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ENDOSCOPIC THERAPEUTICS AND DIAGNOSTICS FOR COLON CANCER: AN UPDATE AND FUTURE PERSPECTIVE

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ABSTRACT

Colorectal cancer is the third most commonly diagnosed malignancy and it afflicts approximately 1 million people around the globe each year. Before the era of national screening programs, the majority of colon cancers were diagnosed at an advanced stage, which required major surgery and led to significant morbidity and mortality rates. Currently, cancer screening programs are not only established, but also widely accepted across the globe. The widespread use of modern endoscopes permits the detection of cancers in early stages, with a low risk of lymph node metastases or distant spread. Endoscopic approaches demonstrated their superiority over conventional surgical techniques and created a precedent for minimally invasive operations for early colon cancer. Subsequently, with improved technology, many patients with colon cancer worldwide have undergone endoscopic resection and this technique has become the standard of care for early colon cancer. Early-stage colon cancer is defined as a disease that appears to have been completely resected without involvement of adjacent organs, lymph nodes, or distant sites. Endoscopic mucosal resection and endoscopic submucosal dissection have been used for early colon cancer, however, recently a more advanced therapeutic endoscopy technique endoscopic full-thickness resection has also been introduced as a therapeutic option for advanced colonic cancer resection. This article provides an overview of the available endoscopic therapeutics for colon cancer and the diagnostics role of endoscopic ultrasound, with a perspective on recent advances, and also sheds light on the safety, indications, and complications for each endoscopic resection approach for colon cancer.

KEYWORDS: Colon cancer; Early stage colon cancer; Advanced colon cancer; Endoscopic therapeutics; Endoscopic resection techniques.

INTRODUCTION

In the USA, 5000 to 6000 new cases of colon cancer are recorded each year, and the incidence seems to be rising.[1, 2] Colon cancer frequently has strong malignant tendencies yet are asymptomatic.[3,4] Endoscopy and other imaging techniques raise suspicion for the diagnosis of colon cancer, which is then validated through tissue biopsy and immunohistochemistry staining.[5-7] For the last one decade, laparoscopic resection remains the preferred treatment of choice for colon cancer[8] However, endoscopy has advanced quickly, and endoscopic resection is now more frequently used as a successful alternative treatment for non-metastatic colon cancer. It has advantages over laparoscopic resection including precise localization of the tumor, less blood loss, shorter procedure time and hospital stay, and most importantly preservation of the stomach. The appropriate resection technique is selected based on the size and location of the cancerous lesion. Endoscopic resection techniques such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and endoscopic full-thickness resection (EFTR) have demonstrated that colon cancer can be safely and effectively removed with minimal damage compared with the traditional surgical approaches.[9-11] A good prognosis for colon cancer is linked to early histological diagnosis and complete resection, hence these techniques should only be used in certain individuals by endoscopists with specialized training and experience. In this study, we provide the latest update on advances in endoscopic resections of colon cancer with the diagnostic role of endoscopic

ultrasound and also shed light on the safety, indications, and complications of each endoscopic resection approach for colon cancer, to help surgeons and gastroenterologists appropriately screen and manage patients to reduce mortality from the colon cancer.

Role of endoscopic ultrasonography (EUS) in the diagnosis of colon cancer

Due to improvements in minimally invasive endoscopic methods and possible advantages of neoadjuvant therapies for advanced but treatable tumors, the staging of colon cancer has grown in importance. For tumor examinations, EUS is a flexible technique.[12–15] In contrast to CT scans, it does not expose the patient to radiation and can accurately identify all layers of the intestinal wall. EUS, like CT, has a restriction on peritoneal involvement, though. For the EUS procedure to produce effective outcomes, qualified hands must be present. It can be difficult to place the scope properly, and non-perpendicular tumor planes during an inspection may cause the stage of the tumor to be incorrectly determined. Inaccurate measurements may result from non-perpendicular planes in the reconstruction of CT scan images. EUS may be prohibited or restricted by stenotic tumors, and it may be difficult or even impossible to keep tiny tumors on stalks in position for high-quality pictures. Since CT is not a dynamic study, images can be reviewed multiple times and evaluated by different professionals when in question. CT also has the advantage of being a quick process that can detect distant metastases.[16–19] Lastly, the only way to definitively distinguish between tumor tissue and fibrosis, edema, and cellular infiltration at the tumor front is by histology.

