Antonello Trecca
Editor

Ileoscopy

Technique, Diagnosis, and Clinical Applications

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Foreword by Shin-ei Kudo

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To my father, Pasquale Trecca

Foreword

It is a great pleasure to see the publication of *Ileoscopy*, edited by Dr. Antonello Trecca. Dr. Trecca studied endoscopic diagnosis and treatment of early cancers of the gastrointestinal tract at the National Cancer Center Hospital, Tokyo, Japan. He is an expert in magnifying endoscopy, including pit pattern diagnosis, and also has an excellent understanding of the importance of depressed type early colorectal cancers.

Colonoscopy (from diagnostic to technical aspects, including magnifying endoscopy, insertion technique, and endoscopic treatment) is an essential tool in the gastrointestinal field. With the emergence of the magnifying colonoscope, pit pattern analysis enables a diagnosis with a close relation to histologic diagnosis.

Today, there are plenty of textbooks of colonoscopy, but fewer of terminal ileoscopy. The importance of terminal ileoscopy during routine colonoscopy, however, should not be underestimated. We can diagnose many ileal diseases with terminal ileoscopy without using capsule endoscopy or balloon enteroscopy.

This book is dedicated to the role of exploration of the terminal ileum in lower gastrointestinal endoscopy. It covers both technical aspects and the modern diagnosis and treatment of small intestinal diseases in a very accessible format. It will be an indispensable guide not only for colonoscopists but also for gastroenterologists and surgeons.

I hope that this book will find the wide readership it doubtlessly deserves.

Prof. Shin-ei Kudo
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Preface

The challenge for the authors of a medical/scientific monograph is to communicate both their passionate interest in and their dedication to the subject matter, whether a disease, a new technique, an original therapeutic approach, or the most recent trends in clinical and experimental research. Of equal importance is to consider the scope of the audience, which may include students, interns, and residents but also highly experienced professionals.

We have kept these goals in mind in our exploration of the difficult subject of digestive endoscopy, specifically, of the terminal ileum, and the most important issues related to the use of this technique in various disease settings. Each chapter consists of a thorough discussion of a particular topic, which is illustrated by a large number of detailed images.

In the field of modern gastroenterology, digestive endoscopy continues to be the focus of enormous interest because of the many achievements over the last several decades: from the introduction of capsule endoscopy to the development of enteroscopy. These imaging capabilities have greatly expanded our knowledge of intestinal diseases while opening up new frontiers in their more accurate treatment.

Exploration of the terminal ileum during total colonoscopy has gained much greater acceptance within the profession based on the diagnostic accuracy of terminal ileoscopy with respect to ileocecal pathologies, including neoplasias of the cecal region. In addition, terminal ileoscopy documents the completeness of colonoscopy and points the way to the optimal procedure for further study of the intestine. This capability is such that we provocatively refer to ileoscopy as the fast track to the diagnosis of gut diseases.

The multidisciplinary approach taken by the authors of this volume to the accurate study of the ileocecum is highlighted by the contributions of experts in radiology and surgery, providing a closer look at several intestinal diseases. Particular emphasis has been placed on endoscopic imaging of the different disease stages and on analyzing the results obtained with the new techniques in terms of their ability to enhance diagnostic accuracy.

We would like to thank all the authors who actively participated in realizing this book, for their clinical efforts and scientific contributions. To our readers: we hope that we have been able to contribute to your professional development and to have inspired in you the same passionate interest that has resulted in this book.

Rome, September 2011 Antonello Trecca

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The editor would like to thank Raffaele Gurrieri, for the illustrations drawn for Chap. 1 with passion and competence, and Astrid Gurrieri, for her unflagging contribution to the book.

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1 Terminal Ileoscopy: Technique

Antonello Trecca, Giuseppe Cerno, Emilio Gentile Warschauer, Gabriele Marinozzi, and Fabio Gaj

1.1 Introduction

The basic requirement for the intubation of the terminal ileum is knowledge of the anatomy of the ileocecal region and of the main appearances of the ileocecal valve (ICV), accompanied by an appropriate level of technical skill in performing colonoscopy.

