Mini-Review

Endoscopic Approach for Superficial Colorectal Neoplasms

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Key Words

Early colorectal cancer · Endoscopic mucosal resection · Endoscopic submucosal dissection · Laterally spreading tumor

Abstract

Background: Colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females, with an estimated 1.4 million cases and 693,900 deaths in 2012. Colonoscopy is the cornerstone for the detection and prevention of CRC. In addition, endoscopic treatment for CRC at an early stage can effectively improve patients' quality of life and cure rate. **Summary:** This review focuses on endoscopic approaches, including white light endoscopy, chromoendoscopy, magnifying endoscopy and therapeutic endoscopy, for the evaluation and treatment of superficial colorectal neoplasms. **Key Message:** Understanding the preoperative evaluation, indications and techniques of endoscopic mucosal resection/endoscopic submucosal dissection as well as postoperative surveillance for superficial colorectal neoplasms is critical for providing appropriate management to the patients. **Practical Implications:** Endoscopic therapy, a method preserving organ function and improving quality of life, is a widely applied microinvasive treatment for superficial colorectal neoplasms. This review describes the basics and developments of endoscopic approaches and may facilitate daily practice for superficial colorectal neoplasms.

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Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide [1]. Colonoscopy is a widely accepted method for detecting and treating CRC at an early stage to decrease CRC incidence and mortality. Presently, superficial colorectal neoplasms, including

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precancerous lesions and early cancer, can be detected and evaluated by white light endoscopy, chromoendoscopy and magnifying endoscopy, and be resected by endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), which are minimally invasive and have become the preferred choices. In this review, the basic and progressive knowledge, including the risks of lymph node metastasis, preoperative evaluation methods and therapeutic techniques for superficial colorectal neoplasms, are summarized.

The Risks of Lymph Node Metastasis

Endoscopic resection requires lesions with a limited risk of lymph node metastasis. Accumulating evidence has demonstrated that tumor size, invasion depth, lymphovascular invasion, tumor budding, and histological tumor grade are associated with lymph node metastasis. Although those risk factors are related to lymph node metastasis, only a few factors can be predicted currently before resection.

Depth of Invasion

Tumors limited to the mucosal layer have a negligible risk of lymph node metastasis [2]. Presently, at least two classification systems exist to predict lymph node metastasis. The Kikuchi classification system is used for non-polypoid lesions and divides the submucosa into three layers: sm1 = the upper third of the submucosa, sm2 = the middle third of the submucosa, and sm3 = the lower third of the submucosa (fig. 1) [3]. The frequency of lymph node metastasis for sm1 and sm2 has been reported to be 2 and 8% [4], and the risk of lymph node metastasis for sm3 has been described to be 12–25% [5].

Haggitt's classification is applicable in pedunculated polypoid lesions and defines the depth of invasion according to the following criteria: level 1 = carcinoma invading through the muscularis mucosae but limited to the head of the polyp, level 2 = carcinoma invading to the level of the neck (the junction of the head and stalk), level 3 = carcinoma invading any part of the stalk, and level 4 = carcinoma invading into the submucosa of the bowel wall below the level of the stalk but above the muscularis propria (fig. 2) [3]. Many studies have shown that the ratio of nodal metastasis is <1% for polyps with a Haggitt level 1, 2 or 3 [6, 7]. A recent retrospective multicenter study reported that the frequency of lymph node metastasis was 0.0% when tumor cell infiltration was limited to the head of the polyp, while the rate of lymph node metastasis increased to 6.2% once the tumor cells extended into the neck of the polyp [8]. In addition, Ueno et al. [9] set another standard to measured invasion and found that the lymph node metastatic potential was 2.5 vs. 18.2% when submucosal invasion width was less or more than 4,000 μm , and 3.9 vs. 17.1% when submucosal invasion depth was less or more than 2,000 μm .

Tumor Size/Macroscopic Morphology

Tumors with larger size have a higher risk of submucosal invasion. The frequency of submucosal invasion is <1% when the lesion size is <1.0 cm. However, the rate of submucosal invasion reaches 30% when the diameter is >2.0 cm in polypoid lesions (type 0-Ip or 0-Is) [10]. Laterally spreading tumors (LST) are classified into granular type (LST-G) and non-granular type (LST-NG). Yamada et al. [11] reported that submucosal invasion was detected in 159 of 408 LST-NG cases (39%) and that in 54% of those 159 cases invasion was deep ($\geq 1,000 \mu\text{m}$). The presence of a submucosal mass-like elevation, depression, and invasive pit pattern were risk factors for deep submucosal invasion, while submucosal invasion was detected in 80 of 414 LST-G cases (19%), 79% of those 80 cases showing deep invasion. Risk factors for deep submucosal invasion were the presence of a large nodule, depression, and

Fig. 1. Kikuchi levels of invasion in sessile (non-polypoid) submucosal invasive cancers (pT1 adenocarcinomas).

