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## Endoscopic therapy for early colorectal cancer: a retrospective study

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Appropriate treatment options for early colorectal cancer (ECRC) smaller than 20 mm remains controversial. Here, we studied the efficacy and safety of endoscopic therapy for ECRC smaller than 20 mm. About 191 patients with colorectal lesions entered into our study from January 2017 to December 2019. Lesions were divided into two groups according to sizes: smaller than 10 mm group and 10-20 mm group. Most cases of ECRC were found in the left colon (70.15%), and the male to female ratio was 1.81:1. A very smaller proportion of colorectal lesions smaller than 10 mm in size were submucosal carcinoma (0.077%), whereas 3.85% of colorectal lesions between 10 mm and 20 mm in size were submucosal carcinoma ( $P=0.049$ ). Cold snare polypectomy (CSP) was found to be a safe and efficient for lesions smaller than 10 mm. For the lesions smaller than 10 mm, the rate of en bloc resection reached 100%, whereas only 81.82% of the lesions of 10-20 mm in size could be resected en bloc and for these cases, endoscopic mucosal resection (EMR) were better therapeutic options. Endoscopic CSP is an appropriate therapeutic approach for ECRC of less than 10 mm in size, whereas for lesions smaller than 10 mm in size but with submucosal infiltration, EMR should be considered. For submucosal carcinoma (SM-carcinoma), endoscopic submucosal dissection (ESD) or surgery should be considered as better options.

**Keywords:** Cold snare polypectomy, dysplasia, Endoscopic mucosal resection, Endoscopic submucosal dissection, Tumor

Colorectal cancer (CRC) is one of the most common malignant tumors affecting 1.93 million people all over the world<sup>1</sup>. In China too, incidence, morbidity and mortality of colorectal cancer have increased over the recent years<sup>2,3</sup>. In China Cancer Statistics, CRC ranks fifth among all malignant tumors in terms of incidence and mortality with a total of 376,000 new cases and 191,000 deaths in 2015, hence constituting a serious health threat to the society<sup>2</sup>. Early diagnosis and early treatment are key determinants for the prognosis of CRC<sup>4-6</sup>. Early CRC can be cured and a

5-year survival rate of up to 90% can be achieved, while the patients with advanced CRC often show a poor 5-year survival rate of <10%<sup>7-10</sup>. Early colorectal cancer (ECRC) is defined as colorectal cancer confined to the mucosa or submucosa irrespective of the presence of regional lymph node metastasis<sup>4</sup>. Surgery is the mainstay in the management of CRC.

In recent years, endoscopic resection has been proven to be an effective therapeutic method for precancerous lesions and ECRC. Commonly used endoscopic techniques include Cold snare polypectomy (CSP), Endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD)<sup>11,12</sup>. Most of the small adenomas and early cancers in gastrointestinal tract can be easily removed by CSP or EMR<sup>13,14</sup>. However, CSP and EMR may not always be available and large tumors may be difficult to remove by these techniques. As such, local recurrence after resection by CSP or EMR may occur<sup>15-17</sup>. Consequently, ESD was developed in the late 1990s in Japan but it was then considered too risky at that time because this technique was often associated with severe complications such as perforation and bleeding. According to the 2017 Guidelines of European Society of Gastrointestinal Endoscopy (ESGE), whole removal technique including EMR, ESD and surgery should be used for superficial invasive tumors<sup>18</sup>, whereas cold and hot trap removal should be used for lesions <20 mm<sup>15-18</sup>.

We present here our investigation on the efficacy and safety of endoscopic therapy for ECRC smaller than 20 mm with 191 patients with colorectal lesions entered into our study from January 2017 to December 2019.

