

# Comparison between endoscopic submucosal snaring with circumferential mucosal incision (ESS-CMI) and endoscopic submucosal dissection (ESD) in treating colonic neoplasm - a cost-effective retrospective study

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## Research article

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# Abstract

**Background** To evaluate and compare the safety, efficacy and cost of endoscopic submucosal snaring with circumferential mucosal incision (ESS-CMI) with endoscopic submucosal dissection (ESD) in various types of colonic neoplasms. **Methods** Patients who were admitted in our endoscopic center for colonic neoplasm therapy were screened, with the Chinese item of “endoscopic submucosal dissection” and the English abbreviation of ESD, for the period between January 2011 and December 2017. Initially enrolled patients were further categorized into ESD and ESS-CMI groups after careful assessment of detailed operation procedures. Data on patients’ and colonic neoplasm’s characteristics, recurrence, treatment, follow-up and disease status were collected after medical records review. Further cost-effective analysis includes two main aspects: treatment effect and complication as well as the cost and efficiency. **Results** A total of 278 patients was selected. Though there were no significant differences in basic anthropometric and disease status data such as age, gender, neoplasm type, degree and the method of follow up, the location of rectum, the longest side and the surface area were significantly higher in ESD group than those in ESS-CMI group. For ESS-CMI, further cost-effective study showed the similar treatment effect and complication rate but significantly decreased cost, operation time and average hospital stay, when compared with ESD. Further subgroup analysis showed that there were no significant differences between the ESS-CMI successful and failure groups. **Conclusion** ESS-CMI might become a new and better choice for colonic neoplasm therapy, based on its decreased operation cost but similar treatment efficacy and complication rate as ESD.

## Background

Colonic neoplasm has been considered as one of the most common tumors in the world<sup>1</sup> and is roughly categorized into two subtypes, according to the origination from mucosal and submucosal layers. The mucosal layer originated colonic neoplasm usually includes carcinoma, tubular/villous adenoma, laterally spreading tumor (LST), polyp, et al. The submucosal layer originated colonic neoplasm has the official name as submucosal tumor (SMT), which is characterized as neoplastic lesions covering by normal overlying mucosa and includes carcinoid, gastrointestinal stromal tumor (GIST), lymphoma, leiomyoma, lipoma, et al. Among them, large sessile polyps and LSTs are increasingly encountered during colonoscopy procedure, reaching approximately 1% in screening population<sup>2,3</sup>.

The treatment of colonic neoplasm mainly contains endoscopic and surgical ways, depending on its severity (the degree of atypical hyperplasia, intestinal wall invasion and metastasis). Concerning endoscopic therapy, the original method is snaring, which is quite simple and much more suitable for pedunculated neoplasm. In 1980s, endoscopic mucosal resection (EMR) has been gradually developed from Japan<sup>4</sup>, where local liquid injection into the submucosal layer decreases the perforation rate and increases the cut area and range of colonic neoplasm<sup>5</sup>. However, as restricted by the scope of snare, usually the neoplasm larger than 2 cm is difficult for complete resection by a single EMR procedure. Therefore, the endoscopic piecemeal mucosal resection (EPMR) was introduced in 2005 as the

complementary for routine EMR <sup>6</sup>. Nevertheless, though the complete resection range is increased by EPMR, the problem of unable to evaluate the vertical and side cutting edge still exists, which calls for further endoscopic technique development.

As an offshoot of EMR, endoscopic submucosal dissection (ESD) was developed and introduced as a revised method of doing en bloc resection of large mucosal lesions, permitting a more thorough and useful pathologic evaluation in regard to the completeness of resection and depth of invasion <sup>7</sup>. Accumulating evidences support the superior effect of ESD over EMR in colonic neoplasm treatment <sup>8,9</sup>. Nevertheless, comparing with EMR, the increased en bloc resection rate of ESD is theoretically, to some extent, at the cost of increased operation time, cost and complications (rate of perforation and bleeding). Such situation might be more obvious in the sessile type of neoplasm 2 cm or larger and in the cecum/right colon location of neoplasm, since the wall of the right colon is thinner and prone to perforation.

Therefore, we are wondering whether there exists a revised form of ESD, which maintains its advantage of en bloc resection but decreases its shortage as previously mentioned. Theoretically, on one hand, sufficient submucosal injection may provide the equal opportunity of vertical edge negativity for both the procedures of submucosal snaring and dissection; on the other hand, once careful circumferential mucosa incision is well done, the side edge negativity would be easier to achieve. Based on this hypothesis, we combined the procedure of circumferential mucosa incision, partial procedure of ESD, with ensuing submucosal snaring, naming it as “ESS-CMI”. Actually, such procedure has already been unconsciously performed in treating large and difficult colonic neoplasms for EMR and ESD. But it is proposed by us with the formal name “ESS-CMI” for the first time. To further make the safety, feasibility and cost-effective comparison with ESD, we retrospectively collected and analyzed data of 278 patients receiving endoscopic treatment of colonic neoplasm.

