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Editor

Endoscopic Submucosal Dissection

Principles and Practice

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Videos to this book can be accessed at
http://www.springerimages.com/videos/978-1-4939-2040-2

ISBN 978-1-4939-2040-2 ISBN 978-1-4939-2041-9 (eBook)
DOI 10.1007/978-1-4939-2041-9
Springer New York Heidelberg Dordrecht London

Library of Congress Control Number: 2014955223

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Foreword

It was 1996 when I and my colleagues, the Endoscopy Group at the National Cancer Center Hospital, Tokyo, Japan, first developed and used the IT knife in endoscopic submucosal dissection (ESD) for early gastric cancer, and it is unbelievable how fast almost two decades have passed since then. Because surgical treatment, such as esophagectomy, gastrectomy, and colectomy, deteriorate patient condition despite clinical benefit, and because ESD obtains undoubtedly much better quality of life with comparable outcome, ESD has been widely accepted as a standard treatment for early cancer in the gastrointestinal tract and has rapidly spread throughout not only Japan but also many East Asian countries.

We know that doctors in Western countries have seen and experienced not many early-stage cancers or superficial lesions of the GI tract, and because those lesions were not in the majority, they have not provoked physicians' interest. However, I think the situation is changing by a certain degree, and I feel more enthusiasm from Western countries as well.

Successful ESD requires sound surgical skills, aptitude for early tumor detection and accurate assessment and diagnosis of tumor extension and depth, and knowledge about treatment indications. ESD has contributed to the development of more advanced diagnostic procedures using NBI with magnifying endoscopy, and has led to the start of many prospective clinical trials. Furthermore, on the basis of ESD, the endoscopist's work has expanded extensively to cover even peroral endoscopic myotomy (POEM), laparoscopy and endoscopy cooperative surgery (LECS), and endoscopic full-thickness resection (EFTR). Yet, we continue to make ceaseless efforts to push to more new frontiers.

Dr. Fukami, the editor, has worked in both Japan and the USA, and, therefore, he keenly feels the necessity for introduction of all aspects of ESD to Western doctors. Many pioneers and experts of ESD approved of his appeal and contributed to it. I believe this textbook will be a great help to both Eastern and Western endoscopists wanting to create new frontiers. Join us and together let us open up new possibilities for endoscopic therapy.

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Preface

Endoscopic submucosal dissection (ESD) was born in Japan in the 1990s with much enthusiasm to overcome the shortcomings of endoscopic treatment for early gastric cancer. Then, many dedicated physicians explored the expansion of this technique to treat an even wider array of mucosal diseases in the gastrointestinal tract. I was lucky to see the early stages of the ESD procedure in Japan, following its evolution to the established ESD procedure that is now perceived as exceptionally elegant, intricate, and effective in carefully selected patients providing cure from cancer without invasive surgery. ESD has evolved to become a much safer and more capable mucosal resection technique, and has now expanded to treat even submucosal tumors (such as stromal tumors) and also into achalasia treatment (POEM).

ESD spread easily to neighboring countries, for they shared the similar disease prevalence of gastric cancer, but it has taken more time to come to Western countries. Early adaptors of ESD from the Western world learned by hands-on training in Japan or with explant models supervised and trained by ESD experts. Literature on outcome and some techniques is available, but we have limited resources for learning ESD in English.

There was a desperate need for an ESD textbook to teach the much-needed basics for learning and performing ESD, from diagnosis of mucosal disease by evaluation with advanced imaging to understanding the indications and limitations of endoscopic treatment, the actual procedural steps, including tips and tricks, to coping with complications, and how to follow up patients after ESD.

It has been an exceptional privilege, pleasure, and an honor to work with worldwide experts in the field to create this first English textbook for ESD.

I truly hope everyone will enjoy this book full of pearls of wisdom shared by the experts so that they may learn safe and effective ESD. This book is dedicated to help all levels of endoscopists who are eager to learn ESD.

I would like to express my respect and deep appreciation to all the exceptional authors who contributed to this book. As well, my gratitude goes to Jacob Gallay and Andy Kwan, who have been dedicated to the success of this first English ESD textbook.