### Subjects and Methods

A total of 191 consecutive patients with 201 colorectal lesions of less than 20 mm in size, including high-grade dysplasia (n=110) and ECRC (n=91), who undertook CSP, EMR or ESD from January 2017 to December 2019 in the Digestive Endoscopy Center of Beijing Shijitan Hospital Affiliated to the Capital Medical University, Beijing China, were included in this retrospective study. Patients were divided into two groups according to the size of the lesions: Group I: those with lesion sizes ≤10 mm; and Group II: those with lesion sizes between 10 mm and 20 mm. Patients with deep submucosal

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invasive carcinoma, inflammatory bowel disease (IBD), intestinal tuberculosis, familial adenomatous polyposis (FAP), other invasive carcinomas and circumferential tumors requiring surgical resection or incomplete pathological data were excluded from this study. The clinicopathological information including gender, age, lesion site, endoscopic features, operation method, postoperative pathological features and postoperative complications (including bleeding, perforation, and infection) were collected. All patients were informed of the risks and benefits of CSP, EMR and ESD, and written consent from each patient was obtained. The study was approved by the Human Ethics Committee of the Beijing Capital Medical University.

#### Procedures, pre- and post-operative management

Anticoagulant and antiplatelet drugs, if any, were discontinued at least seven days before the CSP, EMR and ESD procedures. In addition, narrow band imaging (NBI) endoscopy was performed to assess the lesion sizes prior to the CSP, EMR and ESD procedures.

#### Cold snare polypectomy (CSP)

CSP is suitable for the treatment of small colorectal polyps because of its shorter procedure time and lower rate of delayed bleeding than HSP or EMR. The “pull technique” was used where polyp is ensnared, pulled into the colonoscope channel and transected with simultaneous suctioning<sup>19-21</sup>.

#### Endoscopic mucosal resection (EMR)

The key procedures for EMR include submucosal injection to make protrusion and snaring of protruded area. Generally, 10% glycerin solution or hyaluronic acid solution is injected underneath the submucosa to form a fluid cushion that lifts the target lesions. The elevated lesions can then be captured by snare and removed without excessive thermal damage on both muscle layer and the specimen<sup>22-24</sup>.

#### Endoscopic submucosal dissection (ESD)

ESD was performed with the patient under general intravenous anesthesia and constant monitoring of cardiopulmonary functions (heart rate, blood pressure, and oxygen saturation). Five mL of solution containing 5% indigo carmine and 1% epinephrine is injected underneath the submucosa using a 23-gauge disposable needle and a mucosal incision is created along the normal mucosa approximately 5 mm away from the tumor. Next, a hook knife or SB-knife was used to dissect the submucosal connective tissues beneath the tumor. During the dissection, the solution was injected repeatedly when necessary. At the completion of the resection, all visible vessels of the

artificial ulcer bed were thoroughly coagulated with argon plasma coagulation to prevent postoperative bleeding<sup>24-27</sup>.

#### Post-procedural care

After removing the lesions, specimens were retrieved with forceps or basket. The margins were carefully investigated to ensure complete lesion resection before completing the operation. Hemostatic forceps or metal clips were used to manage intraoperative bleeding. Delayed bleeding as defined by significant blood loss (>3 units) was treated with endoscopic hemostasis. Patients without adverse events were permitted to drinking water the first day and eating soft food on the second day after the operation. Generally, patients can start the normal diets on postoperative days 4 or 5.

An *en bloc* resection was defined as an excision of the tumor in one piece without fragmentation. The resected specimens were carefully examined. Based on the Guidelines of the Japanese Society for Cancer of colon and rectum (JSCCR)<sup>28</sup>, a histological complete resection was defined as an *en bloc* resection with negative horizontal and vertical margins, and a R0 resection was defined as a histological complete resection without lymph node metastasis.

#### Definition of complications

Intraoperative complications were assumed if there was clinical evidence during the procedure (for examples, transmural cut for perforation, and massive bleeding). The delayed bleeding was defined as significant blood loss of three hemoglobin units after completion of the ESD procedure<sup>29</sup>.

#### Statistical analysis

Statistical analysis was performed using SPSS Version 21.0/IBM. All measurement data of normal distribution were expressed as  $\bar{x} \pm s$ , and the counting data were expressed as the composition ratio and rate. A  $\chi^2$  test or continuous correction  $\chi^2$  test was used to analyze the bidirectional unordered R×C comparisons between groups. A *P* value of <0.05 or <Bonferroni adjusted value was considered statistically significant.

