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Management and risk factors for incomplete resection associated with jumbo forceps polypectomy for diminutive colorectal polyps: a single-institution retrospective study

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Abstract

Background Cold forceps polypectomy is simple and widely used in clinical practice. However, there are concerns about the risk of incomplete resection using this technique. In recent years, it has been reported that polypectomy with jumbo forceps (JF) is an effective treatment modality for diminutive polyps (DPs) because JF are able to remove large tissue samples with the combined advantage of a higher complete histological resection rate for DPs than standard forceps. To our knowledge, no studies have evaluated the risk factors for incomplete resection when polypectomy with JF is performed for DPs.

Methods From among 1129 DPs resected using JF at Hiroshima City Asa Citizens Hospital between November 2015 and December 2016, we retrospectively evaluated the clinical outcomes of 999 tumors with known histopathology and investigated the relationship between incomplete resection and clinicopathological factors.

Results Most lesions [985 (87%)] were low-grade dysplasia and 14 (1%) were high-grade dysplasia. The en bloc resection rate was 92% (918/999) and the histological en bloc resection rate was 78% (777/999). Multivariate analysis showed that the significant independent predictors of incomplete resection were tumor size ≥ 4 mm [odds ratio (OR) 3.8; 95% confidence interval (CI) 2.65–5.37; $p < 0.01$], non-tangential direction of forceps in relation to the tumor (OR 1.73; 95% CI 1.21–2.45; $p < 0.01$), and lack of muscularis mucosae in the pathological specimen (OR 15.7; 95% CI 9.16–27.7; $p < 0.01$).

Conclusions This study identified significant independent predictors of incomplete resection of DPs which may be helpful when planning polypectomy with JF.

Keywords Cold forceps polypectomy · Diminutive colorectal polyps · Risk factors for incomplete resection · Tangential direction of forceps · Muscularis mucosae

Colorectal carcinoma is a common cause of cancer-related mortality worldwide [1]. Colonoscopy is the primary screening test for colorectal carcinoma, and adequate polypectomy during screening colonoscopy is important to prevent progression and decrease mortality [2–4]. At least 60% of all colonic polyps detected during screening colonoscopy in an asymptomatic average-risk population [5, 6] are diminutive in size (≤ 5 mm).

Cold forceps polypectomy (CFP), which is performed without a high-frequency device, is often used to remove benign polyps ≤ 5 mm in size and is associated with a low risk of adverse events, such as perforation or postoperative hemorrhage [7]. However, despite the widespread use of CFP, there have been few studies of the clinical efficacy of this technique, and most have raised concern about incomplete resection of polyps [8–11]. The microscopically incomplete polyp resection rate has been reported to be 8–38% [8–11], and precise histopathological diagnosis is difficult. In recent years, it has been reported that polypectomy with jumbo forceps (JF) (cold polypectomy using jumbo forceps which are larger than standard forceps) is an effective treatment modality for diminutive polyps (DPs)

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[12, 13], but there have been very few studies describing detailed histopathological analysis of specimens obtained using JF, and little is known about the risk factors for histologically incomplete resection. To our knowledge, no studies have evaluated the risk factors for incomplete resection associated with using JF for the removal of DPs.

In this study, we retrospectively evaluated the clinicopathological characteristics and clinical outcomes in patients who underwent removal of DPs by JF and sought to identify predictors of incomplete resection.

Patients and methods

Ethics

The study protocol was approved by the institutional review board at Asa Citizens Hospital (Hiroshima, Japan) and conducted in accordance with the tenets of the Declaration of Helsinki.

Patients and study design

This retrospective study was conducted at a single institution. Data were obtained from the medical records held at Asa Citizens Hospital. Figure 1 shows a flowchart for patient selection in this study. In total, 1151 patients with 3222 colorectal polyps underwent endoscopic treatment at Asa Citizens Hospital between November 2015 and December 2016. Lesions that were treated by endoscopic mucosal resection ($n = 1966$) or endoscopic submucosal dissection ($n = 119$) and lesions that were pedunculated and/or larger than 5 mm in size ($n = 8$) were excluded. Finally, data for 581 patients (392 men, 189 women; mean age 66 ± 9.4 years) with 1129 colorectal polyps up to 5 mm in size who underwent JF polypectomy were diagnosed as adenomatous polyps using narrow band imaging (NBI) magnifying endoscopy. Patients with inflammatory bowel disease or polyposis syndrome and patients who were pregnant, were unable to provide informed consent, or had poor bowel preparation were excluded from the study.