## Methods

### Ethics

The current study was approved by the institutional review board of Zhejiang university and conducted in accordance with the Declaration of Helsinki. The study design and manuscript preparation fully followed the guidelines from the STROBE statement. Informed written consent was obtained from all patients before endoscopic treatment.

### Patients

The study design is a retrospective observational cohort study. We firstly screened the data in our endoscopic system with the Chinese item of “endoscopic submucosal dissection” and the English abbreviation of ESD, for the period between January 2011 and December 2017. The search restriction also includes “patients receiving colonoscopy”. Patients receiving ESD were selected according to the Japanese Gastroenterological Endoscopy Society Guidelines <sup>10</sup>. Actually, some patients who receive so

called “ESD” is just using submucosal snaring instead of submucosal dissection, after successful circumferential mucosa incision. We categorized those patients into the group of ESS-CMI. The rest patients were further categorized into the ESD group. The primary goal of endoscopic resection is effective and safe treatment without severe complications such as mass bleeding and perforation need for surgery. Data on patients’ and neoplasm’s characteristics, recurrence, treatment, follow-up and disease status (type, severity and location ) were collected after medical records review and prepared for further analysis. Recurrence was defined as the detection of local recurrence or distant metastasis during follow-up.

All lesions were incidentally identified by screening colonoscopy with various symptoms such as hematochezia, defecation difficulty, change of defecation habit, et al. The biopsy with histological evaluation were obtained and evaluated by independent pathologist prior to the procedure. All patients received enhanced contrast CT scan to evaluate the disease and rule out potential metastasis. Some patients were also further evaluated by endoscopic ultrasonography.

### **Procedures of ESD and ESS-CMI**

As shown in Figure 1, the common base for ESD and ESS-CMI is circumferential mucosa incision using a single-channel endoscope (GIF-Q260, Olympus, Tokyo, Japan) and electrosurgical generator with microprocessor controlled current (VIO 300D Endo Cut Q Effect 3; ERBE Elektromedizin, Tuebingen, Germany), including the sequential steps as: roundly labeling at the site 5mm outside the border line of the neoplasm with Argon plasma coagulation (ERBE, Elektromedizin, Tuebingen, Germany) or Dual knife (Olympus, Tokyo, Japan); injecting saline solution mixed with indigo carmine and noradrenalin into the submucosal layer under the neoplasm; performing circumferential incision at 5 mm outside the marking spot using Dual knife or Hook knife (Olympus, Tokyo, Japan). After thorough circumferential incision and fully lifting of the submucosal layer, the following procedure was furcated. For ESS-CMI, the single submucosal snaring was performed while for ESD, the submucosal layer was directly dissected using the same knife or IT knife (Olympus, Tokyo, Japan). Thereafter, the similar procedures of hemostasis and perforation prevention were routinely carried out for both ESS-CMI and ESD. During the process, precoagulation was performed on visible vessels by using hemostatic forceps (FD-410R, Olympus, Tokyo, Japan).

Sequential steps were carried out for sample management. At first, resected specimen was generally evaluated, including the length of longest side and the square of surface area. Light microscopy was then applied to determine the histological type, depth of invasion, lateral and vertical resection margin involvement and lymphovascular invasion. The degree of hyperplasia was determined by independent pathologist and divided into mild, moderate and severe. Mitotic count and Ki-67 index were assessed for determination of tumor grade under request. For those SMTs that are difficult to diagnosis, appropriate immunohistochemical staining was used.

### **Cost-effective analysis**

Generally, the cost-effective analysis includes two main aspects: treatment effect and complication as well as the cost and efficiency. Among them, en bloc resection was defined as resection of the entire lesion in a single piece. The treatment effect was evaluated by the combination of negativity of vertical cutting edge (NVCE), negativity of side cutting edge (NSCE), no interstitial infiltration (NII) and no vascular infiltration (NVI). The treatment complications usually include mass bleeding in operation that needs emergent surgery (MBO), delayed hemorrhage (DH), intra-operative perforation (IP), delayed operative perforation (DP). The cost and efficiency mainly include operation time (OT), relative operation time (ROT, OT/surface area), overall cost, operation related equipment cost (OREC) and average hospital stay (AHS). OT was defined as the period from identification of the neoplasm to completion of the dissection/snaring and bleeding/perforation control. Perforation was defined as rectal wall penetration observed during the endoscopic procedure or detected after endoscopy by radiology. Hemorrhage was defined as massive bleeding in the operation or hematochezia after operation that required hemostasis or transfusions. En bloc resection was defined as one-piece resection endoscopically. Endoscopic complete resection was defined as en bloc resection endoscopically without tumor involvement to the lateral and the vertical margins of the resected specimens.