1.2 Anatomy of the Ileocecal Region

The cecum is the first part of the large intestine and it occupies the right iliac fossa. Guarding the opening of the ileum (the terminal portion of the small intestine) into the cecum is the ICV [1]. The cecum is located below a transversal plane running along the ileocecal-colic sphincter (Fig. 1.1). It forms a rounded sac between 6 and 10 cm long, with an internal diameter of 5–6 cm and a capacity of 200–300 ml. Three teniae coli enfold this region, defined as anterior, posterolateral, and posteromedial on the basis of their position. The posteromedial tenia coli forms the entrance into the terminal ileum. The longitudinal axis of the cecum and that of the right colon together create an obtuse angle that opens forward and medially. The cecum is lodged together with the terminal ileum and is completely covered by the peritoneal wall. It is separated from the ileum by the ICV (also called the Bauhin valve), which is composed of two segments—an upper lip and a lower lip—that are formed by intrusion of the circular muscle layer of the ileum into the lumen of the large intestine. A narrow membranous ridge continues at the ends of the aperture medially and laterally, where the lips meet, giving rise to the frenula of the valve. The circular muscle fibers of the ileum and those of the cecum combine to form the circular sphincter muscle of the ICV, whose role is to limit the rate of food passage into the cecum and to prevent material from returning to the small intestine. The valve acts through the contraction of the frenula in response to overstretching of the cecum, but it has minimal sphincteric action, a fact that explains the common observation of barium reflux into the terminal ileum during a barium enema examination. Intestinal occlusion results in a persistent contraction of the ICV, with consequent rupture of the cecum (called diastasis rupture), or its relaxation, with continuous reflux of the feces and the overstretching of the terminal ileum. The ileum comprises three-fifths of the small intestine, although there is no absolute point at which the jejunum ends and the ileum begins. In broad terms, the jejunum occupies the upper left part of the abdomen below the subcostal plane (that is, at the level of the 10th rib), while the ileum is located in the lower right part. It has numerous convolutions and is attached to the posterior abdominal wall by the mesentery, an extensive fold of serous-secreting membrane that is missing at the level of the terminal ileum, thereby determining its complete mobility in the abdominal cavity. The arterial blood supply to the large intestine comes from branches of the superior and inferior mesenteric arteries (both of which are branches of the

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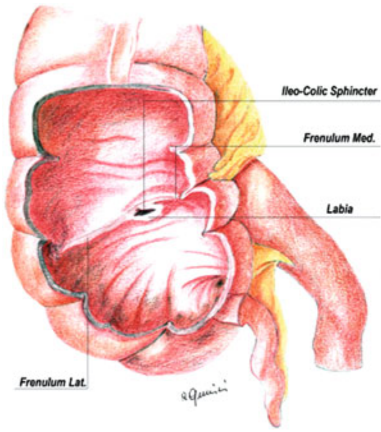

Fig. 1.1 The anatomy of the ileocecal region

abdominal aorta) and the hypogastric branch of the internal iliac artery (which supplies blood to the pelvic walls and viscera, the genital organs, the buttocks, and the inside of the thighs). The vessels form a continuous row of arcades from which vessels arise to enter the large intestine. Venous blood is drained from the colon via branches that form arcades, analogous to those of the arteries. The blood from these veins eventually drains into the superior and inferior mesenteric veins, which ultimately join with the splenic vein to form the portal vein. The ileocecal region has both parasympathetic and sympathetic innervation. The vagus nerve provides parasympathetic innervation. Sympathetic innervation is provided by branches of the superior mesenteric plexus, a nerve network underneath the solar plexus that follows the blood vessels into the small intestine and finally terminates in the Auerbach plexus, which is located between the circular and longitudinal muscle coats, and in the Meissner plexus, which is located in the submucosa. Numerous fibrils, both adrenergic (sympathetic) and cholinergic (parasympathetic), connect these two plexuses.

1.3 Ileocecal Valve Appearances

The ICV may show a spectrum of normal findings at double-contrast barium enema, appearing as a round, ovoid, or triangular structure with a maximum height of nearly 4 cm. The valve may be large, asymmetric, or smoothly lobulated. In a series of 106 patients, the ICV was visible in 91 (86%), being round or ovoid in 71 patients (78%) and triangular in 20 (22%). At colonoscopy, all patients with a normal valve at double-contrast barium enema examination had a normal valve, whereas the two patients with a valve suspicious for tumor at barium enema examination had neoplasms (one carcinoma and one villous adenoma). In a comparative study between double-contrast barium enema and ileoscopy, a macroscopically normal appearance of the ICV was detected in 30 patients. Among these patients, 60% were diagnosed with mild, 26.7% with moderate, and 13.3% with severe endoscopic ileal inflammation. The ICV was affected by Crohn's disease (CD) in 70 patients, in whom significantly more severe ileal inflammation ($p < 0.005$) was detected than in patients with a normal-looking ICV. The authors of that study concluded that ileal exploration should be attempted in every patient suspected of having CD, because, although the appearance of the ICV correlates with the severity of ileal inflammation, a normal-looking ICV does not correspond to normal ileal mucosa in many cases [2].

