Case Rep Gastroenterol 2015;9:120–125
DOI: 10.1159/000382074

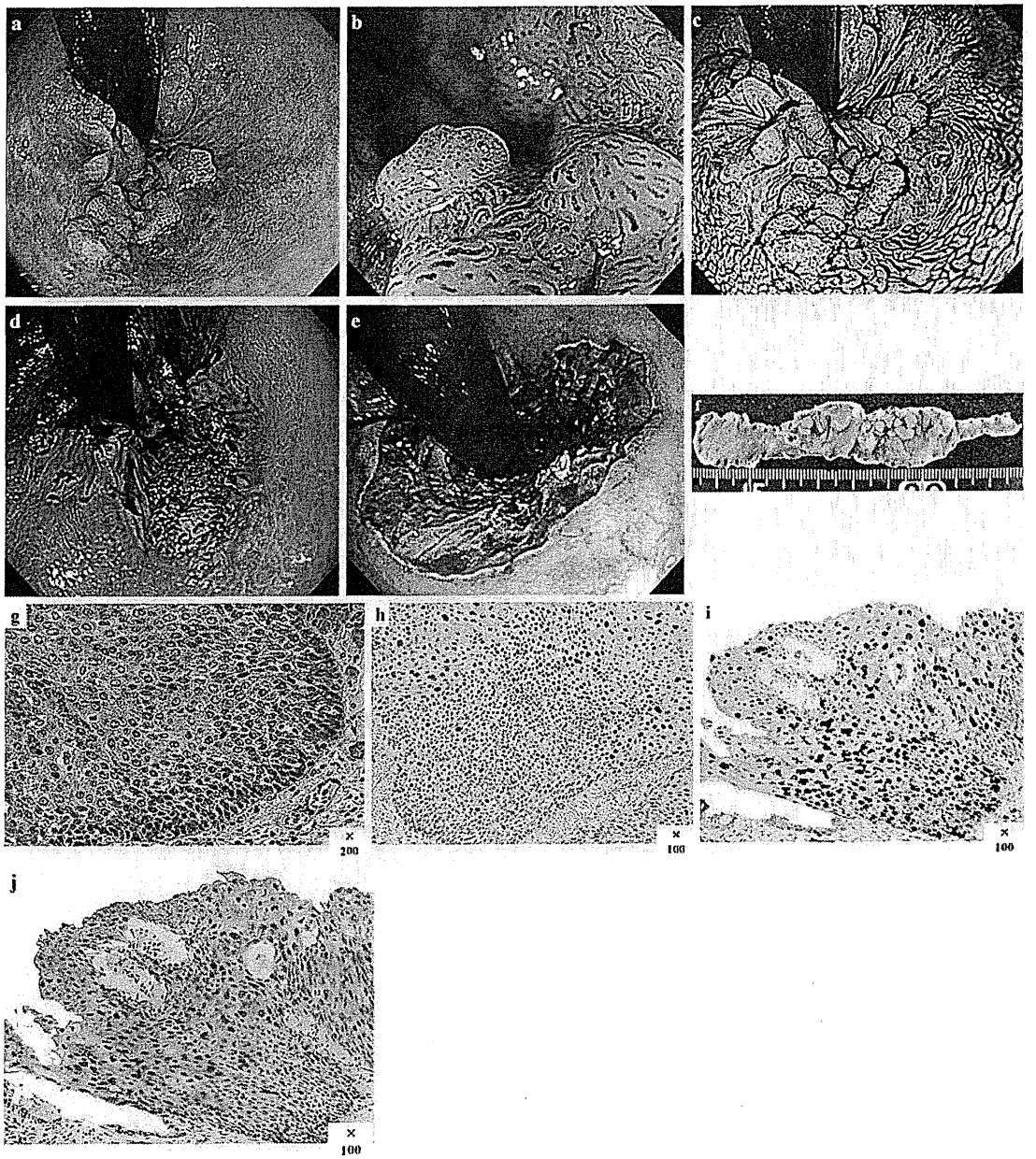

Fig. 2. **a** A white, papillary, flat, elevated lesion, 25 mm in size, was identified from the dentate line to the anal canal. **b** NBI showed irregular vascular patterns (dilatation, tortuous running, caliber changes, and different shapes) at the elevated lesion. **c** A chromoendoscopy with indigo-carmine dye showed the edge of the lesion clearly and revealed a lobulated, elevated lesion. In addition, this lesion was clearly visible inside the dentate line. **d** The lesion was identified by chromoendoscopy with iodine staining as the stained area. **e** The rectal area after en bloc resection showing the entire circumferential ulcer. **f** Macroscopic findings from the resected specimen. **g** The tumor was composed of SCC in situ. The vertical and horizontal cut ends of the tumor were both negative. The histopathological diagnosis was of SCC in situ without vessel invasion. **h–j** An immunohistochemical evaluation showed strong expressions of p53 (**h**), Ki-67 (**i**), and p16 (**j**).

T(9)

ORIGINAL ARTICLE: Clinical Endoscopy

Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study

Yutaka Saito, MD, PhD,[1] Shoichi Saito, MD, PhD,[2] Shiro Oka, MD, PhD,[3] Yasuo Kakugawa, MD,[1] Minori Matsumoto, MD,[1] Hiroyuki Aihara, MD, PhD,[2] Ikue Watari, MD, PhD,[3] Taiki Aoyama, MD, PhD,[3] Sadaharu Nouda, MD, PhD,[4] Takanori Kuramoto, MD, PhD,[4] Kenji Watanabe, MD, PhD,[5] Naoki Ohmiya, MD, PhD,[6] Kazuhide Higuchi, MD, PhD,[4] Hidemi Goto, MD, PhD,[6] Tetsuo Arakawa, MD, PhD,[5] Shinji Tanaka, MD, PhD,[3] Hisao Tajiri, MD, PhD[2]

Tokyo, Hiroshima, Nagoya, Osaka, Japan

Background: Colon capsule endoscopy (CCE) is a new procedure for colon imaging. Limited information is available regarding visualization of flat colon lesions and patient acceptability in Japan.

Objective: The aims of this study were to evaluate the sensitivity of CCE in detecting polyps and other lesions compared with optical colonoscopy (OC) and to evaluate its safety and acceptability in a cohort of Japanese patients.

Design: A prospective, open-label, clinical study in Japan.

Setting: Multicenter.

Patients: Patients referred for OC because of personal history of polyps $\geq$6 mm or any other colon lesion that required endoscopic or surgical treatment.

Interventions: CCE followed by therapeutic colonoscopy.

Main Outcome Measurements: The primary endpoint was per-patient sensitivity of CCE in detecting significant colon lesion. The secondary endpoints were CCE safety and patient acceptability.

Results: Sixty-six of the 72 patients enrolled in the study were evaluated for efficacy. The per-patient sensitivity was 94% (95% confidence interval [CI], 88.2%-99.7%). The per-polyp sensitivity was 86.6% (95% CI, 81.3%-91.9%) when pathology-confirmed polyps were considered true positives. There were no adverse events related to CCE, and the acceptability of CCE was high.

Limitations: All patients had previously confirmed colon lesions, which may have falsely elevated the sensitivity of CCE.

Conclusion: CCE had a high sensitivity for detecting significant colon lesions. CCE was safe and had a high level of patient acceptability. (Clinical trial registration number: University Hospital Medical Information Network, UMIN000007258.) (Gastrointest Endosc 2015;82:861-9.)

Abbreviations: CCE, colon capsule endoscopy; LST, laterally spreading tumor; OC, optical colonoscopy.

DISCLOSURE: *The sponsor of this trial is Given Imaging K.K., who provided statistical analysis and material support. All authors disclosed no financial relationships relevant to this article.*

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2015.02.004

Received May 25, 2014. Accepted February 3, 2015.

Current affiliations: Endoscopy Division, National Cancer Center Hospital, Tokyo (1), Division of Gastroenterology and Hepatology/Endoscopy, Tokyo Jikei University School of Medicine, Tokyo (2), Department of Endoscopy, Hiroshima University Hospital, Hiroshima (3), The 2nd Department of Internal Medicine, Osaka Medical College (4), Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka (5), Department of Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan (6) (Presently Educational Corporation Fujita School, Fujita Health University Hospital).

Reprint requests: Yutaka Saito, MD, PhD, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan.

If you would like to chat with an author of this article, you may contact Dr Saito at ytsaito@ncc.go.jp.

In recent years, it has been reported that the decrease in the incidence and mortality from colon cancer may be related to the use of optical colonoscopy (OC).[1] Polyp resection by OC may reduce the mortality rate from colon cancer by 50%.[2] Periodic colon cancer screening is effective for colon cancer prevention. However, based on the research by the Japanese Society of Gastrointestinal Cancer Screening,[3] only 53.6% of individuals with positive fecal occult blood testing received a follow-up OC examination, probably because of groundless fear or shame of undergoing OC.[4]

Colon capsule endoscopy (CCE) is a new, noninvasive procedure for colon imaging.[5] Compared with OC, CCE may be a more acceptable method of colon imaging for patients[6] because there is no discomfort caused by insertion of an endoscope or accompanying gas insufflation.

The reported sensitivity of the first generation CCE (PillCam COLON; Given Imaging Ltd, Yoqneam, Israel) for detecting patients with polyps $\geq$6 mm is 39% to 79%.[5-11] A second generation product (PillCam COLON 2; Given Imaging Ltd, Yoqneam, Israel) has been developed to improve the sensitivity. The field of view from each capsule head has been widened from 156 to 172 degrees, and the battery life has been substantially increased.[12] The fixed 4 fps of the first generation capsule was improved by using an adaptive frame rate function in which the frame rate switches automatically from 4 frames per second (fps) when the capsule is virtually stationary to 35 fps when the capsule moves rapidly.