## **Follow up**

All patients were periodically followed up by colonoscopy between approximately 6-12 months after endoscopic resection. If recurrent or remnant tumor was suspected, biopsy from the resected scar was performed.

## **Statistics**

Continuous variables were expressed as the means and standard deviations, while the differences in the groups were analyzed using unpaired t test or Mann-Whitney test as appropriate. For categorical variables,  $X^2$  test is used. if the total sample is over 40 and the frequency of each cell in the crosstabs is over 5, pearson-chi-square is used; if the total sample is less than 40 or the frequency of any cell in the crosstabs is less than 5, fisher's exact test is sued. P value <0.05 was considered statistically significant. SPSS version 19.0 was used for the whole analysis .

# **Results**

## **Base line characteristics**

After thorough endoscopy data search and careful evaluation, a total of 278 patients was finally selected. The anthropometric, disease status and pathology of those patients were summarized in Table 1. Briefly, of those patients, the average age is 57.62 year and the percentage of male gender is 60.4%. Rectum ranks the highest occurrence place (57.6%) of colonic neoplasm while Descending colon occupies the lowest place (2.2%). Concerning the severity of colonic neoplasm, the routine biopsy before operation showed that atypical hyperplasia of mild degree has the highest percentage of 17.6% while cancer has the lowest percentage of 1.4%. In contrast, the biopsy of ESD/ESS-CMI showed that atypical hyperplasia

of moderate degree has the highest percentage of 23.4% while no hyperplasia has the lowest percentage of 6.8%. The types of colonic neoplasm were also varied, where carcinoid has the highest rate of 28.4% while GIST, Hamartoma, Hemangioma and lipoma all have the occurrence rate less than 1%. The average longest side of colonic neoplasm is 2.25 cm and the average surface area is 5.99 cm<sup>2</sup> once the timed area was over 1 cm<sup>2</sup>. Though 59.7% patients was loss of follow up, the most common follow up method was colonoscopy (38.8%).

The patients were further categorized into ESD (n=132) and ESS-CMI (n=146) groups according to the endoscopy procedure. Among above mentioned parameters of age, gender, type, degree and location of colonic neoplasm, longest side and surface area of neoplasm and the method of follow up, the location of rectum, the longest side and the surface area were significantly higher in ESD group than those in ESS-CMI group (65.2%, 2.51±1.39, 7.09±7.10 vs 50.7%, 2.02±1.38, 5.01±7.98, respectively).

### **Cost-effective analysis**

To deeply evaluate and compare the cost and efficiency of ESD and ESS-CMI, we generally analyzed the parameters related with resection effect, operation cost and time, complication, recurrence rate and average hospital stay. In general, as shown in Table 2, There were no significant differences in the rates of en bloc resection, NSCE, NVCE, NII, NVI, MBO, DH, IP, DP and recurrence, indicating the similar treatment effect and safety of ESS-CMI when compared with ESD. Nevertheless, the significantly decreased values of OT, overall cost, OREC and AHS indicated that ESS –CMI were much cheaper and efficient than ESD. The decreased cost, operation time and average hospital stay but similar treatment effect and complication rate advocated the application of ESS-CMI in colonic neoplasm therapy.

We defined the failure of ESS-CMI as the unsuccessful en bloc resection and compared the characteristic parameters between patients with successful ESS-CMI and those were unsuccessful (Table 3). There were no significant differences in Age, longest side, surface area, neoplasm location, neoplasm severity and neoplasm type between patients with successful and failed ESS-CMI.

## **Discussion**

With the development of colonoscopy technique and the colon screening program, the discovery rate of colonic neoplasm has also been increasing, which accelerates the treatment method innovation, especially for those large neoplasms. Currently, except for EMR and EPMR, most LSTs and large sessile polyps are treated by wide-field EMR (WF-EMR) in the West, as it is documented to be a safe, effective and durable therapy<sup>11</sup>. Nevertheless, restricted by the limited size of snare, usually the neoplasm larger than 4 cm is difficult for WF-EMR, while the routine remedial EPMR has its own shortage, as it can not obtain the specimen as a whole and hence set the obstacle for accurate pathology evaluation. In contrast, ESD is the dominant technique for those neoplasms in the East, for its ability to achieve en bloc resection in over 80% of cases<sup>12,13</sup>. An advantage of ESD is the direct visualization of the submucosal layer beneath the tumors during submucosal dissection<sup>14</sup>.

