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Clinical Study Protocol

Comparison of Two Electrosurgical Modes for Endoscopic Submucosal Dissection of Superficial Colorectal Neoplasms: A Prospective Randomized Study

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Endoscopic submucosal dissection (ESD) is reportedly one of the standard treatment strategies for large superficial colorectal neoplasms in Japan because of its high *en bloc* resection rate. A few technical issues regarding ESD should be considered, one of which is the selection of the Endo-cut I mode versus the Swift-coagulation mode as the electrosurgical unit mode setting during submucosal dissection. We seek to determine which of these two modes is more suitable for submucosal dissections of colorectal tumors with regard to procedure time and safety.

Key words: endoscopic submucosal dissection, electrosurgical mode, colorectal tumor

Endoscopic submucosal dissection (ESD) is one of the standard treatments for large gastrointestinal superficial neoplasms in Japan because of its high *en bloc* resection rate [1]. There have also been quite a few reports about ESD for colorectal neoplasms [2,3]. However, colorectal ESD still has a few improvable technical issues. One of these issues is the selection of the Endo-cut I mode versus the Swift-coagulation mode as the appropriate electrosurgical unit mode during submucosal dissection.

An electrosurgical unit has 2 basic electrocautery patterns: the cut current and the coagulation current. A cut current causes a more rapid increase in the target tissue temperature to >100°C, causing the cellular water to boil and the cells to rupture, leading to cleavage of the tissue that lies along the electrode. A coagulation current causes a slower increase in temperature within cells (between 70°C and 100°C) and causes the cells to dehydrate and shrink without bursting. The Endo-cut I mode is characterized by alternating a cutting current and the lowest peak voltage coagulation current. The continuous low voltage coagulation current of <200 peak voltage creates pure coagulation, which is called SOFT coagulation.

Conversely, a coagulation current is also able to create an incision effect when the current density is high and the contact area is narrow. The Swift coagulation mode is characterized by a pulse modulated sine wave with 20% of the high voltage, which allows both cutting and coagulation [4]. The Endo-cut I mode provides effective mucosal incision but has relatively low hemostatic ability. Conversely, the Swift-coagulation mode is designed to enhance coagulation more than the Endo-cut I mode.

To perform gastrointestinal ESD, it has generally

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been said that Swift-coagulation is suitable for the submucosal dissection phase because of the superiority of its hemostatic effect. However, the colorectum has fewer blood vessels than the esophagus. The Endo-cut I mode provides high-performance submucosal dissection and mucosal cutting, but its use is thought to increase the risk of bleeding and perforation in the colorectum where the wall is thinner than other gastrointestinal tracts.

Currently, the electrosurgical unit mode used during submucosal dissection phase in colorectal ESD depends completely on the preference of the operator. We decided to select the two modes conventionally used at our institution. There is no published report about which mode is more suitable; therefore, there are no criteria for operators to use. The aim of our planned study is to determine whether the Endo-cut I mode or the Swift-coagulation mode is more suitable for submucosal layer dissection during colorectal ESD.

Endpoints

The primary outcome is the total procedure time of colorectal ESD. The secondary outcomes are as follows: adverse events including perforation and postoperative bleeding, the number of times a coagulation hemostat was used, and the complete *en bloc* resection rate. Adverse events will be prospectively evaluated from the patients' records. The number of times homeostatic forceps were used will be counted by reviewing the automatically recorded intraoperative video. The *en bloc* resection rate and the complete resection rate will be evaluated after pathological examination. For our study, perforation will be deemed to have occurred when the ESD operator detects the perforation endoscopically during the ESD and the presence of free air is confirmed by abdominal X-ray by the morning following the ESD. Postoperative bleeding will be deemed to have occurred if the patient notices hematochezia within several hours after the ESD, and if hemostasis is required with emergency colonoscopy or the hemoglobin level is seen to have dropped by > 2 g/dl at the time of follow-up.

