Endoscopy in Early Gastrointestinal Cancers, Volume 2

Treatment

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Editors

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Foreword

Here, I am very much pleased to introduce this book entitled *Endoscopy in Early Gastrointestinal Cancers* from Springer. This book consists of two parts, that is, Volume I focuses on “diagnosis” and Volume II focuses on “treatment.” All the contributors of this book are the members of ANBIIG (Asian Novel Bio-Imaging and Intervention Group). I would like to mention introductory remarks for Volume 2—*Treatment* in the preface here.

The history of endoscopy over the past three decades has been marked by steady and rapid progress in endoscopic treatment, arising from the development of the video endoscope in 1983, which resulted in more progress in the subsequent years. The period during the 1980s was characterized by improvements in endoscopic treatment of early gastrointestinal cancers using endoscopic mucosal resection (EMR). In the 2000s, the rapid dissemination of endoscopic submucosal dissection (ESD) has led to further advances in endoscopic treatment, while the introduction of the HDTV endoscope to the market in 2002, together with more recent innovations such as image-enhanced endoscopy (IEE) and magnifying endoscopy, has provided the basis for new diagnostic study.

Historically, ANBIIG was founded as non-governmental organization (NGO) in 2013. At first, the workshops have been conducted more than 45 times during the first 4 years, and more than 2000 young doctors received comprehensive training. Throughout the training, we came to realize the necessity to establish an actual consensus on how much Asian practitioners have common knowledge of endoscopic diagnosis related to IEE.

“ANBIIG Consensus Meeting” was started in January 2016, aiming to figure out the consensus in the Asian present situation in the field of endoscopic diagnosis of early gastrointestinal cancers. The policies of ANBIIG activities comprise the aim, the means, and also the performers taking part in health care practices. These policies were “Originated in Asia,” “Developed by Asia,” and “Optimized for Asia.” We set our destination to be most suitably optimized and implemented in Asia. In reality, there is a big difference between Asian and Western countries in many ways, such as the frequency of disease, ways of thinking, and practices.

We, having charge of clinical practices in Asia, are striving to provide meaningful results from our research by Asian endoscopists, widely. Back in the day, we used to learn most of medicine from Western countries. However, I believe that we have now reached “Asian Endoscopic Revolution.”

I would like to emphasize that the importance and benefits of ANBIIG Consensus in Asia are being realized now. For example, IEE diagnosis was unified as Asian Guideline, which is to deliver consistent diagnostic procedures as daily practices with the same contexts, to prevent any deviations in teaching and learning procedures, skills, and knowledge on IEE and also to optimize IEE practices in Asia. It is important to lift up the level of standard in the field of Asian endoscopic diagnosis, which will lead to an early diagnosis and treatment. Also, it is expected that Asian endoscopic medicine will develop and expand globally from now.

I regard this consensus as the best compass for the journey on "Asian IEE Ocean," which certainly guides young and ambitious Asian practitioners to master IEE diagnosis. And it will increase the number of IEE practitioners in Asia for sure.

In this book, based on the above background, indication for endoscopic resection of early GI cancers, real procedure of endoscopic mucosal resection (EMR), real procedure of endoscopic submucosal dissection (ESD), management of non-curative resection and local recurrence after endoscopic resection, complications of endoscopic resection, and management for each organ are stated by experts in an easy to understand and detailed manner. In the last chapter, special ESD case illustrations are mentioned for every country as in Japan, China, Korea, and Hong Kong SAR, which makes it educational and fascinating.

I hope that doctors who are about to start ESD, those who are confronted with difficulties during conducting ESD in real, and also those who are at the side to direct ESD would read this book of practices widely in Asia. And then, all those doctors can enter the matured world of endoscopic resection of early GI cancers and perform your value in advanced level. It would be grateful for me if those who read this book could heal as many patients as they could as one of skillful practitioners of Asia Pacific Society for Digestive Endoscopy.

I believe that the contents covered by this book will give our readers the confidence to take on the unity of clinical medicine in the field of endoscopic diagnosis, which has surmounted the problems associated with conventional manners, and advance new functional studies.

Finally, I would like to express my deepest gratitude to the many doctors and compiling staff who contributed to this book even though they were very busy.

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Foreword

I wish to congratulate the success of experts from the Asian Novel Bio-Imaging and Intervention Group (ANBIIG) to publish these important books on diagnostic and therapeutic for early gastrointestinal cancers. Gastrointestinal cancers are among the commonest cancers worldwide with significant risks in cancer-related mortality. Gastric and esophageal cancers had been an important cause of cancer mortality in Asia, with 70% of patients with gastric cancers coming from Asia. Recently, there is an increase in the number of patients diagnosed to have colorectal cancers worldwide which incurs concerns from gastroenterologists, surgeons, oncologists as well as the government in diagnosis and treatment of these cancers. To impact on the prognosis, it is essential to diagnose these gastrointestinal cancers at an early stage.

Image-enhanced endoscopy had been tremendously advanced over the past decade, with the clinical application of technologies including narrow band imaging and magnifying endoscopy demonstrating the effect of improving recognition and characterization of early gastrointestinal cancers. The mission of ANBIIG is to provide a learning platform for education and training of novel endoscopic imaging and therapeutic technologies for Asian endoscopists. I must congratulate the success of ANBIIG in achieving this goal, as more than 110 workshops in Asia, providing training for more than 7,000 healthcare professionals. Moreover, two consensus papers were published on standards and quality of endoscopy for diagnosis of early gastrointestinal cancers.

One of the important initiatives for education and training of ANBIIG is to publish two books focusing on the diagnosis and endoscopic treatments. These books served as important educational material to propagate exchange of knowledge in these areas. Serving as an advisor for ANBIIG, I am delighted to see these books published with high quality in the content.

With the current advances in artificial intelligence and robotics, I look forward to future technological advances in diagnosis and treatment of early gastrointestinal cancers as well as additional chapters on these topics in the second edition of these books.

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Contents

1 Overview

Takuji Gotoda

Abbreviations

EGC	Early gastric cancer
EMR	Endoscopic mucosal resection
EMRC	EMR with cap-fitted panendoscope method
EMRL	EMR using multiband ligation
ESD	Endoscopic submucosal dissection
IT knife	Insulated-tip diathermic knife
LNM	Lymph node metastasis

Endoscopic resection for early gastrointestinal cancer is the most satisfactory treatment option, because of its minimally invasive curative potentials [1]. Endoscopic resection enables complete pathological staging of cancers that are important for metastatic potential [2]. Patients stratified as having no or lower risk of lymph node metastasis (LNM) than the risk of surgical mortality are ideal candidates for endoscopic resection [3, 4]. The optimal staging method for early gastrointestinal cancer is to assess the pathology through one-piece resected material [5, 6]. In addition, one-piece resection with negative vertical and horizontal margins is to reduce the risk of locally recurrent disease.

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The first endoscopic resection was reported with colorectal polypectomy using a radiofrequency electrosurgical unit in 1973 [7]. The first endoscopic polypectomy used to treat pedunculated or semipedunculated early gastric cancer (EGC) was reported in Japan in 1974 [8].

The "strip biopsy," as an early method of endoscopic mucosal resection (EMR), was devised in 1984 [9]. A technique called ERHSE (endoscopic resection with local injection of hypertonic saline epinephrine solution) was developed in 1988 to obtain excised material with less tissue damage that causes proper pathological staging [10]. EMR with cap-fitted panendoscope method (EMRC) was developed in 1992 for the resection of early esophageal cancer and can be applied directly to resection of EGC [11, 12]. EMR technique using ligation was then extended to EMR using multi-band ligation (EMRL), utilizes band ligation to create a "pseudopolyp" [13, 14]. The EMRC and EMRL techniques were having the advantages of being relatively simple and safe. However, these methods cannot be used to remove lesions larger than 2 cm in one piece [15, 16]. Fragmental excision of lesions larger than 2 cm increases the risk of local cancer recurrence and inappropriate pathological staging [17, 18].

Insulated-tip diathermic knife (IT knife) was devised to improve one-piece resection rate of endoscopic resection for EGC at the National Cancer Center Hospital Japan in the late 1990s. IT knife has a ceramic ball tip, which prevents

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perforation from puncturing the wall during the application of cautery. The knife was also applied to be used for dissecting the submucosa directly, then leads to the name of endoscopic submucosal dissection (ESD) methods, which is now widely known and clinically used [19–21]. Subsequent studies have reported that ESD is effective for endoscopic resection of large lesions “one-piece” and allowing a proper pathological staging. Anyway, one-piece endoscopic resection regardless of tumor size, location and/or submucosal fibrosis can be now possible [22]. However, all steps should be carried out by standard single-channel endoscope, which means ESD requires higher endoscopic tricks. Very recently, ESD has been tried to improve an easier procedure using several supportive devices [23, 24].

The major advantage of endoscopic resection is the ability to provide an accurate pathological staging without precluding future surgical therapy [25, 26]. After endoscopic resection, pathological assessment of depth of cancer invasion, degree of cancer differentiation, and involvement of lymphatics or vessels allows the prediction of the risk of LNM [27]. The risk of developing LNM or distant metastasis is then weighted against the risk of surgery [28, 29]. However, endoscopic resection, which is local treatment without lymph node dissection presents important tradeoffs such as less morbidity but also causing a higher risk of metachronous diseases during the follow-up periods [30]. Patients’ preferences and particularly fear of recurrence is an important element in choosing the optimal therapy.

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2 Indication for Endoscopic Resection of Early GI Cancers: Esophagus

Kenichi Goda

Esophageal cancer has two main subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC is the predominant form and accounts for 90%. However, for the last few decades, a shift in the epidemiology has been seen in the West, where the incidence of adenocarcinoma currently exceeds that of squamous cell types, particularly among white men [1, 2].

Patients with esophageal carcinoma, including advanced-stage cancer, have a poor prognosis. The overall 5-year survival of patients with esophageal carcinoma ranges from 15 to 25%. In contrast, the disease-specific 5-year survival rate of patients with early-stage cancer is excellent, 100% for mucosal squamous cell carcinomas [2]. Diagnoses made at earlier stages are associated with better outcomes than those made at later stages [3].

Surgical treatment such as esophagectomy has been played a central role for esophageal cancer. Esophagectomy, however, is significantly invasive therapy which has the risks for operative mortality even in the minimally invasive esophagectomy [4]. Esophagectomy inevitably leads to dysphasia and lowers the quality of life for the patients.

Endoscopic resection (ER) is the lowest invasive therapy which can be a curative treatment for the patient with early-stage esophageal carcinoma [1]. Understanding of indication for endoscopic resection is very important because incorrect estimation of the indication will result in a non-curative resection that delays additional treatment or may increase the risk for local or metastatic recurrence.

No clinical evidence of lymph node (cN0) or distant (cM0) metastases by pretreatment imaging (CT, MRI, or EUS) is an important indication because endoscopic resection enables only local removal of a cancerous lesion. A metastasis rate of the regional lymph node increases in proportion with invasion depth. Thus, predicting invasion depth is crucial for determining the precise indication for endoscopic resection [5, 6]. Metastasis rates of the regional lymph node were established by a large number of surgical resection cases with extensive histological investigations [5–8]. High-grade intraepithelial neoplasms (HGINs) were included in noninvasive squamous cell carcinomas (carcinoma *in situ*, T1a-EP). Relationships among subclassification of invasion depth of superficial esophageal SCC (Fig. 2.1), the rate of lymph node metastasis, and the indication of ER are listed in Table 2.1.

Tumor depth up to the lamina propria mucosa (T1a-EP or -LPM) having a lymph node metastasis rate of 0% or negligible (≦3.3%) is an absolute indication. The invasion depths of muscularis mucosa (T1a-MM) and micro-submucosal invasion of ≤200 μm (T1b-SM1) are suggested

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Fig. 2.1 Subclassification of invasion depth of superficial esophageal squamous cell carcinoma

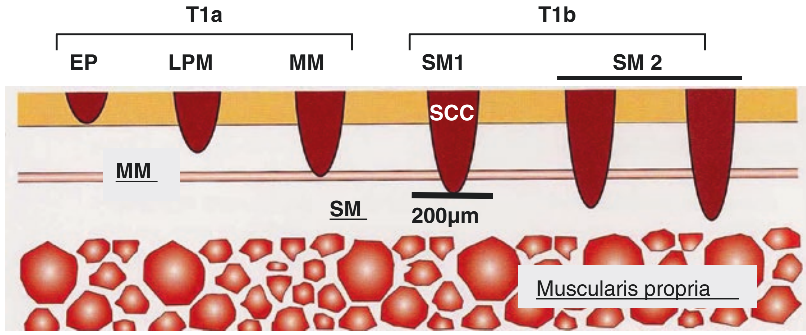

Table 2.1 Relationships among subclassification of invasion depth of superficial esophageal squamous cell carcinoma, the rate of lymph node metastasis, and the indication of endoscopic resection (ER)

T stage	Depth	LN metastasis (%)	Indication for ER
T1a	EP Ca *in situ* ⊇ HGIN	0	Absolute
	LPM Lamina propria mucosae	0 (≦3.3)	
	MM Muscularis mucosa	0~12.2 (0%: G1 or 2, ly0, v0)	Relative
T1b	SM1 ≤ 200 μ	8~26.5 (0%: G1 or 2, ly0, v0)	
	SM2	22~61	Investigative

EP, Carcinoma in situ (Tis) includes high-grade intraepithelial neoplasia (HGIN), *LPM*, Tumor invades lamina propria mucosa, *MM* Tumor invades lamina muscularis mucosa, *SM1* Tumor invades the submucosa to a depth of 200 μm or less from the muscularis mucosa, *SM2* Tumor invades the submucosa to a depth more than 200 μm; G1 or 2: Not having both of high-grade nuclear atypia and infiltrative growth pattern

as a relative indication because lymph node metastasis rates of the tumors are 0~12.2% and 8~26.5%, respectively, and 0% in the cases without high-grade nuclear atypia, infiltrative growth pattern, and vascular invasion (ly0, v0). The tumors with substantial submucosal invasion (SM2, deeper than 200 μm) having a lymph node metastasis rate of 22~61% is suggested as an investigative stage (functionally speaking, a contraindication) [5, 8]. The latest guideline recommended that additional treatment with surgical resection or chemoradiotherapy is strongly recommended in patients with "T1a-MM with positive vascular invasion" and "pT1b-SM including SM1" following endoscopic resection [9].

The former Japanese guideline showed that an absolute indication is limited to lesions of less than two-thirds of the circumferential extension because circumferential extension affects technical resectability as well as the risk of postoperative stricture after endoscopic resection [10, 11]. The reasons are as follows: Improved ER skill allowed removal of extensive circumferential tumors and the prophylactic method to prevent post-ER structure was developed by steroid use (oral prednisolone [12–14]. It, however, needs to know that full circumferential ER can occur refractory stricture even after steroid use.

With regard to esophageal adenocarcinoma (EAC), tumor depth in the mucosa (T1a) is subclassified into superficial muscularis mucosa (SMM), lamina propria mucosa (LPM), and deep muscularis mucosa (DMM) because double layers of the muscularis mucosa are often shown in Barrett's esophagus. EACs invading up to the DMM have been good indication for ER because studies indicated no or negligible lymph node metastasis rate (<5%, 0–4.7%) [15, 16]. Little is, however, known about lymph node metastasis rate if the tumor shows undifferentiated histological type and ulcer formation.

Aforementioned, Japanese guideline divided SCC submucosal invasion into SM1 and SM2 at the 200 μm from the MM, and SM1 is a relative indication for ER. However, SM1 has not defined clearly in EACs. Several studies on ER of early Barrett's cancer confined to SM1, 200 μm from the MM, showed excellent results with no death from EAC (0% of cause-specific mortality rate) during a follow-up period of approximately 3 years. Recent studies from Europe yielded encouraging results that showed that submucosal EAC with invasion depth up to 500 μm, no poorly differentiated component, and no vascular invasion may be included in the expanded indication (i.e., relative indication) for ER because of very low LN metastasis rate (0 or 2%) [17, 18]. A recent multicenter study in Japanese population also demonstrated no LN metastasis was detected in patients with mucosal cancer without vascular involvement and a poorly differentiated component or in patients with cancer invading the submucosa (1–500 μm) without vascular involvement (ly0, v0), a poorly differentiated component, and 30 mm in diameter [19]. These studies suggest that submucosal EAC (≦500 μm invasion) without risk factors have may be good candidates for relative indication criteria for ER.

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3 Indications for Endoscopic Resection of Early Gastric Cancer

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3.1 Introduction

Over the years, therapeutic endoscopy for early gastric cancer has advanced from endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD), dramatically increasing the rate of en bloc resection. In conventional EMR, lesions can be resected quickly, easily, and safely, but piecemeal resection may be necessary for large lesions and those accompanied by ulcer scar. Consequently, residual and recurrent tumors and inaccurate pathological diagnoses were major problems associated with EMR. In contrast, ESD enables en bloc resection of lesions that are considered difficult to resect en bloc by EMR [1]. The merits of en bloc resection are the reduced risk of residual and recurrent tumors and the accuracy of pathological diagnoses. However, the risk of accidental complications such as perforation and bleeding is higher in ESD than in EMR [2, 3], highlighting the importance of understanding the indications for endoscopic resection. The indications for endoscopic treatment depend on the risk of lymph node metastasis and the practicability of en bloc resection. Lesions with a risk of lymph node metastasis require surgery combined with lymph node dissection as a first-choice treatment option and should not be an indication for endoscopic treatment. This chapter explains the indications for endoscopic treatment of early gastric cancer and the procedures involved in determining these indications.

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3.2 Theoretical Indications

The most important prerequisite is that endoscopic treatment is indicated for only lesions with no risk of lymph node metastasis. Previous studies investigated the risk of lymph node metastasis in gastric cancer, but all were single-center studies [4, 5]. Subsequently, Gotoda et al. retrospectively examined a large number of patients (≥5000) treated with gastrectomy (surgical resection) and lymph node dissection to clarify the association between various pathological factors of primary cancer and lymph node metastasis, e.g., tumor invasion depth, tumor size, histological type, presence of ulceration, and vascular invasion [6]. They identified lesions that were not accompanied by lymph node metastasis and therefore could be cured by locoregional treatment, including therapeutic endoscopy. These indications were established based on postoperative pathological findings from surgical resection specimens, but the problem with these findings is that the pathological specimens were not prepared according to the conventional method used to prepare endoscopic resection specimens by sectioning at 2-mm intervals.

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In the first version of the gastric cancer treatment guidelines issued by the Japanese Gastric Cancer Association in 2001, differentiated-type mucosal cancer, ≤2 cm in diameter, and no accompanying ulceration were defined as absolute indications [7], and the guidelines recommended endoscopic treatment for this group of lesions. Then, lesions with a low risk of lymph node metastasis, such as those reported by Gotoda et al., were introduced into the second and later versions of the guidelines as expanded indications, promoting a wider application of ESD in clinical practice across Japan. In actual clinical practice, endoscopic treatment is indicated for the lesions as below [8], (1) mucosal lesions ≤3 cm in diameter, histologically of differentiated type with ulceration; (2) mucosal lesion, histologically of differentiated type, no size specification due to the absence of ulceration; (3) mucosal lesion ≤3 cm in diameter, histologically of undifferentiated type without ulceration; and (4) submucosal carcinoma 1 (SM1) ≤ 3 cm in diameter and histologically of differentiated type (Fig. 3.1). However, because of insufficient scientific evidence about the low risk of lymph node metastasis, the fourth version of the guidelines published in 2014 [9] recommended that a clinical study be conducted to investigate this group of lesions. To address the validity of this expansion of indications, the Japan Clinical Oncology Group (JCOG) conducted prospective multicenter studies on the JCOG 0607 (for differentiated-type cancer) and JCOG 1009/1010 (for undifferentiated-type cancer) trials. The JCOG 0607 study reported that differentiated-type mucosal cancer ≥2 cm in diameter without ulceration and differentiated-type mucosal cancer ≤3 cm in diameter with ulceration were not accompanied by lymph node metastasis, and therefore, they may be included in absolute indications for therapeutic endoscopy [10]. The JCOG 1009/1010 study is currently ongoing, and we look forward to the results. The fifth version of the gastric cancer treatment guidelines is scheduled to undergo revisions that include the categorization of indications into absolute, expanded, and relative indications. Absolute indication is defined as <1% (95% CI) of nodal metastasis plus long-term results similar to those of gastrectomy with lymphadenectomy. Expanded indication is defined as <1% (95% CI) of nodal metastasis, but lacking long-term results in similar with those of gastrectomy with lymphadenectomy. And early gastric cancer except the above criteria is defined as a relative indication. Standard treatment for the lesions in relative indication should be gastrectomy with lymphadenectomy. However, endoscopic treatment is taken into consideration, depending on the patient's status. After ESD, curability should be evaluated carefully using the ESD specimen (Fig. 3.2). In the light of the outcomes of the JCOG 0607 study, differentiated-type mucosal cancer of ≥2 cm

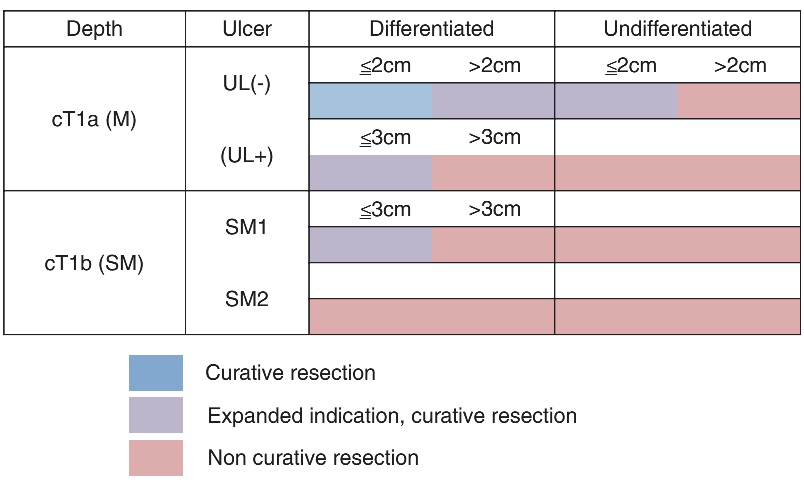

Fig. 3.1 Evaluation of curability of endoscopic resection proposed by Japan Gastroenterological Endoscopy Society

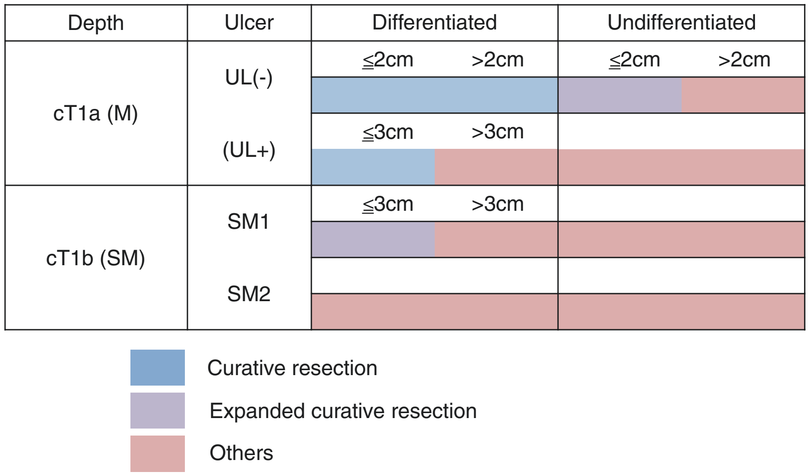

Fig. 3.2 Evaluation of curability of endoscopic resection in fifth edition of Japan Gastric Cancer Association guideline

without ulceration and differentiated-type mucosal cancer of ≤3 cm with ulceration are scheduled to be included in the absolute indications for endoscopic treatment. In another multicenter study, Hatta et al. graded five risk factors for lymph node metastasis among lesions that are currently excluded from the indications. Scores were set at 3 points for lymphatic invasion and 1 point each for ≥30 mm in diameter, positive vertical margin, venous invasion, and submucosal invasion >500 μm. A total score of 0–1 point was defined as low risk (2.5%), 2–3 points as intermediate risk (6.7%), and 5–7 points as high risk (22.7%) [11]. Thus, the indications for endoscopic treatment should be expanded with caution, but the expansion is anticipated to continue gradually in the future.

3.3 Technical Indications

As described in the previous section, the fundamental indication for endoscopic treatment is lesions with no risk of lymph node metastasis. However, from a technical point of view, the indications should be lesions that have no risk of lymph node metastasis and are resectable en bloc with negative margins. The size limit of lesions for en bloc resection is set at ≤20 mm for EMR. In recent years, most cases of early gastric cancer are treated with ESD in Japan, with progressively fewer chances of performing EMR. However, lesions located in the greater curvature of the stomach have a high risk of bleeding during ESD, increasing the technical difficulty. In contrast, these lesions are managed relatively easily in EMR owing to a better surgical view. EMR and ESD should, therefore, be used differentially and appropriately according to the location and size of lesions.

In ESD, en bloc resection is performed no matter how large the lesion is because there is no size limit. However, because the possibility of achieving curative resection decreases as the size of tumor increases, the diagnosis of tumor invasion depth and demarcation should be made carefully. Also in ESD, because large lesions can be resected, it is important to consider functional impairment after ESD. For example, various measures have been established for esophageal ESD because of the association between extensive resection and stricture [12, 13]. Extensive resection of the area involving the cardia and the pyloric antrum increases the risk of stricture even though the overall incidence of stricture is low in gastric ESD [14, 15]. Furthermore, extensive resection of the lower part of the stomach results in peristaltic dysfunction in some patients, resulting in difficulty with ingestion of food. Currently, technological advances allow extensive resection, so it is more important to consider postoperative functional outcomes before performing ESD.

3.4 Diagnostic Process for Determining Treatment Indications

Tumor invasion depth, tumor boarder, and tumor differentiation need to be carefully assessed and evaluated comprehensively when deciding the indications for endoscopic treatment of early gastric cancer.

3.4.1 Depth of Tumor Invasion

Tumor invasion depth in early gastric cancer is evaluated based on findings of white light endoscopy, with emphasis on surface irregularity, thickness, color tone, and converging rugae, interrupted rugae, peristalsis, and air-induced deformation. Abe et al. graded lesions according to margin elevation, tumor diameter (>30 mm), remarkable redness, and uneven surface using white light endoscopy, and reported the utility of their scoring system [16]. Because of the subjective nature of diagnosis made based on the findings of white light endoscopy, endoscopic ultrasound is used for more objective diagnosis. However, the utility of endoscopic ultrasound in diagnosing tumor invasion depth has been controversial, generating both positive and negative opinions [17–19]. Because the targets of ESD are small and shallow lesions, the use of a miniature scanning probe is recommended. Diagnosis of tumor invasion is made based on the recognition of a hypoechoic mass in the submucosal layer which is hyperechoic image. Evaluating invasion depth requires careful attention to the vascular structures in the submucosal layers because submucosal vasculature is an important predictor of intraoperative bleeding, and here lies the technical difficulty of ESD. Submucosal layers rich in blood vessels have a high risk of intraoperative bleeding, and thus may also be useful for surgical decisions and treatment schedules in addition to treatment indications [20, 21]. A small number of studies have reported that the narrow-band imaging with magnification endoscopy (NBI-ME) is useful for evaluation of invasion depth for early gastric cancer [22, 23], but this is still debatable. Our previous study showed that observation of dilated blood vessels in NBI-ME revealed a significantly high possibility of submucosal cancer. However, because the study was a retrospective single-center study, a prospective study is needed to verify these results in the future.

3.4.2 Identification of Tumor Extent

In addition to white light endoscopy, chromoendoscopy and NBI-ME are commonly used to confirm tumor extent in recent years. Chromoendoscopy with indigo carmine or indigo carmine plus acetic acid has higher diagnostic accuracy compared with conventional white light [24–26]. The utility of chromoendoscopy is especially high for differentiated-type lesions, lesions in the upper part of the body, and 0-II b and 0-II c lesions, which are difficult to demarcate in white light imaging. Conversely, NBI-ME enables highly objective diagnosis of tumor boarder via comprehensive observation of micro-surface pattern and micro-vascular pattern, and is fast becoming a commonly used modality in clinical practice. Today, VS classification proposed by Yao et al. [27] and the modified version of diagnostic algorithms [28] are both used in clinical settings (Fig. 3.3). The diagnosis of neoplasia is made by examining the regularity of micro-surface pattern at low to median magnifications and then the micro-vascular pattern at higher magnifications. In a prospective multicenter study, Ezoe et al. reported that the diagnostic accuracy of NBI-ME was higher than that of white light endoscopy [29]. Nevertheless, it is extremely difficult to accurately diagnose undifferentiated-type lesions and gastric cancer after eradication of *Helicobacter pylori* using NBI-ME because these lesions are not exposed over the surface of the mucosa [30, 31]. In such cases, it may be necessary to perform step biopsy in the parts outside the tumor extent. Further study is needed to clarify whether conventional diagnostic clas-

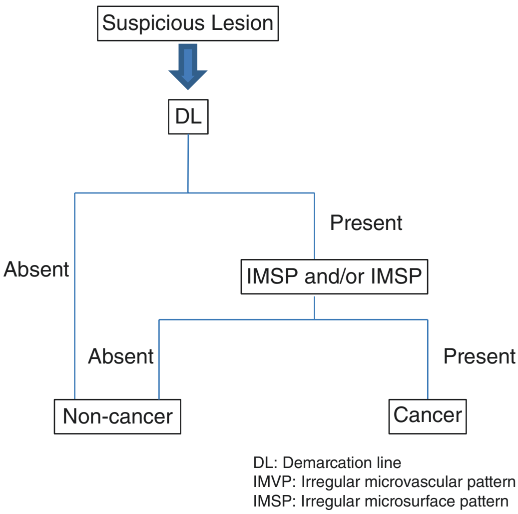

Fig. 3.3 Diagnostic algorism of NBI magnification for early gastric cancer. This algorism was modified VS classification proposed by Dr. Yao

sification and algorithm of NBI-ME can be used for lesions comprising both differentiated and undifferentiated types, lesions that develop after eradication of *H. pylori*, and lesions with no *H. pylori* infection.

3.4.3 Diagnosis of Tumor Differentiation

On white light imaging, differentiated-type adenocarcinoma appears as reddish regions with irregular borders against the background mucosa with atrophic changes, while whitish depressed lesions with clear borders are suspected to be undifferentiated-type adenocarcinoma. These features cannot be used when diagnosing small lesions and lesions accompanied by erosion or ulceration, and therefore, in addition to white light endoscopy, a biopsy is needed to make a histopathological diagnosis. The evaluation of micro-surface patterns and micro-vascular pattern enables histopathological diagnosis in NBI-ME. Taking advantage of the ability of NBI-ME to provide detailed information about vasculature, Nakayoshi et al. classified vascular structures into those in which the network was maintained (fine network pattern) and those in which there was no network (corkscrew pattern). Their findings suggest that the fine network pattern and corkscrew pattern correspond to differentiated- and undifferentiated-type cancers, respectively [32].

3.5 From Diagnosis to Treatment

The above diagnostic approaches and modalities are used to determine treatment indications. When the indication for endoscopic treatment is unclear, computed tomography or abdominal ultrasound should be performed to verify the absence of lymph node metastasis and distant metastasis. Endoscopic treatment should not be indicated in patients with suspected metastasis. It is also important to decide treatment indications and predict the occurrence of comorbidities comprehensively in patients with comorbidities. Despite Japan's current rapidly aging society, no consensus has yet been reached regarding the lesions to be included among indications for endoscopic treatment in elderly patients.

Treatment strategies should be determined after meticulously evaluating various pathological factors, the patient's age, and comorbidities, and only after providing adequate information and obtaining informed consent. Treatment should be administered in accordance with the experience and skill of the endoscopist and the facility. For cases beyond the endoscopist's capability, it is important to refer the patient to more experienced endoscopists or specialized facilities because endoscopic treatment should not be performed to satisfy the ego or fulfill one's desire.

Endoscopic treatment is a minimally invasive and excellent treatment from the perspective of postoperative quality of life. However, with wrong treatment indications, the life of patients is at risk. I believe appropriate treatment indications established based on the findings of accurate preoperative diagnosis will improve outcomes and ultimately lead to cure for patients.

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4 Indication for Endoscopic Resection of Early GI Cancers: Colon

Qing-Wei Zhang and Xiao-Bo Li

4.1 Introduction

With the increasing implementation of a national colorectal cancer screening program, early colorectal neoplasia will be detected more frequently [1]. Early colorectal neoplasia is confined to the colonic mucosa or submucosa, with some of them resected locally. As a less invasive resection method, endoscopic resections are nearly same effective in resection of early colorectal neoplasia compared with surgery. The methods of endoscopic resection include polypectomy and conventional endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD). With the advancement of EMR and ESD, invasive colorectal cancers confined to the submucosa (T1 CRC) can also be resected endoscopically. However, it should be mentioned that lymph node metastases are present in 8–13% of T1 CRC [2–5], which need additional surgery.

In this chapter, we reviewed previous studies about endoscopic resection of early colorectal neoplasia including T1 CRC and described the endoscopic indication and choice of the method of endoscopic resection or surgery for early colorectal neoplasia.

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4.2 Therapy Principle: Which Kind of Patients Could Be Sent for Resection Endoscopically or Surgically?

When a colorectal neoplasia is detected, endoscopic resection or surgery is performed to resect the lesion. But before clinical decision to resect the lesion, the patient's general condition should be assessed comprehensively.

Age, one of factors influencing trade-off between risk and benefit of endoscopic or surgical resection, is usually associated with comorbidities. Many elderly patients (≥75 years) have poor condition owing to comorbidities. Although some studies have reported elderly patients had equivalent clinical outcomes of colorectal ESD compared with younger patients and risk of complications did not differed between two groups [6, 7], conditions of elderly patients should be comprehensively assessed considering whether the expected advantage outweighs the risk of complications associated with the resection, comorbidities of the patient, and the average life expectancy. Mortality predictive models such as the Schonbery Index could be used to classify individuals into different risk groups before performing endoscopic or surgical treatment [8].

Another factor that should be considered is the antithrombotic agent. Antiplatelet drugs are one type of antithrombotic agent. A meta-

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analysis of five observational studies showed that clopidogrel contributed to the risk of bleeding comparing post-polypectomy bleeding among individuals who continued clopidogrel and who did not [9]. Therefore, their cessation are advised by the BSG, ESGE, and American Society of Gastrointestinal Endoscopy (ASGE) and cessation of clopidogrel, prasugrel, and newer antiplatelet agents at around 7 days would be appropriate [10–12]. For warfarin, a study found an increased risk of post-polypectomy bleeding when continuing warfarin (OR = 13.57, $P < 0.001$) in a cohort of 5993 patients undergoing colonoscopic polypectomy [13]. BSG guidelines recommended that warfarin cessation at 5 days with INR < 1.5 before endoscopic resection [10]. For aspirin, conflicting reports existed and BSG, AGSE guideline advises that it could be continued [10, 11] because several studies have shown no difference with aspirin use in post-polypectomy bleeding [14–16]. The above statement is mainly for low-risk patients. For individuals with high-risk of thromboembolic events, risk of bleeding versus risk of thromboembolism is suggested to be assessed and explained to patients. When cessation of anticoagulants or antiplatelet medications comes with comorbidity, endoscopists should seek specialist advice [8].

4.3 Endoscopic Resection Principle: How to Choose a Endoscopic Resection Technique?

When a patient finally decides to undergo endoscopic resection, the next step is to choose endoscopic resection technique. With the advancement of endoscopy, there now has been several techniques for resection, including cold forceps polypectomy (CFP), cold snare polypectomy (CSP), hot snare polypectomy (HSP), advanced technique endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). We will discuss the choice of endoscopic resection technique for different types and sizes of colorectal tumors.

4.3.1 Pedunculated-Type Tumors: HSP or EMR

Pedunculated-type (Ip) tumors without clinical stalk invasion are an indication of polypectomy regardless of tumor size [17, 18]. Since histological en bloc resection rate is high and the rate of adverse events is extremely low, Japan Gastroenterological Endoscopy Society (JGES) suggests that Ip tumors including early colorectal carcinoma receive HSP as the initial ER method [19]. However, an important issue should be mentioned that post-polypectomy bleeding (PPB) is cautioned, especially tumors with thick stalk. Large Ip tumors usually have large blood vessel within the stalk, causing increased risk of PPB [20]. Studies have shown that pretreatment placement of detachable snare at the base of stalk or injection with epinephrine reduces PPB in lesions with stalk more than 10 mm [21]. Moreover, the combination of detachable snare and injection of epinephrine reduces PPB compared with injection of epinephrine alone [22, 23]. Recently published ESGE guideline recommended the stalk injected with adrenaline or mechanical hemostasis in the Ip tumors with head ≥20 mm or stalk ≥10 mm before endoscopic resection. In our medical endoscopic center, pretreatment placement of clips and resection with EMR with submucosal injection of a combination of glycerol, methylene blue, and epinephrine is used for Ip tumors with thick stalk (≥10 mm). In conclusion, HSP is suggested for Ip tumors and EMR with pretreatment placement of clips is safe for the treatment of Ip tumors with thick stalk [24].

4.3.2 Non-pedunculated Colorectal Tumors

4.3.2.1 Diminutive and Small Polyps (<10 mm): Cold Polypectomy

Diminutive polyps are very common as 60–70% of patients undergoing colonoscopy have diminutive polyps [25]. Most of the diminutive polyps, especially rectum, are hyperplastic polyps with no risk of malignant transformation. For diminutive polyps, studies investigated the natural progression of unresected polyps and results showed diminutive polyps have slow growth and even regression without risk of interval cancers within recommended the surveillance intervals [26, 27]. A birth cohort analysis of 3.6 million participants of screening colonoscopy demonstrated that time it takes 21–28 years for progression of non-advanced adenoma to cancer [28]. Studies also showed that nearly 90% of adenomas detected in patients younger than 65 years do not progress to cancer within the affected individual's life span [26, 27, 29]. Therefore, JGES suggest typical diminutive hyperplastic polyps present in the rectosigmoid may be left untreated [30]. For diminutive polyps with an exception for rectosigmoid polyps, the current standard clinical care is to resect it. A US survey of 2003 showed that the most applied endoscopic resection method for 1–3 mm polyps is CFP (50%) followed by hot forceps (33%) and that method for 4–5 mm polyps is HSP (31%) followed by hot forceps (21%) [31]. With an incomplete resection rate of about 15% and increased risk of complication, ESGE guideline has recommended against the use of hot biopsy resection for diminutive polyps [32]. Recently, two prospective randomized studies demonstrated that CFP has similar histologic eradication to CSP in lesions confined to 1–3 mm but CFP is inferior to CSP in lesions with 4–5 mm [33, 34]. In conclusion, it is suggested that CSP or CFP be used for 1–3 mm lesions and CSP used for 4–5 mm lesions with discouragement of hot forceps polypectomy.

A study involving patients undergoing screening colonoscopy found that advanced histopathology in 7% of small polyps (6–9 mm) [25]. The current clinical practice is endoscopic resection of it. Conventional polypectomy usually uses hot snare to remove small polyps, which causes thermal damage affecting the estimation of the completeness of the resection. Recently, a meta-analysis analyzed efficacy and adverse effects of CSP in small polyps with HSP in several randomized controlled trials and concluded that CSP has similar curability to hot polypectomy [35]. Compared with HSP, CSP allows for better interpretation of histopathology and resected margins. Recently published ESGE guideline also supports the use of CSP for resection of small polyps (5–9 mm) [24]. Another issue, rate of polypectomy complications, should be discussed. A meta-analysis including six randomized controlled trials has shown similar complication rates. Also, a randomized controlled trial has shown immediate and delayed bleeding rates of CSP are significantly lower for cold compared to hot snare polypectomy [36]. In conclusion, CSP is suggested for resection of small polyps.

4.3.2.2 Laterally Spreading Tumors (≥10 mm): Hot Polypectomy or Advanced Technique

Flat and sessile polyps larger than 10 mm are termed laterally spread tumors (LSTs). Suspicion of malignancy should be always be kept when polypectomy is conducted for large tumors.

For intermediate size lesions (10–19 mm), CSP usually cannot resect tumors in en bloc way and biopsy forceps is also not effective for achieving complete resection. So HSP is preferred for 10–19 mm tumors with a relative high risk of carcinoma compared with small lesions [37]. However, the Complete Adenoma Resection study demonstrated that HSP has higher incomplete resection rates for 10–19 mm polyps compare with small polyps (17.3% vs. 6.8%) [38]. Also, en bloc resection cannot always be achieved using only HSP without submucosal injection. When 10–19 mm lesions are detected with suspicion of malignancy, advanced technique EMR should be chosen for en bloc resection and complete resection. In conclusion, HSP or EMR is suggested for en bloc resection of intermediate size tumors.

For tumors larger than 20 mm, more complex situations should be discussed. One is subclassification and endoscopic appearance of LSTs. LSTs are classified into granular type (LST-G) and non-granular type (LST-NG). The former consists of a "homogenous type" and a "nodular mixed type," and the latter consists of a "flat elevated type" and a "pseudo-depressed type." For homogenous LST-G, the presence of carcinoma or submucosal invasion is extremely low [39, 40]. Therefore, piecemeal EMR (pEMR) is allowed [41]. Although pEMR is associated with high recurrent risk of 16% in the Australian Colonic EMR (ACE) study, recurrent adenomas were usually unifocal and diminutive and 93% were managed endoscopically successful [42]. However, when large tumors are resected by pEMR, margins are suggested inspection by magnifying endoscopy at the resection, which has been proved with lower recurrence rate retrospectively [43]. Closer surveillance colonoscopy should also be followed and risk of recurrent adenoma can be classified by the validated Sydney EMR Recurrence Tool (SERT) [44], a validated 4-point score stratify the incidence of residual or recurrent adenoma based on characteristics of the index EMR, including laterally spreading lesion size, high-grade dysplasia and intra-procedural bleeding requiring endoscopic control (IPB) (Table 4.1). It is concluded that lesions with score 0 could safely undergo first surveillance at 18 months, whereas lesions with score 1–4 require surveillance at 6 and 18 months [44]. For nodular mixed LST-G, submucosal invasion is more likely to be present in the large nodule [45] (Fig. 4.1a) and mixed LST-G should be resected by en bloc ESD. For pseudo-depressed LST-NG (Fig. 4.1b), submucosal invasion is highly frequent in the depressed areas [45] and should be performed en bloc resection by ESD. For flat elevated LST-NG, whether en bloc resection should be performed according to the detailed preoperative diagnosis, such as Kudo Vi type under magnifying chromoendoscopy [46] (Fig. 4.1c), JNET 2B under magnifying NBI [47] (Fig. 4.1d).

Table 4.1 The Validated Sydney EMR Recurrence Tool (SERT) to stratify the incidence of residual or recurrent adenoma

Risk factor	Score
LSL size ≥40 mm	2
IPB	1
High-grade dysplasia	1
Total	4

LSL Laterally spreading lesion, *IPB* intra-procedural bleeding requiring endoscopic control

Another issue is suspicion of carcinoma and submucosal invasion. In this situation, pEMR should be avoided and en bloc resection should be performed by en bloc EMR or ESD.

Studies have shown that pEMR can result in higher recurrence in malignant tumors than benign lesions [48, 49]. A meta-analysis showed that compared with en bloc EMR, recurrence rate for non-pedunculated neoplasia was 20% for pEMR compared with low recurrence rate of 3% for en bloc EMR [50]. Another study has identified pEMR of malignancy as an independent risk factor for incomplete resection [51]. Unlike en bloc resection, pEMR results in poorer quality of histological specimen and resection margins, invasion depth and completeness of resection cannot be analyzed precisely. The former two factors are two important factors that decide whether additional treatment is needed. Evaluation of resection margins is important because it decides whether the completeness of resection is achieved and positive resection margin is a risk factor for residual tumors [52]. Butte analyzed 143 malignant tumors with polypectomy followed by colectomy and found residual invasive cancers in 16% (8/50) of cases with <1 mm (positive) polypectomy margin, 21% (7/33) of cases with indeterminate polypectomy margin, and zero (0/44) of cases with ≥1 mm (negative) polypectomy margin (P = 0.009) [53], indicating that resection margins should be precisely evaluated whether additional treatment should be performed. Also, submucosal invasion depth is associated with risk of lymph node metastases. A study from the United States reviewed 7543 patients with T1 carcinoma and found that invasion into the lower third (sm3) is an independent risk factor for lymph node metastases [53]. Meanwhile, a Japanese collaborative study analyzed the association between depth of submucosal invasion and lymph node metastasis and <1000 μm submucosal invasion have a negligible risk of lymph node metastases [54], which is an endoscopic indication for T1 carcinoma.

Unlike pEMR, en bloc resection by ESD or EMR may be effective as both a diagnostic and a therapeutic tool for tumors with suspicious malignancy. ESD has been widely used

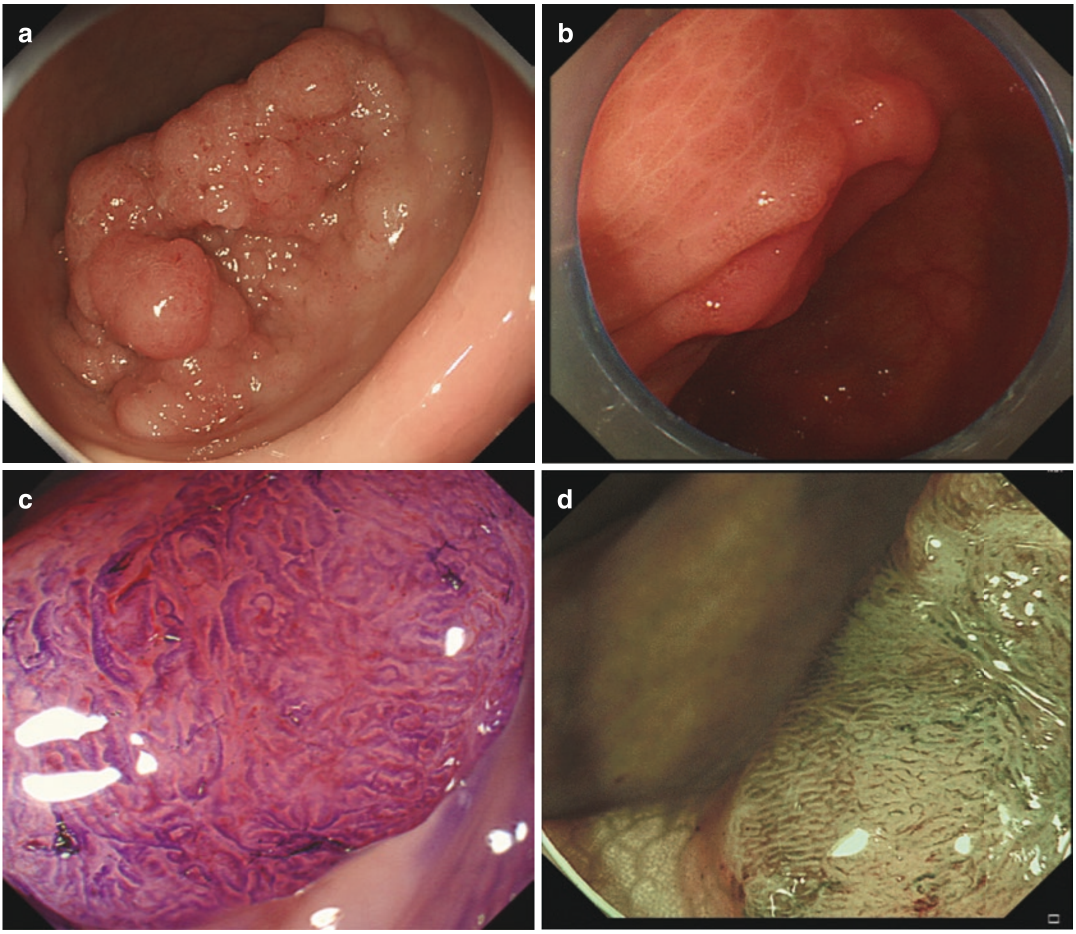

Fig. 4.1 Endoscopic appearance for colorectal neoplasia needing en bloc resection. (**a**) A depressed area in a pseudo-depressed type laterally spreading tumor with non-granular type (LST-NG). (**b**) A large nodule in a nodular mixed type laterally spreading tumor with granular type (LST-G). (**c**) Kudo pit pattern Vi-low type under magnifying chromoendoscopy observation using crystal violet. (**d**) JNET classification 2B under magnifying endoscopy with narrow-band imaging (ME-NBI)

in Asian countries and Japanese Colorectal ESD Standardization Implementation Working Group has proposed the draft of colorectal ESD (Table 4.2). En bloc resection has a higher complete resection rate and lower risk of lesion recurrence than piecemeal resection [48, 55]. Meanwhile, en bloc resection allows precise histological analysis of resection margins, depth of invasion, and other risks of poor outcomes. Recent updated meta-analysis showed that ESD has reached a high en bloc resection rate of 93% in Asian countries but a relatively lower en bloc resection rate of 81.2% in non-Asian countries [56]. For curative resection, curative resection rate of ESD in non-Asian countries was as low as 71.3% with a curative resection rate of 85.6% in Asian countries. A multicenter Japanese retrospective study reported outcomes of T1 carcinomas with submucosal invasion initially treated with ESD. Results showed that 5-year recurrence-free survival and recurrence rates were 98 and 0.8% in low-risk cases without additional surgery (negative vertical margin; well or moderately differentiated adenocarcinoma; absence of lymphovascular invasion; invasion depth < 1000 μm), but 5-year recurrence-free survival of 87 and 97% were reported for outcomes of ESD and ESD with

Table 4.2 Indications for ESD for colorectal tumors in the Japan Gastroenterological Endoscopy Society (JGES) guidelines

1. Lesions for which en bloc resection with snare EMR is difficult to apply
LST-NG, particularly LST-NG (PD)
Lesions showing a VI-type pit pattern
Carcinoma with shallow T1 (SM) invasion
Large depressed-type tumors
Large protruded-type lesions suspected to be carcinoma
2. Mucosal tumors with submucosal fibrosis
3. Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis
4. Local residual or recurrent early carcinomas after endoscopic resection

LST-NG non-granular type laterally spreading tumor, *PD* pseudo-depressed type

additional surgery in high-risk tumors (positive vertical margin; poorly differentiated adenocarcinoma; presence of lymphovascular invasion; invasion depth > 1000 μm), respectively [57]. Meanwhile, recently published retrospective study from Europe analyzed whether additional surgery following endoscopic resection of high-risk T1 CRC does not have a negative effect on patients' outcomes compared with primary surgery and observed no increased risk of LNM or recurrence after secondary surgery compared with primary surgery [58]. Thus, an attempt for an en bloc resection of a possible T1 CRC without evident signs of deep invasion seems justified in order to prevent surgery of low-risk T1 CRC in a significant proportion of patients. Therefore, after en bloc resection by EMR or ESD for T1 CRC, histopathology should be assessed precisely to decide whether additional surgery should be performed. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines recommended that high-risk T1 CRC be considered when any one of the following risk factors of lymph node metastasis present by histopathology: (1) depth of submucosal invasion <1000 μm; (2) positive lymphovascular invasion; (3) poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous carcinoma and (4) grade 2/3 budding at the site of deepest invasion. JSCCR guidelines recommend additional surgery for T1 CRC [59].