However, ESD is technically challenging, more time and resource consuming, and has greater frequency of serious complications than WF-EMR. Though some revised ESD methods such as dental floss traction have been developed, its perforation rate still reaches as high as 5.7%, much higher than that of 1.4% in WF-EMR<sup>15</sup>. We believe that the procedure of circumferential mucosal incision is pivotal in ESD. After such incision, the snare is more easy to enclose the whole neoplasm from the submucosal layer. More importantly, we can control the degree and scale of incision to make a single successful snaring of the whole neoplasm. Therefore, we combine the CMI process with the process of snaring in EMR and create a novel procedure as ESS-CMI. Theoretically, no matter how big the neoplasm is, the ESS-CMI could be successfully performed, once the circumferential incision is completed.

Another important colon neoplasm is colonic neuroendocrine tumor, also named as carcinoid. It arises from the deep portion of gland, invades through the muscularis mucosa into the submucosa and therefore resembles subepithelial tumor<sup>16</sup>. Rectum is the most common occurrence site for GI carcinoid, where approximately 80% rectal carcinoids are 10 mm or less in size and contained within the submucosal layer, making them suitable for endoscopic removal<sup>17</sup>. Due to the high incomplete resection rate (14% to 62%), EMR is considered inadequate for treatment of rectal carcinoid<sup>18</sup>. Though ESD is now regarded as a valuable endoscopic treatment for rectal carcinoid for its higher en bloc resection rate, the perforation and hemorrhage rate are also increased, with prolonged hospital stay and increased medical cost<sup>19</sup>. As an alternative choice, recently developed endoscopic submucosal resection with a ligation device (ESMR-L) is an effective and safe procedure for carcinoid. However, the limitation that the size of neoplasm should be less than the size of ligation band (usually 10mm) is also obvious, putting an obstacle for large carcinoid therapy using the same method<sup>20</sup>. Therefore, as we mentioned before, ESS-CMI might be more suitable for rectal carcinoid, for its unlimited neoplasm size, similar en bloc resection rate as ESD and decreased medical cost and complications.

For colonic tumor, negative resection margins, well or moderate differentiation, absence of vascular or lymphatic invasion, depth of submucosal invasion of <1000 um and low-grade tumor budding are histological parameters associated with a low risk of lymph node metastasis and local recurrence<sup>21</sup>. Our study showed less medical expenses and shortened operation time of ESS-CMI. More importantly, such increased efficiency is not at the cost of effectiveness, as there were no significant differences in the complication and en bloc resection rates between ESD and ESS-CMI groups. Therefore, our results advocated the application of ESS-CMI in different types of colonic neoplasm.

There are several limitations should be admitted. Firstly, Since there were no significant different factors between the ESS-CMI successful and failure groups by univariate analysis, the ensuing multivariate analysis can not be performed. Secondly, the retrospective design of this study may decrease the results' credibility and further well organized cohort study (RCT will be the best) is urgently needed. Thirdly, due to the low number of ESS-CMI and ESD cases (especially for those patients with ESS-CMI failure), the subgroup analysis based on the type of colonic neoplasm such as LST and LST can not be carried out, which needs further revision in the future.

## Conclusion

The techniques that comprise the separate procedures of ESS-CMI have been widely performed. However, the combination of endoscopic submucosal snaring with circumferential mucosal incision to make a new concept as ESS-CMI is, for the first time, proposed by us. Our cost-effective retrospective study confirmed the similar effectiveness and complication rate of this novel treatment as ESD, but with less cost, operation time and hospital stay. Therefore, ESS-CMI might become a new choice for colonic neoplasm therapy.

## Abbreviations

AHS: average hospital stay; DH: delayed hemorrhage; DP: delayed operative perforation; EMR: endoscopic mucosal resection; EPMR: endoscopic piecemeal mucosal resection; ESD: endoscopic submucosal dissection; ESMR-L: endoscopic submucosal resection with a ligation device; ESS-CMI: endoscopic submucosal snaring with circumferential mucosal incision; GIST: gastrointestinal stromal tumor; IP: intra-operative perforation; LST: laterally spreading tumor; MBO: mass bleeding in operation; Nil: no interstitial infiltration; NSCE: negativity of side cutting edge; NVCE: negativity of vertical cutting edge; NVI: no vascular infiltration; OREC: operation related equipment cost; OT: operation time; ROT: relative operation time; SMT: submucosal tumor; WF-EMR: wide-field EMR.