The indications for colonoscopy included abdominal symptoms such as constipation, screening after a positive fecal immunohistochemical test, planned polypectomy, surveillance after endoscopic or surgical treatment, and post-cancer surveillance. JF polypectomy was not performed for lesions suspected to be high-grade dysplasia or submucosal invasive carcinoma (T1) based on endoscopic assessment. JF polypectomy can be regarded as a biopsy procedure, and thus was carried out irrespective of whether the patient was on antithrombotic therapy. However, a prothrombin time-international normalized ratio < 3 was confirmed in all patients who had taken warfarin in the 7 days before the procedure.

We evaluated the clinical outcomes of 999 tumors for which a histopathological analysis had been performed and investigated the relationship between incomplete resection and clinicopathological factors. Complete resection was defined as successful when additional bites for resection were not needed and both the lateral and vertical resection margins of the specimen were tumor free. We classified the tumors for which a histopathological analysis had been performed into a completely resected tumor group and an incompletely resected tumor group, and then investigated

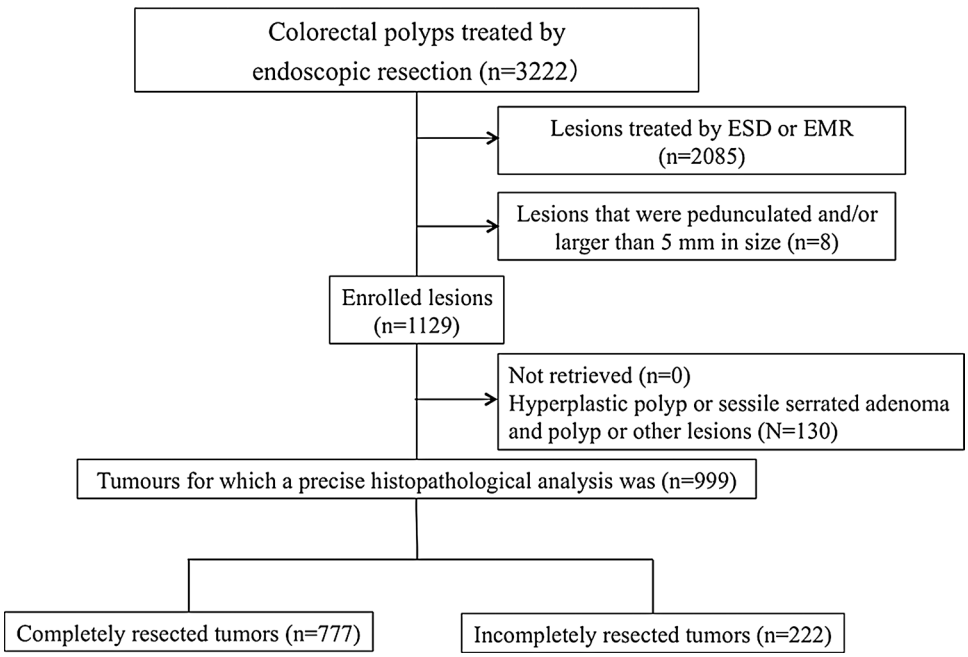

Fig. 1 Flowchart for patient selection in this study

the relationship between incomplete resection and clinicopathological factors.

Procedure

The JF polypectomy procedures were performed by nine physicians. For bowel preparation, patients followed a low-residue diet and took 10 mL sodium picosulfate 1 day before the examination followed by ingesting up to 2 L of polyethylene glycol-ascorbic acid solution (MoviPrep; Ajinomoto Pharma Co., Ltd., Tokyo, Japan) on the day of colonoscopy (repeat split dosing, 0.3 L of polyethylene glycol-ascorbic acid solution + 0.15 L of water). Bowel preparation was continued until all rectal fluid evacuated was clear. A high-definition colonoscope (CF-H260AI, CF-H260AZI, PCF-H260AZI, CH-HQ 290; Olympus Optical Co. Ltd., Tokyo, Japan) was used for all patients. After insertion of the colonoscope, the characteristics of the polyps were recorded, including size, location, and macroscopic type according to the Paris classification.

Cold polypectomy using JF

Cold polypectomy with JF was performed as described previously [14] (Fig. 2) using a Radial Jaw four device (Boston Scientific, Natick, MA), which has a jaw volume of 12.4 mm^3 (compared with 5.3 mm^3 for standard forceps). The best procedure is to estimate the volume of the lesion by matching it to the open width of the jumbo forceps, adjust the orientation of the forceps if the direction is incorrect, decompress the colon to reduce the strain on the mucosa, draw the lesion into the forceps cup, and pluck it away. If residual polyp tissue was detected at the polypectomy site, additional bites were made with the same forceps until complete removal was achieved. After CFP, the absence of residual tissue was confirmed by magnifying endoscopy with NBI after adequate irrigation of the excision site. To determine whether the direction of the forceps affected how much the lesions could be resected completely, we classified the direction of the forceps according to whether it was tangential or non-tangential relative to the tumor (Figs. 3, 4).