In conclusion, for large LSTs, en bloc EMR and ESD are suggested as both a diagnostic and therapeutic tool. However, pEMR is also allowed when adenomatous lesions or focal carcinoma in adenomas ≥2 cm in diameter with attempting resection carcinomatous area, not into segmentation.

4.4 Conclusions

According to the current studies of endoscopic resection for early colorectal neoplasia and guideline, a diagram is drawn for choice of different endoscopic resection methods for different sizes and types of tumors. HSP is suggested for Pedunculated-type tumors. When resecting pedunculated-type tumors with thick stalk, EMR, prophylactic mechanical hemostasis like pretreatment placement of clips at the stalk or combination of them is suggested. For non-pedunculated-type tumors, CSP is suggested for diminutive and small size tumors and CFP is also feasible for diminutive 1–3 mm tumors. For LST tumors, a detailed observation of the appearance of tumors should be performed before treatment. If carcinoma component is not suspected, HSP or EMR is suggested for intermediate tumors. En bloc EMR and ESD are preferred for large tumors but pEMR can be feasible with subsequent frequent surveillance colonoscopy if en bloc not feasible or not safe. If carcinoma component is suspected, en bloc EMR or ESD is suggested for suspected Tis or superficial T1 carcinoma but surgery is suggested for suspected deep submucosal T1 carcinoma (Fig. 4.2).

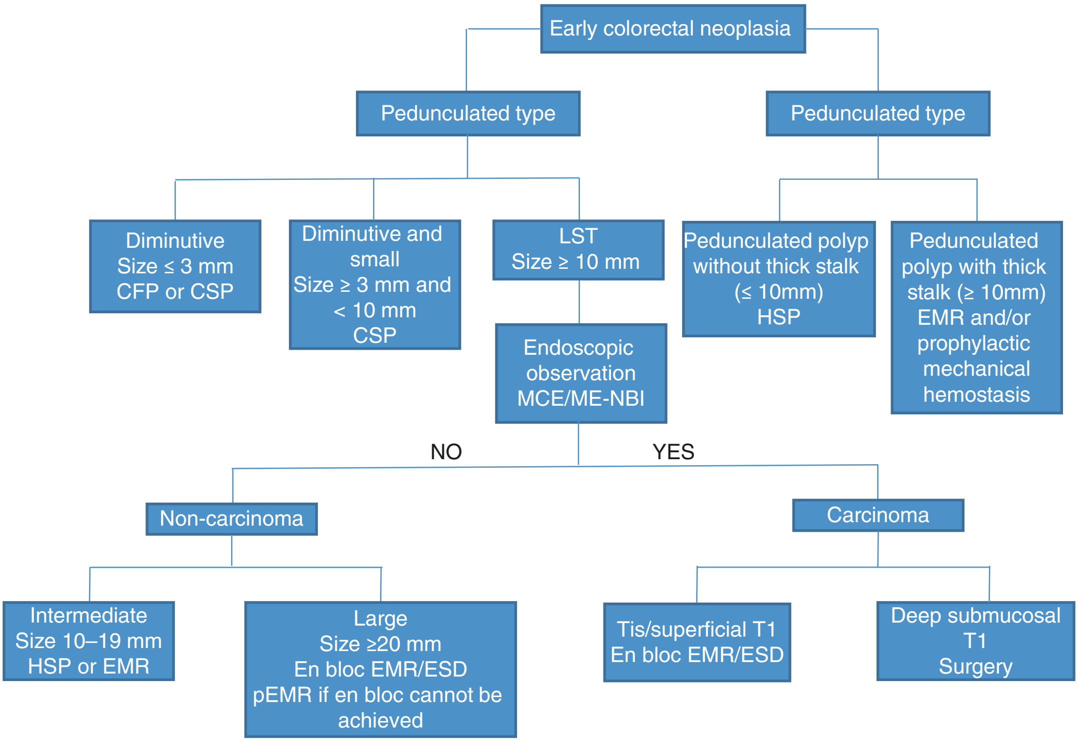

Fig. 4.2 A diagram showing choice of different endoscopic resection methods for colorectal tumors with different sizes and suspected malignancy. This diagram was adjusted from the ESGE guideline for colorectal polypectomy and endoscopic mucosal resection. *CFP* cold forceps polypectomy, *CSP* cold snare polypectomy, *LST* laterally spreading tumor, *HSP* hot snare polypectomy, *EMR* endoscopic mucosal resection, *MCE* magnifying chromoendoscopy, *ME-NBI* magnifying endoscopy with narrow-band imaging, *pEMR* piecemeal endoscopic mucosal resection

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5 EMR for Esophagus

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5.1 Introduction

Due to advances in endoscopic diagnosis, early-stage esophageal neoplastic lesions, e.g., superficial esophageal cancer, are being detected more frequently. A study has shown that endoscopic therapy for early-stage esophageal neoplastic lesions results in similar cancer-free survival and morbidity when compared with surgical resection [1]. Thus, recently endoscopic treatment, which minimizes the risk of adverse events, has become widely accepted as an alternative to surgical treatment.

There are two main types of endoscopic treatment for esophageal neoplastic lesions, resection, and ablation. The advantage of endoscopic resection (ER) is that the resected lesion can be examined histopathologically to reveal the extent and infiltration depth. ER can be divided into endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). We herein describe indications, methods, and techniques of esophageal EMR.

5.2 Indications

Indications for esophageal EMR should be considered carefully, because it is desirable for lesions to be resected in an en bloc fashion with negative margins (R0 resection) [2, 3]. In cases of endoscopic piecemeal mucosal resection (EPMR), precise histopathological evaluation of margins, tumor depth, and vascular invasion cannot be obtained. Furthermore, EPMR is reported to be associated with a high risk (25.2%) of local recurrence, while there is a lower risk (2.6%) in lesions treated by en bloc resection [4].

In cases of esophageal squamous cell carcinoma (ESCC), the criterion for choosing between EMR and ESD mainly depends on the size of the lesion. The EMR procedure is reported not to be reliable for lesions over 15 mm in diameter and unsuitable for lesions over 20 mm [5]. For larger lesions, ESD, which enables R0 resection regardless of lesion size, is recommended. However, ESD is technically more difficult than EMR with a higher risk of adverse events and longer procedure times. The degree of the endoscopist's proficiency in each procedure, the workspace environment, and the patient's general condition should also be taken into consideration when deciding which procedure to perform.

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The indications for endoscopic treatment of gastrointestinal submucosal tumors (SMT) are still controversial. SMTs in the esophagus are mainly benign leiomyomas, but some esophageal stromal tumors have malignant potential. Case reports and series demonstrate the possibility that EMR (or ESD, peroral endoscopic tumor resection (POET) [6]) is an alternative to simple observation or surgical resection for the management of esophageal SMTs [7, 8].

5.3 Methods and Techniques

Although EMR is technically less demanding than ESD, it can become difficult, because the esophagus is narrow and since its thin wall constantly moves together with respiration and heartbeat.

Thus some variations of EMR techniques such as two-channel EMR (strip biopsy method) and cap-fitted EMR (EMRC) have been developed.

In this paragraph, the method of EMR for esophagus including these two techniques, two-channel EMR and EMRC, to achieve safe and effective resection is described.

5.3.1 Anesthesia and Sedation

For esophageal EMR, either general anesthesia or conscious sedation is usually performed to reduce the patients' discomfort and increase procedural safety. General anesthesia performed by a well-skilled anesthesiologist minimizes patient discomfort, but can often only be performed at advanced institutes with sufficient manpower. Conscious sedation can be performed more simply, but when the sedation level is insufficient, the patients' body movement and respiratory fluctuation may make the procedure difficult. When performing EMR under conscious sedation, pharyngeal anesthesia using lidocaine spray or gel is recommended to decrease discomfort of the throat during the procedure [9]. In both methods of sedation, careful monitoring of the patients is required.

5.3.2 Marking

To identify the border of flat or depressed-type lesions is often difficult with only white light observation. The use of magnifying endoscopy, optical enhancement, and chemical staining has been reported to be effective for these lesions. Especially in cases of squamous cell carcinoma, iodine staining is the golden standard for detection and demarcation of these neoplasms [10]. However, preoperative iodine staining may complicate demarcation of the lesions due to mucosal damage [11], and endoscopists should take this into account. In cases of Barrett's esophagus-related adenocarcinoma, observation with both chromoendoscopy and magnifying narrow-band endoscopy may be necessary to accurately demarcate the lesion [12]. Marking around the demarcation line is especially effective for subtle and indistinct lesions, and placing marking dots 2–5 mm outside the lesion using the tip of the electrosurgical snare or an argon plasma coagulation (APC) device can help confirm the orientation and demarcation of the lesion during the procedure.

5.3.3 Injection

An endoscopic injection needle should be inserted from the proximal side of the lesion. After insertion, the depth of the needle should be adjusted so that it enters the submucosal layer. An adequate amount of normal saline (according to the lesion size) is injected through the needle until the target mucosal lesion is lifted up sufficiently. Indigo carmine may be added to the saline for providing blue color to the lifted mucosa and diluted adrenalin saline solution (approximately 1:100,000) may be added for preventing bleeding after the resection. Injection directly into the lesion may be a cause of seeding and should be avoided if possible.

Observing the lesion during and after submucosal injection is very important to decide whether or not to proceed with the procedure. The non-lifting sign, which means that the lesion cannot be elevated with injection, signifies either invasion of the cancer to the submucosal layer or submucosal fibrosis from prior biopsy or ulceration. There is a high risk of perforation in non-lifting cases, and thus the EMR procedure should be discontinued when the non-lifting sign is recognized.

5.3.4 Tissue Grasping

5.3.4.1 Two-Channel EMR

The two-channel EMR (strip biopsy method) requires a double-channel endoscope and grasping forceps (Fig. 5.1). A snare (oval or crescent type according to the operator's preference) and grasping forceps are passed through the different channels. Before snaring, the area near the lesion is grasped by the forceps and is pulled gently into

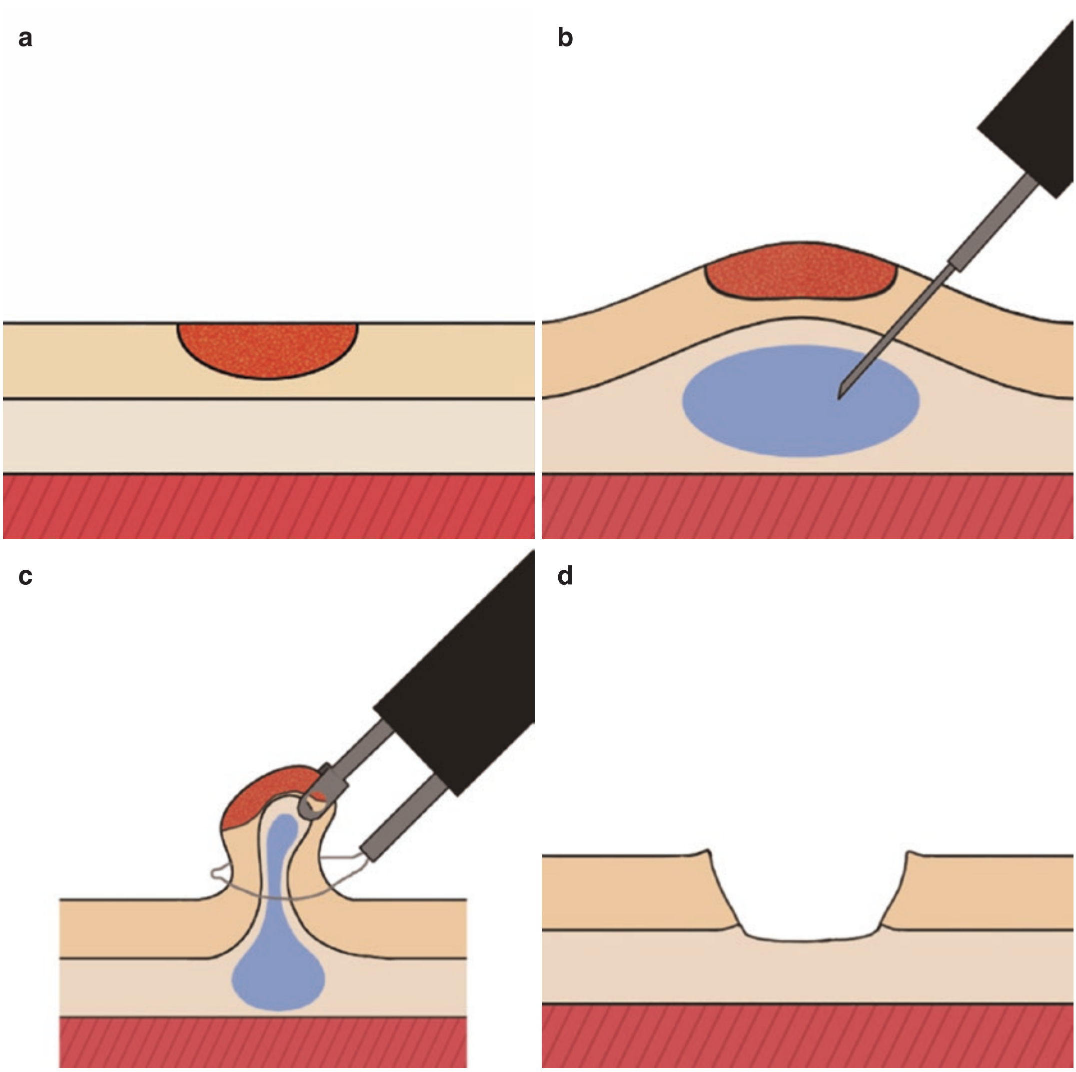

Fig. 5.1 Schematic illustration of two-channel EMR technique. The flat lesion is observed (**a**). After the saline injection (**b**), the lesion is lifted with grasping forceps and the snare is placed at the base of the target area (**c**). The mucosal defect after the resection is observed (**d**)

the opened snare. Then the snare is closed enabling real-time confirmation of target area snaring.

The advantage of two-channel EMR is that pulling the lesion proximally may increase the longest diameter of the resected specimen. On the other hand, the disadvantage is that the procedure may be relatively complicated because of using multiple devices.

A point to be aware of when performing two-channel EMR is not to grasp the lesion directly with the forceps for this may cause damage to the specimen and complicate precise histopathological evaluation.

5.3.4.2 Cap-Fitted Endoscopic Mucosal Resection

The EMRC method (shown as Fig. 5.2) was first described in 1992 [13]. There are several types of translucent plastic caps designed for EMRC. The use of a crescent-type snare with a thin wire is recommended for this procedure. The lists and characteristics of commonly used devices are shown in Fig. 5.3. A cap is fitted to the top of the endoscope. Prelooping the snare is performed in an area where the scope can be fixed perpendicular to the mucosa. At first, the cap is placed against the normal mucosa to seal the outside of the cap, next the snare wire is opened through the instrumental channel of the endoscope and opened so the wire is fixed along the rim of the cap. Cooperation between the endoscopist and assistant is necessary to accurately fix the snare wire along the rim of the cap. Then the lifted mucosa including the lesion is pulled well into the inside of the cap by fully suctioning, followed by tight snaring. The outer sheath is pushed up to confirm that the targeted area is ensnared and to release excessive tissue.

The advantage of EMRC is that suctioning the target area can also increase the longest diameter of the resected specimen. On the other hand, the disadvantage is that insufficient volume of saline injection may increase the risk of perforation.

One point to be aware of while snaring, the target area tends to be tied more widely toward the anal side. It is necessary to place the opened snare precisely at the base of the target area including all the oral side dots.

Endoscopic images of resection of ESCC by EMRC is shown in Fig. 5.4.

5.3.5 Tissue Resection

After grasping the tissue with a snare, it is necessary to be careful to release the excess tissue to avoid damage to the muscularis propria. Entrapment of the muscularis propria can be confirmed by gently moving the snare back and forth. If the muscularis propria is entrapped not only the target lesion but also the whole wall may be seen to move. In this case, loosening the grasped snare slightly and pulling the snare toward the lumen may help to release the potentially entrapped muscularis propria. Moving the snare forward and backward may be also useful. If there is still a possibility that the muscularis propria is ensnared, the snare should be opened fully and snaring of the target area should be performed once again.

Then the target area should be pulled slightly toward the lumen side to minimize the thermal burning effect on the muscularis propria. Most high-frequency generators have two electrosurgery modes specialized for cutting or coagulation, and the appropriate configuration of them is important during resection. Ideal resection is to obtain a histologically assessable resected specimen without adverse events. Insufficient coagulation can cause bleeding from blood vessels, on the other hand, excessive coagulation can cause perforation and thermal effect on the edge of the specimen. When it requires extended time to resect, there is a possibility that the muscularis propria may be entrapped within the snare. In that case, the snare should be opened fully and snaring of the target area should be performed once again.

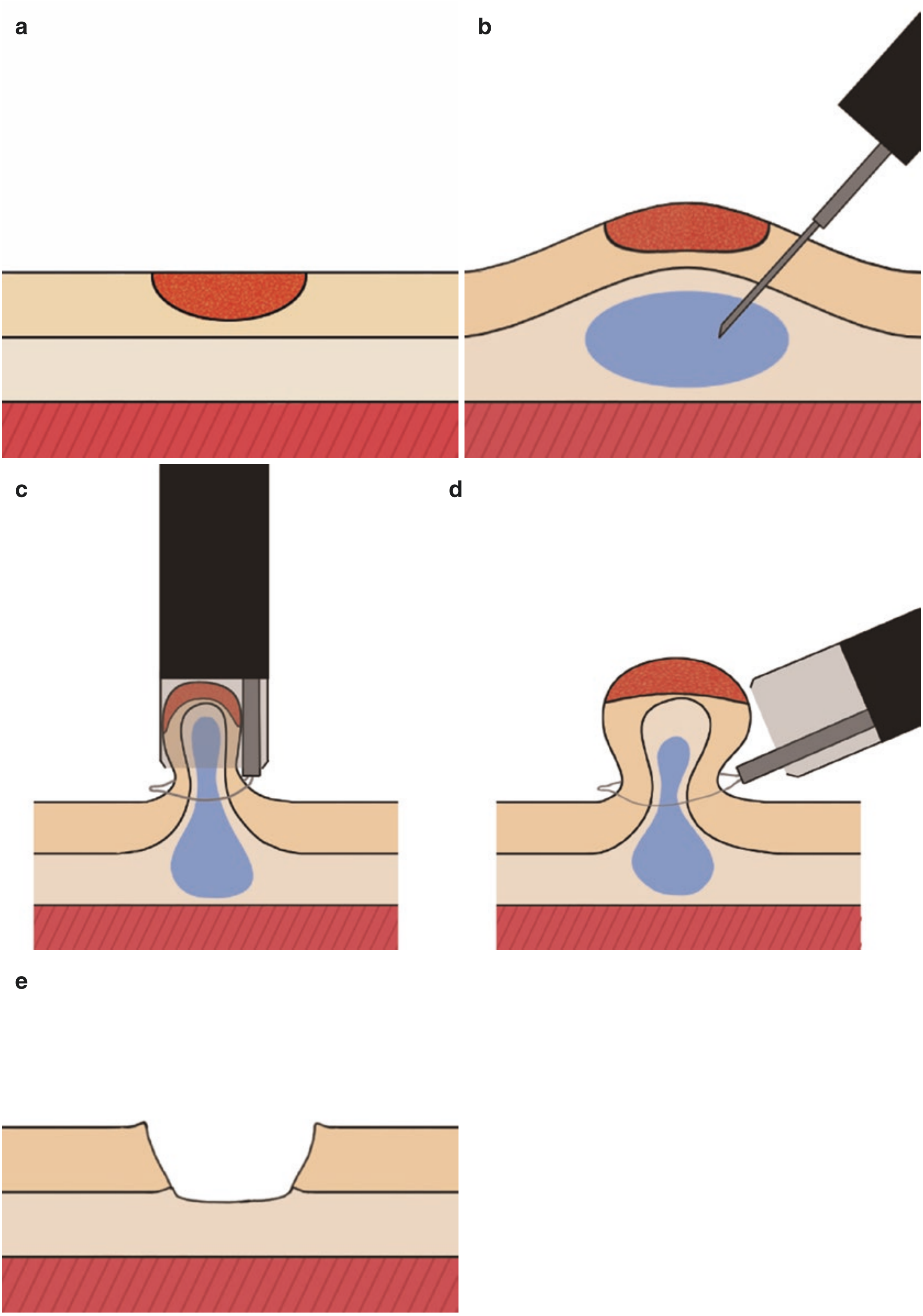

Fig. 5.2 Schematic illustration of EMRC technique. The flat lesion is observed (**a**). After the saline injection (**b**), the snare is prelooped on the edge of the cap. The lesion is drawn into the cap using suction and the lesion is allowed to be into the snare (**c**). The outer sheath is pushed up to confirm that the targeted area has been ensnared (**d**). The mucosal defect after the resection is observed (**e**)

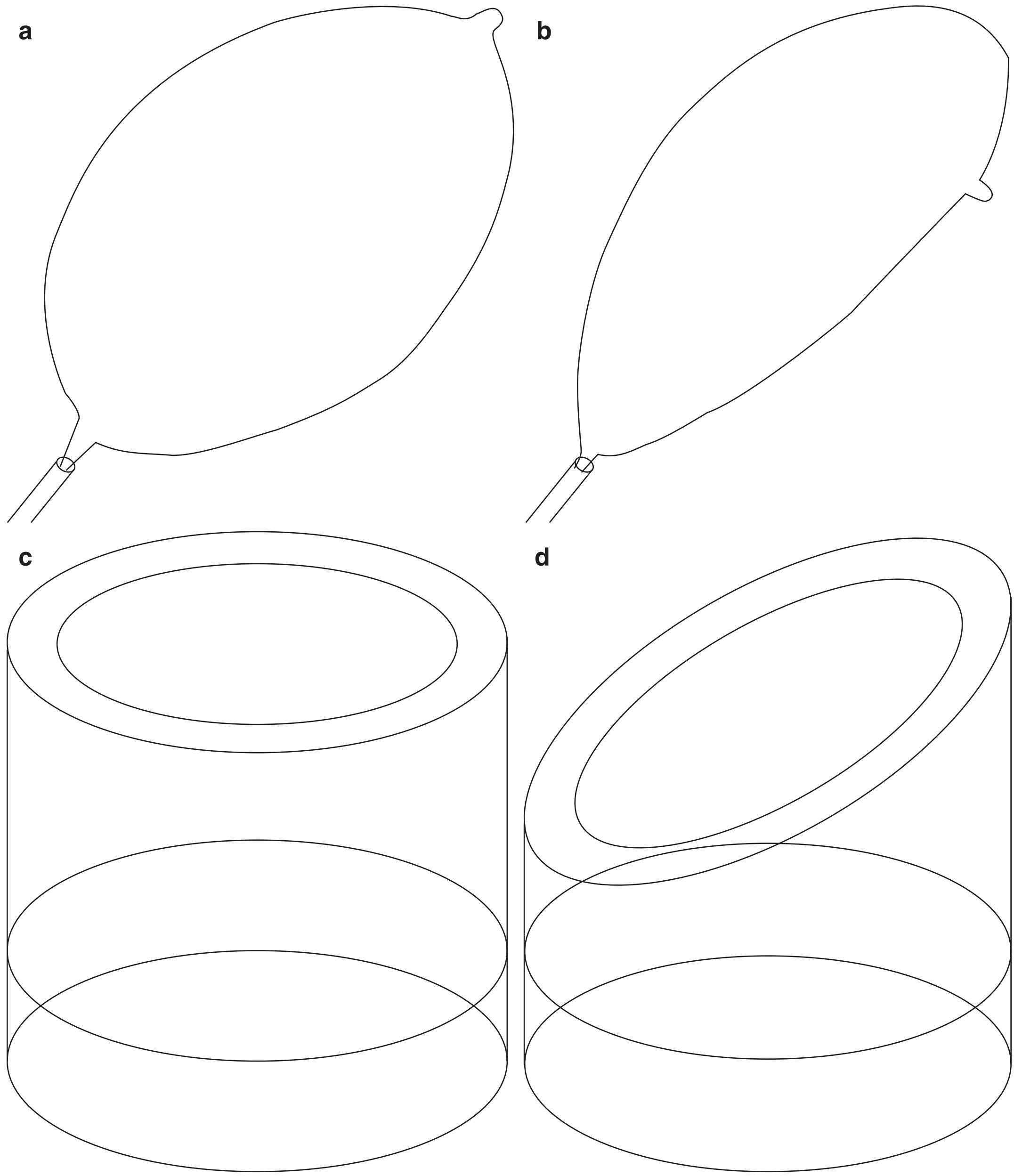

Fig. 5.3 The lists and characteristics of snares and caps. The use of a crescent electrosurgical snare has been advised for easier prelooping. The caps for EMRC have a shallow circumferential rim on the inside and the snare can be prelooped on the edge of the cap. (**a**) Oval electrosurgical snare. (**b**) Crescent electrosurgical snare. (**c**) Straight distal cap with rim. (**d**) Oblique distal cap with rim. (**e**) Wide Oblique distal cap with rim

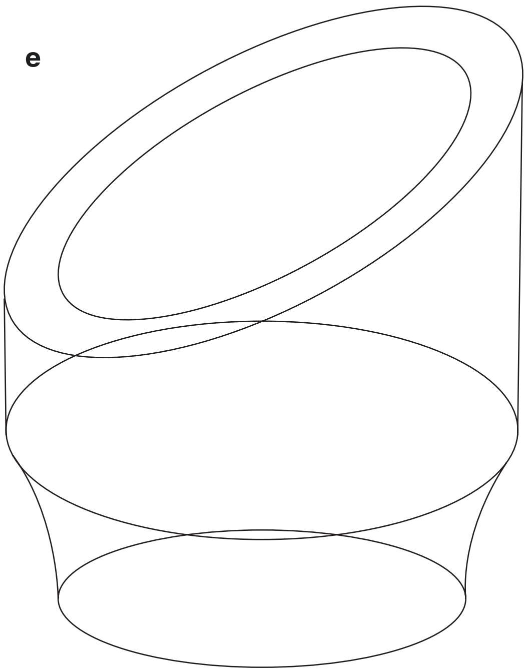

Fig. 5.3 (continued)

5.3.6 After Resection

The resected site should be examined to confirm that there is no residual lesion. If there is a possibility of residual lesion on the edge of the ulcer, additional snaring and resection or ablation therapy with argon plasma coagulation or coagulation forceps are recommended. However, in those cases, accurate pathologic diagnosis and cancer staging cannot be obtained and more cautious endoscopic monitoring is required.

When the mucosal defects due to ER are larger than 3/4 of the circumference of the esophagus, prophylactic treatment for prevention of stricture is recommended. Methods such as steroid injection, oral steroid administration, and PGA sheet with fibrin glue [14] are standardized prophylactic methods. Minor bleeding can be controlled successfully by grasping the bleeding vessels with a tip of snare or hemostastic forceps.

Perforation is rare [15, 16], but should it occur, closure of the perforation should be performed by clips when possible, and the patient should be managed conservatively with intravenous antibiotics with null per mouth. Furthermore, a gastrointestinal surgeon should be consulted. Delayed perforation is extremely rare, but may also require surgical intervention.

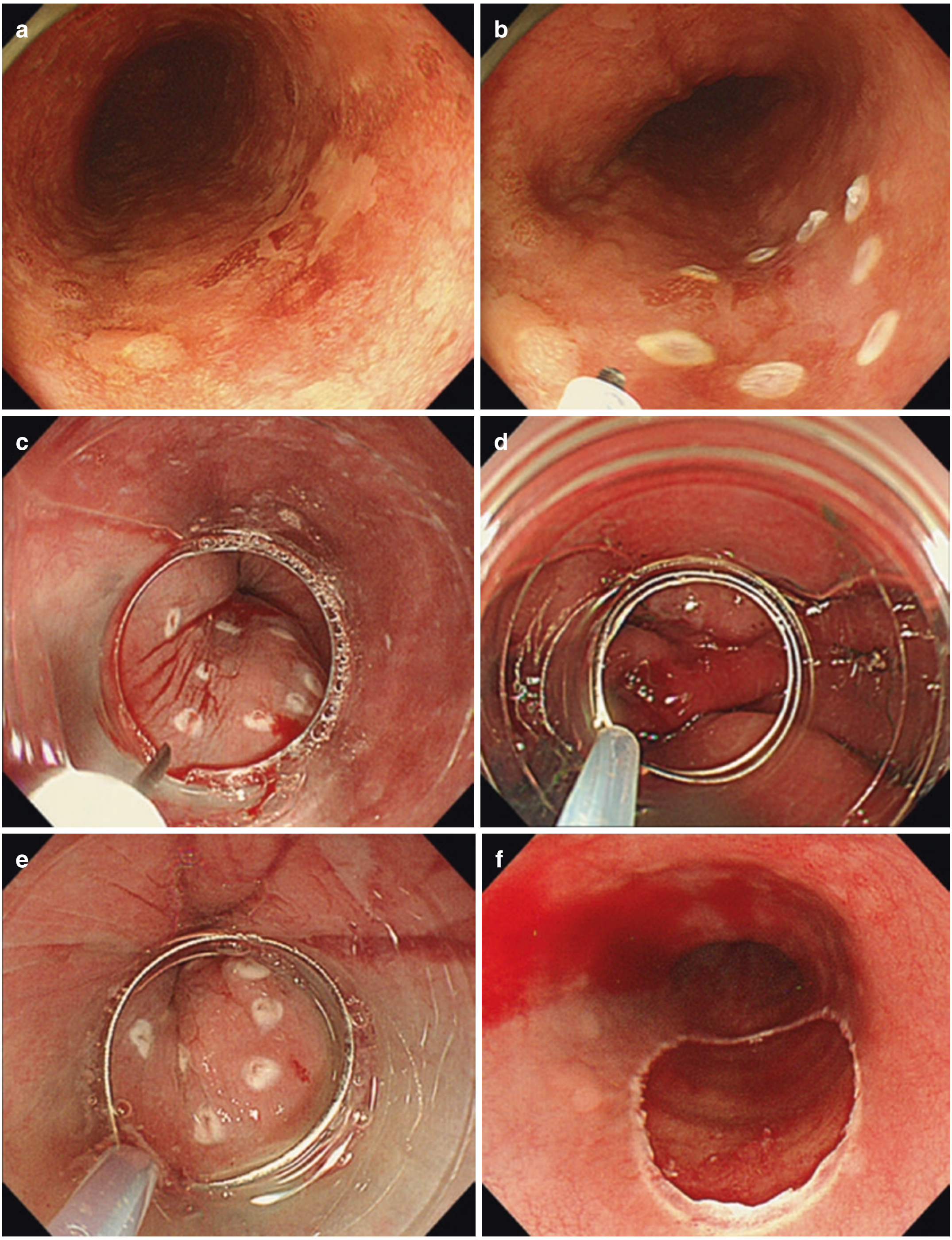

Fig. 5.4 EMRC for superficial cancer of the esophagus (type 0-IIb) in the mid-esophagus. (**a**) Endoscopic appearance of the lesion after chemical staining (Lugol). (**b**) Marking around the lesion was performed with the tip of the snare. (**c**) Submucosal injection was performed with normal saline. (**d**) A crescent-type snare was prelooped along the rim of the cap in an area where the scope could be fixed perpendicular to the mucosa. (**e**) The snare was maneuvered so that the base of the snare was positioned at the base of the target area. (**f**) The resected area was observed after endoscopic mucosal resection to confirm that resection of the target area was successful

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6 Endoscopic Mucosal Resection for Gastric Neoplasia

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6.1 Background

Early gastric cancer (EGC) is defined as an adenocarcinoma confined to the mucosa or submucosa (T1a or T1b) of the stomach regardless of the nodal status (any N). EGC can be difficult to diagnose as the majority of patients are asymptomatic. The only exceptions are countries where nation-wide screening program is implemented, such as Japan and Korea, in which the diagnostic rates of EGC are reported to be more than 50%. With appropriate treatment, it is possible to achieve a 5-year survival rate up to 97–99% for intramucosal tumors and 96% for those involving submucosa [1].

The standard treatment for EGC in the past century used to be gastrectomy with radical nodal dissection. These conventional surgical methods have been associated with significant morbidity rates ranging from 9.6 to 18.7%. The mortality rate varied among different centers, but it could be as high as 10% [2]. Post-gastrectomy syndrome including early satiety, malnourishment, dumping, and bilious reflux were rather common. They constitutively lead to low quality of life in a considerable proportion of patients in the long term.

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6.2 Development of EMR

Since the 1980s, advancement in endoscopic technology has slowly revolutionized the therapeutic approach for EGC. Statistics based on large cancer databases in Japan revealed that differentiated type of mucosal carcinoma (T1a) was associated with very low risks of nodal spread. This sparked off the notion of treating small superficial lesions using endoscopic technique, intending to achieve less peri-procedural morbidities and a lower mortality rate without compromising the odds of long-term cure. Endoscopic mucosal resection (EMR) was developed.

Among all the available options of EMR, the very first one was described by Tada in 1984 (published in Japanese in 1988) [3]. It was termed "strip biopsy" which entails injection elevation of the tumor-bearing mucosa, followed by snare polypectomy using diathermy under endoscopic guidance. With this approach, full thickness of the mucosa and part of the submucosal tissue were removed. In Tada's report, strip biopsy was performed in 137 lesions in 133 cases. Up to 65% of the lesions were completely resected. Additional surgical or further endoscopic therapy was applied to the remaining cases, of which 16 cases were confirmed to have been perfectly resected by gastrectomy. Some 71 patients who were not candidates for surgery because of their physical condition were followed endoscopically for 2–48 months, and no recurrence was noted.

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The performance of strip biopsy using a single-channel endoscope could be technically challenging because the snare might glide over the surface of tumors, especially in those lying in a tangential angulation. In 1988, Hirao et al. reported a technical variant called endoscopic resection with local injection of hypertonic saline epinephrine solution (ERHSE) [4]. The hypertonic solution provided a more sustained elevation effect so that a circumferential mucosal incision could be made around the tumor using a needle knife. An endoscopic snare was then applied to anchor along the incision line to facilitate resection of the tumor in a more controlled manner. This technique had been used by other authors, who also reported high success rates in en bloc resection of tumors larger than 15 mm in maximal diameter.

Two other technical variations were subsequently developed: endoscopic mucosal resection with a cap-fitted endoscope (EMR-C) as described by Inoue et al. in 1993 and endoscopic mucosal resection using a ligating device (EMR-L) described by Chaves et al. in 1994 [5, 6]. These technical procedures allowed the resection of fragments up to 10–15 mm in diameter. However, studies from other groups later demonstrated that these three methods were limited to removal of tumors smaller than 15 mm. For bigger lesions, resection was often ending up in a piecemeal manner. It makes pathological assessment difficult, especially in the determination of clearance of lateral and deep margins. This increased the rate of positive resection margin and risk of local recurrence.

In 1998, Hosokawa and Yoshida developed a special endoscopic knife, called the insulation-tipped electrosurgical knife (IT knife) [7]. It consists of a conventional diathermic needle knife with a ceramic ball tip. This led to the rapid development of a new technique called Endoscopic Submucosal Dissection (ESD). In a nutshell, ESD at that time started by making a circumferential mucosal incision around the pathology according to the endoscopist's discretion, and followed by IT knife dissection in the deeper part of the submucosa, along the surface of the muscularis propria. This procedure ensures a higher success rate of en bloc resection of larger tumors, thus reduces the risk of local recurrence.

6.3 Indications/Contraindications

Before the availability of endoscopic knife and technique of ESD, the older version of Japanese guidelines for endoscopic treatment of EGC is confined to differentiated mucosal carcinoma smaller than 2 cm [8]. These lesions have a low risk of lymphatic spread and a low recurrence rate after EMR. The presence of submucosal invasion, scar, or ulceration, on the other hand, were considered as contraindications. In larger gastric lesions, however, EMR does not seem to be as beneficial as ESD since it is associated with a higher incidence of piecemeal resection and a local recurrence rates have been reported to range from 2% to as high as 35% [9].

6.4 Efficacy

In a meta-analysis comparing the effectiveness of ESD with EMR for early gastric cancer, 12 studies with a total of 3806 gastric lesions were studied. A total of 1734 ESD and 2072 EMR were included. It was shown that EMR had a significantly lower en bloc resection rate than ESD (43% vs.91.9%) [10]. The observation was true in both primary and recurrent EGC. In further subgroup analysis across different sizes of the gastric lesions, curative resection rate was significantly superior for the ESD group (79.5 vs. 59%).

In another more stringent meta-analysis comprising 9 retrospective studies with a total of 3548 gastric lesions (2053 EMR; 1495 ESD), it was shown that ESD required longer operative time than EMR with a weighted mean difference of 59.4 minutes. However, ESD had a significantly higher en bloc resection rate than EMR (OR: 9.69; 95% CI 7.74–12.13) [11]. The observation was also true for histologically confirmed complete resection rate (OR 5.66; 95% CI 2.92–10.96). It is noteworthy that even on follow-up, ESD group had a significantly lower recurrence frequency than the EMR group by an odds ratio of 4.67.

More updated pooled analysis further confirms significantly lower local recurrence rate for the ESD group (OR = 37.83; 95% CI 7.20–198). In a subgroup analysis, the ESD group had a significantly lower local recurrence rate than the EMR group even after follow-up for over 5 years [12]. Ahn et al. compared the curability and safety outcomes of EMR and ESD of EGC based on both the absolute and the extended indications according to the published Japanese Gastric Cancer Treatment Guidelines of 2010 [13]. In the absolute indication group, both EMR and ESD had similar curative resection rates of 94.4% (EMR) and 97.8% (ESD). However, the en bloc resection rate was slightly lower in the EMR group (72.4 vs. 96.8 vs. %). In the extended criteria, ESD showed better results than EMR for both en bloc (95.5 vs. 65.9%) and curative resection (91.1 vs. 83.0%). Local recurrences were similar in EMR and ESD groups for both absolute and extended indications. However, metachronous lesions were more commonly seen in the EMR groups under both indications.

6.5 Complications

ESD is technically more challenging and has higher bleeding and perforation risks when compared with EMR. On the other hand, increasing generalization of ESD over the past decade has led to improved technical competency, which results in the reduction of ESD-related complications in recent years. More importantly, the slightly higher complication rates in ESD has not resulted in serious clinical disadvantages. In the meta-analysis by Park et al., the intraoperative risk was 2.16 times higher for the ESD group (18.82%) than in the EMR group (7.73%) [10]. However, the postoperative bleeding risk was similar in both groups. Perforation occurs less often than bleeding, but is considered the most serious complication in ESD. There is a slightly higher perforation rate in the ESD group (4.54%) vs. the EMR group (1.03%), especially for primary EGC. In most studies, perforation could be treated with conservative management such as endoscopic clipping. No mortality related to perforation was found, and perforation rates are expected to decrease with greater operator experience.

6.6 Conclusions

The role of EMR for superficial neoplasia for the upper gastrointestinal tract is mainly for lesions smaller than 1.5 cm in maximal diameter. Its historical role in the management of early gastric and esophageal cancer is now mostly replaced by ESD due to the cumulated evidence of better en bloc resection rates and lower risk of long-term recurrence and metachronous neoplasia.

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7 Endoscopic Mucosal Resection: EMR for the Colon

Han-Mo Chiu

7.1 Introduction

Endoscopic mucosal resection (EMR) was developed to enable resection of non-polypoid gastrointestinal neoplasms. It was the primary method of resecting early gastric cancers until the introduction of endoscopic submucosal dissection (ESD) in the early 2000s. Currently, ESD has become the standard treatment for early noninvasive gastric or esophageal cancers as it can achieve a significantly higher rate of en bloc resection, thereby reducing the risk of recurrence and achieve curative resection. In contrast, EMR still plays an important role in treating colorectal neoplasms, as the majority of these neoplasms are benign and small. For a number of reasons, EMR is considered a first-line treatment option for colorectal neoplasms. First, the majority of recurrent or residual neoplasms after resection of a benign neoplasm are still benign therefore re-EMR is considered as safe and justified. Second, ESD is highly technically demanding and time consuming, and thus should be reserved for lesions at higher risk of invasion that require en bloc resection, and those considered technically difficult for EMR. A recent cost-effectiveness analysis comparing EMR, universal ESD, and selective ESD (ESD for only selected lesions, and EMR for the majority of lesions) revealed that most of the large, laterally spreading tumors could be curatively resected with EMR, and a selective ESD strategy would be a more cost-effective way of treating such lesions [1]. Third, recent studies have demonstrated that more than 95% of neoplasms can be eradicated after two procedures [2, 3].

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7.2 Instruments, Devices, and Materials for EMR

7.2.1 Preparation

Excellent bowel cleansing is important to achieve adequate visualization of the lesion during the procedure, and also for safety should an unexpected perforation occur. To achieve better bowel preparation, split dosing or same day administration of a cleansing agent is highly recommended prior to EMR, especially for large lesions. The author personally uses 2 liters of PEG-ELS for bowel prep for ordinary screening or diagnostic colonoscopy, but 1 plus 2 liters split dosing for endoscopic piecemeal resection (EPMR) or ESD for large neoplasms.

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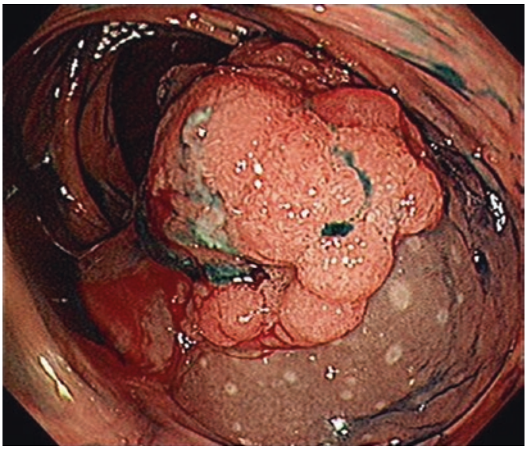


Fig. 7.1 Good cushion that created with hypertonic solution (glycerol solution)

7.2.2 Selection of Submucosal Injection Fluid

Submucosal injection fluid is crucial for creating a good cushion to facilitate lesion resection. Usually, hypertonic fluid (glycerol [10% glycerin and 5% fructose in normal saline solution] or succinylated gelatin [Gelofusine®]) is preferred over normal saline as it is retained in the submucosal layer for a much longer period of time, with a better shape, and thereby achieves a higher rate of en bloc resection [4, 5] (Fig. 7.1). A recent meta-analysis found that by using a hypertonic solution for submucosal injection during EMR, resulted in a significant increase in the likelihood of en bloc resection (odds ratio [OR] = 1.91; 95% confidence interval [CI]: 1.11–3.29) and decrease in residual lesions (OR = 0.54; 95% CI: 0.32–0.91) as compared with normal saline [2]. The difference is more remarkable when resecting flat neoplasms, such as a non-granular-type laterally spreading tumor (LST-NG), or depressed neoplasms. A hypertonic solution, such as dextrose/water, may also achieve adequate dissection, but has the disadvantage of causing cell damage and affecting the pathological diagnosis when the concentration exceeds 20% [6].

7.2.3 Selection of Snare

A stiff snare is preferred for EMR, as it can facilitate entrapment of surrounding normal mucosa at the margin of the neoplasm. Boston Captivator or Captivator II series (Boston Scientific) snares are good choices as they are available in various sizes (10–33 mm), shapes (round, oval, crescent, or hexagonal), and stiffness for treating neoplasms with different morphology, size, and location. In principle, a large snare is used for the first few cuts and a smaller one for the remaining tissue at the resection margin.

7.2.4 Electrosurgical Generator Unit

The majority of currently available electrosurgical generator units possess sophisticated microprocessors and software enabling them to generate a variety of electrosurgical waveforms, which influence the end result of the electrosurgical energy. An electrosurgical generator unit equipped with a blended current function is crucial for a safe and effective EMR procedure. The term blended current refers to a waveform with duty cycles between 12 and 80%, indicating that there is a blend of the proportion of cells that have burst (cutting current) and those that have been desiccated (coagulation current) [7] (Fig. 7.2). Performing EMR with only coagulation current may cause deep tissue injury, and possibly a delayed perforation and should be avoided. The author uses an Olympus ESG-100 electrosurgical generator unit, which is compact and easy to use, with the setting of pulse coagulation 2, 50 Watt for EMR procedures.