## Declarations

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Availability of data and materials

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

JX and YMS carried out the data collection and drafted the manuscript; ZYX and ZRH participated in the design of the study and were involved in the statistical analysis; HY and ZXX participated in ESD operation. JF conceived of the study and supervised in its design and coordination. All authors read and approved the final manuscript.

#### Ethics approval

This study was performed according to the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocol using animals was approved by the institutional review board of the First Affiliated Hospital of Zhejiang University.

#### Consent to Publish

Not applicable.

#### Competing Interests

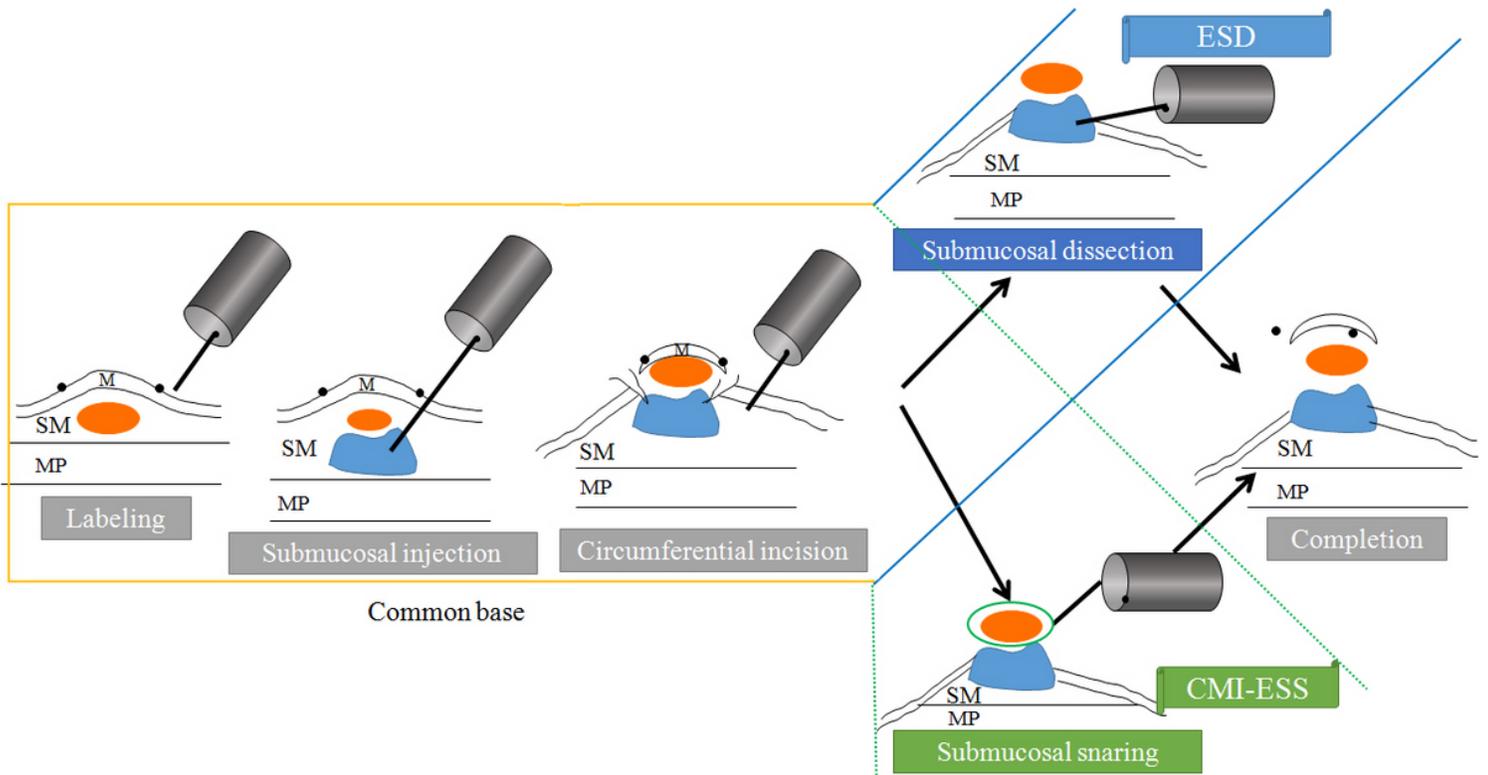
The authors declare that they have no competing interests.

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## Figures



**Figure 1**

Schematic presentation of ESD vs ESS-CMI

## Supplementary Files

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