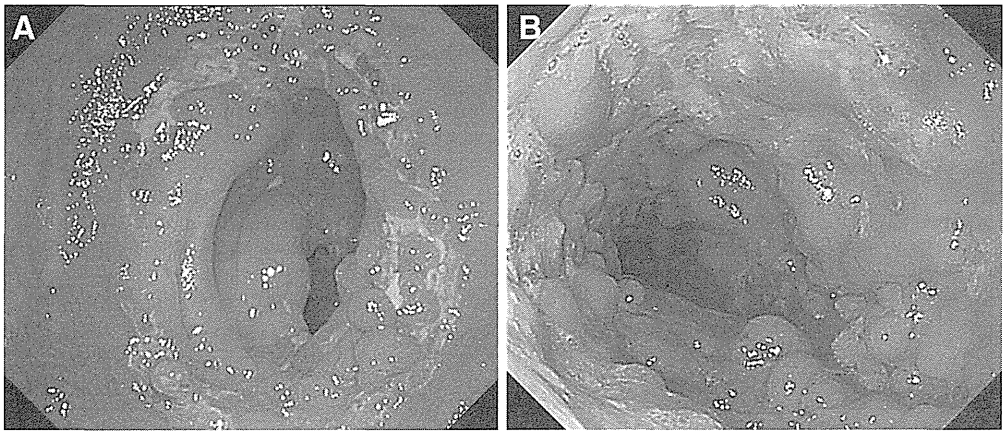

Fig. 2 Differential diagnosis of intestinal BD. **a** Annular ulcers in patients with active TB. **b** Longitudinal ulcers and a cobblestone appearance in a patient with CD

Differential diagnosis of intestinal BD

Intestinal tuberculosis (TB), Crohn's disease (CD), and other diseases with intestinal ulceration should be excluded. Ruling out intestinal TB is especially important, because the immunosuppressive therapy used to treat BD, including corticosteroids and anti-TNFα mAbs, can exacerbate intestinal TB. Methods of diagnosing intestinal TB include tissue culture, tissue PCR and interferon-gamma release assays (IGRA), in addition to general examinations such as chest X-ray and tuberculin test. Endoscopic findings of intestinal TB often include annular ulcer and scarred areas with discoloration (Fig. 2a).

The differential diagnosis between intestinal BD and CD is often difficult, since several extraintestinal manifestations, such as oral ulcers and arthralgia, are seen in both diseases. Typical endoscopic and radiological findings in patients with CD include longitudinal ulcers and a cobblestone appearance (Fig. 2b). Anal lesions are more common in CD than in intestinal BD. Balloon small intestinal endoscopy and capsule endoscopy have recently been reported to be useful for the diagnosis and monitoring of patients with intestinal BD [20–23] (Fig. 1c).

Pathogenesis of intestinal BD

Genetic factors

Few cases of familial intestinal BD have been reported to date, suggesting the contribution of genetic factors in its pathogenesis [24, 25]. Recently, genome-wide association studies (GWAS) have identified several genes associated with susceptibility to BD including the interleukin (IL)-23R, IL-10, STAT, and HLA-B51 genes [26–29]. However, few genetic factors associated with the phenotype of intestinal BD have been identified. The positive ratio of HLA-B51 has been reported to be lower in patients with intestinal BD associated with myelodysplastic syndrome (MDS) than in BD patients without intestinal involvement [18]. The number of copies of the *DEFA1* gene, which encodes α-defensin-1, has been reported to correlate with intestinal involvement in BD [30], and familial cases of BD with intestinal lesions have been reported to be associated with NEMO mutations [31].

Immunological abnormalities

Susceptible genes identified by GWAS strongly suggest that abnormal immunological responses may play a role in the pathogenesis of BD. However, the precise mechanisms underlying the pathogenesis of intestinal BD have not yet been identified. Abnormal innate immune responses have been reported to be associated with intestinal BD [30, 32]. Moreover, tissue samples taken from intestinal lesions of BD have been found to express interferon gamma (IFNγ), TNFα and IL-12 mRNAs, indicating skewed Th1 responses [33]. Similarly, an investigation of cytokine expression in ileal biopsy specimens from patients with intestinal BD reported Th1 skewing [34]. Recent reports showing the efficacy of anti-TNFα mAb suggest the importance of TNFα in the pathogenesis of intestinal BD.

Trisomy 8 and intestinal ulcers

Although BD and MDS are two different disease entities, some BD patients have bone marrow disorders such as MDS and aplastic anemia. MDS is a clonal hematologic disease with cytogenetic abnormalities. The most common chromosomal abnormality in BD patients with MDS is trisomy 8. A review of 62 Japanese patients with BD-associated MDS found that, among the 45 patients with abnormal karyotypes, 39 (86.7 %) had trisomy 8 [35]. Similarly, an analysis of the clinical features of 13 patients with BD and bone marrow disorders found that seven (54 %) had trisomy 8 [36]. Trisomy 8 may also be

associated with the development of intestinal ulcers in patients with MDS [37]. The mechanisms by which trisomy 8 is associated with intestinal ulcers has not been determined, although autoimmune mechanisms play a role in the development of hematopoietic disorders such as MDS and aplastic anemia [38, 39]. Gene expression analysis of $CD34^+$ hematopoietic cells in patients with trisomy 8 showed over-expression of proinflammatory cytokines [40]. In addition, trisomy 8 was associated with low copy numbers of the human beta-defensin 2 gene, which plays a role in human innate immunity [41]. Interestingly, a case report showed atypical endoscopic findings of intestinal ulcers in patients with BD and trisomy 8 [42], differing from the typical endoscopic findings of a giant oval punched-out ulcer at the ileocecum. Further investigations are needed to assess the similarities and differences between intestinal BD and intestinal ulcers in BD patients with trisomy 8.

Management and therapy

Conventional treatments and disease prognosis

Clinical evidence regarding the management of patients with intestinal BD is limited. Among the agents used empirically, 5-aminosalicylic acid (5-ASA), systemic corticosteroids, thalidomide, colchicine and immunosuppressive agents have been used. A study in Korea showed that 5-ASA/sulfasalazine therapy could maintain remission in patients with intestinal BD, although younger age (<35 years), higher C-reactive protein (CRP) level, and higher disease activity were associated with a poor response to 5-ASA/sulfasalazine [43]. Mesalazine was shown to have benefits in the treatment of esophageal ulcers in a patient with intestinal BD [44]. Corticosteroids are generally used to induce clinical remission in intestinal BD patients with moderate to severe activity [15, 45–47]. Immunosuppressants have also been used successfully. For example, a retrospective analysis of 272 patients with intestinal BD in a single center described the efficacy of thiopurine maintenance therapy. Of these 272 patients, 67 (24.6 %) received their first course of thiopurine therapy in the center, with 39 (58.2 %) of these 67 patients maintained on thiopurines. The cumulative 1-, 2-, 3- and 5-year relapse rates after remission were 5.8, 28.7, 43.7, and 51.7 %, respectively [48]. Methotrexate (MTX) has also been used to treat refractory intestinal BD [49]. Oral tacrolimus was effective in a patient with intestinal BD [50], and thalidomide, an agent with anti-inflammatory and immunomodulatory properties, has also been found to be effective [51–53].

In response to a request to standardize treatment of intestinal BD, the Japanese Inflammatory Bowel Disease Research Group, supported by the Japanese Ministry of Health, Labour and Welfare, proposed the first set of consensus statements in 2007 for the management of intestinal BD [9]. This consensus recommended systemic corticosteroids for induction therapy and thiopurines for refractory intestinal BD as standard therapies, with anti-TNFα mAb described as optional.

Despite reports showing the beneficial effect of medical therapies, patients with intestinal BD often require surgical treatment and may develop post-operative recurrence. Thus, intestinal BD, in at least a subpopulation of patients, should be considered a progressive disorder that causes disability, similar to CD. Since it is difficult to predict which patients will experience complicated disease courses, therapy should be individualized and depend on monitoring of individual patients. In our retrospective analysis of 20 patients, ocular and ileal lesions were risks for surgery [54]. Postoperative recurrence of intestinal ulcers was observed in seven of nine patients with intestinal BD who had undergone a total of 15 operations [55]. A retrospective analysis of 72 Korean patients with intestinal BD who underwent surgery showed that 42 (58.3 %) experienced recurrence after surgery, with 22 (30.6 %) requiring re-operations. The cumulative 2- and 5-year recurrence rates after surgery were 29.2 and 47.2 %, respectively [56]. A retrospective evaluation of 130 patients with intestinal BD during the first 5 years after diagnosis revealed five different clinical courses, with the most frequent being persistent remission or mild clinical activity (56.2 %) and only 16.2 % having a severe clinical course. Younger age, higher erythrocyte sedimentation rate (ESR), CRP concentration, and disease activity index, and lower albumin concentration at diagnosis were factors associated with poor patient prognosis [57].