With these improvements, the sensitivity of the second generation CCE for detecting colon polyps of $\geq$6 mm has been increased to 84% to 91%.[12-18] It should be noted that post-preparation bowel cleansing by using the rinse and suction technique during OC cannot be used in CCE. Therefore, the diagnostic accuracy of CCE can be highly affected by the quality of the bowel preparation.[8,19-20]

In recent years, it has been pointed out that laterally spreading tumors (LSTs) as well as polypoid tumors[21] are important contributors to the development of colorectal cancer. However, very limited information is available on the diagnostic yield of CCE for LSTs.

The purpose of the trial was to assess the diagnostic utility, safety, and patient acceptability of CCE in patients with significant colon lesions requiring endoscopic or surgical treatment, as determined by prior diagnostic OC.

METHODS

This was a prospective, multicenter, open-label, clinical trial, approved by the internal review board in each hospital, in accordance with the ethical principles of the World Medical Association's Declaration of Helsinki (Japanese Pharmaceutical Law, 14-3, and 80-2) and the Ministerial Directive on the Conduct of Clinical Studies of Medical Devices (Good Clinical Practice [GCP]: March 23, 2005, Ministry of Health, Labor, and Welfare). This trial was conducted from December 2011 through May 2012. All patients were provided with a detailed explanation of the study, and informed consent was obtained from all patients before enrollment in the trial.

Patients included in the trial were Japanese individuals aged $\geq$18 years who underwent a diagnostic OC that demonstrated a polyp $\geq$6 mm or any other lesion that required endoscopic or surgical treatment as determined by the physician (significant lesions) within the 3 months before enrollment. In the prior OC procedure, all observed lesions were recorded. Biopsy and therapeutic procedures such as excision, endoscopic marking, and clipping were not performed. All individuals included in the trial agreed to go through a CCE procedure within 1 month of being screened for eligibility for the trial. Because of ethical reasons, individuals without significant findings were not included in the trial.

CCE includes an ingestible video capsule, which naturally moves through the colon, captures images of the mucosa, and transmits them wirelessly to a data recorder carried by the patient. These images are subsequently uploaded to a computer, where software compiles them into a video for reading.

The exclusion criteria for this study were (1) dysphagia; (2) known or suspected occlusion, stenosis, or a fistula of the digestive tract, as determined by abdominal radiograph, abdominal US, medical history, surgical history, or clinical findings (this excludes cases in which absence of small-bowel stenosis was confirmed by double contrast study); (3) history of abdominal surgery (such as a colostomy or bypass procedure); (4) presence of an embedded medical device, such as a cardiac pacemaker; (5) plans to undergo an MRI; (6) any GI motility disorder that may affect the test; (7) any serious cardiac condition; (8) any allergy or contraindication to the drugs used in the study; (9) pregnancy, planned or suspected pregnancy, or breastfeeding; (10) any patient whose clinical condition would make it impossible to carry out the study protocol or limit participation in the clinical trial; (11) any rapidly advancing lesion that may require surgical treatment; and (12) participation in a concurrent clinical study.

The CCE system provided by Given Imaging Ltd consists of the second-generation, ingestible video capsule (PillCam COLON 2), a data recorder (DR3), and a computerized work station loaded with RAPID software, allowing the physician to read and analyze the capsule video and report the findings.

Test procedure

This study was conducted in tertiary-care centers with extensive experience in therapeutic endoscopy. For this reason, patients referred to these centers are mostly patients with colon lesions needing a specialized therapeutic strategy. According to this specific recruitment, we chose this original study design to evaluate capsule sensitivity by enrolling patients with at least one lesion. The study flow is shown in Figure 1, and the schedule of the trial is

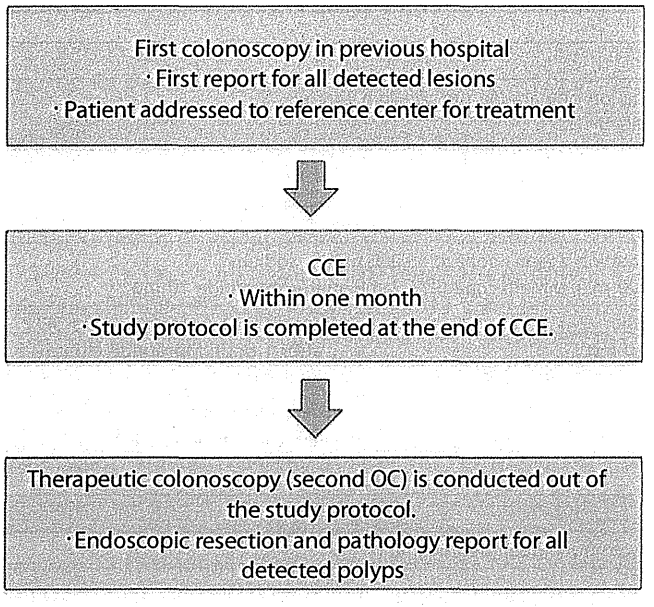

Figure 1. Participants who underwent a diagnostic OC within 3 months before enrollment, which demonstrated a polyp ≥6 mm or any other lesion that required endoscopic or surgical treatment as determined by the physician. In the prior OC procedure, all observed lesions were recorded. Biopsy and therapeutic procedures such as excision, endoscopic marking, and clipping were not performed. *CCE,* colon capsule endoscopy; *OC,* optical colonoscopy.

TABLE 1. Schedule of the clinical trial

Before test
Patient selection by screening investigator
Informed consent
Day prior to test
Diet restriction
Laxative preparation
Test day
Ingestion of CCE
Administration of drug during procedure
Excretion of CCE
Completion of test
Subjective assessment
CCE video reading by reading investigator and reading committee member
Comparison of reading results
Deliberation between reading investigator and reading committee member when results are different
Final result reading
Reading investigator records the final result

CCE, Colon capsule endoscopy.

shown in Table 1. Screening investigators from each clinical site were assigned to enroll the patients.

To ensure the quality of reading, each capsule video was read by two independent physicians who were blinded to the patient's clinical history and who had no access to the result of the colonoscopy performed in the referring hospital. According to the study design, the reader was aware that at least one lesion of interest existed, but no further information was available.

A site reading investigator and a reader from an independent reading committee were assigned to read each capsule. When there were disagreements in reading the CCE-2 videos, the final decision was made by consensus deliberation between the two readers.

The patient acceptability of CCE-2 was determined by using a subjective categorized questionnaire survey.

Overall colon cleanliness was determined by a 4-point grading scale consisting of excellent (no more than small bits of adherent feces), good (small amount of feces or dark fluid not interfering with the examination), fair (enough feces or dark fluid present to prevent a reliable examination), and poor (large amount of fecal residue precluding a complete examination), based on a previously published report.[5]

Therapeutic colonoscopy

Finally, a therapeutic colonoscopy was performed according to the results of both the capsule and the first OC. This was not a part of the study initially; however, it was added because it allowed confirmation of previous findings. All of the lesions detected previously were examined carefully and resected following the usual techniques used in each center.

Histologic diagnoses were based on the Japanese classification of cancer of the colon and rectum and the Vienna classification. Submucosal cancers (T1a, submucosal invasion < 1000 μm from the muscularis mucosae and T1b, submucosal invasion ≥1000 μm) are defined as cancer. Intramucosal cancer (Tis) is classified as high-grade dysplasia, and adenomatous lesion is defined as low-grade dysplasia.

Sample size calculation

The efficacy sample size was calculated by estimating 85% sensitivity in detecting patients with polyps that require endoscopic or surgical treatment, with a 95% confidence interval (CI) of ± 10%, resulting in 49 patients. For the safety sample size, the probability of a rare adverse event occurring was considered to be 5%, and the degree of confidence was considered to be 95%, resulting in 60 patients. Adding a margin of 20% to the 60 patients required for safety resulted in a study sample size of 72 patients.

CCE test method

The recommended bowel preparation regimen is presented in Table 2. The preparation began at noon the day before the procedure. The test ended when capsule excretion was confirmed.

Evaluation of the CCE videos by the readers included identification of colon lesions, grading of colon cleanliness, capsule transit times, and excretion time. Each colon lesion was evaluated for its type, neoplastic appearance, size, shape,

TABLE 2. Recommended regimen schedule

Day -1	From noon	Low-residue diet	
	7-10 PM	Laxative for colorectal examination preparation (magnesium citrate hypertonic solution) 50g/180ml	
	Before bedtime	Sennoside × 2 T	
Day 0	8:30 AM	PEG-ELS 1.5 L. Add up to 500 mL of agent if cleansing level not sufficient.	
	10:45 AM	Ingestion of CCE: mucus elimination agent (Pronaze 40,000 unit + sodium bicarbonate 2 g + water 100 mL), dimethicone (2%) 2 mL, metoclopramide 10 mg	
	Detection of small bowel	When CCE reaches the SB within 1 hour: Mosapride citrate 20 mg, magnesium citrate isotonic solution 50g/900ml	When CCE does not reach the SB after 1 hour: Mosapride citrate 20 mg
			After confirming the SB: magnesium citrate isotonic solution 50g/900ml
	+1 h	PEG-ELS 1 L	
	+1 h	Mosapride citrate 20 mg	
	+2 h	Snack + magnesium citrate isotonic solution 34g/600ml	
	+2 h	Snack + PEG-ELS 1 L	
	+2 h	Bisacodyl suppository 10 mg	

Test ends when the CCE is excreted.
CCE, Colon capsule endoscopy; *PEG-ELS*, polyethylene glycol electrolyte lavage solution; *SB*, small bowel.

and location. For purposes of localization, the colon was divided into 5 segments: cecum, ascending colon, transverse colon, descending colon and/or sigmoid colon, and rectum. The colon cleansing level was graded separately for the entire colon and each segment of the colon. When the capsule was not excreted within the operating time, the final location of the capsule was noted. Patient acceptability of CCE was evaluated with a questionnaire consisting of subjective assessments of embarrassment, fear, pain, ease of ingestion, bowel preparation, and drug administration. Adverse events and technical failures were reported.