Fig. 2. Haggitt levels of invasion in pedunculated (polypoid) submucosal invasive cancers (pT1 adenocarcinomas).

invasive pit pattern [11]. However, Uraoka et al. [12] revealed that the possibility of submucosal invasion was about 14% in LST-NG lesions and that the existence of sclerous wall change, invasive pattern, and larger tumor size (>20 mm) were independent risk factors. In addition, LST-G lesions with a low rate (7%) of submucosal invasion are generally observed below the largest nodule or depression, which can be used to predict submucosal invasion before endoscopic treatment [12].

Preoperative Evaluation of Lesions

Conventional Endoscopy with White Light Imaging

Tumor invasion depth was related to the macromorphology of the lesion, such as tumor size, loss of lobulation, excavation, stalk swelling, demarcated depressed area, fullness and fold convergence. Different endoscopic factors have been assessed for each type: ‘stalk swelling’ for only the pedunculated type, ‘loss of lobulation’ and ‘excavation’ for the pedunculated and sessile types, ‘fullness’ and ‘fold convergence’ for the superficial type, and ‘size’ and ‘demarcated depressed area’ for all three types. A retrospective study showed that the overall accuracy for differentiating intramucosal or slight submucosal invasion (sm1 invasion) from deep submucosal invasion (sm2 invasion or deeper) is 84.2% in the pedunculated type, 88.6% in the sessile type and 92.5% in the superficial type [13].

Magnifying Chromoendoscopy

High-magnification observation with indigo carmine dye can be used to characterize lesions based on pit patterns (types I–V, Kudo classification). Presently, the type V pit pattern is subclassified into type V_I and type V_N . Type V_I is an index of adenoma with severe dysplasia or sm1 carcinoma, while type V_N is an indicator of invasion more than sm1 [14]. To date, several trials have demonstrated that Kudo’s pit pattern classification is a highly accurate

diagnostic method in differentiating neoplastic from non-neoplastic lesions. Recently, a meta-analysis showed that pooled sensitivity is 89.0% and specificity 85.7% for the diagnosis of colorectal neoplastic polyps [15].

Narrow-Band Imaging

Narrow-band imaging is an optical imaging technology which can enhance real-time visualization of the mucosal surface structure and vascular pattern and is able to determine whether the lesion is tumorous or non-tumorous, as well as what is its invasion depth. Sano classified the capillary pattern (CP) as type I, II, IIIA and IIIB on the basis of its visibility, caliber variation, tortuosity, and stoppage. CP type IIIB is correlated with deep submucosal invasive carcinomas [14]. Ikematsu et al. [16] reported that the sensitivity and specificity of CP types IIIA and IIIB in differentiating intramucosal or slight submucosal invasion from deep submucosal invasion is 84.8 and 88.7%, respectively. Moreover, the Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification has been recently developed and validated to allow endoscopic prediction of colorectal polyp histology and differentiation between hyperplastic (type 1) and adenomatous (type 2) colorectal polyps, the overall accuracy being 75% and the overall negative predictive value 85% [17]. A limitation of the NICE classification is that it does not specifically incorporate sessile serrated adenomas into the classification.

Endoscopic Ultrasonography

Endoscopic ultrasonography can be used to stage rectal epithelial lesions. A previous study showed that endoscopic ultrasonography had higher diagnostic accuracy than pit patterns based on magnifying endoscopy in T staging [18], whereas another study found that the diagnostic accuracy of those methods was similar [19]. Recently, Mukae et al. [20] found that the sensitivity and specificity of endoscopic ultrasonography in estimating the deep invasion depth of early CRC was 90 and 87%, respectively.