7.3 Resection Techniques

Endoscopic mucosal resection is also known as an "inject and cut technique." The diseased mucosa is lifted up from the muscular layer by the submucosal

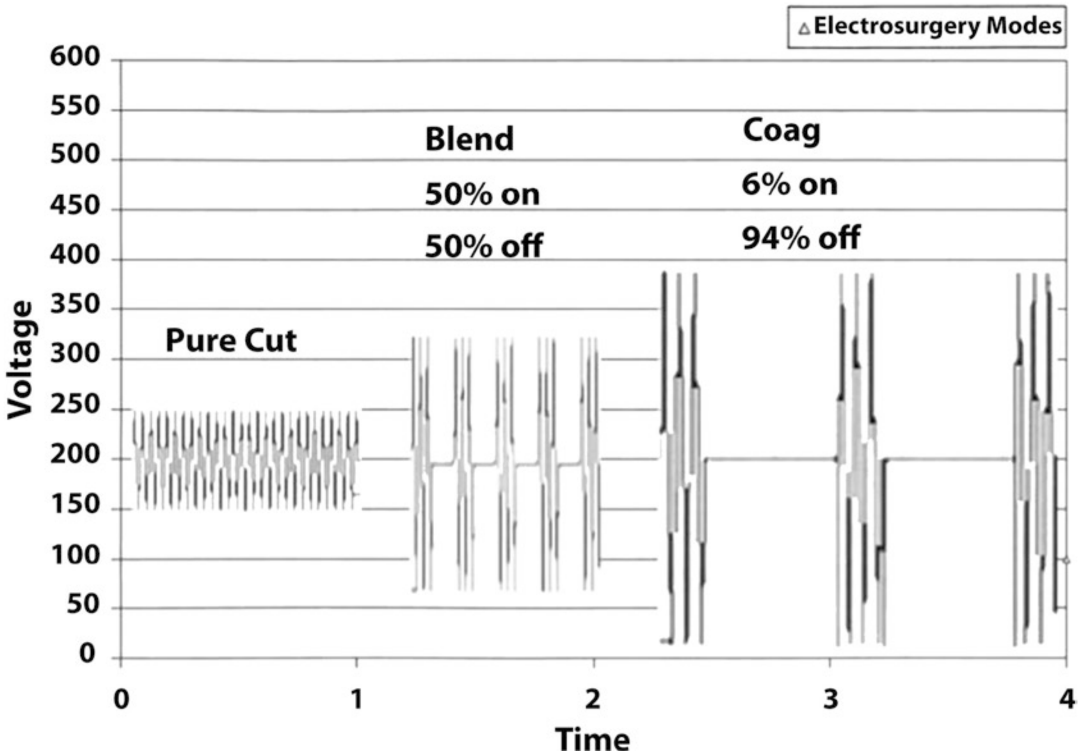


Fig. 7.2 The electrosurgical current modes commonly used in GI endoscopy.[7] Blended current is a mode that uses preset duty cycles ranging from 12 to 80%

fluid cushion created by the submucosal injection, captured, and strangulated using the electrosurgical snare, and then resected. The followings are the steps for performing safe and effective EMR:

- *Determination of the lesion margin*

  Delineation of the lesion margin can be easily achieved using sprayed indigo-carmine dye spraying for identifying the boundary of neoplastic and nonneoplastic pit pattern. Narrow-band imaging (NBI) can also be used, but chromoendoscopy is preferred, if available, as the boundary of some lesions (e.g., sessile serrated adenomas or depressed neoplasms) cannot be visualized well with NBI.
- *Patient positioning*

  Adjusting the patient position is sometimes required for obtaining the best EMR visualization. The lesion should ideally be placed at the 5 or 6 o'clock position so that it can be easily accessed by the snare via the working channel, which is also located at the 6 o'clock position of the colonoscope. It is also advisable to place the lesion at anti-gravity direction because this can help lift the lesion after submucosal injection (the injection can increase the volume and weight of the lesion, and hence move toward the direction the gravitational force is acting), avoid accumulation of fluid that can interfere with the EMR procedure, and the accumulation of blood which can hinder achieving hemostasis should bleeding be encountered (Fig. 7.3).
- *Submucosal injection*

  Forcing the injection needle toward colon wall may sometimes injury the muscularis

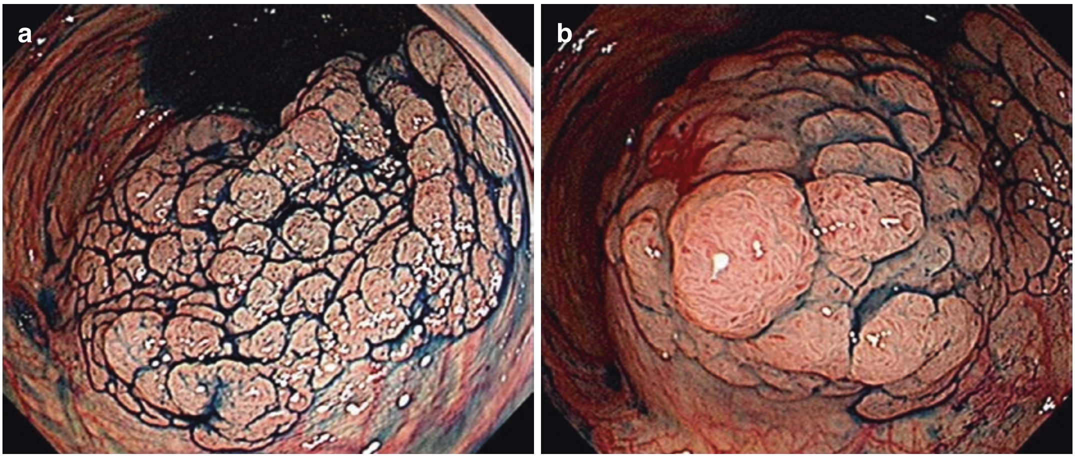


Fig. 7.3 Positioning of patient and lesion for EMR. (**a**): Lesion is placed at anti-gravitational direction and also at 5–6 o'clock position and indigo-carmine dye is visible at the gravitational direction. (**b**): After submucosal injection, the weight of the lesion increased and provided a good traction force toward the gravitational direction

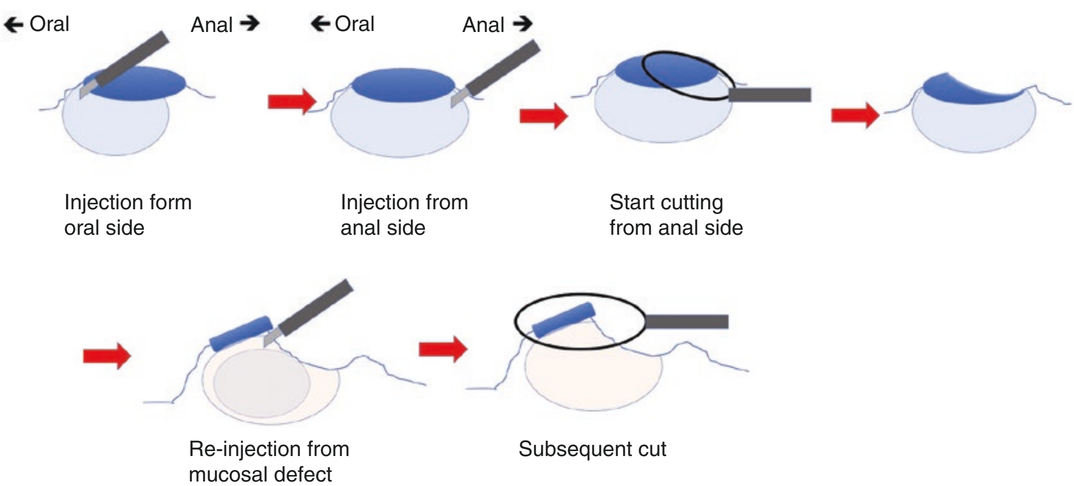


Fig. 7.4 Technique and flow of submucosal injection

propria, or cause transmural injury. Placing the needle tip in the mucosal layer may cause formation of a hematoma, which can hinder subsequent procedures. Instead, dynamic injection should be performed, with elevation of the tissue into the lumen and toward the tip of colonoscope (Fig. 7.4: illustration).

- *Resection (lesions less than 20 mm)*

  En bloc snare excision is appropriate for lesions less than 20 mm, and sometimes up to 25 or 30 mm. En bloc resection is associated with a lower recurrence rate as compared with piecemeal resection. Aligning the snare at the edge of the neoplasm is an important first step for cutting (Fig. 7.5). If a large en bloc resection is to be attempted, it is effective to align the longitudinal axis of the snare with the longest axis of the lesion, which maximizes the tissue capture capacity.

- *Resection (lesions larger than 20 mm)*

  For larger lesions, EPMR is the preferred technique. Before beginning EPMR, a

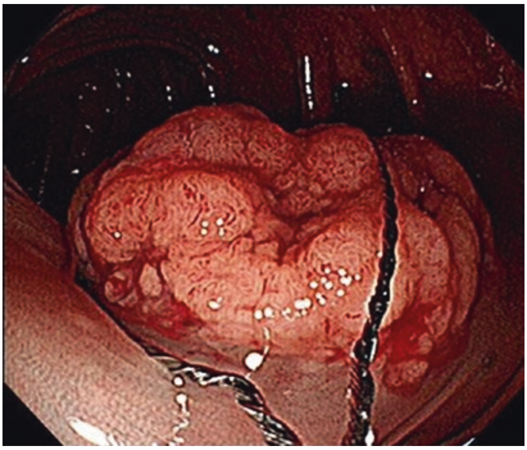


Fig. 7.5 Aligning the snare at the edge of the neoplasm is an important first step for cutting

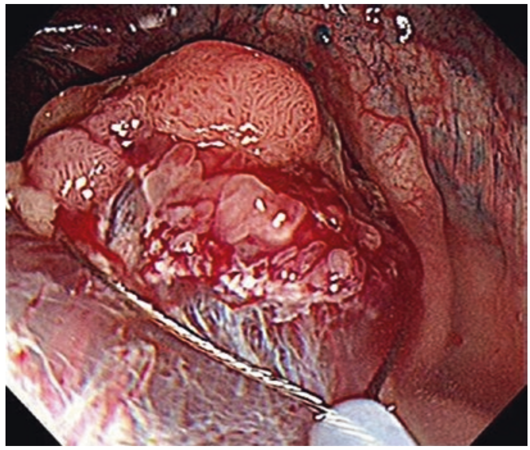


Fig. 7.6 Using the edge of the advancing mucosal defect as a step for the next snare placement

detailed inspection of the surface capillary pattern with NBI, or the pit pattern with chromoendoscopy, is mandatory. Should there be any suspicion of submucosal invasion (type V_I pit pattern), then planned EPMR by resecting the large nodular part as a whole, where submucosal invasion is commonly existent, followed by cutting other portion of the lesion with additional several cuts. For lesion with a higher risk of multifocal invasion (such as LST-NG-PD), en bloc resection with ESD is preferred over EPMR.

Usually, EPMR can be started at one edge of the lesion (usually the anal side, or the site where a large nodule or suspicious cancerous portion is located), and then proceed cranially in a stepwise manner. Align the snare at the edge of the advancing mucosal defect to minimize the occurrence of tissue islands within the defect (Fig. 7.6). It is advisable to include a 2–3 mm margin of normal mucosa during cutting, and use the edge of the advancing mucosal defect as a convenient step for the next snare placement. This can reduce the risk of adenoma islands, and subsequent residual or recurrent lesions (Fig. 7.7). The step-by-step process of EPMR for a large laterally spreading tumor is demonstrated in Fig. 7.8a–m. It is also important to image the muscular plane of the colon wall, and the resection plane should be parallel with it to avoid transmural injury and resultant perforation.

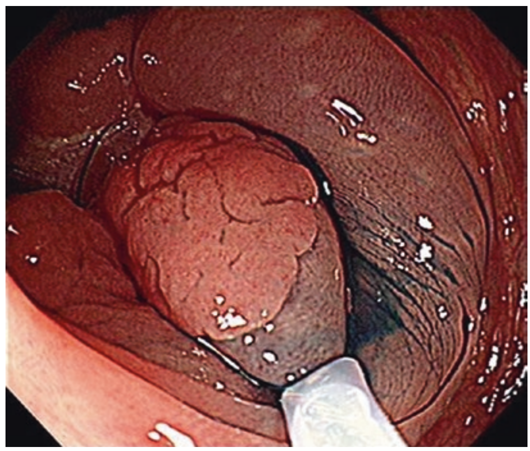


Fig. 7.7 Including little margin of normal mucosa to avoid residual neoplasm after resection

For lesions that are suspicious for malignancy (invasive or noninvasive), marking (tattooing) with a carbon solution after endoscopic resection is necessary to identify the lesion site during additional laparoscopic colectomy, or at surveillance colonoscopy. Technically, we create a cushion with a submucosal injection solution (as used in EMR) at the opposite side of the resection wound, then inject the marking solution into this cushion. A marking made in this manner will remain visible for a year or more.

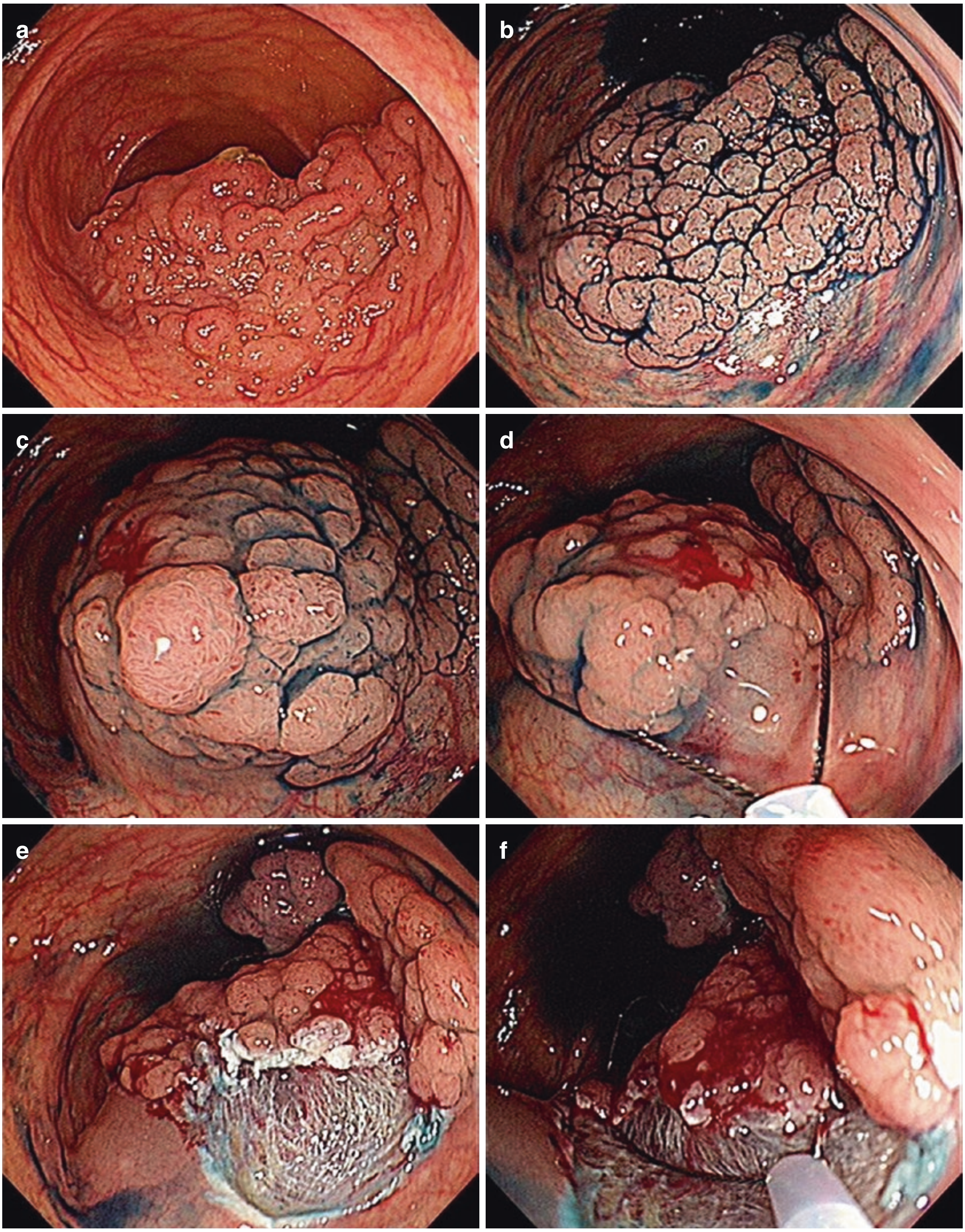


Fig. 7.8 Piecemeal EMR technique for a large 0-IIa (LST-G) lesion. (**a**): A 7 cm 0-IIa (LST-G mixed nodular type) at transverse colon. (**b**): Chromoendoscopy with indigo-carmine dye praying can delineate the border of the lesion. We can observe that lesion was placed at 5–6 o'clock and anti-gravitational location. (**c**): After submucosal injection. (**d**): First cut of EMR started from the anal side. (**e**): Resection wound after first cut. (**f**): Second cut. (**g**): Resection wound after the second cut. (**h**): Third cut. (**i**): Resection wound after third cut. (**j**): Final cut. (**k**): Resection wound after completion of the procedure. (**l**): Chromoendoscopy with indigo-carmine dye can help identifying residual neoplastic tissue. (**m**): Retrieval of resected specimen with Roth Net Retriever

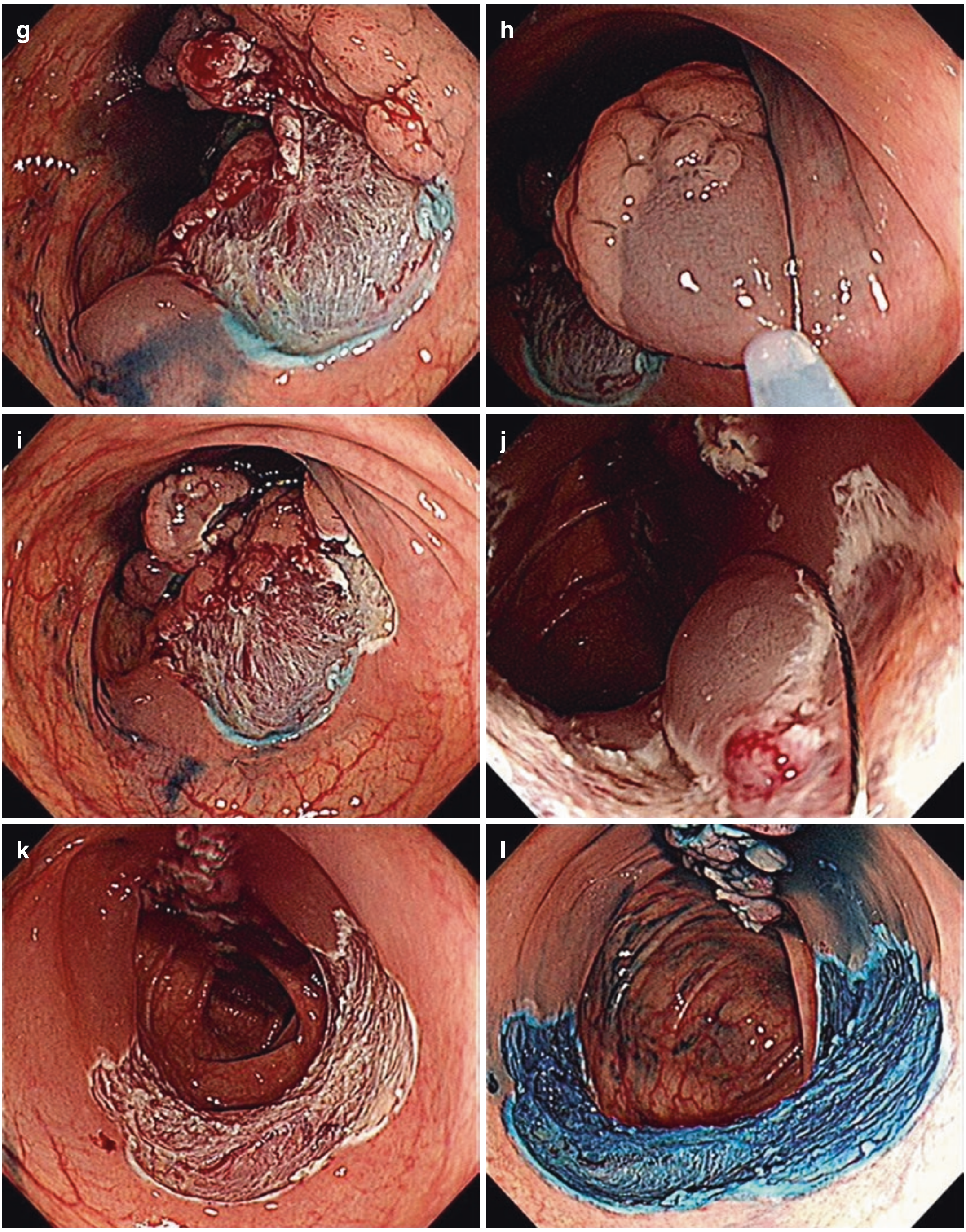
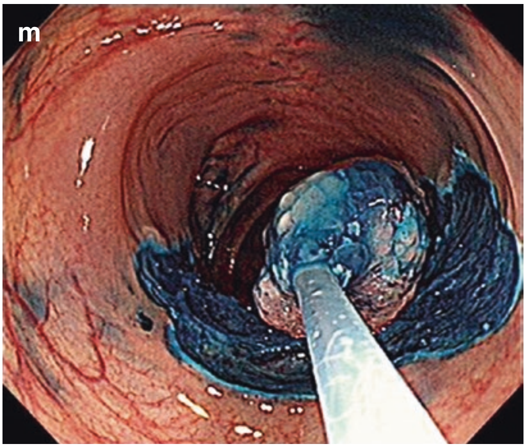


Fig. 7.8 (continued)



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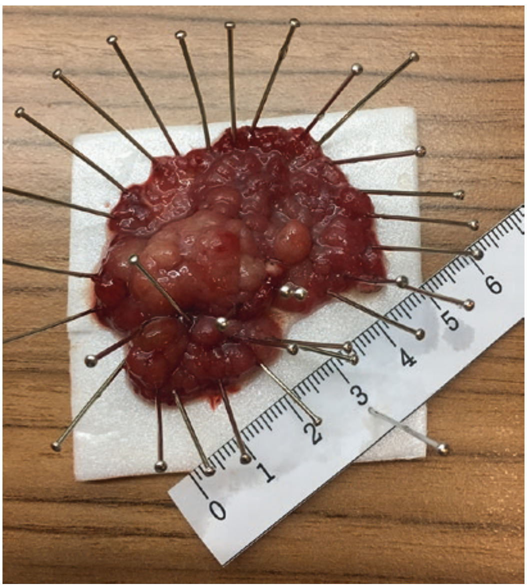

Fig. 7.9 Endoscopically resected specimen pinned on a Styrofoam board

7.4 Management of the Specimen

Endoscopically resected specimens should be pinned on a cork or Styrofoam board to facilitate pathological assessment of the lesion (Fig. 7.9). Ideally, specimens of a large lesion that has been resected in a piecemeal manner should be reconstructed and pinned, though sometimes complete reconstruction is difficult. When complete reconstruction cannot be performed, the pieces of the lesion that are highly suspicious for malignancy should be identified to avoid the risk of underdiagnosis (overlooking the existence of deep invasion pathologically). The author very frequently communicates and discusses the specimen with our pathologist, and correlates endoscopic with pathological findings. This process is very important for providing feedback on the accuracy of the endoscopic diagnosis.

7.5 Post-procedural Care

Post-procedural care for EMR is similar to that of ordinary polypectomy. For large lesions (e.g., ≥5 cm) that have been removed by EPMR, the patient is kept fasting overnight, then a liquid followed by a soft diet is begun the next day. Patients are also instructed to avoid vigorous exercise or alcohol intake during the week after the procedure to reduce the risk of post-procedural bleeding.

If injury of the muscle layer occurs during the procedure, prophylactic antibiotics should be prescribed and there should be a longer period of fasting, and the timing of resuming oral intake will depend on the clinical condition and recovery of the patient.

7.6 Surveillance and Treatment of Residual Neoplasms

Surveillance after EMR, especially EPMR for large lesions, is mandatory to detect and treat residual neoplasms and avoid the risk of post-colonoscopy colorectal cancer (CRC). According to the US Multi-society taskforce and European Society of Gastrointestinal Endoscopy (ESGE) guidelines, surveillance colonoscopy is recommended within 6 months after piecemeal resection of a large adenoma [8–10]. The risk of residual neoplasm or recurrence has been reported to be associated with the number of pieces in a piecemeal resection, and lesion size, location, and morphology [11, 12]. The approximate risk of residual or recurrent neoplasm after large field EMR was reported to be 16%, and the neoplasm is usually unifocal and diminutive. Late recurrence occurs in 4% of cases, and recurrence can be managed endoscopically in 93% of cases [3].

If the residual lesion can be lifted with submucosal injection, then re-EMR is an appropriate procedure (Fig. 7.10a–c), but a hot biopsy (Fig. 7.11a–c) can also be performed for tiny residual lesions. If a residual lesion cannot be managed with repeat conventional EMR (significant non-lifting or lesion cannot be entrapped into the snare) or hot biopsy (lesion size larger than a cup of the forceps), then precut EMR (using the snare tip for the mucosal incision and then snaring (Fig. 7.12a–d) or even ESD should be considered (Fig. 7.13a–c).

For cancerous residual lesions (Fig. 7.14a and b), surgery is recommended because of the potential risk of a non-detected invasive cancer (either endoscopically or pathologically) and regional lymph node metastasis.

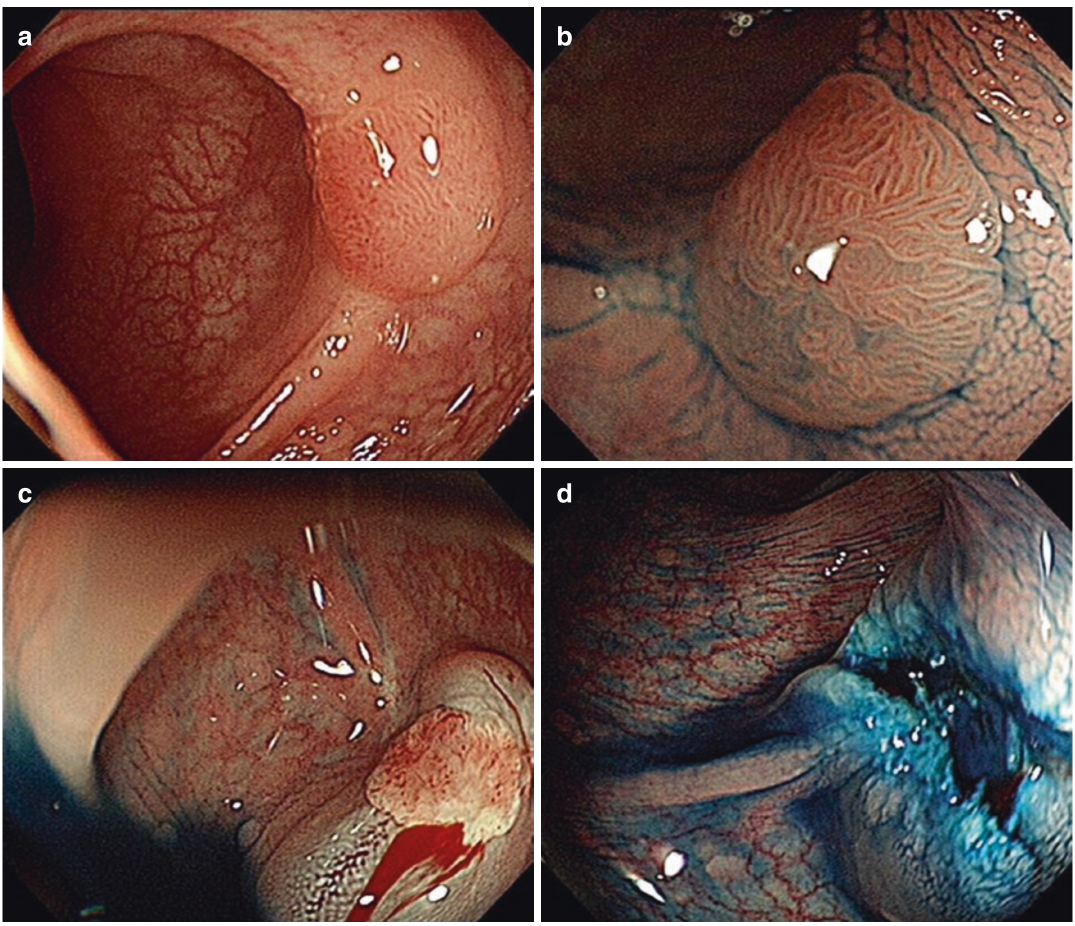

Fig. 7.10 Management of residual neoplasm: Re-EMR. (**a**): White light endoscopy. (**b**): Chromonedoscopy with indigo-carmine dye. (**c**): Successful lifting of the residual lesion with submucosal injection. (**d**): EMR wound

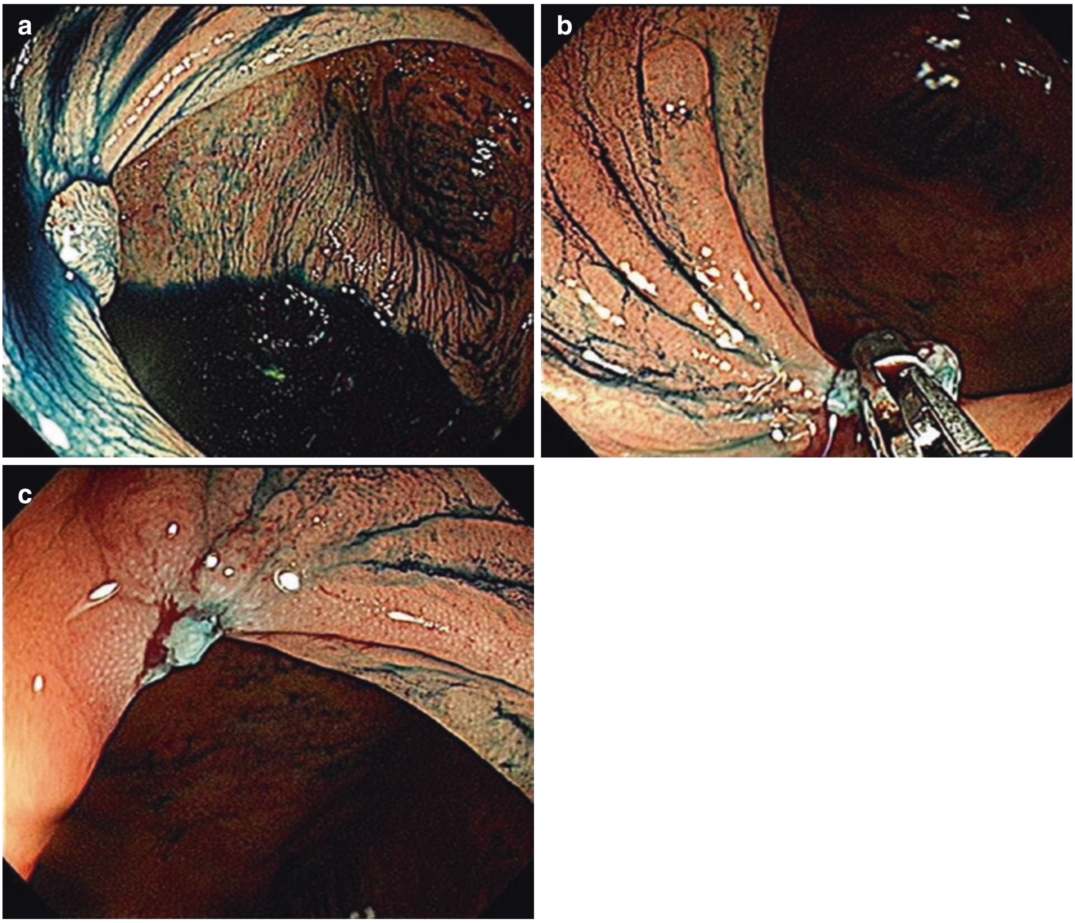

Fig. 7.11 Management of residual neoplasm: Hot biopsy. (**a**): Residual neoplasm. (**b**): Apply hot biopsy forceps. (**c**): After hot biopsy

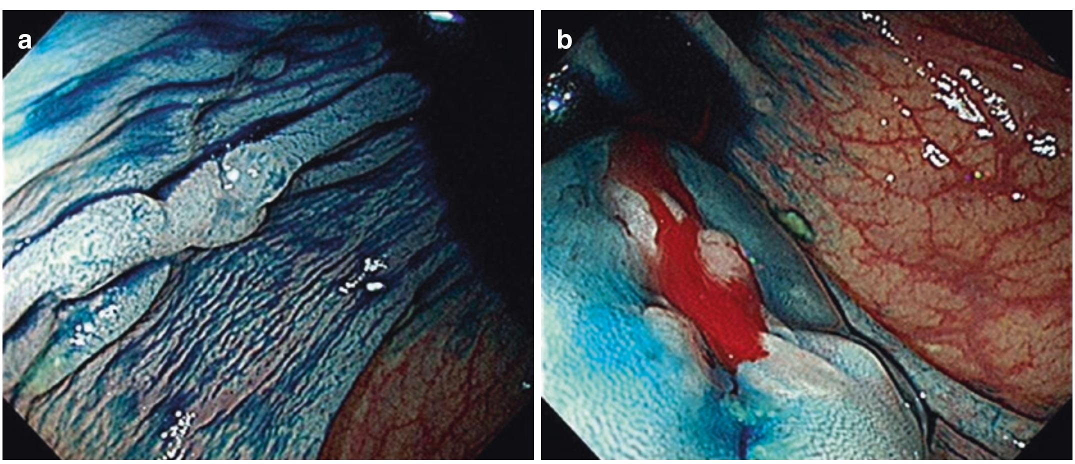

Fig. 7.12 Management of residual neoplasm: Precut EMR. (**a**): Residual neoplasm. (**b**): Significant non-lifting sign after submucosal injection. (**c**): Precutting (incision of surrounding mucosal). (**d**): Resection wound

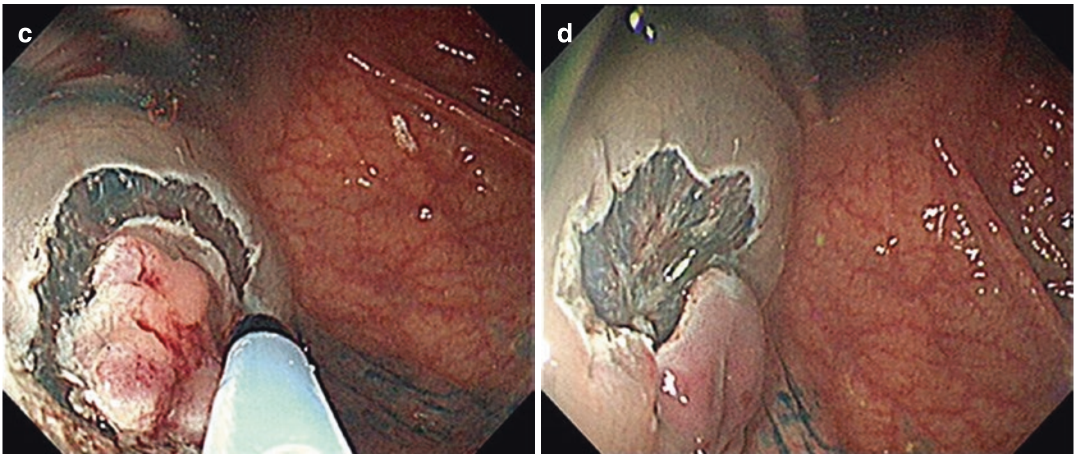

Fig. 7.12 (continued)

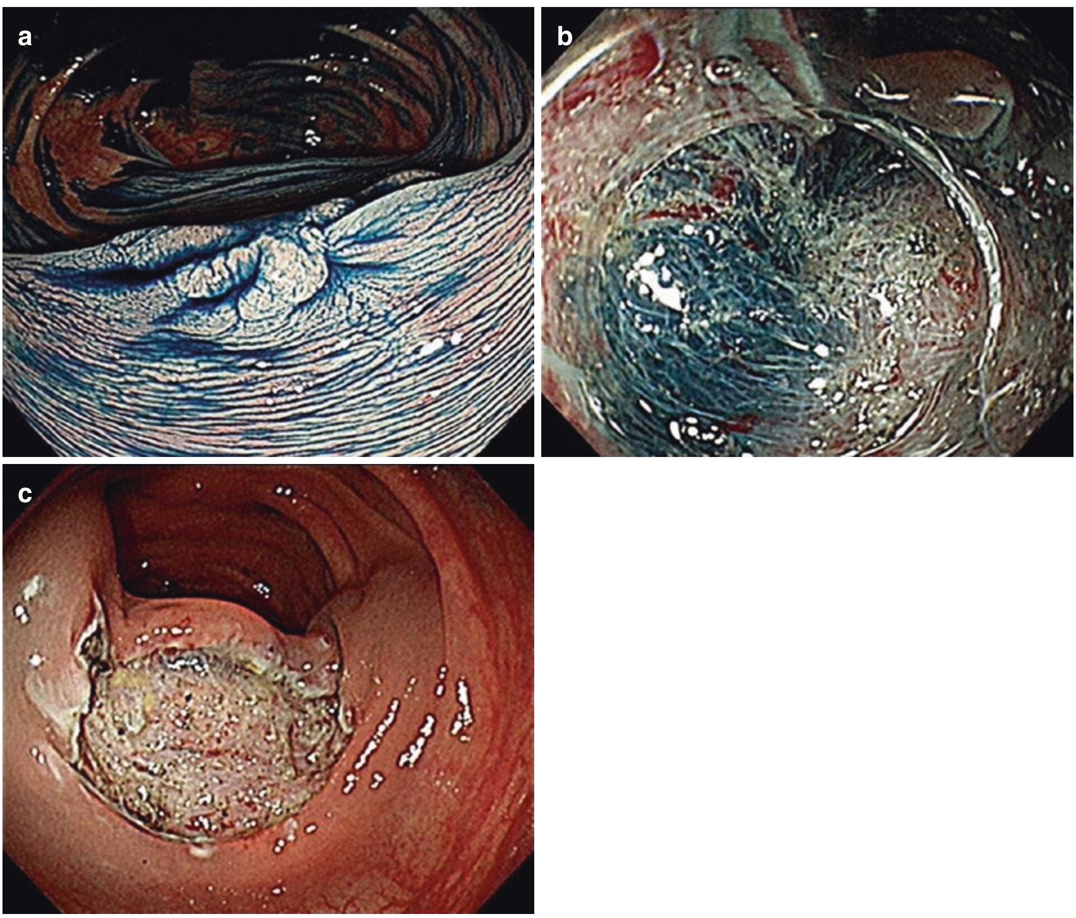

Fig. 7.13 Management of residual neoplasm: ESD. (**a**): Residual neoplasm with significant scarring and fold contraction due to previous procedure. (**b**): Submucosal dissection. (**c**): ESD wound

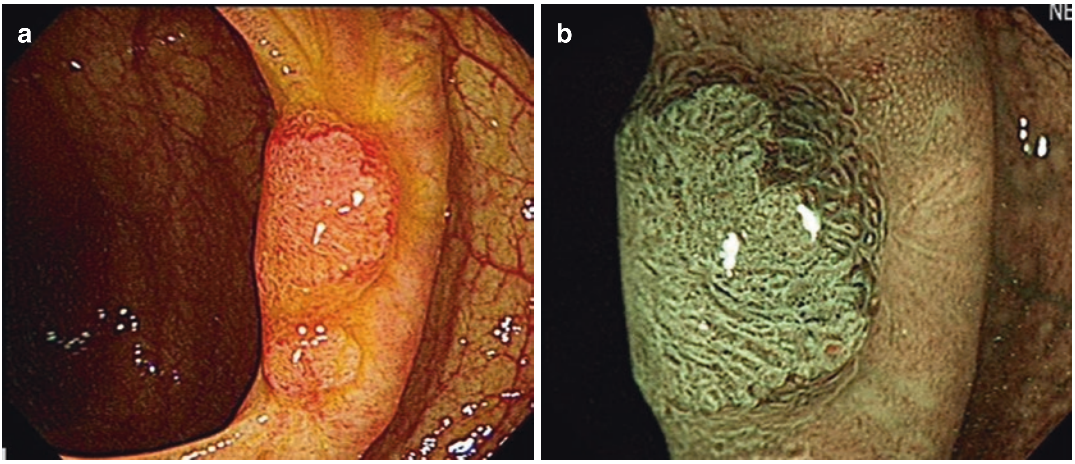

Fig. 7.14 Cancerous recurrence after EPMR. (**a**): While light endoscopy revealed reddish residual lesion on previous EPMR scar. (**b**): NBI revealed cancerous recurrence

7.7 What Lesions Should Not Be Treated with EMR?

If there is very significant non-lifting after submucosal injection, then EMR may carry the risk of muscle layer injury or perforation. When non-lifting occurs, severe submucosal fibrosis is likely present and the lesion should be managed by ESD technique in consideration of procedural safety and completeness of resection. If there is any sign of invasive cancer (e.g., Kudo type V pit pattern, bulging of the lesion with fold convergence; refer to diagnosis chapter) then there is a large risk of regional or distant lymph node metastasis and surgical resection should be performed. For lesions located at specific locations such as the anal verge or ileocecal valve, re-EMR for a residual neoplasm is usually technically very difficult owing to the anatomical space constraint (difficult to open the snare). For such lesions, an ESD technique should be initially performed.

7.8 Summary

Along with evolving endoscopic technologies, an increasing number of endoscopists are now performing endoluminal treatment for colorectal neoplasms in their daily practice. EMR, together with conventional polypectomy, can be used to manage more than 95% of the colorectal neoplasms. Because of the utility of EMR, every endoscopist should learn and master this technique.

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8 History, Instruments, and Preparation for ESD

Shiaw Hooi Ho and Noriya Uedo

8.1 History

Beginning with the introduction of endoscopic polypectomy using high-frequency electroresection in the 1970s [1], endoscopic resection techniques have evolved tremendously with time. Apart from the conventional endoscopic mucosal resection (EMR) technique, various other EMR techniques were introduced in the 1980s and 1990s: strip biopsy EMR technique was introduced in 1984 [2] while cap-EMR technique was introduced in 1992 [3]. Despite development of all these EMR techniques, the ability of EMR to achieve en bloc resection for colorectal lesion >2 cm was around 70% even in high volume centers because the size of resected specimen is limited by the size of snares [4]. This becomes a problem when strict en bloc resection is required for resection of upper gastrointestinal (GI) lesions which are mainly cancerous. This became a main reason why later the endoscopic submucosal dissection (ESD) was developed.

Initial concept of ESD has begun around the year 1988 as a technique called ERHSE (endoscopic resection with local injection of hypertonic saline epinephrine solution) to ensure a free 5-mm mucosal margin around the early gastric cancer before EMR [5]. This technique was known today as hybrid ESD. In the initial description of this technique, mucosal markings were made around the lesions followed by creation of submucosal fluid cushion (SFC) below the markings. Needle knife was then used to make a circumferential mucosal incision outside the marking. This was then followed by lifting of the specimen by creation of SFC below it and the placement of snare along the "circumferential groove" created by the mucosal incision. This hybrid ESD excels in ensuring a tumor-free horizontal margin during endoscopic resection of small lesions but is not applicable for large lesions owing to the increasing difficulty in ensnaring the lesion in an en bloc fashion. Later, in the late 1990s at the National Cancer Center Hospital Japan, an insulated tip (IT) knife was invented to perform the mucosal incision in a safer manner. This subsequently led to the use of such knife to achieve submucosal trimming and eventually, complete submucosal dissection, i.e., ESD of what we know of today. Current practice of ESD is generally divided into five stages: (1) identification of lesion's border with (usually for esophageal and gastric lesions) or without mucosal marking (for colonic polyps with clearly visible border); (2) creation of SFC below the lesion's border intended for the mucosal incision. This is followed by either complete (usually small gastric

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lesion) or partial (esophageal and colonic lesions or any large lesions) mucosal incision depending on lesion's location, size, and intended method of dissection; (3) submucosal dissection with on-the-spot management of bleeding; (4) treatment of mucosal defect following ESD and (5) specimen retrieval and handling.

ESD has engaged strong interest among practitioners in the field of GI endoscopy. It was shown to be able to provide en bloc resection for early GI neoplasia. As such, not only does it provide minimally invasive curative endoscopic resection, it also provides the whole specimen for accurate histopathological assessment for curability. Perhaps, ESD is one of the most satisfying endoscopic procedures to be performed owing to the various points as illustrated above. Due to its slow learning curve, acquiring a competent skill in performing good-quality ESD requires much practices. Studies from Japan indicated that 30–50 supervised ESDs are required to achieve a competent level. Despite its demand for skilled endoscopists, ESD is a relatively safe procedure with overall high efficacy even in centers with low volume for ESD [6].

ESD technique in opening up the submucosal space has led to the development of other techniques that harp on the advantage gained from the access to this "once-secluded" area. A decade after the introduction of ESD, per-oral endoscopic myotomy (POEM) was introduced by Inoue et al. to treat achalasia cardia. At around the same time, other submucosal tunneling techniques were mushrooming such as natural orifice transluminal endoscopic surgery (NOTES), submucosal tunneling endoscopic resection (STER), and endoscopic submucosal excavation (ESE) for the resection of submucosal lesion, POEM for the treatment of gastroparesis (G-POEM) and Zenker's diverticulum (Z-POEM), etc. All these techniques were now referred to as "third space endoscopy". Based on this similar concept, refined ESD technique was introduced recently as a pocket creation method to aid in the resection of large lesion [7]. By using such a method, various favorable factors pertaining to the success of ESD can be further enhanced such as the scope stability, retention of SFC, and ease of submucosal dissection.

8.2 Instruments

Generally, various devices and instruments are available to conduct an ESD procedure. It is mostly up to the individual preference when it comes to the selection of the primary instrument, i.e., the knives. A summary of the types of ESD knives, their characteristics, and their suggested usage is shown in Table 8.1.

8.2.1 Knives

8.2.1.1 Straight-tip Needle Knife Type

Straight-tip needle knife type equipment is the most popular ESD knives as it can be used in most of the stages in ESD, i.e., mucosal marking, mucosal incision, and submucosal dissection. Furthermore, its short tip allows accurate and pinpoint dissection and is a useful tool in dissecting the submucosal plane in areas of fibrosis. To top it off, most of the needle knife-type devices now come with water jet capability (for SFC) and this feature certainly aid in shortening the procedure time. As a general rule, the dissecting direction for a needle knife type device is from the center outwards to the periphery.

Examples of other straight-tip needle knife type devices are Dual Knife (Olympus) (Fig. 8.1a), Flex Knife (Olympus) (Fig. 8.1b), Flush Knife (Fujifilm) (Fig. 8.1c), Hybrid Knife (ERBE) (Fig. 8.1d), Jet B-Knife (Zeon Xemex) (Fig. 8.1e), and Splash M-Knife (Pentax) (Fig. 8.1f). Among these needle knife type ESD knives, Jet B-Knife is the only bipolar knife. It is believed that the risk of deep injury is reduced by the bipolar circuit design. Hybrid Knife is the only needle knife type ESD knives that is equipped with a high-pressure jet function, which enables it to emit a water jet capable of penetrating the mucosa layer. Owing to this unique feature, it reduces procedure time by minimizing the time spent on exchanging endoscopic accessories. However, a separate single-use pump needs to be purchased along with the knife.

