Retrospective Cohort Study
High total Joule heat increases the risk of post-endoscopic submucosal dissection electrocoagulation syndrome after colorectal endoscopic submucosal dissection

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Abstract

BACKGROUND
We hypothesized that thermal damage accumulation during endoscopic submucosal dissection (ESD) causes the pathogenesis of post-ESD electrocoagulation syndrome (PECS).

AIM
To determine the association between Joule heat and the onset of PECS.

METHODS
We performed a retrospective cohort study in patients who underwent colorectal ESD from May 2013 to March 2021 in Japan. We developed a novel device that measures swift coagulation time with a sensor adjacent to the electrosurgical coagulation unit foot switch, which enabled us to calculate total Joule heat. PECS was defined as localized abdominal pain (visual analogue scale ≥ 30 mm during hospitalization or increased ≥ 20 mm from the baseline) and fever (temperature ≥ 37.5 degrees or white blood cell count ≥ 10000 µ/L). Patients exposed to more or less than the median Joule heat value were assigned to the high and low Joule heat groups, respectively. Statistical analyses included Mann-Whitney U and chi-square tests and logistic regression and receiver operating characteristic curve (ROC) analyses.

RESULTS
We evaluated 151 patients. The PECS incidence was 10.6% (16/151 cases), and all
patients were followed conservatively and discharged without severe complications. In multivariate analysis, high Joule heat was an independent risk factor. The area under the ROC curve showing the correlation between PECS and total Joule heat was high [0.788 (95% confidence interval: 0.666-0.909)].

**CONCLUSION**

Joule heat accumulation in the gastrointestinal wall is involved in the onset of PECS. ESD-related thermal damage to the peeled mucosal surface is probably a major component of the mechanism underlying PECS.

**Key Words:** Post-endoscopic submucosal dissection electrocoagulation syndrome; Joule heat; Colorectal endoscopic submucosal dissection; Colorectal neoplasms; Electrocoagulation; Gastrointestinal tract

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**Core Tip:** We investigated the association between Joule heat and the onset of post-endoscopic submucosal dissection electrocoagulation syndrome (PECS), using originally developed a device to measure swift coagulation time with a sensor adjacent to the electrosurgical coagulation unit foot switch which enabled us to calculate total Joule heat. High Joule heat was an independent PECS risk factor. Moreover, the area under the operating characteristic curve showing the correlation between PECS and total Joule heat was high. Joule heat accumulation is involved in the onset of PECS. submucosal dissection-related thermal damage of the peeled mucosal surface is probably a major component of the mechanism underlying PECS.

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**INTRODUCTION**

Colorectal endoscopic submucosal dissection (ESD), a minimally invasive operation, is the best endoscopic procedure for en bloc resection of superficial colorectal tumors[1-4]. However, ESD is associated with severe complications, with rates of perforation and bleeding of 2% to 14% and 0.7% to 3.1%, respectively[4-10]. Post-ESD electrocoagulation syndrome (PECS) is another notable adverse event that can occur after colorectal ESD. The incidence of PECS is 9% to 40%, although most cases improve with conservative therapy[11-15]. In addition, PECS sometimes manifests as a delayed perforation. Therefore, physicians require clinically useful PECS predictors to identify patients who are at risk[12,16].

Currently, two main hypotheses explain the mechanism underlying PECS. One suggests that ESD exposes the mucosa, which is then infected by intestinal bacteria, resulting in inflammation[13,17]. The other proposes that the peeled mucosal surface is inflamed by thermal damage during ESD[13,18]. Interestingly, a clamping closure method performed to prevent intestinal bacteria from infecting the exposed mucosa did not reduce the onset of PECS[19]. In contrast, few studies have examined the impact of thermal damage during ESD on the onset of PECS.