Non-Lifting Sign

The non-lifting sign, first reported by Uno and Munakata [21], is useful to predict the depth of carcinoma invasion and is widely used in clinical practice. One multicenter study observed that the sensitivity and specificity of non-lifting sign versus conventional colonoscopy are 61.5 vs. 84.6% and 98.4 vs. 98.8%, respectively [22]. Thus, the non-lifting sign should not be accepted to assess invasion depth for its lower sensitivity and accuracy. However, this sign can be used to predict technical difficulties. In addition, superficial colorectal tumors exhibiting a positive non-lifting sign may result from peristaltic motion or fibrosis caused by biopsy, so once the lesion is diagnosed as superficial carcinoma, biopsy should be avoided.

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy has emerged as a valuable tool for gastrointestinal endoscopic imaging since its introduction in 2004. As an *in vivo* virtual biopsy technique, confocal laser endomicroscopy allows real-time histological diagnosis free from conventional biopsy. It has been proven to have high sensitivity and specificity in the diagnosis of colorectal neoplasia. Xie et al. [23] reported that the sensitivity and specificity of real-time confocal laser endomicroscopy in identifying colonic adenomas were 93.9 and 95.9%, compared with histological results. A recent meta-analysis including 11 studies revealed that confocal laser endomicroscopy has a high diagnostic accuracy for neoplastic and non-neoplastic colonic lesions [24].

Table 1. Indications for colorectal endoscopic treatment [51, 52]

<i>EMR</i>	
1	5- to 20-mm flat lesions
2	Sessile lesions (Is, >10 mm) suspected to be villous adenoma or sessile serrated adenoma/polyp
3	Suspicious high-grade intraepithelial neoplasia or slight submucosal invasion lesions (≤20 mm) expected to be able to complete resection by EMR
<i>EMPR</i>	
1	20- to 30-mm LST-G-type lesions
2	Large LST lesions (>30 mm, hospital without ESD technology)
<i>ESD</i>	
1	Large (>20 mm) lesion amenable to endoscopic treatment in which en bloc EMR resection is difficult. <ul style="list-style-type: none"> – LST-NG >20 mm, particularly LST-NG (PD) – LST-G >30 mm – Lesions showing a VI-type pit pattern – Carcinoma with shallow T1 (submucosal) 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

Technical Aspects of Endoscopic Approaches for Early CRC

Indications and Contraindications for Colorectal Endoscopic Treatment

Endoscopic resection of superficial tumor requires limited risk of lymph node metastasis and feasibility of en bloc resection. Indications for colorectal endoscopic treatment are presented in table 1, contraindications in table 2.

Bowel Preparation

Excellent bowel preparation is critical for the detection of precancerous lesions or early CRC. Besides, it is a key element in avoiding adverse events such as bacterial peritonitis following iatrogenic colonic perforation. In our hospital, patients typically receive split use of 2 liters of polyethylene glycol, the first time on the night before the procedure, the second in the morning prior to EMR/ESD.

Carbon Dioxide Insufflation

The efficacy of carbon dioxide insufflation during endoscopic procedures has been emphasized in recent years. It is reported that patient discomfort is considerably lower in the carbon dioxide group, probably because of a more rapid absorption of carbon dioxide than under conventional air insufflation. Increasing evidence revealed that carbon dioxide insufflation reduces pain to the patient and the risk of pneumoperitoneum in case of perforation as well as the occurrence of abdominal complaints [26].

Submucosal Injection

The maintenance of adequate submucosal elevation by injection is a key component influencing EMR/ESD procedures. An optimal injection solution should (1) achieve and

Table 2. Contraindications for colorectal endoscopic treatment [52]

Absolute contraindications

- 1 Lesions with deep invasion, lymph node metastasis or distant metastasis
- 2 Grade III or above by American Society of Anesthesiologists classification and cannot tolerate endoscopic surgery
- 3 Unable to undergo bowel preparation (with intestinal obstruction)
- 4 Other contraindications for colonoscopy

Relative contraindications

- 1 Lesions with technical difficulty and high risk of perforation (such as intestinal circumferential lesions, involving multiple folds)
- 2 Familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer
- 3 With advanced cancer in another part of the intestine and can be one-time surgical resection
- 4 With other organ malignancies and short life expectancy
- 5 Tumor location not suitable for endoscopic treatment

Elective endoscopic treatment

- 1 With blood diseases, coagulation disorders and patients taking anticoagulants, coagulation having not been corrected
- 2 Acute inflammation of the intestinal tract, such as active ulcerative colitis
- 3 High fever, weakness, severe abdominal pain, low blood pressure
- 4 Poor bowel preparation or the patient does not cooperate

maintain the necessary submucosal lifting height and duration [27], (2) not influence the histological evaluation, and (3) be easily prepared with low cost and no toxicity [28]. Currently, various submucosal injection solutions have been developed, including normal saline, fibrinogen mixture, dextrose, glycerol, sodium hyaluronic acid, succinylated gelatin, hydroxyethyl starch, and mesna. One meta-analysis showed that, compared with normal saline, other submucosal injection solutions have a significant increase in terms of en bloc resection rate (82 vs. 77%) and complete resection rate (89 vs. 79%). However, there was no significant difference in the incidence of total complications [29].