Table 8.1 Types of ESD knives and their characteristics

Types of ESD knives	Model name (according to alphabetical order)	Figures	Water-jet capability (Y = yes; N = no)	Mono- or bipolar design (M = mono; B = bi)	Marking	Precut	Mucosal incision	Fibrosis	Hemostasis
Straight-tip needle knife type	DualKnife (Olympus)	8.1a	Y	M	O	O	O	O	~
	FlexKnife (Olympus)	8.1b	N	M	O	O	O	O	~
	Flush Knife (Fujifilm)	8.1c	Y	M	O	O	O	O	~
	Hybrid Knife (ERBE)	8.1d	Y	M	O	O	O	O	~
	Jet B (Xemex)	8.1e	Y	B	O	O	O	O	~
	Splash M-Knife (Pentax)	8.1f	Y	M	O	O	O	O	~
Bended-tip needle knife type	HookKnife (Olympus)	8.1g	Y	M	O	O	O	O	~
	Triangle Tip (TT) Knife (Olympus)	8.1h	Y	M	O	O	O	~	~
Blunt-tip type	Insulated Tip (IT) Knife (Olympus)	8.1ia and 8.1ib	N	M	X	X	O	~	~
	Mucosectom (Pentax)	8.1j	N	M	X	X	~	~	~
	Safe Knife (Fujifilm)	8.1k	N	M	~	~	O	X	~
	Swanblade (Pentax)	8.1l	N	M	~	~	~	~	~
Scissor type	Clutch Cutter (Fujifilm)	8.1m	N	M	O	O	O	O	O
	Stag-Beetle (SB) Knife (Sumitomo)	8.1n	N	M	O	O	O	O	O

O = suitable; ~ = somewhat suitable; X = not suitable

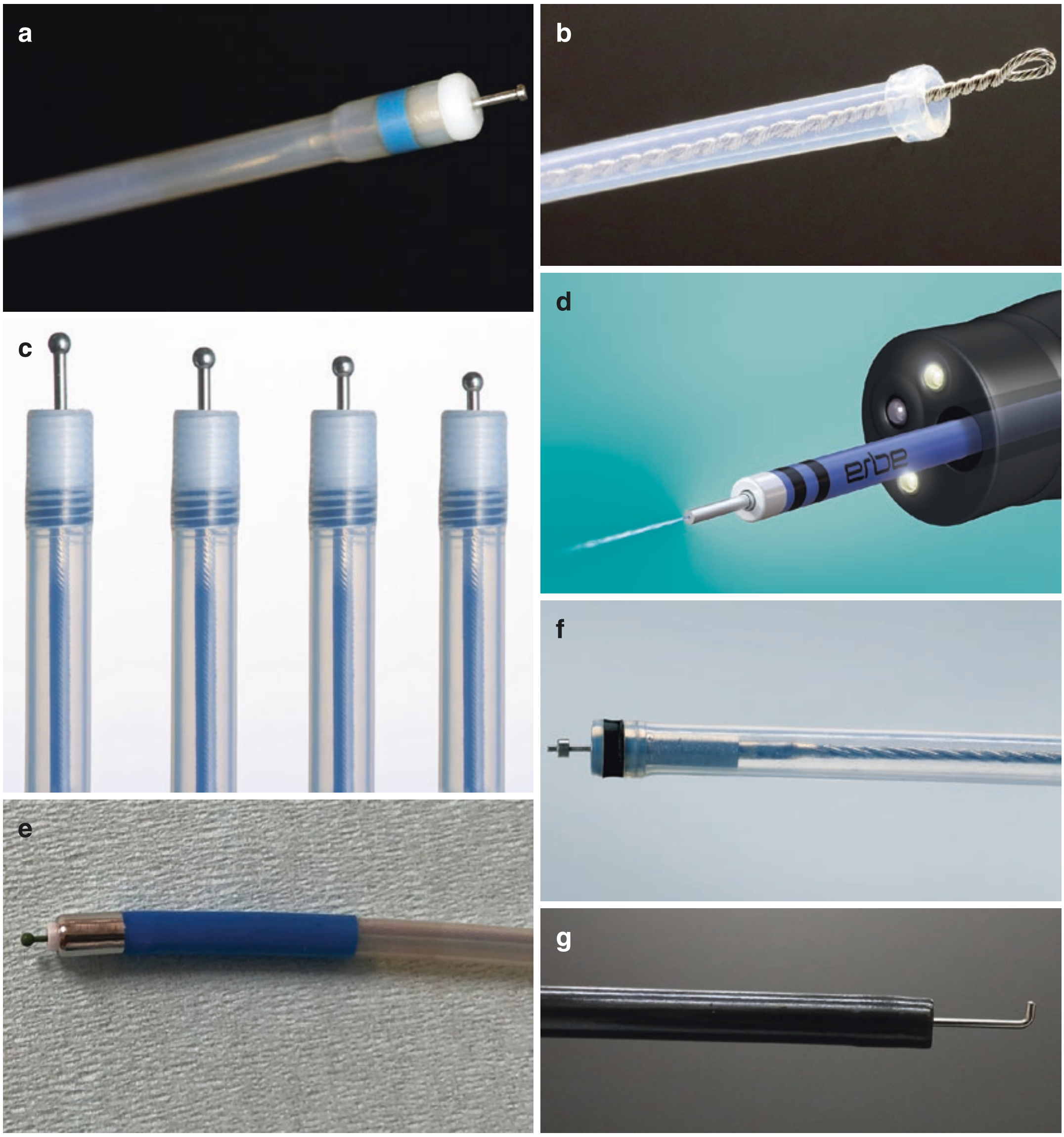


Fig. 8.1 (**a–n**): Types of ESD knives. (**c**, **k**, **m**): Figures courtesy of Endoscopy Systems Division of FUJIFILM Corporation. (**d**): Figure courtesy of ERBE Elektromedizin GmbH. (**e**): Figure courtesy of Dr. Seiichiro Abe, National Cancer Center Hospital, Tokyo, Japan. (**f**, **j**, **l**): Figures courtesy of PENTAX Medical. (**n**): Figure courtesy of Sumitomo Bakelite Co. Ltd

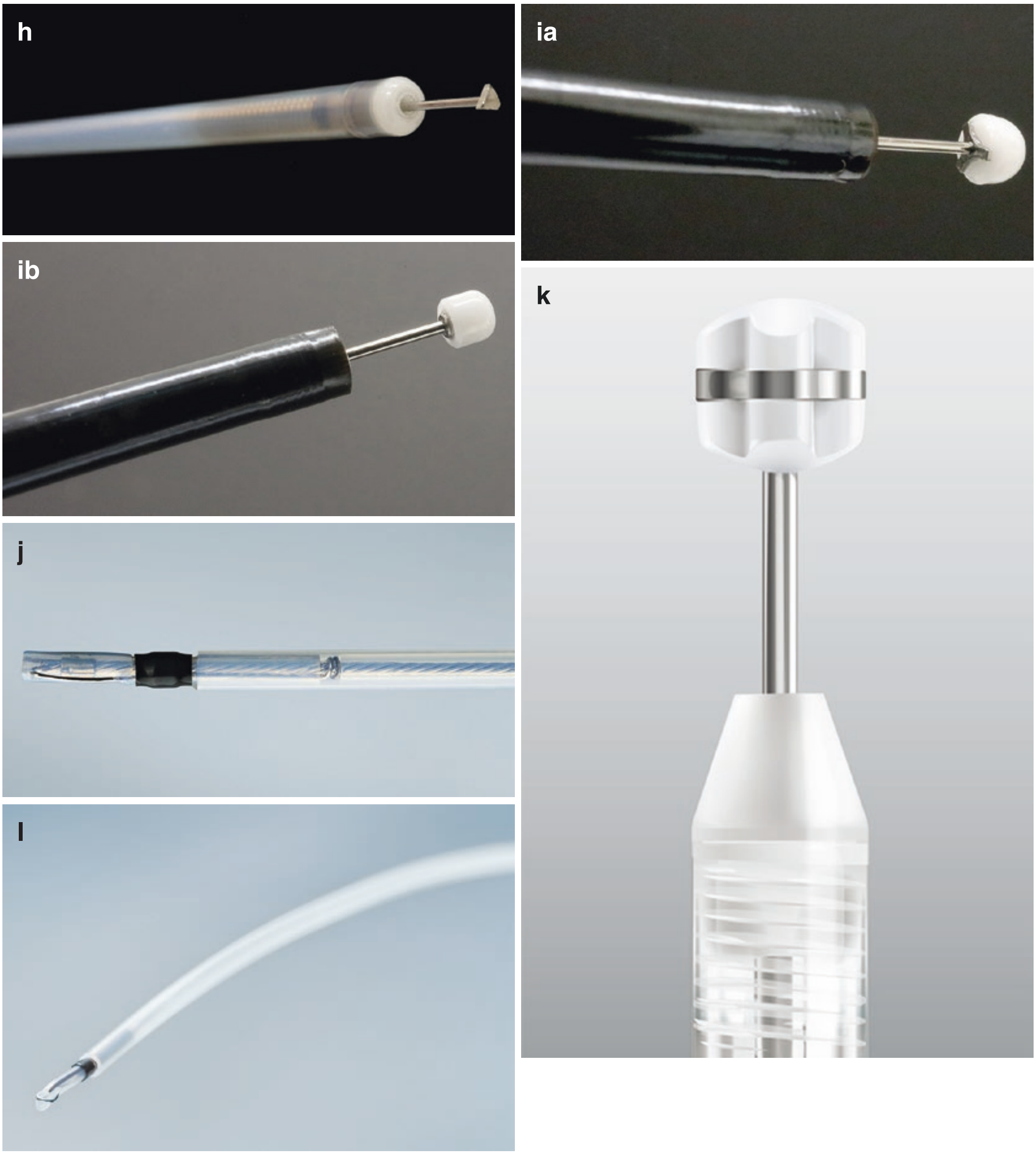


Fig. 8.1 (continued)


m


n

Fig. 8.1 (continued)

8.2.1.2 Bended-tip Needle Knife Type

Bended-tip needle knife type device such as Hook Knife (Olympus) (Fig. 8.1g) facilitates dissection in the fibrotic submucosal area. Not only does it function like other needle knife type devices, the bended-tip allows a small amount of submucosal tissue to be "hooked" and dissected. The safety feature is that the "hooked" tissue can be pulled back toward the scope when the dissecting current is run through the knife thus preventing untoward injury.

Another kind of bended-tip needle knife type device is Triangle Tip (TT) Knife (Olympus) (Fig. 8.1h) that is widely used in Per-Oral Endoscopic Myotomy (POEM) procedure and also in some ESD procedures. Currently, both Hook Knife and TT knife are equipped with water jet function.

8.2.1.3 Blunt-tip Type

Insulated-Tip (IT) Knife (Olympus), a blunt-tip device, was the first knife designed and dedicated to ESD use. It has a ceramic tip at the distal end which is nonconducting. This nonconducting part prevents the current transmission from tip of the needle to deep tissues and thus reducing the risk of inadvertent perforation or bleeding. Now, in its second generation, various improvements to the design of the ceramic tip were made to improve the dissection and safety profile. In IT Knife 2 (Fig. 8.1ia), 3 electrodes were added to the inner part of the ceramic tip to facilitate dissection. In IT Knife Nano (Fig. 8.1ib), the ceramic tip was made smaller with an attached circular plate rather than the 3 electrodes as seen in IT Knife 2.

As a general rule, the dissecting direction of a blunt-tip device is opposite to a needle knife type device, i.e., the dissection should be started by hooking onto one of the peripheral edges and move medially toward the center likened to the swinging movement of a Katana sword.

Other examples of blunt-tip-type devices are Mucosectom (Pentax) (Fig. 8.1j), Safe Knife (Fujifilm) (Fig. 8.1k), and Swanblade (Pentax) (Fig. 8.1l). Mucosectom and Swanblade do not have ceramic tips. Instead, they have rotatable side cutting wires placed near to the end of their respective distal plastic sheaths. Safe Knife, has a nonconducting tip similar to IT Knife, but has additional cutting wire laid around its nonconducting tip.

8.2.1.4 Scissor Type

Scissor-type devices are relatively new in the market. Monopolar in its design, its scissor blades were covered with insulation coating element on the external side and can be rotated 360 degrees. Since it utilizes the concept of both a scissor and a grasper, the intended tissue to be dissected will have to be "grasped" first and be pulled back slightly before applying the cutting current giving it a safer operating condition. Furthermore, as the tissue is grasped before cutting current is applied, the scope is stabilized by the knife to a certain extent and hence, unintended scope movement can be minimized. This advantage is not seen in other type of ESD knives.

Examples of scissor-type devices are Clutch Cutter Knife (Fujifilm) (Fig. 8.1m) and Stag-Beetle (SB) Knife (Sumitomo Bakelite) (Fig. 8.1n). It was shown that scissor-type devices carry a high safety profile, similar en bloc resection rate, R0 resection rate and survival benefit when compared to other larger colonic ESD series using conventional needle knife type or blunt-tip type ESD knives [8].

8.2.2 Electrosurgical Unit

Modern electrosurgical unit (ESU) is equipped with many intelligent and safety features. Better understanding of the ESU is impartial for therapeutic endoscopists to enable efficient and high quality endo-electrical surgery and, when the situation arises, to allow them troubleshooting and making the necessary adjustment.

ESU used in medical practice utilizes high-frequency alternating current (AC) in the range 300 kHz to 3 MHz to generate thermal effect to cut (dissection) and coagulate (hemostasis) the tissues [9–12]. This high-frequency range is needed to avoid neuromuscular activation. Properties of the output AC are determined by peak voltage (Vp), duty cycle, and crest factor. A Vp of more than 200 V induces an electric arc for cutting the tissue (Fig. 8.2). It is important to understand that the tissue is cut by a thermal effect at this electric arc (sparking), but not by mechanical force, in electrical surgery. Below 200 V, only heating with resultant dehydration and desiccation can be achieved. Duty cycle refers to the percentage of time that the current is actually being delivered. Crest factor refers to the ratio of the peak amplitude to its average amplitude. Cutting current, in general, have a low crest factor than coagulating current. A current of more than 200 Vp and 100% duty cycle is called a pure-cut current, while a current of less than 200 Vp or 6% duty cycle, a pure-coagulation current. Current with duty cycle in between this range is called a blended current. All these properties can be individually adjusted to achieve different tissue effects as required. In ERBE VIO300D, such currents are named, in the ascending order of increasing effect in coagulation, as Auto Cut, Dry Cut, Swift Coagulation, Forced Coagulation, and Soft Coagulation (Fig. 8.3). Some ESU has distinctive proprietary cutting mode such as the ERBE EndoCut mode that consists of alternating Auto Cut and Soft Coagulation modes (Fig. 8.4). It is theoretically developed to reduce the risk of bleeding during tissue cutting. However, the pragmatic benefit of EndoCut mode is automatic discontinuation of Auto Cut current with set "duration," facilitating control of amount and direction of cut.

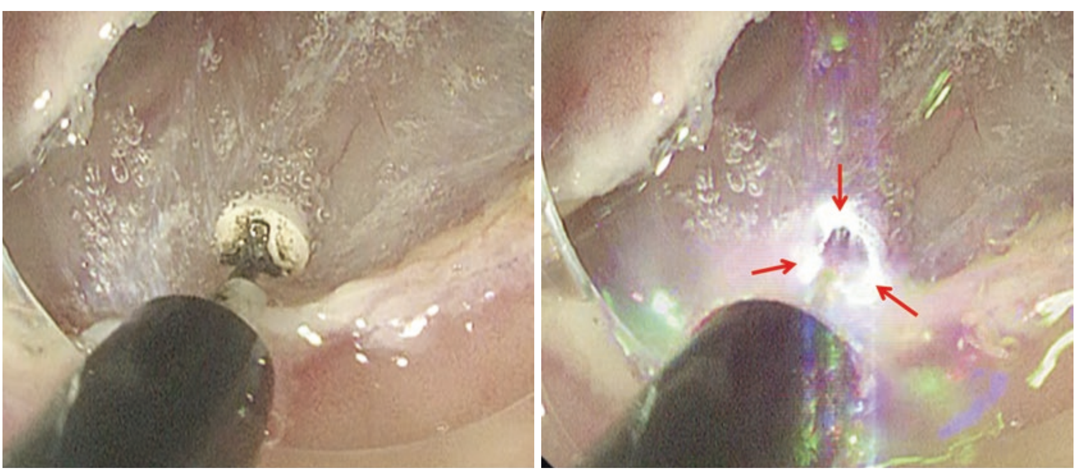


Fig. 8.2 Concept of electric arc. A Vp of more than 200 V induces electric arc from an active electrode. Notice the electric arc is discharged at areas with high current density (red arrow)

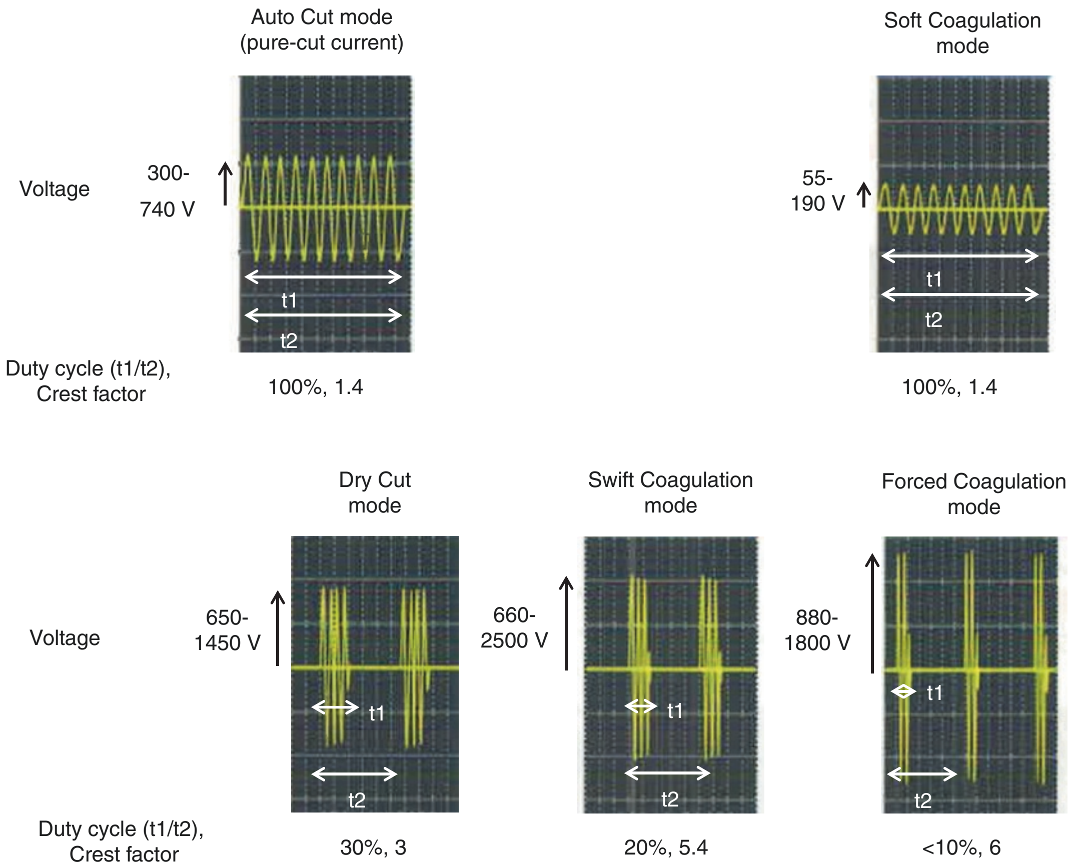
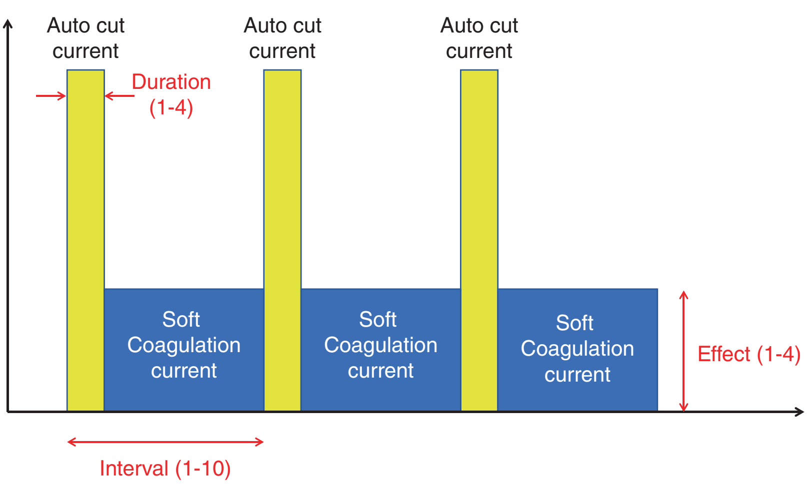


Fig. 8.3 Types of current in electrosurgery. Properties of AC outputs in each modulation (VIO300D). Auto Cut uses continuous sinusoidal wave (duty cycle 100%) with peak voltage (Vp) of 740 V. Blended currents (Dry Cut, Swift Coagulation, and Forced Coagulation) use intermittent waves that are modified for Vp, duty cycle and crest factor. Soft Coagulation uses continuous sinusoidal wave with low voltage (Vp 190)

Fig. 8.4 Principle of ERBE Endo Cut mode. Auto Cut and Soft Coagulation currents are emitted alternately. Time of Auto Cut current is adjusted by "Duration" and this affects cutting property. Strength and time of the Soft Coagulation current are adjusted by "Effect" and "Interval" and these do not affect cutting property



One known difficulty in conventional electrocautery is that as the dissection progresses and further tissue desiccation takes place, if the power output were to remain the same, the tissue impedance increases, leading to inevitable decrease in electric current, and subsequent inefficient tissue dissection. Furthermore, because a contact area between the knife and the tissue changes dynamically during ESD procedure, current density also changes accordingly. If unregulated, both changes in current voltage and density may lead to unstable thermal effects (cut and coagulation). Modern ESU is equipped with intelligent real-time sensor that can detect a real-time change in the circuit impedance. Hence, the power can be constantly and automatically adjusted so that the voltage can be regulated and maintained at desirable level within the pre-set limits. "Wattage" determines the upper limit of the output power and "EFFECT" controls level of output voltage that affects depth of thermal effect (Fig. 8.5). Therefore, wattage should be set at high enough value in order to avoid deficient thermal effect, and actual degree of thermal effect is better to be controlled by the level of "EFFECT" and duration of foot pedal activation. Some recommended settings for ERBE VIO300D, VIO3, and Olympus ESG300 are listed in Tables 8.2, 8.3, and 8.4, respectively.

The difference in thermal effects on the vital tissue depends on speed and degree of increasing temperature. The Cut modes, or the Coagulation modes with high current density (narrow contact area), can induce extremely rapid rise in temperature > 100 °C, and causes vaporization of the intracellular liquid, which leads to the rupturing of the cell membrane. This phenomenon is represented as cutting of the tissue. The Coagulation modes with low current density (wide contact area) cause slow increase in temperature > 100 °C, which results in dehydration and desiccation of the tissue. This can be used for hemostasis of oozing hemorrhage or cauterization of thin vessels, however, it is not enough for hemostasis of spurting hemorrhage or coag-

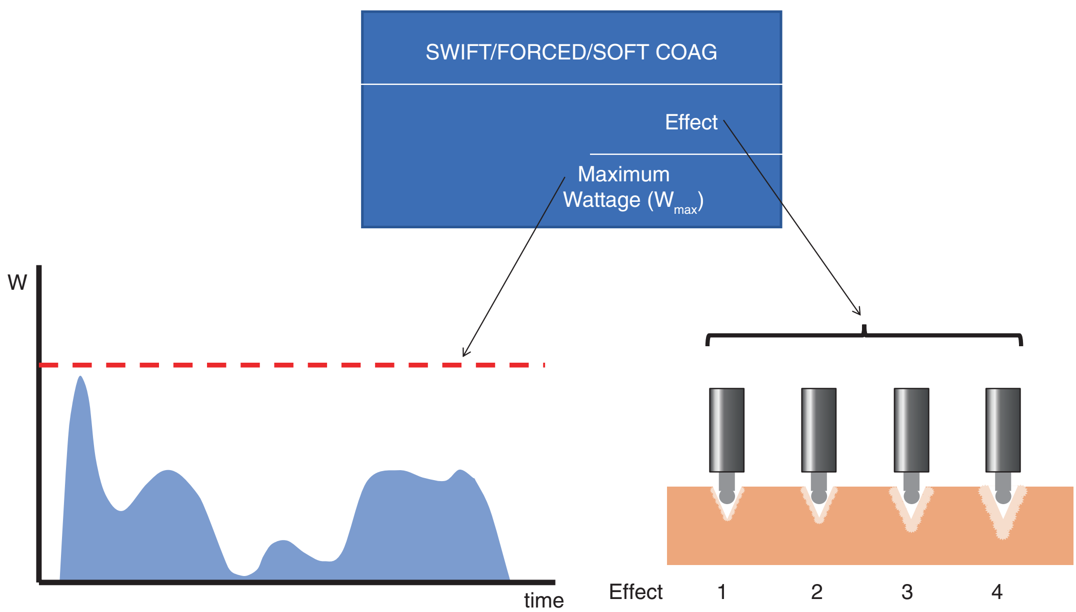


Fig. 8.5 Principle of coagulation mode. In Coagulation modes, the intelligent real-time sensor detects a real-time change in the circuit impedance, and real-time output power (w, blue-colored area) is dynamically adjusted to maintain the output voltage within the pre-set upper limit wattage level (W_{max}, red dotted line) as determined by the operator. "Effect" controls the level of output voltage and changes amount (depth) of tissue coagulation (brown-colored area)

Table 8.2 Recommended Electrosurgical Unit Settings for ERBE VIO300D

	Knife	Marking	Mucosal incision	Submucosal dissection	Hemostasis
Straight-tip needle knife type	Dual knife, Flush knife, etc	• Forced COAG, Effect 2, 20–30 W • Soft COAG, Effect 4, 40 W	• EndoCut I, Effect 2–3, Duration 3, Interval 3 • Dry CUT, Effect 5, 40–60 W	• Forced COAG, Effect 2, 40–50 W • Swift COAG, Effect 3–4, 40–80 W • EndoCut I, Effect 2–3, Duration 3, Interval 3 (submucosa without vessels)	• Forced COAG, Effect 2, 40–50 W (oozing bleeding from thin vessels)
Bended-tip needle knife type	Hook knife, etc	• Forced COAG, Effect 2, 20–30 W • Soft COAG, Effect 4, 40 W	• Dry CUT, Effect 5, 40–60 W • EndoCut I, Effect 2–3, Duration 3, Interval 3	• Forced COAG, Effect 2, 40–50 W • Swift COAG, Effect 3–4, 40–80 W • Spray COAG, Effect 2, 40–60 W	• Spray COAG, Effect 2, 40–60 W (oozing bleeding from thin vessels)
Blunt-tip type	IT-knife 2, etc		• EndoCut I, Effect 2, Duration 3, Interval 3 • Dry CUT, Effect 5, 40–60 W	• Swift COAG, Effect 3, 80-100W • Forced COAG, Effect 2-3, 50–60 W • EndoCut I, Effect 2, Duration 3, Interval 3 (submucosa without vessels)	• Swift COAG, Effect 3, 80–100 W (oozing bleeding from thin vessels)
Scissor type	Clutch Cutter, SB knife	• Forced COAG, Effect 3, 20–30 W	• EndoCut Q, Effect 1, Duration 1–3, Interval 1	• EndoCut Q, Effect 1, Duration 1–3, Interval 1 • (vessel coagulation: Soft COAG, Effect 5–6, 80–100W)	• Soft COAG, Effect 3–5, 40–100W
Hemostatic forceps	Coagrasper, etc.				• Soft COAG, Effect 5–6, 80–100W

ulation of thick vessels. In such a situation, the Soft Coagulation mode using low current-voltage (55–190 V) is effective. Although the Soft Coagulation mode does not generate electric arc but it deeply denatures the tissue including thick vessels (Fig. 8.6). Operator-dependent factors, such as speed of cutting and foot pedal activation time, also affect the final effect on the tissue.

To achieve efficient electrical conduction and ensure adequate energy output, the neutral electrode plate should be positioned as close to the operational area as possible (upper arm, flank, or thigh, Fig. 8.7).

8.2.3 Endoscopes for ESD

Endoscopes used for ESD should ideally be slim, flexible (high degree of upward/downward angulation and small bending radius), equipped with water jet capability and their working channel should at least be 2.8 mm in diameter. However, suctioning of air, water, and blood often take place simultaneously with ESD, hence, a larger working channel such as 3.2 mm or above would be more preferable. Such endoscope should ideally be high definition with zoom or dual focus capability to facilitate recognition of border during ESD. Double channel therapeutic endoscopes may come in handy in situation which requires the concomitant use of two devices such as strip-biopsy EMR, mucosal defect closure using combined endoloop and hemoclips technique.

Specialized endoscope such as multibending double-channel endoscope (Olympus GIF-2TQ260M) allows ESD to be performed in locations with a difficult angle such as the gastric cardia, the fornix, greater curvature of upper

Table 8.3 Recommended Electrosurgical Unit Settings for ERBE VIO3

	Knife	Marking	Mucosal incision	Submucosal dissection	Hemostasis
Straight-tip needle knife type	Dual knife, Flush knife, etc	• Forced COAG, Effect 0.6–0.8 • Soft COAG, Effect 6–6.2	• EndoCUT I, Effect 1–2, Duration 3–4, Interval 3 • Dry CUT, Effect 2.2–5.0	• Forced COAG, Effect 6.6–7 • Swift COAG, Effect 3.4–4 • EndoCUT I, Effect 1-2, Duration 3–4, Interval 3 (submucosa without vessels)	• Forced COAG, Effect 6.4 (oozing bleeding, thin vessel)
Bended-tip needle knife type	Hook knife, etc	• Forced COAG, Effect 0.6–0.8 • Soft COAG, Effect 6–6.2	• EndoCUT I, Effect 1–2, Duration 3–4, Interval 3 • Dry CUT, Effect 2.2–5.0	• Forced COAG, Effect 6.6–7 • Swift COAG, Effect 3.4–4	• Forced COAG, Effect 6.4 (oozing bleeding, thin vessel)
Blunt-tip type	IT-knife 2, etc		• EndoCUT I, Effect 2, Duration 3–4, Interval 3	• Forced COAG, Effect 6.6–7 • Swift COAG, Effect 3.4–4 • EndoCUT I, Effect 1–2, Duration 3–4, Interval 3 (submucosa without vessels)	• Forced COAG, Effect 6.4 (oozing bleeding, thin vessel)
Hemostatic forceps	Coagrasper, etc.				• Soft COAG, Effect 6.4–8

Table 8.4 Recommended Electrosurgical Unit Settings for Olympus ESG300

	Knife	Marking	Mucosal incision	Submucosal dissection	Hemostasis
Straight-tip needle knife type	Dual knife, Flush knife, etc	• Forced COAG, Effect 2, 40 W • Soft COAG, Effect 3, 80 W	• Pulse CUT Fast, Effect 2–3, 40–100 W	• Forced COAG, Effect 3–4, 40–50 W • Pulse CUT Fast, Effect 2-3, 40–100 W (submucosa without vessels)	• Forced COAG, Effect 3–4, 40–50 W (oozing bleeding, thin vessel)
Blunt-tip type	IT-knife 2, etc		• Pulse CUT Fast, Effect 3, 120 W	• Power COAG, Effect 3, 80–120 W • Pulse CUT Fast, Effect 3, 120 W (submucosa without vessels)	• Power COAG, Effect 3, 80–120 W (oozing bleeding, thin vessel)
Hemostatic forceps	Coagrasper, etc.				• Soft COAG, Effect 3, 80 W

body, anterior wall of the body, and incisura. It has a distal segment with 4-way angulation and a proximal segment with 2-way angulation. However, this specialized multibending double-channel endoscope may not be readily available in many countries.

8.2.4 Submucosal Fluid Cushion

Creation and sustaining an adequate SFC is an integral part of a safe ESD procedure. Generally, indigo carmine is added onto the SFC mixture to enhance the visibility of the SFC in the

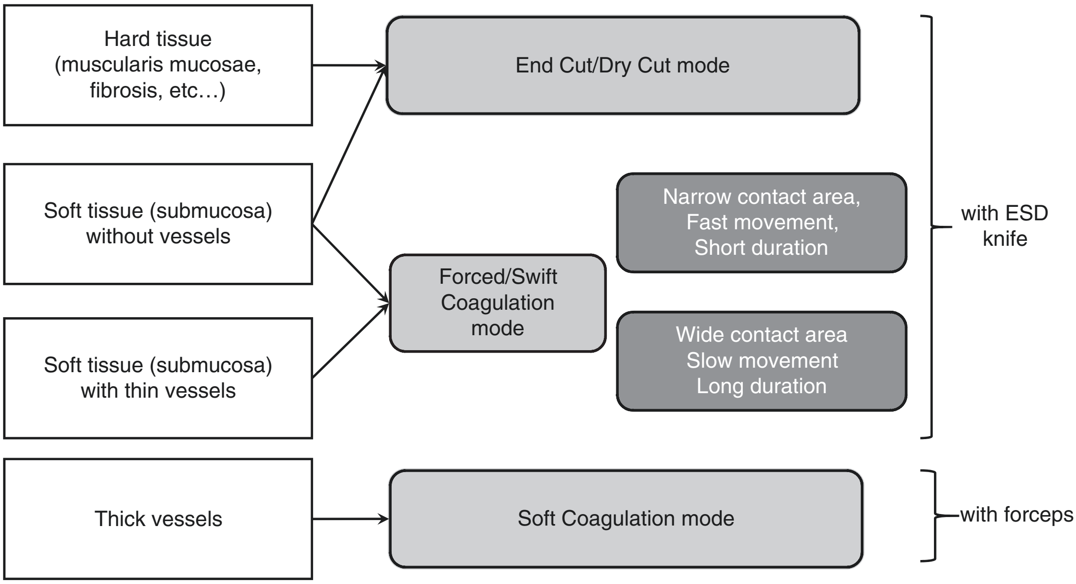


Fig. 8.6 Principle of mode selection, contact area and device control, and device selection

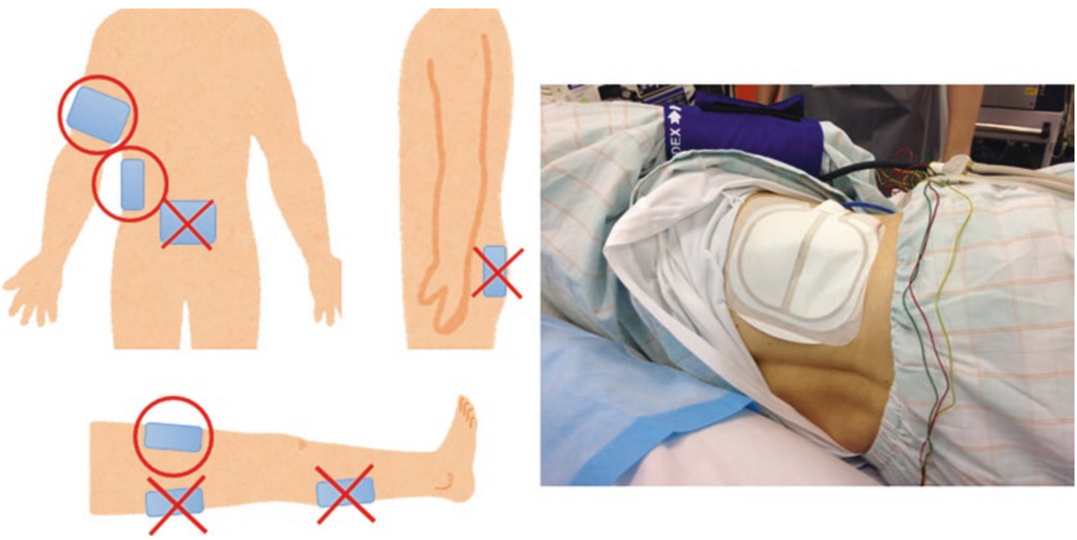


Fig. 8.7 Positioning of neutral electrode plate. Adequate place to attach the neutral electrode plate must be ensured. The neutral electrode plate is positioned at the area close to operation field (upper arm, flank, or thigh). Areas with a thick layer of fat (the stomach, back of thigh, or the buttocks) should be avoided

submucosal plane. The bluish hue produced by indigo carmine in this mixture provides excellent contrast with the surrounding orangish and pinkish tissue and whitish muscularis propria, thus help the endoscopists to better recognize the submucosal dissection plane. In general, most experts prefer low concentration indigo carmine because of its better recognition of submucosal fibers and vessels.

The ability of one fluid to provide sustained elevation varies from one to another. Conventional fluid for SFC is normal saline. Other types of fluid used as SFC are dextrose 50%, glycerol, succinylated gelatin, fibrinogen, hydroxyethyl starch (HES), and sodium hyaluronate solution (MucoUp). Prospective randomized studies confirmed the utility of 0.4% sodium hyaluronate solution (in comparison with normal saline) in providing higher en bloc resection with better resectability and requirement of less submucosal injection volume [13, 14]. A recent meta-analysis drew similar conclusion that the newly developed submucosal injection solutions (such as fibrinogen mixture, dextrose, glycerol, sodium hyaluronate solution, succinylated gelatin, hydroxyethyl starch, and mesna) significantly increased en bloc and complete resection rate and at the same time, reduced bleeding rate when compared with normal saline [15].

8.2.5 Hemostatic Forceps

Bleeding is a common occurrence in ESD, especially in gastric or rectal ESD. Minor bleeding can be treated effectively using the coagulation mode of the ESD knives. However, severe bleeding would require hemostatic forceps like Coagrasper (Olympus) (Fig. 8.8) or simply a hot biopsy forceps. When not treated promptly and adequately, such brisk severe bleeding, or even minor bleeding, may discolor the submucosal tissue, and degrade the endoscopic visualization and electric conduction in the operation field. Hemostatic forceps are generally divided into monopolar type and bipolar type. Soft coagulation mode is often selected to achieve sealing of the vessels.

Fig. 8.8 Coagrasper

In the attempt to secure hemostasis, prompt decision to switch to a coagulation device like Coagrasper is equally important to prevent deep tissue injury by the prolonged and repeated use of the coagulation mode of the ESD knives. In the case of a bleeding vessel, the physical "pinching" effect alone from the device should stop the bleeding. This help in confirming whether the targeted vessel is correctly grasped and clamped, and avoid "heat sink effect" by flowing blood. If bleeding still persists despite the initial pinch, it will be better to select another area before applying the current to prevent unnecessary thermal injury. One important tip in performing prophylactic ablation of the blood vessel is that the targeted vessel should be exposed adequately by further trimming of the submucosal tissue around the vessel before grasping the targeted vessel.

Delayed bleeding after ESD ranged from 1.8 to 15.6% in most of the Far Eastern series [16]. One retrospective study of gastric ESD highlighted the advantage of preventive post-ESD coagulation (PEC) of visible vessels on the resection wound in reducing the risk of delayed bleeding (with preventive PEC, 3.1%; without preventive PEC, 7.1%; $p < 0.01$) [17]. Vigorous PEC is not necessary in the colon because of the low incidence of delayed bleeding and the potential risk of delayed perforation.

8.2.6 Assisting Devices and Methods

8.2.6.1 Traction Devices and Accessories

Patient's positioning should always be explored first to achieve natural traction by gravity. In circumstances where patient's positioning is not feasible, various devices and methods are available to provide traction during ESD. The "up-lifting" pull provided by such devices or methods is invaluable during ESD. They will come in handy in situations when there is inadequate submucosal plane exposure following SFC injection due to the difficult location of the lesion, fibrosis formation, etc. Application of these devices or methods will allow better exposure of the submucosal plane to facilitate efficient and safe dissection.

Such devices and methods are generally divided into external and internal traction types [18]. External traction types are clip-with-line method [19], external forceps method [20], clip-and-snare method [21], and double-scope method [22]; while internal traction types are S-O Clip [23] and clip-band technique [24]. Some traction methods especially the external traction type may not be applicable in a long loopy bowel such as right-sided colon due to the loss of the traction force over the bends. In these locations, internal traction type may be useful.

8.2.6.2 Transparent Hoods

Transparent hood is indispensable in all stages of ESD procedure. During mucosal incision, it provides a fixed and stable distance between the scope and the mucosa and thus allowing safe mucosal incision. During submucosal dissection, not only does it splay open the mucosa from the muscularis propria exposing the working submucosal layer, it helps to achieve a focused endoscopic view and an optimal and stable dissection distance in the submucosa. In the event of bleeding, ESD hoods allow the vessel to be adequately exposed and at times, it can be used to provide temporarily tamponade while waiting for instrument exchange. During specimen retrieval, part of the specimen can be retracted into the hood allowing easier specimen retrieval from the respective luminal sphincter.

Certain specialized hood such as Fujifilm short ST Hood allows easier entrance into the submucosal plane and enables the submucosal plane to be “stretched” open more easily due to the tapered tip configuration. Expert reports recommended the use of such hood for ESD in difficult anatomy such as colon and duodenum [25, 26].

8.2.6.3 Carbon Dioxide Insufflation

CO_2 is popular in modern day endoscopy. Its rapid absorbability provides a more comfortable environment during lengthy endoscopic procedures such as ESD. In the event of perforation, the leak will result in less discomfort and will tend to be completely resorbed much faster than regular air. It was reported in meta-analyses of RCT that the use of CO_2 in gastric ESD resulted in less post-procedural abdominal discomfort and a lower risk of overall adverse events when compared with air insufflation [27, 28]. There were no observed differences in peri-procedure respiratory functions, abdominal circumference, hospital stay, sedation dosage, and procedural time.

8.3 Preparation

8.3.1 Pre-procedure

Pre-procedural preparation differs from center to center. Upper GI procedures normally require a fasting of at least 4– 6 h. However, a procedure like POEM would require a longer fasting time due to the high tendency of food residue in the stagnant and dilated esophagus. While for the lower GI procedure, thorough bowel cleansing, in a measure more stringent than screening colonoscopy, is mandatory in order to achieve ideal bowel preparation. “Clean” bowel is not only important for border identification but also resulted in less contamination in the event of bowel perforation. Specific instruction and requirements for ESD in each of the anatomic locations (i.e., esophagus, stomach, and colon) are discussed in the following three sub-chapters.

8.3.2 Intra-procedure

The most important intra-procedural aspects are sedation and patient’s monitoring. While there are no strict guidelines as to which type of sedation is best suited for certain ESD procedure, generally a moderate to deep sedation is required. If setting allows, general anesthesia is preferred for a more controlled environment during ESD. Some dedicated medical personnel in handling the sedation and monitoring will be indispensable during ESD procedure.

8.3.3 Post-procedure

Mucosal defects induced by ESD may lead to delayed bleeding (especially in the upper GI tract due to the caustic effect from gastric acid) or delayed perforation (especially in the duodenum). Although there is no strong evidence to recommend routine closure of the post ESD wound, several methods and techniques can be attempted. Small defects can be closed with hemoclips alone. However, larger defects would require the use of advanced techniques such as mucosal-incision-and-clip method [29], endoloop-and-clip method (require the use of double-channel endoscope) [30] and string-clip-suturing method [31]. The important message is to choose an appropriate technique according to the indication, expertise, and size of the mucosal defect.

It is also vital to remember that ESD does not end with the endoscopic procedure. In fact, the true success of an ESD procedure can only be evaluated at the post-procedural histological assessment. In general, the histological finding of positive margin, poorly differentiated component, lymphovascular involvement, and invasion beyond the muscularis mucosae of >200 um in the esophagus, >500 um in the stomach, or >1000 um in the colon would imply non-curative resection. Further endoscopic resection or salvage surgery will then be necessary to complete the oncological treatment. ESD sample should be handled with utmost care. It should be adequately spread out and fixed to a board with pins. Oral and anal direction should be labelled to facilitate the orientation during the histopathological examination.

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9 ESD for the Esophagus

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9.1 Introduction

The traditional approach to esophageal cancer consists of open or thoraco-laparoscopic surgery, chemoradiotherapy or both. Surgery has consistently been associated with increased morbidity and mortality. An older large cohort study famously reported fairly high mortality rates ranging from 9.5 to 15.3% [1]. These numbers have improved drastically since the introduction of minimally invasive transthoracic esophagectomy. In a multicenter cohort study of over 1000 procedures, mortality from surgery ranged between 1.0 and 4.6% [2]. The benefits of endoscopic resection over surgery have been reported in a study by Zhang and colleagues who evaluated the perioperative mortality of esophagectomy compared to ESD in 596 patients with T1a or T1b esophageal cancers. The mortality of surgery was five times higher than that of ESD [3]. In addition, esophagectomy was associated with higher episodes of severe adverse events (27.7 versus 15.2% for surgery and ESD, respectively). In a median follow-up of 21 months, the all-cause mortality and cancer recurrence/metastasis was similar across both cohorts (10.9% versus 7.4% and 8.9% versus 9.1%, respectively, for surgery and ESD). Current data do suggest similar efficacy when ESD is compared to surgery not only in the esophagus but also in the stomach and colon [4, 5]. Nevertheless, ESD is an advanced endoscopic resection technique and has one of the highest complication rates in therapeutic endoscopy. As with other procedures requiring manual dexterity, the complication rate is inversely associated with the procedural volume. Odagiri and colleagues reported an average complication rate of 3.3% for esophageal ESD. Perforation or perforation associated complication rates varied almost fourfold depending on hospital's ESD volume per year: very low volume centers (≤8 cases) having a complication rate of 4.8%; low volume (9–17 cases), 4.5%; high volume (18–38 cases), 2.5%; and very high volume (≥39 cases), 1.3% [6]. As opposed to perforation, post-ESD bleeding appears to be very rare (0–0.7%) [7]. However, even when these complications occur, surgery is rarely needed [8].

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9.2 Indication

Although a higher en bloc resection is achieved with ESD, there may be little clinically proven advantages of this method compared to a less complex procedure, Endoscopic Mucosal Resection (EMR) [9]. Currently, EMR may be considered for lesions that are <1 cm in size and deemed to be restricted to the superficial mucosa by advanced imaging techniques.

ESD is indicated for larger superficial neoplasia that cannot be resected en bloc using the EMR technique and/or when invasion is predicted to reach the superficial submucosal layer. Before proceeding with the ESD, an in depth understanding of advanced imaging techniques is paramount (please refer to Volume 1 for details on Endoscopic Imaging of superficial esophageal neoplasia). Occasionally, it may be difficult to totally rely on endoscopic imaging alone. Therefore, endoscopic resection (either ESD or EMR) is now frequently used as a "staging procedure."

The Japanese Esophageal Society (JES) guidelines for ESD state that endoscopic resection is deemed sufficient as treatment of early esophageal cancer for T1a lesions up to the lamina propria and affecting less than two-thirds of the circumference of the organ. A broadened criteria (relative indication) includes invasion up to 200 μm into the submucosa (sm1, 10]. The ESGE guidelines have a slightly different approach toward curative ESD and recommends that it should be confined to the superficial mucosa and not have lymphovascular invasion [11]. The ESGE also recognizes that for SCC, invasion up to 200 μm is most likely curative if there are no other high-risk criteria. The JES highlights that their guidelines are mostly based on SCC, which has a higher lymph node metastatic rate compared to esophageal adenocarcinoma (EAC). In line with this, a Japanese study looking at EAC has proposed similar thresholds as the ESGE for EAC which has a relative indication for submucosal invasive tumors extending up to 500 μm into the submucosa [12]. The indications according to ESGE and JES for both SCC and EAC have been summarized in Table 9.1.

Finally, it is important to touch on the use of antithrombotic agents and its influence on procedural bleeding. It has been shown that Aspirin may not influence bleeding during or after ESD in contrast to other antiplatelet and anticoagulant agents [7]. One should liaise with the patients' general practitioner and/or specialist in order to discuss the risks and benefits of discontinuing these medications prior to performing an ESD.

Table 9.1 Endoscopic submucosal dissection in esophagus—standard and extended indication flowchart

Indication for esophageal ESD		ESGE guidelines		JES guidelines[a]	
		Standard	Extended	Standard	Extended
Squamous cell carcinoma	Size	Any	Any	<2/3rds of circumference	Any
	Depth	m2	m3/sm1 (≤200 μm)	T1a (up to lamina propria)	sm1 (≤200 μm)
	Histology	Any	Well-differentiated	Any	Any
	Lymphovascular invasion	No	No	Unclear[b]	Unclear[b]
Esophageal adeno carcinoma	Size	Any	Any	≤3 cm	–
	Depth	m3	sm1 (≤500 μm)	sm1 (≤500 μm)	–
	Histology	Any	Not poorly differentiated	Not poorly differentiated	–
	Lymphovascular invasion	No	No	No	–

[a]Indication for esophageal adenocarcinoma based on Ishihara et al. [12]

[b]Unclear if lymphovascular invasion status alone determines whether the lesion was completely resected or not [13]

9.3 ESD Procedure

9.3.1 Preparation

As in all therapeutic endoscopic procedures, most ESDs are performed under General Anesthesia (GA). This prevents aspiration and provides better overall control for the proceduralist. The sedation duration should ideally be tailored to patient and lesion characteristics (e.g., ESD in larger lesions could last for several hours, complicated by more intraprocedural bleeding and require numerous reinsertions of the endoscope). Using CO_2 is mandatory in ESDs.

9.3.2 Marking

This step begins with the clear delineation of the margin of the lesion. Either or both virtual chromoendoscopy (e.g., narrow band imaging—NBI) and vital stain (e.g., Lugol iodine) can be used (Fig. 9.1). The type of accessory used to perform the marking largely depends on personal experience and the equipment available but usually consists of either argon plasma coagulation or the same knife that will be used for incision/submucosal dissection (e.g., ERBE knife, dual knife J, and triangular tip knife J), in the "coagulation mode." This should be performed on normal mucosa surrounding the lesion with at least a 2-mm normal margin "clearance" (Fig. 9.2). It is advisable that on the oral extremity, an additional marking be placed to make the orientation of the specimen easier after the procedure is completed. Therefore, one can inform the pathologist of the orientation of the specimen, which could be crucial when margins are compromised. In accordance with this, one must note that the marking line should not be breached during mucosal incision.