For per-polyp sensitivity analysis, any lesion seen during the first OC in the proximity of the location established during CCE was defined as the same lesion. For polyp size estimation, ± 75% difference between the OC and the CCE size estimation was considered as the same lesion.

Data analysis

The statistical analysis was conducted by Given Imaging Ltd by using SPSS software version 20 (IBM, Tokyo, Japan). The primary endpoint of the trial was the sensitivity of CCE per-patient analysis in detecting lesions for which endoscopic or surgical treatment was required, as determined by prior OC. CCE was determined to be clinically effective if the sensitivity reached 85% (95% CI, ± 10%). In addition, the efficacy was assessed and characterized as (1) fairly effective: detected the significant lesion, CCE was excreted during the operating time, and no adverse events occurred; (2) effective: detected the significant lesion, CCE was not excreted in operating time, and no adverse event occurred; (3) minimally effective: detected the significant lesion, but an adverse event and/or defect occurred; and (4) not effective: did not detect the significant lesion.

The secondary endpoints were per-polyp analysis of the findings detected by both the OC and CCE procedures in terms of total number of polyps, colon location, polyp size, and visual classification. The analysis was performed based on a proportion test by using Z test and chi-square test methods. A P value $< .05$ indicated a significant difference between the OC and CCE. In the case of non-polyp findings such as erosion and ulcer, the proportion test was conducted in terms of number of each lesion, colon location, and visual classification.

The right side of the colon was defined as the cecum, ascending colon, and transverse colon, whereas the left side of the colon as descending colon, sigmoid colon, and rectum. The adequate cleansing level (excellent or good) of the entire colon and of each segment was evaluated, and correlation analysis between cleaning level of the entire colon and CCE sensitivity was performed.

The capsule excretion rate and the final location when the capsule was not excreted within the operating time were evaluated. The gastric transit time, small-bowel transit time, colon transit time, and the excretion time were evaluated. In addition, the entire video time was categorized as "<4 hours" group, "4 to <6 hours" group, "6 to <8 hours" group, "8 to <10 hours" group, "10 hours (excreted within the operating time)" group, and "10 hours (not excreted within the operating time)" group to evaluate the capsule excretion rate.

The type, number, severity, treatment, outcome, and duration of adverse events were reported as well as the number and type of technical failures. In addition, safety was assessed and categorized as (1) very safe: no adverse events and product was thought to be very safe to use; (2) safe: minor adverse events occurred, which required no treatment, and product was thought to be safe; (3) fairly

TABLE 3. Total numbers of polyps

No. of polyps		OC	CCE	*P* value
Total (%)		167	247	Z test .0232
Per location	Cecum	18	17	Chi-square test .0191
	Ascending colon	28	39	
	Transverse colon	41	35	
	Descending/sigmoid colon	56	105	
	Rectum	24	51	
Per size	≥6 mm	99	158	Z test .0232
	≥10 mm	63	76	Z-test .327 Not significant
Per visual classification	Advanced cancer	0	0	Chi-square test .6646 Not significant
	Protruding	115	165	
	Superficial	52	82	
	Depressed	0	0	

OC, Optical colonoscopy; *CCE,* colon capsule endoscopy.

safe: adverse events occurred, which were treatable, and product was thought to be fairly safe, and (4) unsafe: severe adverse events occurred, and product was thought to be unsafe. For the subjective assessment of the acceptability of CCE, the rate of each relevant parameter was calculated.

RESULTS

Patients

Seventy-two patients were enrolled between December 2011 and May 2012. Four patients withdrew because of personal reasons, and 1 additional patient was excluded because of noncompliance with procedural recommendations. Therefore, 67 patients were included in the final analysis of safety. Additionally, 1 patient was excluded from the evaluation of efficacy because of a CCE technical failure (the capsule operating time was too short and the colon mucosa was not visualized), resulting in 66 patients evaluated for efficacy. The number of male and female patients was 51 and 16, respectively, and the average (± standard deviation) age was 59.7 ± 10.2 years.

Evaluation

The primary endpoint was assessed in the 66 patients with significant lesions, as established by the initial OC, which was set as the criterion standard. CCE detected the significant lesions in 62 of the 66 patients, resulting in a sensitivity of 94% (95% CI, 88.2%-99.7%).

The number of polyps according to each factor is shown in Table 3. CCE detected 247 polyps of any size, compared with 167 polyps detected by OC (P = .0232; Z test).

Regarding the location, the first OC detected 87 lesions, and CCE detected 91 lesions in the right side of the colon, whereas the first OC detected 80 lesions, and CCE detected 156 lesions in the left side of the colon (P = .0191; Z test).

For polyps ≥6 mm, CCE detected a total of 158 polyps compared with 99 polyps detected by the first OC (P = .0232; Z test). For polyps ≥10 mm, CCE detected a total of 76 polyps, compared with 63 polyps detected by the first OC (P = .327; Z test).

Regarding tumor morphology, CCE detected 165 protruding polyps and 82 flat polyps (including LST), compared with 115 protruding polyps and 52 flat polyps (including LST, which also were detected by CCE) by the first OC (Fig. 2A-C) (P = .6646; Z test).

For the subjective assessment of the acceptability of CCE, the proportion of patients who reported *not at all* and *almost none* for embarrassment, fear, and pain were 95.5% (63 patients), 83.3% (55 patients), and 98.5% (65 patients), respectively (Fig. 3). In addition, 58 patients (87.9%) reported that CCE ingestion was very easy or easy, which shows that the acceptability of the CCE was very high. In the assessment of bowel preparation, a relatively low number of patients reported *quite easy* (9.1%, 6 patients) or *fairly easy* (13.6%, 9 patients), and most of them reported *moderate* (57.6%, 38 patients). A relatively large number of patients reported *fairly hard* and *quite hard* for administration of drug (60.6%, 40 patients) (Fig. 4).

The cleansing level of the entire colon was graded as adequate in 93.9% of patients (62/66). The per-segment adequate cleansing level was 92.4% (61/66) for cecum, 93.9% (62/66) for ascending colon, 95.4% (62/65) for transverse colon, 93.8% (61/65) for descending and/or sigmoid colon, and 83.3% (50/60) for rectum. CCE sensitivity for detecting lesions that require endoscopic or surgical treatment in patients with adequate cleansing levels in the entire colon was 95.2%. The sensitivity in patients with an inadequate cleansing level was 75.0%.

The capsule excretion rate was 56.1% (37 patients) in the "<4 hours" group, 4.5% (3 patients) in the "4 to < 6 hours" group, 12.1% (8 patients) in the "6 to < 8 hours" group, 4.5% (3 patients) in the "8 to < 10 hours" group, and 7.6% (5

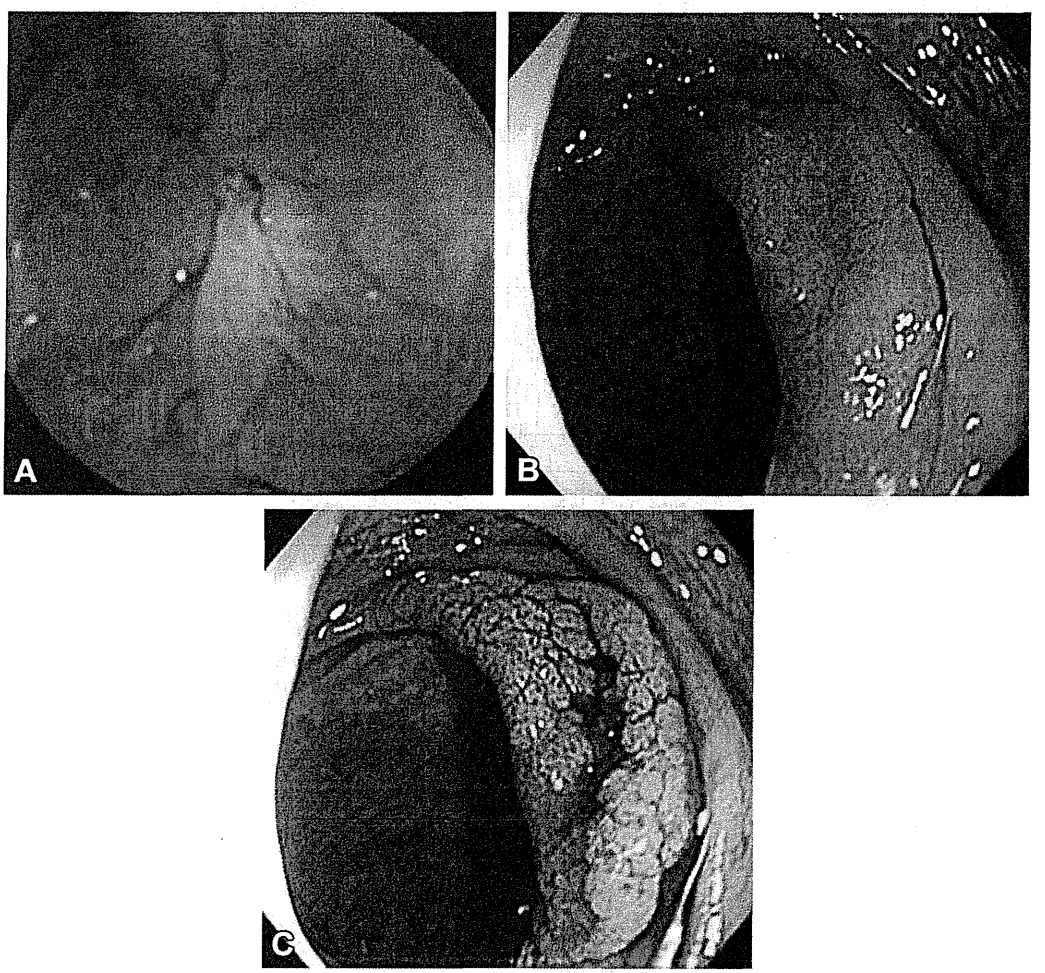

Figure 2. A, Image from a 68-year-old female. A slightly flat, elevated lesion was visualized on the left side of this capsule endoscopy image. **B,** A 40-mm, slightly flat, elevated lesion was visualized in the sigmoid colon. **C,** After indigo carmine dye spraying, the margin of this flat lesion became apparent and was diagnosed as 0-IIa (non-granular type laterally spreading tumor). This tumor was diagnosed as intramucosal neoplasia, and endoscopic submucosal dissection was performed with en bloc resection. Histology revealed a well-differentiated adenocarcinoma (Tis), and a curative resection was achieved.