Techniques of EMR/ESD

EMR is broadly divided into two basic types: non-suction method (submucosal injection-resection) and suction method (transparent cap method and ligation method). In colorectal EMR, the submucosal injection-resection technique is often used, while the transparent cap or ligation technique is rarely used for smaller tumors and associated with the risk of perforation. The injection should elevate the lesion into the lumen and toward the colonoscopy to improve access. Excessive injection should be avoided because this may hinder adequate visualization and create excessive tension within the cushion, which makes snare capture of adequate tissue challenging.

The endoscopic piecemeal mucosal resection (EPMR) technique can be applied for large flat lesions (>2 cm), dividing the lesion into several parts and removing it in several steps. When using EPMR for LST-G (mixed) type lesions, the large nodule (≥ 1 cm) should be resected en bloc first, then the remaining lesions should be removed. During this process, the number of piecemeal specimens must be controlled, because it is difficult to splice tissue specimens for accurate pathological assessment. Besides, a higher number of resected specimens might be associated with a higher risk of local residues/recurrence, so careful colonoscopic surveillance is needed after EPMR [30].

ESD enables direct submucosal dissection, so that early-stage gastrointestinal tumors can be removed with a high en bloc resection rate, and is not limited by lesion size or location. ESD also enables detailed histological evaluation of the specimen and accurate judgment of resection margins. Procedures of colorectal ESD are primarily performed using ESD knives, including a bipolar needle knife, Flex/Dual knife, Hook knife, IT knife, Flush knife and SB knife. The selection of ESD knives is depended on the operator's experience and the type of colorectal neoplasia. After submucosal injection with glycerol and/or sodium hyaluronate, a circumferential incision is made using the ESD knife. Both partial circumferential incision and subsequent submucosal dissection are performed alternately.

Colorectal ESD is technically difficult because of the anatomical features of the colon such as the thin walls, folds and flexures, and colonic peristalsis. This technical difficulty is likely to be associated with complications, especially perforation. Previous studies used long procedure times (more than 120 or 150 min); perforation and piecemeal resection mark the technical difficulty of colorectal ESD, and it was found that technical difficulty was associated with factors including mobility of tumor location (mobile: sigmoid or transverse colon; fixed: rectum, descending colon, ascending colon, or cecum), lesions at a fold or flexure, huge tumor (≥ 5 or ≥ 4 cm), tumors associated with scarring or local recurrence (presence of severe fibrosis) [31–33]. In recent years, in order to obtain adequate tissue tension and clear visibility of the tissue, reduce operating time and improve security, many ESD-assisted methods have been developed, such as the clip-with-line method, the sinker-assisted method, the internal traction method, the outer route method, the double-scope method, the external forceps method and the endoscopic surgical platform [34].

Complications

The complications associated with EMR/ESD procedures, including perforation, bleeding and post-polypectomy electrocoagulation syndrome, are listed in table 3.

Histological Assessment

Curability is evaluated based on the tumor margin of the resected specimen and risk factors for lymph node/distant metastasis. Mucosal (Tis) carcinomas can be radically cured by endoscopic local resection without risk of metastasis. For T1 (submucosal) carcinomas, additional surgery should be carried out in cases with positive vertical tumor margin, submucosal invasion depth $>1,000$ μm , vascular or lymphatic invasion, poorly differentiated or undifferentiated adenocarcinoma, signet ring cell carcinoma or mucinous carcinoma, or tumor budding grade 2 or 3 in the deepest part of infiltration [35, 36]. Application of immunohistochemistry for D2-40 and desmin is informative to accurately detect vascular invasion and depth of submucosal invasion. Two large-scale retrospective multi-center cohort studies have shown that for patients with submucosal invasive CRC without the above risk factors, the 5-year overall survival rates were similar whether they were treated by endoscopic resection alone or underwent endoscopic resection with subsequent surgery [37, 38].