Histological assessment of benign diminutive polyps

Histopathological diagnoses were made by an experienced gastrointestinal pathologist (M.K.) in accordance with the criteria of the World Health Organization [15]. Hyperplastic polyps and sessile serrated adenoma and polyp (SSA/P) were excluded from the evaluation of histopathological margins. We anticipated that the muscularis mucosa was included in the lesions that were resected completely because using JF ensured that an adequate amount of each specimen was resected, which enabled precise histopathological assessment. According to the anticipation, all specimens resected by JF polypectomy were categorized according to whether or not the muscularis mucosae was present for detailed histopathological analysis (Figs. 3, 4).

Outcome measures

Primary outcomes were clinicopathological characteristics and clinical outcomes of patients who underwent removal of DPs by JF polypectomy. Secondary outcome was to identify independent predictors of incomplete resection of DPs.

Statistical analysis

Categorical variables were compared using Fisher's exact test or the χ^2 test and continuous variables were compared using the Mann–Whitney U test. Factors that showed a significant association with incomplete resection in univariate analysis were then subjected to multivariate analysis using a logistic regression model. A p value < 0.05 was considered statistically significant. The statistical analysis was performed using JMP software version 9.02 (SAS Institute, Cary, NC).

Results

Patient demographics and clinical characteristics are summarized in Table 1. Sixty-one percent of the lesions were in the right colon, 28% were in the left colon, and 11% were in the rectum. Ninety-four percent of the lesions were protruding or sessile and 6% were flat or elevated. The polyp retrieval rate was 100%. Most lesions were low-grade dysplasia (LGD) (such as tubular adenoma/tubulovillous adenoma); however, 14 (1%) were high-grade dysplasia (HGD). Thirty-four patients (6%) were receiving antithrombotic agents. The most common antiplatelet strategy was aspirin ($n = 8$, 24%) and the most common anticoagulation strategy was warfarin ($n = 4$, 12%).

The overall en bloc (one-bite polypectomy) resection rate was 92% ($n = 918$) and the histological en bloc resection rate was 78% ($n = 777$) (Table 2).

Precise histopathological diagnosis was difficult in 22% of the 999 cases. Lateral margins could not be assessed histologically for tumor involvement in 16% ($n = 155$), additional bites for resection were needed in 8% ($n = 81$), and involvement of the vertical margin could not be histologically determined in 6% ($n = 58$). One patient had delayed bleeding, which was easily managed by endoscopic clipping. There were no cases of perforation (Table 3).

Table 4 shows the results for univariate analysis of factors associated with incomplete resection. In this study, the