In recent clinical research, the sensitivity of EUS and CT for determining T-stage was good and equivalent, but EUS had a much greater specificity for determining tumors with a high blow risk.[20–23] Due to the tiny patient population, it was difficult to evaluate the outcomes for high-risk colon cancer. In the future, EUS might be used in addition to CT scans to help choose patients for neoadjuvant therapy or local transmural treatment. While CT should still be used for staging and the elimination of distant metastases, EUS may be used to identify patients for neoadjuvant therapy who have advanced operable colon carcinoma as well as those who have early cancer without nodal involvement.[24–27]

Endoscopic Submucosal Dissection (ESD) for colon cancer and challenges with colonic ESD

ESD is a minimally invasive endoscopic modality which is sued for the resection of both early and advanced GI lesions.[28-30] ESD has evolved over the last several years and is currently employed beyond its original intent of endoscopic resection of GI lesions. If the complete resection is achieved with the ESD method, surgery can be avoided. ESD is now more frequently suggested as the preferred method for treating colon cancer. The ESD procedure is carried out as follows: 1) Following a careful inspection of the lesion site, make marking around the lesion, 2) submucosal injection to lift the mucosa around the lesion, 3) mucosal and submucosal incision using hook and IT knife, 4) complete the dissection of the lesion, 5) address any event that may arise during the procedure, such as bleeding or perforations, and 6) close the defect wall using endoscopic suturing device or by another means of suturing depending on the expertise and availability.

ESD procedure has the following challenges; 1) Thin colon wall, 2) Limited expandability of the colonic submucosal space, 3) Colonic muscularis propria can be easily disrupted with inadvertent cauterization by the dissection knife or simply via pressure from the tip of the endoscope, 4) Colonic looping, and 5) Lesion's location behind folds or around flexuresoficient manners. That's why in the United States and west use of colonic ESD is not common.[31] However recently, there have been many devices such as traction devices, tissue apposition devices, and closure and stabilization devices to facilitate colonic ESD.[32-34] The traction-assisted ESD allows better visualization of the resection plan, faster dissection, and avoids muscle injury.

ESD also has several drawbacks and restrictions, such as 1) perforation (1% to 8%) 2) bleeding (0% to 15.6), 3) a steep learning curve, 4) longer procedure time, 5) the risk of local recurrence or distant metastasis associated with ESD for colon cancer.[35, 36]

In summary, a lot of previous studies concluded that ESD could be an efficient and safe therapeutic modality for early colon cancer. However, there are still needs for long-term, large sample size randomized controlled, multicenter trials are needed before final recommendations are made in this regard.

Endoscopic full-thickness resection (EFTR) for colon cancer

EFTR technique plays a major role for the management of challenging submucosal lesions that cannot be resected with traditional endoscopic approaches and previously required a surgical resection.[37-39] The EFTR is performed as follows: 1) marking the lesion, 2) submucosal injection for lifting mucosa, 3) incising the mucosa and submucosa, 4) making the circumferential incision around the tumor, 5) incision into the serosa layer around the tumor, 6) full-thickness resection of the tumor including the serosa layer and closing the wall defect using endoclips.

Recent advancements in the use of titanium clips during endoscopy, based on ESD have made it possible to treat gastrointestinal cancers with EFTR.[40] Successful repair of the perforation is the key to the success of the EFTR procedure, preventing the need for further surgical repair and postoperative peritonitis. Furthermore, a brand-new over-the-scope clip (OTSC) technique might work well to close a variety of GI defects.[41-43] Acute gastrointestinal perforations and fistulas are increasingly

being treated with OTSCs. Additionally, submucosal tunneling endoscopy for resection also employs OTSCs. Sometimes we also use the over-tube device and utilize it to put the suturing device inside it. Different international guideline says if the tumor has high-risk features like poorly differentiated adenocarcinoma, signet ring cell carcinoma, mucinous carcinoma, lymph vascular invasion and intermediate-to-high grade tumor budding, these tumors should not have resected by endoscopy.[44]

Perforation is not seen as a complication in EFTR. Bleeding, localized peritonitis, and abdominal distention are among the reported complications of EFTR.[45,46] Additionally, a recent study discovered that the safety and effectiveness of EFTR and laparoscopic resection for colon cancer are equal; however, surgery requires longer procedure time, more blood loss, and a longer length of hospital stay.[47] We believe that EFTR may be a safe and effective alternative to surgical resection for the treatment of colon cancer if the complications rate of EFTR could be reduced.

When to use which technique?

The US Multi-Society Task Force did not specify indications for EMR or ESD for colon cancer **(Figure 1).** Therefore, there is no clear distinction between EMR/ESD indications. However, it is understood that certain lesions will have a higher risk of submucosal invasion such as granular lateral spreading lesions having only a 3.2% chance of submucosal invasion versus nongranular polyps having a 15.3% chance of submucosal invasion.[48] On the other hand, mixed granular and nongranular lesions have a 10% chance of submucosal invasions **(Figure 2).**[49] This showed that nongranular lateral spreading polyps have a higher risk of submucosal invasion, and therefore, should be removed by ESD.