Postoperative Follow-Up

En Bloc Resection Rates of Colorectal EMR/ESD

En bloc resection is desirable as an endoscopic treatment for early CRC. The en bloc resection rate of colorectal EMR is 31.0–66.3%, the complete histological resection rate being

Table 3. Complications of colorectal endoscopic treatment

Complications	Incidence rate, %	Risk factors	Management methods
Perforation [42, 46, 53, 54]	EMR: <1.5 ESD: 0.58–20.4	tumor size, large LST lesions, presence of fibrosis	titanium clip, loop clip, over-the-scope clip
Delayed perforation [55–57]	EMR: 1.4–1.7 ESD: 1.5–2.8	excessive coagulation in the muscularis propria	emergency surgery
Bleeding [43, 58–62]	EMR: 1.0–18.0 ESD: 0–15.6	right-sided lesions, older patient, large tumor size, 0–IIa+ Is lesions, lesions containing villous component, recent aspirin or anticoagulation use, inadequate experience of operators	injection of epinephrine, argon plasma coagulation, coagulation graspers, endoscopic application of clips, snare tip soft coagulation, contact coagulation with the tip of a knife, coagulation with hemostatic forceps
Delayed bleeding [47, 58, 59, 61, 63–65]	EMR: 0.2–7.2 ESD: 0–12.5	location of lesions in the rectum/ cecum, significant bleeding during the process	postoperative blood pressure control, prophylactic clip
Post-polypectomy electrocoagulation syndrome [66–68]	1–8	large tumor size, hypertension, tumor site other than rectosigmoid, non-polypoid configuration of the lesion	broad-spectrum antibiotics (intravenous), fasting until the symptoms disappear, emergency surgery

45.0% [39, 40]. However, the en bloc resection rate of colorectal ESD is significantly higher than that of EMR, which can reach 64–7% [41]. The complete R0 resection rates of colorectal ESD also have a good performance, which can reach up to 53–91% [41].

Local Residual/Recurrence

Residual lesions are among the ‘seeds’ of interval cancer, and colonoscopy surveillance is desirable for early detection of local recurrence. The recurrence rate of conventional colorectal EMR has been described to be 0.8–7.2%, and the ratio is higher for larger lesions [42–45]. The local residual/recurrence rate for difficult cases can even be up to 20.4–27.0% [46, 47]. A recent meta-analysis reported that the mean risk of recurrence after EMR of non-pedunculated colorectal lesions is 15%, occurring in 3% of en bloc resections and 20% of piecemeal resections [39]. In addition, more than 5 piecemeal specimens is an independent risk factor for local recurrence after multiple EPMP [30]. Compared with the EMR group, the local recurrence rate is lower in the ESD group, accounting for 0.1–7.0% [30, 41]. A multi-center prospective study showed that piecemeal resection is the only significant factor associated with local recurrence in ESD [48].

Surveillance Strategy after Endoscopic Treatment

Surveillance improves the patient’s prognosis by early detection and treatment of residual and recurrent lesions. Presently, it is recommended to perform a colonoscopy 6 and 12 months after definitive endoscopic resection of an early-stage carcinoma, and then colonoscopy surveillance yearly. A recent meta-analysis suggested that a follow-up colonoscopy

should be done 6 months after colorectal EPMP [39]. Recommendations made by other studies show that 4 and 12 months are appropriate intervals for first and second surveillance colonoscopy [49]. Generally, for piecemeal resection cases, the colonoscopy should be performed between 3 and 6 months, with regard to the risk factors of recurrence such as size, location, and histological type of the lesion [50].

Future Directions

With the rapid development of endoscopic technology, endoscopic diagnosis and therapy for superficial neoplasm has been established in the last years. However, it is still a challenge to avoid missing lesions during colonoscopy, or to exclude lesions with indications of high risk of lymph node metastasis, including lymphovascular involvement and poor differentiation, before resection. Besides, full-thickness resection may be applied for submucosal cancer without lymph node metastasis. In the future, accurate endoscopic diagnosis of lymph node metastasis will be the cornerstone of lesion selection for therapy and permit real-time stratification of lesions and allocation to appropriate therapy. Besides, rapid advancements in devices and techniques, such as natural orifice transluminal endoscopic surgery and robotic endoscopy (MASTER), promise to facilitate safer procedures and to expand indications. Thus, colorectal endoscopic techniques will help us to achieve the goal of minimally invasive treatment for early CRC patients.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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