL amyloidosis is important because most cases are diagnosed late and have a grave prognosis. The endoscopic findings in both cases were similar in the formation of a submucosal hematoma; however, the clinical courses differed. James *et al*[5] investigated endoscopic findings of AL amyloidosis of the GI tract, including stomach, duodenum and colon, and reported that submucosal hematomas, as well as mucosal erosions and ulcerations, were the most common endoscopic findings. Therefore, gastroenterologists should diagnose submucosal hematomas more frequently than that indicated in past reports.

The pathogenesis of submucosal hematomas in AL amyloidosis remains unclear. Deposition of AL amyloid within vascular walls increases vessel fragility and possibly results in spontaneous bleeding beneath the lamina propria, which results in hematoma formation[5].

Untreated AL has a median 1 year mortality rate of approximately 50%[6] and survival is largely dependent on the degree of cardiac and renal involvement. Recently, high-dose chemotherapy with hematopoietic stem cell transplantation has been performed for patients with good performance status and limited cardiac involvement[1] and the 5-year survival rate in such patients is

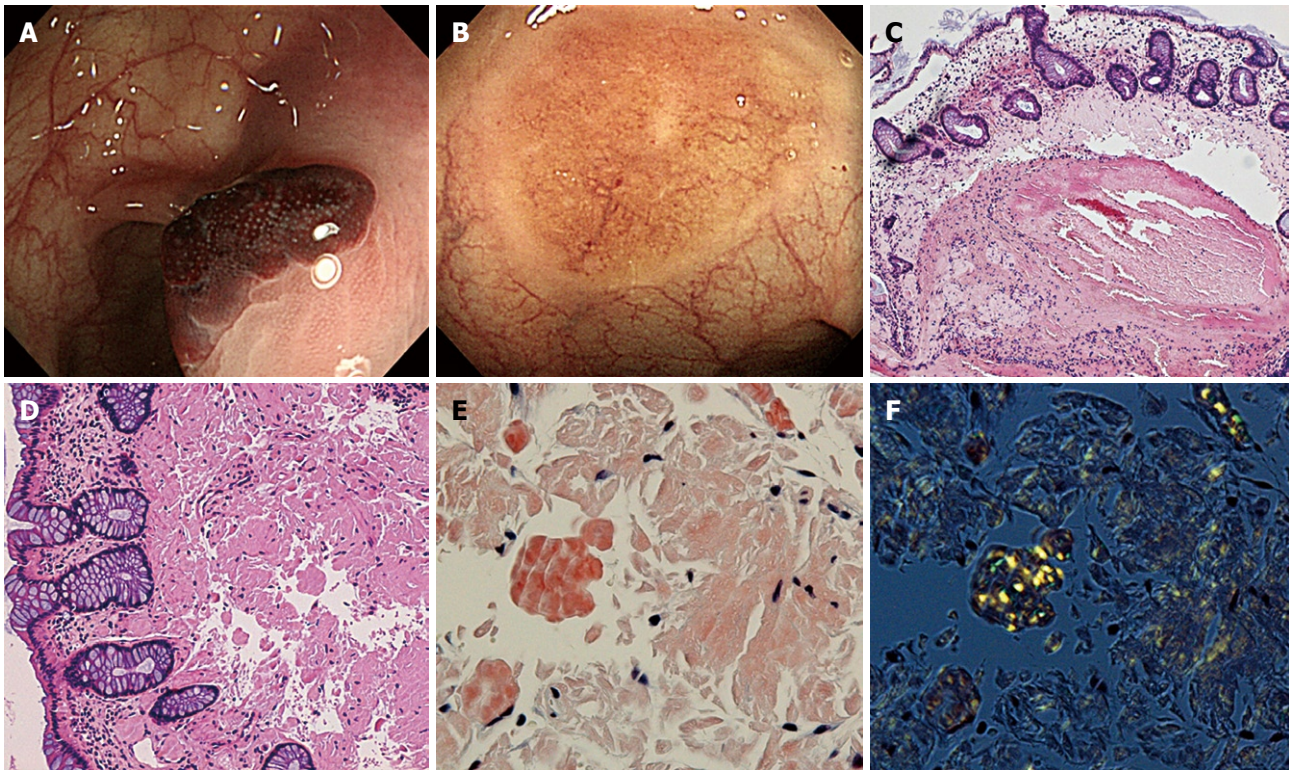

Figure 1 Initial colonoscopy revealed reddish elevated lesions within plaque-like erythema in the sigmoid and transverse colon. A: Initial colonoscopy showing a submucosal hematoma in the transverse colon; B: Repeat colonoscopy showing a discoid discoloration where the submucosal hematoma was located; C: Biopsy from submucosal hematoma showing mucosal hemorrhages and deposition of amorphous material in the lamina propria (hematoxylin-eosin stain); D: Biopsy from discoid lesion showing deposition of amorphous material in the lamina propria and in the vessel walls of the submucosa (hematoxylin-eosin stain); E: Congo red stain showing amyloid deposition; F: Apple-green birefringence under polarized light.