patients) in the "10 hours (excreted within the operating time)" group. The excretion rate for cases where the exact excretion time was unknown, but the capsule was excreted within capsule operation time, was 3.0% (2 patients). The rate for cases in which the capsule was not excreted within the capsule operation time was 12.1% (8 patients). The capsule was excreted within its operating time in 58 of 66 cases (87.9%; 95% CI, 80%-96%). In the 8 patients from whom the capsule was not excreted within the operating time, the final locations were as follows: ascending colon in 1 patient (12.5%), descending and/or sigmoid colon in 5 patients (62.5%), and rectum in 2 patients (25.0%). In the 66 patients used for efficacy analysis, the average gastric transit time, small-bowel transit time, colon transit time, and entire video recording time were 0:48 hour, 1:01 hours, 2:53 hours, and 5:41 hours, respectively.

There were no severe adverse events in this trial. In 1 patient (1.5%), mild vomiting during the procedure was reported, but the patient recovered without any treatment. There was no retention of the capsule in this trial. Seventy capsules were used in the 68 patients, and device failure was reported in 4 patients (5 events) (5.9%). In 2 patients the capsule failed to operate (did not blink) before ingestion when the case was opened. In 1 patient, there was a communication failure between the capsule and the data recorder, causing image loss because of external interference with another device. In 1 patient, the data recorder stopped functioning during the procedure; however, it was replaced with another recorder, and the examination was continued. The data in this case were downloaded successfully. In 1 patient, the operating time of the capsule was too short and consequently, images of the colon were not obtained. This patient was excluded from the efficacy analysis.

In the evaluation of the safety and efficacy of the CCE by the principal investigators, CCE was reported as fairly safe or safe in all 67 eligible patients, and as fairly effective or effective in 88.1% (59 patients).

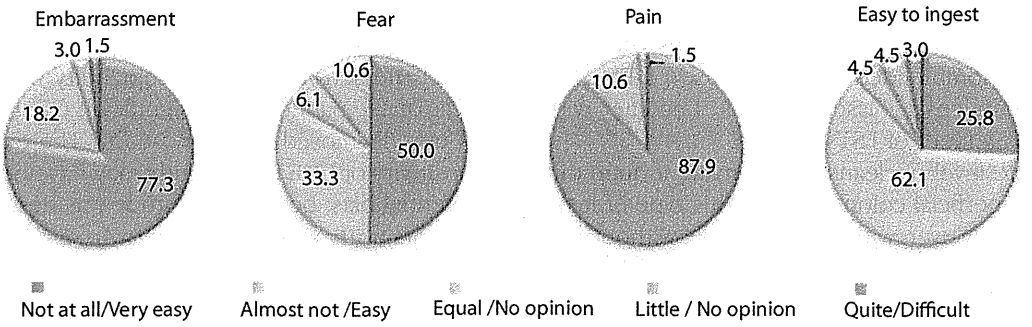

Figure 3. Acceptability of colon capsule endoscopy test (%).

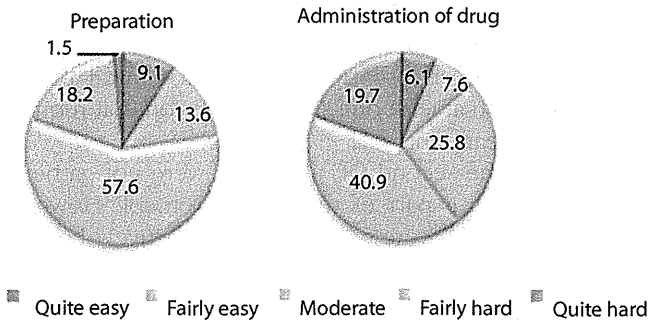

Figure 4. Acceptability of preparation and administration of drug during procedure (%).

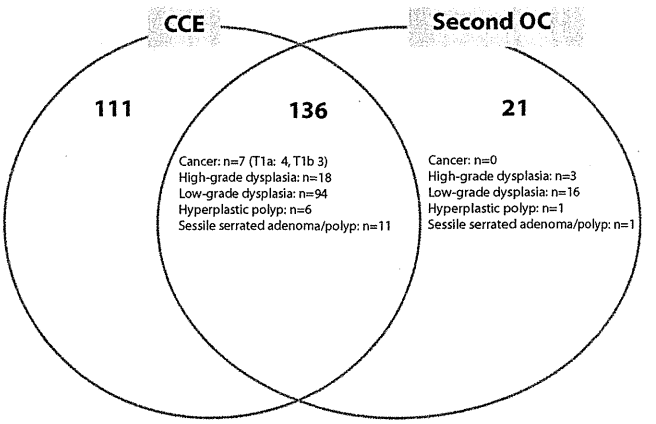

Figure 5. After colon capsule endoscopy, second OCs were performed in 66 patients to remove the lesions. As a result, 268 lesions were confirmed by CCE and/or second OC. *CCE,* colon capsule endoscopy; *OC,* optical colonoscopy.

Second therapeutic colonoscopy

After CCE, a second OC was performed in 66 patients to resect the lesions of interest. As a result, 268 lesions were confirmed by CCE and/or second OC (Fig. 5). The pathology diagnosis was confirmed based on the resected specimens in 66 patients, with 157 lesions resected. Among these 157 lesions, 136 were detected both by CCE and the second OC: 7 cancers (T1a: 4, T1b: 3), 18 high-grade dysplasias, 94 low-grade dysplasias, 6 hyperplastic polyps, and 11 sessile serrated adenomas/polyps. In contrast, 21 lesions were detected by the second OC only: 3 high-grade dysplasias, 16 low-grade dysplasias, 1 hyperplastic polyp, and 1 sessile serrated adenoma/polyp (Fig. 5). The per-polyp sensitivity was 86.6% (95% CI, 81.3%-91.9%) when pathology-confirmed polyps were considered true positives. Regarding the pathologic type, per-polyp sensitivities were 100% (7/7) in cancer, 85.7% (18/21) in high-grade dysplasia, 85.5% (94/110) in low-grade dysplasia, and 89.5% (17/19) in other nonneoplastic lesions, respectively.

DISCUSSION

This trial demonstrates that CCE with a reduced preparation regimen was safe, with a sensitivity of 94% for detecting significant lesions, including LSTs (Fig. 1A-C). Until now, there has been limited information on the accuracy of CCE for flat lesions, which are important contributors to the development of colorectal cancer.

CCE detected 247 polyps of any size compared with 167 polyps detected by OC (significant difference, Z test; $P = .0232$). This could result either from overreading of CCE or from missed lesions during the first OC. It is possible that the CCE reader may have detected the same lesion more than once because of the back-and-forth motion of the capsule. It has been reported that OC has a 95% polyp detection sensitivity,[22] indicating a 5% possible miss rate.

CCE failed to detect significant lesions that were detected by the first OC in 4 of 66 patients (6%). In 2 patients, the capsule reached the sigmoid colon and was not excreted within the operating time. Consequently, 3 rectal polyps were missed (a 12-mm 0-Is polyp in 1 patient and 8-mm 0-Isp and 12-mm 0-Isp in another). The cleansing level was inadequate in 2 patients, which likely explains why 2 lesions were missed in these patients (35-mm 0-IIa + IIc lesion in the ascending colon and 15-mm 0-Isp lesion in the rectum). In the fourth patient, a 15-mm 0-IIa lesion was missed because of location in the descending and/or sigmoid colon behind a fold.

This clinical trial included patients with superficial tumors such as LST (Fig. 1A-C), for which endoscopic treatment is often recommended. In Japan, use of EMR and endoscopic submucosal dissection has become widespread for management of LSTs ≤ 2 cm.[23-25]

An inadequate level of cleansing can make it quite difficult to detect superficial colon tumors. This type of lesion can be missed easily even with OC, especially without prior knowledge of the presence of a flat or depressed lesion. It is important to emphasize that CCE was able to detect flat superficial tumors in this trial.

According to Van Gossum et al,[8] the most important factor for the detection of colon polyps in CCE is the level of colon cleansing. The regimen used in this clinical trial was based on the modified method reported by Kakugawa et al.[19] One of the important point of our modification is setting the 50g magnesium citrate hypertonic solution (180ml) on the day before the CCE. The proportion of patients with an adequate cleansing level was very high, 93.9% (62/66 patients). In addition, the excretion rate for capsules within the operating time was fairly good at 87.9% (58/66 patients). Thus, it is the opinion of the authors that the recommended regimen is adequate in terms of the cleansing level and the excretion rate of the capsule. The fact that a relatively high number of flat lesions was detected also suggests that the cleansing level was sufficient.