We have often encountered patients with PECS who underwent a lengthy colorectal ESD, and previous studies of PECS risk factors implicated prolonged ESD procedures [20,21]. We hypothesized that electrocoagulation is associated with Joule heat capable of causing thermal damage to the gastrointestinal wall during long ESD operations. Therefore, we aimed to determine the association between Joule heat and the onset of PECS.
Materials and Methods

Study design and patient selection
We performed a retrospective study in patients who underwent colorectal ESD at Hitachi General Hospital in Japan from May 2013 to March 2021. Case selection was according to the indications for colorectal ESD established by the Japan Gastroenterological Endoscopy Society guidelines[22]. Therefore, our inclusion criteria were as follows: (1) Laterally spreading tumors of the non-granular type with the Vi-type pit pattern, carcinomas with shallow T1 submucosal (SM) invasion, large depressed-type tumors, and large protruded-type tumors that are difficult to remove en bloc by endoscopic mucosal resection; and (2) Mucosal tumors with SM fibrosis. Patients with multiple colorectal neoplasms or apparent deeply invasive T1 SM carcinoma were excluded. R0 resection was defined as no cancer cells seen microscopically at the primary tumor site. We converted the swift-coagulation mode time, measured by an electrosurgical-coagulation unit with a high-frequency generator (VIO 300D, ERBE Co. Ltd., Tubingen, Germany), to Joule heat.

The Hitachi General Hospital Institutional Review Board approved the study (No. 2019-97, 2020-1), and our research was performed according to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments. The study is registered on the University Hospital Medical Information Network (ID: UMIN000038704, UMIN 000041580). Although our ethics committee waived the requirement for informed consent from each patient because we used anonymized data, we obtained informed consent using an opt-out option on our facility’s website (uniform resource locator below).

PECS definition
PECS was defined as localized abdominal pain and fever without apparent perforation after colorectal ESD. We used a visual analog scale (VAS) to evaluate localized abdominal pain. Nurses who were not research participants administered the VAS. The pain criteria were defined as a score ≥ 30 mm from the postoperative day (POD) 1 to discharge or increased by ≥ 20 mm from the hospital admission VAS score. Our fever criteria were body temperature ≥ 37.5 degrees or white blood cell count ≥ 10000 µ/L from POD 1 to discharge.

Colorectal ESD procedures
All patients underwent bowel preparation (polyethylene glycol, 2 L) before colorectal ESD. Then, the patients were sedated in the endoscopy room using intravenous injections of pentazocine (15-30 mg/kg body weight). We added midazolam (1-3 mg/session) if pentazocine was insufficient for sedation. Electrocardiogram monitoring was performed in each case. The procedures were performed by 10 endoscopists (one expert colorectal endoscopic surgeon and 9 less experienced colorectal endoscopic surgeons). An expert was defined as an endoscopist who performed more than 40 colorectal ESDs[22]. We used a water-jet system colonoscope (PCF-Q260JI, Olympus Corporation, Tokyo, Japan) with a transparent hood (DH-29CR for scope tip, Fujifilm, Tokyo, Japan) attached to the scope tip. Marking, mucosal incision, and mucosal detachment were performed with a dual knife (KD-655Q, Olympus Corporation). We injected 0.4% sodium hyaluronate acid diluted in physiological saline into the SM layer directly below the lesion before mucosal detachment. A coagrasper (FD-411QR, Olympus Corporation) and an endoscopic clip (HX-610-090, Olympus Corporation) were used to obtain hemostasis.

Calculating Joule heat
We used the electrosurgical-coagulation unit to detach the lesion’s colorectal mucosa. We changed the setting mode according to the procedure step and used dry-cut, swift-coagulation, and soft-coagulation modes. We calculated the power applied using the diagram in the manufacturer’s technical manual that shows the relationship between resistance (Ω) and power (W) in the swift-coagulation mode (Supplementary material). As human internal resistance is 1000-1600 Ω[24], the lesion resistance was defined as 1300 Ω. Thus, lesions are detached while the electrosurgical-coagulation unit automatically adjusts the power output. However, this automatic power adjustment is difficult to monitor.

