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ORIGINAL ARTICLE

Risk factors for incomplete polyp resection after cold snare polypectomy

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Abstract

Background Incomplete polyp resection (IPR) is recognized as a risk factor for interval colorectal cancer (ICC), and is, therefore, an important issue in polypectomy. Cold snare polypectomy (CSP) is a procedure that does not involve electrocautery and has no burn effect. Therefore, there is the possibility that the risk of ICC associated with IPR is higher in cases undergoing CSP than in those undergoing hot polypectomy. However, little is known about the risk factors for IPR after CSP.

Purpose Precise identification of the risk factors can lead to prevention of IPR after CSP. Therefore, we performed this observational study for accurate identification of the risk factors for IPR after CSP.

Methods Medical records of a total of 501 patients with 1177 colorectal polyps that were resected at Omori Red Cross Hospital between October 2017 and March 2018 were retrospectively reviewed. The lateral and deep margins of the resected polyps were evaluated to check for the resection completeness.

Results Among the 1177 polyp resections, 1163 were included in the final analysis. IPR was detected in 206 (17.7%) cases. Performance of the resection by a trainee (OR (95% CI) 1.87 (1.328–2.632); $P < 0.001$) was identified as an independent risk factor for IPR in patients undergoing CSP.

Conclusions Performance of the polypectomy by a trainee was identified as a significant risk factor for IPR in patients undergoing CSP. Prospective, randomized studies are necessary in the future to develop effective methods for the prevention/control of IPR after CSP.

Keywords Colorectal polyps · Cold snare polypectomy · Incomplete polyp resection · Interval colorectal cancer

Introduction

The incidence of colorectal cancer (CRC) continues to increase worldwide [1, 2]. Most cases of CRC originate from adenomas [3], and their removal has been shown to reduce the risk of death from CRC [4]. Therefore, the importance of early detection and early treatment is growing, and endoscopic removal of all detected colorectal polyps is currently a standard practice during colonoscopic screening. Hot polypectomy (HP) and endoscopic mucosal resection (EMR), which involve the use of electrocautery, are the most commonly performed endoscopic therapies to resect colorectal polyps. However, there is a major concern about delayed postpolypectomy bleeding (DPPB) as a complication of HP and EMR [5–8]. In contrast, cold snare polypectomy (CSP) does not involve the use of electrocautery and has also been reported to be superior to conventional HP and EMR in terms of the procedure time [9, 10]. In addition, several studies have shown that DPPB is less common after CSP than after conventional polypectomy [11–14]. Therefore, CSP has spread rapidly in recent years because of its convenience and safety.

Although endoscopic polyp resection is highly efficient in preventing CRC, the risk of interval colorectal cancer (ICC) after resection of polyps (HP and EMR) still exists. One of the main causes for the development of ICC is incomplete polyp resection (IPR) [15–20]; therefore, IPR is an important issue after polypectomy. In the cases of HP and EMR, it might be assumed that even in cases of IPR, the burn effect can prevent, at least to some extent, local recurrence and ICC. On the other

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hand, CSP does not involve the use of electrocautery and has no burn effect, and there is the possibility that the risk of local recurrence and ICC associated with IPR is higher in patients undergoing CSP than in those undergoing HP or EMR. Moreover, CSP is also occasionally associated with difficulties in histopathological assessment of the margins of the resected polyps, which might be related to the tissue damage that is caused during the suctioning of the resected polyps through the endoscope channel [12]. IPR after CSP is more common than that after HP or EMR. Therefore, IPR after CSP is an important issue in clinical practice.

Although identification of the risk factors for IPR after CSP is an issue of clinical importance, little is yet known about the risk factors for IPR after CSP. A recent study showed that female gender of the patient was an independent risk factor for IPR after CSP [21]. However, there is only one study about the risk factors for IPR after CSP. Precise identification of the risk factors can lead to prevention of IPR after CSP. Therefore, we performed this observational study in a large study sample for identifying the risk factors for IPR after CSP.

