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ORIGINAL RESEARCH—CLINICAL

Conventional Clips vs Over-the-Scope Clips for Mucosal Defects Closure After Duodenal Endoscopic Submucosal Dissection

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BACKGROUND AND AIMS: Over-the-scope clips (OTSCs) are used for treating gastrointestinal perforations, postoperative anastomotic leakages, and mucosal defect closure after endoscopic resections. However, OTSCs are expensive and associated with fatal complications; therefore, proper OTSC usage is necessary. Criteria of OTSC use for mucosal defect closure after duodenal endoscopic submucosal dissection (ESD) are scarce. We examined closure outcomes with OTSCs and conventional clips in patients undergoing duodenal ESD, analyzed the resected specimen area, estimated the preoperative size of tumors treated with each method, and attempted to clarify the criteria for the use of OTSCs vs conventional clips. **METHODS:** Endoscopic resection was performed for 133 superficial duodenal epithelial tumors from April 2017 to February 2022. Complete closure of mucosal defects after duodenal ESD was attempted for 82 superficial non-ampullary duodenal epithelial tumors, divided into OTSC and control (conventional clips used) groups. Closure outcomes were analyzed. **RESULTS:** The overall rate of complete mucosal defect closure in both groups was 98.8%. Significant between-group differences existed in the median estimated tumor size and median resected specimen area. **CONCLUSION:** Conventional clips work well for mucosal defects $\leq$18 mm after duodenal ESD, but for those >18 mm, a combination of OTSCs may be considered.

Keywords: Bleeding; Duodenum; Endoscopic submucosal dissection; Over-the-scope clip; Perforation

See editorial on page 1136.

Introduction

An over-the-scope clip (OTSC; Ovesco Endoscopy GmbH, Tübingen, Germany) is useful for treating gastrointestinal perforation, postoperative anastomotic leakage, and bleeding.[1] OTSCs are also useful for the complete closure of mucosal defects to prevent adverse events due to exposure to bile or pancreatic juice after duodenal endoscopic submucosal dissection (ESD).[2–4] Additionally, there have been reports of endoscopic resection of duodenal tumors using OTSCs,[5] and OTSCs are gaining recognition in many fields. In cases of gastrointestinal perforations, closure with OTSCs or through-the-scope clips should be considered if the perforation size is < 2 cm; however, a combination of through-the-scope clips and PolyLoop ligating device or endoscopic sutures should be considered if the size is $\geq$ 2 cm.[6] So far, no studies have clearly demonstrated the size of the mucosal defect that requires OTSCs or the criteria for using OTSCs to close mucosal defects after duodenal ESD. The rates of delayed bleeding and delayed perforation after duodenal ESD are very high compared to those observed after ESD of other organs, which is largely because of the exposure of duodenal mucosal defects to bile and pancreatic juice.[7,8] Therefore, complete closure of mucosal defects is necessary to prevent severe adverse events, and OTSCs are often used for this purpose.[2–4] Although OTSC usage results in a high rate of complete closure (>90%), there are some caveats. The OTSC is difficult to deploy if the tumor is in a flexure, such as the superior or inferior duodenal angle, and there is a slight risk of critical bleeding or perforation if deployed incorrectly.[2] Furthermore, OTSCs cost approximately $800 per unit; an additional $900 is required if the twin-grasper method is used. Therefore, considering the medical costs, avoiding the overuse of OTSCs and using them appropriately is desirable.

Our study aimed to determine the appropriate use of conventional clips and OTSCs for complete closure of mucosal defects after duodenal ESD based on the preoperative estimated tumor size and area of the resected specimen.

Methods

Study Design and Ethical Statements

This retrospective cohort study was conducted at Saitama Medical University International Medical Center in Japan. It was

Abbreviations used in this paper: **ESD, endoscopic submucosal dissection; IQR, interquartile range; n, number; OTSCs, over-the-scope clips; SD, standard deviation.**