The curve describing the relationship between power (vertical axis) and resistance (horizontal axis) in the manufacturer’s technical diagram (we used effect 4 in our study) showed that the power corresponding to 1300 Ω is 50 W (Supplementary material). Therefore, we obtained the formula: power consumption (J) = power (W) ×
time (s) from the relationship between power and power consumption. We used this formula to calculate the total Joule heat applied to the lesion.

We developed a novel device to measure the swift coagulation time with a sensor [Miniature Basic Switch (D3V-016-1C23), OMRON Corporation, Kyoto, Japan] adjacent to the foot switch of the electrosurgical coagulation unit (Figure 1). This sensor was activated when the operator stepped down on the foot switch, and the swift-coagulation mode time was recorded by a counter [Total Counter (H7ET-N1), OMRON Corporation]. In cases where the swift-coagulation time was not measured, we retrospectively calculated the time using the data (swift-coagulation mode time/procedure time: Mean 3%) obtained from the measured cases. Patients exposed to more or less than the median Joule heat value (8460 J) were assigned to the high and low Joule heat groups, respectively.

**Post-ESD hospitalization**
In all patients, on POD 1, the vital signs and a blood sample were examined to check for bleeding, the pain VAS was administered, and radiography was performed to check for free air. We considered a fever, localized abdominal pain, or increased C-reactive protein suspicious for delayed perforation associated with PECS. If the pain or fever criteria were satisfied, we performed computed tomography. In the absence of adverse findings, patients resumed eating, starting with dinner on POD 1. If no fever, localized abdominal pain, or bleeding occurred after eating resumed, patients were discharged on POD 6.

**Statistical analysis**
We analyzed continuous and categorical variables using Mann-Whitney U and chi-square tests, respectively. In our multivariate analysis, we performed logistic regression analyses using important factors identified by univariate analysis. We determined the cutoff of the total Joule heat value that predicted the onset of PECS using receiver operating characteristic (ROC) curve analysis. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (version 26, IBM Corp., Armonk, NY, United States). The statistical methods of this study were reviewed by Masanori Ochi from the Department of
Gastroenterology, Hitachi General Hospital, Japan.

RESULTS

Baseline characteristics
Of 170 patients admitted for colorectal ESD, 19 met the exclusion criteria (multiple lesions, n = 6; post-ESD infection, n = 2; perforation during ESD, n = 7; ESD discontinuation, n = 4) (Figure 2). We analyzed the remaining 151 patients [mean age, 67.3 years (range 39-92); male, 62.3%]. Tumors occurred in the right colon (n = 59, 39.1%), left colon (n = 41, 27.2%), and rectum (n = 51, 33.8%). R0 and en bloc resections were achieved in 115 patients (76.2%) and 135 patients (89.4%), respectively; and PECS occurred in 16 patients (10.6%) (Table 1).

Primary outcome
The high (n = 76) and low (n = 75) Joule heat groups showed no statistically significant difference in sex; tumor morphology, location, or depth of pathological invasion; R0 resection rate; or incidence of SM fibrosis (Table 2). Univariate analyses revealed that patient age was significantly greater, and the PECS incidence was significantly higher in the high Joule group than in the low Joule group; the specimen size was also significantly larger in the high Joule group. Compared to the low Joule heat group, the high Joule heat group included more patients who had undergone ESD performed by a trainee, and the difference was significant. In addition, the R0 resection rate was significantly higher in the low Joule group. Multivariate analysis showed that the R0 resection rate [odds ratio (OR), 3.27; 95% confidence interval (CI): 1.26-8.45; P = 0.01] and PECS incidence (OR, 4.83; 95% CI: 1.08-21.50; P = 0.03) were significantly higher and the specimen size (OR, 1.07; 95% CI: 1.03-1.11; P < 0.01) and number of ESD procedures performed by a trainee (OR, 5.30; 95% CI: 2.32-12.10; P < 0.01) were significantly larger in the high Joule heat group than in the low Joule heat group (Table 3).