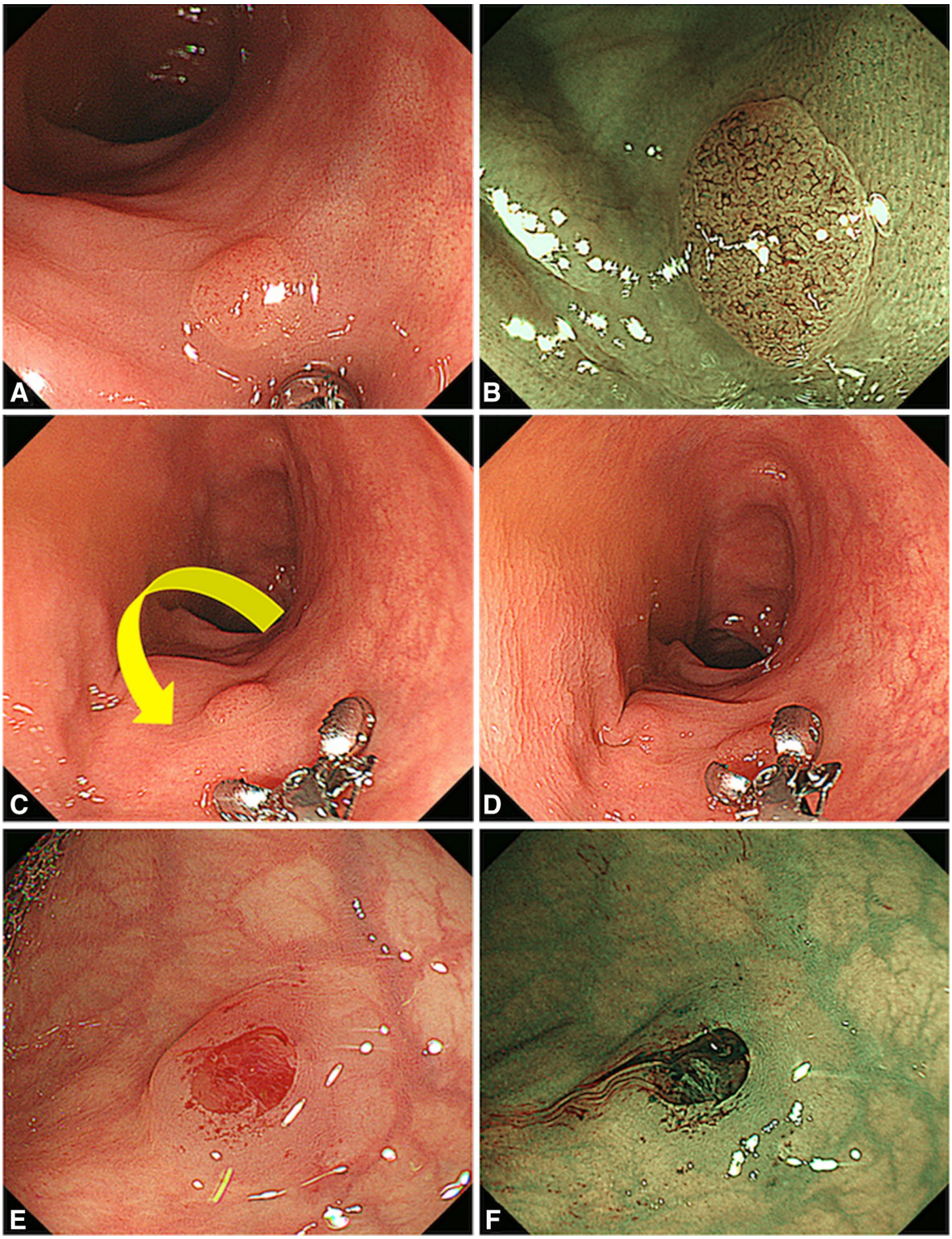

Fig. 2 **A** and **B** Endoscopic images from a 66-year-old man with a 3-mm polypoid-type (Is) lesion in the descending colon taken during cold forceps polypectomy using jumbo forceps. **C** The best procedure is to estimate the volume of the lesion by matching it to the open width of the jumbo forceps and then adjusting the orientation of the forceps if its direction is incorrect. **D** The key to successful cold forceps polypectomy is to decompress the colon in order to reduce the strain on the mucosa, draw the lesion into the forceps cup, and pluck it away. **E** and **F** After cold forceps polypectomy, the absence of residual tissue is confirmed on magnifying endoscopy with narrow band imaging after adequate irrigation of the excision site