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List of Abbreviations

AFI	Autofluorescence imaging
APC	Argon plasma coagulation
BE	Barrett's esophagus
CI	Confidence interval
CLE	Confocal laser endomicroscopy
CO_2	Carbon dioxide
CRC	Colorectal cancer
CRP	C-reactive protein
CRT	Chemoradiation therapy
CT	Computed tomography
D50	50 % Dextrose water
DBE	Double-balloon endoscopy
DW	Dextrose water
EBD	Endoscopic balloon dilation
EDSP	Endoscopic double-snare polypectomy
EDTA	Ethylenediaminetetraacetic acid
EEC	Early esophageal cancer
EFTR	Endoscopic full-thickness resection
EGC	Early gastric cancer
EMR	Endoscopic mucosal resection
EP	Epithelium
EPMR	Endoscopic piecemeal resection
ER	Endoscopic resection
ERHSE	Endoscopic resection with hypertonic saline-epinephrine solution
ESD	Endoscopic submucosal dissection
ESMR-L	Endoscopic submucosal resection with ligation device
ESTD	Endoscopic submucosal tunnel dissection
ETI	Endoscopic triamcinolone injection
EUS	Endoscopic ultrasound
FICE	Fujinon intelligent color enhancement
FNA	Fine-needle aspiration
GEJ	Gastroesophageal junction
GI	Gastrointestinal
GIST	Gastrointestinal stromal tumor
H2RA	H2-receptor antagonist

HA	Hyaluronic acid
HDWLE	High-definition white light endoscopy
HGD	High-grade dysplasia
HPMC	Hydroxypropyl methylcellulose
HS	Hypertonic saline
IPCL	Intrapapillary capillary loop
IRB	Institutional review board
IT	Insulated tip
JES	Japan Esophageal Society
JGES	Japan Gastroenterological Endoscopy Society
KCM	Keratinocyte culture medium
LES	Lower esophageal sphincter
LN	Lymph node
LNM	Lymph node metastasis
LP	Lamina propria
LSS	Light-scattering spectroscopy
LST	Laterally spreading tumor
LST-G	Laterally spreading tumor—granular type
LST-NG	Laterally spreading tumor—non-granular type
M	Mucosa(l)
MC	Methylcellulose
ME	Magnification endoscopy
MGC	Metachronous gastric cancer
MRI	Magnetic resonance imaging
NBI	Narrow-band imaging
NET	Neuroendocrine tumor
NOTES	Natural orifice transluminal endoscopic surgery
NS	Normal saline
OCT	Optical coherence tomography
OR	Odds ratio
OTSC	Over-the-scope clip
POEM	Peroral endoscopic myotomy
POET	Peroral endoscopic tumor resection
PPI	Proton pump inhibitor
PVDF	Polyvinylidene difluoride
SCC	Squamous cell carcinoma
SCMC	Sodium carboxymethylcellulose
SFC	Submucosal fluid cushion
SGN	Synchronous gastric neoplasm
SH	Sodium hyaluronate
SLE	Second-look endoscopy
SM	Submucosa(l)
SMI	Submucosal invasion
ST hood	Small-caliber tip hood
STER	Submucosal tunneling endoscopic resection
TTS	Through-the-scope
US	Ultrasonography

Part I

Introduction

History of ESD

1

Kazuki Sumiyama and Hisao Tajiri

The Quest for En Bloc Resection

The development of current endoscopic tissue resection (ER) techniques began with polypectomy in the 1960s [1, 2]. Since that time, researchers have been seeking a method to sample larger specimens. Various endoscopic mucosal resection (EMR) techniques were developed in Japan during the 1980s and early 1990s as minimally invasive therapeutic options for small early stage gastric cancers. These EMR techniques included strip biopsy [3], endoscopic resection with local injection of hypertonic saline-epinephrine solution (ERHSE) [4, 5], endoscopic double snare polypectomy (EDSP) [6], and also cap-assisted EMR [7, 8], which promoted international acceptance of EMR. The technology in this field has been steadily evolving and has made ER easier, safer, and more reliable. Prior to the development of endoscopic submucosal dissection (ESD), ordinary ER techniques were restricted by resectable specimen size, which was imposed by the caliber of a snare or cap attachment. Therefore, the indication of ER was limited to small lesions less than 2 cm in diameter that were resectable within a single specimen. In fact, the en bloc resection rate of EMR techniques even for small lesions did not reach 70 %, and the resultant incomplete and piecemeal resections could give rise to local recurrence [9–11]. ESD was developed to eliminate the technical limitation of resectable specimen size as a single piece.