PECS and Joule heat correlation analysis
The area under the ROC curve showing the correlation between PECS and total Joule heat was 0.788 (95% CI: 0.666-0.909), and the PECS onset cutoff value was 15390 J (sensitivity, 0.625; specificity, 0.822) (Figure 3).

DISCUSSION
To our knowledge, this study, performed using our novel device, is the first to indicate high total Joule heat exposure during colorectal ESD as a PECS risk factor. Additionally, PECS and Joule heat were highly correlated, and the Joule heat cutoff value where PECS occurred was 15390 J.

PECS is a state of temporary inflammation resulting from transmission of electrocoagulation heat to the resection site muscle layer and serous membrane during endoscopic therapy[18,25,26]. Previously reported PECS risk factors include tumor location[11,13,20,27], SM fibrosis[27], long procedure time[20,21], and specimen diameter[11,13]. Long procedures lead to the occurrence of PECS due to increased electrical current load on the gastrointestinal wall[11]. Additionally, ischemic changes occur in the gastrointestinal wall due to excessive current during incision, dissection, and hemostasis[28]. These reports suggest that Joule heat of the peeled mucosal surface is associated with the occurrence of PECS.

A study of lengthy procedures (mean, 90 min) demonstrated that long procedure time is a PECS risk factor[20]. However, several studies that did not include long procedure time as a PECS risk factor showed that the procedures were short (range, 52-67 min)[11,28,29]. Our study revealed that ESD procedures performed by trainees are associated with the onset of PECS. A previous study showed that ESD procedures performed by trainees are longer than those performed by experienced endoscopists[23]. Because the swift-coagulation mode time probably increases as the procedure time lengthens, high Joule heat accumulation is likely to occur during long ESDs, causing severe damage to the peeled mucosal surface, leading to PECS. Previous studies were limited in that they did not consider the impact of the ESD procedure time on the Joule heat delivered to the lesion. In this study, measurement of swift-coagulation mode time allowed us to investigate the association between PECS and
Table 1 Characteristics of patients who underwent endoscopic submucosal dissection, n (%)

| Patient features                                             | n (%) |
|--------------------------------------------------------------|-------|
| Number of patients                                          | 151   |
| Male                                                        | 94 (62.3) |
| Age (yr), mean ± SD                                         | 67.3 ± 10.9 |
| BMI (kg/m²), mean ± SD                                      | 22.9 ± 3.0 |
| Specimen size                                               |       |
| < 40 mm                                                     | 132 (87.4) |
| ≥ 40 mm                                                     | 19 (12.6) |
| Total Joule heat                                            |       |
| < 8460 J¹                                                   | 75 (49.7) |
| ≥ 8460 J                                                    | 76 (50.3) |
| Tumor location                                              |       |
| Right colon                                                 | 59 (39.1) |
| Left colon                                                  | 41 (27.1) |
| Rectum                                                      | 51 (33.8) |
| Tumor morphology                                            |       |
| 0-Is/Ip                                                     | 29 (19.2) |
| LST-G                                                       | 75 (49.7) |
| LST-NG (0-IIc)                                              | 47 (31.1) |
| Depth of pathological invasion                              |       |
| Tis (M)                                                     | 130 (86.1) |
| T1 (SM)                                                     | 21 (13.9) |
| Histological diagnosis                                      |       |
| Adenoma                                                     | 67 (44.4) |
| Adenocarcinoma                                              | 80 (53.0) |
| Other                                                       | 4 (2.6) |
| ECOG performance status after ESD                           |       |
| 0                                                           | 144 (95.4) |
| ≥1                                                          | 7 (4.6) |
| R0 resection                                                | 115 (76.2) |
| ESD procedure performed by trainees                         | 52 (34.4) |
| Additional endoscopic therapy after ESD                     | 2 (1.3) |
| Additional surgery after ESD                                | 12 (7.9) |
| En bloc resection                                           | 135 (89.4) |
| Intraoperative perforation or penetration                    | 7 (4.6) |
| Submucosal fibrosis                                         | 45 (29.8) |
| PECS                                                        | 16 (10.6) |

¹Patients exposed to more or less than the median Joule heat value (8460 J) were assigned to the high and low Joule heat groups, respectively.