In summary, the indications of endoscopic resections for colonic lesions are expanding to include ileocecal valve and appendiceal orifice lesions.[50, 51] ESD can be used in granular lateral spreading tumors > 3 cm, non-granular lateral spreading tumors, and depressed or fibrotic lesions. EFTR is perfect for fibrotic colonic lesions less than 2 cm in size, and surgery should be reserved for lesions with a high risk of deep submucosal invasion. Poorly differentiated adenocarcinoma, signet ring cell carcinoma, mucinous carcinoma, deep submucosal invasion, lymph vascular invasion, and Intermediate-to-high grade tumor budding are the main indications of surgical resection.[52]

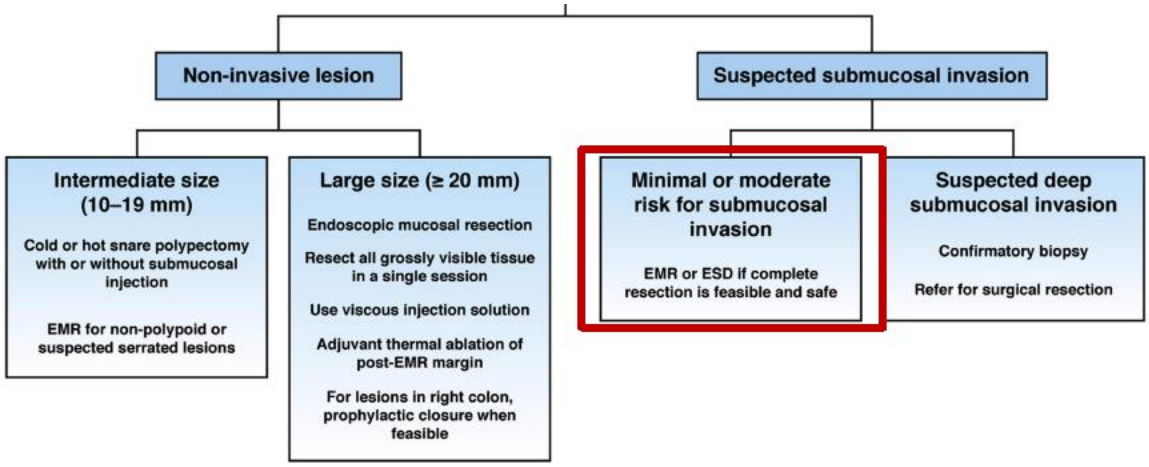

Figure 1: US Multi-Society Task Force Indications for EMR/ESD.

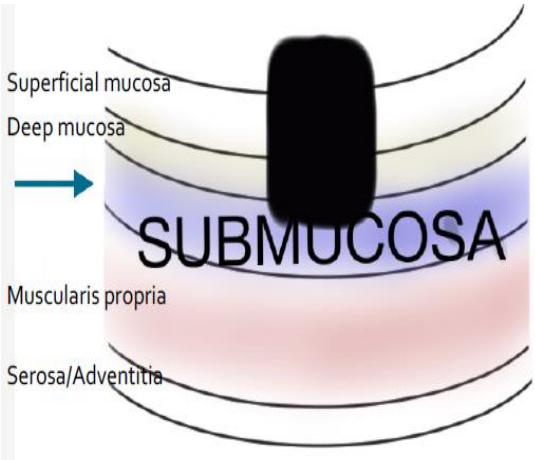

Figure 2: Schematics for planes of dissection showing the lesion in the submucosa.

CONCLUSION

Computed tomography remains the standard image modality currently used in the diagnosis of colonic tumors. However, more recently, EUS is being performed more frequently wherever the resources and expertise are available, and possibly even better, for determining the advancement of the colonic cancer loco regionally, and maybe a good and feasible supplement to CT for optimizing medical and surgical treatments. EUS is very helpful in decision-making on which endoscopic therapy to use for the colonic lesion depending on the depth of the lesion. Currently, ESD is used if the lesion is in the submucosal layer. However, if the lesion is beyond the submucosal layer EFTR is preferred. Although these techniques are there for several years and there have been several clinical trials and multicenter studies on their safety and feasibility. There are still several technological issues that must be fixed before endoscopy may be used more frequently for colon cancer. First of all, we must figure out how to reduce complications rate associated with endoscopic resection (e.g., perforation). Although several devices including OTSC, have been suggested, the majority of them are not appropriate for large or advanced lesions and are not even available worldwide including in China, thus warranting the development of new devices. In addition, there should be a need for uniform training programs for GI fellows and a need for multinational collaborations. Finally, there should be consensus on the indications of each endoscopic resection technique to manage colon cancer. Therefore, technical advancement is required to define the role of endoscopy in treating colon cancer globally. Although hypothetical, the future calls for less invasive approaches, where the role of the EUS technique could be important. Based on the currently available literature, EUS seems to complement current image modalities used in colonic cancers.

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