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World Journal of Gastrointestinal Oncology (World J Gastrointest Oncol, WJGO, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGO covers topics concerning carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. The current columns of *WJGO* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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Clinical Practice Study

Sessile serrated adenoma detection rate is correlated with adenoma detection rate

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Kinoshita H, Niimi K, Ono S, Yoshida S, Yamada A, Kodashima S, Yamamichi N and Hirata Y performed endoscopic procedures, checked the manuscript and suggested improvement; Hayakawa Y and Minatsuki M checked the manuscript and suggested improvement; Ushiku T and Fukayama M provided advice on the histopathological diagnoses, checked the manuscript and suggested improvement; Koike K gave the final approval of the manuscript.

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Abstract

AIM

To investigate the association between adenoma detection rate (ADR) and sessile serrated adenoma (SSA) and significant predictors for sessile serrated adenomas (SSA) detection.

METHODS

This study is a retrospective, single-center analysis. Total colonoscopies performed by the gastroenterologists at the University of Tokyo Hospital between January and December 2014 were retrospectively identified. Polyps were classified as low-grade or high-grade adenoma, cancer, SSA, or SSA with cytological dysplasia, and the prevalence of each type of polyp was investigated. Predictors of adenoma and SSA detection were examined using logistic generalized estimating equation models. The association between ADR and SSADR for each gastroenterologist was investigated by calculating a correlation coefficient weighted by the number of each gastroenterologist's examination.

RESULTS

A total of 3691 colonoscopies performed by 35 gastroenterologists were assessed. Overall, 978 (26.5%) low- and 84 (2.2%) high-grade adenomas, 81 (2.2%) cancers, 66 (1.8%) SSAs, and 2 (0.1%) SSAs with cytological dysplasia were detected. Overall ADR was 29.5% (men 33.2%, women 23.8%) and overall SSADR was 1.8% (men 1.7%, women 2.1%). In addition, 672 low-grade adenomas (68.8% of all the detected low-grade adenomas), 58 (69.9%) high-grade adenomas, 29 (34.5%) cancers, 52 (78.8%) SSAs, and 2 (100%) SSAs with cytological dysplasia were found in the proximal colon. Adenoma detection was the only significant predictor of SSA detection (adjusted OR: 2.53, 95%CI: 1.53-4.20; $P < 0.001$). The correlation coefficient between ADR and SSADR weighted by the number of each gastroenterologist's examinations was 0.606 ($P < 0.001$).

CONCLUSION

Our results demonstrated that ADR is correlated to SSADR. In addition, patients with adenomas had a higher prevalence of SSAs than those without adenomas.

Key words: Sessile serrated adenoma; Sessile serrated adenoma detection rate; Adenoma detection rate; Colonoscopy; Interval colorectal cancer

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Core tip: Sessile serrated adenomas (SSAs) are difficult to detect and are associated with interval colorectal cancer (CRC). To reduce interval CRC and CRC death, SSA detection is important, and evaluation of the sessile serrated adenoma detection rate (SSADR) is crucial. In Western countries, there have been some reports showing the correlation of adenoma detection rate (ADR) and SSADR. However, in Asian countries, little is known about the correlation between ADR and SSADR. We investigated the association between ADR and SSADR and significant predictors for SSA detection in Japanese population. We found that ADR is correlated with SSADR, and patients with adenomas have a higher prevalence of SSAs than those without adenomas.

Ohki D, Tsuji Y, Shinozaki T, Sakaguchi Y, Minatsuki C, Kinoshita H, Niimi K, Ono S, Hayakawa Y, Yoshida S, Yamada A, Kodashima S, Yamamichi N, Hirata Y, Ushiku T, Fujishiro M, Fukayama M, Koike K. Sessile serrated adenoma detection rate is correlated with adenoma detection rate. *World J Gastrointest Oncol* 2018; 10(3): 82-90 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v10/i3/82.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v10.i3.82>

INTRODUCTION

Colorectal cancer (CRC) is one of the major causes of cancer mortality in the world^[1]. Incidence of CRC has been increasing in Japan, and it is now the second leading cause of cancer-related death^[2]. Colonoscopy currently plays a central role in CRC screening^[3-5]. Total colonoscopy has been shown to reduce the risk of death from CRC by removing precancerous adenomas^[5]. Total colonoscopy and detection of adenomas are imperative for preventing CRC. The adenoma detection rate (ADR) has been reported to be an excellent quality indicator of total colonoscopy^[6,7]. ADR is also associated with the risk of interval CRC and death^[8,9].