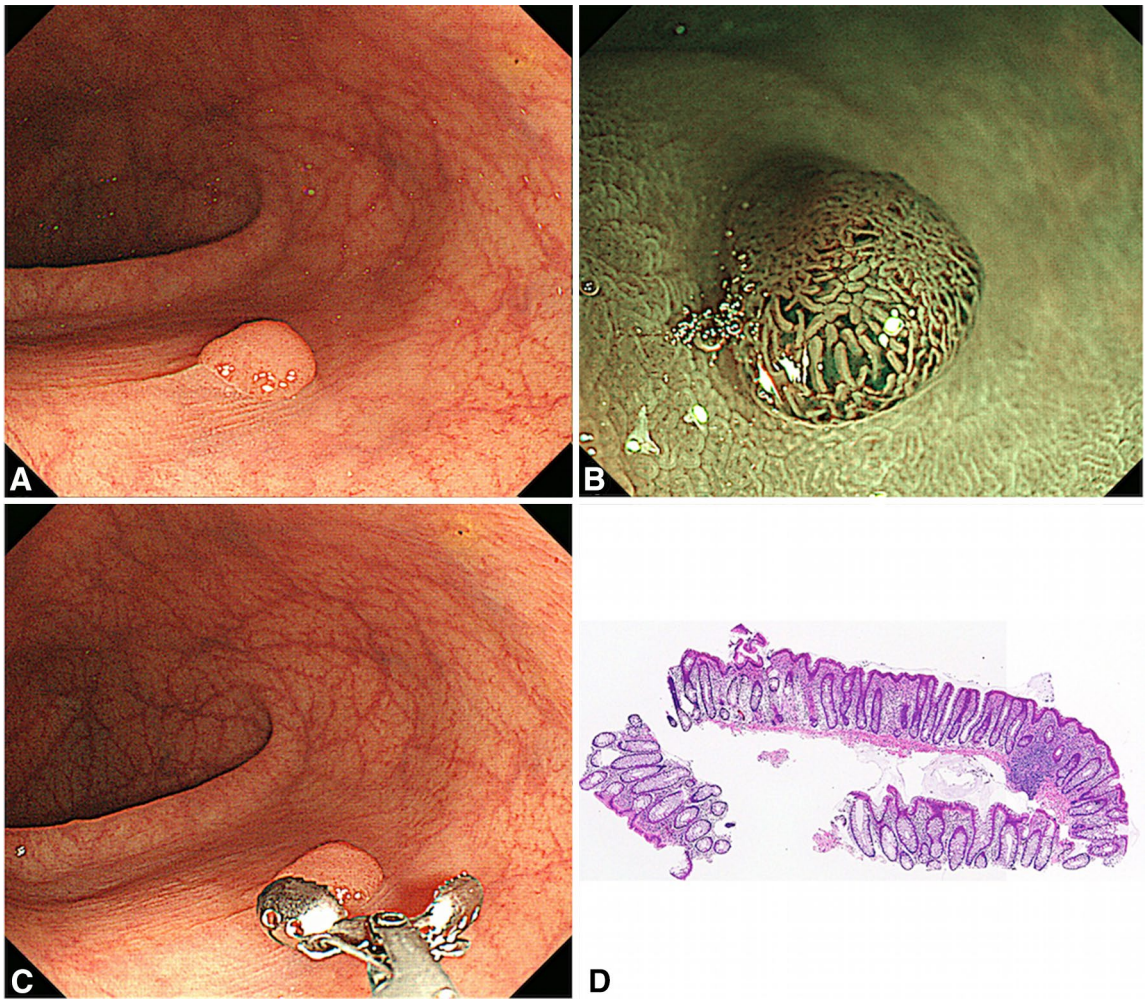

Fig. 3 Endoscopic and histological findings for a diminutive polyp completely resected by Jumbo forceps polypectomy. **A** and **B** Endoscopic images from a 69-year-old woman with a 3-mm polypoid-type (Is) lesion in the sigmoid colon. **C** En bloc resection was performed with the forceps in a tangential direction relative to the tumor. **D** The pathological diagnosis was low-grade adenoma. The lateral and vertical margins were negative and contained muscularis mucosae, which enabled straightforward and accurate pathological assessment

one-bite polypectomy rate decreased when the tumor size was ≥ 4 mm, we analyzed tumor size < 4 mm and ≥ 4 mm to identify independent predictors of incomplete resection of DPs. Tumor measuring ≥ 4 mm, non-tangential direction of the forceps relative to the tumor, and lack of muscularis mucosae in the pathological specimen were significantly more common in the incompletely resected tumor group than in the completely resected tumor group. The same three factors were confirmed to be significant independent predictors of incomplete resection in multivariate analysis (Table 5).

Discussion

To our knowledge, this is the first study to analyze the risk factors for incomplete resection associated with cold polypectomy using JF for diminutive colorectal polyps. JF are larger than standard forceps and are effective for treating DPs [12, 13]. Introduced by Draganov's team, JF were found to be better able to remove large tissue samples and to have the combined advantage of a higher complete histological resection rate for DPs and a shorter withdrawal time than the standard forceps used in colonoscopy [12]. Several reports on the usefulness of JF have recently been published [12, 13, 16]. A recent meta-analysis determined that the use of JF for CFP reduces the risk of incomplete removal of a DP [16]. However, no studies have evaluated the risk factors for incomplete resection associated with JF for DPs.

In this study, we investigated whether the direction of the forceps affected how completely these lesions could be resected and found that it was very important to adjust the tangential direction of the forceps relative to the tumor. Multivariate analysis showed a non-tangential direction of the