9.3.3 Submucosal Injection

Submucosal injection solution customarily consists of a saline/colloid mix with adrenaline and a small amount of coloring agent such as

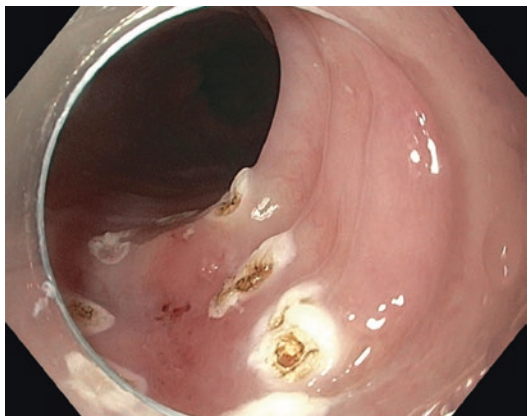

Fig. 9.2 Marking

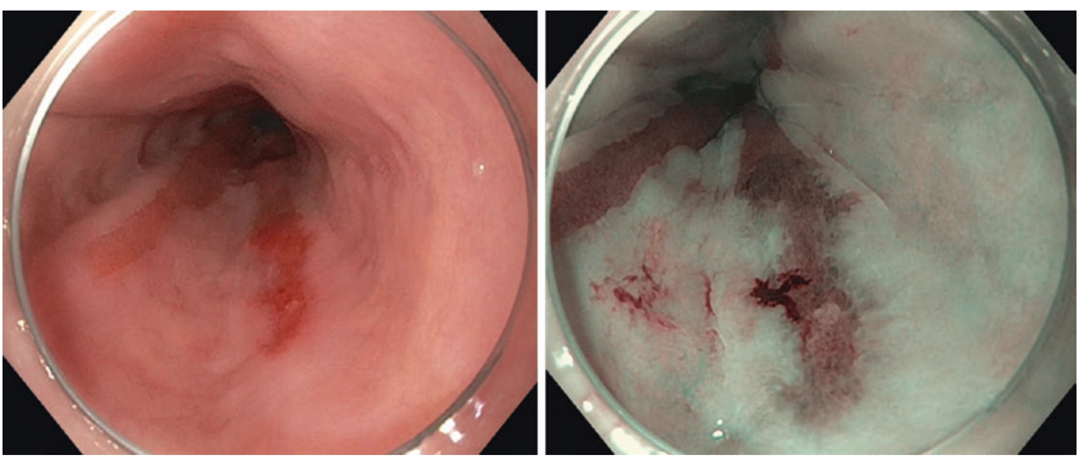

Fig. 9.1 Area of interest on white light and NBI

indigo carmine or methylene blue. The colloid generally used is Gelofusine® (succinylated fluid gelatin), MucoUp® (hyaluronic acid), or mannitol. The exact amount of each is debatable, but a common mix used in the East consists of 100 mL of saline + 1 mg of adrenaline (1:100,000 solution) + 100 mL of hyaluronic acid + 0.4 mL of indigo carmine. This is usually injected with a 25G needle in 2–5 mL aliquots per injection (5–10 mL syringe).

9.3.4 Incision

There are different approaches used for the initial mucosal incision. For instance, for small lesions it is possible to perform an all-round mucosal incision prior to the submucosal dissection. For larger lesions, a 2–3 cm incision on the proximal edge is sufficient, followed by submucosal dissection. As the endoscopist is proceeding with the submucosal dissection, it may sometimes become difficult to progress due to restrain provided by the "un-incised" mucosa. The mucosal incision can then be extended on either side and dissection continued until the mucosal incision on either side are connected at the anal extremity. A number of alternative methods to tackle specific/difficult situations have also been developed, such as the pocket creation method. This consists of a smaller initial mucosal incision and tunneling the submucosa until the anal extremity if reached. The mucosal incisions are then "joined" on either side of the pocket after most of submucosal dissection has taken place.

Whenever possible, the mucosal incision should be extended to the depth of the deepest submucosal layer (Fig. 9.3). This will enable the endoscopist to cut the border loose during submucosal dissection as opposed to further "digging" underneath the incision line (which could be carried out blindly leading to complications). This is optimally and safely achieved in an angled approach (45–60 degrees). Avoiding a 90-degree angle helps in preventing perforations.

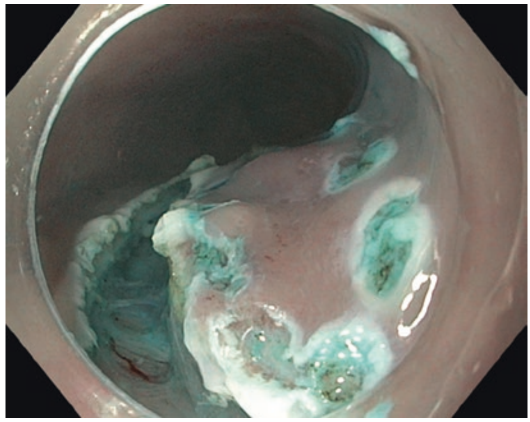

Fig. 9.3 Mucosal incision extended up to deep submucosa

9.3.5 Submucosal Dissection

As per anatomic particularities (e.g., thinner wall and absence of serosa), the esophagus requires more "gentle" knives than the stomach. The most common knives available in the market that can be used for esophageal ESD are the IT knife nano, dual knife (1.5 mm), flush knife (1.5 mm), SB knife Jr., and the ERBE hybrid knife. All of these have their advantages and disadvantages.

The ability to visualize the muscular plane is one of the most important (and maybe one of the most difficult) steps (Fig. 9.4). This could be a drawback of the SB knife Jr. This device requires the assistant to rotate the knife to meet the parallel plane of dissection, hence requiring at least two operators who are experienced in ESD. However, it is thought to lead to less complications, especially for non-experts as it provides more controlled cutting with a "scissor-type" action.

The IT knife nano (and other insulated tip knives) have the peculiarity of needing a mucosal breach before initiating its use (e.g., with a needle knife). This knife does offer additional protection to prevent perforation when compared to the non-insulated tip types. With the IT knife nano, the incision and dissection should be preferably performed in a retrograde or "pulling" fashion (i.e., from anal to oral) or sideways.

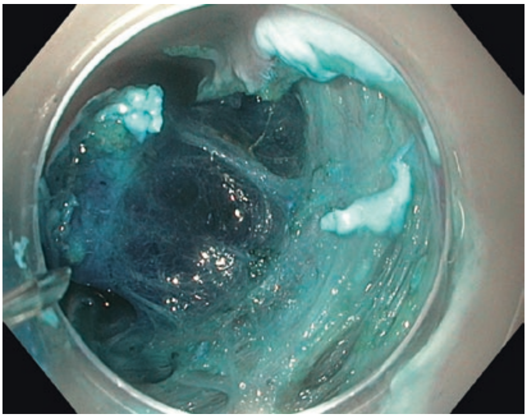

Fig. 9.4 Submucosal dissection

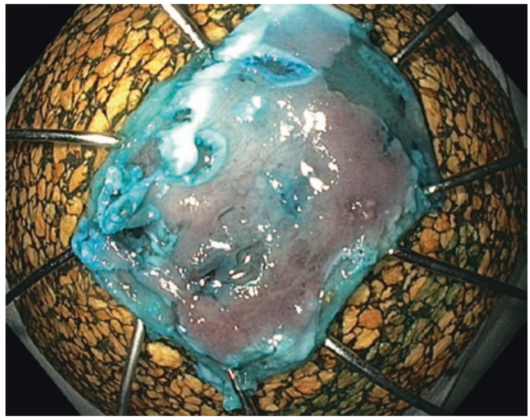

Fig. 9.5 Specimen fixed on cork

Other knives such as the Dual knife J, the triangular tip knife and the ERBE hybrid knife can be used as sole devices, although they do require an injection prior. With the latter knives, incision and dissection should be preferably performed in an antegrade fashion (i.e., from oral to anal) or sideways.

A thin wall, surrounding vital structures (e.g., aorta and mediastinum) and absence of serosa layer make the esophagus a site for particular concern for perforation. When a muscular defect is suspected, the patient vitals should be monitored closely and endoscopic closure of the defect attempted using standard endoscopic clips. If this is successful and the patient is stable, one could continue with the procedure with extra caution. If this is unsuccessful and/or the patient vitals deteriorate, an endoscopy-guided nasogastric tube must be swiftly placed and the procedure aborted. Depending on the endoscopist expertise with advanced endoscopy, other closure devices could be used to deal with the perforation (e.g., Over The Scope Clip-OTSC®, fully covered stents or endoscopic suturing using the OverStitch™).

Another difficulty one may find during esophageal ESD is related to the adequate presentation of the submucosa to the knife. This sometimes can be made easier with the traction technique. It can only be used when a mucosal incision and at least some submucosal dissection has been performed. This technique consists of tying a line (e.g., dental floss) to an endoscopic clip that is advanced through the working channel prior to scope insertion (scope withdrawn, outside the patient). The line should pass outside the scope to enter the distal end of the working channel. After the line is tied, the clip is closed and withdrawn into the working channel. The scope is then introduced into the patient. The clip should then be deployed on the submucosal face of the to-be specimen, on its proximal edge. Once deployed, the clip and hence the specimen will be connected to the line which can be separately captured outside the patient's oral cavity. An assistant could apply proximal and downwards traction which is likely to allow easier access to the submucosa. A snare and clip technique could also be used which may help with both pushing and pulling. Although specialized through-the-scope clips with traction capability have been developed (e.g., S-O clip—Zeon Medical, Tokyo, Japan), these are mostly used for colonic and gastric ESD as they require a broad lumen for optimal performance. Therefore, the manually prepared traction system described above is still preferred for esophageal ESD.

After the completion of resection, the specimen should be retrieved and fixed on a flat surface (e.g., cork with pins) before formalin is added, and then sent for histological evaluation (Fig. 9.5). The pathologist should be informed of the specimen's orientation (e.g., different color pin on the proximal extremity), especially if the margins are not clear. It is also advisable to extensively photo document the resected specimen and the resection bed for future reference. Once the ESD is complete and the specimen retrieved, a final assessment of the ulcer/bed should be done carefully, applying hemostatic forceps (e.g., Coagrasper™) to any visible vessels and clipping any muscular breaches.

As per variations in the abovementioned ESD technique, there are multiple different techniques and devices that could be used and hence should be tailored to the Endoscopist's experience.

9.3.6 Training

It is contentious how many procedures are required to achieve competency as previous experience can have a big impact on the learning curve. Full proficiency with both diagnostic and therapeutic gastroscopy and colonoscopy must be achieved before attempting ESD. In addition, watching a number of ESDs performed by experts is of utmost importance. However, the exact number of observed and mentored ESDs and the site where to start is debatable.

In the East, it is advised that one should begin with 50 gastric antral ESDs before proceeding with more complex areas such as the esophagus. This is mainly because the stomach has thicker submucosa and muscularis propria layers. It is also a common site for early neoplastic lesions in the East, making it a feasible target for early training. In the West, however, this site is difficult to use for training mainly due to the low incidence of early gastric cancers. Therefore, in the West, rectal lesions are generally targeted before progressing to the colon and esophagus [14]. In addition, the availability of mentoring for ESD is much more limited in the West as opposed to the East. These make the consensus of a minimum standard difficult to reach.

It is important to note that familiarity with other endoscopic resection techniques (e.g., EMR) influences the learning curve. Therefore, teaching should be individualized and tailored to the availability of cases and mentoring in each center. In addition, practice on animal models (in vivo or ex vivo) and observation of ESDs in high-volume centers is advised [11].

9.4 Conclusion

ESD of the esophagus is a complex therapeutic endoscopic procedure that allows even large superficial neoplasms to be resected in an en bloc fashion. Special attention must be given prior to the procedure to ensure it is performed for the correct indication; and during the procedure ensuring the lesion is clearly demarcated and cautiously dissected. Attention should also be focused on intra-procedural complications such as bleeding and perforation. In addition, sufficient training is necessary to achieve optimal proficiency.

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10 ESD for Stomach

Takuji Gotoda

Abbreviations

EGC	Early gastric cancer
ESD	Endoscopic mucosal resection
QOL	Quality of life
IT knife	Insulated-tip diathermic knife

10.1 Introduction

Many cases of gastric cancer discovered up to 1970s were in the advanced stage. As represented by the Appleby operation, extended radical surgery was globally accepted as a standard approach to gastric cancer, even in the early gastric cancer (EGC). With the widespread adoption of nationwide screening [1] in Japan and South Korea, and the technological advancement of endoscope in the 1980s, the number of patients diagnosed with gastric cancer has been diagnosed at an early stage. Nowadays, endoscopic resection including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) offer less invasive options to those patients.

In cancer treatment, it is main key point to cure the disease completely. However, if quality of life (QOL) is compromised by procedures that are superior only in terms of reducing marginal risks, patients may experience difficulties in daily life and social rehabilitation after treatment [2, 3]. The stomach not only functions as a storage compartment, but also serves as an external and internal secretion for digestion and absorption. Therefore, if there is no difference of curability between different treatments, long-term QOL needs to be seriously considered when we chose a treatment option, especially in elderly patients [4, 5].

Health care should always be provided with the following considerations: whether ESD is truly minimally invasive, whether a "complete" treatment, as determined according to guidelines such as gastrectomy, is beneficial, and whether treatment is not the best, but more tolerable and acceptable to the patients [6].

10.2 ESD Technique for Stomach

Because ESD has a higher risk of complications such as severe bleeding and perforation than EMR, it still requires high endoscopic skills. Therefore, further innovation and modification are required to standardize ESD procedures worldwide [7, 8]. The traction method using dental floss and a hemoclip (any hemoclip available) can make gastric ESD, especially submucosal dissection easier and safer because of good visibility and tension. Some endoscopic manipulation of ESD is necessary and complicated [9]. IT

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knife and needle-type devices are standard for gastric ESD in Japan. Therefore, in order to standardize gastric ESD procedures not only in Japan and Korea but also in other countries with a low incidence of gastric cancer, this chapter presents simple ESD using a clutch cutter as a non-chip method [10, 11].

Clutch Cutter used for gastric ESD has a 0.4-mm-wide and 5-mm long serrated cutting edge well-grasping function. Since the outside of the forceps is insulated, the electrosurgical current energy is concentrated on the closed blade. Forced coagulation mode (VIO 300D; Erbe, Tübingen, Germany) 30 W (effect 3) is used for marking, ENDO-CUT Q mode (effect 1, duration 3, interval 1), and/or forced coagulation mode are used properly depending on the size and number of vessels during mucosal incision and submucosal dissection, and soft coagulation mode 100 W (effect 5) is often used for the treatment of large vessels or artery.

Because the clutch cutter can rotate in the desired direction around the mucosal incision side of the marking dot, ESD is smoothly carried out after submucosal injection containing indigo carmine (Fig. 10.1a, b). Indigo carmine is added to the submucosal injection solution in order to better identify the blue colored layer. Sodium hyaluronate (MucoUp, Boston Scientific Japan, Tokyo) is useful and effective to make enough submucosal cushion for preventing perforation [12].

After the circumferential cutting is completed, a direct incision is made in the submucosa below the lesion. In this step, the traction method is very useful and the visualization is excellent, making dissection easy, safe, and fast. The hemoclip tied with dental floss is fixed to the lesion site suitable for oral traction. The clip position depends on the location of the lesion. For lesions approaching from the retroflex endoscopy position, the clip is anchored to the anal side edge of the resected mucosa (Fig. 10.1c). In lesions approached from the straight endoscopy position, the clip is anchored to the oral side edge of the excised mucosa. During submucosal dissection, the anchored suture material outside of the patient is pulled to the oral side with gentle manual traction by an operator or assistant. Good visualization and tension of the submucosa are obtained by the inverted flap (Fig. 10.1d).

If small arteries and/or veins are found in submucosal, Clutch Cutter should be controlled first in soft coagulation mode for hemostasis and then cut the tissue in ENDO-CUT Q mode (Fig. 10.1e).

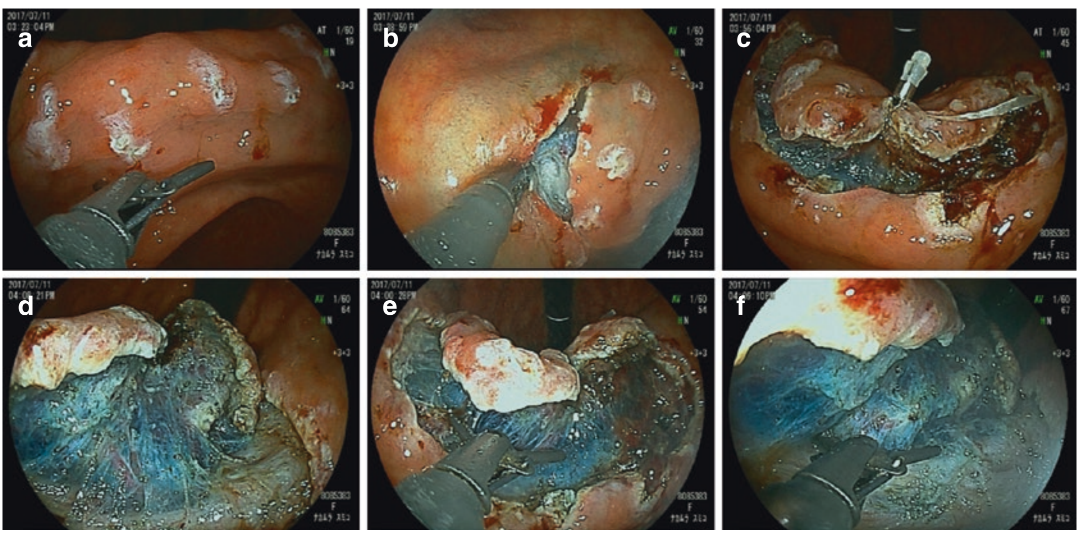

Fig. 10.1 (**a**) Mucosal incision using Clutch Cutter like scissors, (**b**) easy incision by a rotatable device with enough grasping, (**c**) hemoclip—tied by dental floss—as an anchor for traction, (**d**) good visualization and tension of the submucosa by oral traction, (**e**) combination with soft coagulation mode and ENDO-CUT Q mode for submucosal layer with vessels, and (**f**) visualized and safe dissection of submucosal layer using Clutch Cutter

However, please do not hesitate to change Clutch Cutter to Coagrasper G (Olympus Medical Systems), which is very effective in grasping and controlling bleeding vessels. After the management of bleeding vessels, Clutch Cutter can be safely manipulated to dissect connective tissue between the submucosal layer and the muscle layer (Fig. 10.1f). A soft transparent hood (JMDN 38819001, Top Corp, Tokyo, Japan) or a small caliber-tip transparent hood (ST hood, FUJIFILM Medical Co, Ltd) is often helpful to stabilize the operating field and create good triangulation during the dissection of the submucosal tissue [13].

It is widely accepted that ESD has a significant advantage in achieving one-piece resection for EGC. However, ESD using traditional devices is technically difficult and requires intensive training by an expert. Because these knives lack the ability to grasp the targeting tissue, meaning difficult maneuverability under unstable conditions (like one-handed surgery). Comparing these devices, Clutch Cutter is technically simple and easy to perform without any higher skills. Therefore, gastric ESD using Clutch Cutter may be accepted in the countries where EGC incidence is low.

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11 ESD for Colon

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11.1 Introduction

Endoscopic submucosal dissection (ESD) technique, originally developed in Japan, allows *en bloc* resection of early colorectal tumors in any size. Endoscopic mucosal resection (EMR) had been the only treatment available for large colorectal neoplasms before arrival of the ESD. However, *en bloc* resection rate of EMR for lesions greater than 20 mm was unsatisfactory, leading to high proportion of local recurrence. Soon after launching of ESD, it has been confirmed to be superior to EMR with significantly higher rate of *en bloc* resection (ESD 84%, EMR 33%) [1] and lower local recurrence rate (ESD1.4%, EMR 6.8%) [2].

However, colorectal ESD compared to EMR is technically more demanding, time cosuming and has higher rate of perforations [3]. From experiences of colorectal ESD over a decade, it has been clarified that most of the procedure-related complications including perforations are manageable conservatively without surgical operation [4]. We believe that colorectal ESD satisfies an adequate safety even for non-expert to start on after a sufficient training, and standardization of this technique will lead to reduction of unnecessary surgeries in the future. Now, colorectal ESD becomes the key endoscopic treatment for large early colorectal lesions and is disseminating worldwide.

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11.2 Indications

The indications for colorectal ESD is listed in the guideline [5] drafted by Japan Gastroenterological Endoscopy Society (JGES) based on the typing of LST lesions (Fig. 11.1) proposed by Kudo.

1. Lesions for which *en bloc* resection with snare EMR is difficult to apply.
    - LST-NG, particularly LST-NG (PD).
    - Lesions showing a V_I-type pit pattern.
    - Carcinoma with shallow T1 (SM) invasion.
    - Large depressed-type tumors.
    - Large protruded-type lesions suspected to be carcinoma.
2. Mucosal tumors with submucosal fibrosis.
3. Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis.
4. Local residual of recurrent early carcinomas after endoscopic resection.

In general, colorectal neoplasms smaller than 20 mm are compatible with EMR to achieve R0 resection, therefore 20 mm is often referred

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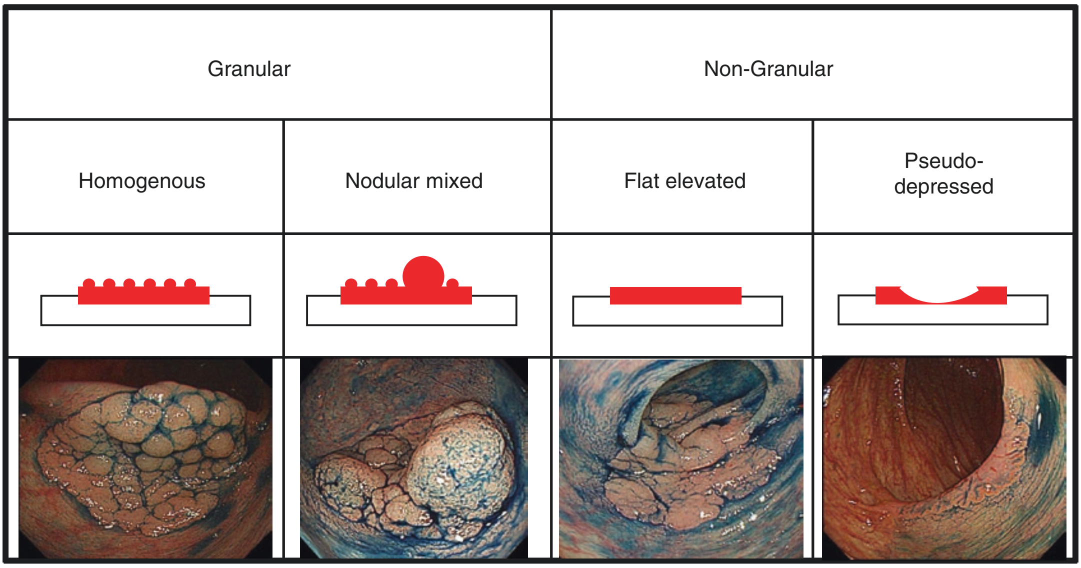

Fig. 11.1 Subtypes of laterally spreading tumors (LST)

as the boundary diameter for selecting ESD treatment. For exceptional cases such as post-therapeutic recurrent lesions, lesions with submucosal fibrosis and any lesions with technical difficulty to allign a snare, ESD may be considered regardless of its size. Given that LST-NG (Pseudo-depressed type) is frequently associated with fibrosis, ESD is more favorable, whereas LST-G (Homogeneous type) is acceptable for piecemeal EMR as they are less likely to invade to deep submucosal layer.

The biological features of the neoplasms are also important factors to decide treatment strategy. ESD is a topical treatment that should only be applied for curative lesions with low risk of lymph node metastasis. As the size of tumor does not always reflect the depth of invasion [6], the prediction of malignant potential and invasion depth should be attempted by carefully observing the lesion using narrrow band imaging (NBI) [7], magnifying endoscopy, chromoendoscopy, or endoscopic ultrasound prior to the therapy. NICE classification [8], JNET-classification [9], and Kudo's pit pattern classification [10] are widely used for pre-ESD diagnosis. NICE type 3, JNET type 3, invasive type V_i and type V_N are the typical findings for submucosal deeply invasive lesions (invasion depth >1000 μm sm) which have higher risk of lymph node metastasis and require surgical treatment with lymph node dissection.

11.3 Before Starting the Procedure

11.3.1 Scopes and Distal Attachment

Scope models such as GIF-Q260J, PCF-Q260AZI (Olympus, Tokyo, Japan) are often favored for colorectal ESD. First reason for selecting these scopes is that the width of the scopes is relatively thin and provides fair flexibility compared with a standard colonoscope model. This helps endoscopists to achieve retroflex position during the procedure and offers various strategic options. Second reason is the equipment of water-jet function which keeps to maitain clear visualization even under situation with active bleeding. The scope selection is influenced by the handling difficulty due to location of the lesion and looping at the sigmoid colon, therefore the practitioner is recommended to confirm the maneuverability of colonoscope before performing ESD. In general, gastroscopes are selected for lesions located in the distal colon, but it may also be used for lesions located in the ascending colon given that sufficient control is achievable. Double balloon endoscopy (EC-450BI, Fujifilm, Tokyo, Japan) is known as an advanced option in the proximal colon when the maneuverability is poor due to looping of a long sigmoid colon [11].

A transparent distal attachment (cap) is uniformy applied to the tip of the endoscope during ESD procedures. Disposable attachments from Olympus (D-201-11,804; Olympus, Tokyo, Japan) or TOP (Elastic Touch F-030; TOP, Tokyo, Japan) are popularly used in Japan. Short-type ST hood (DH-28GR and 29CR; Fujifilm, Tokyo, Japan) is a tapered attachment designed to maintain the position of the tip of the endoscope under mucosa even in cases with poor submucosal lifting. This type of attachment is essential in carrying out pocket-creation method (PCM) described in the latter.

11.3.2 Sedation

An appropriate amount (2–3 mg) of midazoram is administered intermittently to keep conscious sedation during the procedure. An analgesic (pentazocine 15 mg) may be administered when necessary. Note that changing the body position and breath control with help of the patient are both important in colorectal ESD, thus deep sedation should be avoided. 10 mg of scopolamine Butylbromide or 0.5 mg of glucagon are used to control peristaltic movements [12].

11.3.3 Gas Insufflation

Carbon dioxide (CO_2) insufflation is absorbed 160 times faster than conventional air insufflation [13]. The efficacy and safety of CO_2 insufflation have been confirmed with additional benefits of reduced discomfort during and after the colorectal ESD. Luminal distention with CO_2 is also expected to reduce serious complications such as abdominal compartment syndrome and tension pneumothorax due to perforations during the ESD procedure [14].

11.3.4 Electrosurgical Unit (ESU)

All ESD devices are powered by either monopolar or bipolar electric current generated by ESU. Several new ESUs provide a wide variety of functions and effect settings required for safe and effective ESD. Appropriate power and effect setting vary for each ESD device, and the setting should be changed in each stage of ESD. The setting of ESU is relatively simple in colorectal ESD compared to upper gastric lesions as the control of bleeding typically is not difficult. ENDOCUT mode is mainly used for mucosal incision and forced or swift coagulation mode is used for submucosal dissection and mild hemostasis. Soft coagulation mode does not cause cell burst or carbonization therefore vessel coagulation or hemostasis using hemostatic forceps are generally carried out with this mode setting. ICC200 and VIO 300D (Erbe Elektromedizin, Tübingen, Germany) and ESG100 (Olympus, Tokyo, Japan) are widely used as the main ESU for ESDs of any gastrointestinal tract, and specific settings for DualKnife and hemostatic forceps are depicted in Table 11.1.

11.3.5 ESD Knives

DualKnife J (Olympus, Tokyo, Japan) and FlushKnife (Fujifilm, Tokyo, Japan) are commonly used as the main device for colorectal ESD (Fig. 11.2). These "short needle-type" or "non-insulated tip" devices provide a sharp cutting with fair maneuverability. A small disc electrode is placed at the tip of the knife for safety and stabilization of the target tissues, while care to avoid perforation is necessary throughout the procedure. Despite various models with different length of the electrode, 1.5 mm is mostly used as the standard size in the colon and rectum. These devices features integrated submucosal injection fuction, hence we no longer need to change devices for mucosal injection.

ITKnife nano (Olympus, Tokyo, Japan) features speedy cutting and the insulated tip is useful to avoid damage to muscular layer. However,

Table 11.1 ESU setting for DualKnife and hemostatic forceps

ESD stage	Devices	ICC200	ESD setting VIO300D	ESG-100
Mucosal incision	Dual knife	ENDOCUT, [E]2, 40 W	ENDOCUT 1, [E]1, [D]2, [I]2, Dry cut [E]2, 30 W	Pulse Cut low 30 W
Submucosal dissection	Dual knife	Forced Coag, 30 W	Swift Coag, [E]3, 30 W	Forced Coag 2, 30 W
Hemostasis	Dual knife	Forced Coag, 30 W	Swift Coag, [E]3, 30 W	Forced Coag 2, 30 W
	Hemostatic forceps	Soft Coag, 50 W	Soft Coag [E]5, 50 W	Soft Coag, 50 W

[E]: effect, [D]: duration, [I]: interval

Fig. 11.2 Devices for colorectal ESD. Left: DualKnife J, middle: IT Knife nano, right: Coagrasper hemostatic forceps

IT Knife nano requires relatively large motion and it may be technically demanding under poor maneuverability. HookKnife (Olympus, Tokyo, Japan) offers a good visualization of the tissues by hooking and pulling the target area before cutting, therefore this type of knife provides safety operation especially in cases with fibrosis. ClutchCutter (Fujifilm, Tokyo, Japan) and SB Knife Jr. (Sumitomo Bakelite, Tokyo, Japan) are scissors-like devices that grasp target before electrical cutting. Although these devices features the highest level of safety, the dissection speed is slow and it is required to educate assistants to be able to rotate the device to desired direction.

Hemostatic forceps are available from Olympus and Pentax. The tip is designed to be smaller compared to conventional hot biopsy forceps to achieve intensed heat concentration at the tip, which reduces risk of delayed perforation. The use of these forceps in colorectal ESD is not mandatory in all cases because bleeding is mostly controlled easily by coagulating using ESD knife devices. Although switching devices and mode setting are time consuming, hemostatic forceps are expected to provide more promising hemostasis, and precoagulation of vessels avoids carbonization of tissues and helps maintaining clear vision.

11.4 The Procedure

11.4.1 Marking

In contrast to gastric ESD, colorectal neoplasms typically have clear demarcation that generally does not require marking. However, serrated lesions may have unclear margins, therefore marking may be considered as an option before starting submucosal injection. Mucosal tatooing should be considered when the target lesion has been suspected to have potential of deep submucosal invasion.

11.4.2 Submucosal Injection

The duration of mucosal protrusion gained by a single submucosal injection is important for efficient and safe ESD. MucoUp (Seikagaku Corp, Tokyo, Japan) provides a longer time of submucosal cushion that replaces with the conventional saline. MucoUp may be diluted with normal saline or 5% glycerol by 1:1 proportion to reduce the cost of agents. Few drops of indigo carmine are added into the solution to help differentiating the whitish muscular layer from blueish submucosal layer. Adequate amount (2–3 ml per injection) of MucoUp around the margin of colorectal neoplasm should be injected carefully at the start of ESD.

11.4.3 ESD Procedure

One important process before starting ESD is the observation of gravitational direction. Fluid collection should be located at the opposite side of the lesion to avoid the pooling of the fluid in the resection area, while the gravitational force lifts up the dissected lesion and provides a good visualization. Ideally, maneuveravility of the endoscope should be checked before the day of the procedure and appropriate scope model should be selected depending on the maneuveravility. When achievable, the procedure is preferred to be started in the retroflexed position due to various reasons; (1) endoscope synchronizes with the respiratory motion and provides more stable view, (2) the rotation radius is smaller which allows speedy and effective circumferential incision, and (3) the proximal side tend to have poor visibility in the normal position.

The risk factors associated with technical difficulty and adverse events are poor submucosal lifting after injection and lack in maneuverability of scopes. Hence, less experienced endoscopists are recommended to start performing ESD from simple LST-G lesions in the rectum which are expected to have less fibrosis [15]. Here, we introduce two strategies of colorectal ESD and an alternative technique.

11.4.3.1 Conventional Method

Typically, we initiate mucosal incision from the oral side using DualKnife J, with at least a 5-mm margin of the neoplasm in the retroflex position view after submucosal injection (Fig. 11.3). A practitioner should not intend to carry out a shallow mucosal incision as 1.5 mm blade automatically provides sufficient depth of incision, provided that appropriate amount of mucosal injection has been administered. Incomplete incision of muscularis mucosae often causes unnecessary bleeding and carbonization, and additional trimming under poor maneuverability should be minimized because this process is often time consuming and requires delicate handling to avoid perforation. Complete circumferential incision at this early stage is not recommended in the colorectal lesions as it causes the injection agent to leak out rapidly. Hence, around 180–270 degrees of mucosal incision is ideal to go to the next stage.

After partial mucosal incision, the next target will be the submucosa just below the edge of dissected area. Although submucosa is often located perpendicularly, precise control of the scope with aid of transparent attachments provides appropriate view by locating the attachment under peripheral mucosa. The practitioner should aim to continue the submucosal dissection up to about halfway to the anal demarcation of the neoplasm. Once this has been achieved, return the scope to normal position to complete the circumferential mucosal incision from the anal side. Submucosal space is expanded widely with the help of gravity, so the final part of submucosal dissection should have less difficulty.

To maintain the safety of submucosal dissection, recognition of muscular layer is crucial throughout and the practitioner must always keep the direction of dissection horizontal to muscular layer. Although specific hemostatic devices are not used routinely, precoagulation should be considered for cases with thick branch of vessels. After completing the ESD, endoscopists should be watchful on any damaged muscular layer that requires enforcement with clips.

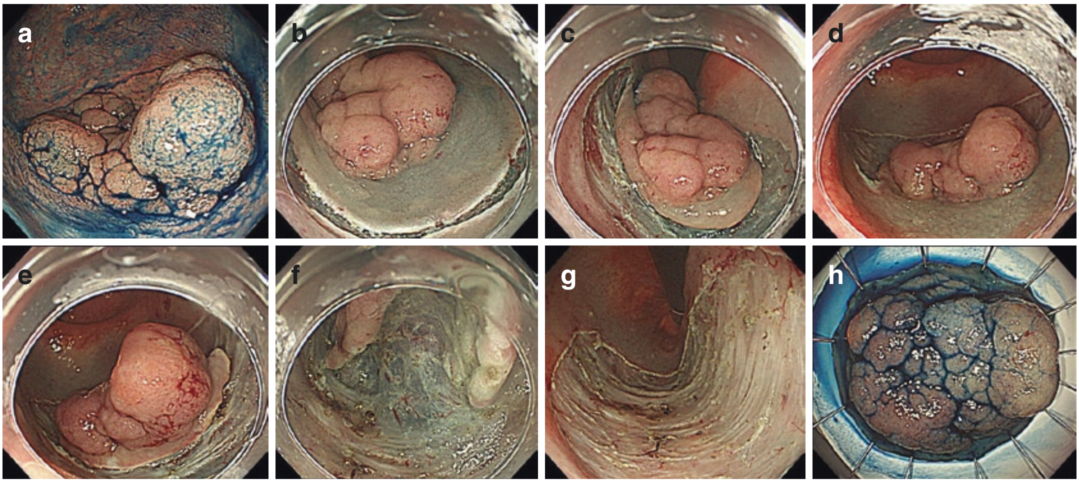

Fig. 11.3 (**a**) 35 mm LST-G nodular mixed type at rectum (Rb). (**b**) Mucosal incision initiated from the oral side in retroflex position. (**c**) Continue mucosal incision and submucosal dissection to approximately 180–270 degrees of the whole circumference. (**d**) Return the scope to the normal position. (**e**) Circumferential incision completed. (**f**) Remaining submucosal layer dissected in retroflex position. (**g**) R0 resection completed without complication. Duration of procedure: 47 min. (**h**) pathology: Intramucosal tubulovillous adenocarcinoma (tub1 + tub2), pHM (−), pVM (−), ly0, v0, pTis (M)

11.4.3.2 Pocket-Creation Method

PCM is a novel strategy of colorectal ESD with confirmed reliability and safety originally reported by Hayashi et al. [16, 17]. This method features creation of a large submucosal pocket using a small-caliber-tip transparent attachment (short-type ST hood) with minimal mucosal incision so that injected fluid does not leak out throughout the procedure. Furthermore, PCM reduces respiratory motion and provides stabilized vision constantly once the endoscope entered the pocket. Identification of muscular layer is easy even when the tumor is located at the fold of intestinal tract, therefore it is often referred to be a safe strategy suitable for inexperienced endoscopists.

An initial mucosal incision is made at 10 mm away from distal side of the tumor and the incision is recommended to be 20 mm wide approximately. Few traces of submucosal dissection were performed to make a pocket. Insert the tip of the endoscope with short type ST hood into the submucosal pocket to continue submucosal dissection with a minimal mucosal incision. An additional mucosal incision and submucosal dissection were made to open the lower side (based on the direction of gravity) of the pocket toward proximal side. Finally, upper side was treated in the same method.

11.4.3.3 Hybrid ESD

"Hybrid ESD" or "precutting EMR" is a modified technique of colorectal ESD and EMR, defined as ESD with snaring after circumferential mucosal incision. One use of this technique is for facilitating the submucosal dissection on relatively small lesions to reduce the procedure time. Secondly, hybrid ESD is also used as rescue treatment in situation where complete resection with ESD is not achievable due to technical difficulty and perforation. However, the *en bloc* resection rate of emergency hybrid ESD is lower than full ESD (66.7% vs. 94.2%) [18], therefore this technique should be limited for cases with unstable vital signs, especially due to perforations.

11.5 Complications

Bleeding

Post-ESD bleeding occurred in 2.04% (124/6077) of patients in a meta-analysis of colorectal ESD

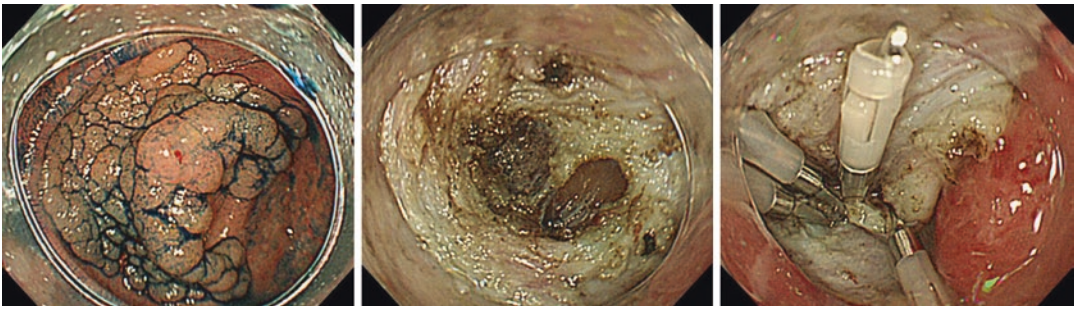

Fig. 11.4 Immediate perforation occurred for LST-G at the cecum. This patient has been managed conservatively after the closure of perforation with clips

[3]. Although severe bleeding event that required blood transfusion or surgical treatment is rare, patients should be informed in detail about the complication before starting the procedure.

Perforation

Perforation is the most common and severe complication in the colorectal ESD (Fig. 11.4), and the rate of 4.8% (296/6077) was reported in a meta-analysis [3]. "Immediate perforation" and "delayed perforation" are often differentiated from each other as the management and outcome of these complications differ. Endoscopic closure of immediate perforations with clips is the key to successful conservative therapy therefore this process must be completed very carefully. In a large case series, nine immediate perforations were managed without surgical treatment after successful closure of perforation [4].

On the other hand, delayed perforation often develops pan peritonitis with sudden abdominal pain and fever. There are no indicators available today to predict successful conservative management. Delayed perforation may be life-threatening, especially for elderly and patients with cardiopulmonary disorders, thus surgery is more prior to conservative therapy despite few successful cases of conservative therapy have been reported.

Stricture

Post-ESD stricture is one of the major complications in the esophagus, but stricture at the rectum also occurs rarely. The frequency of rectal stricture after subtotal (>90%) circumferential ESD and full circumferential ESD were 43.8% and 71.4%, respectively, but none in lesions with less than 90% of circumference [19]. Intravenous, oral or local injection of steroid is expected to reduce the frequency of rectal stricture, and endoscopic balloon dilation (EBD) is an effective treatment for the condition.

11.6 The Efficacy and Long-Term Outcomes

The largest prospective, multicenter study from Japan to assess the efficacy of colorectal ESD included 1111 consecutive colorectal lesions [20]. The *en bloc* and curative resection rates were 88% and 89%, respectively, and the mean duration of procedure was 116 min for tumor size of 35 mm in average. In terms of long-term outcomes, one single-center retrospective study [21] has followed 222 consecutive patients with 224 tumors treated with colorectal ESD for 5 years, resulting *en bloc* resection rate of 89.7% and local recurrence rate of 1.5% (3 out of 201 R0 resected cases). 100% disease-related survival and 94.6% overall survival have been achieved after a median follow-up of 79 months. A meta-analysis [22] combined data from 21 single-arm case series for ESD and transanal endoscopic microsurgery (TEM) evaluating outcomes in the treatment of rectal neoplasms larger than 2 cm. In this analysis, there was a trend toward fewer local recurrences in the ESD group than in the TEM group (2.6% vs. 5.2%).

Although the data from experts in Japan seems to be very promising, one systematic review evaluated the difference between Asian and non-Asian countries, showing that the standard ESD technique is still failing to achieve acceptable levels of performance in non-Asian countries [23]. R0 resection rate and *en bloc* resection rate were significantly lower in non-Asian versus Asian countries (R0: 71.3% vs. 85.6%, *en bloc* 81.2% vs. 93%). Furthermore, the rate of surgery needed was also significantly higher (3.1% vs. 0.8%) for non-Asian. Given that the quality of colorectal ESD by non-experts is clearly not as high as experts, patients should be informed in detail about the risk of incomplete treatment and complications especially when non-experts perform ESD.

11.7 Training

Colorectal ESD is know as a complex procedure which requires extremely high level of technique. Certainly, a specific training course is necessary before starting ESD. However, it is also true that requirement of years of training to start ESD is causing a delay in spreading of this technique worldwide. Determination of an appropriate amount of training is not constant for each endoscopist as they have different levels of skill and learning curb to each other. Nevertheless, there are various options of training available today such as visiting centers with high volume of ESD for observation and learning knowledge of technique and equipment, viewing ESD videos, practicing on animal models, attending to ESD workshops and applying ESD in human for selected safe lesions such as LST-G in the lower rectum.

Classically, the number of experiences in gastric ESD is often referred as the measurement to initiate training on colonic lesions, but appropriate gastric lesions may not be available especially in the Western countries. One study from Japan has pointed that colorectal ESD may be implemented without any experience of gastric ESDs [24] and 30 cases of colorectal ESD under guidance of experts have been appropriate to complete ESD without serious complications [25]. Report from a European center has shown a clear improvement of the outcomes for rectal and sigmoid ESD in 76 consecutive cases. *En bloc* resection rate was improved to 96% in the present data compared to 60% in the first 25 cases, and procedure time was decreased to 136 min from 200 min. Such data suggest that non-experts will be able to overcome the technical difficulty in colorectal ESD without requiring long-term training in the future [26].

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12 Handling of Specimen and Post-ESD Management Protocol

Rapat Pittayanon and Noriya Uedo

12.1 Handling of Specimen

After accomplishing ESD procedure, specimen handling is a fundamental step to obtain the correct histological diagnosis for curability of resection and appropriate further management. The following steps are recommended for handling resected-tissue before passing to a pathologist.

12.1.1 Stretched out Specimen and Pinned

The resected specimen must be stretched out, so that it is approximately the same size at in vivo, and be pinned on the flat board or cork sheet [1–4] loosely [2] (Fig. 12.1). In case of piecemeal resection, it is better to reconstruct all retrieved specimens as much as possible to estimate completeness of resection. Orientation and labelling the margin of specimens; for instance, proximal (P) and distal (D) are very helpful to determine the free margin of malignancy [1–4]. Application of dye helps orientating the specimen. For circumferential esophageal resection, the resected tissue can be placed over a syringe [2] (Fig. 12.2).

12.1.2 Preserved Specimen

Usually, 10–20% formaldehyde solution is used to preserve resected tissue at room temperature for 24–48 h [4]. The optional preservative solution is 4% neutral buffered formaldehyde [2]. The container should have enough space for the entire sheet underneath the specimen and ensure that specimen is completely covered by preservative solution in all directions [2] (Fig. 12.3). This process should be done after resection as soon as possible to prevent cell autolysis when the tissue is dry [4]. We can keep the resected specimen soaking in physiological saline solution to prevent this problem until finishing the procedure [4].

12.1.3 Submit Specimen to Pathologist

Before passing the specimen to a pathologist, it should be confirmed that the container is secured properly. Then, put the container into the

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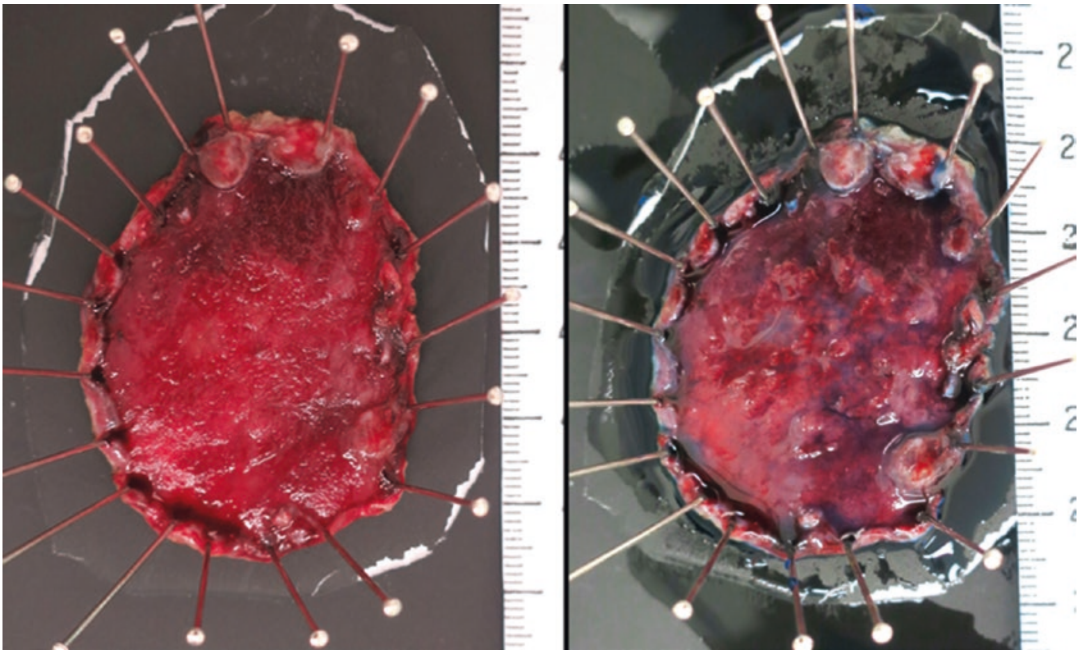

Fig. 12.1 Pinned resected specimen

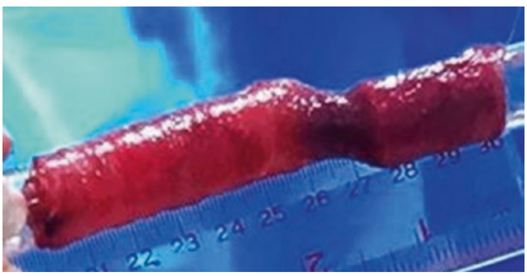

Fig. 12.2 Circular *en bloc* specimen over the syringe

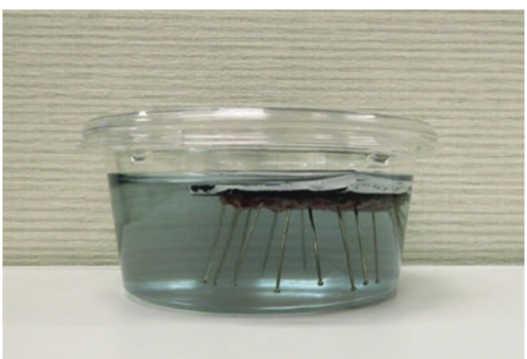

Fig. 12.3 Preserving resected specimen

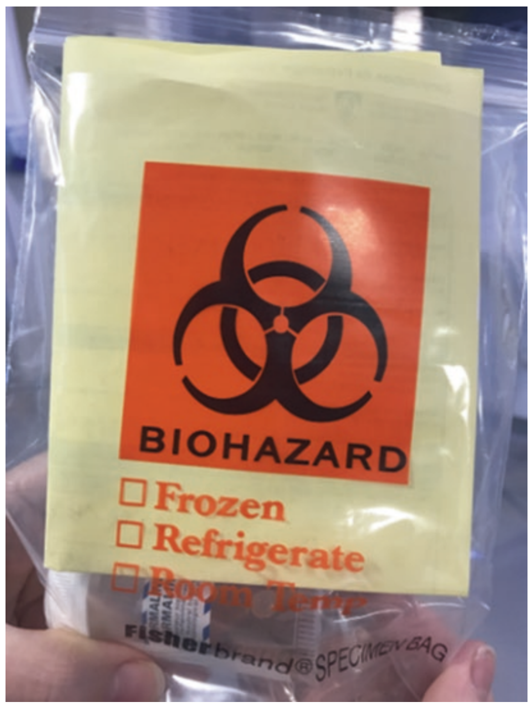

Fig. 12.4 Carry specimen

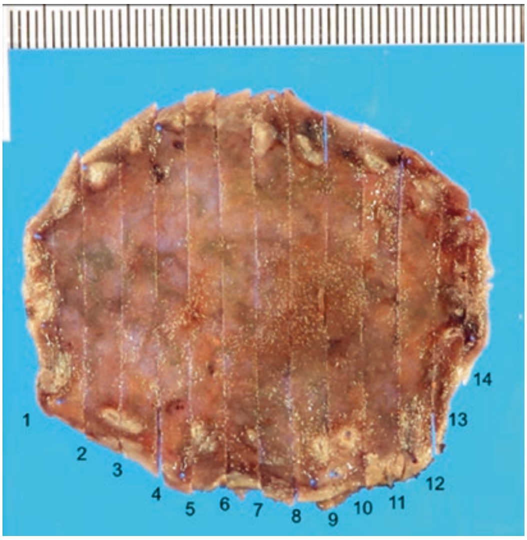

Fig. 12.5 Sectioning of specimen

"Biohazard" bag attached with a pathology request form (Fig. 12.4). Endoscopist should provide accurate clinical information, including previous histology from biopsy if indicated as well as endoscopic findings such as size and location of tumor to pathologist in order to get the precise diagnosis [4]. Finally, carry all together sending to pathologist.