At endoscopy, the ICV may be classified as labial, papillary, or lipomatous based on its morphologic appearance [3, 4]. The labial type has a slit-like opening, the papillary type is dome shaped, and the lipomatous type has a substantial deposit of fat within its lips. However, most non-lipomatous valves will demonstrate streaks of fat within the valve lips. Each ICV subtype may vary in appearance depending on whether the patient is prone or supine or whether the valve is open rather than closed. Another endoscopic classification defines the ICV with the cecum moderately inflated: thin lipped, when the fold has no bulge; single or double bulging, when one or two prominent bulges of the fold are present; and volcanic, when the fold is exuberant and the orifice is visible. Of these, the thin lipped morphology is the most difficult to intubate (Fig. 1.2).

1.4 Ileoscopy: Technique

The correct positioning of the colonoscope in the ileocecal region is an essential step in the intubation of the ICV. Straightening the colonoscope in the left but also in the transverse colon guarantees its good maneuverability, allowing easy passage into the ileum (Fig. 1.3). Once the ICV is reached, its position in the

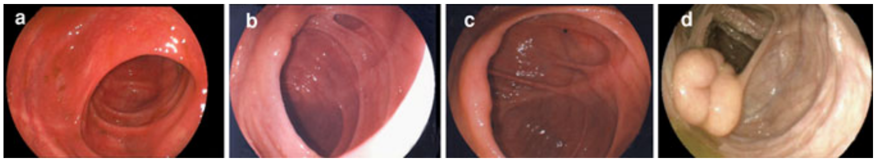

Fig. 1.2 The ileocecal valve morphology. **a** Thin-lipped or labial. **b** Single-bulge or papillary. **c** Double-bulge or papillary. **d** Volcanic or lipomatous

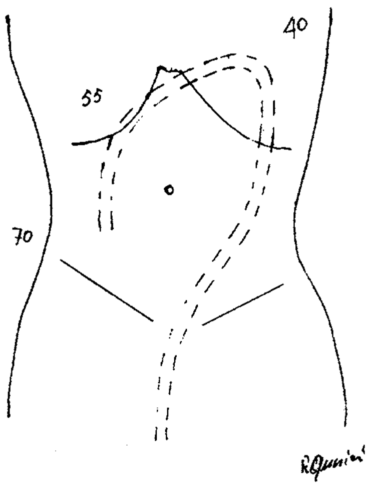

Fig. 1.3 The correct position of the colonoscope for ileoscopy

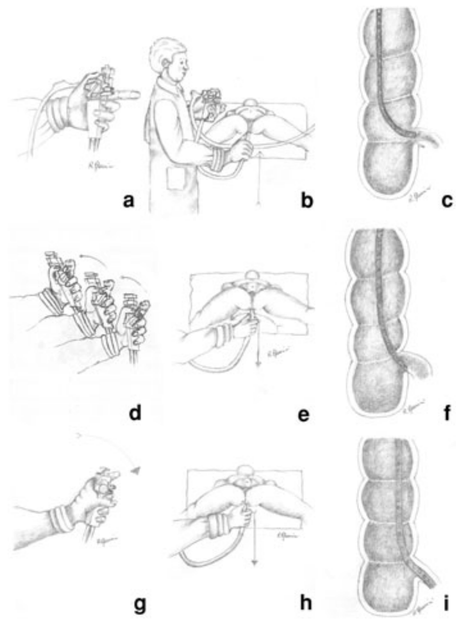

Fig. 1.4 **a**, **d**, **g** Manipulation of the scope using the *left hand* during ileal intubation. **b**, **e**, **h** Position of the patient and manipulation of the scope using the *right hand* during ileal intubation. **c**, **f**, **i** Position of the colonoscope within the intestinal lumen during the different steps of the procedure

intestinal lumen must be considered as well as the decubitus of the patient. With the patient supine and the ICV at the 9 o'clock position, downward deflection is recommended to stretch the lower lip, and anti-clockwise torque with the left hand gently accompanying the scope toward the left (Fig. 1.4). When the patient is in left lateral decubitus, the ICV appears in the 6- or 7-o'clock position and passage into the ileum can be achieved with the same maneuvers. Sometimes the ICV is positioned in the 12- to 1-o'clock position and a combination of upward deflection and clockwise torque (opposite from that described above) may be necessary. In case of a thin-lipped valve, which, as noted above, is the most difficult one to intubate, due to difficult visualization of the upper and lower lips, a retroversion of the tip of the scope in the cecal region can help to identify the valve. In this case, the scope is withdrawn and the tip is straightened, before the instrument is advanced into the ileum (Fig. 1.5). Once the endoscope has entered in the ileal lumen, the ileum must be insufflated with a good amount of air in order to position the scope, avoiding its retreat into the cecum [5, 6]. The use of hyoscine-n-butyl bromide reduces bowel motion and may also facilitate ileal intubation [7]. Exploration of the last 10–15 cm of the ileum is always possible, with advancement of the scope facilitated by abdominal compression. The reported incidence of complications during ileoscopy is essentially null, both in unsedated and sedated patients, especially if the use of biopsy forceps to intubate a difficult valve or insufflating large amounts of air in the ileocecal region is avoided [8–11]. Once the scope is in the ileal lumen, its withdrawal, accompanied by a moderate insufflation of air,