However, the correlation between the cleansing level and sensitivity of CCE could not be evaluated in this trial, because of the small number of patients ($n = 4$) with an inadequate cleansing level.

In the subjective assessment of CCE acceptability, CCE scored highly, in the range of 83.3% to 98.5% for parameters such as embarrassment, fear, pain, and easiness of ingestion. It is, therefore, possible that CCE can contribute an increase in the compliance rate in patients requiring diagnostic imaging of the colon or colorectal cancer screening.

Regarding the preparation and administration of drugs during the procedure, the survey revealed moderate to *quite* hard as responses (77.3% for preparation and 86.4% for administration of drug), highlighting a potential area for improvement in the protocol for CCE.

In terms of safety, no severe adverse events were reported. In only 1 case, mild vomiting during the procedure was reported; however, this was not thought to be related to the capsule device, and the patient recovered without any treatment. In all 67 patients, safety of the CCE test was demonstrated; the CCE test was considered to be useful in 59 cases (88.1%).

Limitations

This clinical trial included patients with previously confirmed significant lesions; therefore, the specificity of CCE could not be evaluated. However, previous reports describe a specificity ranging from 64% to 94%.[11-13] Additionally, CCE detected a greater number of lesions than did the first OC.

The sample size of our study was smaller than that of previous studies because the specific endpoints investigated the sensitivity and acceptability of CCE in a cohort of Japanese patients, with significant colorectal lesions previously diagnosed by colonoscopy. The exceptionally high sensitivity of CCE in this study may have been affected by a potential bias, because the study was designed to evaluate patients with at least one known significant lesion. This could increase physician concentration during capsule reading to find at least the first polyp. This original study design was adapted to our recruitment at expert therapeutic centers, where the majority of patients are referred for treatment of a known lesion. Thus, we were able to evaluate only the sensitivity of the capsule in patients with known lesions. However, the reader did not know the location, the number, or the macroscopic type of the lesions. Capsule endoscopy may have a clinical benefit for patients with at least one significant lesion that requires endoscopic treatment.

Results of the second OC after CCE were not gathered prospectively as a part of the study protocol. However, the following data were collected retrospectively because it was thought to be important to our understanding of CCE. One hundred eleven lesions were detected by CCE-2 only, and thus, pathologic diagnoses of these lesions remains unknown. We suspect that these CCE-2–only detected lesions may be false positives or diminutive lesions located behind folds.

However, we believe it is clinically important for CCE to provide patients with the opportunity to receive treatment by detecting significant lesions in the colon, which is the primary endpoint of this trial, rather than the exact number of lesions detected.

In conclusion, CCE detected significant colon lesions safely, with high sensitivity per patient analysis and acceptability to patients.

ACKNOWLEDGMENTS

We thank Given Imaging Ltd, who sponsored this trial, for the statistical analysis of the results. We express our appreciation to Dr Ara Sahakian, University of Southern California Keck School of Medicine, USA, and Dr Mathieu Pioche, Hospital Edouard Herriot, Lyon, France, for their assistance in editing this manuscript.

REFERENCES

1. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095-105.
2. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal–cancer deaths. N Engl J Med 2012;366:687-96.
3. The 2011 National Summary of Gastrointestinal Cancer Screening. Commission report of the Japanese Society of Gastrointestinal Cancer Screening.

4. Negreanu L, Babiuc R, Bengus A, et al. PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy. World J Gastrointest Endosc 2013;5:559-67.
5. Eliakim R, Fireman Z, Gralnek IM, et al. Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. Endoscopy 2006;38:963-70.
6. Schoofs N, Deviere J, Van Gossum A. PillCam colon capsule endoscopy compared with colonoscopy for colorectal tumor diagnosis: a prospective pilot study. Endoscopy 2006;38:971-7.
7. Sieg A, Friedrich K, Sieg U. Is PillCam COLON capsule endoscopy ready for colorectal cancer screening? A prospective feasibility study in a community gastroenterology practice. Am J Gastroenterol 2009;104:848-54.
8. Van Gossum A, Navas MM, Fernandez-Urien I, et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med 2009;361:264-70.
9. Gay G, Delvaux M, Frederic M, et al. Could the colonic capsule PillCam Colon be clinically useful for selecting patients who deserve a complete colonoscopy? Results of clinical comparison with colonoscopy in the perspective of colorectal cancer screening. Am J Gastroenterol 2010;105:1076-86.
10. Sacher-Huvelin S, Coron E, Gaudric M, et al. Colon capsule endoscopy vs. colonoscopy in patients at average or increased risk of colorectal cancer. Aliment Pharmacol Ther 2010;32:1145-53.
11. Pilz JB, Portmann S, Peter S, et al. Colon capsule endoscopy compared to conventional colonoscopy under routine screening conditions. BMC Gastroenterol 2010;10:66.
12. Spada C, De Vincentis F, Cesaro P, et al. Accuracy and safety of second-generation PillCam COLON capsule for colorectal polyp detection. Therap Adv Gastroenterol 2012;5:173-8.
13. Eliakim R, Yassin K, Niv Y, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy 2009;41:1026-31.
14. Spada C, Riccioni ME, Hassan C, et al. PillCam colon capsule endoscopy: a prospective, randomized trial comparing two regimens of preparation. J Clin Gastroenterol 2011;45:119-24.
15. Hartmann D, Keuchel M, Philipper M, et al. A pilot study evaluating a new low-volume colon cleansing procedure for capsule colonoscopy. Endoscopy 2012;44:482-6.
16. Hagel AF, Gabele E, Raithel M, et al. Colon capsule endoscopy: detection of colonic polyps compared with conventional colonoscopy and visualization of extracolonic pathologies. Can J Gastroenterol Hepatol 2014;28:77-82.
17. Spada C, Hassan C, Munoz-Navas M, et al. Second-generation colon capsule endoscopy compared with colonoscopy. Gastrointest Endosc 2011;74:581-9 e1.
18. Singeap AM, Trifan A, Cojocariu C, et al. Colon capsule endoscopy compared to colonoscopy for colorectal neoplasms diagnosis: an initial experience and a brief review of the literature. Rev Med Chir Soc Med Nat Iasi 2012;116:145-9.
19. Kakugawa Y, Saito Y, Saito S, et al. New reduced volume preparation regimen in colon capsule endoscopy. World J Gastroenterol 2012;18:2092-8.
20. Spada C, Hassan C, Galmiche JP, et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2012;44:527-36.
21. Urakawa T, Saito Y, Matsuda T, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumors in the colorectum. Gut 2006;55:1592-7.
22. **The 2005 Group for study for appropriate methods for cancer screening and establishment of its evaluation method. Colonic cancer screening guideline based on efficacy.**
23. Saito Y, Uraoka T, Yamaguchi Y, et al. A prospective multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). Gastrointest Endosc 2010;72:1217-25.
24. Nakajima T, Saito Y, Tanaka S, et al. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc 2013;27:3262-70.
25. Saito Y, Otake Y, Sakamoto T, et al. Indications for and technical aspects of colorectal endoscopic submucosal dissection. Gut Liver 2013;7:263-9.

Int J Clin Oncol (2015) 20:207–239
DOI 10.1007/s10147-015-0801-z

SPECIAL ARTICLE

Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer

Toshiaki Watanabe · Michio Itabashi · Yasuhiro Shimada · Shinji Tanaka · Yoshinori Ito · Yoichi Ajioka · Tetsuya Hamaguchi · Ichinosuke Hyodo · Masahiro Igarashi · Hideyuki Ishida · Soichiro Ishihara · Megumi Ishiguro · Yukihide Kanemitsu · Norihiro Kokudo · Kei Muro · Atsushi Ochiai · Masahiko Oguchi · Yasuo Ohkura · Yutaka Saito · Yoshiharu Sakai · Hideki Ueno · Takayuki Yoshino · Narikazu Boku · Takahiro Fujimori · Nobuo Koinuma · Takayuki Morita · Genichi Nishimura · Yuh Sakata · Keiichi Takahashi · Osamu Tsuruta · Toshiharu Yamaguchi · Masahiro Yoshida · Naohiko Yamaguchi · Kenjiro Kotake · Kenichi Sugihara · Japanese Society for Cancer of the Colon and Rectum

Received: 14 January 2015 / Accepted: 4 February 2015 / Published online: 18 March 2015

Abstract Colorectal cancer is a major cause of death in Japan, where it accounts for the largest number of deaths from malignant neoplasms among women and the third largest number among men. Many new methods of treatment have been developed during recent decades. The Japanese Society for Cancer of the Colon and Rectum Guidelines 2014 for treatment of colorectal cancer (JSCCR Guidelines 2014) have been prepared as standard treatment strategies for colorectal cancer, to eliminate treatment disparities among institutions, to eliminate unnecessary treatment and insufficient treatment, and to deepen mutual understanding among health-care professionals and patients by making these guidelines available to the general public. These guidelines have been prepared as a result

T. Watanabe (✉) · S. Ishihara
Department of Surgical Oncology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: toshwatanabe@yahoo.co.jp

M. Itabashi
Department of Surgery 2, Tokyo Women's Medical University, Tokyo, Japan

Y. Shimada · T. Hamaguchi
Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

S. Tanaka
Department of Endoscopy, Hiroshima University Hospital, Hiroshima, Japan

Y. Ito
Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Y. Ajioka
Division of Molecular and Diagnostic Pathology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

I. Hyodo
Division of Gastroenterology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan

M. Igarashi
Department of Endoscopy, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

H. Ishida
Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan

M. Ishiguro · K. Sugihara
Department of Surgical Oncology, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

Y. Kanemitsu
Colorectal Surgery Division, National Cancer Center Hospital, Tokyo, Japan

N. Kokudo
Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

K. Muro
Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

A. Ochiai
Pathology Division, Research Center for Innovative Oncology, National Cancer Centre Hospital East, Chiba, Japan

of consensuses reached by the JSCCR Guideline Committee on the basis of careful review of evidence retrieved by literature searches and taking into consideration the medical health insurance system and actual clinical practice in Japan. They can, therefore, be used as a guide for treating colorectal cancer in clinical practice. More specifically, they can be used as a guide to obtaining informed consent from patients and choosing the method of treatment for each patient. As a result of the discussions of the Guideline Committee, controversial issues were selected as clinical questions, and recommendations were made. Each recommendation is accompanied by a classification of the evidence and a classification of recommendation categories, on the basis of consensus reached by Guideline Committee members. Here we present the English version of the JSCCR Guidelines 2014.