#### Results

The baseline and clinicopathological characteristics of the patients are summarized in Table 1. Among the 22,067 patients undertook colonoscopy between January 2017 and December 2019. About 191 cases (including 123 male and 68 females, median age 13±6 years) had a total of 201 colonic tumors. Among these tumors, 67 were smaller than 10 mm (Gr. I) and 134

Variable	Tumor size <10 mm (n=67)	Tumor size 10-20 mm (n=134)	P value
Characteristics			
I	47 (70.2%)	112 (83.6%)	0.172
II	20 (29.9%)	7 (5.2%)	<0.01
LST	0 (0%)	15 (11.2%)	<0.01

were between 10 mm to 20 mm (Gr. II). There were 67 cases in Gr. I, including 39 male children (58.21%) and 28 female (41.79%), with a mean age of 13.4±6.6 years. The median tumor size was 7.0±1.6 mm. More than 64.2% of the tumors were found in the left colon (n=43) and the rest were in the right colon (n=24, 35.8%). There were 134 cases in Gr. II, including 84 male (62.7%) and 50 females (37.3%), with a mean age of 14.8±5.2 years. The median tumor size was 14.8±4.1 mm. Similar to Gr. I, the majority of the tumors were located in the left colon (n=98, 73.1%) and a smaller proportion of the tumors were found in the right colon (n=36, 26.9%).

As shown in Table 1, males had a higher incidence rate of ECRC than females, and more of the colonic tumors were found in the left colon, while only approximately one third of the cases were found in the right colon. No significant difference in the age, sex, and the anatomic location of the lesions was found between the two groups.

#### Endoscopic findings

The colonic lesions were classified into Ip, Is, Isp, Ila, Iib, Iic and LSTs, as per the guidelines of the Paris Classification as given below: Ip, Pedunculated; Isp, Semi-pedunculated; Is, Sessile, higher than height of closed forceps (2.5 mm); Ila, Slightly elevated, below height of closed forceps (2.5 mm); Iib, Completely flat lesion, does not protrude above mucosal surface; and Iic, Slightly depressed, lower than mucosa but depth less than 1.2 mm. Among the 67 cases in Gr. I, 17 cases had Ip lesions (25.4%); another 17 cases had Isp lesions (25.4%); 13 cases had Is lesions (19.4%); and 20 cases had Ila lesions (29.8%). Ila lesions were more common in Gr. I than in Gr. II (29.8% vs. 5.2%,  $P < 0.01$ ). Among the 134 cases in Gr. II, 52 cases had Ip lesions (38.8%); 36 cases, Isp lesions (26.9%); 24 cases, Is lesions (17.9%); 7 cases, Ila lesions (5.2%); and 15 cases had LST lesions (15, 11.2%). Ip lesions were more common in Gr. II than in Gr. I (38.8% vs. 25.4%,  $P < 0.01$ ), and LST lesions were more common in Gr. II than in Gr. I (11.2% vs. 0.0%,  $P < 0.01$ ) (Table 2).

Variable	Tumor size ≤10 mm (n=67)	Tumor size 10-20 mm (n=134)	P value
Age (year)	13.4±6.6	4.8±5.2	0.849
Gender ratio (M:F)	39/28	84/50	0.443
Mean size (mm)	7.0±1.6	14.8±4.1	
Location ratio (Left/Right)	43/24	98/36	0.127
Characteristics			
Ip	17 (25.4%)	52 (38.8%)	<0.01
Isp	17 (25.4%)	36 (26.9%)	0.199
Is	13 (19.4%)	24 (17.9%)	0.110
Ila	20 (29.8%)	7 (5.2%)	<0.01
LST	0 (0%)	15 (11.2%)	<0.01
Treatment options			
Biopsy	3 (4.5%)	0 (0%)	<0.01
CSP	17 (25.4%)	11 (8.2%)	<0.01
EMR	47 (70.1%)	97 (72.4%)	0.172
ESD	0 (0%)	26 (19.4%)	<0.01
Complications			
Perforation	0 (0%)	0 (0%)	
Bleeding	0 (0%)	2 (1.5%)	
Infection	0 (0%)	0 (0%)	
Histology			
HG-IEN	43 (64.2%)	67 (50.0%)	0.143
M-Carcinoma	23 (34.3%)	62 (46.3%)	0.135
SM-Carcinoma	1 (1.5%)	5 (3.7%)	0.049
Completed procedures			
<i>En bloc</i> resection	67 (100%)	129 (98.5%)	0.128