Eligibility Criteria

The patient inclusion criteria are: (1) tumor diagnosed with colonoscopy before ESD, (2) lesions 20-50 mm in dia., (3) suspected lesions of colorectal intramucosal or slight-invasion (SM < 1000 μm) cancer, and (4) suspected lesion with no lymph node or distant metastasis before ESD. The exclusion criteria are (1) non-correctable coagulopathy, (2) severe organ failure, (3) a comorbidity requiring continuous antithrombotic medication, (4) performance status > 2, (5) age < 20 years, (6) no provision of informed consent, and (7) the case is judged inappropriate by the chief medical examiner.

For this study, the following criteria were set as the discontinuation criteria: (1) occurrence of serious adverse events (perforation, major bleeding, *etc.*), (2) a high possibility that a serious adverse event will occur as evaluated by the ESD operator, and (3) difficulty continuing ESD for other reasons.

Design and Study Setting

This study has been designed as a prospective, randomized controlled trial and will be conducted in the endoscopy unit of the Okayama University Graduate School of Medicine, Japan between June 2018 and June 2020. The study has been registered in the University Hospital Medical Network Clinical Trials Registry (UMIN-CTR) as UMIN #000027638.

Ethics

The Institutional Review Board of Okayama University Hospital has approved this study. The approval number is 1805-003. We will obtain written informed consent from a parent or guardian of all of the subjects, preoperatively.

Study Intervention

The study intervention protocol is illustrated in Fig. 1. The study intervention will start after the patient's colonoscopy screening in the division of endoscopy. Subsequently, we will discuss the therapeutic strategy for lesions, including the above criteria, at the endoscopists' conference. The participants will be randomly assigned to treatment groups (Endo-cut I mode group and Swift-coagulation mode group) following simple randomization procedures. The randomization table has been prepared using Excel 2007 (Microsoft, Redmond, WA, USA). The endoscopists will be blinded to this allocation. However, when an