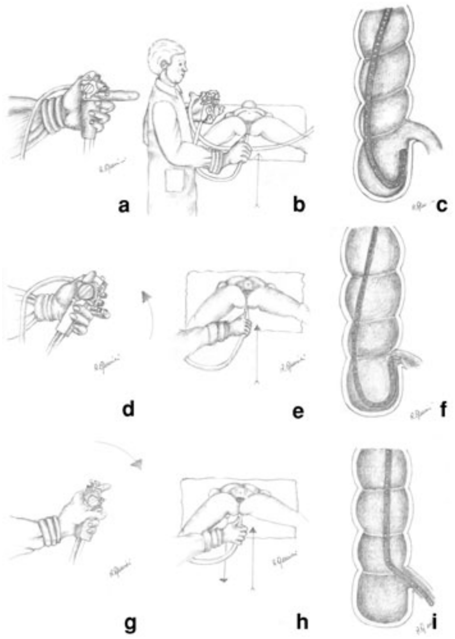

Fig. 1.5 **a**, **d**, **g** Manipulation of the scope using the *left hand* during ileal intubation. **b**, **e**, **h** Position of the patient and manipulation of the scope using the *right hand* during ileal intubation. **c**, **f**, **i** Position of the colonoscope within the intestinal lumen during the different steps of the procedure

enables an accurate evaluation of the endoscopic appearance of the terminal ileum, searching for the presence of hyperemia, aphthoid lesions, erosions, or ulcers. The standard view cannot describe the morphology of the general villous architecture, which instead can be outlined only after the injection of 10–15 ml of saline through the biopsy channel, as confirmed in a prospective, observational study on 216 consecutive completed colonoscopies in which the images of the terminal ileum were significantly more likely than cecal images to be considered convincing in order to verify the extent of colonoscopy ($p < 0.0001$ for all reviewers). The instillation of sterile water in the intestinal lumen was considered by the authors as a prerequisite to obtain accurate photodocumentation [12].

1.4.1 Magnified Ileoscopy

The important clinical results obtained with magnifying endoscopy for the detection and definition of early colorectal cancer led us to reproduce this technique for

Table 1.1 Magnified ileoscopy technique

Step 1: Washing the mucosa with a mucolytic agent
Step 2: Dye-spraying with a solution of 5–8 ml of indigo carmine 0.4%
Step 3: Magnifying view
Step 4: Endoscopic evaluation

Table 1.2 Virtual magnified ileoscopy technique

Step 1: Washing the mucosa with a mucolytic agent
Step 2: Filling the lumen with saline
Step 3: Activating virtual chromoendoscopy
Step 4: Magnifying view
Step 5: Endoscopic evaluation

the study of the terminal ileum (magnified ileoscopy, Table 1.1) [13]. The steps of the procedure are similar to those followed for the colon, including washing the mucosa with mucolytic agents in order to enhance the villous profile and then spraying the lumen with dye (5–8 ml of indigo carmine 0.4%). The dye, with its capacity to pool in any minimal depression, further enhances the villous profile, highlighting the presence of lymphoid follicles and the subtotal or total atrophy of the terminal ileum. The endoscopist, after an accurate evaluation of the sprayed mucosa, can scan the region, identifying the pathological area for study and performing a target biopsy. Magnified ileoscopy allows a much more accurate study of the terminal ileum. It can be used to determine the presence of even subtle changes of the mucosa, such as hyperemia, and of small aphthoid or erosive lesions, which can be missed at conventional view. It also reveals the villous morphology, including the size of the villi, and potential atrophy of the terminal ileum, neither of which are seen on conventional endoscopy. Caution must be exerted by the endoscopist to avoid spraying too much dye, because it can alter the visualization of the mucosa with backflow to the ileocecal region, thus compromising the inspection of this area.