During ESD, the diseased mucosa is radically incised from surrounding non-neoplastic tissues with careful, repetitive needle knife dissections that secure the lateral and vertical surgical margins in a step-by-step process. The concept of the en bloc resection during ESD is universally appreciated as a desirable methodology, which respects the principle of surgical excision of neoplastic lesions with "no touch isolation" as far as possible using direct endoscopic inspection. The en bloc tissue sampling technique enables precise histological assessment of the curability of the treatment and optimizes conditions for complete tumor removal compared to piecemeal resection. These advantages have resulted in rapid adoption of the technique and its application in all areas of the gastrointestinal tract. Reimbursement by the National Health Insurance of Japan was initially approved for gastro-duodenal lesions in 2006; it

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N. Fukami (ed.), *Endoscopic Submucosal Dissection: Principles and Practice*,
DOI 10.1007/978-1-4939-2041-9_1,

was extended for esophageal lesions in 2008, and eventually for colorectal lesions in 2012. A series of studies mostly from East Asia have demonstrated that the use of ESD increased R0 resection rate and, more importantly, reduced local recurrence rate compared to other ER techniques, regardless of the target organ [5, 12–15].

Development of Instruments for Safer and Easier ESD

ESD is characterized and distinguished by two procedural steps: circumferential mucosal incision and submucosal dissection. Circumferential mucosal incision was originally introduced to ensure that the lateral surgical margins remain intact during treatment in ERHSE, which is one of the snare-based EMR techniques. In ERHSE, the final tissue removal is assisted by tissue countertraction using grasping forceps and a dual working channel scope in the same manner as strip biopsy. During the developmental phase of both the ERHSE and ESD procedures, a traditional safety measure developed for polypectomy was employed that used a simple diathermy needle knife for the mucosal layer incision following saline injection. However, a sharp incision with the naked cutting wire tip of the rudimental needle knife was associated with unacceptably high risks of severe bleeding and perforation. Consequently, ERHSE and ESD were not widely adopted by endoscopists until improvements were made to the instruments that resulted in more sophisticated and safer ESD procedures.

An array of needle knives have been developed with unique tip configurations specifically designed for ESD. ESD knives can be divided into two types, according to the safety measure applied: a blunt tip and a tip-cutting knife. The insulated tip knife, or "IT-knife" was developed by Hosokawa and colleagues and was promoted globally as the optimal therapeutic option [16–18]. The IT-knife (Olympus Medical Systems, Tokyo, Japan) is still commonly used for gastric ESD and is a blunt tipped knife, with a small porcelain hemisphere on the tip of the cutting wire. The hemisphere works as a protector to avoid unintended deep cuts and a pivot to tilt and swing the cutting wire tip to align the dissection plane to the submucosal layer. It also acts as a stabilizer to arbitrarily control dissection speed. The Mucosasectome (HOYA/PENTAX, Tokyo, Japan) and SAFEKnife (Fujifilm, Tokyo, Japan) are additional examples of the blunt tip knife (Fig. 1.1). The tip-cutting knives allow multi-directionally emitted electrosurgical cautery from both the tip and side of the cutting wire. It is important to apply cautery only under direct endoscopic visualization of the dissection plane for safe tissue dissection using tip-cutting knives. Many tip-cutting knives share the same basic design and function with minor modifications (Fig. 1.2). Typically, they have a thin and short cutting wire exposure from an insulated outer sheath to provide sharp tissue dissection that

Fig. 1.1 Blunt tip ESD knives. From the *bottom*: IT-knife (Olympus Medical Systems), SAFEKnife V (Fujifilm), Swan Blade (Hoya/Pentax), Mucosectom (Hoya/Pentax)

Fig. 1.2 Tip-cutting ESD knives. From the *left*: Hook knife (Olympus Medical Systems), Dual knife (Olympus Medical Systems), Flex knife (Olympus Medical Systems), Flush knife BT and Flush knife (Fujifilm)