Methods

Patients

Patients referred and scheduled for screening or surveillance colonoscopy were enrolled between October 2017 and March 2018; during this period, 501 patients underwent CSP at Omori Red Cross Hospital. CSP is indicated for colorectal polyps up to 10 mm in diameter, excluding lesions with submucosal invasion and lesions suspected as being cancerous at the preprocedural diagnostic evaluation. Narrow-band imaging, magnifying endoscopy, and chromoendoscopy were used for the diagnosis. We included all patients who underwent CSP, including those that were receiving treatment with multiple antithrombotic agents. However, patients whose resected polyp specimens could not be retrieved were excluded.

In this study, we counted each polyp; two or more polyps resected by the same CSP procedure were counted as two or more polyps. We excluded 14 polyps (specimen retrieval failure). The study protocol was in compliance with Declaration of Helsinki and the Ethics Guidelines for Clinical Research published by the Ministry of Health, Labour and Welfare, Japan. Approval for the study was obtained from the Ethics Committee of Omori Red Cross Hospital on January 11, 2018. The protocol and informed consent forms were approved by the institutional ethics committee of Omori Red Cross Hospital.

CSP procedure

Bowel preparation for the procedure was initiated a day prior to the colonoscopy. Each patient was instructed to consume a low-residue diet and take 5 mg of oral sodium picosulfate on the evening before the colonoscopy. On the day of the colonoscopy, each patient was given 1500 ml of polyethylene glycol (PEG). If the stools were not sufficiently clear, an additional 500 ml of PEG was given to ensure sufficient bowel cleaning. In almost all cases, conscious sedation with midazolam (2–5 mg) and pethidine (17.5–35 mg) was administered at the beginning of the procedure. During the procedure, the blood pressure, heart rate, electrocardiography, and peripheral oxygen saturation were monitored. Intravenous glucagon or scopolamine was administered, as needed, to reduce colonic movements.

A standard or magnifying colonoscope was used in all cases (CF-H260AZI, PCF-Q260AZI, PCF-Q290AZI, PCF-H290ZI; Olympus Co., Tokyo, Japan), with carbon dioxide insufflation. A transparent attachment was used at the tip of the endoscope. Cecum intubation was verified by identification of the appendiceal orifice and ileocecal valve. The location, size, and macroscopic type of all the detected lesions were documented according to the Paris Classification [22]. Retroflexion in the rectum was routinely performed. Polyp resection was performed with a Snaremaster-Plus (Olympus) in all cases. Endoscopists were instructed to measure the polyps using the size of the snare catheter or the snare diameter. All detected colorectal polyps that were up to 10 mm, except for tiny hyperplastic polyps in the rectum and distal sigmoid colon, were resected. We usually perform CSP during the colonoscopy. Every polyp was examined in detail to determine the appropriateness of its resection by CSP. Whether the lesions were resected by HP (or EMR) or CSP was left to the judgment of experts. At our hospital, we usually undertake these steps as a routine in daily clinical practice. The CSP was performed on either an outpatient or inpatient basis. All patients were started on a regular diet from the evening on the day of the CSP.

Data analysis and definition of IPR after CSP

The polyps were categorized according to the pathological margin status after CSP into the negative-margin group, unclear-margin group, or positive-margin group (Fig. 1). Cases where both the lateral and deep margins were free of dysplastic cells were classified into the negative-margin group. Cases where it was unclear whether resection margins were involved or not were classified into the unclear-margin group. Cases where either or both the lateral margin and deep margin contained dysplastic cells were classified into the positive-margin group. Finally, complete resection (CR) group was defined as resection of the lesion with a pathological negative margin [23]. Cases of the unclear-margin group and positive-margin group were classified into the IPR group.