BMI: Body mass index; Is: Sessile type; Ip: Pedunculated type; LST-G: Lateral spreading tumor granular type; LST-NG: Lateral spreading tumor non-granular type; Ilc: Superficial depressed type; Tis (M): Carcinoma in situ or intramucosal carcinoma; T1 (SM): Tumor invades submucosa; R0: Microscopically margin-negative; ESD: Endoscopic submucosal dissection; PECS: Post-endoscopic submucosal dissection electrocoagulation syndrome; SD: Standard deviation; ECOG performance status: Eastern Cooperative Oncology Group performance status.

Our study revealed that the total Joule heat applied to the peeled
Table 2 Clinicopathological factors in the high and low Joule heat groups, n (%)  

|                              | High Joule heat | Low Joule heat | P value |
|------------------------------|-----------------|----------------|---------|
| **Sex**                      |                 |                | 0.54    |
| Male                         | 45 (59.2)       | 49 (65.3)      |         |
| Female                       | 31 (40.8)       | 26 (34.7)      |         |
| **Age (yr), mean ± SD**      |                 |                | < 0.01  |
|                             | 69 ± 11.5       | 66 ± 10.2      |         |
| **BMI (kg/m²), mean ± SD**   |                 |                | 0.77    |
|                             | 22.8 ± 2.3      | 23.0 ± 3.2     |         |
| **Specimen size**            |                 |                | < 0.01  |
| < 40 mm                      | 60 (78.9)       | 73 (97.3)      |         |
| ≥ 40 mm                      | 16 (21.1)       | 2 (2.7)        |         |
| **Tumor location**           |                 |                | 0.84    |
| Right colon                  | 28 (36.9)       | 31 (41.3)      |         |
| Left colon                   | 21 (27.6)       | 20 (26.7)      |         |
| Rectum                       | 27 (35.5)       | 24 (32.0)      |         |
| **Tumor morphology**         |                 |                | 0.56    |
| 0-Is/Ip                      | 18 (23.7)       | 21 (28.0)      |         |
| LST-G                        | 36 (47.4)       | 29 (38.7)      |         |
| LST-NG (0-IIc)               | 22 (28.9)       | 25 (33.3)      |         |
| **Depth of pathological invasion** |             |                | 0.66    |
| Tis (M)                      | 64 (84.2)       | 66 (88.0)      |         |
| T1 (SM)                      | 12 (15.8)       | 9 (12.0)       |         |
| **Histological diagnosis**   |                 |                | 0.12    |
| Adenoma                      | 34 (44.7)       | 33 (44.0)      |         |
| Adenocarcinoma               | 42 (55.3)       | 38 (50.7)      |         |
| Other                        | 0 (0.0)         | 4 (5.3)        |         |
| **Performance status after ESD** |             |                | 0.45    |
| 0                            | 71 (93.4)       | 73 (97.3)      |         |
| ≥ 1                          | 5 (6.6)         | 2 (2.7)        |         |
| R0 resection                 | 50 (65.8)       | 65 (86.7)      | < 0.01  |
| ESD procedure performed by trainees | 37 (55.3)   | 15 (13.3)      | < 0.01  |
| Additional endoscopic therapy after ESD | 1 (1.3)   | 1 (1.3)        | 0.999   |
| Additional surgery after ESD | 8 (10.5)        | 4 (5.3)        | 0.38    |
| En bloc resection            | 69 (90.8)       | 73 (97.3)      | 0.18    |
| Submucosal fibrosis          | 27 (35.5)       | 18 (24.0)      | 0.17    |
| **PECS**                     | 13 (17.1)       | 3 (4.0)        | 0.02    |

BMI: Body mass index; Is: Sessile type; Ip: Pedunculated type; LST-G: Lateral spreading tumor granular type; LST-NG: Lateral spreading tumor non-granular type; Ilc: Superficial depressed type; Tis (M): Carcinoma in situ or intramucosal carcinoma; T1 (SM): Tumor invades submucosa; R0: Microscopically margin-negative; ESD: Endoscopic submucosal dissection; PECS: Post-endoscopic submucosal dissection electrocoagulation syndrome; SD: Standard deviation.