avoids inadvertent deep tissue damage. They have a thick blunt tip of the outer sheath that acts as a bumper to protect tissues and controls the depth of incision, as well as a bent portion or small disk at the tip of the cutting wire to hook tissues to avoid damaging deeper tissue. Other examples of tip-cutting knives are the Hook knife (Olympus Medical Systems) [19], Flex knife (Olympus Medical Systems) [20], Dual knife (Olympus Medical Systems) [21], Flush knife (Fujifilm) [22], and Hybrid knife (ERBE, Erlangen, Germany) [23] (Fig. 1.2) (Appendix). Optimal electrosurgical generator and cutting current modes are essential for a successful ESD procedure. In particular, the development of the EndoCut mode in ERBE systems alerted users to this fact. Various computerized high-tech electrosurgical generators are commercially available at present. These provide an array of options that automatically modulate cutting and coagulating currents corresponding to tissue resistance. The optimal electrosurgical current may vary according to a number of parameters, including the procedural phase of ESD, the types of knives used, the target tissues, and the operators' preference. Use of the sharp cutting current enables both rapid and accurate dissection of the mucosa, whereas controlled dissection with a coagulating blended current is safer for the dissection of well-vascularized submucosal tissues. Most of the bleeding that occurs during ESD can be immediately controlled by cauterization with hemostatic forceps.

The creation of a submucosal fluid cushion (SFC) is a convenient safety measure to prophylactically avoid inadvertent deep muscularis injury during ER. The procedural simplicity of this measure allows it to be applied universally, regardless of technical variations in the resection, tumor location, or skill level of the operator. Classical saline injection is sufficient for most quick snare-based ER techniques. The creation of a more durable and reliable SFC is desirable for performing more time-consuming ESD procedures safely. The efficacy of various viscous and highly osmotic solutions in producing a long-lasting SFC has been tested. For example, Yamamoto and colleagues introduced hyaluronic acid solution as an injectate for ESD [24–26]. Hyaluronate is widely used in the fields of orthopedics and ophthalmology as a lubricant, and the safety of the drug is ensured with a wealth of clinical data in those fields. The Ministry of Health, Labour and Welfare of Japan approved 0.4 % hyaluronic acid solution as an injectate for ER and it is now commercially available (MUCOUP, Johnson & Johnson, Tokyo, Japan). Because hyaluronate is not readily accessible for the majority of gastroenterologists working outside of Japan, cheaper alternatives such as glycerol, dextrose [27–29], and hydroxypropyl methylcellulose (HPMC) solutions are also used for ESD [30, 31]. Many researchers are still investigating the development of improved needle knives and injectate for submucosal dissection [32–36]. The pathway of ER development clearly demonstrates that the challenges associated with ESD cannot be completely eliminated with a single development, and can be overcome only with a multidisciplinary approach.

Challenges for Globalization and Future Prospects

The efforts of many researchers and technological developers have made ESD both safer and easier, and as a result the ESD technique is now widely practiced in Japan as a first-line therapeutic option for early gastrointestinal neoplasms. The indications of ER could be expanded for larger lesions by ESD. In the extended indications for gastric cancer, there is no limitation on tumor size for differentiated (intestinal type) mucosal cancers without ulceration. An enormous amount of data has been obtained from meticulous histological analysis of ESD specimens following a strict, standardized pathological protocol. These results have indicated that the therapeutic outcomes of ESD for the extended indications of purely differentiated lesions are comparable with those of surgical resection [15, 37]. However, ESD is not yet the global method of choice for ER techniques. The social acceptance of ESD is geographically diverse, and the technique is predominantly practiced in East Asia. ESD requires specialized skills to intuitively manipulate flexible endoscopes and needle knives with unique designs that result in longer operation times. As a result, ESD requires optimal training in selected relatively easy cases to gradually obtain a high level of skill that will permit the safe completion of the procedure for challenging cases such as Barrett's and colonic neoplasms, which are the main indications of ER in the West. In fact, the safety of ESD in Western countries that have a lower prevalence of early gastric cancers and lack the appropriate cases for training is not equivalent to the published data for ESD in Eastern countries [12, 38, 39]. It is difficult to establish the knowledge and skill bases for adequate preoperative assessment of the precise delineation of lesions. These basic attributes are mandatory to achieve a satisfactory outcome from ESD due to the absence of opportunities for screening endoscopies to detect asymptomatic, early cancers in Western countries. Other therapeutic options, including piecemeal resection and even surgical resection, should be considered if overwhelming challenges are encountered during ER.