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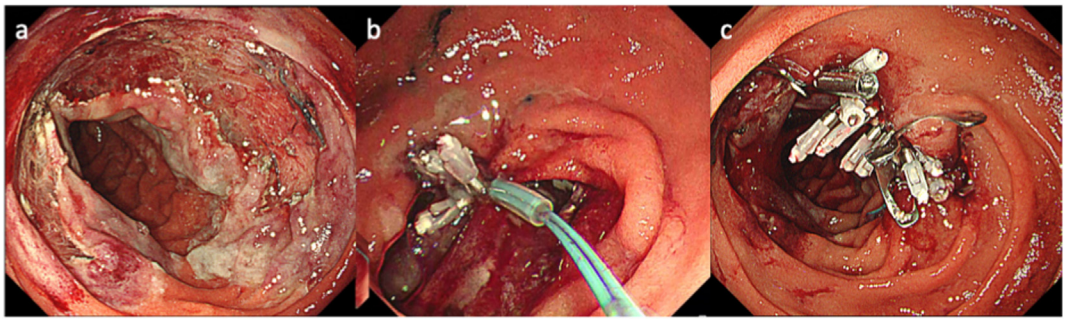

Figure 1. Combination of conventional clips, PolyLoop ligating device sutures, and over-the-scope clips for closing a large mucosal defect (A) Mucosal defect in the descending part of the duodenum after endoscopic submucosal dissection. The resected specimen diameter was 61 × 60 mm. The resected tumor diameter was 60 × 55 mm. (B) The mucosal defect size was reduced using PolyLoop ligating device sutures and conventional clips. (C) Subsequently, the defect was closed with 2 over-the-scope clips using the aspiration method. The closure time was 45 minutes. The remaining mucosal defect was completely closed with additional conventional clips.

approved by the institutional review board of Saitama Medical University International Medical Center (institutional ID: 20-249) and performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Patients

Endoscopic resection was performed for 133 superficial duodenal epithelial tumors at our institution from April 2017 to February 2022. Among them, 7 ampullary tumors, 2 tumors observed during laparoscopy and endoscopy cooperative surgery, and 33 tumors observed during endoscopic mucosal resection were excluded. We also excluded 9 tumors in the duodenal bulb. Finally, 82 superficial non-ampullary duodenal epithelial tumors for which complete mucosal defect closure after duodenal ESD was attempted were included in the analysis. The cases were divided into 2 groups: the OTSC group had 55 cases, and the control group (for which only conventional clips were used) had 27 cases (Supplementary Material).

OTSC and Control Groups

OTSC group. At least one OTSC was used in each case. Depending on the size of the mucosal defect, conventional clips (EZ Clip, HX-610-135, HX-610-090L; Olympus) and PolyLoop ligating device sutures (HX21L1, MAJ339; Olympus) were used with OTSCs (Figure 1).

Control group. Only conventional clips (EZ Clip, HX-610-135, HX-610-090L; Olympus) were used (Figure 2).

Preparation for Duodenal ESD

In general, duodenal endoscopic mucosal resection was performed under intravenous anesthesia in the endoscopy room, and duodenal ESD was performed under general anesthesia in the operating room. However, the procedure was performed under intravenous anesthesia when the risk of performing duodenal ESD under general anesthesia was estimated to be high based on the patient's general condition. Under intravenous anesthesia, our endoscopists adjusted the dosage of midazolam, pethidine, and dexmedetomidine according to the patient's condition. The antispasmodic drugs used were scopolamine for patients with no cardiac disease or benign prostatic hyperplasia and glucagon for patients with these conditions. All duodenal ESDs were performed by a few endoscopists at our institution. All ESD procedures were performed using a therapeutic endoscope (GIF-H290T or GIF-Q260J; Olympus, Medical Systems Co., Tokyo, Japan) with a transparent cap (D-201-11,804; Olympus). Regarding endoscopic devices, we used 1.5-mm DualKnife J (KD655Q; Olympus) to perform mucosal incision or submucosal dissection. Depending on the circumstances of each case, a 3.5-mm Clutch Cutter (Fujifilm Co, Tokyo, Japan) was used as an adjunct. The endoCUT I (effect 1, duration 4, interval 1), forced coagulation (effect 2, 45 W), and soft coagulation (effect 4, 60 W) modes of an electrosurgical generator (VIO 300D; ERBE Elektromedizin, Tübingen, Germany) were used for mucosal incision, submucosal dissection, and hemostatic procedure, respectively. A local injection of 0.4% sodium hyaluronate (MucoUp; Boston Scientific, Tokyo, Japan) combined with a small amount of indigo carmine was administered into the submucosa to elevate it firmly and ensure optimal visualization.