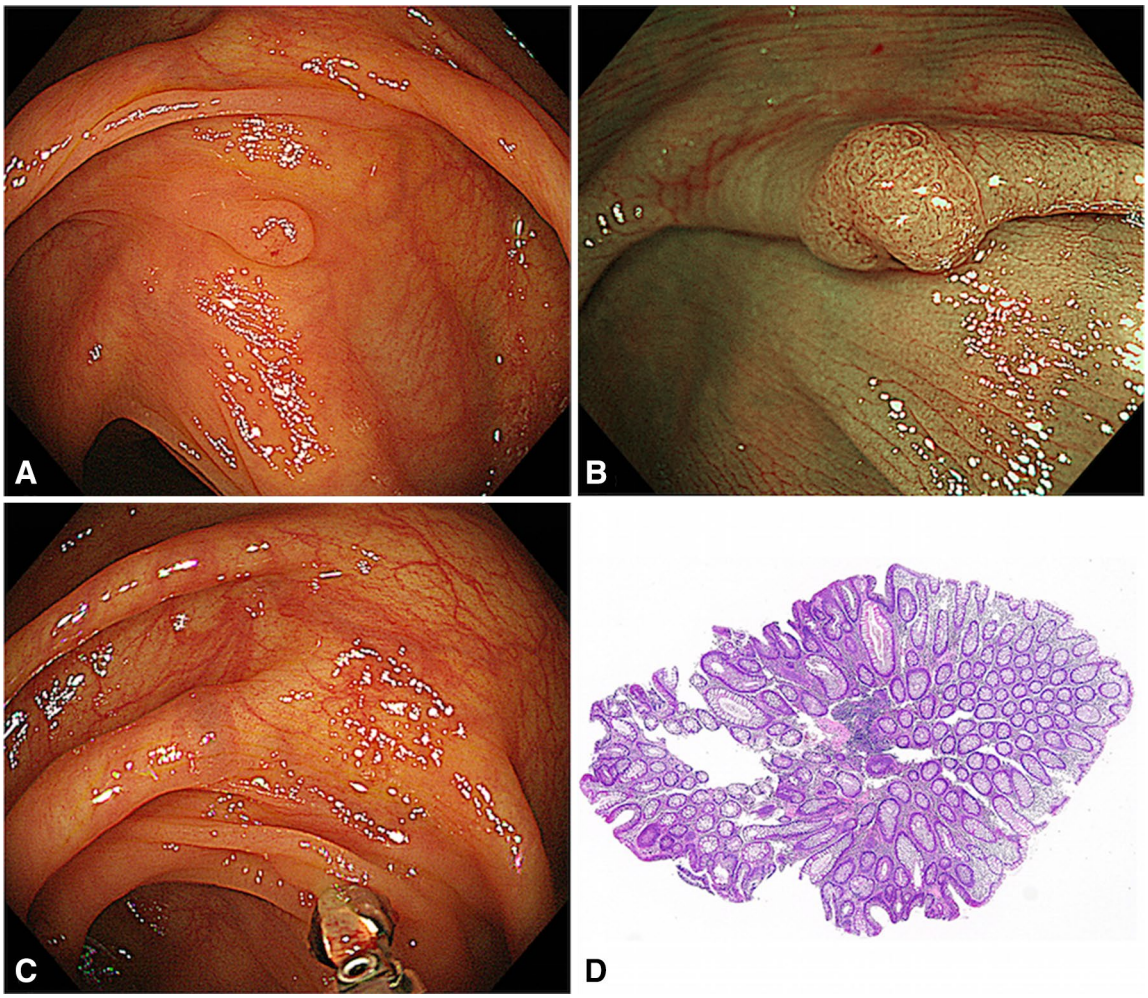

Fig. 4 Endoscopic and histological findings for a diminutive polyp in completely resected by Jumbo forceps polypectomy. **A, B** Endoscopic images from a 66-year-old man with a 3-mm polypoid-type (Is) lesion in the cecum. **C** The lesion was resected en bloc with the forceps in a non-tangential direction relative to the tumor. **D** The pathological diagnosis was low-grade adenoma but the lateral and vertical margins were unclear and the specimen did not contain muscularis mucosae, so accurate pathological assessment was difficult

forceps relative to the tumor to be a significant independent predictor of incomplete resection.

CFP is commonly used to treat DPs and has become a routine procedure performed by all practicing endoscopists. CFP has been reported to be the predominant method for removing polyps measuring 1–3 mm in the US and for removing DPs (≤ 5 mm in size) in Japan [17, 18]. DPs are usually treated with CFP because the risk of adverse events is very low. Among the patients in this study, there was only one case of postoperative hemorrhage. The bleeding occurred on the day after JF polypectomy, but was controlled by endoscopic clipping and did not warrant blood transfusion.

In this study, the overall rate of one-bite polypectomy was 92% (100%, 100%, 96%, 79%, and 72% for lesions 1 mm, 2 mm, 3 mm, 4 mm, and 5 mm in size, respectively). In a multicenter prospective study of the efficacy of JF for the removal of 223 DPs, Uraoka et al. [19] found that the rate of one-bite polypectomy was 85% (100%, 100%, 96%, 88%, and 70% for lesions 1 mm, 2 mm, 3 mm, 4 mm, and 5 mm in size, respectively). The outcomes of JF polypectomy in our study and those in the report by Uraoka et al. are very similar and both are higher than the outcomes in a report on CFP using conventional biopsy forceps [8–11]. Aslan et al. reported high one-bite polypectomy and complete resection rates using JF to remove polyps measuring 4–5 mm in size [13] and Jung et al. reported finding no differences in the size, histology, or location of polyps or in the number of biopsies performed between their complete and incomplete resection groups when performing CFP using standard forceps [10]. In the present study, the one-bite polypectomy rate decreased when the size of the tumor was ≥ 4 mm and multivariate analysis revealed a tumor size of ≥ 4 mm to be a significant independent predictor of incomplete resection.