Various novel, multi-degree-of-freedom therapeutic endoscopes have been developed to enable intuitive performance of complicated surgical procedures with the flexible endoscopic platform. Therapeutic scopes with water-jet capabilities and multi-bending portions are recognized as standard equipment for ESD. The triangulation platform is considered an eventual design of the therapeutic endoscope, which has dual mobile instrumental channels or articulated manipulators at the tip of an endoscope (Fig. 1.3) [40, 41]. These systems provide an operative environment more like laparoscopic surgery rather than ordinary endoscopic intervention. They have been tested with ESD for deflecting the diseased mucosa away from the dissection plane and horizontally swinging a needle knife parallel to the muscularis propria. Ho and colleagues have applied robotics to the triangulation platform and successfully introduced their original master–slave type endoscopic robot to gastric ESD in human patients [42, 43]. At present, all triangulation platforms are still too cumbersome in their current form and need to be miniaturized for use within a narrow GI lumen.

Fig. 1.3 A multi-tasking platform (EndoSAMURAI, Olympus Medical Systems). Reproduction of this image, obtained from Ikeda et al. [40], was permitted by Elsevier

Conclusions

ESD has greatly improved the resectability of early GI neoplasms by ER. The ESD procedure has rapidly increased in sophistication in tandem with instrument developments during the last decade, but there is still room for improvement. In order to truly benefit from the use of ESD, the advantage of en bloc resection should be balanced against the procedural risks. The endoscopists performing ESD must receive appropriate training, and the operative environment should be appropriate for not only the therapeutic procedure but also for preoperative diagnosis and periprocedural management. Recent technological advances, including robotics, may enable the concept of en bloc resection by ESD to be universally accepted in the near future as standard of care for patients with early gastrointestinal neoplastic lesions.

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Part II

Indications

2 Indications of ESD in the Upper Gastrointestinal Tract

Hang Lak Lee and Sang Yong Seol

Introduction

Early gastric cancer (EGC) is defined as a gastric cancer that is confined to the mucosa or submucosa of the stomach, irrespective of the presence of regional lymph node metastasis [1, 2]. Endoscopic submucosal dissection (ESD) is a novel endoscopic treatment that enables a clinician to resect early stage gastric cancer in an en bloc fashion [3]. Endoscopic resection is comparable to conventional surgery in many aspects, but it has the advantage of being less invasive and more economical. The absolute and expanded indications of ESD in the upper gastrointestinal tract are introduced in this chapter, and their usefulness, safety and limitations are discussed.

General Concepts for Application of ESD for EGC

Two main factors are considered to determine the application of ESD for each lesion by each operator (Fig. 2.1). The first is the likelihood of lymph node metastasis and the second is the technical resectability. The former has been determined by the large numbers of surgically resected cases in each organ before establishment of ESD and the latter may be determined by the applied technique, the expertise of the operator, the location of the lesion, and/or their characteristics. In terms of technical resectability, en bloc resection is more desirable than piecemeal resection for accurate assessment of the appropriateness of the therapy, because the depth of invasion and lymphovascular infiltration of cancer cells cannot be accurately assessed by piecemeal resection [4]. Almost all possible node-negative epithelial neoplasms can be resected en bloc by ESD, when they are treated by very experienced hands.

Absolute and Expanded Indications of ESD for EGC

Currently accepted indications for endoscopic resection of EGC include the resection of small intramucosal EGCs of intestinal histology type. The rationale for this recommendation is based on the knowledge that larger lesions or diffuse histology lesions are more likely to extend into the submucosal layer and thus have a higher risk of lymph node metastasis. In addition, en bloc resection of large lesions was not technically feasible until the ESD procedure was developed. Therefore, at present, the accepted indications for EMR according to the gastric cancer treatment

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N. Fukami (ed.), *Endoscopic Submucosal Dissection: Principles and Practice*,
DOI 10.1007/978-1-4939-2041-9_2, © Springer Science+Business Media New York 2015