1.4.2 Virtual Chromoendoscopy

Virtual chromoendoscopy, called narrow-band imaging (NBI), represents another aid to the endoscopist. The NBI system makes use of optical filters within the

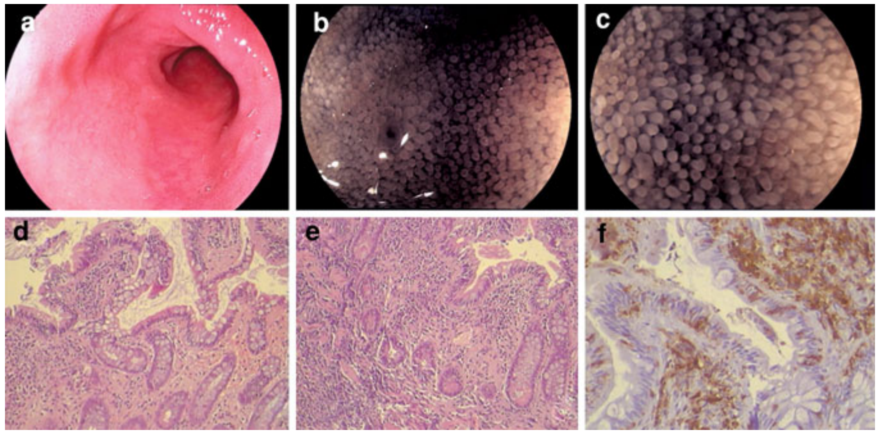

Fig. 1.6 Normal villous morphology. **a** Conventional view of the terminal ileum with normal finding. **b**, **c** Virtual magnified ileoscopy shows the normal villous pattern, with evidence of a single lymphatic follicle. **d**–**f** Histology of the normal villous morphology

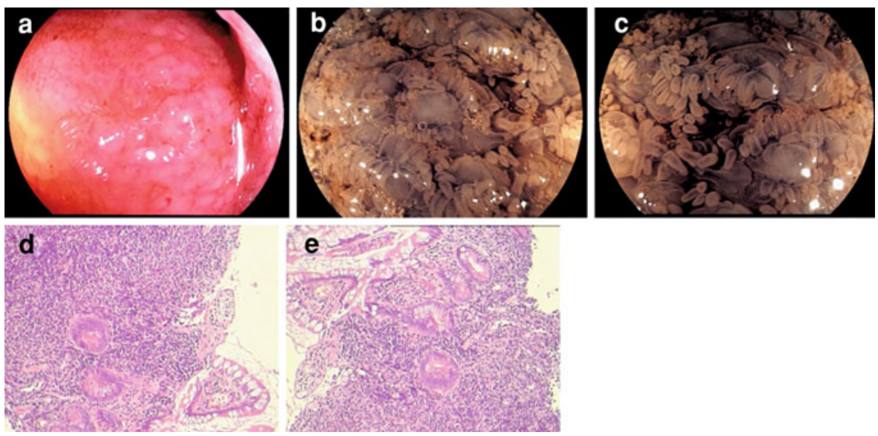

Fig. 1.7 Normal villous morphology with evidence of multiple lymphatic follicles. **a** Conventional view of the terminal ileum, showing diffuse hyperemia. **b**, **c** Virtual magnified ileoscopy with normal villous pattern and multiple lymphatic follicles. **d**, **e** Histology shows non-specific ileitis

light source of a videoendoscope, selecting light in short and limited wavelengths within the hemoglobin absorption band. The most recent development is computed virtual chromoendoscopy imaging, invented by Yoichi Miyake (Faculty of Engineering, Chiba University, Chiba, Japan) and introduced by Fujinon as Fujinon Intelligent Color Enhancement (FICE). FICE is based on the same physical principle as NBI, but due to a new computed spectral estimation technology it is not dependent on optical filters. The FICE technology takes an ordinary endoscopic image from the video processor and arithmetically processes the reflected photons to reconstitute virtual images by increasing the relative intensity of narrowed blue (B) light to a maximum and decreasing narrowed red (R) and green (G) light to a minimum. FICE successfully realizes enhancements and real-time observations of mucosal and microvascular patterns [14–17]. By cutting off the longer wavelengths, FICE improves the contrast of the capillary patterns and enhances the structure of the mucosal surface. Virtual chromoendoscopy thus provides dyeless contrast and constitutes an easy-to-use diagnostic technology. The digital processing system allows switching between conventional images and FICE-NBI images by a simple push of a button on the endoscope [18, 19] (virtual magnified ileoscopy; Table 1.2, Figs. 1.6 and 1.7).