Table 1 Clinicopathological features of diminutive polyps removed by Jumbo forceps polypectomy

Variable	
Patients (*n*)	581
Polyps (*n*)	1129
Sex (%)	
Male	392 (67)
Female	189 (33)
Age [years (mean ± SD)]	66 ± 9.4
Location (*n*, %)	
Right colon	689 (61)
Left colon	317 (28)
Rectum	123 (11)
Lesion size [mm (*n*, %)]	
1–2	267 (27)
3–4	791 (70)
5	71 (3)
Morphology	
Isp	51 (5)
Is	1013 (89)
IIa	65 (6)
Use of antithrombotic drugs	
Yes	34 (6)
No	547 (94)
Histology	
LGD	985 (87)
HGD	14 (1)
Hyperplastic polyp	63 (6)
SSA/P	22 (2)
Other	45 (4)

The left colon refers to the segment distal to the splenic flexure; the right colon refers to the segment proximal to the splenic flexure

LGD tubular adenoma/tubulovillous adenoma, *HGD* high-grade dysplasia, *SSA/P* sessile serrated adenoma and polyp, *SD* standard deviation, *Tis* intramucosal carcinoma

Despite the simplicity and widespread use of CFP in daily clinical practice, there are concerns about the risk of incomplete resection when using this technique. Several recent studies have attempted to detect residual lesions after CFP by immediate microscopic examination of specimens obtained by biopsy or endoscopic mucosal resection of post-CFP ulcer edges and reported incomplete resection rates ranging from 8 to 38% [8–11]. Although these studies revealed high incomplete resection rates immediately after CFP of DPs, that does not necessarily mean that this rate is exactly the same as the actual adenoma recurrence rate during follow-up. Lee et al. reported a confirmed recurrence rate of 4% (44/1111) and a probable recurrence rate of 13% (145/1111) during a median follow-up of 5 years. Most of the recurrences in that study were non-advanced adenoma, and advanced adenoma (defined as adenoma ≥ 1 cm, adenoma with villous histology, or high-grade dysplasia) developed in only 0.5% (5/1111) of all lesions [20]. However, the outcome of CFP in that study should be considered in light of the definition of recurrence, given that a judgment of definite recurrence is difficult and the definition of probable recurrence is ambiguous. We speculate that it is possible to limit the risk of recurrence of DPs by using JF rather standard forceps for CFP, adjusting the tangential direction of the forceps relative to the tumor, and carefully observing the surrounding mucosa after CFP using magnifying endoscopy.

In our study, precise histopathological diagnosis was difficult in 222 (22%) of 999 cases. The lack of thermal fulguration when using JF may create difficulties when trying to confirm the resection margin, resulting in a low complete resection rate. Furthermore, a thermal burn effect cannot be expected to eradicate neoplastic tissue around the forceps. In this study, complete resection was defined as successful when additional bites for resection were not needed and both the lateral and vertical resection margins of the specimen were tumor free. A possible reason for the difficulty in making a precise histopathological diagnosis in 22% of the cases in this study is that the definition of complete resection was stricter than that used in previous studies.

Multivariate analysis showed lack of muscularis mucosae in the pathological specimen to be a significant independent predictor of incomplete resection. From this result, we speculate that an adequate amount of muscularis mucosae in the resected tissue specimen is necessary to be able to perform a precise histopathological assessment. However, whether or not the resected specimen contains muscularis mucosae cannot be predicted when performing JF polypectomy.

Table 2 Treatment outcomes

Lesion size (mm)	Polyps (*n*)	En bloc resection rate (%)	Histological en bloc resection rate (%)
1	4	100 (4/4)	50 (2/4)
2	229	100 (229/229)	85 (195/229)
3	481	96 (463/481)	83 (398/481)
4	224	79 (178/224)	66 (148/224)
5	61	72 (44/61)	56 (34/61)
Total	999	92 (918/999)	78 (777/999)

Table 3 Treatment outcomes

Variables	
Histological en bloc resection rate	777 (78)
Reasons for incomplete resection (overlap)	
Additional bites for resection	81 (8)
Lateral margins could not be assessed	155 (16)
Vertical margins could not be assessed	58 (6)
Complications	
Delayed bleeding [*n* (%)]	1 (0.1)
Perforation [*n* (%)]	0 (0)

Data are presented as the number (percentage)

Table 5 Multivariate analysis of potential risk factors for incomplete resection

Variables	Odds ratio	95% CI	*p* value
Presence of MM			
Negative	15.67	9.16–27.71	< 0.01
Tumor size of ≥ 4 mm	3.77	2.65–5.37	< 0.01
Direction of forceps			
Non-tangential direction	1.73	1.21–2.45	< 0.01

CI confidence interval, *MM* muscularis mucosae

Therefore, the indication for JF polypectomy should remain limited to benign lesions.