Anti-TNFα monoclonal antibodies

The efficacy of anti-TNFα mAbs in intestinal BD was first reported in 2001. Treatment with infliximab (IFX) of two patients with intestinal BD resistant to conventional therapy, including prednisolone, one with 3 mg/kg and the other with 5 mg/kg IFX, resulted in the rapid (within 10 days) reduction of intestinal lesions and extraintestinal manifestations [53]. Remission in both patients was maintained with thalidomide, not IFX. In addition, a patient with chronically active, steroid-dependent BD involving the gastrointestinal tract who was treated with four doses of IFX over a period of 6 months showed a reduction in CD activity index (CDAI) from 270 points before infusion to 13 points by week 2, with remission sustained despite the complete withdrawal of steroids [58]. Colonoscopy 10 weeks after the first infusion showed marked endoscopic and histological improvement. After

these reports suggesting the rapid efficacy of IFX, several groups have assessed the efficacy of anti-TNFα in intestinal BD [59, 60]. For example, six Japanese patients with intestinal BD, all of whom were steroid dependent and refractory to other treatments, received IFX induction therapy (5 mg/kg at 0, 2, and 6 weeks), followed by maintenance therapy every 8 weeks [61]. Four of these six patients achieved and maintained remission with IFX. The other two patients, both of whom had ileal ulceration, required surgery, but one has maintained remission by IFX after surgery. A retrospective analysis of 28 patients with intestinal BD who received at least 1 dose of IFX and were followed-up for a median 29.5 months, resulted in response rates to IFX at 2, 4, 30, and 54 weeks of 75, 64.3, 50, and 39.1 %, respectively, and clinical remission rates of 32.1, 28.6, 46.2, and 39.1 %, respectively [62]. Multivariate analysis indicated that older age at diagnosis (≥40 years), female sex, longer disease duration (≥5 years), concomitant immunomodulator use, and achievement of remission at week 4 were predictive of sustained response. BD patients with intestinal lesions have a risk of multiple operations, but postoperative use of anti-TNFα has not been shown to reduce postoperative relapse rates and risk of multiple operations. IFX was used as rescue therapy for a patient with an unhealed anastomosis site and early recurrent ulcers after bowel resection [63]. IFX has also been reported effective in treating pediatric patients with intestinal BD, including a 15-year-old girl with refractory intestinal BD who responded rapidly to IFX [64] and a pediatric patient with progressive, refractory pediatric BD with intestinal lesions who responded to IFX [65].

Fewer reports have described the clinical efficacy of ADA. One patient with intestinal BD was treated with ADA monotherapy [66], whereas another was diagnosed with intestinal BD despite ADA treatment for underlying ankylosing spondylitis [67]. In Japan, a phase 3, non-randomized, non-controlled, one-arm, clinical trial tested ADA for intestinal BD [68]. Patients were given 160 mg ADA at week 0, 80 mg at week 2, and 40 mg every other week, beginning at week 4. The primary endpoint was 'marked improvement' rate at week 24, with 'marked improvement' defined according to the physicians' global assessment of gastrointestinal symptoms and endoscopic improvement. The 'marked improvement' and complete remission rates at week 24 were 45 and 20 %, respectively. Based on the results of this clinical trial, ADA was approved in Japan to treat intestinal BD in May 2013. A clinical trial has also tested IFX for intestinal BD in Japan, and the second edition of consensus statements for the diagnosis and management of intestinal BD has proposed anti-TNFα mAb as a standard therapy for patients with moderate to severe intestinal BD [68].

Can anti-TNFα mAb change therapeutic strategy of intestinal BD?

CD is regarded as a progressive disability of the digestive tract. Early intervention with anti-TNFα mAbs may alter the natural history of CD and improve the long-term prognosis of patients with this disorder [69]. Sub-types of BD are also progressive diseases, with BD uveitis causing loss of vision and intestinal BD requiring bowel resection. Thus, it is important to determine if anti-TNFα mAb treatment can improve the long-term prognosis of these patients. Although anti-TNFα mAb has been reported to reduce the risk of visual loss in patients with BD uveitis [70], its ability to reduce the risk of surgery in patients with intestinal BD has not been fully investigated. Since clinical symptoms and clinical activity index are often subjective in inflammatory bowel disease (IBD), discrepancies between clinical symptoms and endoscopic findings have been observed in IBD patients. Therefore, endoscopic findings are regarded as more important in evaluating the management of IBD patients. Mucosal healing, defined as endoscopic remission, has become the goal of IBD treatment to improve the long-term prognosis [71]. In contrast, there is no evidence indicating that mucosal healing should be a treatment target for improving the long-term prognosis of patients with intestinal BD, although the concept of 'mucosal healing' may be applicable in the management of these patients (Fig. 3a, b). For example, an analysis of 10 patients with intestinal BD who were treated with IFX and MTX reported that ileocecal ulcerations disappeared in nine of these patients (90 %) 12 months after initiation of IFX [49]. A patient with intestinal BD who was treated with IFX monotherapy successfully maintained clinical remission and complete mucosal healing for 6 years [72]. A retrospective analysis of the correlation between endoscopic parameters and clinical activity index in 167 patients with intestinal BD found that, although the number of intestinal ulcers and volcano-shaped ulcers were predictive of severe clinical index score, the correlation between endoscopic severity and clinical activity index was weak [73].

Thus, as in IBD, anti-TNFα mAb treatment may achieve mucosal healing and improve the long-term prognosis in patients with intestinal BD. To ensure the maximal efficacy of anti-TNFα mAb therapy, the concept of 'early CD' has been proposed. Subgroup analysis of the CHARM trial showed that ADA was superior to placebo in maintaining clinical remission in patients with moderately to severely active CD after 1 year of treatment, regardless of disease duration [74]. Clinical remission rates through 3 years of treatment were highest in the group with the shortest disease duration. However, the optimal timing of anti-TNFα mAb treatment in intestinal BD has not been determined.

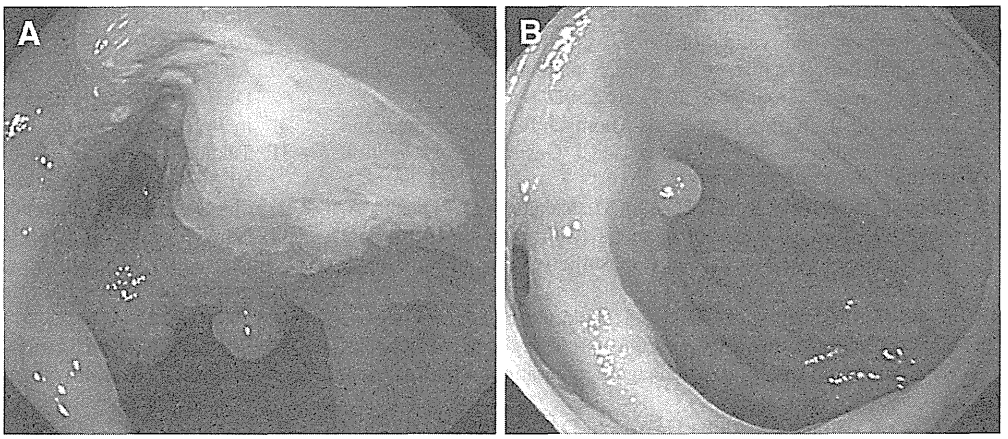

Fig. 3 IFX treatment can induce 'mucosal healing' of intestinal BD lesions. **a** A typical giant *oval-shaped* ulcer observed before initiation of IFX. **b** Dramatic improvement of ileocecal lesions after treatment with IFX (the patient was reported by Maruyama et al. [72])

Despite anecdotal evidence showing the efficacy of combinations of immunomodulators with anti-TNFα mAbs as induction and maintenance treatment in intestinal BD, there is no consensus regarding their use. Even in CD, it remains unresolved whether anti-TNFα mAbs should be used in combination with immunomodulators [75–78]. Although one study reported the effectiveness of MTX plus IFX [49], another described a patient successfully maintained with IFX monotherapy [72].

Conclusion

In reviewing the latest reports on the diagnosis and management of intestinal BD, we found that anti-TNFα mAb is a promising treatment for patients with this disorder. However, several issues remain to be resolved. Genomic analysis of patients with intestinal BD, as well as determining the mechanism of action of anti-TNFα mAbs, may provide insight into the pathogenesis of this disorder. Clinically, it is necessary to formulate global diagnostic criteria and an objective disease activity index. Treatment with anti-TNFα mAbs will likely alter disease prognosis, although these agents are not necessary in all patients with intestinal BD. Most importantly, it is necessary to identify high-risk patients and to monitor their disease activity.

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Disclosures

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Human/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: This review article does not have relevant issues of informed consent disclosure to be reported.

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Magnetically Guided Capsule Versus Conventional Gastroscopy for Upper Abdominal Complaints

A Prospective Blinded Study

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Objectives: Upper gastrointestinal endoscopy is mostly performed under sedation and has a low yield of relevant gastric lesions in patients without alarm symptoms. Simpler screening tests such as capsule endoscopy could be helpful, but gastric visualization is insufficient with the current passive capsules. A magnetically guided gastric capsule was prospectively evaluated in patients with routine indications for gastroscopy.

Methods: A total of 189 symptomatic patients (105 male; mean age 53 y) from 2 French centers subsequently and blindly underwent capsule and conventional gastroscopy by 9 and 6 examiners, respectively. The final gold standard was unblinded conventional gastroscopy with biopsy under propofol sedation. Main outcome was accuracy (sensitivity/specificity) of capsule gastroscopy for diagnosis of major gastric lesions, defined as those lesions requiring conventional gastroscopy for biopsy or removal.

Results: Twenty-three major lesions were found in 21 patients. Capsule accuracy was 90.5% [95% confidence interval (CI), 85.4%-94.3%] with a specificity of 94.1% (95% CI, 89.3%-97.1%) and a sensitivity of 61.9% (95% CI, 38%-82%). Accuracy did not correlate with lesion location, gastric luminal visibility, examiner case volume, or examination time. Of the remaining 168 patients, 94% had minor and mostly multiple lesions; the capsule made a correct diagnosis in 88.1% (95% CI, 82.2%-92.6%), with gastric visibility and lesion location in the proximal stomach having significant influence. All patients preferred capsule gastroscopy.

Conclusions: In a prospective and strictly blinded study, magnetically guided capsule gastroscopy was shown to be feasible in clinical practice and was clearly preferred by patients. Improvements in capsule technology may render this technique a future alternative to gastroscopy.