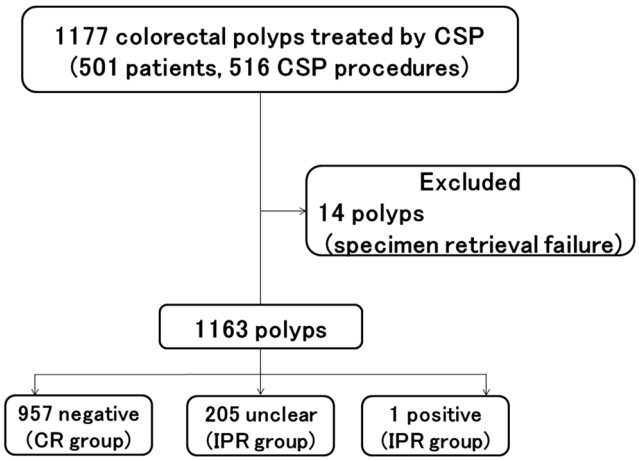

Fig. 1 Study flow. A total of 1163 colorectal polyps were included in this analysis

The primary endpoint was identification of the risk factors for IPR after CSP. To investigate the potential risk factors for IPR after CSP, we investigated the age, sex, polyp location, polyp diameter (< 6 mm/≥ 6 mm), morphology, histopathology, presence/absence of DPPB, presence/absence of immediate bleeding, antithrombotic agent therapy (present/absent), endoscopist's experience (expert/trainee), and the frequency of IPR after CSP. We used a polyp diameter of 6 mm as the cutoff, based on a previous report [21]. DPPB was defined as a fall in the hemoglobin level by at least 2 g/dl below the most recent preoperative level, or necessitation of endoscopic hemostasis and/or blood transfusion, and/or massive melena [24, 25]. Prophylactic clipping after polyp removal was not routinely performed; however, hemostatic clipping was carried out during the procedure for immediate bleeding. Spurting or oozing that continued for more than 30 s was defined as immediate bleeding necessitating hemostatic clipping [26]. This definition was used to avoid the potential for a biased assessment of immediate bleeding. Experts were defined as endoscopists with experience of ≥ 500 colonoscopies and trainees were defined as endoscopists with experience of < 500 colonoscopies. We used the cutoff value for endoscopy experience of 500 colonoscopies, based on a previous report that experience of at least 500 colonoscopies was probably required to ensure reliable independent completion rates [27].

Statistical analysis

The results are presented as means or medians (± standard deviation or range) for the quantitative data, and as frequencies (percentage) for the categorical data. Categorical data were analyzed by the χ^2 test or Fisher's exact test, as appropriate. Data showing normal distribution were compared by the *t* test, and those showing non-normal distribution were compared by the Mann-Whitney *U* test, to assess the statistical significance of differences. $P < 0.05$ was considered as denoting statistical significance. Multivariate analyses were performed using the risk factors that were identified as being significant by the univariate analyses. All statistical analyses were carried out using SPSS statistics, version 18 (SPSS, Chicago, IL, USA).

Results

Study flow

We performed CSP in 501 patients (516 CSP procedures, 1177 polyps) at Omori Red Cross Hospital between October 2017 and March 2018. We excluded 14 polyps (specimen retrieval failure), and data of 1163 polyp resections were included in the final analysis (Fig. 1). Depending on the pathological margin status after CSP, the polyps were divided into three groups: the negative-margin group (957 polyps), the unclear-margin group (205 polyps), and the positive-margin group (1 polyp). The 957 polyps of the negative-margin group were classified into the CR group, while the remaining 206 polyps (including 205 of the unclear-margin group and 1 of the positive-margin group) were classified into the IPR group. The rate of IPR after CSP was 17.7% (206/1163).

Patient characteristics

The clinical characteristics of the patients are presented in Table 1. The total number of patients was 501, and the mean age ± SD of the patients was 69.1 ± 8.2 years. In all, 109 patients were receiving antithrombotic therapy: the indication was ischemic heart disease in 22.9% of patients, atrial

Table 1 Clinical characteristics of the patients

Characteristics of the patients	
Number of patients	501
Sex (M:F)	310:191
Age (mean ± SD)	69.1 ± 8.2
Patients receiving antithrombotic agents	109
Antiplatelet agents	49
Warfarin	9
DOAC	26
Multiple antithrombotic agents	25
Indication for use of antithrombotic agents	
Ischemic heart disease	25 (22.9%)
Atrial fibrillation	32 (29.4%)
Cerebrovascular disease	31 (28.4%)
As preventive medication	21 (19.3%)

CSP, cold snare polypectomy; *DOAC*, direct oral anticoagulants

fibrillation in 29.4% of patients, cerebrovascular events in 28.4% of patients, and as preventive medication in 19.3% of patients.