A newly proposed approach for removal of DPs and small colorectal polyps is the 'predict, resect, and discard' strategy, in which optical guidance and NBI are used to assess the histopathology of a polyp and determine appropriate surveillance intervals. This strategy has been confirmed to be safe and cost-effective for the management of patients with DPs or small colorectal polyps [21–27]. However, this strategy is based on the assumption that all DPs and small neoplastic colorectal polyps would be completely removed. Histopathological evaluation of DPs resected by JF can distinguish between HGD and LGD but not between HGD and T1 carcinoma if the muscularis mucosa was not included in the lesion. Regarding HGD, the exact frequency is unknown because there are few reports about its frequency in DPs. The frequency is considered to be 0.03% [28] in Western countries and 0.2–2.0% [18, 29] in Japan. In our study, 1% (14/1129) of DPs displayed HGD. A possible reason for the difference between the studies is selection bias because we included patients who received endoscopic treatment. Fortunately, follow-up colonoscopy 1 year later did not reveal residual lesions or recurrence in all patients with HGD lesions. Some DPs have been reported to be T1 carcinomas, and there is the potential risk of missing these lesions [29–31]. Therefore, magnifying colonoscopy is beneficial for determining the precise histopathological diagnosis of DPs; if it is still too difficult to distinguish between LGD and HGD, chromoendoscopy is recommended. If HGD is suspected, endoscopic mucosal resection rather than cold/hot biopsy or polypectomy is recommended to determine the precise histopathological diagnosis. If a submucosal injection (usually normal saline solution containing methylene

Table 4 Univariate analysis of potential risk factors for incomplete resection

Variables	Completely resected tumors, *n* (*n* = 777)	Incompletely resected tumors, *n* (*n* = 222)	*p* value
Tumor size (mm)			
≤3	595 (77)	119 (53)	< 0.01
≥4	182 (23)	103 (47)	
Location			
Right colon	504 (65)	144 (65)	NS
Left colon	273 (35)	78 (35)	
Morphology			
Protruding (0-Isp/0-Is)	738 (95)	205 (92)	NS
Flat (0-IIa)	39 (5)	17 (8)	
Direction of forceps			
Tangential	536 (69)	105 (47)	< 0.01
Non-tangential	241 (31)	117 (53)	
Presence of MM			
Positive	755 (97)	156 (70)	< 0.01
Negative	22 (3)	66 (30)	

Data are presented as number (percentage). The left colon refers to the segment distal to the splenic flexure; the right colon refers to the segment proximal to the splenic flexure

MM muscularis mucosae

blue or indigo carmine dye) is performed, the polyp can be lifted onto a cushion of submucosal fluid and a clear margin can be defined, which provides a safety zone for easier snare resection. The 'predict, resect, and discard' strategy should be applied selectively and informed by accurate endoscopic evaluation.

This study has some limitations. First, this was a single-center retrospective study. Second, the JF polypectomy specimens were not pinned and were small and fragile. Thus, the actual vertical margin was not evaluated in some of the specimens. Third, no long-term follow-up data are available. In this article, we did not directly compare JF polypectomy with cold snare polypectomy. However, there is a growing trend toward cold snare excision of polyps with adequate margins, low complication rates, and better complete excision even for 4–5 mm polyps. JF polypectomy appears to be an adequate method for resection of DPs 1–3 mm in size but seems to be insufficient for larger polyps.

In conclusion, JF polypectomy is a straightforward technique that can be performed rapidly and safely and has a polyp retrieval rate of 100%. Only 1 (0.1%) of 581 patients in this study had delayed bleeding, which was easily managed by endoscopic clipping, and there were no cases of perforation. Multivariate analysis showed tumor size ≥ 4 mm, a nontangential direction of the forceps relative to the tumor, and lack of muscularis mucosae in the pathological specimen to be significant independent predictors of incomplete resection of DPs. These findings may provide helpful information when planning JF polypectomy.

Author Contributions NA and SN conceived and designed the study, performed the statistical analysis, interpreted the data, and drafted the manuscript. NA, SN, KS, YO, HT, YS, TA, AF, and SM acquired the data. MK analyzed and interpreted the histopathological data. All authors critically revised the article for important intellectual content and approved the article for publication.

Compliance with ethical standards

Disclosures Naoki Asayama, Shinji Nagata, Kenjiro Shigita, Yutaro Ogawa, Hirosato Tamari, Taiki Aoyama, Akira Fukumoto, Shinichi Mukai, and Mayumi Kaneko have no conflicts of interest or financial ties to disclose.

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