Key Words: gastroscopy, capsule endoscopy, gastric cancer screening

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Flexible endoscopy has been established for the diagnosis and treatment of a large and increasing number of gastrointestinal (GI) disorders during the past 30 years. However, depending on patient characteristics and symptoms, endoscopy detects relevant lesions in only a minority of cases and involves costs and expenditure as well as certain risks mostly related to sedation.[1–4] Thus, similar to colorectal cancer screening, a simple and reliable filter test would be helpful to stratify patients into those without relevant lesions not requiring further invasive methods and a minority of cases in whom flexible endoscopy has to be performed for biopsy or treatment of detected lesions. In countries with gastric cancer screening such as Japan, noninvasive methods such as serum pepsinogen tests have been evaluated, but have not replaced image-based screening by endoscopy or barium swallow.[5,6] For symptomatic patients with upper abdominal complaints, several nonendoscopic strategies outside of cancer screening have been evaluated, such as *Helicobacter pylori* testing and treatment,[7] but these have not been implemented into most national guidelines.

Capsule endoscopy was introduced into gastroenterologic diagnostics primarily for small-bowel imaging, in which conventional endoscopy and radiology have traditionally failed to detect lesions especially if they are smaller and more discrete.[8,9] Attempts to expand the indications for capsule endoscopy to the esophagus[10] and colon[11] have met several obstacles in performance, preparation, organization, and costs, thereby preventing widespread capsule use in these areas. In the stomach, occasional lesions have been detected after esophageal capsule endoscopy or before small-bowel imaging, but the consensus is that the stomach is not a good target organ for passive capsule endoscopy.[12]

Thus, there may be a need for guided capsule gastroscopy to allow for complete visualization of all areas of the stomach. After promising initial results using a capsule guided by a simple external magnet[13,14] or by a more sophisticated magnetic guidance system,[15,16] the current prospective study systematically evaluated the diagnostic accuracy of the latter system of capsule gastroscopy. It was compared with conventional flexible gastroscopy in patients examined for upper GI complaints. Examination of the esophagus and duodenum was not included in this comparative study.

PATIENTS AND METHODS

Patients

During a 6-month period (October 2011 to March 2012), patients with abdominal complaints requiring upper GI endoscopy were included in this prospective comparative trial after providing informed consent. Patients with the following were excluded: dysphagia or symptoms of gastric outlet obstruction, suspected or known intestinal stenoses, postabdominal radiation, overt GI bleeding, known large (> 2 cm) and obstructing tumors (cardia/pylorus) of the upper GI tract, status after upper GI surgery or abdominal surgery altering GI anatomy, under therapeutic anticoagulation, in poor general condition (American Society of Anesthesiologists class III/IV), patients with claustrophobia, metallic parts, electronic implants, artificial heart valves, pregnancy or suspected pregnancy.

The study was approved by the Local Ethical Committee (Comité de Protection des Personnes – Sud Mediterranée V; Scientific study: No. 2010-A01442-37; P reference 11.006) and was performed at the Institut Arnault Tzanck, St. Laurent du Var/France, where the magnetic guidance equipment was installed. Patients were recruited from both gastroenterologic departments at the Institut Arnault Tzanck and the Centre Hospitalier Universitaire of Nice. Examinations were performed by 9 and 6 different examiners for capsule and conventional gastroscopy, respectively, who were all very experienced in upper GI endoscopy (> 10,000 examinations). All capsule examiners received special training in capsule gastroscopy, participating in at least 10 gastric capsule endoscopies. Three of 9 capsule examiners had precious experience with the small-bowel capsule. The training was part of prestudies, which also evaluated different preparation regimens[16]; these examinations were not included in the present study. All authors had access to the study data and reviewed and approved the final manuscript.

Examiners were blinded to previous findings, suspected diagnoses, and patient history, but only received a standardized indication list. Patients were cared for by 2 study fellows (M.A.-H., B.H.). Capsule and conventional gastroscopies were always performed by different examiners who were blinded to the results of the other test.

Capsule Gastroscopy

Guidance System, MGCE Capsule, and MGCE Navigation

The capsule gastroscopy setup has been described in detail elsewhere.[10,17] The magnet of the guidance system has a footprint of 1 × 2 m and generates dynamic magnetic fields and field gradients in 3-dimensional space over the entire stomach at very low intensity. The low magnetic field has a maximum of 100 mT, which is 15 times smaller than the standard 1.5 T magnetic resonance imaging field. Because of the low intensity of the magnetic field, a cooling system is not required and possible side effects for patients with metallic internal devices are reduced.

The capsule measures 31 × 11 mm and contains a permanent magnet to enable guided movements by the magnetic field applied by the guidance system. The capsule is equipped with 2 image sensors—1 at each end—that use a charge-coupled device. It generates images from the forward and backward direction of the capsule movement with image transmission at 4 frames/s. The optics obtain high-quality images of the stomach using a wider field of view and a deeper field of depth compared with the current small-bowel capsule. Comparable to the small-bowel capsule, images are recorded by means of multiple antennas attached to the patient.

In real-time gastric imaging, the capsule images and data are displayed on a dual-monitor panel. The images of both capsule optic sensors are shown simultaneously on the right monitor, whereas the left monitor displays the information about the capsule orientation assessed by the magnetic field. The physician controls capsule movements using 2 joysticks with 5 independent mechanical degrees of freedom. The magnetically guided capsule endoscope (MGCE) can be navigated forward, backward, tilting, which is equivalent to the large–steering wheel movements of an endoscope, or rotating, which is equivalent to the endoscopic small-wheel movements. Movements are possible floating at the water surface or diving at the bottom of the stomach. If the capsule is blocked between the gastric folds it can be dislocated using the jumping function.

Capsule transmission time is about 30 to 40 minutes.

Capsule Procedure

Capsule gastroscopy was always performed first. After overnight fasting, patient preparation included administration of 500 mL of clear water at room temperature and 300 mg simethicone about 1 hour before the procedure. this was followed by 2 × 400 mL of tap water at near body temperature (35°C) within 15 to 20 minutes, to provide an air-water interface in the stomach for capsule navigation. Image receiving antennae were attached to the patient, and the patient was positioned inside the low-field magnetic resonance imaging. Capsule was ingested in a sitting position to facilitate the esophageal passage. The examination was then undertaken with the patient lying in subsequent positions of left lateral, supine, and finally right lateral. In cases of difficulty in capsule navigation, the patient was turned to a different position, sometimes even prone. If necessary, additional water was ingested to create optimal conditions (the capsule requires some water volume for

proper navigation). Findings were documented immediately after capsule gastroscopy without later review by the examiner and/or the research fellow.

Conventional Gastroscopy

Conventional upper GI endoscopy was performed after MGCE with a maximum delay of 1 day but a minimum delay of 4 hours due to water filling of the stomach with the capsule examination. The examination was carried out first blinded and then unblinded (Olympus gastroscopes 180 series; Olympus Corp., Hamburg, Germany) with patients in the left lateral position and under propofol sedation monitored by an anesthesiologist. Only the stomach was inspected for the present study; the esophagus and duodenum were examined for clinical routine reasons, but findings were not noted on the study case report form. Upper GI endoscopy was terminated when the examiner felt the stomach had been adequately inspected, and findings were documented at this stage by the research fellow as dictated by the examiner. Biopsies were taken whenever felt to be appropriate. After this, results of capsule gastroscopy or other clinical or imaging information relevant for the case were revealed by the research fellow to allow reinspection in the case of discrepancy between capsule gastroscopy and blinded gastroscopy. With this information, unblinded gastroscopy was performed in the same gastroscopy session. The combined endoscopic assessment (blinded and unblinded gastroscopy) including biopsy was used as the final gold standard and is called unblinded gastroscopy in the following sections.

Data Recording and Definitions

The following parameters were recorded:

- patient age and sex
- indication for upper GI endoscopy
- details of capsule gastroscopy performance such as
  - examination time
  - assessment of examination quality consisting of
    - (i) overall gastric visibility on a visual analog scale (VAS) of 1 to 10 (1 = excellent; 10 = no visualization)
    - (ii) overall clarity of capsule image 1 to 3 (1 = completely clear; 2 = slightly turbid, no impairment; 3 = turbid, impairment of visibility)
    - (iii) gastric contractile activity 1 to 3 (1 = ignorable; 2 = mild; 3 = strong)
    - (iv) gastric expansion during examination (sufficient/insufficient)
- findings; major findings were defined as localized lesions with diagnostic or therapeutic relevance (ie, those requiring subsequent conventional gastroscopy for biopsy or therapy). Major lesions thus included tumors (adenomas, carcinomas, singular hyperplastic polyps), ulcers, and angiodysplasia. Minor findings were multiple and diffuse findings such as fundic gland polyps, erosions, and marked gastric atrophy. Location (proximal = fundus + cardia; distal = body, antrum + pylorus) and size were noted for major lesions, and location only was noted for minor lesions. The case load of participating examiners within the study was also recorded.

Patient acceptance of capsule gastroscopy (no sedation) versus conventional gastroscopy (including sedation), on a VAS scale of 1 (excellent, no problem) to 10 (very poor, hardly tolerable, interrupted) was recorded, as well as the answer to the question of which examination patients would prefer in the case of further gastroscopy becoming necessary.

Outcome Parameters

The primary outcome parameters were the accuracy (all true positives and negatives/all cases) and the sensitivity, specificity, and predictive values of capsule gastroscopy compared with unblinded gastroscopy with biopsy with regard to major lesions on a per-patient and per-lesion basis, respectively. This definition was chosen, as the concept of capsule gastroscopy as a filter test for gastroscopy is based on the assumption that the imaging function should be equivalent to conventional gastroscopy, which should then be reserved for biopsy or therapy. We thus choose lesions that would require biopsy or removal as major lesions, the precise diagnosis of which can be regarded as the major outcome parameter. Only these major lesions require conventional gastroscopy, whereas minor lesions contribute to the diagnosis but do not require subsequent gastroscopy.

