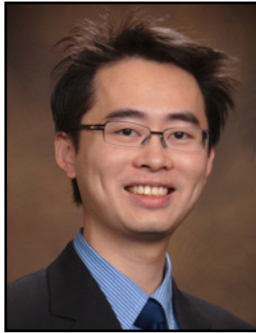


Melvin Schapiro, M.D., Series Editor

# Endoscopic Management of Colorectal Cancer



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**Colorectal cancer (CRC) is one of the most commonly diagnosed cancers in the United States. Until recently, colon cancer found on endoscopic examination has been treated entirely with surgical resection. With the advancement of new endoscopic techniques including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), early CRC that presents with favorable features can be initially removed endoscopically without surgery. In this review we will discuss the expanding role of endoscopic resection in the treatment of colon cancer.**

## INTRODUCTION

**C**olorectal cancer (CRC) is the fourth most commonly diagnosed cancer with an estimated incidence of 132,700 cases in the United States in 2015.<sup>1</sup> Most malignant neoplasms of the colon and rectum arise from non-invasive adenomatous polyps. Malignant colorectal polyps are defined according to the Vienna classification by the presence of cancer cells invading through the lamina propria into the underlying mucosa or submucosa (pT1).<sup>2</sup> With recent development and refinement of endoscopic techniques, endoscopic resection has played an increased role in the resection of early colon cancer. In particular, T1 colorectal cancer with favorable features can be removed by endoscopic techniques.

In this review, we will address various topics including initial endoscopic assessment of the colon

lesion, histology of invasion of depth, risk factors associated with invasive colorectal cancer, endoscopic techniques to remove early colon cancer, and surgical treatment of early colon cancer.

## Endoscopic Assessment

Given the potential for curative endoscopic resection, it is increasingly important to identify which lesions are non-invasive, superficially invasive, and deeply invasive. The depth of invasion guides management as non-invasive lesions can be treated by simple endoscopic mucosal resection, the superficially invasive lesions require en bloc endoscopic resection, and the deeply invasive lesions require surgery. Endoscopic inspection of the shape and surface patterns has now been well validated means to make accurate classification of invasion depth.

Colonic adenomas are classified as either polypoid or nonpolypoid type. Based on the Paris classification,

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polypoid lesions include pedunculated (0-Ip) and sessile-shaped (0-Is) lesions. Nonpolypoid lesions may be subdivided into superficially elevated (0-IIa), flat (0-IIb), depressed (0-IIc), and excavated or ulcerated lesions (0-III). Flat and particularly depressed polyps are more likely to harbor high grade dysplasia and invasive cancer.<sup>3</sup> Using the Paris classification, 0-Ip and 0-Is can be removed by snare polypectomy. Nonpolypoid lesion such as 0-IIa and 0-IIb can be removed EMR en bloc or piecemeal. Depressed lesions categorized as 0-IIc, often signifying early cancer, can also be removed with ESD or en bloc EMR. Lastly, ulcerated lesions represent deep carcinoma and require surgical resection.

Superficial elevated lesions 20 mm or larger are termed lateral spreading tumors (LSTs). LSTs can be divided into granular LSTs, nongranular LSTs, or mixed-type based on surface appearance. Understanding the morphology allows the endoscopist to select the proper technique in removing the colon polyp. Nongranular LSTs are at highest risk for harboring invasive cancer.

Changes in pit patterns seen on the colon surface can aid the endoscopist in determining the degree of neoplasia and depth of invasion. Pit pattern are classically seen with the use of dye spray and are classified by the Kudo system. Type IIIs (small tubular or round pit pattern that is smaller than normal pit) and Type IIIL (tubular or round pit that is larger than the normal pit) are usually associated with tubular adenoma. Type IV (dendritic or gyrus-like pit) is associated with tubulovillous histology. Type V<sub>I</sub> (irregular arrangement) or Type V<sub>N</sub> (loss or decrease of pits) is associated with intramucosal or invasive malignancy.<sup>4</sup>

Surface pit patterns have been incorporated into Narrow Band Imaging International Classification for Endoscopy (NICE) classification systems to aid in management of colonic neoplasia.<sup>5</sup> There are three subtypes of the NICE classification, and it is organized based on color, vessel, and surface pattern. Type 1, 2, and 3a can be treated endoscopically. However, Type 3b indicates likely deep submucosal invasive cancer and needs surgical operation for removal.<sup>6</sup>

### Histologic Invasion Depth

Invasion depth of colorectal carcinoma predicts lymph node metastasis, and pedunculated lesions (Paris 0-Ip) having a lower risk for lymphatic spread than sessile or flat lesions (Paris 0-Is and 0-II). Two models were devised to classify colorectal cancer invasion depth:

Haggitt classification for pedunculated lesions and Kikuchi classification for sessile or flat lesions.