Keywords Colorectal cancer · Guideline · Surgery · Chemotherapy · Endoscopy · Radiotherapy

Introduction

1. Guideline objectives

The incidence and mortality of colorectal cancer have substantially increased in Japan recently. According to vital statistics for Japan in 2012, colorectal cancer accounted for the largest number of deaths from malignant neoplasms among women and the third largest number among men, after lung cancer and gastric cancer. The number of deaths from colorectal cancer per unit population has increased approximately tenfold during the past 50 years. Many new treatment methods have been developed during that time, and their use in combination with advances in diagnostic methods has led to a steady improvement in the results of treatment. However, different treatment is used among medical institutions in Japan that provide medical care for patients with colorectal cancer, and the differences may lead to differences in the results of treatment.

In such circumstances, the JSCCR Guidelines 2014 for treatment of colorectal cancer, which are intended for doctors (general practitioners and specialists) who provide medical care for patients with colorectal cancer in different disease stages and conditions, have been prepared for four purposes:

1. to disseminate standard treatment strategies for colorectal cancer;
2. to eliminate disparities among institutions in terms of treatment;
3. to eliminate unnecessary treatment and insufficient treatment; and
4. to deepen mutual understanding among health-care professionals and patients by making these guidelines available to the general public [1].

Achievements expected as a result of these guidelines are:

1. improvement of treatment of colorectal cancer in Japan;
2. improvement of the results of treatment;
3. reduction of human and financial burden; and
4. increased benefits for patients.

M. Oguchi
Radiation Oncology Department, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

Y. Ohkura
Department of Pathology, Kyorin University School of Medicine, Tokyo, Japan

Y. Saito
Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan

Y. Sakai
Department of Surgery, Kyoto University, Kyoto, Japan

H. Ueno
Department of Surgery, National Defense Medical College, Saitama, Japan

T. Yoshino
Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, Japan

N. Boku
Department of Clinical Oncology, St. Marianna University, Kawasaki, Japan

T. Fujimori
Department of Surgical and Molecular Pathology, Dokkyo Medical University School of Medicine, Tochigi, Japan

N. Koinuma
Department of Health Administration and Policy, Tohoku Pharmaceutical University, Miyagi, Japan

T. Morita
Department of Surgery, Cancer Center, Aomori Prefectural Central Hospital, Aomori, Japan

G. Nishimura
Department of Surgery, Japanese Red Cross Kanazawa Hospital, Ishikawa, Japan

2. How to use these guidelines

These guidelines have been as a result of consensuses reached by the Guideline Committee of the Japanese Society for Cancer of the Colon and Rectum, on the basis of careful review of evidence retrieved by literature searches and taking into consideration the medical health insurance system and clinical practice in Japan. They can, therefore, be used as a guide for treating colorectal cancer in clinical practice. More specifically, they can be used as a guide to obtaining informed consent from patients and choosing the method of treatment for each patient. However, these guidelines provide only general recommendations for choosing treatment strategies for colorectal cancer, and they do not control or limit treatment strategies or treatment methods that are not described herein. These guidelines can also be used as a document to explain the rationale for selecting treatment strategies and treatment methods that differ from those described in the guidelines.

The Japanese Society for Cancer of the Colon and Rectum (JSCCR) is responsible for the statements in these guidelines. However, the personnel directly in charge of treatment, not the JSCCR or the Guideline Committee, are responsible for the outcome of treatment.

Y. Sakata
CEO, Misawa City Hospital, Aomori, Japan

K. Takahashi
Department of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

O. Tsuruta
Division of GI Endoscopy, Kurume University School of Medicine, Fukuoka, Japan

T. Yamaguchi
Department of Gastroenterological Surgery, The Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

M. Yoshida
Department of Hemodialysis and Surgery, Chemotherapy Research Institute, International University of Health and Welfare, Chiba, Japan

N. Yamaguchi
Library, Toho University Medical Center Sakura Hospital, Chiba, Japan

K. Kotake
Department of Surgery, Tochigi Cancer Center, Tochigi, Japan

3. Users

The users of these guidelines are mainly clinical doctors engaged in all aspects of the medical treatment of colorectal cancer.

4. How to develop these guidelines

1) Recording methods

We adopted the concept from the first edition in which the treatment policy algorithm was disclosed and a simple explanation thereof provided, and added further comments with regard to categories requiring additional explanation. Since the 2009 edition, topics of debate have been raised as clinical questions (CQs) and included with recommendations added. In the 2014 edition, this practice was continued, with corrections and additions made to the CQs on the basis of knowledge acquired since the 2010 version.

2) Evidence level and strength of recommendations of CQs

The recommendations added to CQs included the evidence level and the strength of recommendations determined by use of the following guidance.

2-1) Evidence level Papers relating to the CQs were comprehensively collected and evidence in individual papers relating to critical outcomes included in the CQs was divided into groups by study design [2]. The literature level and the body of evidence (Table 1) were evaluated with reference to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system [3–25], before determining the final CQ evidence level (Table 2).

2-2) Strength of recommendations Draft recommendation statements and the strength of the recommendations were based on outcomes and the level of evidence obtained by use of the process described above and were evaluated at a consensus meeting of the Guideline Committee.

The draft recommendations were evaluated on the basis of four categories:

① quality of evidence;
② patients' views and preferences;
③ benefits and harm, and
④ cost effectiveness.

The strength of recommendation (Table 3) was determined by vote, on the basis of the Delphi method, with those reaching a consensus of opinion of 70 % or more committee members determined as having been agreed upon. Items not reaching consensus after a single vote

Table 1 Rating the quality of evidence

Step 1 (evaluation of individual study): study design, evaluation of bias risk, create structured abstract
Step 2 (overall rating for each important outcome across studies):
1. Initial quality of a body of evidence: evaluation of each study design group
•Systematic reviews, meta-analysis, randomized controlled trials = "initial quality A (high level)"
•Observation studies, cohort studies, case control studies = "initial quality C (low level)"
•Case series, case reports = "initial quality D (very low level)"
2. Five possible reasons for downrating the quality
•Risk of bias
•Inconsistency in results
•Indirectness of evidence
•Data imprecision
•High possibility of publication bias
3. Three possible reasons for uprating the quality
•Large effect with no confounding factors
•Dose–response gradient
•Possible confounding factors are weaker than actual effects
4. We evaluate 1->2->3, and assess the quality of a body of evidence

Table 2 Definition of levels of evidence [13]

A (high):	We are very confident in the estimate of the effect
B (moderate):	We are moderately confident in the estimate of the effect: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
C (low):	Our confidence in the estimate of the effect is limited: the true effect may be substantially different from the estimate of the effect
D (very low):	We have very little confidence in the estimate of the effect: the true effect is likely to be substantially different from the estimate of effect

were debated once again, with the results of the first vote disclosed and additional information on the situation relating to clinical practice in Japan provided. Discussion and voting was repeated until a consensus was reached. No strength of recommendation was presented in CQs.

5. Literature search

At first, the literature search was performed for the following 12 broad categories. Then, a further search was conducted, as needed, with additional search techniques.

(1) Endoscopic treatment of colorectal cancer
(2) Treatment of Stage 0 to Stage III colorectal cancer [26]
(3) Treatment of Stage IV colorectal cancer [26]
(4) Treatment of liver metastases of colorectal cancer
(5) Treatment of lung metastases of colorectal cancer
(6) Treatment of recurrent colorectal cancer
(7) Adjuvant chemotherapy for colorectal cancer
(8) Chemotherapy for unresectable colorectal cancer
(9) Adjuvant radiotherapy for colorectal cancer
(10) Palliative radiotherapy for colorectal cancer

Table 3 Strength of recommendation [24]

Strength of recommendation
1 Strong recommendation
Strongly "for" an intervention
Strongly "against" an intervention
2 Weak recommendation
Weakly "for" an intervention
Weakly "against" an intervention

(11) Palliative care for colorectal cancer
(12) Surveillance after surgery for colorectal cancer.