Secondary outcome parameters were: the accuracy (sensitivity, specificity, predictive values) of capsule gastroscopy compared with unblinded gastroscopy with biopsy with regard to minor lesions, on a per-patient and per-lesion basis, respectively; analysis of factors with possible influence (patient characteristics, overall visibility, examination time, examiner case volume, lesion location) on the accuracy of diagnosing major and minor lesions; complications of both examinations; comparison of blinded and unblinded gastroscopy.

Case Number Calculation

Because of limited availability of capsules (n = 220), it was decided to enrich the population with positive findings under conditions of strict blindness for both capsule and gastroscopy examiners to reach a prevalence of major lesions of 20% to 25%. Under these circumstances, the case number of 220, including a dropout rate of 10%, would provide the following confidence intervals (CIs) for sensitivity and specificity: 25% prevalence of major lesions: for sensitivity 90% CI 78%-97%, 80% CI 66%-90%; for specificity 95% CI 91%-98%, 85% CI 78%-90%. These assumptions were partially based on 2 previously published pilot studies.[15,16]

Statistical Analysis

Discrete variables are given as counts and percentages, and continuous variables are given as mean ± SD. Specificity, sensitivity, and positive and negative predictive values along with their exact 95% CIs are given. Hierarchical logistic regression analyses were applied to analyze the effect of various factors of the true positivity of capsule findings. A nominal P-value of <0.05, 2 tailed, was considered statistically significant. No adjustment for multiplicity was performed. Analyses were performed using statistical software SAS v 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics and Examination Details

A total of 215 patients were initially included, but 26 had to be excluded because of secondary refusal of study

TABLE 1. Accuracy Values of Capsule Gastroscopy Compared With Unblinded Gastroscopy as the Final Gold Standard for the Diagnosis of Major Lesions on a Per-Patient (n = 21) and Per-Lesion (n = 23) Basis

	Per Patient (%)	95% CI	Per Lesion (%)	95% CI
Accuracy	90.5	85.4-94.3	89.5	84.3-93.5
Sensitivity	61.9	38.4-81.9	56.5	34.5-76.8
Specificity	94.1	89.3-97.1	94.1	89.3-97.1
PPV	56.5	34.5-76.8	56.5	34.5-76.8
NPV	95.2	90.7-97.9	94.1	89.3-97.1

There were 21 cases with major lesions and 168 without major lesions (ie, 10 normal cases and 158 cases with minor lesions).
CI indicates confidence interval; NPV, negative predictive value; PPV, positive predictive value.

participation (n = 14), capsule impaction in the esophagus during scanning time (n = 3), technical problems (n = 5), protocol violation (n = 2), and inability to swallow the capsule (n = 1). The remaining 189 patients (105 male, 84 female; mean age 53.0 ± 13.7 y) with an indication for upper GI endoscopy such as upper abdominal pain and/or anemia were included in the study.

Major Lesions

The planned enrichment failed to reach the desired level of 20% to 25% patients with major lesions, but ended at a rate of 11%. These 23 major lesions found in 21 patients were 2 adenocarcinomas (tumor size 1.2 and 10.0 cm, both located in the gastric body), 4 submucosal tumors (size/location 1.5 and 0.8 cm in the gastric body, 0.9 cm in the cardia, and 1.0 cm in the antrum), 9 gastric ulcers [mean size 0.8 cm (range, 0.5 to 1.5 cm]; location cardia (n = 2), fundus (n = 1), antrum (n = 6)], 3 single hyperplastic polyps with a maximum size of 5 mm [location fundus (n = 2), pylorus (n = 1)], and 5 focal angiodysplasias [location antrum (n = 2), gastric body (n = 2), cardia (n = 1)]. Two patients each showed 2 lesions (each patient with 1 ulcer and 1 hyperplastic polyp).

Minor Lesions

Minor lesions were marked inflammatory changes with erosions (n = 165), multiple fundic gland polyps (n = 55), gastric atrophy (n = 16), and others (n = 7). Only 10 patients had no minor lesions found on unblinded gastroscopy.

Complications

No complications of capsule or conventional endoscopy were encountered. In the 3 patients who were excluded from the analysis due to capsule entrapment in the esophagus during the scanning time, subsequent upper GI endoscopy found the capsules still in the esophagus; the capsules were pushed gently into the stomach without problems. These patients had no symptoms either before gastroscopy or on follow-up.

Test Performance

Capsule gastroscopy was performed by a total of 9 examiners and upper GI endoscopy by 6. The mean examination time was 10.6 minutes (95% CI, 10.1-11.1) for capsule gastroscopy and 4.0 minutes (95% CI, 3.7-4.2) for blinded gastroscopy, with an additional 1.7 minutes (95% CI, 1.6-1.9) for the unblinded part of gastroscopy. On capsule gastroscopy, examiners' subjective assessment rated 96.3% of all 189 gastric capsule examinations as complete, with rates for pylorus, antrum, body, and cardia ranging from 93.1% to 98.9%, with significant differences between locations favoring the proximal stomach ($P = 0.007$). In addition, subjective ratings for overall visibility, clarity, and absence of significant gastric contractile activity were 80.3% (visibility VAS 1 to 2), 93.1% (clarity 1 to 2 with 67.2% completely clear), and 79.9% (absence of contractile activity; an additional 12.7% had mild contractile activity), respectively. There was no complication with any of the tests performed.

Capsule Gastroscopy Accuracy Compared With Unblinded Gastroscopy

Tables 1–3 show the accuracy results of capsule gastroscopy with regard to major and minor lesions, respectively. Sensitivity was limited for major lesions. Of the responsible factors that could be analyzed, sex was not found to be of relevance in the univariate analysis and was not considered further. None of the other factors analyzed with respect to capsule accuracy for major lesions had significant influence (Fig. 1). Because of the limited case number of major lesions, further factors documented but not shown in Figures 1 and 2 could not be analyzed in this model. With respect to minor lesions, only proximal location had significant influence (Fig. 2). Examples of major findings seen on capsule endoscopy are displayed in Figure 3.

Blinded Versus Unblinded Gastroscopy

Of the 21 patients with major lesions, 1 angiodysplastic lesion seen on capsule gastroscopy was not detected on blinded gastroscopy but was confirmed on subsequent unblinded gastroscopy. In all other patients with major lesions, findings had already been detected by blinded gastroscopy. For minor lesions, blinded gastroscopy was 89.8% to 98.0% sensitive depending on the lesion type and also very specific in the 3 subgroups when compared with

TABLE 2. Accuracy Values of Capsule Gastroscopy Compared With Unblinded Gastroscopy as the Final Gold Standard for the Diagnosis of Minor Lesions on a Per-Patient Basis (n = 168)

	Per Patient (%)	95% CI
Accuracy	88.1	82.2-92.6
Sensitivity	89.2	83.3-93.6
Specificity	70.0	34.8-93.3
PPV	97.9	94.0-99.6
NPV	29.2	12.6-51.1

There were 158 with 1 or (mostly) several minor lesions and 10 cases with normal stomach (ie, the 21 cases with major lesions are not included).
CI indicates confidence interval; NPV, negative predictive value; PPV, positive predictive value.

TABLE 3. Accuracy Values of Capsule Gastroscopy Compared With Unblinded Gastroscopy for the Diagnosis of Subgroups of Minor Lesions on a Per-Patient Basis

	Fundic Gland Polyps		Erosions and Hemorrhagic Gastritis		Gastric Atrophy	
	% (n = 49)	95% CI	% (n = 148)	95% CI	% (n = 17)	95% CI
Accuracy	83.9	77.5-89.1	91.7	86.4-95.4	91.7	86.4-95.4
Sensitivity	75.5	61.1-86.7	93.9	88.8-97.2	29.4	10.3-56.0
Specificity	87.4	80.1-92.8	75.0	50.9-91.3	98.7	95.3-99.8
PPV	71.2	56.9-82.9	96.5	92.1-98.9	71.4	29.0-96.3
NPV	89.7	82.6-94.5	62.5	40.6-81.2	92.6	87.3-96.1

This calculation was based on the 168 patients without major lesions (overlap between groups possible), of whom 158 had 1 or more minor lesion and 10 had none.

CI indicates confidence interval; NPV, negative predictive value; PPV, positive predictive value.

unblinded gastroscopy, although the number of negative cases was small (n = 10) (Table 4).

Patient Acceptance

The mean patient rating was 1.17 (95% CI, 1.11-1.23) for capsule gastroscopy and 1.67 (95% CI, 1.55-1.79) for conventional gastroscopy under sedation ($P < 0.001$). Preference for the type of future gastroscopy if indicated was capsule in all cases (100%).

DISCUSSION

The present study is the first large study to systematically evaluate guided capsule gastroscopy in patients with upper abdominal symptoms. The main outcome was defined as the accuracy of capsule gastroscopy in the diagnosis of major lesions because these lesions would require subsequent conventional endoscopy for biopsy and/or therapy, such as endoscopic biopsy and/or removal for (early) tumors, endoscopic ultrasound for suspected submucosal tumors, biopsy including *H. pylori* testing for ulcers, and coagulation in angiodysplasias. Unfortunately, we could not fully reach our goal of case enrichment of major lesions, which would have allowed for smaller CIs for sensitivity calculation. However, the present rate of 11% major lesions is more realistic for an average gastroscopy setting, and the limited sensitivity of only 62% is unlikely to become substantially better with more lesions; the multivariate analysis showed that examiner experience and case load did not play a role. Thus, it has to be concluded that at the present stage of development, guided capsule gastroscopy would have to be substantially improved before it could be considered as a filter test to stratify patients to undergo conventional gastroscopy, irrespective of cost issues. Previous studies with a different technology only involved small numbers of volunteers as feasibility trials[13,14] or—using the same capsule in a pilot trial and in prestudy testings—did not systematically evaluate a similar patient collective of the same size and did not rigorously test accuracy.[15,16]

There would be several ways of improvements related to both influencing stomach characteristics and modifying capsule technology. Among the former, limited expansion of the stomach yielded by drinking water in capsule gastroscopy compared with air expansion in gastroscopy was probably the most important one. Sufficient intragastric volume of clear fluid is required for good visualization and capsule maneuvering,[15] but ingested water left the stomach too quickly; adding water during the examination did not substantially improve the results as outflow was similarly rapid. The fact that the visibility rating by examiners yielded excellent results, yet detection of focal lesions was poor, points toward the fact that the subjective impression of examiners of visibility probably represents an overjudgment of their own performance. This conclusion is also supported by the low detection rate of singular major lesions versus the high detection rate of minor lesions, which were mostly multiple and thus did not readily escape gastric inspection. That the visualization of minor lesions was significantly better in the proximal stomach was mostly due to antral motility leading to a pushback of the capsule, which could not be counteracted by active capsule maneuvering.