Surface involvement is involved in the development of PECS. Furthermore, using the total Joule heat cutoff value of PECS occurrence could allow the introduction of PECS prevention measures, including online measurement of swift-coagulation mode time during colorectal ESD. For example, an online PECS alert system is promising.
Table 3 Multivariate analysis of risk factors associated with high Joule heat accumulation

| Risk Factor                                      | Odds ratio | 95%CI     | P value |
|--------------------------------------------------|------------|-----------|---------|
| Age                                              | 1.03       | 0.99-1.06 | 0.17    |
| R0 resection                                     | 3.27       | 1.26-8.45 | 0.01    |
| Specimen size                                    | 1.07       | 1.03-1.11 | < 0.01  |
| ESD procedure performed by trainees              | 5.30       | 2.32-12.10| < 0.01  |
| PECS                                             | 4.83       | 1.08-21.50| 0.03    |

PECS: Post-endoscopic submucosal dissection electrocoagulation syndrome; R0: Microscopically margin-negative; 95% CI: 95% confidence interval.

Figure 2 Study flowchart. ESD: Endoscopic submucosal dissection.

Figure 3 Receiver-operating characteristic curve showing the correlation between post-endoscopic submucosal dissection electrocoagulation syndrome and total Joule heat [area under the curve = 0.788 (95% confidence interval: 0.666-0.909)].
**Limits of the study**
First, because this was a retrospective cohort study, we could not rule out poor endoscope operability as a confounding factor. Second, as this was a single-center study, selection bias cannot be excluded. Nevertheless, we imposed strict inclusion and exclusion criteria to mitigate selection bias to the greatest extent possible. Last, the sample size was small. In the future, a prospective study should be performed to establish the validity of our results.

**CONCLUSION**
We found that Joule heat accumulation within the gastrointestinal wall is involved in the onset of PECS. ESD-related thermal damage to the mucosal peeled surface is probably a major component of the mechanism underlying PECS.

**ARTICLE HIGHLIGHTS**

**Research background**
Few studies have examined the impact of endoscopic submucosal dissection (ESD)-related thermal damage on the onset of post-ESD electrocoagulation syndrome (PECS).

**Research motivation**
We hypothesized that electrocoagulation is associated with Joule heat capable of causing thermal damage to the gastrointestinal wall during long ESD operations.

**Research objectives**
We aimed to determine the association between high Joule heat and the onset of PECS.

**Research methods**
We developed a novel device to measure the swift coagulation time with a sensor adjacent to the electrosurgical coagulation unit foot switch, which enabled us to calculate total Joule heat. PECS was defined as localized abdominal pain (visual analogue scale ≥ 30 mm during hospitalization or increased by ≥ 20 mm from the baseline) and fever (temperature ≥ 37.5 degrees or white blood cell count ≥ 10000 µ/L). Patients exposed to more or less than the median Joule heat value were assigned to the high and low Joule heat groups, respectively.

**Research results**
We evaluated 151 patients. The PECS incidence was 10.6% (16/151 cases), and all patients were followed conservatively and discharged without severe complications. In multivariate analysis, high Joule heat was an independent PECS risk factor. The area under the ROC curve showing the correlation between PECS and total Joule heat was high [0.788 (95% confidence interval: 0.666-0.909)].

**Research conclusions**
Joule heat accumulation in the gastrointestinal wall is involved in the onset of PECS. ESD-related thermal damage of the peeled mucosal surface is probably a major component of the mechanism underlying PECS.

**Research perspectives**
Future prospective studies should be performed to establish the validity of our results.

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