Definitions of Outcomes

Complete closure: Several endoscopists retrospectively evaluated the cases for complete closure with reference to the endoscopic findings at the time. En bloc resection: A one-piece resection that included the entire tumor. Procedure time: The time from the initial mucosal incision to tumor resection. Resected specimen area: Calculated using the following equation: the largest diameter of the resected specimen (mm)/2 × the smallest diameter of the specimen (mm)/2 × 3.14. Intraoperative perforation: A perforation that occurred during duodenal ESD. Delayed perforation: A perforation diagnosed using computed tomography after duodenal ESD. Delayed bleeding: Hemorrhage that required additional endoscopic hemostasis after duodenal ESD. Resectability: It was classified into 3 categories based on the final pathological diagnosis, as follows: R0, both the horizontal and vertical margins were negative; RX, either the horizontal or the vertical margin was unclear; and R1, either the horizontal or the vertical margin was positive. Surgery due to adverse events: Cases requiring

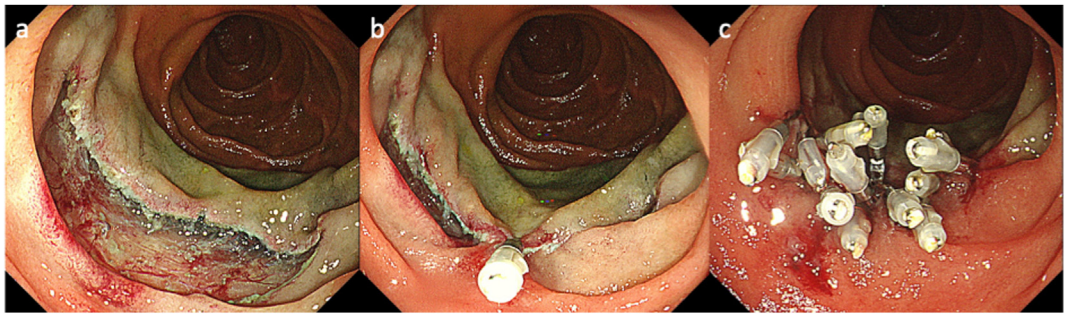

Figure 2. Use of only conventional clips to close mucosal defects (A) Mucosal defect in the descending part of the duodenum after endoscopic submucosal dissection. The resected specimen diameter was 26 × 20 mm. The resected tumor diameter was 18 × 18 mm. (B) First, the center of the mucosal defect was closed with a conventional clip. (C) Next, more conventional clips were added to the remaining mucosal defect, and complete closure was performed. The closure time was 18 minutes.

surgery due to duodenal ESD-related complications. Closing time: Time from re-insertion of the endoscope after specimen retrieval until the end of the closure procedure. Additional treatment: A case that required endoscopic treatment or surgery due to adverse events associated with OTSC application.

Statistical Analysis

First, we compared patient characteristics and duodenal ESD outcomes of the 2 groups to identify case bias, if any. Thereafter, we focused on the preoperatively estimated tumor size and resected specimen area and calculated their median values for each closure method. Binary variables of the 2 groups were compared using Pearson's chi-square test, and continuous variables were compared using the Mann–Whitney U test or Student's *t*-test. All analyses in this study were performed using STATA version 17 (StataCorp, College Station, TX, USA). Finally, $P < .05$ was considered statistically significant.

Results

Characteristics of the Patients

The following background characteristics of the patients were compared between the OTSC (n = 55) and control (n = 27) groups: age, sex, tumor location, occupied circumference, macroscopic classification, estimated tumor size, preoperative biopsy findings, and antithrombotic therapy. Between the 2 groups, there were significant differences in sex (47.8% female vs 11.1 % male; $P = .001$), median estimated tumor size (20 mm vs 15 mm; $P < .001$), and antithrombotic therapy use (0% vs 11.1%; $P = .012$) (Table 1).