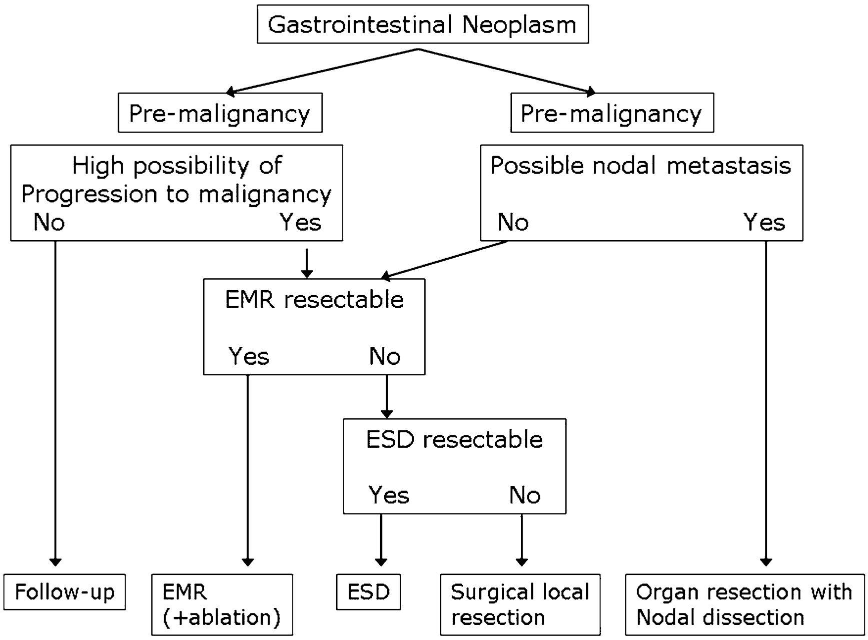

Fig. 2.1 Algorithm for endoscopic submucosal dissection of gastrointestinal neoplasms

Table 2.1 Indications for extension of EMR

Guideline criteria for EMR, Surgery

	Depth					
	M cancer			SM cancer		
	Ulcer (-)		Ulcer (+)	< SM 1		> SM 1
	< 20 mm	> 20mm	< 30 mm	> 30 mm	< 30 mm	Any size
Differentiated						
Undifferentiated						

guidelines published in 2001 by the Japanese Gastric Cancer Association are: (1) well-differentiated elevated cancers less than 2 cm in diameter and (2) small (<1 cm) depressed lesions without ulceration. Also, these lesions must be moderately or well-differentiated cancers that are confined to the mucosa and have no lymphatic or vascular involvement [5, 6]. However, it has been observed clinically that the accepted indications for EMR may be too strict, which leads to unnecessary surgery (Table 2.1) [7].

Further studies by Gotoda et al. have defined new criteria for expanding the indications for endoscopic treatment of gastric cancer. Endoscopic submucosal dissection was developed to dissect directly along the submucosal layer using specialized devices. Preliminary studies have been published on the advantages of ESD over conventional EMR for en bloc removal of larger or ulcerated EGC lesions. Thus, ESD allows for precise histological assessment of the resected specimens, possibly preventing residual disease and local recurrence. Gotoda et al. analyzed more than 5,000 EGC patients who underwent gastrectomy with meticulous D2 level node dissection; they provided important information on the risks of lymph node metastasis, wherein differentiated gastric cancers with no lymphovascular involvement, correlating with a nominal risk of lymph node metastasis, were defined [8].

Table 2.2 Indications for extension of ESD

Guideline for ESD: **Expanded indication,** **Consider surgery,** **Surgery**

	Depth					
	M cancer				SM cancer	
	Ulcer (-)		Ulcer (+)		< SM 1	> SM 1
	< 20 mm	> 20mm	< 30 mm	> 30 mm	< 30 mm	Any size
Differentiated						
Undifferentiated						

Thus, they proposed the expanded criteria for endoscopic resection: (1) mucosal cancer without ulceration, irrespective of tumor size; (2) mucosal cancer with an ulcer <3 cm in diameter; and (3) minute (<500 μm from the muscularis mucosa) submucosal invasive cancer <3 cm in size (Table 2.2). However, extending the indications for ESD remains controversial because the long-term outcomes of these procedures have not been fully documented.

Recent Evidence for Expanded Indications of ESD for EGC

Although the absolute indication is applicable only to mucosal cancer, there have been some studies about ESD for submucosal cancer. Of the 145 well-differentiated tumors that had invaded less than 500 μm into the submucosa and were smaller than 30 mm in diameter, none showed evidence of lymph node metastasis, provided that there was no lymphatic or venous invasion. Based on these findings, it was suggested that the criteria for EMR and ESD as local treatment for EGC should be extended [9–13].

According to a recent study of patients who had surgery for EGC at Seoul National University Bundang Hospital [14], of 132 patients with mucosal cancers, 129 met the extended indications for EMR or ESD while three (2.3 %) had lymph node metastasis. Of the 52 submucosal cancer cases that met the extended indications for EMR or ESD, two (4 %) had lymph node metastasis. Differentiated mucosal cancers without ulcer formation did not have lymph node metastasis, irrespective of size. These data suggest that a well-differentiated mucosal cancer of any size without ulceration may be considered as an extended indication for EMR or ESD. However, data from this study showed that 2.8 % of tumors meeting the extended criteria for EMR or ESD had positive lymph nodes, and the authors suggest that if EMR or ESD had been performed in these patients, it would not have been curative.

