

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.

Hisao Tajiri

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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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Overview

1

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
LNМ	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 (LNМ) 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.

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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Indication for Endoscopic Resection of Early GI Cancers: Esophagus

2

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].

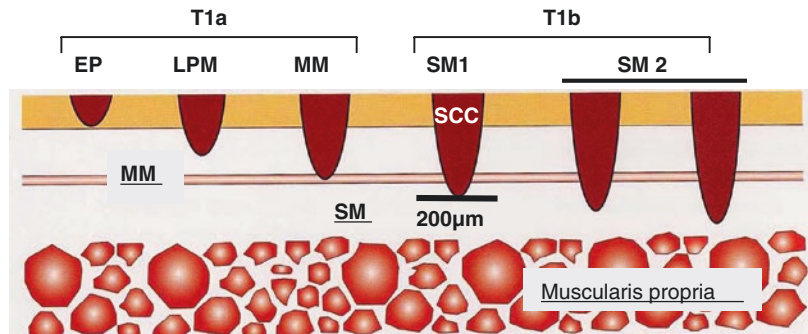
Understanding of indication for endoscopic resection is very important because incorrect estimation of the indication will result in a non-curative resection that delays additional treatment or may increase the risk for local or metastatic recurrence.

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 ($\leq 3.3\%$) is an absolute indication. The invasion depths of muscularis mucosa (T1a-MM) and micro-submucosal invasion of $\leq 200 \mu\text{m}$ (T1b-SM1) are suggested

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



Superficial esophageal cancer: the invasion depth confined to the submucosa regardless of LN metastasis

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 <i>in situ</i> ≥ 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)	Investigative
	SM2	22~61	

EP, Carcinoma in situ (Tis) includes high-grade intraepithelial neoplasia (HGIN), LPM, Tumor invades lamina propria mucosae, 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 recom-

mended 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 stricture 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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