To survey the latest literature, in addition to the papers used for reference in the previous edition, the PubMed and Ichushi-Web databases were selected for the search, and English and Japanese literature was searched in both databases from January 2008 to March 2012. The task of searching was shared by 4 members of the medical library; the 4 members created a search formula by discussion with the Committee members in charge of each item and collected literature during the search period (March

Table 4 Number of scientific articles retrieved and selected

	Number of articles retrieved		Number of articles selected		Number of articles retrieved manually
	PubMed	Ichushi	PubMed	Ichushi	
(1) Endoscopic treatment of colorectal cancer	811	385	80	40	39
(2) Treatment of Stage 0 to Stage III colorectal cancer	469	285	92	14	12
(3) Treatment of Stage IV colorectal cancer	237	102	97	14	13
(4) Treatment of liver metastases of colorectal cancer	812	357	364	79	25
(5) Treatment of lung metastases of colorectal cancer	96	157	46	35	6
(6) Treatment of recurrent colorectal cancer	688	302	147	29	13
(7) Adjuvant chemotherapy for colorectal cancer	639	228	209	32	41
(8) Chemotherapy for advanced or recurrent colorectal cancer	762	149	254	44	154
(9) Adjuvant radiotherapy for colorectal cancer	447	95	115	8	27
(10) Palliative radiotherapy for colorectal cancer	708	39	109	6	29
(11) Palliative care for colorectal cancer	278	181	58	18	10
(12) Surveillance after surgery for colorectal cancer	1,446	1,287	256	57	20
Total	7,393	3,567	1,837	376	389

2012). For categories 7 and 8, however, April 2010 was set as the end of the search period. In addition, secondary documents such as UpToDate and literature collected by manual searching were added and critically examined as needed, and other documents such as minutes and guidelines were included as necessary. In addition to the 8,043 documents extracted in the previous literature search (5,305 PubMed documents and 2,738 Ichushi documents), a further 2,213 documents were selected by use of the study design from the 2,917 documents (2,088 PubMed documents and 829 Ichushi documents) extracted during the literature search for the current edition. and critically examined (Table 4).

6. Funding

Preparation of these guidelines was funded by the JSCCR. No financial support was received from any other organization or corporation.

7. Conflicts of interest

1) The following corporations were disclosed by self-declaration of the Guideline Committee members and Guideline Evaluation Committee members

AstraZeneca K.K., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Olympus Medical Systems Co., Ltd., Van Medical Co., Ltd., Synergy International, Inc., Tsumura & Co., Yakult Honsha Co., Ltd., Kawasumi Laboratories, Inc., Covidien Japan Co., Ltd., Shionogi & Co., Ltd., Daiichi Sankyo Company, Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Bayer Yakuhin Ltd., Pfizer Japan Inc., Bristol-Myers Squib Company, MerkSerono.

2) Overcoming possible conflicts of interest

The members of the Guideline Committee and the Guideline Evaluation Committee were from a diverse range of disciplines, including surgery, internal medicine, radiology, pathology, etc., to minimize the possibility of biased opinion. Each recommendation was determined not the basis of an individual opinion but on the basis of voting by all the committee members, with consensus prioritized.

Treatment guidelines for colorectal cancer

Chapter 1: Treatment strategies for Stage 0 to Stage III colorectal cancer [26]

1. Endoscopic treatment (Fig. 1)

General principles underlying indications for endoscopic resection

- There is little possibility of lymph node metastasis, and the size and location of the tumor make en bloc resection possible.

Indication criteria for endoscopic resection:

(1) Intramucosal carcinoma or carcinoma with slight submucosal invasion
(2) Size does not matter
(3) Any macroscopic type

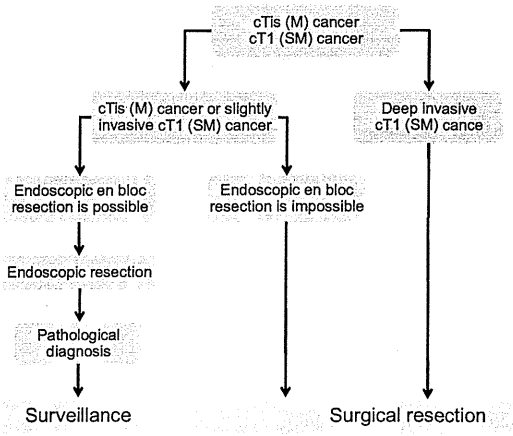

Fig. 1 Treatment strategies for cTis (M) cancer and cT1 (SM) cancer

- Endoscopic treatment is a method of endoscopically resecting lesions in the large bowel and of collecting the resected specimens.
- Endoscopic treatment methods are polypectomy,[note 1] endoscopic mucosal resection (EMR),[note 2] and endoscopic submucosal dissection (ESD).[note 3]
- In determining the indication for endoscopic treatment and the method of treatment, information on the size, predicted depth of invasion, and morphology of the tumor is essential.

Comments

① Endoscopic resection is intended for both diagnosis and treatment. It consists in total excisional biopsy in which curability and the need for additional intestinal resection are assessed by histopathological examination of the resected specimens (CQ-1).

② En bloc resection is desirable for accurate diagnosis of the status of carcinoma invasion in the resection margin and the deepest area.

- 2 cm is the largest size of a tumor that can be easily resected en bloc by polypectomy or snare EMR [27] (CQ-2).
- Colorectal ESD is an "endoscopic resection technique which enables en-bloc resection of a tumor, irrespective of size", which was approved for implementation under health insurance in April 2014 with regard to "early-stage malignant tumors". Given the high likelihood of technically difficult complications (perforations), however, it should only be implemented after sufficient consideration of the level of skill of the endoscopist performing the procedure. Tumors with a diameter between 2 and 5 cm are currently covered by insurance (CQ-3).
- EMRC (EMR using a cap) is reported to involve a high risk of perforation when used for colon lesions.
- If the preoperative diagnosis is cancer accompanied by adenoma (intramucosal carcinoma), piecemeal resection of the adenoma can be performed while avoiding division of the cancerous area. It should be noted, however, that piecemeal resection is associated with a high incidence of incomplete resection and high local recurrence [27].

Note 1 Polypectomy. In this method, a snare is placed on the stalk of the lesion, and the lesion is electrocauterized by use of a high-frequency current. This method is mainly used for protruding lesions.

Note 2 EMR. In this method, the lesion is elevated by local injection of a liquid, for example physiological saline, into the submucosa, and the lesion is electrocauterized the same as in polypectomy. This method includes the snare method [28] and EMR using a cap (EMRC). It is mainly used for superficial tumors and large sessile lesions.

Note 3 ESD. In this technique, the lesion is elevated by local injection of a liquid, for example sodium hyaluronate solution, into the submucosa of the perilesional area; circumferential incision of the mucosa surrounding the lesion, dissection of the submucosa with a special knife, and en bloc resection are then performed [28]. ESD is mainly indicated for large tumors, especially for early cancers that cannot be resected by EMR.

2. Surgical treatment (Fig. 2)

- The extent of lymph node dissection to be performed during colorectal cancer surgery is determined on the basis of the preoperative clinical findings, and on the extent of lymph node metastasis and depth of tumor invasion by the tumor observed intraoperatively.
- If lymph node metastasis is recognized, or suspected on the basis of the preoperative/intraoperative findings, D3 dissection is performed.
- If no lymph node metastases are observed on the basis of preoperative and/or intraoperative diagnostic findings, lymph node dissection is performed on the basis of the depth of tumor invasion [29].

(1) Lymph node dissection is unnecessary for pTis (M) cancer (D0), because pTis (M) cancer is not accompanied by lymph node metastasis; however, D1 dissection can be performed because the accuracy of the preoperative diagnosis of invasion depth may be insufficient.

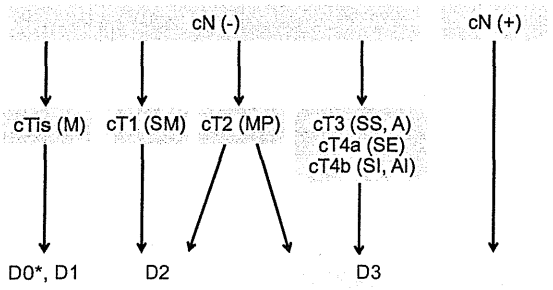

Fig. 2 Surgical treatment strategies for cStage 0 to cStage III colorectal cancer

(2) D2 dissection is necessary for pT1 (SM) cancer, because the incidence of lymph node metastasis is approximately 10 % and because pT1 (SM) cancer is often accompanied by intermediate lymph node metastasis.
(3) Although there is insufficient evidence of the extent of lymph node dissection for cT2 (MP) cancer, at least D2 dissection is necessary. However, D3 dissection can be performed, because approximately 1 % of cT2 (MP) cancer is accompanied by main lymph node metastases (Table 5) and because preoperative diagnosis of depth of invasion is not very accurate.

Surgical treatment for rectal cancer:

- The principle for radical surgery for rectal cancer is TME (total mesorectal excision) or TSME (tumor-specific mesorectal excision) [30–33].

[Indications for lateral lymph node dissection]

- Lateral lymph node dissection is indicated when the lower border of the tumor is located distal to the peritoneal reflection and the tumor has invaded beyond the muscularis propria [30].

[Local excision for rectal cancer]

- Local excision is indicated for cTis (M) cancer and cT1 (SM) cancer (slight invasion) located distal to the second Houston valve (peritoneal reflection).
- Histological investigation of the resected specimen enables determination of the likelihood that treatment will cure the condition completely, and the need for additional treatment (intestinal resection accompanied by lymph node dissection).

[Autonomic nerve-preserving surgery]

- The autonomic nervous system of concern in surgery for rectal cancer comprises the lumbar splanchnic nerves, superior hypogastric plexus, hypogastric nerves, pelvic splanchnic nerves, and pelvic plexus. Taking into consideration such factors as the extent of cancer progression and the presence or absence of macroscopic nerve invasion, preservation of autonomic nerves is attempted to preserve urinary and sexual function as much as possible, if curability is unaffected.

Laparoscopic surgery:

- The indications for laparoscopic surgery are determined by considering the surgeon's experience and skills and characteristics of the tumor, for example the location and extent of progression of the cancer, and patient factors, for example obesity and history of open abdominal surgery (CQ-4).

Comments

[Lateral lymph node dissection]

① An analysis of 2,916 cases of rectal cancer in the project study by the JSCCR showed that the incidence of lateral lymph node metastasis was 20.1 % among patients whose lower tumor border was located distal to the peritoneal reflection and whose cancer invaded beyond the muscularis propria (only patients who underwent lateral lymph node dissection) (Table 5). After performing lateral lymph node dissection for this indication, it is expected that the risk of intrapelvic recurrence decreases by 50 %, and 5-year survival improves by 8 to 9 % [34].
② The incidence of lateral lymph node metastasis was 27 % among patients whose lower tumor border was located distal to the peritoneal reflection and who had lymph node metastasis in the mesorectum.
③ Urinary function and male sexual function may be impaired after lateral dissection, even if the autonomic nervous system is completely preserved.