Haggitt and colleagues stratified the invasion depth into levels 0-4, with carcinoma confined to mucosa (0), polyp head (1), neck (2), stalk (3), and invasion into submucosa of the underlying colonic wall (4).<sup>7,8</sup> For invasion depth levels 1, 2, and 3, there is absent lymph node metastases and local cancer recurrence. For patients with Haggitt level 4 invasion, 27% of cases harbored lymph node metastasis.<sup>9,10</sup>

The other model devised by Kikuchi and colleagues assess the depth of submucosal cancer invasion by dividing the submucosa into thirds (SM1, SM2 and SM3). Colon cancer confined to upper third or SM1 has no risk of lymph node metastasis, but deeper invasion into the submucosa can increase to the risk of lymph node metastasis to up to 25%. Currently, colon cancer confined to the upper third of submucosa layer (SM1) is amendable to endoscopic resection, but deeper invasion into submucosa requires surgical resection.

### Risk Factors of Invasive Colorectal Cancer

Different risk factors for invasive colorectal cancer and lymph node metastasis were introduced by different studies. Invasion into the deepest third of the submucosa (SM3) which likely correlates with a submucosal invasion  $\geq 1$ mm, presence of lymphovascular invasion, location in the lower third of the rectum, poor differentiation, tumor budding, and incomplete polypectomy are independently associated with increased risk of lymph node metastasis and residual cancer and warrant a radical resection.<sup>11-15</sup>

### Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

EMR and ESD are current mainstay treatments for resection of neoplasia. Low-risk colorectal cancers harbor the following features: well to moderate differentiated,  $\geq 2$ mm cancer-free margin and Haggitt invasion level 1-3. These are unlikely to develop recurrence or metastatic disease when amendable for en-bloc EMR with a disease-free and overall survival of 90-96% and 89-96%, respectively.<sup>16-20</sup> On the other hand, Kikuchi SM3 and Haggitt 4 invasion level, submucosal invasion  $\geq 1000\mu\text{m}$ , positive excision margin, lymphatic or venous invasion, and poor differentiation predict residual tumor and lymph node metastasis, warranting radical resection.<sup>20-23</sup>

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ESD is a well-established technique that is mostly performed in Asia although increasingly accepted in the West. In direct comparison with EMR, ESD has a lower neoplasia recurrence rate (14.5% vs. 2.1%).<sup>24</sup> and higher en-bloc resection rate. However, this comes at the costs of a higher perforation (0.8% vs. 1.6-4.9%) and bleeding rate (2% vs. 1.5-2.2%).<sup>25,26</sup> Recent literature recommends colorectal ESD for neoplasia when en-bloc resection is difficult to achieve (mostly >20mm), for non-granular LST, Kudo V pit pattern, non-lifting neoplasia and invasive submucosal cancer  $\geq 1000\mu\text{m}$  infiltration.<sup>24</sup>

### Endoscopic Mucosal Resection

Initially described in 1973, EMR is a technique used for resection of lesions confined to the mucosa or submucosa of the colon. Lesions limited to the mucosa and superficial layers of submucosa are more suitable for EMR.<sup>27</sup> Adenoma of the colon represents one of the most important premalignant lesions of the gastrointestinal tract. Compared to regular snare polypectomy, EMR has a higher successful complete resection rate for large colon polyps (> 2cm).<sup>28</sup> On the other hand, lesions that are greater than 2 cm may require piecemeal mucosal resection.

One of the important features of EMR involves submucosal fluid injection. Typically, a sclerotherapy needle is used to inject the fluid into the submucosa. This provides a cushion to protect the deeper layers of the colonic wall to prevent perforation and bleeding. Common agents used for lifting the base of the lesion include normal saline, hydroxypropyl methylcellulose, glycerol, 50% dextrose, hyaluronic acid, and hypertonic saline. Compared to normal saline, hypertonic solution seems to provide better and longer-lasting elevation. Methylene blue and indigo carmine are used to confirm if the resection is in the correct plane. Approximately, 3 mL to 10 mL of solution is needed to achieve adequate separation from the submucosa, and this reduces the risk of thermal and mechanical injury of the deeper layers. After submucosal injection, a snare is placed on top of the protruding lesion, and the lesion is resected using electrocautery with high-frequency current.

Approximately 5% of cases of large colorectal polyps after EMR can result in intraoperative/immediate bleeding or delayed bleeding (hours to weeks after the procedure).<sup>29-31</sup> Most delayed bleeding occurs within two weeks after EMR. Predictors associated with risk

for post-polypectomy bleeding including polyp size greater than 1 cm to 2 cm, flat or laterally spreading lesions, pedunculated polyp with thick stalk, proximal colon lesions, resection technique, and coagulation status.<sup>32</sup> Immediate bleeding can be controlled by several methods including dilute epinephrine, endoscopic clipping, and bipolar coagulation probe.