Table 1. Characteristics of the Patients in the OTSC Group and Control Group

	OTSC group (n = 55)	Control group (n = 27)	*P* value
Age, mean (SD)	62.3 (11.1)	67.3 (10.3)	.052
Female, n (%)	26 (47.3)	3 (11.1)	.001
Tumor location, n (%)			.093
Bulb	0 (0)	0 (0)	
Superior duodenal angle	5 (9.1)	5 (18.5)	
Descending part	40 (72.7)	22 (81.5)	
Inferior duodenal angle	6 (10.9)	0 (0)	
Transverse part	4 (7.3)	0 (0)	
Occupied circumference, n (%)			.15
< 1/2	51 (92.7)	27 (100)	
> 1/2	4 (7.3)	0 (0)	
Macroscopic classification, n (%)			.52
0-I	2 (3.6)	1 (3.7)	
0-IIa	50 (90.9)	22 (81.5)	
0-IIc	1 (1.8)	2 (7.4)	
0-IIa + IIc	2 (3.6)	2 (7.4)	
Estimated tumor size, mm (IQR)	20 (18–30)	15 (12–15)	<.001
Preoperative biopsy, n (%)			.068
Yes	53 (96.4)	23 (85.2)	
Antithrombotic therapy, n (%)			.012
Yes	0 (0)	3 (11.1)	

n, number; SD, standard deviation.

Outcomes of Duodenal ESD

We included 82 cases in which complete closure of mucosal defects after duodenal ESD was attempted. Of these, 55 cases were included in the OTSC group and 27 in the control group. Complete closure of mucosal defects was successfully achieved in 81 cases; however, it was unsuccessful in one case in the OTSC group. The outcome measures used to evaluate the 2 groups were en bloc resection, procedure time, resected tumor diameter, largest diameter of the resected specimen, smallest diameter of the resected specimen, resected specimen area, intraoperative perforation, delayed bleeding, delayed perforation, surgery due to adverse events, final pathological diagnosis, lymphovascular invasion, resectability, and recurrence. Between the groups, there were significant differences in the median resected tumor diameter (20 mm vs 15 mm; $P < .001$), median largest diameter of the resected specimen (24 mm vs 18 mm; $P < .001$), and median smallest diameter of the resected specimen (18 mm vs 12 mm; $P = .0001$). Moreover, the median resected specimen areas in the OTSC and control groups were 339.1 mm^2 (interquartile range [IQR] = 235.5–604.5 mm^2) and 169.6 mm^2 (IQR = 141.3–266.9 mm^2), respectively (Table 2). The median estimated preoperative tumor sizes were 20 mm (IQR = 18–30 mm) and 15 mm (IQR = 12–15 mm) in the OTSC and control groups, respectively. Spearman's rank correlation coefficient between the estimated preoperative tumor size and resected specimen area was 0.847 ($P < .001$), indicating a strong correlation.

Outcomes of Complete Mucosal Defect Closure after Duodenal ESD

The combined rate of complete mucosal defect closure in the 2 groups was 98.8% (95% confidence interval = 93.39–99.97%). There was no significant difference in the rate of complete mucosal defect closure and closing time between the 2 groups (Table 2). The average number of OTSCs used in the OTSC group (n = 55) was 1.4 (standard deviation = 0.56), and the OTSC was deployed using the suction method in 90.9% (n = 50) and the twin-grasper method in 9.1% (n = 5) of cases. In one case, the OTSC was deployed to the ulcer during ESD, and complete closure failed; however, none of the patients required additional treatment because of adverse events associated with an OTSC (Table 3).

Table 2. Outcomes of Duodenal ESD in the OTSC Group and Control Group

	OTSC group (n = 55)	Control group (n = 27)	*P* value
En bloc resection, n (%)			1.0
Yes	55 (100)	27 (100)	
Procedure time, min (IQR)	45 (30–75)	36 (24–43)	.012
Resected tumor diameter, mm (IQR)	20 (17–29)	15 (12–17)	<.001
Resected specimen, largest diameter, mm (IQR)	24 (22–35)	18 (18–22)	<.001
Resected specimen, smallest diameter, mm (IQR)	18 (15–23)	12 (10–17)	.0001
Resected specimen area, mm^2 (IQR)	339.1 (235.5–604.5)	169.6 (141.3–266.9)	<.001
Intraoperative perforation, n (%)			.27
Yes	6 (10.9)	1 (3.7)	
Delayed bleeding, n (%)			.99
Yes	2 (3.6)	1 (3.7)	
Delayed perforation, n (%)			1.0
Yes	0 (0)	0 (0)	
Surgery due to adverse events, n (%)			1.0
Yes	0 (0)	0 (0)	
Final pathology, n (%)			.11
Adenoma	32 (58.2)	16 (59.3)	
Intramucosal cancer	23 (41.8)	9 (33.3)	
Submucosal	0 (0)	2 (7.4)	
Lymphovascular invasion, n (%)			
Ly0	55 (100)	27 (100)	1.0
V0	55 (100)	27 (100)	1.0
Resectability, n (%)			.35
R0	42 (76.4)	23 (85.2)	
Additional treatment, n (%)			1.0
Yes	0 (0)	0 (0)	
Recurrence, n (%)			1.0
Yes	0 (0)	0 (0)	
Complete mucosal defect closure, n (%)			.48
Yes	54 (98.2)	27 (100)	
Closure time, min (IQR)	10 (5–25)	12 (6–21)	.76

n, number.