12.1.4 Sectioning of Specimen

This is usually performed by a pathologist. However, if there is an area needing special attention, i.e., close resection margin or interesting endoscopic finding, it is better to indicate the cutting direction in the ordering paper or to attend sectioning by a pathologist. Fixed materials should be sectioned serially at a few millimeter intervals parallel to a line that includes the closest resection margin of the specimen [3, 4] (Fig. 12.5).

12.2 Post-ESD Management Protocol

12.2.1 Esophagus, Stomach, and Duodenum

All patients who underwent upper GI-ESD are better to be observed as in-hospital patients. Routine postoperative care including close monitoring of vital signs, observe patient's well-being, continue IV fluid, and adequate pain management is the key approach in the first 2 h after the procedure. The specific issues for post upper GI-ESD management consist of second-look endoscopy, refeeding, medication, and length of hospital stay.

Most evidences of post-ESD management strategy in upper GI tract are mainly from gastric ESD followed by esophageal ESD. Currently, feasibility and safety of duodenal ESD are controversial because of possibility of morbid adverse events [5]. The summary of patient's care in patient underwent gastric ESD is in Fig. 12.6.

12.2.1.1 Second-Look Endoscopy

If the patient has an average risk of bleeding, second-look endoscopy (even with prophylaxis hemostasis) is not routinely recommended because it does not prevent post-gastric-ESD bleeding [6, 7]. Electrical cauterization from prophylaxis hemostasis during second-look endoscopy can potentially induce delayed bleeding [7]. Moreover, post-ESD bleeding can occur within 24-hr after finishing ESD [8, 9], which cannot be prevented by scheduled endoscopy over a day. In contrast, patients with chronic kidney disease (CKD) with ongoing hemodialysis may need a different strategy. The detail of post-ESD management in this specific group is described in the topic of special conditions below.

The second-look endoscopy in post esophageal ESD may be recommended at 2–3 weeks post procedure in patients with lesion of more than three-fourth the circumferential extension in order to find the evidence of esophageal stricture [10, 11]. Re-scope during admission dose not routinely perform, except in case of suspicion of bleeding.

12.2.1.2 Refeeding

From a multicenter survey in Japan, all ten high-volume hospitals permit food intake prior to post-gastric ESD day 3 [8]. Four of ten hospitals allow refeeding a day after procedure whereas the rest of those extend to the second day. However, refeeding time depends on the experience of the individual endoscopist, the chance of perforation and

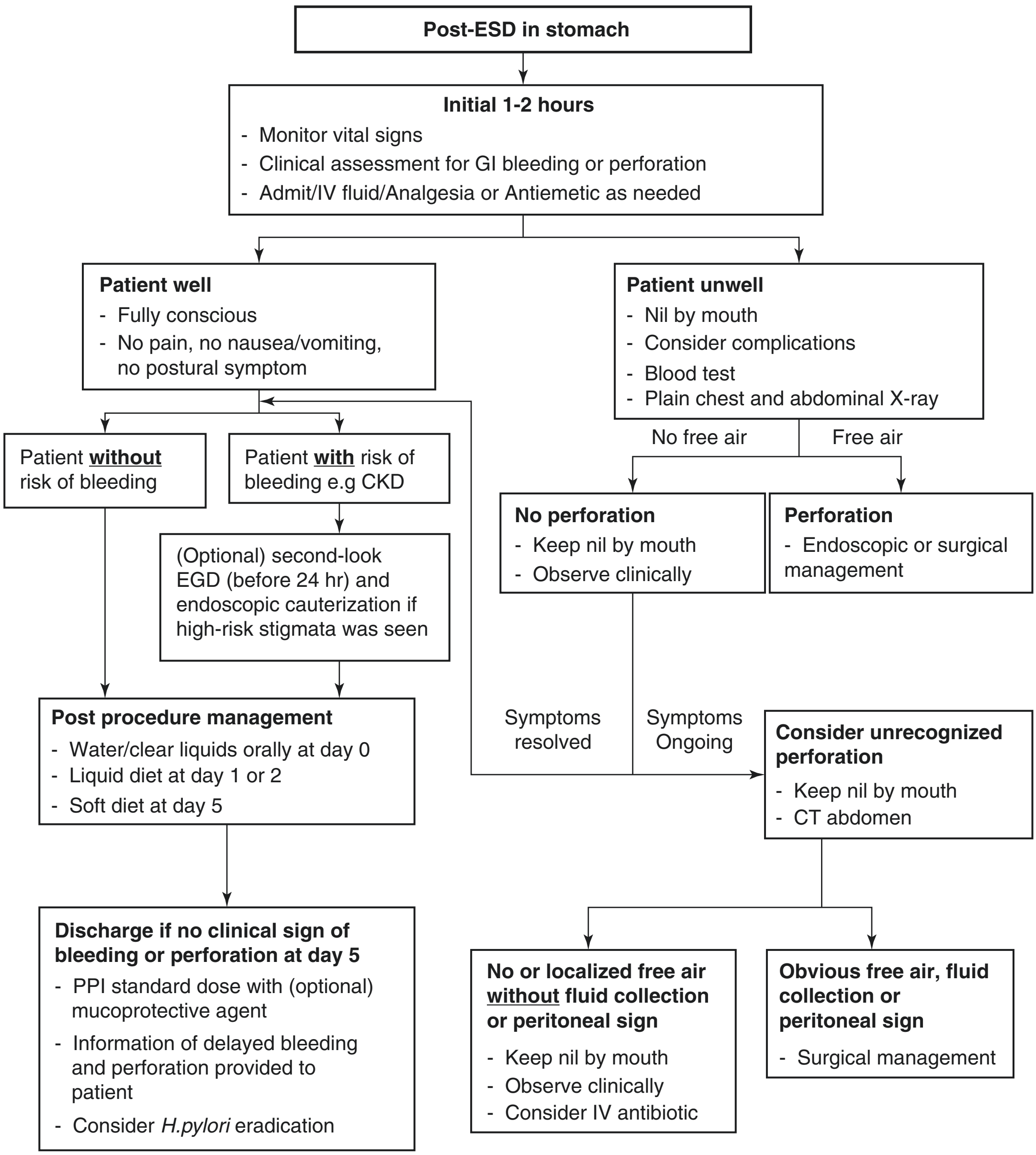

Fig. 12.6 Schema of post-gastric-ESD management

patient's condition [8]. In case with intraprocedural perforation, if the perforation hole was completely closed with clips, patient may start feeding at day 3–4 after nasogastric suction and intravenous antibiotic administration [12]. Delayed perforation develops in <0.5% of gastric ESD cases and peritoneal symptom presents within 24 h in such patients [13]. If patients look unwell, they should keep nil per oral and observe the clinical signs (Fig. 12.6). Most patients are allowed to start with a clear liquid diet and then gradually step up to soft diet by day 5 after gastric-ESD [6].

In terms of esophageal ESD, a small amount of water is permitted 3 h after the procedure. If no complication occurred, patient can have a light meal the next day [10].

12.2.1.3 Medication

Esophagus

From the expert opinion, if the lesion located near esophago–gastric junction (EGJ), proton pump inhibitor (PPI) can be prescribed to prevent delay healing from acid irritation. Of those, healed ulcer could be achieved at 5 weeks post-procedure, irrespective of lesion location, and extension [14]. However, there is still lack of evidence that demonstrate the clinical benefit, for instant prevention of chest pain, bleeding, or stricture, as well as ulcer healing rate of PPI in patients with squamous cell carcinoma and the lesion located higher than EGJ [15]. In addition, routine antibiotic prophylaxis after esophageal–ESD is not necessary because the incidence of bacteremia is less than 1% [16].

Submucosal steroid injection to the wound just after the resection reduces stenosis in patients received esophageal ESD [17] but is not enough effective in patients with tumor extension >75% of circumference [18]. A retrospective study revealed that tapered oral steroids within 8 weeks in patients undergoing semicircular or complete circular ESD might eliminate subsequent esophageal dilatation [19]. On the other hand, in entire circumferential ESD cases, the recent retrospective study reported that there is no correlation between oral steroid administration and post-ESD stricture in multivariate analysis [20]. Consequently, development of an effective prophylactic method to prevent stricture in extensive whole circumferential esophageal ESD cases is still warranted.

Stomach and Duodenum

PPI is the first-line treatment to prevent post-ESD bleeding and to promote artificial ulcer healing in the stomach [21]. Uedo et al. reported the better efficacy of PPI on prevention of post-gastric-ESD delayed bleeding compared with H_2-receptor antagonists [22], and, later it was confirmed in the meta-analysis of six randomized control trials [23]. Expert consensus in China recommends using intravenous PPI twice a day right after ESD for 2–3 days, followed by oral standard dose PPI once a day for 4–8 weeks regarding the risk of delayed bleeding [21].

A meta-analysis suggested the usefulness of mucosal protective, Rebamipide, add-on therapy to PPI for better ulcer healing than PPI alone [24]. However, all RCT comparing PPI alone and combination treatment (PPI plus Rebamipide) evaluated ulcer healing by endoscopy, and did not show evidence for reduction of delayed bleeding rate [24, 25].

Nevertheless, there is still a lack of information to establish optimal dosage and duration of PPI for preventing delayed bleeding. From the Japanese survey, 60% of endoscopists prescribe 2 months of PPI to post-ESD patients whereas 30 and 10% usually order 4 weeks and 2 weeks of PPI, respectively [8]. The healing speed of ESD-derived ulcer was associated with the initial ulcer size [26]. In addition, complete ulcer healing could be achieved without continuous PPI [27, 28]. A prospective study revealed that, with 2-week standard dose PPI, post-ESD ulcer completely healed at 8 weeks after ESD without bleeding in 80% (44 from 55) of patients with single, non-ulcerative early gastric cancer [27]. Although, scaring is the ultimate endpoint of tissue healing, almost all delayed bleeding after gastric ESD occurs within 14 days [29]. Taking these aspects into consideration, effectiveness of at least 2-week PPI on prevention of delayed bleeding in post-ESD patients could be investigated in a well-designed clinical trial. Nevertheless, 4–8 weeks PPI administration with/without adjunctive Rebamipide may serve as an optional treatment in patients at high-risk bleeding conditions.

There is no evidence for using antacids such as aluminum hydroxide to neutralize gastric acid and prevent post-ESD complications. *Helicobactor pylori* (*H. pylori*) eradication is strongly recommended to prevent metachronous gastric cancer in patients undergone ESD for early gastric cancer [30], but there is no evidence to support the effectiveness of *H. pylori* eradication on the promotion of ulcer healing and prevention of delayed bleeding.

12.2.1.4 Length of Hospital Stay

One retrospective study investigated post-gastric-ESD ulcer on the second-look endoscopy and showed that no high-risk stigmata including adherent clot, non-bleeding visible vessel, oozing, and spurting bleeding were found at day 8 after ESD [31]. The protocol in most upper GI ESD studies in Japan indicated that the hospitalization was around 1 weeks (varying from 5 to 10 days) even no complication occurred and it is allowed by the social insurance system [10, 32]. Majority (>70%) of delayed bleeding occurs within 1 week after gastric ESD but the reminder happens even after that. Hence, length of hospital stay should be approximately 5–10 days, respective of sociomedical condition and individual physician's decision.

12.2.2 Colon and Rectum

After colonic or rectal ESD, Japanese guideline recommends hospitalization [4], but Western practice indicates hospitalization is not always necessary if the lesion is less than 2 cm [33, 34]. However, in every patient, they should be monitored closely for 1–2 h before discharge from the hospital to observe unexpected complications. If any signs of complication occurred, they can proceed to early management promptly (Fig. 12.7).

12.2.2.1 Refeeding

If no complication occurred, patients will be allowed to drink water or clear liquid diet a couple of hours after ESD and start soft diet at the following day [33, 35]. Refeeding should be initiated after confirming the absence of inflammation as well as bleeding and perforation [4]. Pain and fever may be caused by inflammation of the peritoneum occurs in 9.5% of post-colorectal ESD cases [36]. Most patients with conservative treatment can be carried out, it is important to adopt careful measures such as prolongation of the fasting period while considering the possibility of delayed perforation. Delayed perforation occurs in 0.1–0.4% of patients within 24 h [4]. Nevertheless, abdominal pain should be monitored after initial oral intake [33].

12.2.2.2 Medication

In general, no medication is required in patients after colonic ESD, but probably in anorectal lesion. Prophylaxis antibiotics can be considered in patients undergoing anorectal ESD, especially larger than 3 cm to prevent bacteremia from direct bacterial translocation to systemic circulation [34, 37]. Moreover, if the lesion involves a dentate line, adequate pain control should be aware [34, 37]. These patients should maintain soft stool for 1–2 weeks; thus stool softener may be prescribed [37].

12.2.2.3 Length of Hospital Stay

Patient undergoing ESD in lower GI tract does not always require admission in hospital if the size of the lesion is smaller than 2 cm [33] or if the lesion located in the rectum. However, the physicians are able to observe patient's condition in hospital overnight depends on the opinion and experience of the individual physician [4]. One Japanese study in 382 colonic ESD patients suggested that these patients could discharge on 3 postoperative days [38]. One Swedish study by a Japanese endoscopist suggested patients with uncomplicated ESD should be treated as a day surgery [39].

12.2.3 Special Conditions

12.2.3.1 Patient with Antithrombotic

According to the recent British and European guidelines [40] as well as Japanese guidelines [41], ESD is categorized as a high-risk procedure, therefore antithrombotic agents are basically recommended discontinuing before ESD procedure. Risk of thromboembolic event should be weighed against the risk of post-ESD bleed-

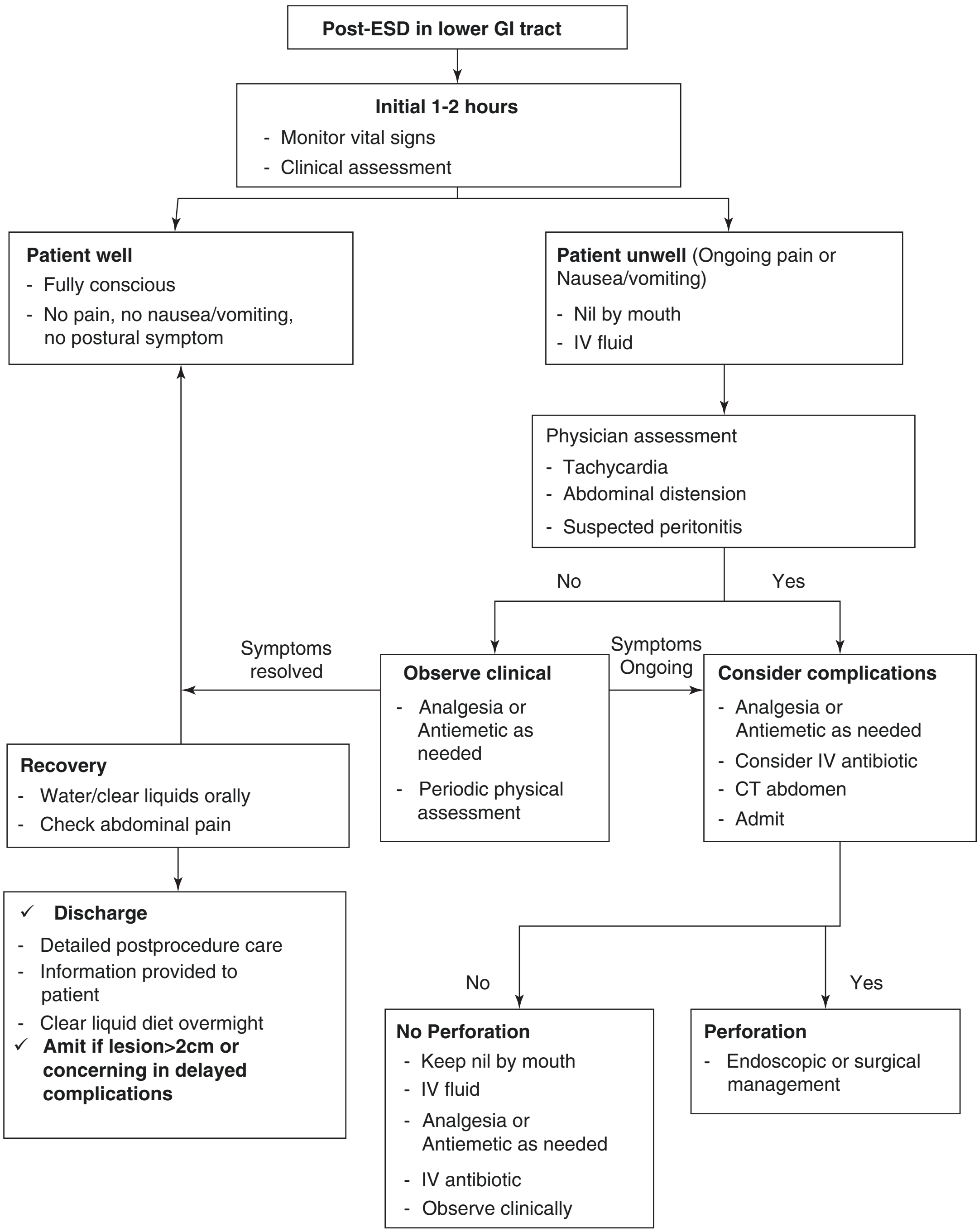

Fig. 12.7 Schema of post-ESD management in the lower GI tract. Modified from Klein A and Bourke MJ Gastroenterology Clinics of North America 2015 [34] and Ma MX and Bourke MJ Best Practice & Research Clinical Gastroenterology 2016 [33]

ing. In patients at high risk of thrombosis, aspirin can be continued. Antithrombotic should be resumed as soon as the definite hemostasis is confirmed [21, 40, 41]. It is appropriate to restart oral aspirin and nonaspirin antiplatelet on the following day if hemostasis is secured [41, 42]. In terms of conventional anticoagulant, warfarin is able to resume within 24 h after ESD in low risk at thromboembolism patient [21, 43] or postpone to 72 h post-procedure for a patient at high risk of rebleeding [21]. On the other hand, unfractionated heparin or low molecular weight heparin should be prescribed at 2–6 h after accomplishing the procedure to patient with high risk thromboembolism until INR reaches the therapeutic range [41, 43]. Due to the rapid onset of action in direct oral anticoagulant (DOAC), heparin can be discontinued immediately after taking DOAC [41].

Resuming antiplatelet and anticoagulant increases risk of bleeding in both acute and delay onset after 2 weeks [41]. Therefore, continuous monitoring of sign of bleeding is necessary [21, 41]. Moreover, the patients have to be fully informed of the bleeding risk and given the written consent [41].

12.2.3.2 Patient with Chronic Kidney Disease

Post-gastric-ESD bleeding rate increases in patients with CKD [44, 45]. The bleeding rate in patients with hemodialysis was 33%, compare to 9.4% in non-hemodialysis [45] and less than 6% in general population [46]. This high bleeding rate is explained by the fact that artificial membrane of dialysis activates blood platelet and coagulating factors resulting in reduction of these hemostasis cofactors in circulation [47]. A retrospective study in 79 CKD patients undergone gastric ESD revealed that most patients (88%) required coagulation of exposed vessels during second-look endoscopy [45]. They suggested that hemodialysis patients having ESD in upper GI tract may have benefit from second-look EGD before 24 h.

In addition, impaired renal function in CKD patients attributes to poor drug clearance and potentiating drug interaction. Medications that mainly excrete by kidney should be concerned in these patients to prevent drug toxicity [21]. There is no relevant data in patients undergoing ESD in lower GI tract.

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13 Surveillance Protocol After Endoscopic Resection

Takuji Kawamura

13.1 Introduction

Due to recent progress in endoscopic treatment, a lot of gastrointestinal cancers or premalignant lesions are successfully removed using this technique and patients' quality of life is considerably improved as a result. However, the risk of secondary cancers after endoscopic resection is likely higher than that after surgery, because metachronous cancer may develop from the preserved organ. Therefore, appropriate surveillance after endoscopic resection is essential.

In this section, the surveillance protocol after curative endoscopic resection is discussed. Management of non-curative resection and local recurrence after endoscopic resection will be described in the other section.

13.2 Esophageal Cancer

13.2.1 Squamous Cell Carcinoma

Long-term outcomes after endoscopic resection of esophageal squamous cell carcinoma (SCC) are related to the depth of invasion. Compared with epithelial (EP) or lamina propria (LPM) cancer, the hazard ratio for metastasis was reported to be 13.1 for cancer with invasion into muscularis mucosa (MM), 40.2 for cancer with ≤0.2 mm invasion into the submucosa (SM1), and 196.3 for cancer invading >0.2 mm into the submucosa (SM2) [1]. When invasion depth is limited within EP/LPM, good prognosis is expected with endoscopic resection only. However, synchronous and metachronous SCC in the esophagus, head and neck frequently occurs [2–4]. Therefore, appropriate surveillance after endoscopic resection of esophageal SCC, including of the head and neck region, is necessary.

Usually, we can easily identify esophageal SCC as Lugol-voiding lesions (LVL) on Lugol chromoendoscopy. Multiple LVLs in the background esophageal mucosa are sometimes observed in patients with esophageal SCC, and multiple LVLs are recognized as one of the important risk factors for metachronous SCC [5, 6]. Katada et al. divided patients with esophageal SCC into three groups, based on the number of LVLs per endoscopic view: no lesion, 1–9 lesions, and 10 or more lesions [2]. They reported that metachronous esophageal SCCs were detected in 4% of patients without LVL, in 9.4% of patients with 1–9 LVLs, and in 24.7% of patients with 10 or more LVLs over the 2-year study period.

Alcohol consumption and insufficient alcohol metabolism are known to be important risk factors for esophageal SCCs. Risk of developing metachronous multiple SCCs of the esophagus are decreased by alcohol abstinence [2].

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No randomized controlled study has looked at the appropriate frequency of surveillance after endoscopic resection. In a Japanese multicenter cohort study, Lugol chromoendoscopy of the esophagus and upper gastrointestinal endoscopy were performed at 3-month intervals for up to 6 months after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Subsequently, these examinations were carried out at 6-month intervals [7].

13.2.2 Adenocarcinoma

As for esophageal cancer, squamous cell carcinoma (SCC) is the prevailing histological type in Asia, whereas adenocarcinoma (AC) is more common in Western countries. Some Western studies reported favorable prognosis after endoscopic resection for AC of the esophagus, while local and metachronous recurrence rates were relatively high [8, 9]. Eradication of long-segment Barrett's esophagus after endoscopic resection of AC is recommended to reduce the development of metachronous lesions [9, 10]. On the other hand, the majority of esophageal AC arises from short-segment Barrett's esophagus in Japan. A lower recurrence rate was reported after endoscopic resection of AC compared with SCC in Japan, therefore, the surveillance interval required after endoscopic resection of AC may be longer than that for SCC in this country [11].

13.3 Gastric Cancer

In the 2014 Japanese Gastroenterological Endoscopy Society (JGES) guidelines, "curative resection" is defined as en bloc resections that are <2 cm in diameter, predominantly differentiated type, intramucosal (pT1a) carcinoma, no finding of ulceration (scar) and vascular infiltration [i.e., UL(−), ly(−), v(−)], and with negative surgical margins [12]. Furthermore, "curative resection for expanded indications" is defined as en bloc resected lesions that are: (1) ≥2 cm in diameter, predominantly differentiated type, pT1a, and UL(−); (2) <3 cm, predominantly differentiated type, pT1a, and UL(+); (3) <2 cm, predominantly undifferentiated type, and pT1a, UL(−); (4) <3 cm, predominantly differentiated type, pT1b (SM1, defined as cancer invasion <500 μm from the muscularis mucosae); and ly(−), v(−), with negative surgical margins [12].

Excellent long-term prognosis has been observed if curative resection for absolute or expanded indications was achieved by endoscopic resection [13–19]. Oda et al. reported that no recurrences were observed in any of the 1601 patients that underwent curative resections, and as for patients with curative resections for expanded indications, the recurrence rate was just 0.2% (3/1205 patients) in a multicenter questionnaire study conducted in Japan [16]. We have to pay more attention to local recurrence when we apply the conventional EMR technique, not ESD, because many lesions cannot be curatively resected by conventional EMR compared with ESD [15].

The main problem concerning long-term outcome is synchronous or metachronous multiple gastric cancers. Kato et al. reported that synchronous multiple gastric cancers were seen in 9% of patients who underwent gastric ESD, and 19% of synchronous cancers were missed at their first ESD procedure [20]. Metachronous multiple gastric cancer increases with time, and Abe et al. showed that the cumulative incidence rates of metachronous cancers were 9.5% at 5 years, 13.1% at 7 years, and 22.7% at 10 years [14]. Therefore, long-term follow-up is necessary for the detection of metachronous cancers.

It is known that *Helicobacter pylori* (*HP*) infection is strongly associated with the development of gastric cancer [21]. The occurrence of metachronous gastric cancer after endoscopic resection should be reduced by *HP* eradication [22, 23]; therefore, Japanese guidelines recommend *HP* eradication in *HP*-positive patients [12]. However, several reports have shown that the incidence of metachronous cancer did not decrease after *HP* eradication [20, 24, 25]. As such, appropriate surveillance should be considered even after successful *HP* eradication [26].

There is no standard surveillance protocol after endoscopic resection for gastric cancer.

Japanese guidelines only suggest follow up with esophagogastroduodenoscopy (EGD) at intervals of 6–12 months after endoscopic resection, for the detection of metachronous gastric cancers [12]. Hahn et al. reported that patients with long surveillance intervals (>12 months) have higher risk of recurrent adenocarcinoma, additional gastrectomy, and larger recurrent tumor size than those with short surveillance interval (≤12 months) [27]. In common Japanese clinical practice, the first surveillance EGD is often performed 1–3 months after endoscopic resection for the detection of synchronous gastric cancers. EGD at 6-month intervals for several years is often carried out, and annual follow up is performed in the long term to detect metachronous cancers [20]. It is reported that metachronous cancer is limited to early stage and can be resected by endoscopic procedures, as long as the appropriate surveillance with endoscopy is carried out [20].

13.4 Colorectal Cancer

Endoscopic polypectomy for colorectal adenomatous lesions prevents the development of colorectal cancer [28]; therefore, colorectal polypectomy is widely performed worldwide for premalignant polyps. Recent advancement of endoscopic techniques allows en bloc resection of larger lesions, and early-stage colorectal cancer can also be treated, in part, by endoscopic procedures [29]. Generally, carcinoma in situ (Tis) (mucosal [M]) does not metastasize to lymph nodes or distant organs; therefore, the resected lesion is judged as curative resection, when the lesion can be removed en bloc and the tumor is limited to the mucosal layer [30]. When the resected lesion is pT1 (submucosal [SM]) carcinoma, subsequent therapeutic surgery should be considered. However, when the resected lesions satisfy all of the following conditions, the risk of metastasis is low and the lesion is usually judged as curative resection [30]; vertical tumor margin negative; papillary adenocarcinoma or tubular adenocarcinoma; SM invasion depth <1000 μm; no vascular invasion; tumor budding grade 1.

In the United States (US) and European guidelines, the recommended surveillance interval after colorectal polypectomy among average-risk patients depends on the findings of baseline colonoscopy [31, 32]. In American guidelines, baseline findings are classified in detail, and the recommended interval is divided according to these findings (Table 13.1) [31]. European guidelines divide patients into low, intermediate and high-risk groups based on findings at baseline colonoscopy (Table 13.2) [32]. In Asia-pacific regions, several counties also have their own guidelines [33], but current Japanese guidelines, which recommend follow-up colonoscopy should be done within 3 years after polypectomy, is no more detailed than Western guidelines [30]. We always have to take into consideration missed lesions during colonoscopy [34] and to confirm baseline risk of colorectal cancer, colonoscopy may need to be performed twice [35, 36].

There are no definitive guidelines after endoscopic resection of T1 colorectal cancer. When the lesion is judged as curative resection, endoscopic surveillance intervals might be the same as after surgical intervention for invasive cancer. In US guidelines, the first surveillance colonoscopy is recommended to be performed 1 year

Table 13.1 Recommended colonoscopy intervals among average-risk individuals in 2012 US guidelines [31]

Recommended surveillance interval	Baseline colonoscopy: most advanced finding(s)
10 years	No neoplasia, Small (<10 mm) hyperplastic polyps in rectum or sigmoid
5–10 years	1–2 small (<10 mm) tubular adenomas
5 years	Sessile serrated polyp(s) <10 mm with no dysplasia
3 years	3–10 tubular adenomas, one or more tubular adenomas ≥10 mm, one or more villous adenomas, adenoma with high-grade dysplasia (HGD), sessile serrated polyp(s) ≥10 mm, sessile serrated polyp with dysplasia, traditional serrated adenoma
<3 years	>10 adenomas
1 year	Serrated polyposis syndrome

Table 13.2 Recommended colonoscopy intervals among average-risk individuals in 2012 European guidelines [32]

Recommended colonoscopy interval	Risk category	Baseline colonoscopy: most advanced finding(s)
None (Routine screening)	Low risk	1–2 small (<10 mm) adenomas
3 years	Intermediate risk	3–4 small adenomas or at least one adenoma of size ≥10 mm and <20 mm
Within 1 year	High risk	5 or more adenomas, or an adenoma ≥20 mm

after surgery for patients who have undergone curative resection of colorectal cancer [37]. The risk of metachronous cancer continues throughout life; therefore, long-term follow up using colonoscopy would be necessary. According to US post-surgery guidelines, when no neoplasia is detected during the 1-year examination, the next colonoscopy is recommended after 3 years. If no neoplasia is detected in this examination, the next recommendation is after 5 years, and subsequent surveillance is recommended at 5-year intervals.

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14 Management of Non-curative Resection and Local Recurrence After Endoscopic Resection: Non-curative ER in Esophagus

Hon Chi Yip and Philip W. Y. Chiu

14.1 Manuscript

Despite careful preprocedural assessment of esophageal neoplasia, non-curative endoscopic resection (ER) for carcinoma of esophagus would still occur in a proportion of patients. These include lesions with involved margins or tumors with high risk of lymph node metastasis. In addition, local recurrence after complete endoscopic resection could be detected during surveillance endoscopy. This chapter would focus on the management of these conditions with separate discussion on squamous cell carcinoma and Barrett's related adenocarcinoma.

14.2 Esophageal Squamous Cell Carcinoma

14.2.1 Definition of Non-curative Endoscopic Resection

There are two prerequisites to define a successful endoscopic resection of early squamous cell carcinoma (SCC) of esophagus: First, the risks of lymph node involvement should be minimal; second, the lesion should be completely resected with negative margins. When both criteria are fulfilled, endoscopic resection could be considered curative. According to the latest Japanese Guidelines on treatment of carcinoma of esophagus, tumors confined to the mucosal epithelium (T1a-EP) and lamina propria mucosae (T1a-LPM) are considered as absolute indication for endoscopic resection [1]. From studies of surgically resected specimens, these tumors had a negligible risk of lymph node metastasis [2, 3]. Tumors within the muscularis mucosae (T1a-MM) or superficial layer of submucosa (SM) less than 200 μm (T1b-SM1) have low risk of lymph node metastasis of less than 10%. These are considered as relative indications for endoscopic resection in the absence of other adverse factors such as lymphovascular permeation on histology. Tumors invading into deeper submucosal layer (T1b-SM2 or beyond) have a substantial risk of 20–45% lymph node involvement, hence endoscopic resection should be regarded as non-curative. Previous studies basing on the results of endoscopic submucosal dissection (ESD) for superficial esophageal neoplasia demonstrated a non-curative resection rate of around 15–24% as determined by the depth of invasion [4–7].

Moreover, endoscopic resection would also be considered as non-curative when the resection margins are involved. In this situation, a detailed pathological review of the specimen is necessary to determine the site of positive margin, in partic-

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ular whether the vertical or horizontal margin is involved. Retrospective cohort studies have consistently demonstrated a higher rate of en bloc resection and curative resection rate with ESD when compared to EMR for superficial esophageal neoplasia [4, 6].

14.2.2 Management of Non-curative ER of Esophagus

As mentioned above, superficial esophageal neoplasia which has invaded the deep submucosal layer have high risk of lymph node metastasis and should be considered as non-curative endoscopic resection. Further treatment options should be offered, including surgical resection with radical lymphadenectomy or primary chemoradiation. In the recent decade, minimally invasive esophagectomy using thoracoscopy and laparoscopy has become a major trend worldwide. The potential of reducing pulmonary complications with minimally invasive esophagectomy has been demonstrated from randomized study in Western countries [8]. Moreover, the use of thoracoscopic esophagectomy may be associated with superior lymph node clearance in the mediastinum due to the magnified and altered view of the surgical field provided by the high definition video laparoscope [9]. A randomized study (JCOG-1409) is currently underway in Japan to demonstrate the non-inferiority in survival between thoracoscopic and open esophagectomy [10].

Esophagectomy, whether performed with a minimally invasive or open approach, is still associated with high risk of postoperative morbidities. In particular, pulmonary complications and recurrent laryngeal nerve palsy are not uncommon after surgery, and would result in significant morbidities to patient's postoperative recovery. Primary chemoradiation is an alternative option in this situation. Studies using primary chemoradiation as the initial management have shown comparable survival with surgery alone, but local relapse remains a concern [11, 12]. The clinical efficacy of adjuvant chemoradiation to salvage non-curative endoscopic resection remained controversial. In a recent small case series involving 43 patients with SM invasive esophageal SCC after ESD, 11 patients who received adjuvant chemoradiation had a 3-years relapse-free survival of 76.6%, compared to 82.2% in the 15 patients who received surgery [13]. A phase II clinical trial (JCOG-0508) is currently conducted and ongoing in Japan to address the role of adjuvant chemoradiation for management of non-curative endoscopic resection, and the long-term result of the study is eagerly awaited [14].

Selection of patients for additional treatment would also depend on their premorbid condition and tolerance to major surgery. This requires proper preoperative assessment in the patient's general condition as well as specific organ functions including cardiopulmonary and renal reserve. In a patient with significant comorbidities and poor condition, it may be safer to perform surveillance alone if they are at high risks of complications from surgery or chemoradiation.

When pathological assessment of endoscopic resection specimens showed positive margin, a detailed review with the pathologist would be necessary. If the vertical margin is involved, this would be regarded as a deep SM invasion particularly after ESD, and the management would follow the above principles. If the horizontal margin is involved in histology, a repeated endoscopic examination with image enhanced endoscopy and magnification is generally recommended as a first step to identify the potential residual or recurrent tumor. In this scenario, second endoscopic resection is possible but technically more demanding due to significant scarring after initial endoscopic resection. ESD, as compared with endoscopic mucosal resection (EMR), is a better treatment given its superior performance in tackling with submucosal fibrosis. Endoscopic ablative therapy such as photodynamic therapy and radiofrequency ablation may be an alternative option when repeated endoscopic resection is deemed impossible [15, 16]. However, there will be no histopathology available, and local ablation will lead to even more difficult endoscopic resection if further local recurrence occurs in the future.

14.2.3 Surveillance and Local Recurrence After ER of Esophagus

Local recurrence and metachronous carcinoma can both occur after primary endoscopic resection of esophagus. It is, therefore, mandatory to perform surveillance endoscopy after curative resection of early esophageal neoplasia. (1) Local recurrence can usually be detected upon image enhanced endoscopy, including 1. The presence of iodine-unstained area adjacent to resection scar and cancer cells identified on the biopsy specimen; (2) Dark brownish area upon narrow band imaging and presence of abnormal IPCL patterns upon magnification. Metachronous neoplasia is defined as newly detected neoplasia away from the original tumor site at least 12 months after the primary endoscopic resection. At the moment, there are no universal guidelines on the interval of surveillance endoscopy after curative endoscopic resection of esophagus. In general, most centers would perform endoscopic surveillance frequently in 3–6 months during the first year after ER, gradually increasing the interval to annually if no new lesion is detected. During surveillance, the routine use of Lugol's iodine chromo-endoscopy and Narrow Band Imaging (NBI) technology, in addition to conventional white light endoscopy, is helpful to identify small areas of local recurrence [17, 18].

In a recent meta-analysis of eight cohort studies comparing ESD versus EMR of early esophageal cancers, a significantly lower local recurrence rate was found with ESD (0.3% vs. 11.5%, OR = 0.08; 95%CI: 0.03–0.23; $p < 0.001$) [19]. Subgroup analysis identified a particularly significant better local recurrence rate when lesion size is >20 mm (OR = 0.05; 95%CI: 0.01–0.28; $p = 0.0006$) and with no heterogeneity.

When local recurrence is detected on surveillance endoscopy, repeat staging is necessary to determine the extent of the disease. For recurrence localized in the esophagus, repeated endoscopic resection should be considered if preoperative assessment showed low suspicion of deep SM invasion. Similar to endoscopic re-resection when specimen showed positive lateral margin, re-ESD is a better option as significant scarring is expected from previous resection. The risk of perforation remains a concern if significant fibrosis is encountered at the submucosal plane.

14.3 Barrett's Related Esophageal Adenocarcinoma

The principles of management of non-curative ER of esophageal adenocarcinoma are similar to that of esophageal SCC. However, esophageal adenocarcinoma is commonly associated with underlying Barrett's esophagus and has a much higher prevalence in the Western countries. As a result, there are some distinctive features in the management of this condition.

Definition of non-curative ER of adenocarcinoma of the esophagus is slightly different from that of SCC. Tumors that are confined to the mucosa (T1a) disease have minimal risk of lymph node metastasis and are considered a suitable case for endoscopic resection [20, 21]. In contrast, a 50% rate of lymph node involvement was reported for tumors that invade the SM layer (T1b) [22]. Studies from the west have attempted to subdivide the SM into three equally thick layers, and a lower risk of lymph node metastasis was reported at around 10–20% for SM1 lesions [23, 24]. Current guidelines suggested that T1a tumor without significant adverse features could be safely resected with endoscopy, while T1b tumors should be subjected for multi-disciplinary discussion to determine the appropriate treatment modality [25]. In a highly selected group of patients whose T1b tumors showed good differentiation and absence of lymphovascular permeation, endoscopic resection could be a viable option. In addition, ablative therapy such as radiofrequency ablation and photodynamic therapy has been advocated to reduce the risk of recurrence for the remaining non-dysplastic Barrett's mucosa after successful ER.

Recurrence of Barrett's esophagus after endoscopic therapy is common >20%, but only a small proportion of these lesions contains dysplastic mucosa [26, 27]. Repeated endoscopic treatment is usually possible when only dysplastic mucosa is identified. When invasive adenocarcinoma is detected, surgical resection in the form of en bloc esophagectomy is the preferred option to ensure complete clearance of the disease.

14.4 Summary

Management of non-curative ER of esophagus requires a detailed pathological review of the ER specimen. Repeated endoscopic resection is possible in selected patients, while esophagectomy and chemoradiation remain the gold standard in the treatment of locally advanced esophageal carcinoma with lymph node metastasis.

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15 Management of Non-curative Resection and Local Recurrence after Endoscopic Resection: Non-curative ER in Stomach

Kohei Takizawa

15.1 Introduction

Endoscopic resection (ER) for early gastric cancer (EGC) is considered for tumors that have a very low possibility of lymph node metastasis (LNM) and are suitable for en bloc resection [1]. If the risk of LNM is less than 1 and 3% in pT1a and pT1b cancers, respectively, we assume that similar outcomes can be achieved with ER as with surgical resection [2]. According to the analysis of a large number of surgical resection cases [3, 4], indications for tumor-related factors are classified as absolute indications, expanded indications, and out of indications (Fig. 15.1). Before ER, we endoscopically diagnosed tumor size, depth of invasion, and the presence of ulcer findings (UL). However, after ER, there is often some discrepancies between the endoscopic diagnosis and pathological diagnosis. Although the histological type was decided pathologically by biopsy, there are also discrepancies between the pathological diagnosis based on the forceps biopsy before ER and that based on the totally resected specimens after ER. Moreover, Lymphatic and vascular invasion (ly, v) are one of the most important predictors of LNM, but can be determined only after ER. Therefore, there are two evaluations before ER (Indication) and after ER (Curability). We should consider whether additional treatment after ER is necessary or not according to the pathological results (Fig. 15.2).

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15.2 Definition of Curability

Tumor removal in a single piece without macroscopically residual disease was defined as “en bloc resection.” En bloc resection showing lateral and vertical margins to be tumor free on histological examination was defined as “complete resection,” and that showing cancer cells at the resection margin was defined as “incomplete resection.” Multiple fragment resection was also defined as incomplete resection, even if it resulted in tumor-free vertical margins with no macroscopic residual disease because the lateral margin could not be evaluated. The resection is judged as “Curative resection (CR)” when all of the following conditions are fulfilled: en bloc resection, tumor size ≤2 cm, histologically of differentiated type, pT1a, negative horizontal margin (HM0), negative vertical margin (VM0), and no lymphovascular infiltration (ly(−), v(−)).

The resection is considered as CR for tumors of expanded indications when all of the following conditions are fulfilled: en bloc resection, HM0, VM0, ly(−), v(−), and: (a) tumor size >2 cm, histologically of differentiated type, pT1a, UL(−), (b) tumor size ≤3 cm, histologically of differentiated type, pT1a, UL(+), (c) tumor size ≤2 cm, histologically of undifferentiated type, pT1a,

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Fig. 15.1 ESD Indications. Classification of indications according to tumor-related factors. cT1a (M), intramucosal cancer (preoperative diagnosis); UL, finding of ulceration (scar)

	cT1a (intramucosal)			
	UL-		UL+	
	≤2cm	>2cm	≤3cm	>3cm
differentiated	Absolute indication	Expanded indication	Expanded indication	Out of indication
undifferentiated	Expanded indication	Out of indication	Out of indication	Out of indication

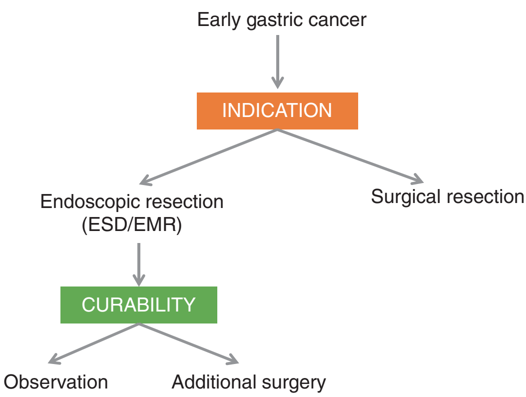


Fig. 15.2 Treatment strategy of early gastric cancer

UL(−), or (d) tumor size ≤3 cm, histologically of differentiated type, pT1b (SM1,<500 μm from the muscularis mucosae).

Resection that does not satisfy any of the above criteria is considered "non-curative resection (NCR)." There are two types of NCR. If the result is en bloc resection of a differentiated-type carcinoma with positive horizontal margin (HM1) as the only non-curative factor, it was classified as "incomplete curative resection (ICR)" [5].

15.3 Treatment Strategy after Non-curative Resection

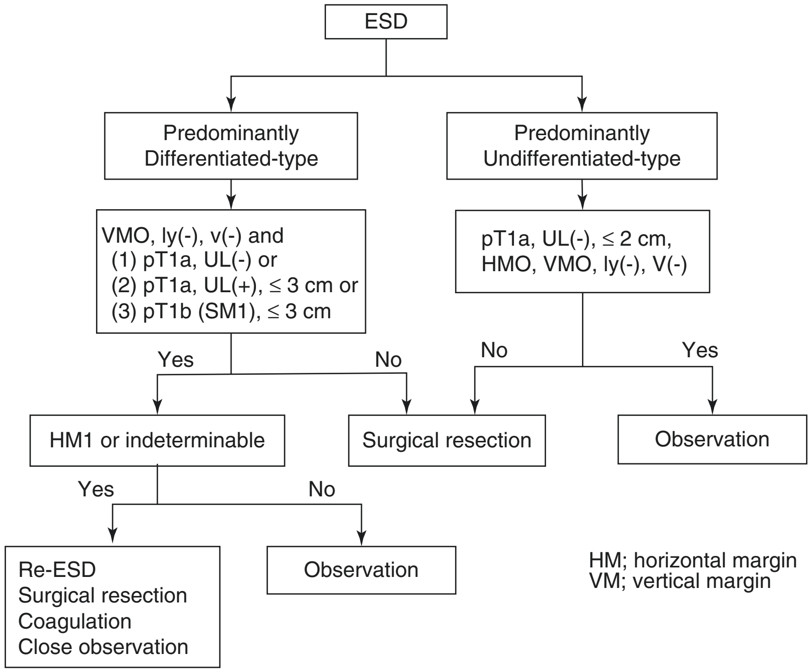
According to the Japanese guideline [1, 2], surgical treatment should be performed after NCR. However, ICR cases actually carry a very low risk of harboring LNM, nonsurgical treatments such as repeated endoscopic submucosal dissection (ESD), endoscopic coagulation using LASER or argon-plasma coagulator, or close observation expecting a burn effect of the initial ESD could be proposed as alternatives and delivered upon the patient's informed consent (Fig. 15.3).

Open or laparoscopic surgical resection is indicated in the following cases: (1) <3 cm, predominantly differentiated type, pT1a, and UL (+); (2) <3 cm, predominantly differentiated type, and pT1b (SM1) lesions, if the combined size of the endoscopically determined remnant lesion plus the lesion in the resected specimen exceeds 3 cm, or if the submucosally invasive part of a lesion is either resected piecemeal or has positive margins [2].

15.4 re-ESD for Locally Recurrent Lesion

As mentioned before, Japanese gastric cancer treatment guidelines describe close observation without gastrectomy as an acceptable option when HM1 or piecemeal resection of a differentiated-type adenocarcinoma is the only non-curative factor [1]. Moreover, the guidelines allow for ESD to be performed as a part of an investigational therapy when a locally recurrent EGC is detected during a close follow-up.