Therefore, future technical requirements for capsule gastroscopy include implementation of a lens-cleaning system, as is available with conventional endoscopy, and a stronger guidance system, which currently appears to be too weak and requires faster speed of movement with stronger force, but also a better capability of keeping the capsule in place more steadily. More force would probably also help to actively pass the pylorus and to keep the capsule in the esophagus. The latter appears to be particularly important, as detection of esophageal lesions such as reflux erosions, Barrett esophagus, or varices will be important indications for upper GI endoscopy performed by guided capsules in the future.

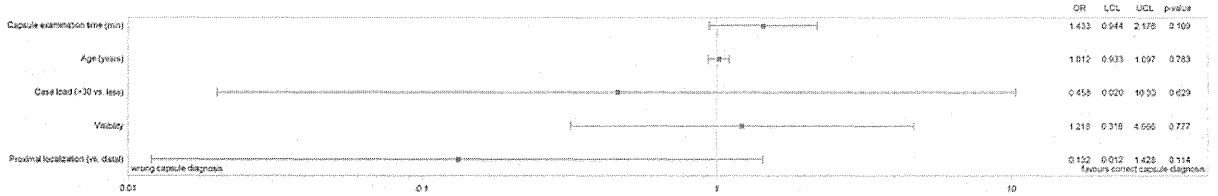

FIGURE 1. Factors influencing sensitivity in the diagnosis of major lesions; lesion-based analysis (see also Table 1). For definitions see text. LCL indicates lower confidence limit; OR, odds ratio; UCL, upper confidence limit.

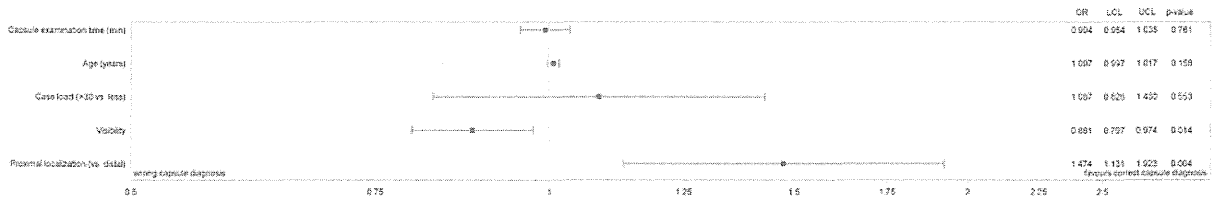

FIGURE 2. Factors influencing sensitivity in the diagnosis of minor lesions: lesion-based analysis (see also Table 2). For definitions see text. LCL indicates lower confidence limit; OR, odds ratio; UCL, upper confidence limit.

In 3 cases the capsule was still found in the esophagus on subsequent conventional endoscopy; patients did not have any symptoms nor any esophageal pathology, and the examiners decided to push the capsule into the stomach during gastroscopy. Capsule entrapment in the esophagus has been described with esophageal stenosis,[18] and despite the fact that passage times of small-bowel capsules are very rapid in most patients, they are significantly delayed in a few cases.[19] Thus, it can be assumed that capsules would have passed spontaneously in these 3 cases. In contrast, a special technical modification would be required to perform capsule endoscopy in the esophagus, one that keeps the capsule in the esophagus for longer on a regular basis.[10,17]

In conclusion, current models of steerable capsules should be improved to be further studied as a filter test in clinical routine for gastric examination, such as for gastric cancer screening in Japan. Only then would it make sense to discuss cost issues, including equipment and time needed for performance and reading as well as other factors such as nurse performance, etc. Further refinements are to be

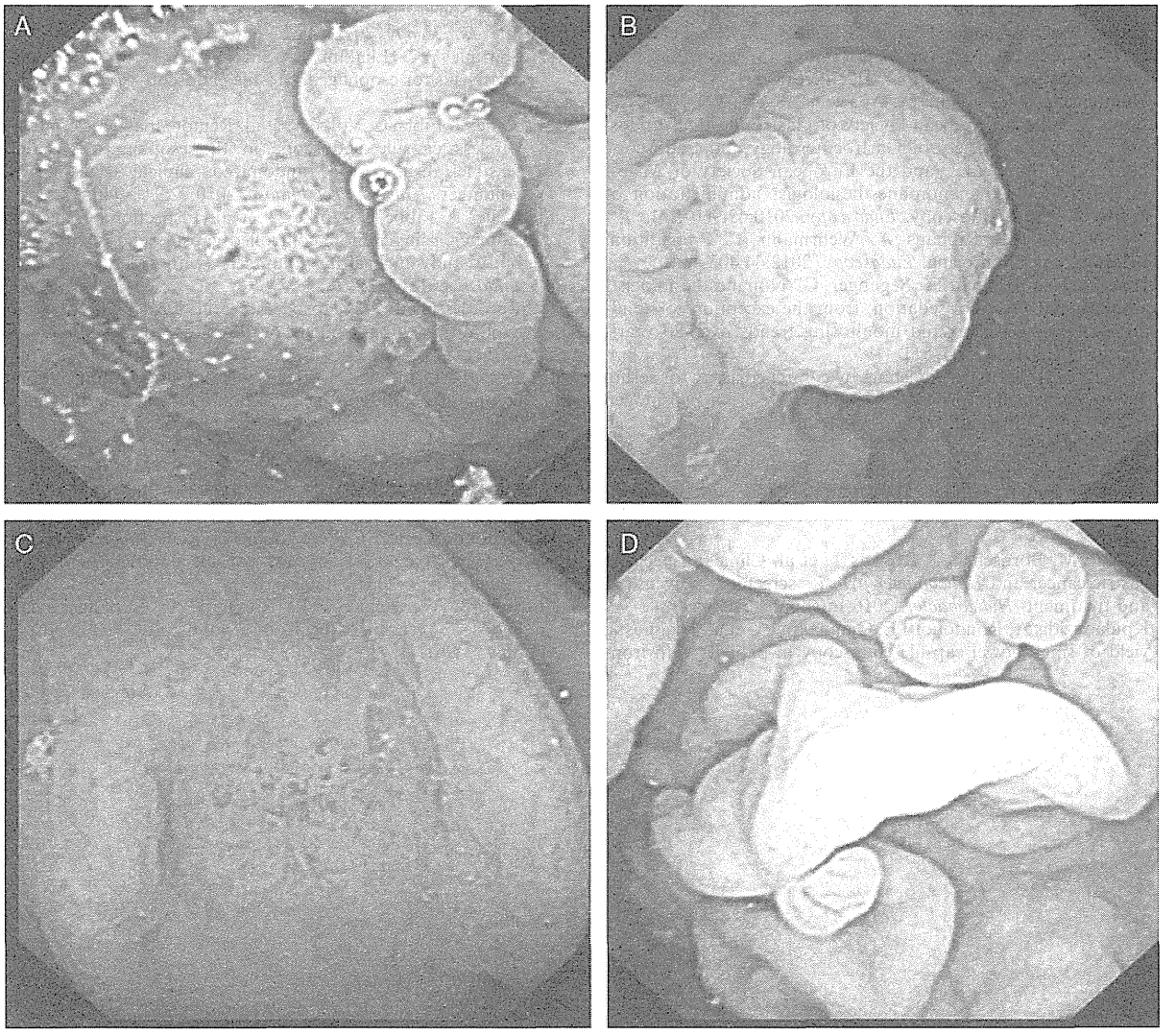

FIGURE 3. Examples of gastric pathology on capsule gastroscopy: (A) gastric cancer; (B) submucosal tumor; (C) diffuse erosions; and (D) multiple fundic gland polyps.

TABLE 4. Sensitivity and Specificity Values of Blinded Compared With Unblinded Gastroscopy as Gold Standard

	Sensitivity	95% CI	Specificity	95% CI
Major lesions (per lesion) (n = 23)	95.6	78.1-99.9	—	—
Minor lesions (per patient) (n = 168)	98.1	94.6-99.6	100	69.2-100
Subgroups				
Fundic gland polyps (n = 49)	89.8	77.8-96.6	100	97.0-100
Erosions and hemorrhagic gastritis (n = 148)	98.0	94.2-99.6	95.0	75.1-99.9
Gastric atrophy (n = 17)	94.2	71.3-99.9	99.3	96.4-100

CI indicates confidence interval.

expected and then studies with similar methodology as well as patient uptake and outcome studies have to be conducted to define the role of guided upper GI capsule endoscopy in the clinical setting.

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Review

Current status of capsule endoscopy through a whole digestive tract

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More than a decade has passed since small-bowel capsule endoscopy (CE) was first reported. Small-bowel CE is a non-invasive tool that allows visualization of the entire small-intestinal mucosa and facilitates detection of small-intestinal abnormalities. Several studies have shown benefit of small-bowel CE for certain disorders. Because it is non-invasive, CE has been applied to other organs including the esophagus, stomach, and colon. The main indications for esophageal CE (ECE) are screening for gastroesophageal reflux disease/Barrett's esophagus, and esophageal varices. However, the clinical benefit of ECE is unconfirmed. Magnetically guided CE (MGCE) was developed to visualize the gastric mucosa. MGCE is a new concept with room for improvement of capsule navigation and the preparation protocol. Recently, two new small-bowel CE tools were released. First-generation colon CE (CCE-1) has moderate sensitivity and specificity compared with colonoscopy for colorectal neoplasia surveillance. To obtain higher accuracy, a second-generation CCE (CCE-2) was developed with a high sensitivity for detecting clinically relevant polypoid lesions. A possible application of CCE is for inflammatory bowel disease. In the near future, CE may include diagnostic and therapeutic functions such as magnifying endoscopy systems, targeted biopsy forceps, and drug delivery systems.