Regarding the expansion of indications to EGC with undifferentiated histology, the supporting data are continuously being reported. Ye and colleagues reported that EGC with undifferentiated histology has no lymph node involvement, provided that the cancer is smaller than 25 mm and is confined to the mucosa or upper third of the submucosa and has no lymphatic involvement [15]. A similar study for signet ring cell carcinoma was reported by Park et al. [16]; EGC with signet ring cell histology has a high risk for nodal and organ metastases, while smaller cancers of less than 25 mm that are confined to the SM2 layer and have no lymphovascular involvement demonstrated no lymph node involvement.

In another Korean study on the lymph node metastasis of poorly differentiated adenocarcinomas, a retrospective analysis was performed on 234 patients with poorly differentiated EGC who underwent radical gastrectomy with D2 lymph node dissection [17]. Of the 234 lesions with poorly differentiated EGC, half ($n = 116$) showed submucosal invasion in the resection specimen, and 25.9 % (30/116) of those were limited to the upper third (SM1). Of the lesions confined to the mucosa, lymph node metastasis was found in 3.4 % (4/118). With minor submucosal infiltration (SM1), the lymph node metastasis rate was non-existent (0/30). However, with SM2/3 invasion, the lymph node metastasis rate increased sharply to about 30 %. Therefore, poorly differentiated EGC confined to the mucosa or with minimal submucosal infiltration could be considered for curative ESD due to the low risk of lymph node metastasis. Another Korean study [18] focusing on endoscopic resection for undifferentiated-type cancer such as poorly differentiated adenocarcinoma and signet ring cell carcinoma showed interesting results. In this study, a total of 58 lesions with undifferentiated EGC (17 poorly differentiated; 41 signet ring cell) were treated by endoscopic resection. The en bloc and complete resection rates in poorly differentiated cases were 82.4 % and 58.8 %, whereas those in signet ring cell were 85.4 % and 70.7 %, respectively. Interestingly, all of the histologically incomplete resections in poorly differentiated cases were vertical cut end-positive, whereas 83.3 % of these resections in signet ring cell were lateral cut end-positive. The recurrence rate was 5.1 % in complete resection during the follow-up period. Therefore, the authors suggested that endoscopic resection may be a feasible local treatment for undifferentiated EGC if complete resection can be achieved. However, the indication for poorly differentiated cancers is still controversial. Further follow up periods and accumulation of a larger number of cases are still required to clarify this issue.

Yamaguchi et al. reported clinical outcomes of ESD according to indication criteria. A total of 589 EGC lesions were divided into the guideline group and the expanded group [6]. En bloc, complete, and curative resections were achieved in 98.6 % and 93.0 %, 95.1 % and 88.5 %, and 97.1 % and 91.1 % of the guideline and expanded criteria lesions, respectively; the differences between the two groups were significant for all types of resection. The expanded criteria lesions were at significantly higher risk for ESD-associated bleeding and perforation. Overall survival was adequate, irrespective of indication, and the disease-specific survival rates were 100 % in all groups.

Limitations of ESD

However, more aggressive cases have been encountered. Walter et al. reported one case [19] with early gastric cancer that was initially treated by ESD. Esophagogastroduodenoscopy showed a slightly elevated, centrally depressed lesion about 15 mm in diameter with a very small ulceration in the center (type IIa + IIc) and biopsies showed only focal high-grade intraepithelial neoplasia. The resected specimen showed a submucosal infiltration depth of greater than 500 μm. Therefore, the patient underwent gastrectomy. The postoperative stage was pT1 (sm3), pN0 (0/58), cM0, L0, V0, G2 (UICC stage Ia). Three months later, an ultrasound revealed a new mass in the liver, and biopsy showed a rapidly growing metastasis of the gastric adenocarcinoma. This case highlights the risk of affected lymph nodes in early gastric cancer and the consequent risk of metastasis, which increases with greater depth of infiltration into the submucosa.