Characteristics of the colorectal polyps

The characteristics of the colorectal polyps are presented in Table 2. The total number of polyps resected was 1177 and the number of lesions that were included in the final analysis was 1163. In all, 86 (7.4%) of the resected polyps were located in the rectum. The mean polyp size was 4.58 ± 1.81 mm, and the predominant morphological type was the type IIa morphology. There was only case of piecemeal resection. Of the total, 276 (23.7%) polyps were resected by trainees, and 887 (76.3%) polyps were resected by experts. The rate of immediate bleeding during CSP was 5.4% (63/1163); however, there were no cases of DPPB in this study. With regard to the histopathology, 992 (85.3%) of the resected polyps (the majority) were low-grade adenomas. There was no case of carcinoma (0%) in this study. A total of 206 polyps (including 205 of the unclear-margin group and 1 of the positive-margin group) were classified into the IPR group.

Table 2 Clinical characteristics of colorectal polyps resected by CSP in the total sample

Characteristics of the polyps	
Number of polyps (resected: 1177)	1163
Polyp location	
Colon	1077 (92.6%)
Rectum	86 (7.4%)
Polyp diameter, mm (mean ± SD)	4.58 ± 1.81
Morphology type	
Is	343 (29.5%)
Isp	80 (6.9%)
IIa	740 (63.6%)
Type of resection	
En bloc	1162 (99.9%)
Piecemeal	1 (0.1%)
Number of polyps resected by endoscopists' experience	
Trainees	276 (23.7%)
Experts	887 (76.3%)
Immediate bleeding	
Yes	63 (5.4%)
Prophylactic clipping	
Yes	70 (6.1%)
DPPB	
Yes	0 (0%)
Histopathology	
Low-grade adenoma	992 (85.3%)
High-grade adenoma	2 (0.1%)
Hyperplastic polyp	110 (9.5%)
SSA/P	59 (5.1%)
Carcinoma	0 (0%)
Pathological margin	
Negative	957 (82.3%)
Unclear	205 (17.6%)
Positive	1 (0.1%)

CSP, cold snare polypectomy; *DPPB*, delayed post polypectomy bleeding; *SSA/P*, sessile serrated adenoma/polyp

Factors associated with IPR after CSP

The results of univariate analysis and multivariate analysis performed to identify the risk factors for IPR after CSP are presented in Table 3. The IPR group included 206 polyps, and the CR group included 957 polyps. Of the 206 cases of IPR after CSP, 82 polyps (39.8%) were resected from patients who were ≥ 75 years old ($P = 0.034$). Among the polyps of the protruded morphology type, IPR occurred in 89 cases ($P = 0.026$). With regard to the influence of the endoscopist's experience, the rate of IPR was higher in the polyp resections performed by trainees than in those performed by experts. There were no significant differences in any of the other variables (sex, location of the polyps, polyp diameter, proportion of patients receiving antithrombotic agent therapy, histopathology, proportion of patients with immediate bleeding) between the CR and IPR groups.

We also performed multivariate analysis using the risk factors that were identified as being significant by the multivariate analysis. Multivariate analysis identified performance of the CSP by trainees (OR (95% CI) 1.87 (1.328–2.632); $P < 0.001$) as an independent risk factor for IPR. While patient age is ≥ 75 years and the protruded morphology type were identified as significant factors by univariate analysis, and therefore considered as potential risk factors for IPR, multivariate failed to confirm these as significant independent risk factors for IPR.