1.5 Conclusions

Terminal ileoscopy during colonoscopy is of pivotal importance for the detection and definition of ileal pathology. The endoscopist should be familiar with the ileocecal anatomy and with the different possible morphologies of the ICV. Following brief but indispensable training, proficiency in ileal intubation can be achieved after 50 procedures. The principles of the technique should be kept in mind by both the trainee and the expert in order to simplify intubation of the last 20 cm of the ileum. A broad spectrum of ileal diseases can be excluded during investigation of this region, which has been significantly improved by the contribution of recent technological advances, mainly magnified ileoscopy.

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2 The Importance of Complete Colonoscopy and Exploration of the Cecal Region

Kuangi Fu, Takahiro Fujii, Takahisa Matsuda, and Yutaka Saito

2.1 The Importance of a Complete Colonoscopy

Ever since case-control studies demonstrated the ability of flexible sigmoidoscopy (FS) to decrease colon cancer mortality by 60–70%, it has become the most frequently recommended modalities for colon cancer screening [1]. Recent reports, however, have shown that FS may miss proximal neoplasms or cancers [2]. Moreover, the National Polyp Study found that the incidence of colorectal cancer (CRC) in an adenoma-bearing cohort that had undergone clearing colonoscopy was reduced by 76–90% compared to reference populations [3]. It is obvious that examination of the left colon alone misses right-sided lesions. Thus, while colonoscopy is more time-consuming and resource-demanding, in addition to causing greater patient discomfort and with a higher rate of complications due to bowel cleansing and the endoscopic procedure, it is widely appreciated as the most sensitive colonic imaging test for adenomas. An additional advantage of colonoscopy is that it allows the removal of precancerous polyps at the time of their detection.

A right-sided aging-related shift in the location of the initial development of colorectal adenomas was recently reported, based on repeated colonoscopies in subjects with no neoplasms [4]. Recurrent adenomas after polypectomy also tend to develop at locations proximal to the initial adenomas [5]. Accordingly, total colonoscopy is needed for surveillance, regardless of the initial adenoma site. Moreover, the distribution of carcinoma and of adenomatous polyps in the colorectum likewise shows a proximal shift with age and female gender [6, 7]. Clinically, right-sided cancer is likely to be detected at a more advanced stage, with severe symptoms such as passage trouble or abdominal mass. Morphologically, the frequency of tumors with a flat-type appearance is significantly higher in right-sided than in left-sided colon cancers, while polypoid-type lesions are substantially more dominant in the left colon [8]. Histopathologically, poorly differentiated, mucinous, and signet-ring cell tumors are frequently seen in the right colon [9]. From a molecular aspect, the right-sided tumors that predominate in the elderly are those with a high frequency of CpG island methylation and those with microsatellite instability (MSI), in which there is often methylation of the promoter region of the hMLH1 mismatch repair gene [10]. A newly proposed disease entity, serrated polyps, comprises hyperplastic polyps, traditional serrated adenomas (TSAs), and sessile serrated adenomas (SSAs), which have also been described as sessile serrated polyps (SSPs) [11]. SSAs/SSPs are more prevalent in the proximal colon and lack classic dysplasia but may have mild cytologic atypia, whereas TSAs are more prevalent in the rectosigmoid and have cytologic dysplasia. SSAs/SSPs, particularly those with foci of classic histologic dysplasia, are considered the likely precursor lesions to sporadic MSI-H colon cancer, as determined in studies of their molecular profiles, which have shown inactivation through methylation of genes such as the MLH-1 DNA repair genes and/or

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Table 2.1 Endoscopic treatment at the National Cancer Center Hospital, Tokyo, Japan (January 1998 until September 2006)

	Adenoma (14,285)	M-Ca (1,717)	SM-Ca (302)	Total (%)
Cecum	860 (87.2%)	119 (12.1%)	7 (0.7%)	986 (6.0)
Ascending	2,942 (90.2%)	283 (8.7%)	35 (1.1%)	3,260 (20.0)
Transverse	4,004 (93.3%)	244 (5.7%)	42 (1.0%)	4,290 (26.3)
Descending	1,723 (92.8%)	122 (6.6%)	11 (0.6%)	1,856 (11.4)
Sigmoid	3,298 (84.2%)	513 (13.1%)	104 (2.7%)	3,915 (24.0)
Rectum	1,458 (73.0%)	436 (21.8%)	103 (5.2%)	1,997 (12.3)
Total (%)	14,285 (87.6)	1,717 (10.5)	302 (1.9)	16,304 (100.0)

0-6-methylguanine DNA methyltransferase (MGMT) [12]. The presence of SSAs/SSPs (≥10 mm in size) is also reported to be a risk factor for CRC, particularly of the proximal colon [13].