Key words: capsule endoscopy, double-balloon enteroscopy, esophageal capsule endoscopy, gastroesophageal reflux disease, inflammatory bowel disease

INTRODUCTION

MORE THAN A decade has passed since small-bowel capsule endoscopy (CE) was first reported by Iddan *et al.*[1] in 2000. Small-bowel CE is a non-invasive tool that allows visualization of the entire small-intestinal mucosa and facilitates detection of small-intestinal abnormalities. Several studies have shown the benefit of small-bowel CE for certain disorders, such as obscure gastrointestinal bleeding (OGIB),[2] suspected Crohn's disease (CD),[3,4] small-bowel tumors,[5] and small-intestinal mucosal injury associated with non-steroidal anti-inflammatory drug use.[6] Small-bowel CE systems and protocols, such as angle of view, analysis software, prokinetics, and bowel preparation, have been improved. Furthermore, because it is non-invasive, CE has been applied to other organs, including the esophagus, stomach, and colon. In the present article, we focus on past and current status of CE through the entire digestive tract.

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ESOPHAGEAL CE

GASTROESOPHAGEAL REFLUX DISEASE (GERD) is common and is increasing in Japan[7,8] and in Western countries.[9,10] The prevalence of esophageal varices (EV) in cirrhotic patients is approximately 80%,[11] and management of EV is crucial for cirrhotic patients. Detection and observation of esophageal disease using a non-invasive tool is beneficial for patients. Thus, CE is appropriate for screening for esophageal abnormalities. In Japan, esophageal CE (ECE) is not available and is not covered by health insurance.

In a pilot study of a prototype ECE, Eliakim *et al.*[12] examined 17 patients with esophagus-related complaints using an esophageal capsule that acquires video images from both ends of the device at 4 frames/s. They reported excellent results with 100% sensitivity and 80% specificity compared with conventional esophagogastroduodenoscopy. A first-generation esophageal CE (ECE-1) (PillCam Eso®; Given Imaging, Ltd, Yokneam, Israel) was approved by the US Food and Drug Administration in 2004. ECE-1 has a dual camera that obtains images at a combined rate of 14 frames/s[13,14] and is the same size as the small-bowel CE (11 × 26 mm) with a 20-min operating time. A second-generation esophageal endoscope (ECE-2) (PillCam Eso2®; Given Imaging, Ltd),

Table 1 Diagnostic accuracy of esophageal capsule endoscopy for esophageal disease

Reference	Target disease	No. subjects	Capsule type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Eliakim *et al.*[12]	GERD/BE	106	ECE-1	92	95	97	88
Koslowsky *et al.*[14]	GERD/BE	25	ECE-1	100	74	77	100
Lin *et al.*[17]	BE	90	ECE-1	67	84	22	98
Galmiche *et al.*[18]	ESEM	89	ECE-1	79	94	83	92
	GERD			60	100	100	95
Gralnek *et al.*[15]	ESEM	28	ECE-2	100	74	64	100
	GERD			80	87	57	95
Sharma *et al.*[19]	ESEM	100	ECE-1	77	85	87	74
	GERD			50	90	56	88
Eisen *et al.*[20]	EV	32	ECE-1	100	89	96	100
Lapalus *et al.*[21]	EV	21	ECE-1	81	100	100	57
Pena *et al.*[22]	EV	20	ECE-1	68	100	100	14
de Franchis *et al.*[23]	EV	288	ECE-1	84	88	92	77
Frenette *et al.*[24]	EV	50	ECE-1	63	82	73	74
Lapalus *et al.*[25]	EV	120	ECE-1	77	86	69	90
Schreibman *et al.*[26]	EV	37	ECE-1	65	67	95	15
Chavalitdhamrong *et al.*[27]	EV	65	ECE-1	78	58	NR	NR
Laurain *et al.*[28]	Recurrent EV	80	ECE-1, 2	65	83	65	83

BE, Barrett's esophagus; ECE-1, first-generation esophageal capsule endoscope; ECE-2, second-generation esophageal capsule endoscope; ESEM, endoscopically suspected esophageal metaplasia; EV, esophageal varices; GERD, gastroesophageal reflux disease; NPV, negative predictive value; NR, not reported; PPV, positive predictive value.

released in 2007, has a wider angle of view, a rate of 15 frames/s, and a better image quality.[15]

A specific ingestion protocol is required to slow down transit of the capsule through the esophagus. The patient lies on their right side and, after ingestion of the capsule, swallows sips of 15-mL water through a straw from a glass every 30 s.[16]

The main indications for ECE are screening for GERD/Barrett's esophagus (BE) and EV. As shown in Table 1, ECE sensitivity was substantially variable between studies, ranging from approximately 50% to 100% for BE/endoscopically suspected esophageal metaplasia and GERD. ECE sensitivity for EV was similar, ranging from approximately 60% to 100%.

The actual performance of ECE is still unknown. A third-generation esophageal endoscope (ECE-3) (PillCam Eso3®; Given Imaging, Ltd) has already been released, with a wider 174° angle of view and a higher 35 frames/s rate. We need more clinical evidence using ECE-3 and an improved protocol for ECE.

GASTRIC CE

THE STOMACH IS a large luminal organ. Passive CE cannot explore the entire gastric wall only by passive movement of the CE. Several small pilot studies using guided CE have been reported.[29–33] The magnetically guided capsule endoscope (MGCE) was developed in a joint project of Olympus Medical Systems Corporation (Tokyo, Japan) and Siemens Healthcare (Erlangen, Germany) to create a prototype device that provides endoscopic visualization of the stomach.[34–36] Currently, MGCE is the only CE system evaluated in a large-scale clinical comparative study. The MGCE capsule is 31×11 mm and equipped with two cameras that take images at 4 frames/s and optics designed to obtain sufficiently high-quality images of the relatively larger stomach space, with a wider field of view and deeper depth of field compared with current small-bowel capsules (Olympus EC Type 1). To maneuver by magnetic power, the MGCE contains a permanent magnet allowing the capsule to be guided inside the stomach by a magnetic field applied externally by the guidance system. Figure 1 shows the observation method of MGCE. Figure 2a shows that small erosions can be visualized by MGCE. Figure 2b shows a distinctive MGCE image of the gastric cardia without using a scope.

The first pilot study comparing MGCE with standard gastroscopy for gastric examination was conducted in 2010 at the Institut Arnault Tzanck in Saint Laurent du Var, France, with the participation of three Japanese facilities (The Jikei University, Showa University Northern Yokohama Hospital, and our institution). In this study, MGCE missed 14 findings

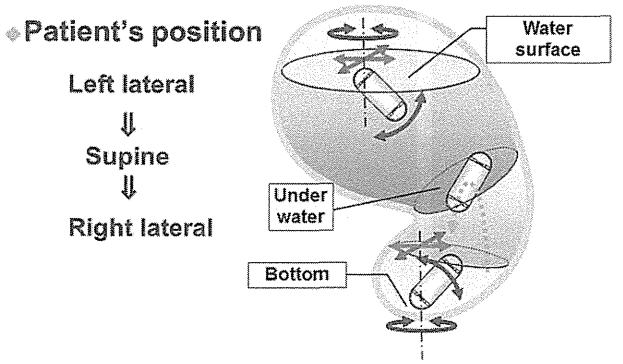

Figure 1 Observation method for magnetically guided capsule endoscopy (MGCE). In a stomach expanded and filled with water, MGCE can observe from the water surface and underwater like a submarine. To obtain a complete stomach examination, the patient's position needs to be changed from left lateral to supine and finally to right lateral.

and gastroscopy missed 31 findings that were seen with MGCE; the overall diagnostic yield was similar for both modalities. To confirm the performance assessment of MGCE, a second large-scale trial was conducted at the Institut Arnault Tzanck with two European and three Japanese institutions,[37] but the MGCE performance results were not very good. Symptomatic patients from two French centers subsequently and blindly underwent MGCE and conventional gastroscopy. Although 189 patients were included in this trial, only 23 major lesions were found in 21 patients, with 94.1% specificity (95% confidence interval [CI]: 89–97%) and 61.9% sensitivity (95% CI: 34.5–77%). MGCE is a new concept with room for improvement of capsule navigation and patient protocol, including preparation for cleanliness and stomach expansion, In the near future, MGCE may become a first-line non-invasive screening device with high patient acceptance.

SMALL-BOWEL CE

Obscure gastrointestinal bleeding

SMALL-BOWEL IMAGING REMAINS the major indication for CE, primarily for OGIB. The diagnostic yield of small-bowel CE for OGIB ranges from approximately 30% to 70%.[38–48] The diagnostic yield of CE for significant lesions depends on various factors. Earlier CE (within 1 week of bleeding) correlates with a higher diagnostic yield.[39,45] Other factors associated with a higher detection rate include inpatient status,[40,49] overt gastrointestinal bleeding requiring transfusion,[38,40,45] increased age,[43,48,49] and warfarin use.[43] Some reports showed that small-bowel CE was superior to radiographic barium.[2,50,51] In a meta-analysis of three studies, the diagnostic yield for CE and small-bowel barium studies for clinically significant findings was 42% and 6%, respectively ($P < 0.0001$).[2] Another study reported a higher diagnostic yield for OGIB with small-bowel CE compared with computed tomography (CT) angiography but similar to that of standard angiography; the CE findings led to therapeutic intervention in 47% of enrolled patients.[52]

Double-balloon enteroscopy (DBE) is another option to investigate the small intestine, with added therapeutic capabilities. Arakawa *et al.*[53] reported the diagnostic yield of small bowel CE and DBE as 54% and 64%, respectively ($P = 0.12$). Another prospective study reported similar diagnostic yields for small-bowel CE and DBE.[54] Being less invasive is an advantage of small-bowel CE, but a disadvantage is the impossibility of treating the detected lesion endoscopically. Used in conjunction, small-bowel CE and DBE complement the other device's limitations.