#### Efficacy and safety

In Gr. I, three cases had Is, Isp, and Ila lesions respectively, and the size of these lesions were 4–6 mm. Upon biopsy resection and histopathology, these lesions were found to be high-grade dysplasia. Among the 17 cases receiving CSP, and the lesions were Ila (n=9) or Is (n=8), and histopathology all revealed high-grade dysplasia. Among the 47 cases undertaking EMR, 23 cases had high-grade dysplasia, another 23 cases had mucosal carcinoma (M-carcinoma), and one case had submucosal carcinoma (SM-carcinoma). All lesions were of 5–10 mm in size. Of special note, the 6 mm SM-carcinoma was a type Ila lesion, with depression on the surface, acanthosis at the base, and an infiltration depth of 600 μm but clear vertical and lateral margins. No complications such as bleeding, perforation and infection occurred immediately after and 3–6-month post the endoscopic procedures. Our data indicated that SM-carcinoma of <10 mm was rare, and the infiltration depth was rarely deeper than 1000 μm. Overall, CSP and EMR were effective and safe procedures for the treatment of colonic lesions of ≤10 mm.

In Gr. I, eleven cases received CSP and the lesions were high-grade dysplasia (n=9) or M-carcinoma

(n=2). Among which two cases had positive vertical and lateral margins. EMR was performed in 108 cases. Histopathologically, most of them were type I lesions (n=82), two had SM-carcinoma (including one Isp lesion with expansive appearance, and one Is lesion with fold convergence). The lesions invaded into the submucosal tissues by 760  $\mu\text{m}$  and 800  $\mu\text{m}$ , respectively and the vertical and lateral margins were all positive. These two lesions were treated with surgery after endoscopic therapy. Twenty-six cases were treated with ESD (including 11 cases with LST lesion, 13 cases with Is lesion, and two cases with Ila lesion). In three cases, surgery was performed one week after endoscopic treatment because of submucosal infiltration and incomplete resection. Two cases with Is lesion had depressed area endoscopically and by histopathology, the lesions were SM-carcinoma with an invasion depth of 1000  $\mu\text{m}$ . One case had Ila lesion with erosion and expansive appearance, and histopathologically, moderately to poorly differentiated adenocarcinoma with an invasion depth of 700  $\mu\text{m}$  was revealed. In this case, the vertical and lateral margins were all negative. Two cases (1.49%) occurred post procedure bleeding who were treated with coagulation therapy. Overall, SM-carcinoma was more common in Gr. II than in Gr. I ( $P=0.049$ ), ESD was more common in Gr. II than in Gr. I ( $P < 0.01$ ), CSP was less common in Gr. II than in Gr. I ( $P < 0.01$ ).

## Discussion

Our study has shown that most of the ECRC are in the left colon. Consistent with the published data<sup>30,31</sup>, these lesions are more common in men than in women with a male to female ratio of 1.81:1. Lesion size is an important indicator for the invasion depth and a key determinant for selecting the treatment approach for advanced colorectal neoplasms<sup>32,33</sup>. It was previously reported that 7.4-14% of colorectal polyps larger than 20 mm were SM-carcinoma<sup>32-35</sup>, whereas others reported that only 0.07 to 5.8% of the polyps less than 20 mm were SM-carcinoma<sup>34,35</sup>. In our study, 0.08% of polyps smaller than 10 mm in size were SM-carcinoma and 3.9% of polyps between 10 and 20 mm in size were SM-carcinoma. These characteristics are consistent with what have been reported by others<sup>32-35</sup>. It shows that tumors of small size are still possibly be SM-carcinoma. The reported morphological features of SM-carcinoma include loss of normal lobulation, excavation (a crumbled, damaged area of the tumor