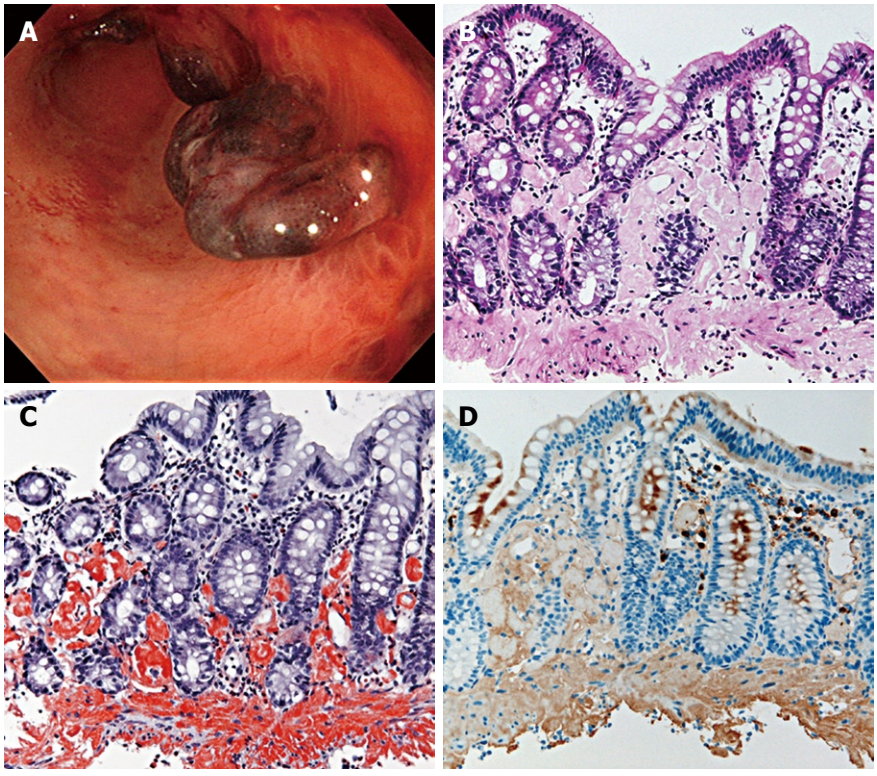

Figure 2 Endoscopic biopsies were performed for the submucosal hematomas. A: Colonoscopy showing submucosal hematomas from the ascending colon to the rectum; B and C: Biopsy showing mucosal hemorrhages and deposition of amorphous material in the lamina propria and in the vessel walls of the submucosa (hematoxylin-eosin stain and direct fast scarlet stain); D: Staining with κ was positive.

60%. Patients in whom involvement is limited to the GI tract should be immediately referred to a hematologist for consideration of treatment.

In conclusion, the endoscopic detection of submucosal hematomas in a setting of GI bleeding should raise suspicion of AL amyloidosis, which might lead to improved prognosis of AL amyloidosis.

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Events Calendar 2012

January 19-21, 2012
American Society of Clinical Oncology 2012 Gastrointestinal Cancers Symposium
San Francisco, CA 3000, United States

January 19-21, 2012
2012 Gastrointestinal Cancers Symposium
San Francisco, CA 94103, United States

January 20-21, 2012
American Gastroenterological Association Clinical Congress of Gastroenterology and Hepatology
Miami Beach, FL 33141, United States

February 2-4, 2012
14th Dusseldorf International Endoscopy Symposium 2012
Dusseldorf, Germany

February 24-27, 2012
Canadian Digestive Diseases Week 2012
Montreal, Canada

March 1-3, 2012
International Conference on Nutrition and Growth 2012
Paris, France

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting
San Diego, CA 92121, United States

March 12-14, 2012
World Congress on Gastroenterology and Urology
Omaha, NE 68197, United States

March 30-April 2, 2012
Mayo Clinic Gastroenterology and Hepatology
San Antonio, TX 78249, United States

March 31-April 1, 2012
5th Annual Endoscopy Directors Meeting Endoscopy Unit Management in the 21st Century: Issues, Solutions, and Plans for the Future
Washington, DC 20057, United States

April 8-10, 2012
9th International Symposium on Functional GI Disorders
Milwaukee, WI 53202, United States

April 15-17, 2012
European Multidisciplinary Colorectal Cancer Congress 2012
Prague, Czech

April 19-21, 2012
Internal Medicine 2012
New Orleans, LA 70166, United States

April 20-22, 2012
Diffuse Small Bowel and Liver Diseases
Melbourne, Australia

April 22-24, 2012
EUROSON 2012 EFSUMB Annual Meeting
Madrid, Spain

April 28, 2012
Issues in Pediatric Oncology
Kiev, Ukraine

May 3-5, 2012
9th Congress of The Jordanian Society of Gastroenterology
Amman, Jordan

May 7-10, 2012
Digestive Diseases Week
Chicago, IL 60601, United States

May 17-21, 2012
2012 ASCRS Annual Meeting-American Society of Colon and Rectal Surgeons
Hollywood, FL 1300, United States

May 18-23, 2012
SGNA: Society of Gastroenterology Nurses and Associates Annual Course
Phoenix, AZ 85001, United States

May 19-22, 2012
2012-Digestive Disease Week
San Diego, CA 92121, United States

June 18-21, 2012
Pancreatic Cancer: Progress and Challenges
Lake Tahoe, NV 89101, United States

September 8-9, 2012
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 8-9, 2012
Florida Gastroenterologic Society 2012 Annual Meeting
Boca Raton, FL 33498, United States

September 15-16, 2012
Current Problems of Gastroenterology and Abdominal Surgery
Kiev, Ukraine

October 4-6, 2012
EURO-NOTES 2012: NOTES and Advanced Interventional Endoscopy
Prague, Czech Republic

October 19-24, 2012
American College of Gastroenterology 77th Annual Scientific Meeting and Postgraduate Course
Las Vegas, NV 89085, United States

November 3-4, 2012
Modern Technologies in Diagnosis and Treatment of Gastroenterological Patients
Dnepropetrovsk, Ukraine

December 1-4, 2012
Advances in Inflammatory Bowel Diseases
Hollywood, FL 33028, United States

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INSTRUCTIONS TO AUTHORS

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hyperten sion, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data
Write as mean ± SD or mean ± SE.

Statistical expression
Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Abbreviations
Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
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Biology: *H. pylori*, *E coli*, *etc.*

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