[Aggregate data from the colorectal cancer registry]

① The incidence of lymph node metastasis according to site and depth of tumor invasion, prevalence of curative resection, and 5-year survival is shown in Tables 6, 7, and 8 [29].
② Five-year survival after curative resection of pStage 0 to pStage III colorectal cancer according

Table 5 Lateral lymph node dissection and lateral lymph node metastasis of rectal cancer

	No. of patients	No. of patients who underwent lateral dissection	Prevalence of lateral dissection	No. of patients with lateral metastasis	Incidence of metastasis (percentage of all patients)	Incidence of lateral metastasis (percentage of patients who underwent lateral dissection)
RS						
sm	124	0	0	0	0.0	0.0
mp	127	6	4.7 %	0	0.0	0.0
ss/a_1	316	24	7.5 %	0	0.0	0.0
se/a_2	177	8	4.5 %	0	0.0	0.0
si/ai	32	14	43.8 %	1	3.1	7.1
Total	776	52	6.7 %	1	0.1	1.9
Ra						
sm	138	5	3.6 %	0	0.0	0.0
mp	149	18	12.1 %	0	0.0	0.0
ss/a_1	230	58	25.2 %	4	1.7	6.9
se/a_2	181	59	32.6 %	7	3.9	11.9
si/ai	15	8	53.3 %	0	0.0	0.0
Total	713	148	20.8 %	11	1.5	7.4
RaRb + Rb						
sm	234	37	15.8 %	2	0.9	5.4
mp	372	218	58.6 %	20	5.4	9.2
ss/a_1	350	230	65.7 %	28	7.7	12.2
se/a_2	412	319	77.4 %	75	18.0	23.5
si/ai	59	48	81.4 %	17	28.8	35.4
Total	1,427	852	59.7 %	142	9.8	16.7

(Project study by the JSCCR: patients in years 1991–1998)

Table 6 Incidence of lymph node metastasis according to primary site and depth of tumor invasion

	No. of patients	Extent of lymph node metastasis detected histologically				
		n_0 (%)	n_1 (%)	n_2 (%)	n_3 (%)	n_4 (%)
All sites						
sm	3,151	90.7	7.3	1.9	0.0	0.1
mp	3,590	77.3	17.4	4.2	0.9	0.3
ss/a_1	11,272	54.6	29.9	12.0	2.3	1.2
se/a_2	6,101	35.9	34.4	20.2	5.7	3.8
si/ai	1,502	43.0	27.6	16.4	6.7	6.3
Total	25,617	57.1	26.3	11.9	2.9	1.9
Colon						
sm	1,957	91.4	6.8	1.8	0.0	0.0
mp	1,747	79.3	16.3	3.5	0.6	0.3
ss/a_1	7,333	56.6	28.1	11.7	2.4	1.2
se/a_2	3,363	37.4	34.0	19.3	5.6	3.7
si/ai	960	44.6	28.6	14.7	5.5	6.6
Total	15,360	58.6	25.4	11.3	2.8	1.8
Rectosigmoid						
sm	337	88.7	9.5	1.8	0.0	0.0
mp	429	80.4	17.0	2.6	0.0	0.0
ss/a_1	1,584	53.9	33.0	10.2	1.3	1.7
se/a_2	789	34.2	38.4	20.8	3.2	3.4
si/ai	187	44.9	24.6	19.3	4.8	6.4
Total	3,326	55.7	29.3	11.4	1.6	2.0
Rectum						
sm	839	89.7	7.7	2.0	0.1	0.4
mp	1,373	73.9	19.2	5.4	1.4	0.1
ss/a_1	2,310	48.8	33.3	14.2	2.7	1.0
se/a_2	1,904	33.9	33.6	21.5	6.8	4.1
si/ai	328	38.1	26.2	19.8	10.4	5.5
Total	6,754	54.3	27.0	13.3	3.6	1.8
Anal canal						
sm	18	94.4	0.0	5.6	0.0	0.0
mp	41	70.7	9.8	7.3	7.3	4.9
ss/a_1	45	60.0	22.2	8.9	6.7	2.2
se/a_2	46	32.6	21.7	23.9	15.2	6.5
si/ai	27	33.3	25.9	14.8	18.5	7.4
Total	177	54.8	17.5	13.0	10.2	4.5

National registry of patients with cancer of the colon and rectum of the JSCCR: patients in years 2000–2004

Depth of invasion and the degree of lymph node metastasis were determined according to the rules listed in the "Japanese Classification of Colorectal Carcinoma" (6th edition)

to site was: all sites 82.2 %, colon 83.8 %, rectosigmoid 81.7 %, Ra-Rb rectum 79.3 % (patients in years 2000–2004).

Chapter 2: Treatment strategies for Stage IV colorectal cancer [26] (Fig. 3)

- Stage IV colorectal cancer is associated with synchronous distant metastasis to any of the organs: liver, lung, peritoneum, brain, distant lymph nodes, or other organ (e.g., bone, adrenal gland, spleen).
- If both the distant metastases and the primary tumor are resectable, curative resection of the primary tumor is performed, and resection of the distant metastases is considered.
- If the distant metastases are resectable but the primary tumor is unresectable, in principle, resection of the primary tumor and distant metastases is not performed, and another treatment method is selected.
- If the distant metastases are unresectable but the primary tumor is resectable, the indication for resection of the primary tumor is determined on the basis of the

Table 7 Curative resection rate according to stage (lower rows: no. of patients)

Stage	I	II	IIIa	IIIb	IV	All stages
All patients	98.7 %	96.2 %	91.9 %	81.8 %	–	78.0 %
	5,455	7,336	5,635	2,572	4,300	25,298
Colon	99.1 %	96.6 %	92.4 %	83.6 %	–	77.2 %
	3,028	4,688	3,208	1,379	2,787	15,090
Rectosigmoid	99.5 %	96.6 %	92.5 %	80.2 %	–	78.0 %
	615	961	835	288	560	3,259
Rectum	97.9 %	95.0 %	90.9 %	80.5 %	–	79.9 %
	1,764	1,644	1,564	866	929	6,767
Anal canal	95.8 %	86.0 %	78.6 %	61.5 %	–	70.9 %
	48	43	28	39	24	182

National registry of patients with cancer of the colon and rectum of the JSCCR: patients in years 2000–2004

Extent of curative resection = number of patients with histological curability A cancer/total number of patients who underwent surgery

Staging was performed according to the rules listed in the "Japanese Classification of Colorectal Carcinoma" (6th edition)

Table 8 Cumulative 5-year survival according to site (lower rows: no. of patients)

Stage	0	I	II	IIIa	IIIb	IV	All Stages
Cecum	91.0 %	93.7 %	83.5 %	73.0 %	65.4 %	12.5 %	68.2 %
	79	185	249	207	113	204	1,037
Ascending colon	93.9 %	91.2 %	85.8 %	79.1 %	63.4 %	19.1 %	71.4 %
	125	338	656	416	211	410	2,156
Transverse colon	88.9 %	91.4 %	85.2 %	78.5 %	65.7 %	20.8 %	74.0 %
	105	277	428	244	138	210	1,402
Descending colon	100.0 %	94.1 %	85.3 %	82.0 %	52.9 %	21.1 %	75.4 %
	43	146	224	166	52	117	748
Sigmoid colon	94.2 %	92.3 %	85.8 %	83.0 %	64.7 %	22.0 %	73.7 %
	154	852	1,124	837	363	736	4,066
Rectosigmoid	89.4 %	91.5 %	84.8 %	78.0 %	60.0 %	19.8 %	71.6 %
	54	366	539	473	175	322	1,929
Upper rectum	98.0 %	95.3 %	84.6 %	75.9 %	57.7 %	11.6 %	72.4 %
	67	356	464	471	173	263	1,794
Lower rectum	97.5 %	88.3 %	81.7 %	70.0 %	51.4 %	11.6 %	70.5 %
	142	718	486	473	332	298	2,449
Anal canal	100.0 %	78.7 %	90.9 %	46.9 %	61.2 %	15.7 %	60.0 %
	4	16	14	16	19	17	86
Colon	93.0 %	92.3 %	85.4 %	80.4 %	63.8 %	19.9 %	72.8 %
	506	1,798	2,681	1,870	877	1,677	9,409
Rectum	97.6 %	90.6 %	83.1 %	73.0 %	53.5 %	14.8 %	71.3 %
	209	1,074	950	944	505	561	4,243
All sites	94.0 %	91.6 %	84.8 %	77.7 %	60.0 %	18.8 %	72.1 %
	773	3,254	4,184	3,303	1,576	2,577	15,667

National registry of patients with cancer of the colon and rectum of the JSCCR: patients in years 2000–2004

Only adenocarcinomas (including mucinous carcinomas and signet-ring cell carcinomas) were counted

Survival was calculated by use of the life table method with death from any cause as an event

Five-year censoring = 20.5 % (3,208/15,667)

Staging was performed according to the rules listed in the "Japanese Classification of Colorectal Carcinoma" (6th edition)

clinical symptoms of the primary tumor and the effect on prognosis (CQ-5).

② Distant metastasis associated with peritoneal dissemination (CQ-6).

Comments

① The incidence of synchronous distant metastasis is shown in Table 9.

- Complete resection is desirable for P1.
- Complete resection is considered for P2 when easily resectable.
- The efficacy of resection of P3 has not been demonstrated.