Another obstacle in EMR and ESD is the presence of micrometastasis [20–24]. Even after curative surgical resection for EGC, the recurrence rate is about 1.7–3.4 %, which could be the result of micrometastasis. According to Cai and colleagues, tumor size, macroscopic type, accompanying ulcers, and depth of invasion are strongly associated with micrometastasis in lymph nodes. Therefore, tumors with suspected submucosal invasion, large size, accompanying ulcers, and undifferentiated histology may have a risk of recurrence owing to micrometastasis, which may indicate the inappropriateness of EMR or ESD.

One more problem should be solved as follows: (1) We cannot be aware of the presence of ulcers before ESD and, as a result, it is very difficult to resect the lesion. We also have to pay attention to the fact that there are some differences in the definition of ulceration among physicians. (2) The way lesion size is measured is also somewhat different among institutions. Therefore, a uniform, standard way for measuring lesion size may become necessary in the future.

Long-Term Follow-Up Data

Long-term follow-up data are needed for the clinical application of the expanded indication. One Japanese study [25] from the National Cancer Center Hospital, involving a total of 1,955 EGC patients enrolled from January 1999 to December 2005, showed that there were no significant differences in the overall 5-year survival rates of the curative resection group, as defined by the expanded criteria, and the non-curative resection group after additional surgery. These data suggest that ESD using the expanded criteria can show excellent long-term outcomes.

Indication of ESD for NETs and GISTs

Neuroendocrine tumors (NETs) can show a broad range of clinical behaviors. In general, NETs are limited to the mucosa or submucosa and less than 11–20 mm in size, demonstrating a low frequency of lymph node and distant metastasis, and thus can be managed with local excision such as ESD or EMR. However, complete histological resection may not always be easy to achieve by using EMR because most gastrointestinal NETs are not confined to the mucosa, but rather, invade the submucosa, which results in frequent involvement of the resection margin. Therefore, ESD must be used for gastrointestinal neuroendocrine tumors. One recent study showed that complete resection was performed in 28 stomach NETs among a total of 29 lesions, and all of them were confined to the submucosa [26].

Gastrointestinal stromal tumors (GISTs) can arise at any location in the gastrointestinal tract. With the rapid advances in endoscopic skill and the development of minimally invasive technologies, there are more choices for treatment of GISTs. Davila et al. first reported endoscopic resection of small superficial GISTs in 2003. According to previous studies, it seems that endoscopic resection is technically feasible and effective for small gastric GISTs. However, with the progress of ESD techniques, ESD now appears to be an effective treatment for large-sized GISTs in both the esophagus and stomach. Long-term follow-up data about the recurrence or metastasis is required, however.

Indication of ESD in Esophagus and Duodenum

According to the guidelines of the Japanese Esophageal Society for the diagnosis and treatment of esophageal squamous cell carcinoma, endoscopic management of esophageal cancer is principally indicated based on 2 factors: low likelihood of lymph node metastasis and technical resectability of the tumor [27]. Some studies have indicated that high-grade intraepithelial neoplasia, including non-invasive squamous cell carcinoma and intramucosal invasive squamous cell carcinoma limited to the lamina propria without vessel infiltration, have no lymph node metastasis [28, 29]. The location and characteristics of the lesion, and the experiences of the endoscopists, determine the technical resectability.

Superficial duodenal cancers without lymph node metastasis can be cured by endoscopic resection. In 1992, endoscopic mucosal resection of duodenal neoplasia was first described. Technically, duodenal ESD is considered more difficult. The proper muscle layer of the duodenum is very thin and soft. It is even thinner than in the esophagus and colorectum. Therefore, the duodenal wall is more prone to perforation by ESD. Patient selection for ESD in the duodenum should be made cautiously, with consideration of all difficulties and risks. Although there have not been any large long-term follow up studies about duodenal cancers, the indication criteria for gastric ESD can also apply to duodenal lesions. Because surgical resection procedures for duodenal lesions are complicated and invasive, duodenal ESD can be beneficial.

For further discussion of the details regarding indication and technique for ESD in the upper GI tract, please see Chaps. 10, 11, and 13.

Conclusions and Future Prospects

ESD makes it possible to perform complete resection of lesions larger than 20 mm, as well as those with ulceration, regardless of location. There is much clinical data suggesting that ESD may be adequate for both the standard guidelines and the expanded criteria lesions. However, ESD requires highly skilled endoscopists, and a suitable training program is required for permeation of this technique. In the future, long-term follow-up data, newer technology, and more highly developed techniques will be needed to treat EGC according to the expanded indications.

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