Sethi *et al.*[55] recently reported the diagnostic and therapeutic yield of single-balloon enteroscopy (SBE) in patients with suspected small-bowel disorders and the impact of preceding small-bowel CE on these outcomes. The overall diagnostic yield for small-bowel disease by small-bowel CE was 62%, and the total diagnostic and therapeutic yield of SBE was 60% and 28%, respectively. The diagnostic and therapeutic yield of SBE with prior small-bowel CE was 68% and 35% versus 44% and 12% for SBE without prior CE ($P = 0.002$ and $P = 0.001$), respectively. Sethi *et al.*[55] recommend carrying out small-bowel CE before SBE to improve diagnostic and therapeutic yield.

OGIB is subdivided into occult (iron-deficiency anemia [IDA] and/or positive fecal occult blood tests) and overt OGIB. Many studies have evaluated the performance of small-bowel CE for occult OGIB.[38,56–66] A 2012 meta-analysis of 24 studies including 1960 patients with IDA[67] reported a 47% overall diagnostic yield of small-bowel CE (95% CI: 42–52%), although there was significant heterogeneity among the studies. When only patients with IDA confirmed by hemoglobin and ferritin values were included, the diagnostic yield increased to 66.6% (95% CI: 61.0–72.3%).

Small-intestinal polyps and tumors

Small-bowel tumors account for 5–7% of patients presenting with OGIB and are the most common cause in patients under age 50 with OGIB.[68] Common small-intestinal tumors are adenocarcinomas, lymphomas, gastrointestinal stromal tumor (GIST), neuroendocrine tumors, and metastasis. Since the introduction of small-bowel CE, the detection rate of small-bowel tumor has been increasing.[69] Submucosal

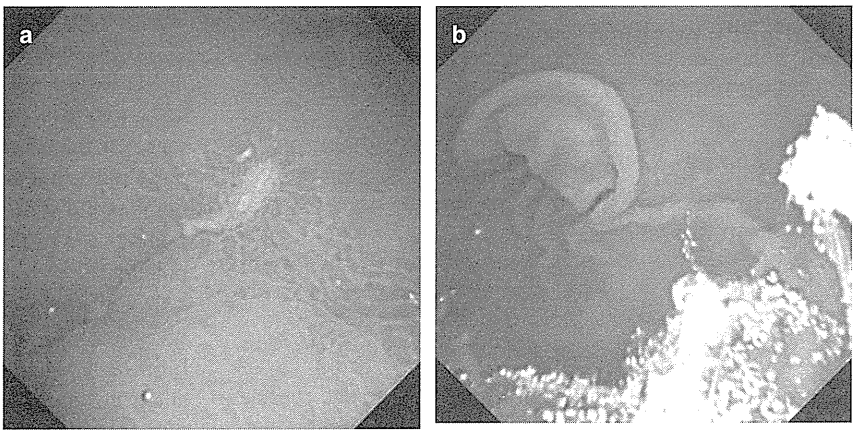

Figure 2 Magnetically guided capsule endoscopy image. (a) Small erosion surrounding edematous mucosa is visualized. (b) Gastric cardia without scope.

tumors such as GIST are often missed by CE, but Urgesi *et al.*[70] reported that CE was able to diagnose small-bowel GIST in nine of 10 cases otherwise missed by traditional endoscopic and radiological imaging. Another retrospective study by Zagorowicz *et al.*[71] reported that CE missed three small-bowel tumors (two GIST and one mesenteric tumor), although the sensitivity and specificity of CE for small-bowel tumor detection were 83.3% and 100%, respectively. Rapid transit through the proximal jejunum, duodenum, and periampullary region poses a potential limitation for investigating the proximal small bowel and periampullary region by CE.[72,73]

Small-bowel CE has been used to evaluate hereditary polyposis syndromes such as familial adenomatous polyposis (FAP) and Peutz-Jeghers syndrome. A small case series comparing the number of polyps detected by a small-bowel follow-through (SBFT) series and small-bowel CE showed that small-bowel CE was a valuable alternative to a barium-contrast series in patients with Peutz-Jeghers syndrome or FAP.[74] Ohmiya *et al.*[75] reported that fluoroscopic enteroclysis detected fewer Peutz-Jeghers polyps than DBE, whereas CE had detection rates similar to those of DBE. The polyp-detecting accuracy of small-bowel CE has been shown as equal to magnetic resonance imaging (MRI) for detecting polyps >15 mm, although the detection rate for 5–15-mm polyps was much higher, and those <5 mm were detected only by small-bowel CE.[76]

CE is not an appropriate method for detecting and characterizing duodenal and upper-jejunum polyps because of the rapid transit of the capsule. Although there is no clear consensus, small-bowel CE may be beneficial for evaluating small-intestinal polyps and tumors. A negative examination, however, should not preclude further investigation by other modalities if patients have persistent symptoms and/or a lesion is highly suspected.

Crohn's disease

Another indication for small-bowel CE is suspected/diagnosed CD. Many studies have shown that small-bowel CE is useful in patients with suspected/diagnosed CD[4,77–79] in Western countries, whereas in Japan, until 2012, small-bowel CE was contraindicated for diagnosed CD to avoid capsule retention. In July 2012, the Japanese Ministry of Health, Labour, and Welfare approved small-bowel CE (PillCam® SB 2 plus; Given Imaging, Ltd) and a patency capsule (PillCam® patency) for all small-bowel diseases including diagnosed CD. In a nationwide survey of 40 Japanese institutions, Esaki *et al.*[80] identified 94 patients with diagnosed CD and 80 patients with suspected CD who were examined by small-bowel CE. Small-bowel CE identified mucosal injuries in 88% of diagnosed CD and in 73% of suspected CD, and the capsule retention rate was not statistically different between patients with diagnosed CD and those with suspected CD (7.4% *vs* 6.3%, $P = 1.0$). They concluded that small-bowel CE is useful for evaluating small-bowel mucosal injuries in Japanese patients with CD, but possible intestinal stricture should be carefully investigated before carrying out small-bowel CE.

Multiple modalities such as SBFT, balloon-assisted enteroscopy, MRI, CT, and CE are used to diagnose CD. CE is convenient for patients but is contraindicated for patients with severe small-intestinal strictures. In suspected CD, colonoscopy and SBFT should be initially carried out. In established CD, CE should be carried out after ileocolonoscopy/SBFT and CT.[81]

Newly developed small-bowel CE

Recently, two new small-bowel CE devices were released. One is a third-generation small-bowel CE (PillCam® SB3)

Figure 3 Antenna sensor array belt and holster for the recorder with real-time viewer. The patient is fitted with a belt containing an antenna sensor array that can track the capsule and provide images to a real-time viewer.

developed by Given Imaging, Ltd with one camera equipped with an adaptive frame rate system that can automatically increase from 2 to 6 images/s when the capsule is accelerated by peristalsis. To our knowledge, the utility of third-generation small-bowel CE has not been reported. The other capsule is a second-generation small-bowel CE (EC-10) developed by Olympus Medical Systems Corporation (Tokyo, Japan) that is now available in Western countries but not in Japan. This capsule has a new sensor with a wider angle of view, better image quality, and longer battery life compared with EC-1. The EC-10 system is installed with EC-10 capsule localization software (3D Track Function®; Olympus Medical Systems Corporation). The patient is fitted with a belt containing an antenna sensor array that can track the capsule and provide images to a real-time viewer (Fig. 3). Figure 4 shows a representative image of our case. Marya *et al.*[82] evaluated the EC-10 capsule localization software in comparison with radiographs in 30 healthy volunteers and concluded that the 3D track software provides capsule localization consistent with radiological observations. The clinical impact of 3D Track Function is still unknown and requires further validation in a large prospective clinical trial.

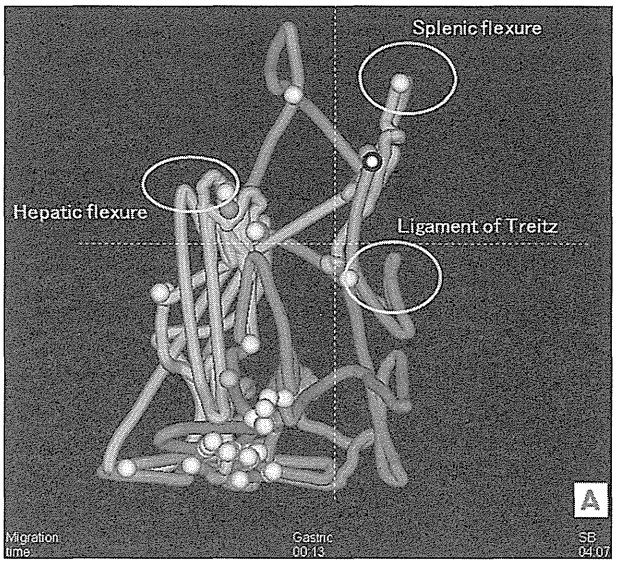

Figure 4 3D track image of our case. The pink line shows the track of the capsule in the stomach, the green line shows the small-intestinal track, and the purple line is the colonic track. The new EC-10 capsule localization software can clearly visualize the area of the ligament of Treitz and the hepatic and splenic flexures.