Discussion

IPR is a risk factor for ICC, even in cases of HP and EMR [15–20]. Therefore, there is the possibility that the risk of local recurrence and ICC associated with IPR is higher in cases undergoing CSP than in those undergoing HP or EMR, since CSP does not involve the use of electrocautery and has no burn effect. CSP has spread rapidly in recent years and it is expected that the number of CSP cases will continue to increase. Therefore, IPR after CSP is an important issue in clinical practice. This study, conducted in a consecutive series of over 1000 polypectomies, showed that performance of the procedure by trainees was an independent risk factor for IPR after CSP.

Table 3 Univariate and multivariate analysis performed to identify the risk factors for IPR after CSP

	Univariate analysis			Multivariate analysis	
	IPR group	CR group	*P* value	OR (95% CI)	*P* value
Number of polyps (= 1163)	206	957			
Age (years)			0.034	1.33 (0.967–1.828)	NS
≥75	82 (39.8%)	305 (31.9%)			
<75	124 (60.2%)	652 (68.1%)			
Sex			NS		
Male	134 (65.0%)	636 (66.5%)			
Female	72 (35.0%)	321 (33.5%)			
Location			NS		
Rectum	17 (8.3%)	69 (7.2%)			
Colon	189 (91.7%)	888 (92.8%)			
Polyp diameter (mm)			NS		
≥6 mm	53 (25.7%)	232 (24.2%)			
<6 mm	153 (74.3%)	725 (75.8%)			
Morphology			0.026	1.20 (0.868–1.669)	NS
Protruded (0-Is, Isp, Ip)	89 (43.2%)	334 (34.9%)			
Superficial, elevated (0-IIa)	117 (56.8%)	623 (65.1%)			
Antithrombotic agents			NS		
Present	55 (26.7%)	206 (21.5%)			
Absent	151 (73.3%)	751 (78.5%)			
Endoscopists' experience			< 0.001	1.87 (1.328–2.632)	< 0.001
Trainees	73 (35.4%)	203 (21.2%)			
Experts	133 (64.6%)	754 (78.8%)			
Histopathology			NS		
Adenoma	169 (82.0%)	825 (86.2%)			
Hyperplastic polyp, SSA/P	37 (18.0%)	132 (13.8%)			
Immediate bleeding			NS		
Yes	15 (7.3%)	48 (5.0%)			
No	191 (92.7%)	909 (95.0%)			

IPR, incomplete polyp resection; *CSP*, cold snare polypectomy; *CR*, complete resection; *NS*, not significant; *SSA/P*, sessile serrated adenoma/polyp

Several studies have addressed about the association between the learning curve and proficiency of colonoscopy in trainee fellows. Lee et al. [28] reported that experience of a minimum of 150 colonoscopies is required to ensure reliable completion rates. Another study suggested that competence in diagnostic colonoscopy in a trainee fellow group requires experience of more than 500 colonoscopies [27]. Concerning the adenoma detection rate (ADR), the ADR increased markedly with the level of training [29]. In addition, several studies have addressed the association between the skill level for polypectomy and experience in colonoscopy for trainee fellows. Choi et al. [30] reported that the resection completeness of polyps depended on the experience level of the endoscopist in the trainee fellow group, and as the number of procedures increased, a higher rate of CR was achieved. In the trainee fellow group, inadequate experience in the procedure was closely associated with poor polypectomy outcomes, which could be attributed to their overall poor skills in polypectomy owing to factors such as lack of adequate familiarity with the manipulation of the scope, snare, and determination of the cutting plane of the snare, resulting in their inability to secure an adequate margin [31]. Choi et al. [30] reported that such limitations of trainee fellows could be overcome by accumulated cumulative experience. These findings support the need for adequate education and supervision by expert endoscopists to ensure proficiency of trainees in endoscopic procedures, and suggest that trainee endoscopists might require careful and close attention before he/she acquires adequate skill to achieve CR [32]. Considerable training and experience are required for optimal performance of polypectomy, including securing adequate resection margins. Therefore, endoscopic quality improvement programs should include training for improving polypectomy completeness, besides increasing the ADRs, because CR rates could be

improved by practice and IPR is associated with the occurrence of ICC [15, 20]. It is desirable to conduct a prospective study in the future to determine whether fellowship education and supervision could change the outcomes of polypectomy.