In the setting of delayed bleeding, patients can be managed conservatively if hematochezia ceases at the time of admission because rebleeding from the EMR site is uncommon. If there is no sign of active bleeding or gross blood noted during bowel preparation, colonoscopy can be deferred unless patient requires re-initiation of anticoagulation agent. Otherwise, for patients with ongoing hematochezia or other signs of GI bleeding, urgent colonoscopy should be performed.

A recent systemic review and meta-analysis indicates that the general recurrence rate of colorectal lesions is around 13.1% after EMR.<sup>33</sup> Piecemeal resection was associated with higher recurrence rate compared to en-bloc technique, with odds ratio of 4.4. Although some studies suggest that the application of prophylactic APC at the resection edge results in lower risk of recurrence of colonic lesions, more data is needed to confirm the optimal methods.<sup>34</sup> Fortunately, most recurrences after EMR or ESD can be treated with further resection, resulting in long term cure.<sup>35</sup>

### Endoscopic Submucosal Dissection

ESD is primarily used for lesions confined to the mucosa or superficial submucosa measuring greater than 20 mm in diameter. ESD has the advantage of achieving en-bloc resection regardless of lesion size, which results in lower recurrence.<sup>36</sup> It is performed when the lesion needs to be resected en bloc to evaluate the histological features. Granular LST, nodular type measuring  $\geq 30$  mm or nongranular LST measuring  $\geq 20$  mm are also lesions to be considered for ESD.<sup>37</sup> ESD is also indicated for lesions that are difficult to resect with conventional EMR, including lesions that show non-lifting signs after submucosal injection and recurrent lesions at the same location.<sup>36</sup> The technique is not suited for lesions with deep submucosal invasion. It should be noted, that there is no randomized controlled trial of EMR versus ESD for colorectal neoplasia. Until such data is available, the optimal method of resecting such lesions remains unknown.

At the start of the procedure, the lesion is marked circumferentially by applying soft coagulation current.

Submucosal injection is performed initially to provide a fluid cushion. The main solutions used for ESD are normal saline, glycerol, and hyaluronic acid. Normal saline is usually adequate for gastric ESD as the gastric wall is thicker. However, for colon and esophagus, longer lasting solution is needed to lift the mucosal wall.<sup>38</sup> After the injection, a mucosal incision is made with short needle knife, and afterward, the lesion is further dissected from the other layers of the bowel wall by using electrocautery knives. There are two types of ESD knives used during procedure including needle knives and insulated tip knives.<sup>38</sup> It is essential to continue the dissection through the submucosal layer and avoid injury to the muscularis propria. Carbon dioxide insufflation is recommended because this is rapidly reabsorbed in the event of perforation. In a case-control series, the use of carbon dioxide for insufflation was associated with shorter operating times, lower use of sedation medication, and reduced procedural and post-procedural pain.<sup>39,40</sup>

There are many risk factors that strongly correlate with increased difficulty in performing this procedure. One prospective study with 247 lesions demonstrates that location of the lesion particularly at the hepatic and splenic flexure, locally recurrent lesion, tumor size  $\geq 50$  mm, and tumor spreading across  $\geq 2$  folds were strong independent risk factors for longer procedure duration or perforation.<sup>41</sup>

Recent studies have focused on the efficacy and safety of colorectal ESD. A recent meta-analysis and systemic review of 22 studies provided data on 2841 ESD lesions. Analysis from the study shows that ESD is extremely effective in achieving complete en-bloc resection in 88% of lesions that are  $\geq 20$ mm.<sup>42</sup>

### Endoscopic Versus Surgical Treatment for Colorectal Cancer

No randomized controlled trials have compared endoscopic resection vs. transanal full thickness resection vs. radical resection. EMR of high-risk T1 colorectal cancer had a reported recurrence rate of 20.1% compared with 3.7% following radical resection.<sup>43</sup> Based on recent study, endoscopic resection is only acceptable for low-risk T1 colorectal cancer.<sup>20,43</sup>

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### CONCLUSION

For early T1 colorectal cancer, EMR and ESD offer safe and effective alternatives to surgical resection. It is critical to select the appropriate patient to undergo endoscopic resection, and this can be accomplished through careful endoscopic and histologic assessment. Currently, colon cancer confined to SM1 is amenable to endoscopic resection, and deeper invasion into submucosa requires surgical resection. Additional studies looking at the complete resection rate, recurrence, and complications comparing EMR and ESD with surgical treatment for early colorectal cancer is warranted. ■

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