2.2 The Importance of Exploring the Cecum

It has been known for many years that colorectal adenoma and CRC have different distributions in the colon. The anatomic distribution of adenomas in the colon was described in previous reports (e.g., [14]) that included autopsy and endoscopic studies. Autopsy studies show a relatively even distribution of adenomas throughout the colon whereas cancer is more frequent in the distal colon and rectum. In those studies, the incidence of adenomas located in the cecum varied from 2 to 67%. However, in some reports fewer than 200 cases were evaluated. By contrast, endoscopic studies evaluated more than 200 cases (one was based on 6,942 cases), reporting cecal adenomas in 2–20%. Based on data from the National Cancer Center, the incidence of early colorectal neoplasia involving the cecum, as determined from tumors resected endoscopically, is 6.0% (Table 2.1) whereas the incidence of CRCs located in the cecum, as determined from surgically removed tumors, is 6.8% (Table 2.2). Although the incidence of colorectal neoplasia in the cecum is lower than in other sites, it should be kept in mind that some non-polypoid neoplasias, including SSAs/SSPs or laterally spreading tumor, can occur at this site, especially at the periphery of the appendiceal orifice, and are endoscopically detectable. Obviously, visualization of the appendiceal orifice and ileocecal valve confirms a complete total colonoscopy.

2.3 Case Presentation

2.3.1 Case 1

A 74-year-old woman underwent total colonoscopy because of a positive fecal occult blood test. During conventional endoscopic observation, a superficially reddish area was detected on the ileocecal valve (Fig. 2.1a). Narrow-band imaging revealed a flat brownish lesion (Fig. 2.1b). Chromoendoscopy, performed using indigo-carmine spraying, further demonstrated a non-granular type of laterally spreading tumor (LST-NG), 20 mm in diameter, on the ileocecal valve (Fig. 2.1c). Magnification with chromoendoscopy using indigo-carmine and crystal-violet staining showed a type IIIL pit pattern, according to Kudo's classification, which is a good indication for endoscopic resection (Fig. 2.1d, e). The tumor was completely removed en bloc with endoscopic submucosal dissection (Fig. 2.1f). Histologically, the lesion was identified as a tubular adenoma with high- and low-grade atypia, with the cut end free of adenoma.

2.3.2 Case 2

A 48-year-old man underwent total colonoscopy because of a positive fecal occult blood test. A flat elevated lesion was detected in the cecum near the orifice of the appendix (Fig. 2.2a). Chromoendoscopy using indigo-carmine day spraying showed a lesion covered by a small amount of mucus, even after vital water washing (Fig. 2.2b). Magnification after chromoendoscopy revealed an elongated type II pit pattern at the periphery, with features similar to those of a type IIIL pit pattern (Fig. 2.2c). A dilated type II pit pattern

Table 2.2 Surgery at the National Cancer Center Hospital, Tokyo, Japan (January 1998 until September 2006)

	Early (618)	Advanced (2,651)	Total (%)
Cecum	39	183	222 (6.8)
Ascending	73	322	395 (12.1)
Transverse	58	215	273 (8.4)
Descending	26	117	143 (4.4)
Sigmoid	166	660	826 (25.3)
Rectum	256	1,154	1,410 (43.0)
Total (%)	618 (18.9)	2,651 (81.1)	3,269 (100.0)