In this study, we achieved a good total CR rate with a negative pathological margin (82.3%) and there were no cases of carcinoma (0%). Each polyp resected by CSP was examined in detail to determine the appropriateness of its resection. Whether the polyp resection was performed by HP (or EMR) or CSP was left to the judgment of experts. If carcinoma was suspected, the polyps were resected by HP or EMR, and not by CSP. We were able to diagnose correctly; this may have influenced the good results obtained in respect of the histopathology and the pathological margin.

The definition of CR and IPR is not standardized. In this study, CR was defined by histological examination of the polypectomy specimens, and we used a tumor-free condition of the horizontal margins of the resected specimen as determined by histopathology as our definition of CR of a polyp after CSP. Cases with an unclear-margin and positive-margin were classified into the IPR group. It is possible that some of the cases with an unclear margin actually had a clear margin (CR group). Dwyer et al. [33] reported performance of additional biopsies from the polypectomy site as a method for assessing the completeness of endoscopic resection. Matsuura et al. [21] reported that the best method for determining the completeness of polyp resection is EMR of the polypectomy base. However, additional biopsy or additional EMR from the CSP site may not be feasible in all cases of CSP and would be associated with an increased risk of complications, most notably DPPB and perforation. In addition, the advantage of the CSP procedure is its convenience, and additional biopsy or EMR would increase the complexity of the procedure. Although the muscularis shrinks after polypectomy and it is difficult for the pathologist to accurately identify the resection margin after CSP, histopathological determination of a negative resection margin for assessing CR is a more popular and acceptable method in routine clinical practice. Japanese pathologists are trained to examine the lateral margins of all polyps and to report the results of completeness of polyp resection. The pathologists at our hospital are also experienced in determining the margin status and we believe that we are able to maintain a high quality. In regard to the deep margins, we inspected the resultant wound carefully in all cases to confirm that there was no residual lesion after the CSP. Tutticci et al. [34] reported that the protrusions within the cold snare defect (CSDPs) do not represent vascular structures, do not contain residual polyps, and are not associated with adverse outcomes in short-term follow-up. It is significant that the CSDPs did not represent residual polyps or tumor components. Therefore, we believe that the resections were complete.

There were several limitations of this study. First, this study was a retrospective review conducted at a single center; however, it had the advantage of a large sample size. Second, there was no randomization protocol between the trainees and experts. However, there were a sufficient number of polyp resections included in the present study and multivariate analysis identified performance of the procedure by trainees as an independent risk factor for IPR after CSP. Therefore, the characteristics of the polyps might not have had any influence on our results. Taking into consideration these limitations, we propose to conduct a prospective, multicenter, randomized controlled trial to confirm our results. Third, we have not followed up the patients to identify local recurrence or ICC after IPR. Therefore, it cannot be mentioned whether IPR after CSP is actually a risk factor for local recurrence or ICC. However, previous studies have shown that IPR is one of the main causes for predisposing to the development of ICC [15–20]. In addition, the main objective of this study was not to investigate the rate of local recurrence or ICC incidence in the IPR cases—it was accurate identification of the risk factors for IPR after CSP, and main outcome was risk factors for IPR after CSP. We would like to perform another long-term follow-up study to determine the rate of local recurrence rate and ICC incidence in the cases of IPR after CSP in the future.

In conclusion, our results indicated that performance of CSP by trainees was a significant risk factor for IPR after CSP. IPR is recognized as a risk factor for the development of ICC, and the issue of IPR is therefore of great clinical significance. Adequate education and supervision by expert endoscopists to ensure proficiency of the trainees in the performance of endoscopic procedures are necessary for improving trainee's skills. Prospective, randomized studies are necessary in the future to develop effective methods for the prevention/control of IPR after CSP.

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Author contributions JA, HC, TH, TG, and AN conceived the study. JA, KA, JT, TN, HK, and MN performed the CSP. JA and RF recruited the study participants. Analysis and interpretation of the data was conducted by JA, NM, and HC. All the authors have read the final manuscript and approve of its submission for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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