Table 3. Outcomes of Complete Mucosal Defect Closure in the OTSC Group

OTSC group (n = 55)	
Complete mucosal defect closure, n (%)	
Yes	54 (98.2)
Number of OTSCs used, mean (SD)	1.4 (0.56)
OTSC deployment method, n (%)	
Suction method	50 (91)
Twin-grasper method	5 (9)
Additional treatment, n (%)	
Yes	0 (0)

n, number; SD, standard deviation.

Discussion

The risks of delayed bleeding and delayed perforation caused by exposure to bile and pancreatic juice are very high, especially during duodenal ESD. In this study, we aimed to determine the indications for using OTSCs rather than conventional clips after duodenal ESD based on the preoperative tumor size and area of the resected specimen. The effectiveness of prophylactic closure of mucosal defects after duodenal ESD has been reported,[9] and OTSCs are often used for this.[2–4] OTSCs use allows for complete and firm closure of mucosal defects after duodenal ESD. In this study, the rate of complete closure of mucosal defects with OTSCs was very high (>95%); however, there are some caveats. The OTSC may be difficult to deploy if the tumor is located in a flexure, such as the superior or inferior duodenal angle, and there is a small risk of severe bleeding or perforation if the OTSC is incorrectly deployed. OTSC removal devices have been developed in other countries to correct failed OTSC deployment[10]; however, such correction is not practical. OTSC deployment is characterized by a single attempt and requires skill. It has been reported that multiple OTSC deployments have resulted in a gap between OTSCs and perforation in the same area because of exposure to bile or pancreatic juice.[3]

We compared the closure of mucosal defects after duodenal ESD between the OTSC and control groups and examined the appropriate criteria for the use of OTSCs based on the resected specimen area. The median resected specimen areas in the OTSC and control groups were 339.1 mm^2 and 169.6 mm^2, respectively. Additionally, the median estimated preoperative tumor sizes were 20 mm and 15 mm in the OTSC and control groups, respectively. The estimated preoperative tumor size strongly correlates with the resected specimen area, and unless the tumor shape is very distorted, the resected specimen area can be calculated using the estimated preoperative tumor size. In the control group of the present study, the median estimated preoperative tumor size was 15 mm (minimum = 10 mm; IQR = 12–15 mm; maximum = 18 mm), and the median resected specimen area estimated from the estimated preoperative tumor size was 176.6 mm^2 (minimum = 78.5 mm^2; IQR = 113.0–176.6 mm^2; maximum = 254.3 mm^2). Based on the fact that the maximum estimated resected specimen area (254.3 mm^2) ranged from 25% to 75% of the control group measurements and that complete closure of the mucosal defect was possible for all cases in the control group during this study, closure of the mucosal defect was possible using only conventional clips if the estimated preoperative tumor