that may prevent observation of the surface structure), demarcated depression (depressed demarcations on the tumor surface), stalk swelling (a thickened and expanded stalk), fullness (a bursting appearance due to expansive growth of the tumor), fold convergence towards the tumor, bleeding ulcers, pit patterns and non-lifting signs<sup>33-35</sup>. The pit pattern is further divided as invasive or non invasive, where invasive patterns are characterized by irregular and distorted crypts in demarcated areas, whereas non-invasive patterns are characterized by lesions with normal mucosa, star-shaped crypts, or regular crypts with or without demarcated areas or irregular pits without demarcated areas. A positive non-lifting sign refers to a lesion where only the surrounding mucosa but not the lesion can be lifted following submucosal injection, whereas a negative non-lifting sign refers to a lesion that can be easily elevated<sup>32,33</sup>.

An assessment of the above patterns prior to endoscopic therapy may provide important information on the tumor nature and depth of invasion. In our study, a case of colonic lesion smaller than 10 mm was found to be SM-carcinoma with a demarcated depression on the tumor surface. Five cases with the lesion size of 10-20 mm were found to be SM-carcinoma with demarcated depression, fullness, and spontaneous bleeding. As per the 2017 Guideline of European Society of Gastrointestinal Endoscopy (ESGE), CSP is the treatment of choice for sessile or flat superficial colorectal neoplasia smaller than 10 mm<sup>10</sup>, whereas biopsy forceps (CBF) is not recommended for such lesions because of high rates of incomplete resection. In a randomized control trial of CSP vs. CBF, the rate of residual neoplastic tissue found after polypectomy for lesions sized 5-7 mm was significantly lower in the CSP group than in CBF polypectomy group (6.2% vs. 29.7%;  $P=0.013$ )<sup>16,17</sup>. In our study, three cases of Is, Isp and Ila lesions with the sizes of 4-6 mm were treated with CBF, and the post-procedure pathology revealed high-grade dysplasia with negative vertical and lateral margins. Due to insufficient sample size, we were unable to compare the efficacy and safety of CSP, EMR, ESD. CSP was performed in 17 cases of lesions smaller than 10 mm and 11 cases of lesions 10-20 mm, two of these cases with pedunculated lesions had incomplete resection with positive lateral margins. Two of these cases with sessile lesions had postoperative bleeding which was successfully managed endoscopically. We felt that CSP is an adequate safe and efficient

treatment for lesions smaller than 10 mm. For lesions of 10-20 mm in size, there was an increased possibility of incomplete resection, especially for flat lesions. In a retrospective study of 248 polyps sized 10-19 mm, complete resection was achieved in 89.5% of cases by CSP and in 95.6% of cases by EMR. In a retrospective study that evaluated piecemeal CSP outcomes for sessile polyps of size >10 mm, 30 lesions between 10 mm and 19 mm were completely retrieved without any adverse events such as delayed bleeding, post-polypectomy syndrome, or perforation. Of 27 patients who underwent follow-up colonoscopy within 6 months, 98.6% did not have residual carcinoma tissue at the resection site. For sessile or flat superficial colorectal neoplasia 10-19 mm, EMR was recommended by ESGE as a preferred treatment. However, for SM-carcinoma, ESD is treatment of choice, especially for flat, sessile and LST lesions.

### Conclusion

Our data have confirmed the efficacy and safety of CSP for endoscopic *en bloc* resection of high-grade dysplasia and ECRC of  $\leq 10$  mm in size, whereas EMR is the preferred approach for endoscopic *en bloc* resection of high-grade dysplasia and ECRC sized 10-20 mm but without submucosal infiltration. For SM-carcinoma lesions, ESD and surgery are better options.

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### Conflict of Interest

Authors declare no competing interests.

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