Fig. 15.3 Treatments after ER (from Guideline [1])



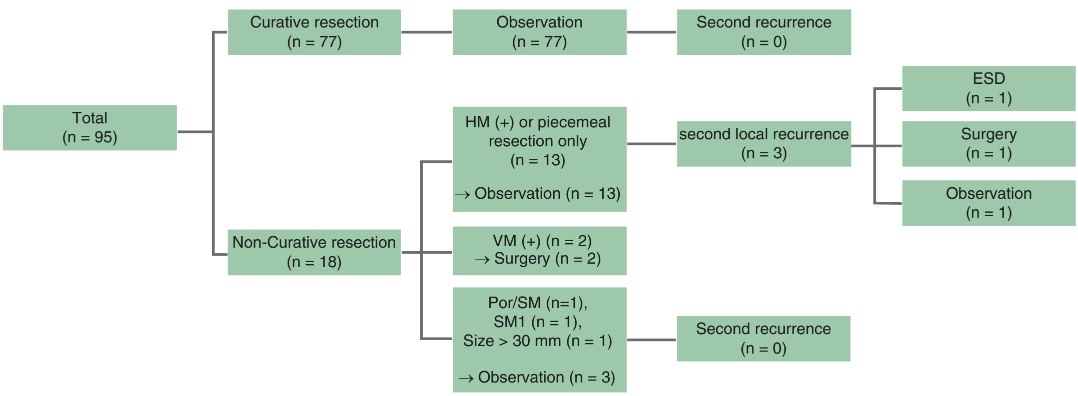


Fig. 15.4 Clinical courses after re-ESD (from Sekiguchi et al. [6] Fig. 15.1). Clinical courses of the 95 patients who underwent endoscopic submucosal dissection for local recurrence following endoscopic resection. *ESD* endoscopic submucosal dissection, *HM* horizontal margin, *Por* poorly differentiated adenocarcinoma, *SM1* tumor infiltration into the submucosal layer <500 μm from the muscularis mucosae; *VM* vertical margin

Sekiguchi et al. investigated about re-ESD for locally recurrent early gastric cancer after ER [6]. Ninety-five patients with 95 locally recurrent EGCs following their ER underwent re-ESD. The prior endoscopic resection procedures were endoscopic mucosal resection (EMR) in 75 cases and ESD in 20. Of the 95 cases, en bloc resection was achieved in 90.5%, R0 resection in 84.2%, and curative resection in 81.1%. Median procedure time was 70 min; no bleeding requiring blood transfusion was seen. There were six perforations (6.3%), with one necessitating emergency surgery. Within a median follow-up period of 76.4 months (range, 10.5–170.0 months), second local recurrences occurred in three patients (Fig. 15.4). Five-year overall survival (OS) and disease-specific survival (DSS) rates were 92.8 and 100%, respectively. They showed that re-ESD was safe and effective with favorable long-term clinical outcomes for locally recurrent EGC following ER. According to these results, re-ESD can be performed for locally recurrent lesions. However, it is still investigational therapy and it requires very high skill, therefore it should be performed only by experts at high-volume center.

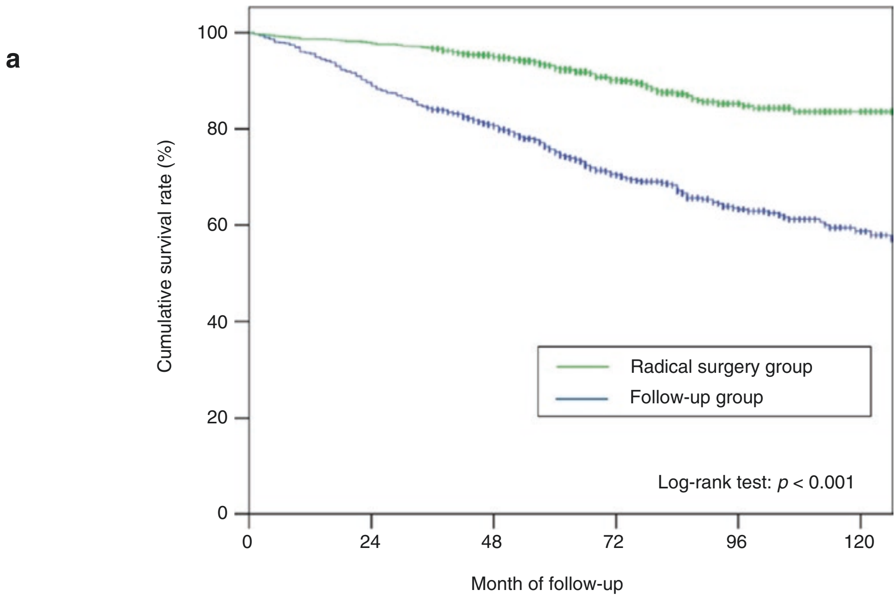
15.5 Additional Surgery for NCR

Japanese guidelines indicate that gastrectomy with lymph node dissection should be conducted in such cases, given the low mortality rate of <1% and the favorable long-term prognosis. However, factors such as age, various underlying comorbidities, and quality-of-life considerations often lead to conservative follow-up of patients in these situations. Hatta et al. conducted a multicenter cohort study demonstrating the long-term outcomes in patients who did not meet the current curative criteria for ESD in EGC [7]. Of 15,785 patients who underwent ESD for EGC at 19 institutions between 2000 and 2011, 1969 patients not meeting the curative criteria were included in this study. Based on the treatment strategy after ESD, patients were divided into radical surgery (n = 1064) and follow-up (no additional treatment, n = 905) groups. Nearly half of the patients (46.0%) received no additional treatment rather than radical surgery after ESD for EGC. OS and DSS were significantly higher in the radical surgery group than in the follow-up group (Fig. 15.5). However, the difference in 3-year DSS between the groups (99.4 vs. 98.7%) was rather small compared with the difference in 3-year OS (96.7 vs. 84.0%). LNM was found in 89 patients (8.4%) in the radical surgery group.

Next, they developed the risk-scoring system for LNM using multivariate logistic regression analysis in 1101 patients who underwent radical surgery after having failed to meet the curative criteria for ESD of EGC [8]. Five risk factors for LNM were weighted with point values: three points for lymphatic invasion and 1 point each for tumor size >30 mm, positive vertical margin, venous invasion, and submucosal invasion ≥500 μm. Then, the patients were categorized into three LNM risk groups: low (0–1 point: 2.5% risk), intermediate (2–4 points: 6.7%), and high (5–7 points: 22.7%) (Table 15.1). Next, the system was internally validated by survival analysis in another 905 patients who also did not meet the criteria and did not receive additional treatment after ESD. In the validation stage, cancer-specific survival differed significantly among these groups (99.6, 96.0, and 90.1%, respectively, at 5 years; $p < 0.001$) (Fig. 15.6). They demonstrated that this scoring system predicted cancer-specific survival in patients who did not meet the curative criteria after ESD for EGC. ESD without additional treatment may be an acceptable option for patients at low risk.

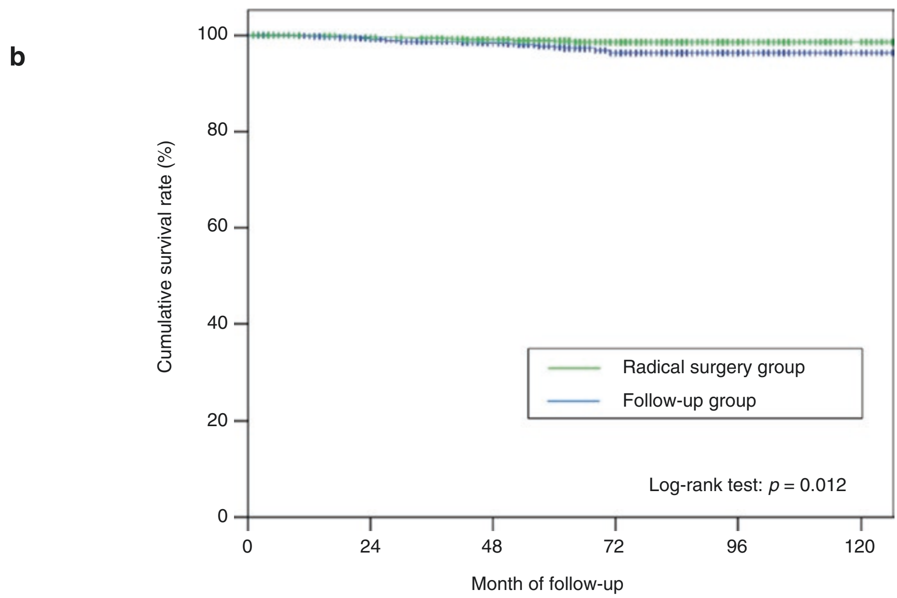
15.6 Elderly Patients after Non-curative ESD

When ESD for EGC results in a non-curative resection, additional surgery is recommended according to the Japanese gastric cancer treatment guidelines. However, for elderly patients, the contribution of additional surgery to their life prognosis is still controversial. We investigated the survival outcomes of radical surgery compared with observation only in elderly patients after non-curative ESD [9]. We reviewed existing data of all elderly patients (older than 80 years) who had undergone ESD for EGC at a prefectural Cancer Center between September 2002 and December 2013. We compared the overall and relapse-free survival rates after non-curative ESD between with and without additional surgery. According to the pathological results of ESD, the patients were divided into two groups: high-risk and low-risk. “High-risk” was defined as positively or/and v, or submucosal deep (SM2) invasion. Of the 111 non-curative ESD patients, 24 patients underwent additional surgery and 87 were followed without surgery. There was no significant difference between the groups in Performance Status, American Society of Anesthesiologist score, comorbidities, and previous cancer history (Table 15.2). Patients who did not undergo surgery tended to be older. The rate of high-risk



Number at risk

	0	24	48	72	96	120
Radical surgery group	1,064	1,042	942	457	192	75
Follow-up group	905	811	675	372	198	80



Number at risk

	0	24	48	72	96	120
Radical surgery group	1,064	1,042	942	457	192	75
Follow-up group	905	811	675	372	198	80

Fig. 15.5 Hatta (from Hatta et al. [7] Figs. 2 and 3). (**a**) OS rate for patients who did not meet the current curative criteria for ESD of EGC. The 3-year OS rate was 96.7% in the radical surgery group and 84.0% in the follow-up group, which was significantly different (p < 0.001). *OS* overall survival, *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer. (**b**) DSS rate for patients who did not meet the current curative criteria for ESD of EGC. The 3-year DSS rate was 99.4% in the radical surgery group and 98.7% in the follow-up group, which was significantly different (p = 0.012). *DSS* disease-specific survival, *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer

Table 15.1 Distribution of risk classification for LNM (from Hatta et al. [8] Table 3)

Risk category	Total points	Patients ($n = 1101$)	LNM ($n = 94$)	Rate of LNM (%)
Low	0–1	403	10	2.5
Intermediate	2–4	465	31	6.7
High	5–7	233	53	22.7

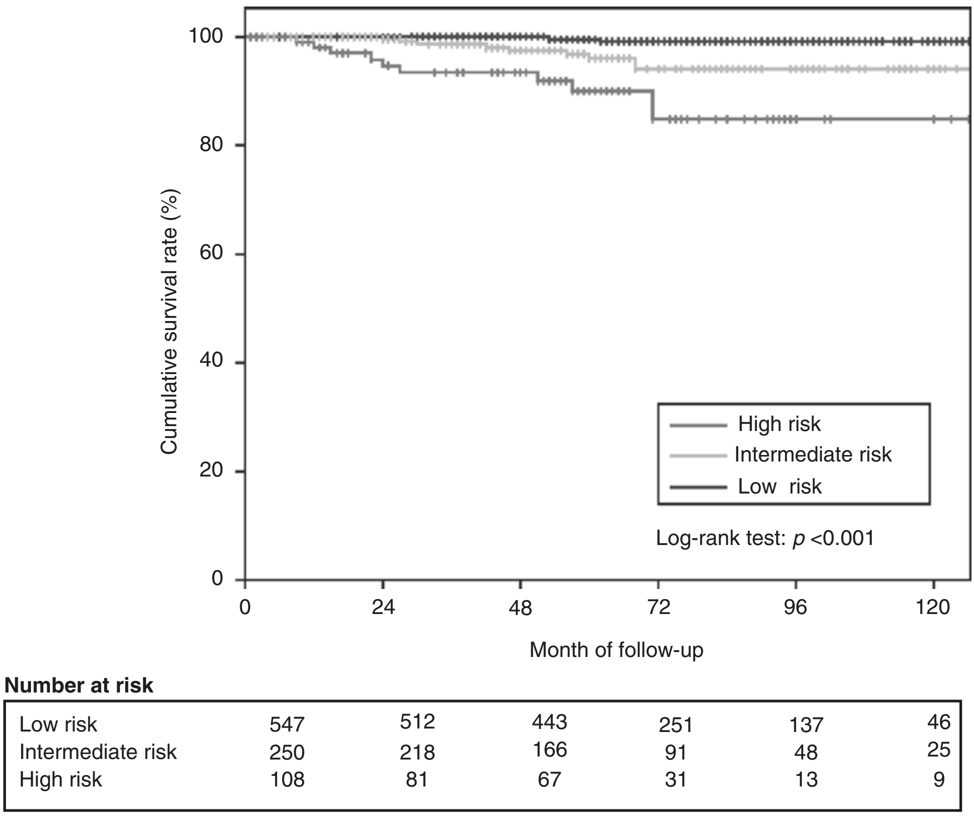
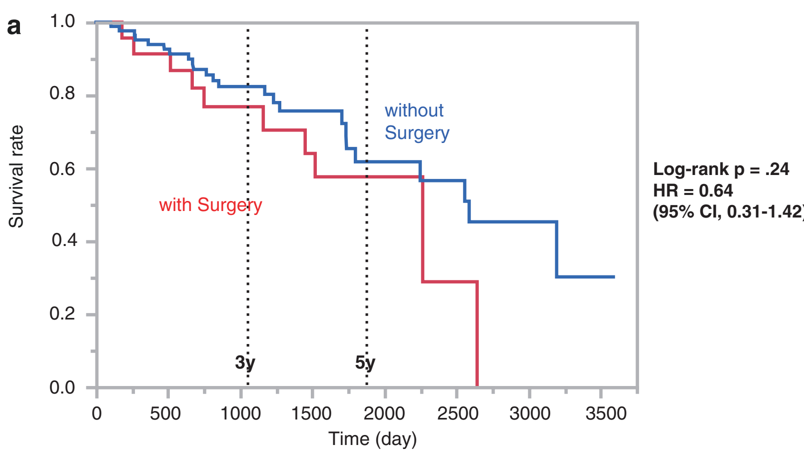


Fig. 15.6 Hatta (from Hatta et al. [8] Fig. 2a). Cancer-specific survival according to the risk category in the validation cohort. The cancer-specific survival differed among three risk groups in the validation cohort ($p < 0.001$)

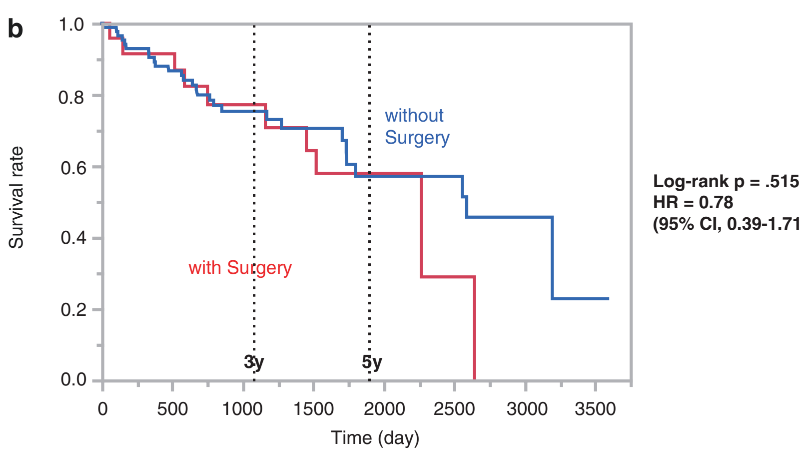
Table 15.2 Patients and lesion characteristics

		With additional surgery	Without additional surgery	P value
Gender	Male/female	18/6	59/28	0.52
Age (years old)	Median (range)	82 (80–89)	83 (80–93)	0.03
ECOG PS	0.1/2.3	23/1	72/15	0.29
Previous cancer history	+/–	7/17	18/69	0.90
Comorbidities	+/–	11/13	55/32	0.22
ASA-PS	2/3	16/8	57/30	0.92
Location	U/M/L	4/11/9	21/39/27	0.88
Pre-ESD indication	Absolute-Expanded Out of indication	15 9	48 39	0.62
Histology	Differentiated Undifferentiated	19 5	64 23	0.91
High risk (SM2 or ly/v+)		23 (96%)	42 (48%)	<0.01

patient was 96% in additional surgery group, and 48% in no additional surgery group. The median follow-up period in additional surgery group and no additional surgery group was 38 and 36 months, respectively. In additional surgery group, 3 patients (13%) died as a result of gastric cancer and 7 patients (29%) died from other causes. In no additional surgery group, 4 patients (5%) died from gastric cancer, and 19 patients (21%) died from other causes. Overall 5-year survival rates in additional surgery group and no additional surgery group were 58 and 62% (log-rank p = 0.24, HR: 0.64 (95% CI 0.31–1.42)) (Fig. 15.7a). There was no significant difference in overall and relapse-free survival (log-rank p = 0.515, HR: 0.78 (95% CI 0.39–1.71)) between the groups (Fig. 15.7b). In high-risk patients, overall 3- and 5-year survival rate tended to be higher in additional surgery group than no additional surgery group (80%



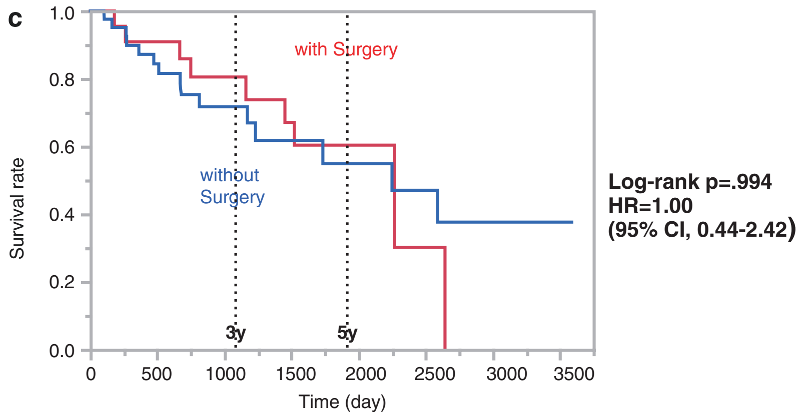
	n	median (m)	3-year	5-year
without Surgery	87	86	**82%**	62%
with Surgery	24	76	**77%**	58%



	n	median (m)	3-year	5-year
without Surgery	87	86	**75%**	57%
with Surgery	24	76	**77%**	58%

Fig. 15.7 (**a**) Overall survival (n = 111): Overall 3-year survival rates in additional surgery group was 77% and without surgery group was 82%. (**b**) Relapse-free survival (n = 111): Three-year relapse-free survival rates in additional surgery group was 77% and without surgery group was 75%. (**c**) Overall Survival in high-risk group (n = 65): In high-risk patients, overall 3-year survival rate tended to be higher in additional surgery group than no additional surgery group (80 vs. 72%)

Fig. 15.7 (continued)



vs. 72%, 60% vs. 55%) (Fig. 15.7c). According to multivariate analysis, additional surgery was not an independent factor indicating a longer survival (HR: 1.86 (95% CI 0.67–4.93)). In our retrospective study, additional surgery following non-curative ESD could not improve OS compared with nonsurgical observation only. For the patients with histological findings of lymphovascular involvement or massive submucosal penetration, additional surgery might contribute to the extension of life expectancy. Thus, additional surgery after non-curative ESD may not be considered for all elderly patients, but for high-risk patients.

15.7 Conclusion

According to the pathological evaluation after ER, close observation without additional surgery is an acceptable option if a positive horizontal margin of differentiated-type adenocarcinoma is the only non-curative factor. When locally recurrent EGC is subsequently detected, re-ESD could be performed first.

For the patient with non-curative resection, additional surgery must be considered, especially for high-risk patients according to the risk-stratified system, such as e-Cura system. However, for low-risk patients, additional surgery should be considered carefully based not only on the tumor-related factors, but also on the patient factors, such as age, comorbidities, PS, dementia, and Patient's and family's opinions on life and death.

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Management of Non-curative Resection and Local Recurrence after Endoscopic Resection

16

Yoji Takeuchi, Noriya Uedo, and Ryu Ishihara

16.1 Introduction

Most candidates for endoscopic resection (ER) are premalignant lesions or early-stage cancers. Therefore, most patients undergoing ER are curable. Actually, ER is less invasive than surgical intervention, and it provides a better quality of life, but endoscopists should always consider curing the patients in any way. Incomplete endoscopic excision of neoplastic lesions has been consistently shown to increase the risk of post-colonoscopy colorectal cancer [1]. Additionally, a recurrent lesion after incomplete ER is associated with severe fibrosis in its submucosa and a low successful en bloc resection rate, regardless of the ER technique [2]. Since the endoscopic diagnosis and ER are not always perfect and we have salvage therapies, such as additional ER or surgery, endoscopists need to know how they should treat the lesions for which curative resection with ER cannot be achieved. Herein, we describe the management of non-curative resection and local recurrence after ER for colorectal neoplasms.

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16.2 What Is Non-curative Resection?

The goals of ER are to achieve complete removal of neoplastic tissue and to assess the curability. Therefore, non-curative resection is indicated when (1) the resection is incomplete and (2) the removed specimen does not fulfill the curative criteria.

Complete resection can be achieved when no tumor involvement is seen on the horizontal margin and vertical margin of the resected specimen (R0 resection) [3]. On the other hand, incomplete resection is considered when tumor involvement is seen on the horizontal or vertical margin of the resected specimen (R1 resection), horizontal and/or vertical margins of the resected specimen cannot be accurately assessed (RX resection), or a macroscopic residual tumor is recognized (R2 resection) [3]. In case of piecemeal resection, which is removal of the lesion in multiple fragments, since tumor involvement is seen on the lateral margin and tumor involvement on the lateral margin cannot be accurately assessed pathologically (Fig. 16.1a–e), piecemeal resection can be considered incomplete resection in the strict sense. Additionally, it is sometimes impossible to retrieve all the fragmented specimen and pathological diagnosis cannot be accurate in such a case. Furthermore, since many reports have suggested a higher incidence of recurrence after piecemeal resection [4–7], piecemeal resection

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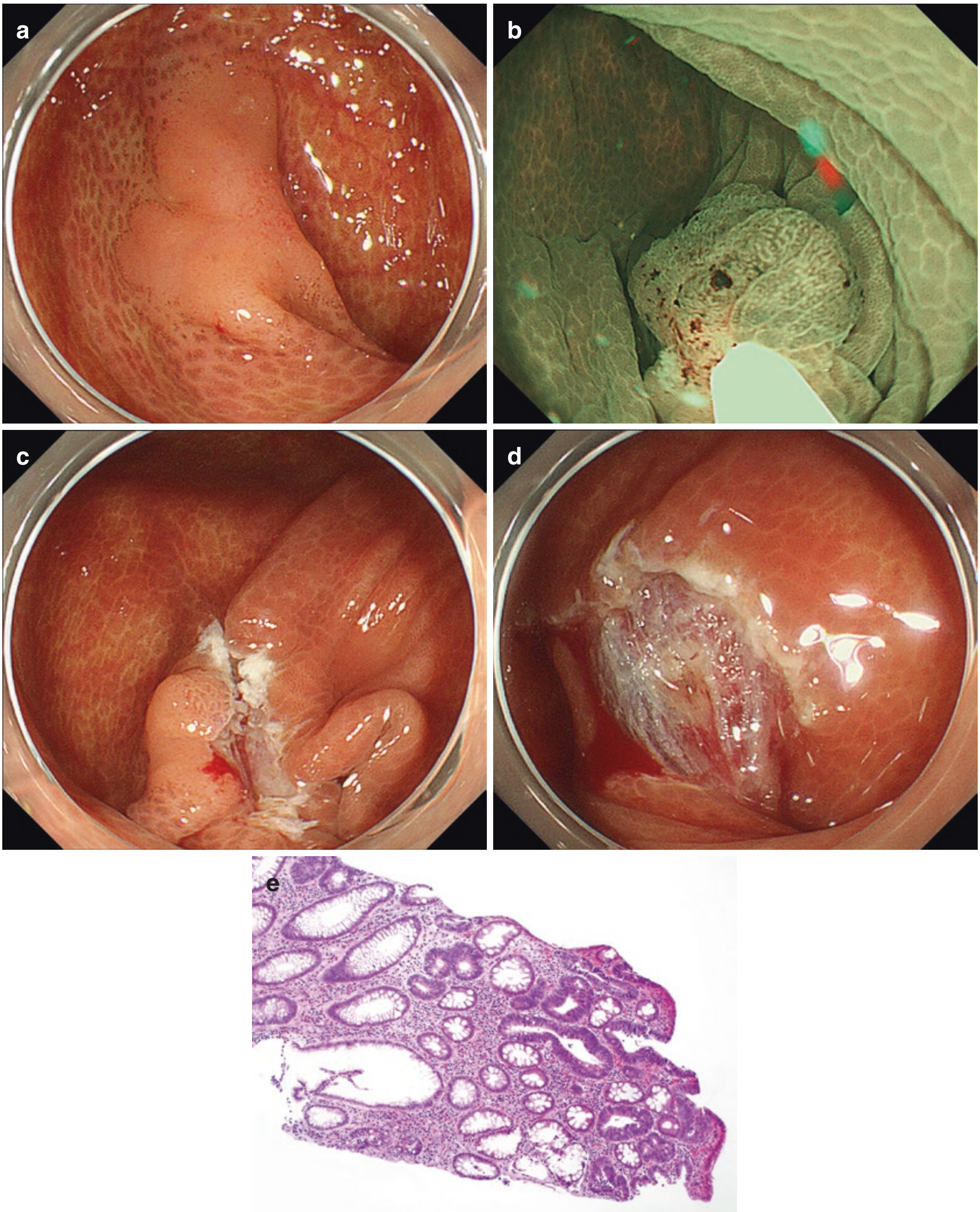

Fig. 16.1 Piecemeal resection of a lateral spreading tumor (LST) in a 79-year-old female patient. (**a**) A non-granular-type LST at the hepatic flexure. (**b**) Underwater endoscopic mucosal resection for the LST. (**c**) Polyp residue after the first attempt of snaring. (**d**) A mucosal defect after piecemeal resection without apparent polyp residue. (**e**) Polyp involvement on the lateral margin of the resected specimen. Completeness of the resection cannot be assessed accurately

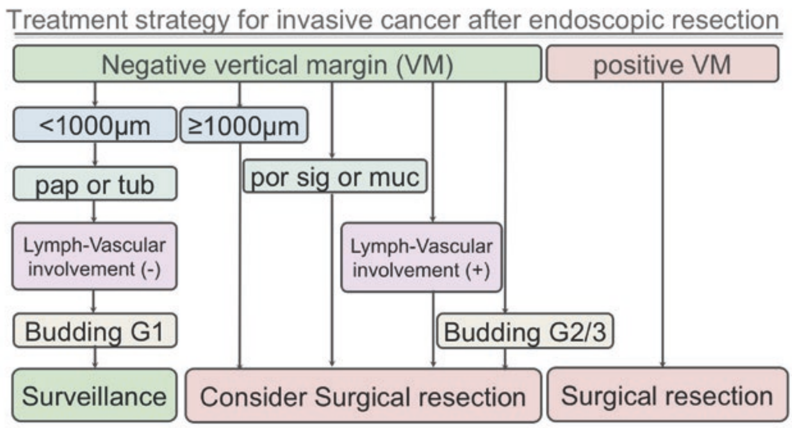

Fig. 16.2 Treatment strategy for invasive cancer after endoscopic resection [9]. The lesions with risk factors for lymph node metastasis or a positive vertical margin should be considered for additional surgery. *Pap* papillary adenocarcinoma, *tub* tubular adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet ring cell carcinoma, *muc* mucinous carcinoma

is not complete resection. However, most candidates for colorectal endoscopic resection are a benign adenoma, and polyp residue just after endoscopic removal is relatively easy to find compared to residue of other organs (e.g., the esophagus and stomach). Therefore, many endoscopists have considered that complete resection can be achieved even in case of piecemeal resection, and sometimes they call such resection in a piecemeal manner "complete resection" [8]. Endoscopists need to pay attention to the definition of complete resection and whether complete resection was achieved en bloc or piecemeal in each patient. In a multicenter, prospective trial, it was reported that most patients (93%) with recurrence were managed endoscopically, but strict surveillance was mandatory [8]. Therefore, complete resection with piecemeal resection and en bloc complete resection should be at least treated separately.

General principles underlying curative resection are defined based on the lesions with little risk of lymph node metastasis because ER cannot treat lymph node metastasis [9]. Curative criteria, which include lesions with little risk of lymph node metastasis, were defined based on a retrospective analysis of surgically resected specimens [10]. It has been reported that intramucosal cancer and submucosal (SM) invasive cancer <1000-μm deep without lymphovascular involvement, poorly differentiated/signet-ring cell/mucinous carcinoma, and budding grades 2 and 3 have no possibility of metastasis (low-risk SM cancer) [10, 11]. Therefore, if the lesion invades a depth ≥1000 μm or has lymphovascular involvement, poorly differentiated/signet-ring cell/mucinous carcinoma, or budding grades 2 and 3, it should be considered for non-curative resection (Fig. 16.2) [9].

16.3 What Should Be Done for Non-curative Resection?

In the case of R2 resection, another intervention should be considered since complete pathological assessment cannot be done and the same repetitive procedure would not be effective. Surgical resection would be ideal to obtain a pathological diagnosis, but ablation therapy using electrocautery, argon plasma coagulation, or laser therapy can also be alternative therapies [12, 13].

A case of R1 or RX resection is considered to have no macroscopic tumor residue. Since tumor residue of colorectal neoplasms is easy to recognize endoscopically, most patients who have undergone R1 or RX resection have no tumor residue in situ. Especially, an assessment of the lateral margin of colorectal polyps smaller than 10 mm is unreliable for detecting polyp residue. We investigated the rate of polyp residue after cold snare polypectomy in a prospective study; 67% of the lateral margin assessments were not adequately assessed on the horizontal margin, but polyp residue was observed only in 3.9% of the lesions in additional endoscopic mucosal resection (EMR) specimens [14]. Therefore, endoscopists usually do not need to consider lateral margin assessment of the resected specimen after complete endoscopic removal of colorectal polyps, and the European Society of Gastrointestinal Endoscopy (ESGE) recommends that if the horizontal margin is positive but no other high-risk criteria are met, endoscopic surveillance/re-treatment could be considered instead of surgery [15].

In case of piecemeal resection, the patient would be followed up without any additional therapy when there is no pathological finding suggestive of SM invasion because intramucosal lesions have no risk of lymph node metastasis, only a risk for local resection, which can be removed endoscopically [8]. However, it is generally known that the incidence of recurrent polyps is significantly high, so an early surveillance period is recommended. Especially, Sakamoto et al. reported that the removal of five or more neoplastic specimens is an independent risk factor for local recurrence after piecemeal resection, and careful surveillance should be performed for such lesions [16]. Hotta et al. reported that piecemeal resection has a higher incidence of local recurrence, but it can be treated with endoscopic therapy 6 months after piecemeal resection, as recommended [8]. The ESGE guideline recommends endoscopic follow-up within 6 months for lesions after piecemeal resection of adenomas larger than 10 mm [17]. The US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society guidelines also recommend short intervals (2–6 months) for a follow-up evaluation to verify complete removal after piecemeal resection [18].

For lesions that do not fulfill the curative criteria, surgical colorectomy with lymph node dissection should be considered because they are associated with a risk of lymph node metastasis (Fig. 16.2). Some retrospective studies have reported good long-term outcomes, and standard surveillance is recommended in Japanese guidelines in case of SM invasive cancer that fulfills the curative criteria (low-risk SM cancer) [19, 20]. Additionally, they showed that the risk of lymph node metastasis in SM cancers without any risk factor, except for the depth of invasion (lymphovascular involvement, poorly differentiated/signet-ring cell/mucinous carcinoma, and budding grades 2 and 3), is quite low even if the lesion invaded the deep SM layer [11, 20]. Therefore, clinicians should consider such risk of lymph node metastasis and patients' background characteristics, such as age, comorbidity, and lesion location.

Of course, when tumor involvement is seen on the vertical margin of the resected specimen of SM cancer, the tumor depth of the lesion cannot be assessed accurately, and surgical colorectomy should be recommended (Fig. 16.2) [3].

16.4 What Should Be Done for Local Recurrence after Endoscopic Resection?

Usually, additional endoscopic treatment is performed for local recurrence after endoscopic resection when the original lesion is an intramucosal neoplasm. Hotta et al. reported that 94% of patients with a recurrent lesion underwent additional endoscopic resection, and 6% underwent additional surgery [7]. In a multicenter prospective study, 93% of local recurrences were successfully treated endoscopically [8]. Although most patients with local recurrence can be treated with endoscopic therapy, additional endoscopic mucosal resection is technically challenging because severe fibrosis develops at the resection site. The fibrosis prevents elevation of the lesions with an SM fluid injection. Therefore, a recurrent lesion after endoscopic resection is considered one of the indications for ESD (Fig. 16.3a–d) [21]. However, ESD for a recurrent lesion is technically difficult and requires a long procedure time, and en bloc

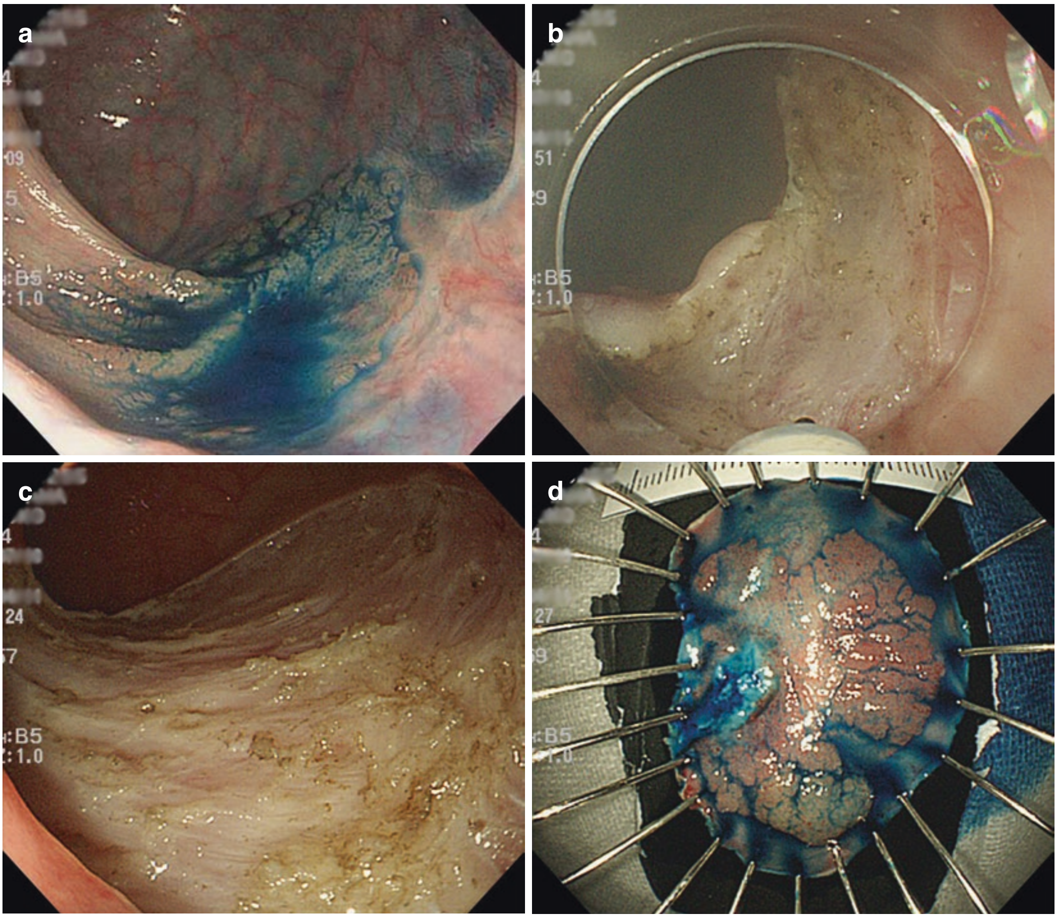

Fig. 16.3 Endoscopic submucosal dissection for a recurrent rectal lesion after piecemeal endoscopic resection and local surgical resection. (**a**) A granular type large lateral spreading tumor after piecemeal endoscopic resection and surgical resection of the rectum. (**b**) Severe fibrosis in the submucosal layer under the recurrent lesion during endoscopic submucosal dissection (ESD). (**c**) Mucosal defect after ESD. (**d**) The en bloc resected specimen

resection rates for recurrent lesion with EMR (39%) and ESD (56%) were still low in a previous report [2].

Underwater EMR (UEMR), which was invented and reported by Binmoeller et al. in 2012, is also a useful technique for treating recurrent colorectal neoplasms after endoscopic resection (Fig. 16.4a–d) [22]. Kim et al. reported that the rates of en bloc resection for recurrent lesions (47% vs. 16%, $p = 0.002$) and endoscopic complete resection were significantly higher in the UEMR group than in the conventional EMR group (89% vs. 32%, $p < 0.001$) [23]. The recurrence rate on follow-up colonoscopy was significantly lower in the UEMR group than in the conventional EMR group (10% vs. 39%, $p = 0.02$). In this trial, UEMR was a significant independent predictor of successful en bloc resection and complete endoscopic removal. However, the larger size of a recurrent lesion was a negative independent predictor of successful en bloc resection and complete endoscopic removal. Therefore, we perform ESD for recurrent lesions larger than 10–15 mm and UEMR for recurrent lesions equal to or smaller than 10–15 mm.

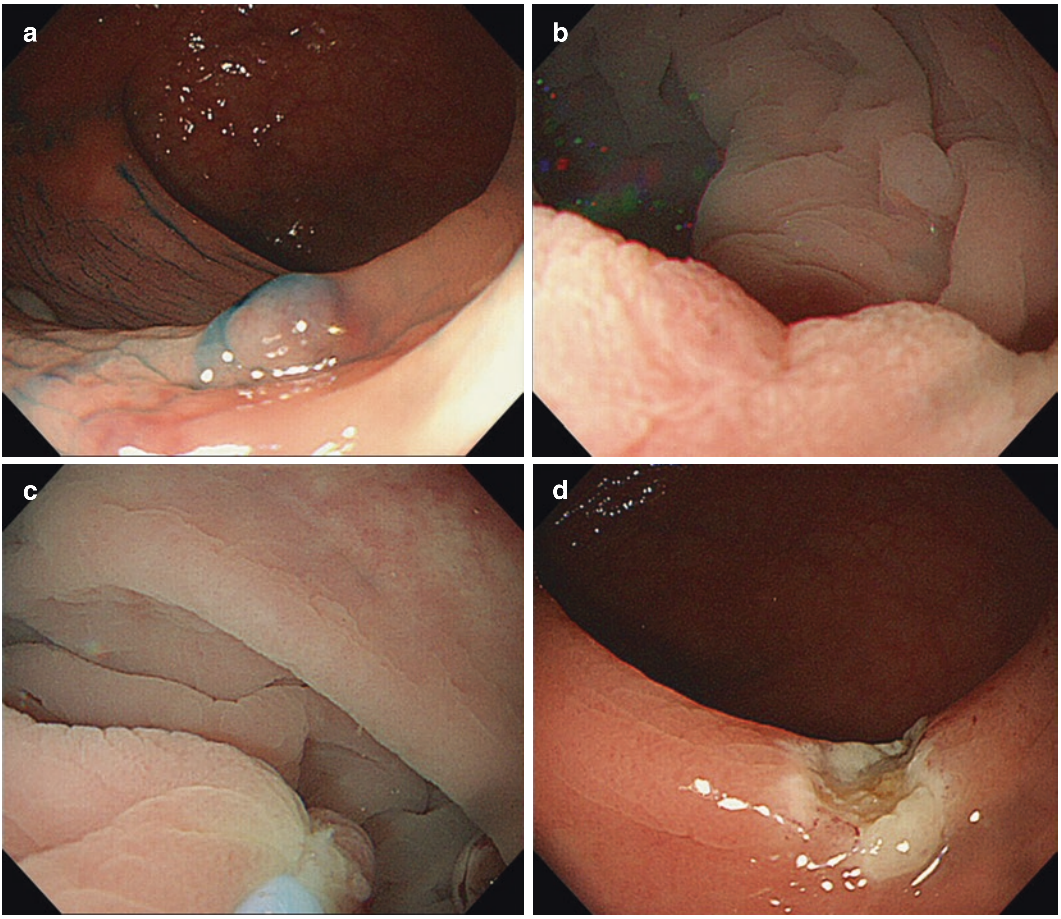

Fig. 16.4 Underwater endoscopic mucosal resection (UEMR) for a recurrent lesion after incomplete endoscopic resection. (**a**) Small polyp residue after incomplete endoscopic resection is observed at the hepatic flexure. (**b**) Underwater observation of the lesion. The lesion looks like it is floating in the water. (**c**) The lesion is snared with the surrounding mucosa. (**d**) Mucosal defect after UEMR without apparent polyp residue

16.5 Conclusions

Most patients who undergo incomplete resection for a cure can be treated with salvage endoscopic therapy, such as UEMR or ESD, with an appropriate surveillance interval. Patients with non-curative lesions should undergo salvage colectomy with lymph node dissection, but endoscopists should consider the risk of lymph node metastasis and patients' background characteristics (e.g., age, comorbidity, and location of the lesion). Since endoscopic therapy is not always perfect, endoscopists should know what should be done for patients with non-curative resection.

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17 Complications of Endoscopic Resection and Management: Esophagus and Stomach

Yoshiki Sakaguchi, Mitsuhiro Fujishiro, and Kazuhiko Koike

17.1 Standard Precautionary Measures

Complications may occur in any endoscopic procedure, and standard precautionary measures should be routinely utilized.

17.1.1 Sedation

Appropriate sedation for the prevention of body movement or gag reflex should be utilized routinely. General anesthesia for longer procedures should be considered when possible.

17.1.2 Carbon Dioxide Insufflation

Carbon dioxide insufflation is absorbed easily, and decreases discomfort during long endoscopic procedures. In addition, it decreases the severity of gas leakage in cases of perforation, which can be crucial especially in cases of mediastinal emphysema.

17.1.3 Sufficient Submucosal Injection

Sufficient lifting with submucosal injection should be maintained throughout resection to prevent the snare or dissection device from contacting the muscularis propria. The use of solutions such as hyaluronic acid and glycerol may improve the lifting effect, and are recommended especially for long ESD procedures.

17.1.4 Endoscopic Devices

Endoscopic devices for the treatment of common complications such as hemorrhage and perforation should be prepared before each procedure.

17.2 Major Complications of Esophageal Endoscopic Resection

Radical esophagectomy has traditionally been the standard for treatment of esophageal neoplasms, but along with recent advances in endoscopic imaging such as optical enhancement, an increasing number

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of esophageal neoplasms are being discovered at an early stage. Due to the risks and morbidity associated with esophagectomy, endoscopic resection (ER) with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) is widely recommended for these superficial lesions [1, 2]. However, the narrow lumen and thin wall of the esophagus make endoscopic resection technically difficult, and there is a risk of severe complications associated with these procedures due to the location in the mediastinum.

17.2.1 Perforation and Mediastinal Emphysema

Risk Factors Perforation is one of the most common intra-operational complications during esophageal ER, and has been reported to occur at a rate of 2.6–10% during ESD and 0–3% for EMR [3]. Perforation may occur for a variety of reasons, including background factors such as the location of the lesion or fibrosis of the submucosa, but there is still insufficient literature on significant risk factors (Fig. 17.1).

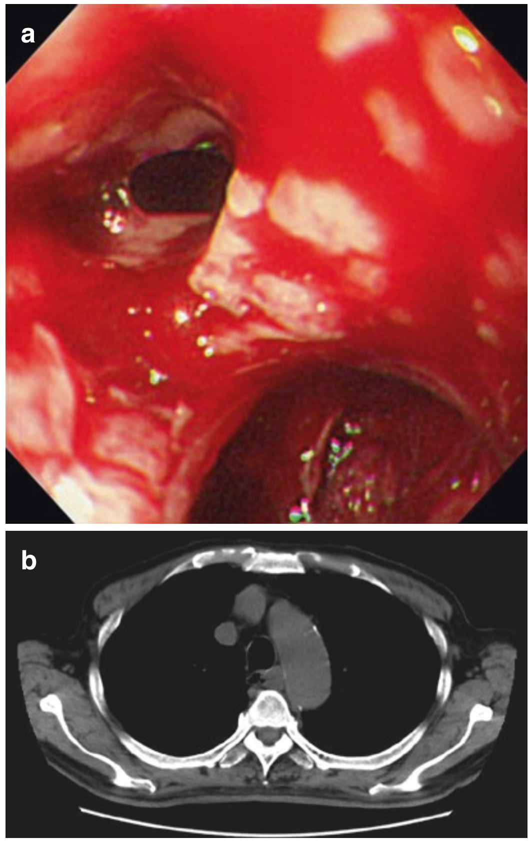

Fig. 17.1 (**a**) Left: Esophageal perforation (bottom right) into the extraluminal space caused by direct penetration of the endoscope through the muscularis propria. The esophageal lumen can be seen in the upper left. (**b**) Right: CT scan revealed mediastinal emphysema which was minimized by carbon dioxide insufflation. The patient was managed conservatively and discharged after 2 weeks

Diagnosis The most easily detectable sign of intra-operational perforation is a defect in the muscularis propria. Due to the thinness of the muscularis propria and lack of the serosa in the esophagus, mediastinal emphysema, and mediastinitis may occur even in cases where there is no apparent damage to the muscularis propria [4], and patients should be carefully screened for complications after endoscopic resection. Palpation of the neck for clinical indications such as snowball crepitation can be useful for early detection of perforation, and a chest X-ray after the endoscopic procedure should be routinely performed. CT scans are also used for the diagnosis and assessment of severity of the complication.

Management Endoscopic closure of the defect is recommended for intra-operational perforation. Clip closure is the standard method of closure, but must be performed with caution because the clips may cause additional damage to the surrounding thin muscularis propria, resulting in an even wider perforation. Alternative methods such as the over-the-scope-clip (OTSC) and shielding with polyglycolic acid (PGA) sheets have also been introduced in recent years. After closure of the defect, patients can often be managed conservatively, with intravenous antibiotic treatment. However, in cases with strong chest pain or fever, a CT scan should be performed to check for severe mediastinal emphysema or mediastinitis. These complications may be life threatening, and cooperation with a surgeon is mandated. Especially in cases of delayed perforation, a surgeon should be consulted immediately.

Tips During Resection Endoscopic techniques such as lifting the lesion away from the muscularis propria before EMR, and moving the tip of the endoscopic resection device away from the muscularis propria during ESD, should also be utilized to minimize the risk of perforation. Only minimal coagulation of visible vessels should be performed during and after resection because excessive thermal damage to the muscularis propria can lead to delayed perforation.

17.2.2 Stricture

Risk Factors Due to the narrow lumen of the esophagus, postoperative stricture may occur after widespread resection. The circumference and longitudinal length of the resected area [5] are known to be risk factors for postoperative stricture, and prevention of stricture is recommended after resection of over 3/4 the circumference of the esophagus [1]. In cases of total circumferential resection, stricture occurs almost invariably (Fig. 17.2).

Diagnosis Postoperative stricture often occurs 3–6 weeks after resection. Early symptoms include dysphagia and vomiting, and endoscopy should be considered in these cases.

Management Endoscopic balloon dilation or bougie dilation are standard methods for treatment of stricture through which an endoscope cannot pass. Both methods have been reported to be similarly effective [6, 7], but balloon dilation has been reported to have a lower risk of complication during dilation of complex strictures [8]. Other methods such as electrosurgical incision, stent placement, and steroid injection have also been introduced for refractory strictures in recent years.

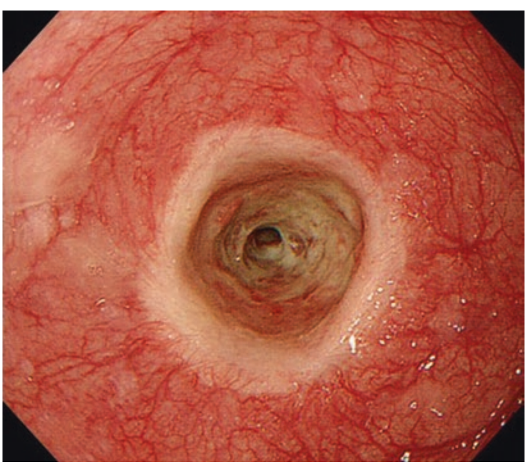

Fig. 17.2 Esophageal stricture following total circumferential endoscopic submucosal dissection. The patient required 16 sessions of endoscopic balloon dilation

Tips During Resection Resection should be limited to as close to the margins of the lesion as technically possible, to prevent an overly wide defect. Steroid injection into the submucosa of the resected area, and oral steroid administration are commonly performed prophylactic methods for the prevention of stricture. However, delayed perforation may occur after steroid injection and systemic infections may occur after oral steroid administration. Evaluation of risk factors that may influence the selection of prophylactic measures should be performed prior to resection. In addition, while the risks associated with prophylactic measures are minimal, they can be mortal, and informed consent for prophylactic measures should also be obtained prior to resection. Alternative methods such as stent placement, shielding with polyglycolic acid sheets with/without steroid injection [9, 10], and tissue-engineered cell sheets have also been introduced in recent years.