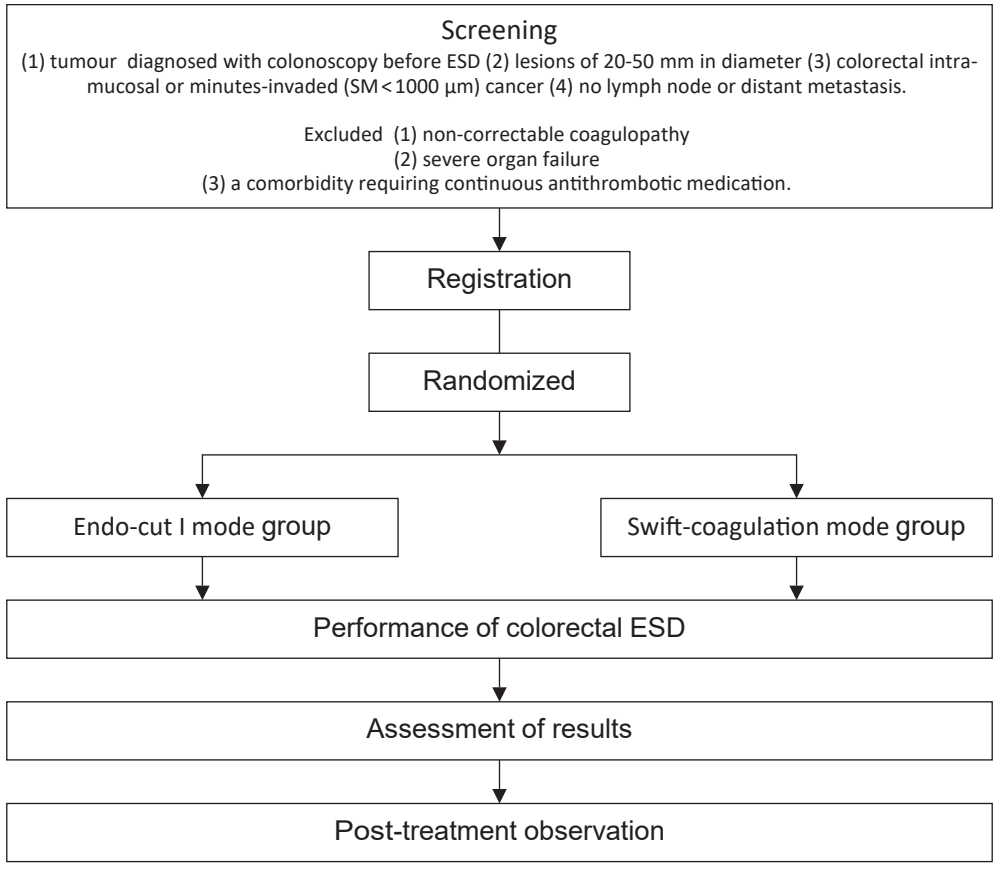

Fig. 1 The patient flow chart. ESD: endoscopic submucosal dissection.

ESD is performed, it is not feasible to blind the endoscopist to the treatment allocation.

General Setting of the ESD

The ESD will be performed under intravenous sedation using midazolam colonoscopy with a water jet function and a distal attachment cap (Olympus, Tokyo) for all cases. Tumor outlines will be delineated by chromoendoscopy with indigo carmine or narrow-band imaging. Each ESD will be conducted using the Dual knife® (Olympus) only for mucosal incision and submucosal dissection. As the tool used as a hemostat forceps, only the Coagrasper® (FD-410LR; Olympus) will be used. As an electrosurgical unit, we will use the VIO® 300D (Erbe, Tübingen, Germany) in all cases. Each knife is a dual knife with an Endo-cut I mode (Effect 1, duration 3, interval 3 for a marginal incision) and a Swift-coagulation mode (Effect 2, 35W). The Coagrasper has a soft-coagulation mode (Effect 5 80W) for hemostasis.

The operator in this study will be the endoscopist at our institute who has performed approx. 60 cases of colonic and approx. 70 cases of stomach ESD. All lesions will be resected using the same process, as follows. Step 1: A mucosal incision will be performed to make a flap to insert the colonoscope under the mucosa. Step 2: Submucosal dissection will be performed.

In this study, when the knife reaches the submucosal layer, the dissection phase will proceed promptly in the assigned mode. The time at which the mucosal incision phase ends and the submucosal dissection phase begins depends completely on the visual judgment of the operator. The total procedure time will be calculated by adding the time taken to perform Steps 1 and 2.

Data Collection

Investigators will collect the following data: patient

age, body weight, and gender; the pathological diagnosis of the tumor, vital signs during colorectal ESD, peripheral blood general and biochemical examination results, operation time, and adverse events.

Statistical Considerations

The sample size has been calculated based on the initial results for colorectal ESD at our institution. The mean procedure time for colorectal ESD is usually 70 min using a dual knife. We hypothesize that the procedure time using only the Endo-cut I mode will reduce the time by 15%, *i.e.*, approx. 60 min. Therefore, a total of 64 patients will be required in each group to detect a significant difference in a two-sided test with a significance level of 0.05 and a power of 80%. The outcomes of the present study, such as the procedure time, will be expressed as the mean ± standard deviation. Continuous variables will be compared using Student's *t*-test. Categorical variables will be compared using the χ^2-test or Fisher's exact test, as appropriate. The significance level has been set at $p < 0.05$. The statistical analyses will be performed using the JMP 10.0 software package for Windows (SAS Institute, Cary, NC, USA).

Discussion

To our knowledge, this study is the first single-arm prospective interventional study to determine which mode of the electric system of the VIO 300D electrosurgical unit is more appropriate for colorectal ESD.

A standard strategy for selecting the Endo-cut I mode or the Swift-coagulation mode for the dissection of the submucosal layer during colorectal ESD has not been established. It is hoped that this trial will assist in the establishment of a standard strategy for colorectal ESD. There has been no report regarding the selection of the electrical mode while performing ESD. This study will present findings that will most likely prove to be a unique resource well into the future.

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