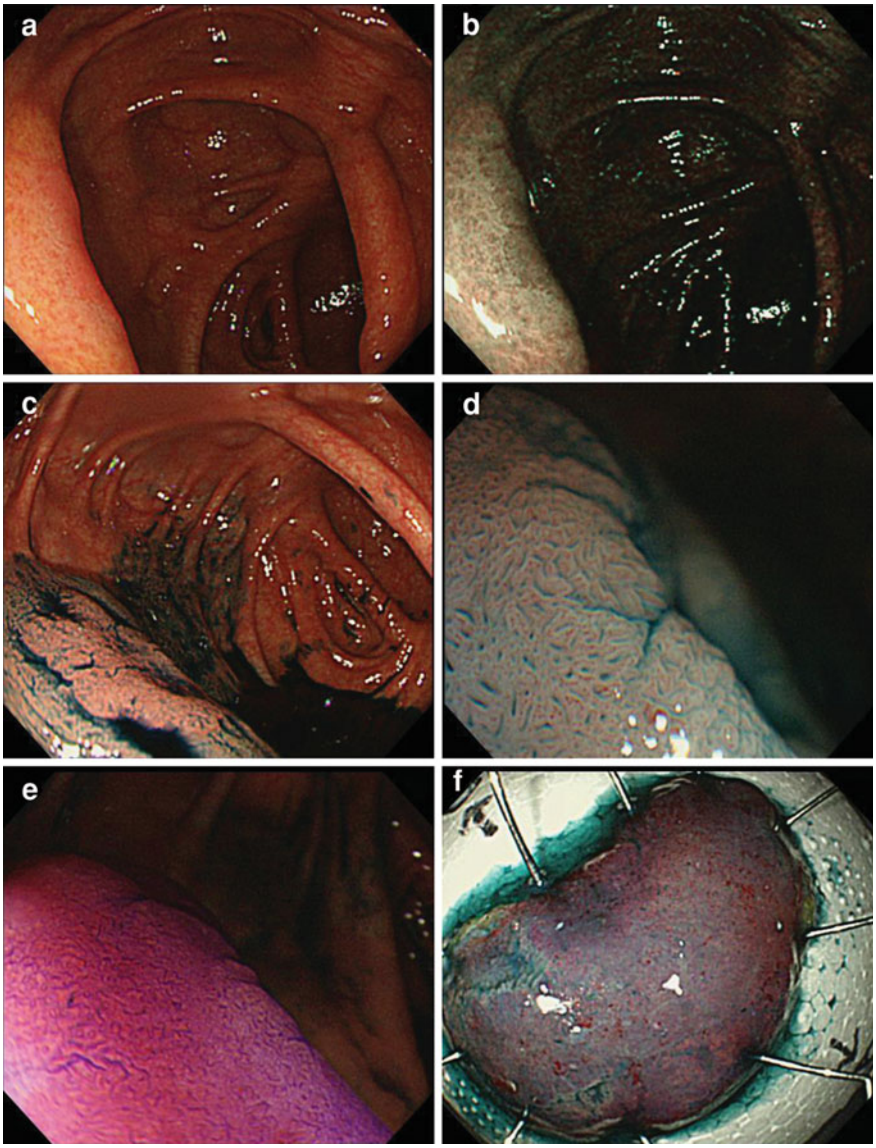

Fig. 2.1 **a–f** A non-granular type of laterally spreading tumor (LST-NG), 20 mm in diameter, is seen on the ileocecal valve

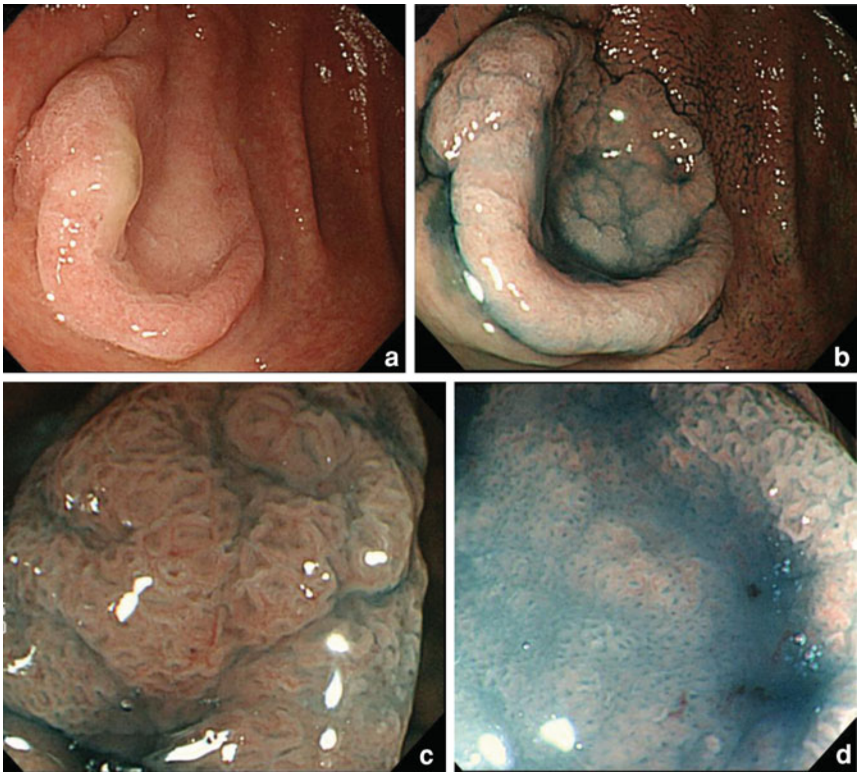

Fig. 2.2 a–d A sessile serrated adenoma/polyp is detected in the cecum adjacent to the orifice of appendix

was detected in the central flat area (Fig. 2.2d). These endoscopic results suggested a large hyperplastic polyp, or an SSA/SSP. The lesion was completely removed en bloc with endoscopic mucosal resection (the conventional lift and cut technique). Histologically, the lesion was identified as an SSA/SSP.

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