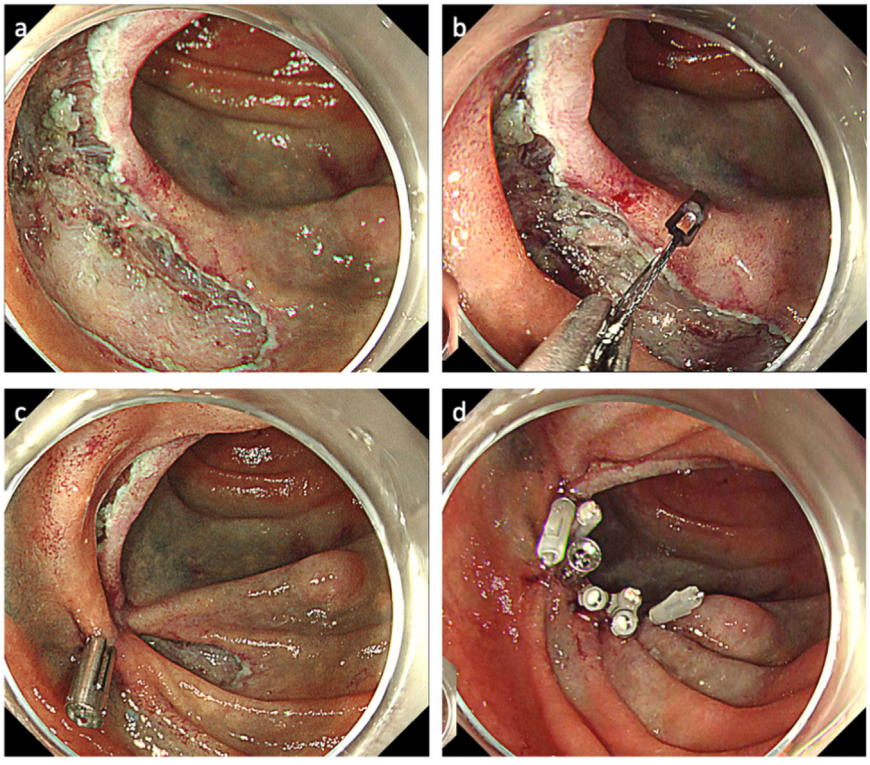

Figure 3. Use of a re-openable clip to close mucosal defects (A) Mucosal defect in the descending part of the duodenum after endoscopic submucosal dissection. The resected specimen diameter was 28 × 20 mm. The resected tumor diameter was 22 × 18 mm. (B) First, the center of the oral side of the mucosal defect was grasped, and closure was attempted. Because the clip is re-openable, it can be used as often as necessary. (C) Release of the clip. (D) Next, conventional clips were added to the residual mucosal defect, and it was completely closed. The closure time was 15 minutes.

size was ≤18 mm. Therefore, for mucosal defects after duodenal ESD, complete closure can be expected with conventional clips only if the estimated preoperative tumor size is ≤ 18 mm. If the size is > 18 mm, it may be advisable to use a combination of OTSCs, PolyLoop ligating device sutures, clip-and-threads,[11] or conventional clips for complete closure of the mucosal defect. During duodenal ESD, for which the risk of adverse events is much higher than ESD in other organs, it is useful to estimate the resected specimen area based on the estimated preoperative tumor size and consider the strategy for closing mucosal defects after the procedure. This will enable safe and economical duodenal ESD in the future. Recently, a re-openable clip (SureClip 16 mm; Micro-Tech Co. Ltd., Nanjing, China), which has a larger opening width than a conventional clip, has become popular (Figure 3). In the future, we would like to investigate the effectiveness and safety of closure devices on mucosal defect closure in a larger number of duodenal ESD patients using re-openable clips and novel traction devices in addition to conventional clips and OTSCs. Various reports on suture techniques should also be considered, such as hold-and-drag closure, endoscopic purse-string suturing, slip knot clip suturing, string clip suturing, and loop clip closure methods.

In addition to the limitation of this study as a single-center retrospective study, the performance of the procedure by a few endoscopists could have led to crucial selection bias. However, duodenal ESD is not as common as ESD in other organs and should be performed by a skilled endoscopist at that facility, so this study design is acceptable. We would like to accumulate more cases in the future in order to verify whether our results are common in clinical practice.

Conclusion

Conventional clips are effective for mucosal defects ≤18 mm after duodenal ESD, but OTSCs should be considered for those >18 mm. OTSCs are adequate and safe therapeutic devices. This study should contribute to the appropriate use of OTSCs in the future.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2023.07.004.

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Authors' Contributions:
Study conception and design: Ryuhei Jinushi , and Tomoaki Tashima. Acquisition of data: Ryuhei Jinushi, and Tomoaki Tashima. Analysis and interpretation of data: Ryuhei Jinushi. Drafting of the manuscript: Ryuhei Jinushi. Critical revisions of the manuscript: Ryuhei Jinushi, Tomoaki Tashima, Akashi Fujita, Yuki Tanisaka, Yumi Mashimo, Masafumi Mizuide, Sakue Masuda, Kazuya Koizumi, and Shomei Ryozawa.

Conflicts of Interest:
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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research. The institutional review board of Saitama Medical University International Medical Center (institutional ID: 20-249).

Data Transparency Statement:
The data that support the findings of this study are available from the corresponding author (Ryuhei Jinushi) upon reasonable request.

Reporting Guidelines:
Helsinki Declaration.