17.2.3 Hemorrhage

Both intra-operational and post-operational hemorrhage are relatively rare in the esophagus. Should they occur, endoscopic hemostasis with hemostatic forceps or endoclips should be considered. Special care should be taken not to damage the surrounding muscularis propria (Fig. 17.3).

17.3 Major Complications of Gastric Endoscopic Resection

Endoscopic resection with EMR and ESD are also recommended for superficial gastric neoplasms [2, 11] as a minimally invasive method of treatment.

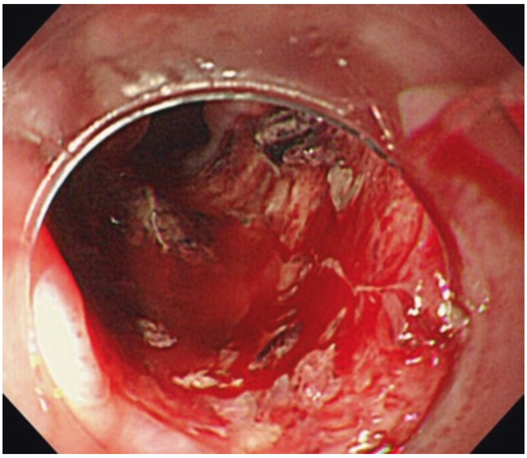

Fig. 17.3 Delayed hemorrhage after esophageal endoscopic resection. The patient was managed by coagulation with hemostatic forceps

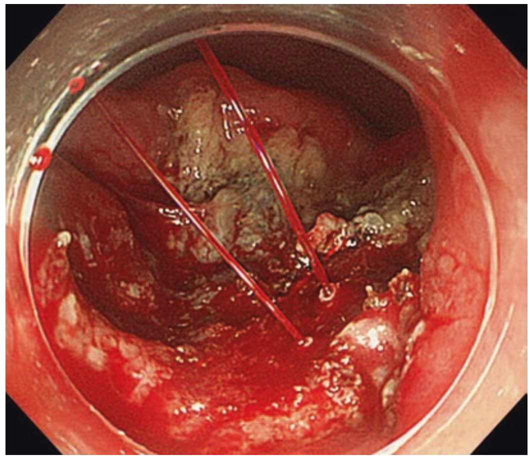

Fig. 17.4 Intra-operational hemorrhage during gastric endoscopic submucosal dissection was managed by hemostatic forceps. The patient did not have a significant decrease in hemoglobin levels

17.3.1 Hemorrhage

Risk Factors Hemorrhage frequently occurs during endoscopic resection of gastric lesions. Hemoglobin levels may decrease by over 2 g/dL during endoscopic resection in up to 7% [12], and resection of the gastric body is associated with a higher rate of intra-operational hemorrhage (Fig. 17.4). Delayed hemorrhage is reported to occur in up to 15.6% of gastric ESD [12] and with similar rates for gastric EMR [13]. Risk factors associated with delayed hemorrhage include larger resection size, tumor location (lesser curvature of antrum) [12] (Fig. 17.5).

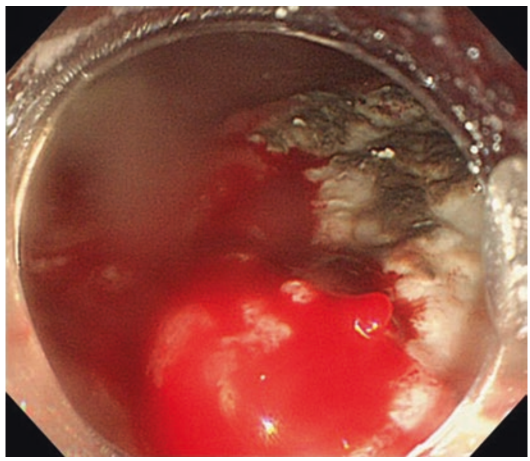

Fig. 17.5 Delayed hemorrhage after gastric endoscopic resection. The vessel responsible for active bleeding was identified and managed with hemostatic forceps

Diagnosis Clinical symptoms of hemorrhage include hematemesis and melena. After the endoscopic procedure, both clinical symptoms and laboratory test results should be carefully monitored for signs of hemorrhage. In cases with either clinical symptoms of hemorrhage, or a significant decrease in hemoglobin levels, emergency endoscopy should be considered.

Management Proton pump inhibitors (PPI) should be administered for a minimum of 2 weeks after resection for the prevention of delayed hemorrhage [14]. Cases of delayed hemorrhage can often be controlled by endoscopic hemostasis with hemostatic forceps or endoclips. Blood transfusion should be administered as required. In rare cases of massive bleeding where endoscopic hemostasis is not technically feasible, conversion to emergency surgery or embolization with vascular interventional radiology (IVR) should be considered.

Tips During Resection Prophylactic hemostatic coagulation of visible blood vessels after resection on the mucosal defect is recommended for prevention of delayed hemorrhage.

17.3.2 Perforation

Risk Factors Intra-operational perforation occurs at a rate of 1.2–8.2% during gastric ESD, and at lower rates for gastric EMR (Fig. 17.6) [13]. Tumor location (gastric body), larger tumor size, and fibrosis have reported to be independent risk factors. Delayed perforation occurs in approximately 0.45%, and while rare, often requires emergency surgery.

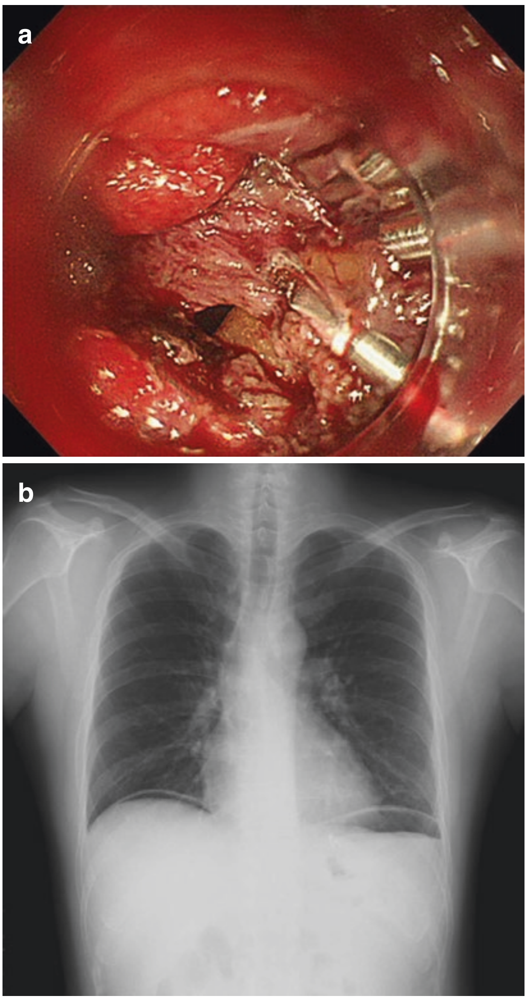

Fig. 17.6 (**a**) Left: Intra-operational perforation during gastric endoscopic submucosal dissection with the omentum visible. Conventional endoclips were used to close the perforation. (**b**) right: Intra-abdominal free air the day after resection. Leakage of air was minimized by carbon dioxide insufflation and the patient was managed conservatively with no symptoms

Diagnosis Intra-operative perforation can be diagnosed endoscopically, and/or by the presence of free air on a plain radiograph or abdominal CT just after ESD procedure.

Management In cases of intraoperative perforation, endoscopic closure should be performed. Along with standard endoclips, OTSCs, suture devices, and snaring devices have been introduced for this procedure. Massive gas leakage into the abdominal cavity may be a cause for shock due to vasovagal reflex or abdominal compartment syndrome, and abdominal paracentesis should be considered in cases of severe abdominal swelling. Intravenous antibiotic treatment should be administered, and cooperation with a surgeon is mandated, especially in cases of delayed perforation.

Tips During ESD As in esophageal ER, excessive muscular damage should be avoided to prevent perforation. Tips to avoid muscular damage include sufficient lesion lifting, taking care to move the resection device so as not to contact the muscularis propria, and avoiding blind resection in a situation where the submucosal layer cannot be seen.

17.3.3 Stricture

Risk factors Post-operative stricture has been reported to occur in 0.8–1.9% of gastric ESD cases [15, 16]. Endoscopic resection of over 3/4 the circumference of the cardia/pylorus is the most significant risk factor for stricture. On the other hand, there have been no previous reports of stricture in either the body, angulus, or fundus.

Diagnosis As in esophageal ER, early symptoms include dysphagia and vomiting, as well as abdominal pain. Endoscopy should be performed for these cases, and dilation should be performed when the endoscope cannot pass through the stricture. However, unlike the esophagus, there are cases where patients demonstrate clinical symptoms similar to those of stricture despite the fact that significant stricture cannot be endoscopically detected. These may be caused by suppression of peristalsis due to gastric deformity, and fluoroscopy may be effective for the diagnosis of this condition.

Management Although there are few reports on the treatment of postoperative gastric stricture due to the low incidence, EBD is an effective method of treatment. Due to the anatomic location of the stricture, guidewire-assisted dilation may be safer in cases of severe stricture. Dilation may not be as effective for cases of symptomatic stricture caused by gastric deformity, and these cases may require surgery for symptom management.

Tips During Resection As in esophageal ER, resection should be limited to as close to the margins of the lesion as technically possible. Steroid injection may be effective for prophylaxis of stricture, but due to the low incidence of this complication, there is as of yet insufficient documentation concerning prevention of stricture.

17.4 Other Complications

17.4.1 Electrocoagulation Syndrome

Patients may experience symptoms such as pain and fever within 24 h after endoscopic resection and demonstrate leukocytosis in laboratory tests. Perforation should be ruled out in these cases, but these symptoms are often manifestations of electrocoagulation syndrome. Electrocoagulation syndrome develops when the electric current applied during resection extends to the muscularis propria and serosa. This causes a transmural burn, which in turn causes a localized inflammatory response. The incidence of electrocoagulation syndrome of the esophagus and stomach has not been sufficiently documented, but can be managed conservatively. Antibiotics may be required in some cases.

17.4.2 Laryngeal Edema

In cases which require long operational times, although rare, there is a risk of laryngeal edema due to mechanical stimulus by the endoscope. The use of an endoscopic overtube should be considered for difficult cases as well as cases that might require frequent endoscope insertion. The respiratory condition of the patient should be constantly monitored during the procedure. After completion of the endoscopic procedure, the larynx should be carefully observed to check for edema. In cases of severe edema, an otolaryngologist should be consulted. While laryngeal edema due to endoscopic resection can often be managed conservatively with the use of steroids, some cases may require intubation or tracheotomy.

17.4.3 Aspiration Pneumonia

Aspiration pneumonia is a less frequent complication than bleeding and perforation reported to occur in approximately 1% of ESD, which requires longer procedure times than EMR [12]. Main risk factors for aspiration are longer procedure times, older age, and male gender. Cases of aspiration pneumonia can often be managed conservatively with antibiotic treatment, but caution is required in the management of elderly patients.

17.4.4 Venous Thromboembolism

Asymptomatic venous thromboembolism (VTE) has been reported to occur in 10.0% [17] of ESD cases. This is speculated to occur due to immobility for a long period of time, which raises the risk of clot formation. Although there is insufficient documentation concerning the prevention of VTE, sufficient intravenous fluids, and the use of compression stockings may be effective in lowering the risk.

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18 Complication of Endoscopic Resection and Management: Colon

Shinji Tanaka

Main accidental complications during colonoscopic resection are perforation and bleeding. The definition of perforation and bleeding in relation to colonoscopic resection is defined in "Japan Gastroenterological Endoscopy Society (JGES) guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection 2020" [1] as follows: Perforation is the condition in which the abdominal cavity is visible from the colorectal lumen because of mural tissue defects. The presence of free air is not always detected on X-ray examination. In contrast, the condition in which the tissue defect reaches other parenchymal organs is defined as penetration. Various definitions have been proposed for bleeding, such as a decrease in hemoglobin by >2 mg/dL or the requirement for blood transfusion [2]. However, these definitions have not been established on the basis of solid evidence. The presence of marked bloody stool after treatment or the requirement for a certain measure for hemostasis after treatment is often defined as delayed bleeding.

In above JGES guidelines, with regard to the frequency of complication of endoscopic resection, perforation rates during endoscopic resection are reported to be 0%, 0–0.8%, and 2–10.7% for EMR, and ESD, respectively. Moreover, the delayed bleeding rates are reported to be 1.4~1.7%, and 1.5~2.8% for polypectomy, EMR, and ESD, respectively. I introduce the data from Japan Society for Cancer of the Colon and Rectum (JSCCR) [3] and JGES [4] in Tables 18.1 and 18.2. Although additional surgery after ESD perforation is relatively high, it is due to initial stage of colorectal ESD learning curve in Japan and various skill levels of hospitals. JGES multicenter prospective cohort study (data from 69 institutions) in Table 18.2 showed the effectiveness and safety regardless the size of lesion. Also, additional operation rate in cases with perforation is low.

18.1 Management of Perforation

Colon is a long liminal organ with many flexures and folds, then maneuverability of the scope is often bad. In addition to this, as the colonic wall is thinner than that of the stomach, the risk of perforation during the procedure is higher in the colon than in the stomach. Although there is no peptic ulcer in the colon and rectum, large colorectal lesion often accompanies by submucosal fibrosis due to prolapse of the lesion and peristalsis of the colonic wall. When perforation occurs during the procedure, clipping using a clip should be carried out as far as possible, regardless of the location (Figs. 18.1, 18.2,

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Table 18.1 Adverse events in colonoscopic treatment from multisurvey questionnaires by Japan Society for Cancer of the Colon and Rectum (JSCCR)

Adverse events	Hot biopsy n=14,382	Polypectomy n=34,433	EMR n=36,083	ESD n=688	Total n=85,586
Delayed bleeding	38 (0.3)	444 (1.3)	520 (1.4)	12 (1.7)	1,014 (0.1)
additional surgery	0 (0)	1 (0.2)	1 (0.2)	0 (0)	2 (0.2)
Perforation	2 (0.01)	6 (0.02)	33 (0.09)	23 (3.3)	64 (0.07)
additional surgery	1 (50)	4 (66.7)	18 (54.5)	14 (60.9)	37 (57.8)

EMR: endoscopic mucosal resection
ESD: endoscopic subumucsal dissection
*p<0.01 (%)

Oka S, Tanaka S, et al. Dig Endosc 2010; 22: 376–80

Table 18.2 Outcome of colorectal ESD in multicenter prospective cohort study by Japan Gastroenterological Endoscopy Society (JGES)

Items: %	maximum diameter of lesion ≤ 50 mm	maximum diameter of lesion 50 mm <	Total
en bloc resection rate	95.1 (1233/1297)	94.0 (251/267)	94.9 (1484/1564)
complete en bloc resection rate	84.2 (1092/1297)	73.8 (197/267) (p<0.01)	82.4 (1289/1564)
operation time (min)	80.1±53.7	96.1±5.9	93.1±69.1
perforation rate	3.1 (40/1297)	4.9 (13/267)	3.4 (53/1564)
delayed bleeding rate	2.2 (28/1297)	5.6 (15/267) (p<0.01)	2.7 (43/1564)
operation rate in cases with perforation	15.0 (6/40)	15.4 (2/13)	15.1 (8/53)
total operation rate of perforation cases	0.46 (6/1297)	0.75 (2/267)	0.5 (8/1564)

Between 2009 and 2011 among about 69 institutions

and 18.3). If closure of the perforation is complete, additional surgical rescue can usually be avoided by giving intravenous antibiotics injection and fasting. Of course, it is necessary to discuss and decide the timing of the emergency surgery carefully in cooperation with surgeons. Nevertheless, in cases of incomplete closure of the perforation, emergency surgery should be carried out as soon as possible as the risk of pan-peritonitis is extremely high in this situation. In cases with rectal lesion below the peritoneal reflection, perforation into the abdominal cavity would not occur as a result of anatomical features; however, penetration into the retroperitoneum occurs and, consequently, mediastinal emphysema or subcutaneous emphysema

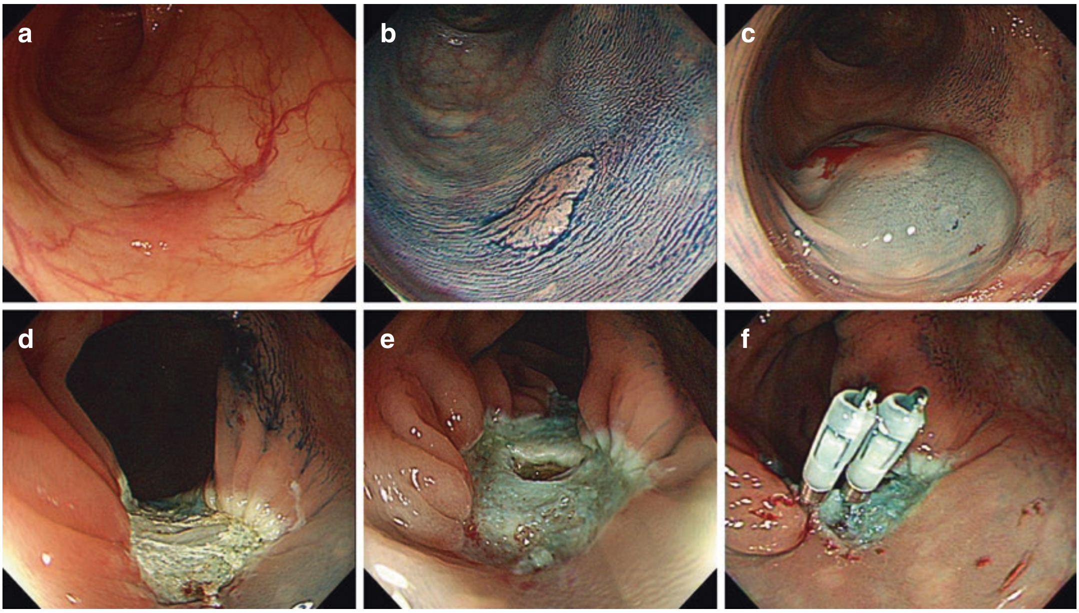

Fig. 18.1 Case with perforation after EMR. (**a**) Superficial elevated lesion 10 mm in diameter, (**b**) indigo carmine dye spraying view of this lesion, (**c**) view of after injection of glycerol, (**d**) view of after EMR, (**e**) small perforation hole is seen in ulcer bed after EMR, and (**f**) clipping was conducted complete closure of perforation hole

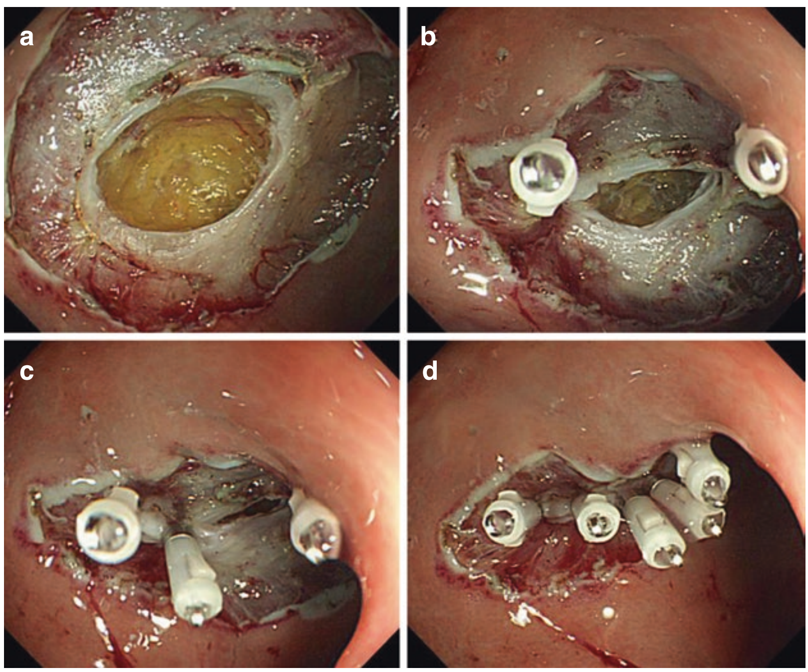

Fig. 18.2 Case with perforation after hybrid ESD. (**a**) Large perforation hole after hybrid ESD. (**b**) At first, clippings were conducted at the bilateral side of the hole, then, hole became remarkably small. (**c**) The third clipping was done. (**d**) Two more clippings were added and complete closure was obtained

may occur. Also, we have to pay attention to the prevention from Fournier's syndrome. Recently for large perforation, Over-The-Scope-Clips (OTSC®) is available for closure [5]. When delayed perforation occurs, basically surgical operation should be conducted as soon as possible.

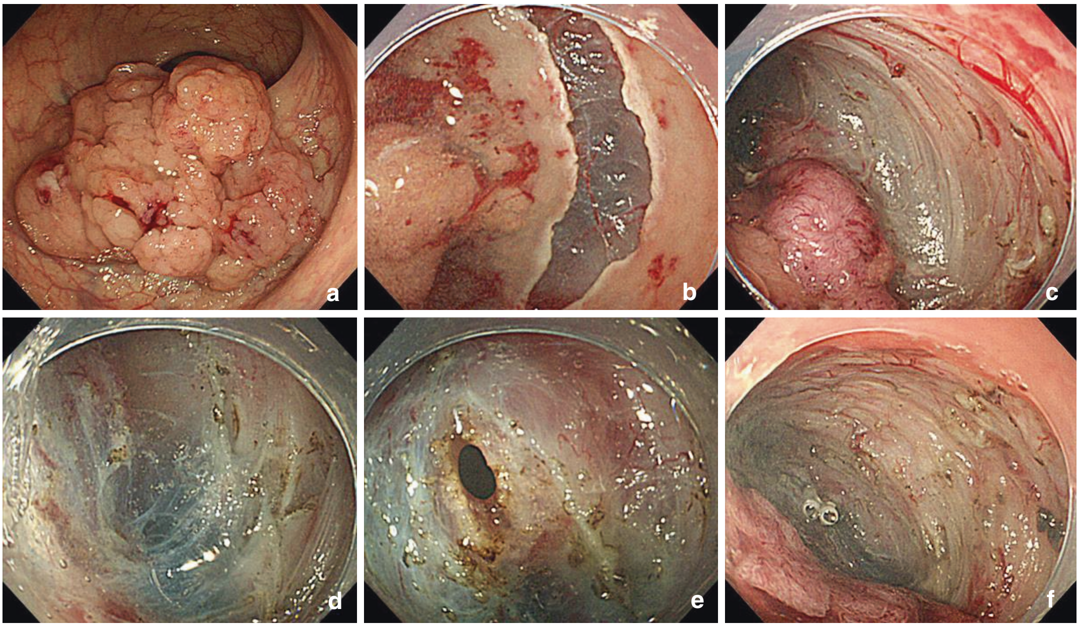

Fig. 18.3 Case with perforation during ESD. (**a**) Sessile polypoid lesion 40 mm in diameter. (**b**) View of after mucosal incision at the surrounding normal mucosa of the lesion. (**c**, **d**) Submucosal dissection is ongoing. (**e**) Microperforation occurred due to contact of the tip of needle-type knife to the muscle layer. (**f**) Complete closure of the perforation hole was conducted by clipping using two clips

18.2 Prevention and Management of Bleeding

For bleeding associated with endoscopic resection, clipping or coagulation is appropriate. In case of minor bleeding from a small vessel, contact coagulation with the tip of a knife or coagulation with hemostatic forceps is usually used for hemostasis. In cases of severe bleeding from a large vessel or artery, hemostatic forceps are indispensable. To avoid delayed perforation caused by thermal damage, the bleeding point should be grasped precisely with hemostatic forceps, and the application of electrocoagulation should be minimized. Serious delayed bleeding that requires blood transfusion seldom occurs in the colon. Emergency endoscopy is usually required to treat exposed blood vessels in the case of continuous bloody stool.

A randomized controlled trial reported that preventive clipping after endoscopic resection did not decrease the delayed bleeding rate (0.98% with clipping and 0.96% without clipping) [6]. Recent Japanese study also supports this result [7]. However, at present, regarding ESD no robust evidence has been obtained by randomized controlled trials for the efficacy of suturing the ulcer bed after ESD wound to prevent delayed bleeding.

Regarding the endoscopic resection for cases with antithrombotic therapy, we have to consider the kind of drugs, background of patients such as comorbidity, and risk of bleeding in each therapeutic procedure as a whole [8].

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Special ESD Cases Illustrations

19

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Abbreviations

EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
GI	Gastrointestinal
LST	Laterally spreading tumor
NBI	Narrow-band imaging
TAR	Trans anal resection

19.1 Case 1

A 67-year-old woman was referred to our hospital for the treatment of an anorectal residual polyp after treatment at another hospital. Trans anal resection (TAR) was performed previously as an initial treatment. The histology showed carcinoma in situ with positive resection margins. Residual adenoma was detected at the surveillance colonoscopy, which was performed 2 years after the initial treatment, and EMR using snare and hot biopsies were attempted. However, residual adenoma was observed at the 3-year surveillance colonoscopy. A colonoscopy performed at our center showed a 20 mm polypoid lesion extending to the anal canal as well as multiple surrounding scars (Fig. 19.1a). Magnifying endoscopy with narrow-band imaging (NBI) showed dilated microvessels with a regular arrangement. Chromoendoscopy with magnification following crystal violet staining revealed a regular blanched pit pattern. The diagnosis was residual adenoma. The lesion extended to the anal canal, and scars were also found at the one-third circumference of the anal canal (Fig. 19.1b). Rectal tumors extending to the dentate line are technically difficult to excise because of their anatomical features, i.e., the narrow space and complex shape of the anal canal, the thin submucosal layer containing fibrotic tissues (termed “musculus submucosae ani”), the rich vasculature of the rectal venous plexus, and the presence of sensory nerves in the anoderm [1]. There is also the theoretical risk of systemic bacteremia because of direct drainage via the venous plexus to the systemic circulation [2]. Moreover, in this case, poor lifting of the lesion after submucosal injection was considered likely due to possible widespread submucosal fibrosis. Thus, we predicted that it would be difficult to remove the residual adenoma by EMR using a snare. Accordingly, we decided to use ESD to achieve complete removal.

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19.1.1 ESD Setting

- Endoscope: A gastroscope with a water-jet system (GIF-Q260J; Olympus Medical Systems Corp., Tokyo, Japan)

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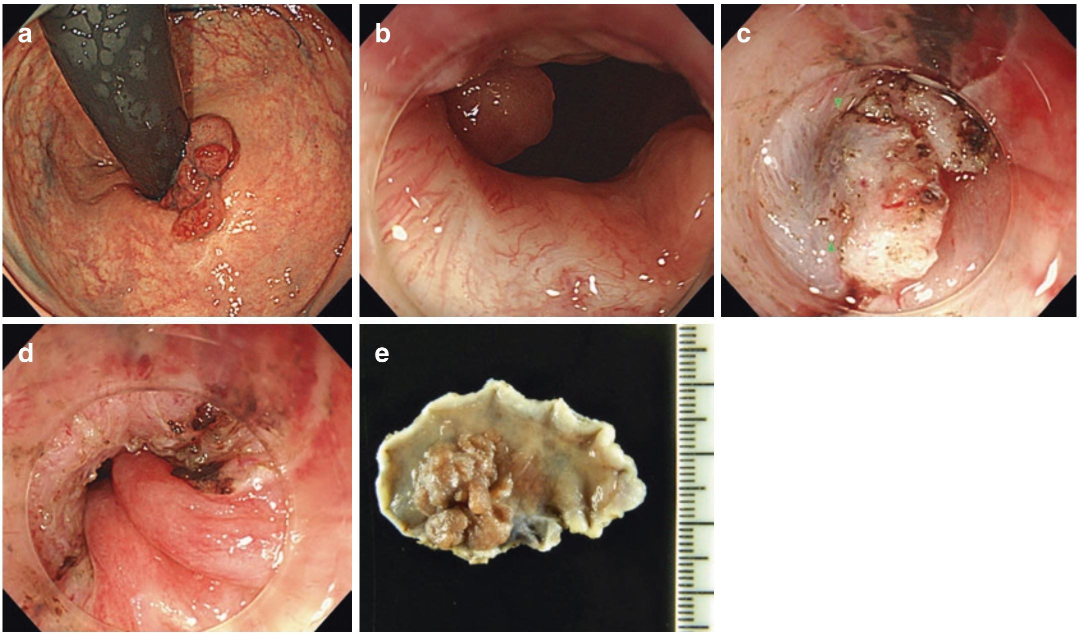

Fig. 19.1 (**a**) Colonoscopy revealed a 20 mm rectal polyp extending to the anal canal with surrounding multiple scars. (**b**) There was a widespread scar in the anal canal due to previous trans anal resection. It would have been difficult to make a mucosal incision to create a mucosal flap on the anal side that was far away from the scar. (**c**) After a mucosal flap was successfully created on the left side of the lesion at the anal canal, the submucosal layer could be directly visualized using the mucosal flap (green arrowheads). (**d**) The ulcer bed at the anal canal. (**e**) The resected specimen

- Device: Dual knife and ITknife nano™ (Olympus)
- Fluid: Hyaluronic acid plus Glycerol (1: 1) tinged with indigo carmine
- Electrosurgical unit: VIO300D (cut mode; Endocut Q 80W effect 3, coagulation mode; SWIFT 60W)
- Coagulation forceps: Coagulaspar (Olympus), SOFT 40W
- Sedation: Midazolam and pethidine
- Other: Carbon dioxide insufflation

19.1.2 Technical Problems

The potential technical problems were as follows: (1) poor visualization from the narrow lumen; (2) a possible risk of bleeding due to the presence of rectal venous plexus; (3) pain due to unique innervation; (4) a risk of systemic bacteremia due to the unique vascular supply; (5) the complex shape of the submucosa at the anal canal; and (6) possible submucosal fibrosis due to previous treatment.

19.1.3 ESD Technique Modifications

We modified the ESD procedure as follows: (1) A transparent hood was attached to the tip of the endoscope to improve visualization. (2) A gastroscope was used to improve scope operability in the narrow surgical space. (3) Local injection of 1% lidocaine (100 mg/10 mL) was used prior to ESD to reduce the pain. (4) Prophylactic antibiotics were administered intravenously after ESD. (5) A needle-type knife (dual knife) was used to accurately trace the complex resection line at the anal canal. (6) Indigo carmine was used so that blue-tinged fluid would improve the visualization of the submucosal layer with fibrotic tissue. (7) A highly viscous fluid, hyaluronic acid, was used to create a good cushion. (8) A small-caliber-tip transparent hood (ST hood, DH-28GR; Fujinon, Japan) was used to make it easy to enter the submucosal layer.

19.1.4 ESD Procedure

The key to the success of the ESD procedure is to enter the submucosal layer using a mucosal flap after mucosal incision. Entering into the submucosal layer enables stable endoscope maneuver under direct vision of the resection line. A larger mucosal flap is helpful for treating lesions with fibrosis. In this particular case, creating a large mucosal flap at the distal side of the lesion was considered difficult because wide field submucosal dissection was not feasible in the anal canal. Therefore, we made an initial mucosal incision to create a mucosal flap 10 mm to the left of the tumor. Because there was no scar there, a good submucosal cushion could be created by submucosal injection. After a mucosal flap was created, a mucosal incision was performed around the anal side, and submucosal dissection was started. Using a mucosal flap, the thin submucosal layer could be observed directly as a transparent layer (green arrowheads, Fig. 19.1c). When dissecting thin submucosa with fibrosis, one must use a horizontal approach with ESD knives in order to minimize thermal damage to the muscular layer. Meticulous rotation of the endoscope enabled safe and efficient submucosal dissection with direct visualization of the thin submucosal layer. The anal canal area was carefully dissected, and then circumferential mucosal incision and submucosal dissection were performed in the retroflex position in the remaining area that did not involve the anal canal. Finally, en bloc resection was successfully performed without any complications (Fig 19.1d). The procedure was completed within 2 h. Although the patient did not have pain during or after the procedure, she developed a slight fever (37–38 °C). This resolved 3 days after ESD, and she was discharged without any symptoms. The resected specimen measured 40 × 25 mm, and the lesion within it was 20 × 20 mm (Fig. 19.1e). Histological analysis revealed tubular adenoma with high-grade dysplasia (Vienna classification 4.1) with negative lateral and vertical margins. A 1-year surveillance colonoscopy showed a flat anorectal scar with no residual adenoma and no stenosis.

19.2 Case 2

A 66-year-old woman was referred to our hospital for surgical treatment of advanced gastric cancer that was detected by esophagogastroduodenoscopy after she complained of epigastralgia. Although she had no lower gastrointestinal (GI) symptoms, surgeons recommended that she undergo a colonoscopy, since she had not had one previously. Colonoscopy showed an 80 mm granular-type laterally spreading tumor (LST) at the ascending colon. The LST lesion had a large nodule (>10 mm) at its center with a flat elevation base. Magnified endoscopy with NBI showed a dilated, tortuous microvascular structure, corresponding to Japan NBI Expert Team Classification Type 2A. Magnified chromoendoscopy with crystal violet staining revealed a regular tubular pit, corresponding to the Type IV pit pattern in Kudo's classification. The diagnosis was intramucosal cancer with no submucosal invasion; thus, we recommended ESD as the initial treatment. Open gastrectomy with lymph node dissection was planned for the gastric cancer because it was diagnosed at an advanced stage with positive lymph node metastasis. We performed ESD for the colonic LST (Fig. 19.2).

19.2.1 ESD Setting

- Endoscope: An intermediate-length colonoscope with a water-jet system (PCF-Q260J; Olympus)
- Device: Dual knife and ITknife nano™ (Olympus)
- Fluid: Hyaluronic acid plus glycerol (1:1) tinged with indigo carmine
- Electrosurgical unit: VIO300D (cut mode; Endocut Q 80W effect 3, coagulation mode; SWIFT 60W)

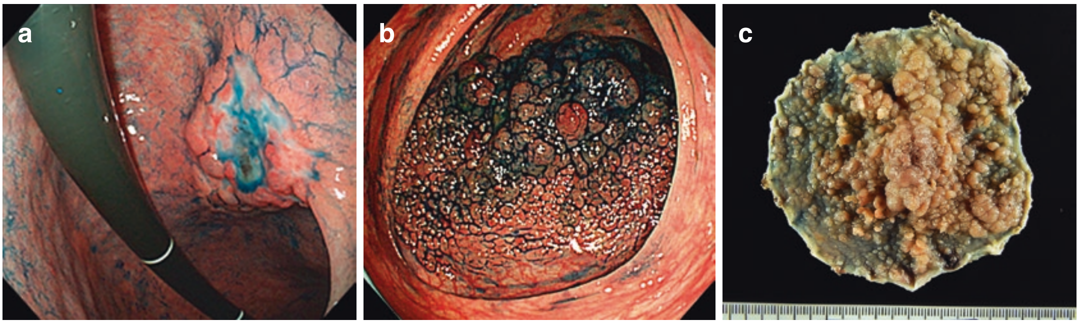

Fig. 19.2 (**a**) Retroflex gastroscopy showed a 30 mm excavated gastric cancer at the anterior wall of the antrum. (**b**) An 80-mm laterally spreading mixed nodular granular-type tumor can be seen over a semilunar fold of the ascending colon. (**c**) The resected specimen of the laterally spreading tumor suggested en bloc resection with macroscopically tumor-free lateral margins

- Coagulation forceps: Coagulaspar (Olympus), SOFT 40W
- Sedation: Midazolam and pethidine
- Other: Carbon dioxide insufflation

19.2.2 Technical Issues

The potential technical issues were as follows: (1) The presence of semilunar folds. (2) The possible presence of thick vessels under the large nodule.

19.2.3 ESD Technique Modifications

We modified the ESD procedure as follows: (1) An ITknife nano™ was used for submucosal dissection. (2) A Dual Knife rather than an ITknife nano™ was used to dissect fibrotic tissue.

19.2.4 ESD Procedure

Initially, a mixed solution of hyaluronic acid and glycerol was injected submucosally. To confirm that the injection correctly targeted the submucosal layer, we performed a test injection using only a glycerol solution. After confirming adequate submucosal lifting, we then used a syringe with a mixed solution of hyaluronic acid and glycerol. Next, a one-third mucosal incision was made on the anal side using a needle-type knife (Dual Knife). Two or three additional mucosal incisions allowed us to place the endoscope into the submucosal layer. We then used an ITknife nano™ for submucosal dissection. Repeated submucosal injections helped maintain an adequate submucosal fluid cushion and improved our visualization of the submucosal tissues. When thick vessels could be seen within the submucosal layer, prolonged application of a coagulation current allowed us to dissect the vessels without extensive bleeding [3]. The ITknife nano™ was thus effective for this safe and time-saving procedure. En bloc R0 resection was achieved without any complications. Histological analysis showed an 80-mm intramucosal cancer (Tis) with negative margins.

19.3 Discussion

Here we presented two cases: in Case 1, ESD was used as salvage therapy for anorectal residual neoplasms after several previous treatments; in Case 2, ESD was used for the optimal management of a large synchronous colonic LST in a patient with advanced-stage gastric cancer. Case 1 demonstrated the advantages of using ESD rather than trans anal surgical procedures in the anorectal region. TAR can be performed as a local resection method as an alternative to surgery; however, the rate of local recurrence is high and there can be severe complications [4]. In recurrent cases, salvage resection to treat local recurrence would be increasingly difficult due to severe submucosal fibrosis. Moreover, when the tumor extends into the anal canal, surgical resection would result in the loss of the anus itself (along with anal function), greatly reducing the patient's quality of life. Thus, the overuse of surgery for nonmalignant rectal tumors that extend into the dentate line should be avoided in order to keep medical costs down and to ensure higher quality of life [5, 6]. ESD was not used for anorectal lesions in the past due to considerable technical difficulties during the early phase of development of this technique. However, recent advances in endoscopic equipment and techniques make it possible to now offer ESD to patients with anorectal lesions [7]. In our previous reports, ESD for rectal tumors extending to the dentate line was feasible and showed high rates of complete tumor removal and en bloc resection (95.6%), with a perforation rate was 4.4%. Minor postoperative complications were common, including high-grade fever over 38.0 °C (22%), persistent anal pain (26%), and proctostenosis (2%); however, these were not serious complications.

In the current case, en bloc R0 resection and detailed histological evaluations were achieved by ESD even for a severely scarred lesion that recurred after TAR. The possibility of residual neoplasm development and the subsequent risk of metastasis were completely eliminated by ESD. Thus, curative therapy using ESD for anorectal lesions as an alternative to surgical options would have great value in terms of preserving anal organ function.

Survival has improved for patients with gastrointestinal cancer owing to advances in surgery and adjuvant chemotherapy, but synchronous neoplasms in other parts of the GI tract must also be addressed. In our previous report, patients with gastric cancer showed a twofold greater prevalence of high-risk adenomas than healthy individuals [8]. Screening colonoscopy that is performed in patients with gastric cancer prior to surgery sometimes detects large colorectal neoplasms, as for case 2. In case 2, the large size and the morphology of an 80-mm granular-type LST nodular mixed-type lesion raised the possibility that there could be submucosal invasion. Indeed, a previous study showed that approximately 19% of granular-type LST nodular mixed-type lesions ≥40 mm was submucosal invasive cancers [9]. Certain histological findings pertaining to invasion depth, tumor differentiation, tumor budding, lymph-vascular permeation, and margin status, are significant independent risk factors for lymph node metastasis in submucosal invasive colorectal cancer [10]. The histological findings that are linked to lymph node metastasis are difficult to see in specimens that are resected in multiple pieces. In case 2, the surgeon notified us that complete removal of the lesion was necessary and that the histology of the LST needed to be determined prior to gastrectomy to avoid secondary colectomy after gastrectomy. In general, pathological findings related to metastatic risks, such as tumor invasion depth, lymph-vascular permeation, tumor budding, and resection margin, are carefully evaluated for a few weeks. The waiting time prior to pathological reports of the ESD specimen could raise concerns in patients because of the delay prior to the curative gastrectomy. The patient hoped to undergo ESD for her LST without delay. We should plan the ESD within a week after the diagnosis to reduce the waiting time. A time-saving ESD procedure is needed, because we perform many colonoscopies every day. In this context, ESD using the ITknife nano™ is useful for achieving en bloc resection in a shorter period. A definitive pathological assessment helps physicians develop an optimal treatment strategy for patients with two malignancies, i.e., advanced gastric cancer plus superficial colon cancer. Case 2 demonstrated that ESD could be part of an optimal treatment strategy with minimal invasiveness in patients with synchronous cancerous lesions in multiple organs.

These two case reports illustrate how ESD can be used to minimize the use of surgery to treat patients with complex lesions. In case 1, ESD eliminated the need for more extensive surgery by achieving complete en bloc resection at a delicate site. In case 2, ESD minimized the need for the patient to undergo two surgeries, i.e., colectomy and gastrectomy, by eliminating the need for colectomy due to the complete removal and favorable histology of a huge LST.

To summarize, ESD offers a way to minimize the need for invasive treatment in patients with GI cancers. To facilitate and spread the use of ESD, GI endoscopists and surgeons should continue to share their knowledge of this technique and their experiences and results and should discuss the use of this treatment strategy in patients.

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20 Special ESD Cases Illustrations: China

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Case 1
A large LST-G approximately sized 4 × 3 cm was found in the rectum near the anus (Fig. a, b). We used magnifying endoscopy with narrow-band imaging to carefully observe this lesion. Under magnifying endoscopy, it showed with regular tubular pattern with regular vessels, which was classified as JENT 2A (Fig. c, d). Also, positive regular WOS was observed. Finally, we considered it colorectal tubular adenoma and it could be resected with ESD. ESD was performed from the anal direction to the proximal direction and it was successfully dissected (Fig. e, f). Final histopathology was tubular adenoma.

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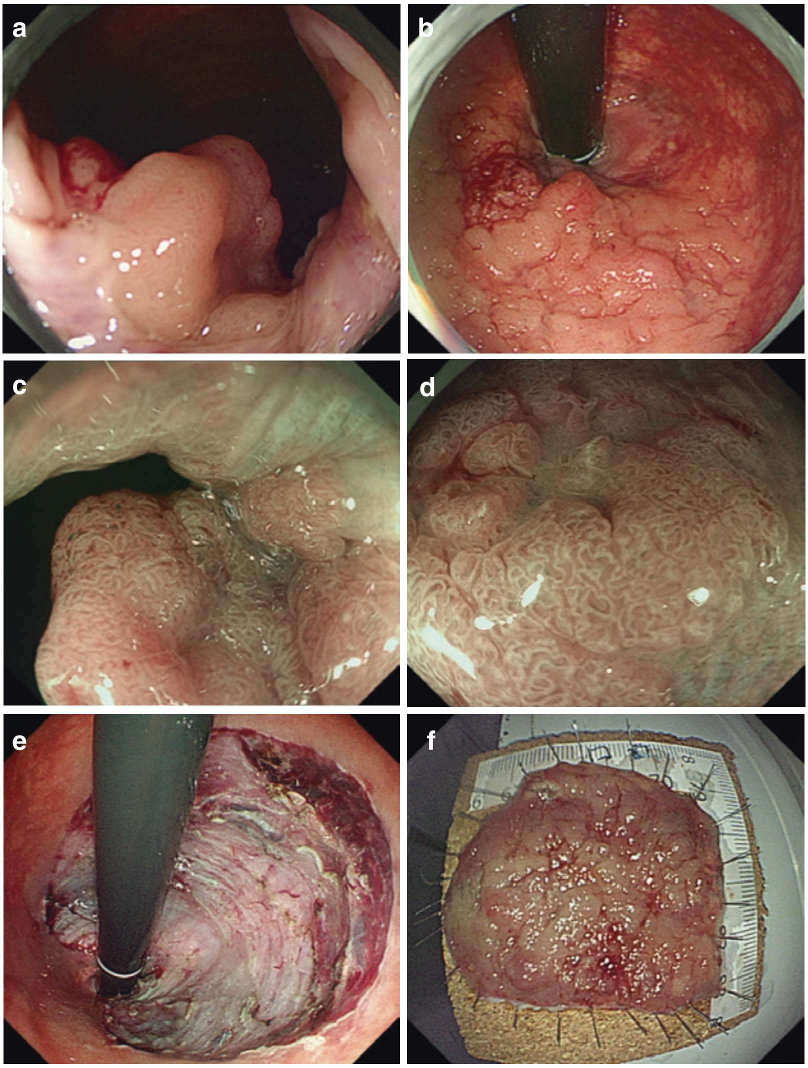
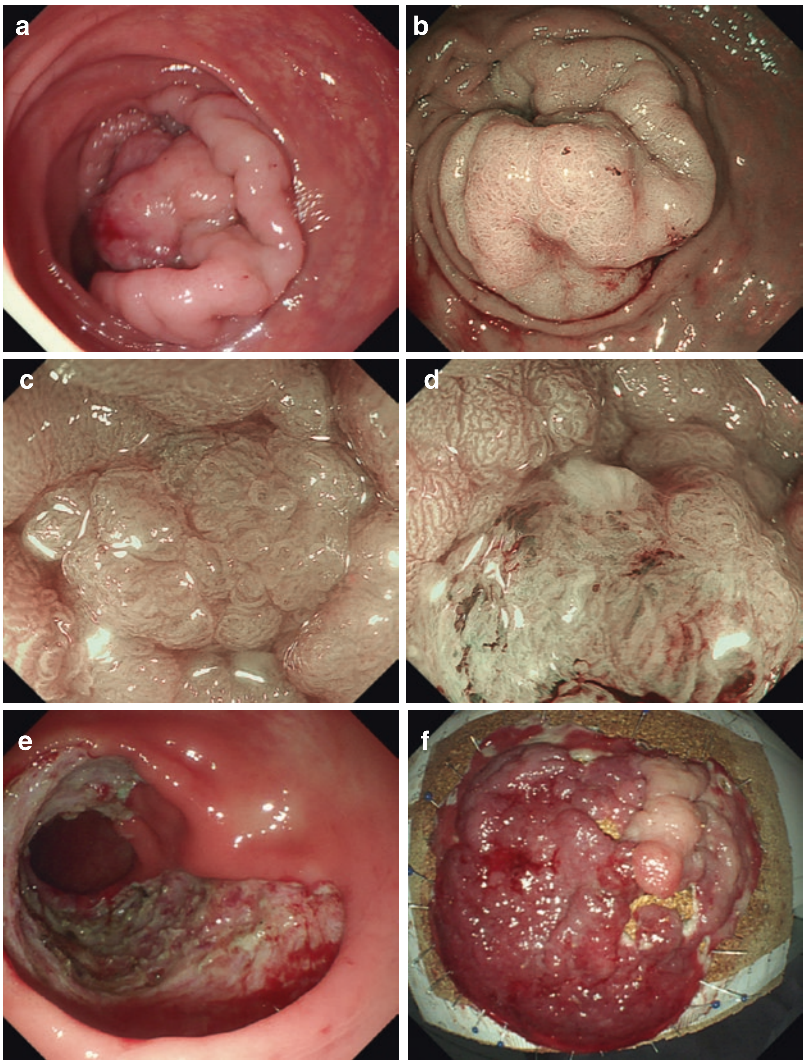

a
b
c
d
e
f

Case 2

A large LST-G with mixed nodule approximately sized 7 × 7 cm was found in the rectum occupying 3/4 of the lumen (Fig. a). We used magnifying endoscopy with narrow-band imaging to carefully observe this lesion. Under magnifying endoscopy, it showed with regular tubular pattern with regular vessels, which was classified as JENT 2A (Fig. b, c). Also, positive regular WOS was observed. However, in the largest nodule located in the middle of the lesion, surface and vessel pattern seemed obscure and at least JENT 2B could be diagnosed (Fig. d). We finally did an ESD for this lesion and postoperative bleeding was conducted (Fig. e, f). Also, clip was used to close the mucosa with impaired muscularis propria. Final histopathology was villous adenoma with localized malignancy in the largest nodule. Submucosal invasion could be diagnosed with 4.5 mm from the muscularis mucosae but without lymphatic invasion.



Case 3
A large LST-G with nodules approximately sized 4 × 3 cm was found in the ileocecal junction (Fig. a). We used magnifying endoscopy with narrow-band imaging to carefully observe this lesion. Under magnifying endoscopy, it showed with regular tubular pattern with regular vessels in most areas, which was classified as JENT 2A (Fig. b, c). However, in the depressed area in the middle of the lesion, surface and vessel pattern seemed irregular and JENT 2B could be diagnosed (Fig. d), which was suitable for ESD. Finally, successful ESD was performed and postoperative clip was placed to the dissected mucosa (Fig. e, f). Final histopathology was tubular adenoma with high-grade dysplasia.