COLON CE

COLON CE (CCE) was first reported in 2006.[83] First-generation CCE (CCE-1) has some technical differences from the small-bowel capsule, being approximately 6 mm longer with dual cameras that can acquire images from both ends, optics with more than twice the coverage area of the small-bowel capsule, automatic light control, and a rate of 4 frames/s. CCE has been mainly used for colorectal cancer screening.[84–90] Table 2 shows the diagnostic accuracy of CCE for significant findings (polyps ≥6 mm or ≥3 polyps). Van Gossum *et al.*[84] reported that CCE-1 has a moderate sensitivity (64%) and specificity (84%) compared with colonoscopy for surveillance of colorectal neoplasia. Others have shown variable sensitivity (39–100%) and specificity (70–95%) of CCE-1 (Table 2).

To obtain higher accuracy, a second-generation CCE (CCE-2) was developed.[96] CCE-2 is equipped with a high-frame-rate camera that can take 4–35 pictures/s when the capsule is accelerated by peristalsis.[96] In a European study, Spada *et al.*[87] reported a high sensitivity of CCE-2 for the detection of clinically relevant polypoid lesions but a low specificity (64%) for ≥6-mm polyps, explained by a substantial number of false-positive polyps because of size mismatch. For example, 20 (80%) of the 25 false-positive cases with CCE-2 (6–9 mm, 21 cases; ≥10 mm, four cases) were

Table 2 Diagnostic accuracy of colon capsule endoscopy for significant findings†

Reference	Indication for colonoscopy	No. subjects	Capsule type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Eliakim *et al.*[83]	Known/suspected colonic disease, CRC screening	91	CCE-1	50	83	40	88
Schoofs *et al.*[91]	Known/suspected colonic disease, CRC screening	41	CCE-1	77	70	59	84
Van Gossum *et al.*[84]	Known to have colonic disease ≤18 y/o, suspected colonic disease ≥50 y/o	328	CCE-1	64	84	60	86
Gay *et al.*[92]	Personal history of CRC/polyps, family history of CRC/polyps ≥50 y/o, known/suspected colonic disease, CRC screening	128	CCE-1	76	76	78	74
Sacher-Huvelin *et al.*[93]	Asymptomatic patients with personal or family history of CRC, CRC screening	545	CCE-1	39	88	47	85
Pilz *et al.*[94]	Symptomatic patients with personal or family history of CRC ≤40 y/o, CRC screening ≥50 y/o	59	CCE-1	50	76	20	93
Spada *et al.*[95]	≥18 y/o, ≤75 y/o	40	CCE-1	62	85	67	82
Spada *et al.*[86]	≥18 y/o, ≤75 y/o	60	CCE-1	100	95	78	100
Eliakim *et al.*[96]	Known/suspected colonic disease	104	CCE-2	89	76	46	97
Spada *et al.*[87]	Known/suspected colonic disease	117	CCE-2	84	64	62	85
Hartmann *et al.*[97]	Known/suspected colonic disease	50	CCE-1	91	94	83	97

†Polyps ≥6 mm in size or ≥3 polyps.
CCE-1, first-generation colon capsule endoscope; CCE-2, second-generation colon capsule endoscope; CRC, colorectal cancer; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; y/o, years old.

because of size mismatching (i.e. <6- or <10-mm polyp with colonoscopy measured as ≥6 or ≥10 mm with CCE-2).

A CCE procedure requires a substantial multi-step preparation for colon cleansing and the capsule booster. The European Society of Gastrointestinal Endoscopy Guideline[89] recommends giving 4 L polyethylene glycol (PEG) before the CCE and booster preparations to improve capsule egestion rates and to complete visualization of the colonic mucosa. In patients without contraindications, sodium phosphate solution is recommended as a booster. In Japan, sodium phosphate solution is not available, and magnesium citrate is used instead.[98,99] To improve patient acceptance, Hartmann *et al.*[97] reduced the preparation to 2.75 L PEG plus ascorbic acid for colorectal cancer screening. Kakugawa *et al.*[98] also used a reduced regimen with 2 L PEG and 1.8 L magnesium citrate (3.8 L total). These studies showed moderate CCE completion rates of 76% (37/49)[97] and 71% (22/31).[98] CCE preparation should be modified for better patient acceptance.

Pioche *et al.*[100] reported the feasibility and usefulness of CCE-1 for colonoscopy failure or contraindication. In 107 patients with colonoscopy failure or general disease that excluded colonoscopy with anesthesia, CCE was completed in 100 patients (93.5%) with positive findings in 36 patients (diagnostic yield 33.6%), among whom 23 underwent therapeutic intervention. Alarcon-Fernandez *et al.*[101] evaluated the efficacy of CCE-1 in helping physicians make decisions about patients with incomplete colonoscopy; CCE exceeded the most proximal point reached by prior colonoscopy in 29 patients (85.3%) and allowed formulation of a specific medical plan for 20 patients (58.8%). They concluded that CCE might be an alternative procedure to complete colon examination in patients with non-occlusive incomplete colonoscopy. Also evaluating incomplete colonoscopy, Triantafyllou *et al.*[102] carried out CCE immediately after colonoscopy in one-third of enrolled patients; CCE-1 reached or went beyond the colon segment at which colonoscopy stopped in 68 patients (91%). Negreanu *et al.*[103]

Table 3 Modified bowel preparation for ulcerative colitis (reproduced from Usui *et al.*[99])

Day	Timing	Procedure
Previous day	Lunch, snack, dinner	Low-fiber diet
Examination day	9:00 a.m.	700 mL PEG
	11:00 a.m.	Swallowing CCE-2 with mosapride citrate 20 mg and dimethicone 40 mg
	12:00 a.m.	Confirm CCE-2 in the small intestine
		Add metoclopramide 10 mg if CCE-2 remains in the stomach
		Magnesium citrate 34 g (900 mL) within 30 min and mosapride citrate 20 mg after confirmation of CCE-2 in the small intestine
	3:00 p.m.	Magnesium citrate 23 g (600 mL) in case CCE-2 has not yet been egested
	6:00 p.m.	Dinner
		CCE-2 recording continues until battery runs down or CCE-2 is egested

CCE-2, second-generation colon capsule endoscope; PEG, polyethylene glycol solution.

assessed feasibility and accuracy of CCE-2 in detecting significant lesions in colorectal cancer risk patients unable or unwilling to undergo colonoscopy with positive findings in 34% of the analyzed patients and a 77% capsule excretion rate in 12 h. They concluded that CCE-2 was effective in detecting significant lesions and might be considered an adequate alternative diagnostic tool in patients unable or unwilling to undergo colonoscopy.

CCE may be appropriate for inflammatory bowel disease (IBD). Small-bowel CE and balloon-assisted enteroscopy are already used for small-intestinal investigation in IBD patients,[81,104] but the efficacy of CCE in IBD is not confirmed. Regarding CD, only one case study ($n = 6$) was reported by Negreanu *et al.*[105] The main target disease among IBD for CCE is ulcerative colitis (UC). Sung *et al.*[106] conducted the first multicenter study using CCE-1 to assess mucosal inflammation in 100 suspected or diagnosed UC patients and compare the assessment by CCE-1 and conventional colonoscopy. They reported 89% sensitivity to detect active colonic inflammation (95% CI: 80–95%) and 75% specificity (95% CI: 51–90%). Positive and negative predictive values of CCE for colonic inflammation were 93% (95% CI: 84–97%) and 65% (95% CI: 43–83%), respectively. They concluded that CCE-1 was a safe procedure to monitor mucosal healing in UC, but is not recommended to replace conventional colonoscopy. In a pilot study ($n = 13$), Meister *et al.*[107] found disease activity scores (modified Rachmilewitz score) judged by CCE-1 and colonoscopy to significantly differ. They recommended the preferential use of standard colonoscopy to assess inflammation in UC patients rather than CCE-1. In contrast, Ye *et al.*[108] found significant correlation in severity ($\kappa = 0.751$, $P < 0.001$) and extent ($\kappa = 0.522$, $P < 0.001$) of UC between CCE-1 and conventional colonoscopy.

Our group conducted the first study to assess the feasibility of using CCE-2 to evaluate mucosal inflammation severity in patients with UC.[109] We also attempted to reduce bowel preparation time for UC with a low-volume (2 L) PEG and prokinetics (mosapride citrate and metoclopramide) regimen. Our CCE-2 procedure was completed within 8 h in 69% of the patients, but <50% of patients achieved a good or excellent cleansing level. The Matts endoscopic scores determined by CCE-2 were strongly correlated with scores obtained by conventional colonoscopy (average $\rho = 0.797$). We conducted a second CCE-2 study[99] to improve the colon-cleansing regimen for UC patients with the modified bowel preparation shown in Table 3. Patients received a maximum 2.2 L lavage solution (PEG and magnesium citrate) in two or three divided doses. In our second CCE-2 study, 85% of enrolled patients achieved total colon observation using the modified reduced-volume preparation regimen. Comparing the diagnostic accuracy of CCE-2 with colonoscopy as the gold standard for evaluating disease activity in pediatric UC, Oliva *et al.*[110] found 96% sensitivity (95% CI: 79–99%) and 100% specificity (95% CI: 61–100%) for CCE-2. They concluded that CCE-2 was accurate in evaluating mucosal inflammation severity in pediatric UC.

FUTURE PERSPECTIVES

CAPSULE ENDOSCOPY HAS been applied to the entire digestive tract since small-bowel CE was developed. CE possesses several important diagnostic advantages, mainly excellent visualization of the digestive tract without pain. CE may include specialized functions such as image-enhanced endoscopy.[111–113] In available CE systems, RAPID software (Given Imaging, Ltd) has been installed in the flexible spectral imaging color enhancement system, raising the possibility of improving the contrast of vascular and mucosal patterns.[113,114] Aihara *et al.*[112] and we reported[111] enhanced visibility of prototype small-bowel CE equipped with white-light light-emitting diodes selected specifically to increase