However, there have been some reports indicating that total colonoscopy is less effective in reducing the risk of cancer in the proximal colon^[10,11]. The presence of sessile serrated adenomas (SSAs) in the right colon, which would progress *via* the serrated pathway to CRC, is thought to be a potential reason. A serrated pathway is an alternative pathway in which serrated polyps replace the traditional adenoma as precursor lesions to CRC^[12]. CRCs derived from serrated pathways account for 20%-30% of all CRCs^[13,14]. SSAs are usually flat or sessile, and are occasionally covered by a mucous cap^[13]. They are difficult to detect because of their subtle morphology, and even when detected, are often incompletely resected. In addition, some SSAs are reported to progress to invasive cancer in a short period of time^[15,16]. Therefore, SSAs are thought

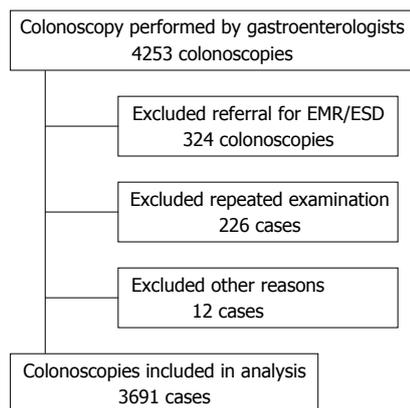


Figure 1 Study flow chart. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

to be strongly associated with interval CRC^[16,17]. To reduce interval CRC and CRC-related death, detection of SSAs is important, and evaluation of the SSA detection rate (SSADR) is crucial. Recently, there have been few reports suggesting that SSADR is associated with ADR^[17,18]. However, to the best of our knowledge, there has been no report in Asian countries showing a correlation between ADR and SSADR. In this context, we investigated the association between ADR and SSADR with significant predictors for SSA detection in total colonoscopy screening or surveillance in the Japanese population.

MATERIALS AND METHODS

Patients

This study is a retrospective, single-center analysis. We extracted data on total colonoscopies performed at the University of Tokyo Hospital between January and December 2014 by reviewing electronic medical records. All total colonoscopies performed by gastroenterologists were included in this analysis. Indications for total colonoscopy were classified as surveillance total colonoscopy, positive fecal occult blood test, screening for other symptoms (*e.g.*, abdominal pain, anemia, and chronic diarrhea), and others. The following colonoscopies were excluded: repeated examinations during the study period and referral colonoscopies for endoscopic mucosal resection/endoscopic submucosal dissection (Figure 1). All gastroenterologists involved in this study had more than 5 years of experience in total colonoscopy.

In this study, we classified the pathology of each resected polyp into the following categories: low- or high-grade adenoma, cancer (including intramucosal cancer), SSA, or SSA with cytological dysplasia (Figures 2 and 3). Polyps that were resected but not histologically evaluated, and endoscopically detected polyps that were not resected, were determined to be non-neoplastic. The histological definition for SSAs was in accordance with the definition of the Japanese Society for Cancer of the Colon and Rectum^[19]. SSAs had two or more of

the following features in more than 10% of the serrated area: (1) Dilated crypt; (2) irregularly branching crypt; and/or (3) dilation of the base of the crypt which often has a boot, L, or inverted T shape. SSA with cytological dysplasia was defined as a dysplastic area, similar to conventional adenoma^[19,20]. In our institution, the comprehensive retrospective analysis of each patient's medical record was approved by our ethics committee (No. 2058); this study is included in that category. The present study was performed in accordance with the Declaration of Helsinki.

Procedure

The bowel preparation method in our institution was as follows: (1) 10 mL of 0.75% sodium picosulfate the day before endoscopy; and (2) 2-4 L of polyethylene glycol (Niflec: EA Pharma, Tokyo, Japan) on the morning of the endoscopy.

Video processor unit EVIS LUCERA SPECTRUM or EVIS LUCERA ELITE (Olympus Corporation, Tokyo, Japan) and single-channel lower gastrointestinal endoscope (PCF-Q260AZI, PCF-Q260AI, PCF-PQL, CF-240AI; Olympus Co.) were used. The choice of the endoscope was left to the discretion of each endoscopist.

Almost all colonoscopies were performed without sedation, but in some special cases where patients could not tolerate the colonoscopy procedure, conscious sedation using diazepam with or without pentazocine was administered.

Examination items

The polyp detection rate and location of each polyp were investigated. The proximal colon was defined as the area proximal to the splenic flexure (transverse colon, ascending colon, and cecum), while the distal colon was defined as the area distal to the splenic flexure (descending colon, sigmoid colon, and rectum). ADR was calculated as described in previous literature^[6,21]: the proportion of colonoscopies where at least one colorectal low- or high-grade adenoma or cancer was detected. SSADR was calculated in the same way: the proportion of colonoscopies where at least one SSA or SSA with cytological dysplasia was detected.

Factors possibly related to adenoma detection and SSA detection was assessed: (1) Patients' age; (2) patients' sex; (3) years of colonoscopy experience of the endoscopist; (4) withdrawal time; (5) cecal intubation rate; and (6) bowel cleansing level. Withdrawal time was defined as the time from identification of cecum to identification of anus in colonoscopy cases where no polyps were removed. The bowel cleansing level was classified as "adequate" or "non-adequate" according to the ASGE/ACG task force recommendations. "Adequate" was defined as the examination allowed for the detection of polyps > 5 mm in size^[6,22].

Statistical analysis

Characteristics of patients were summarized and compared between the presence (+) or absence (-)

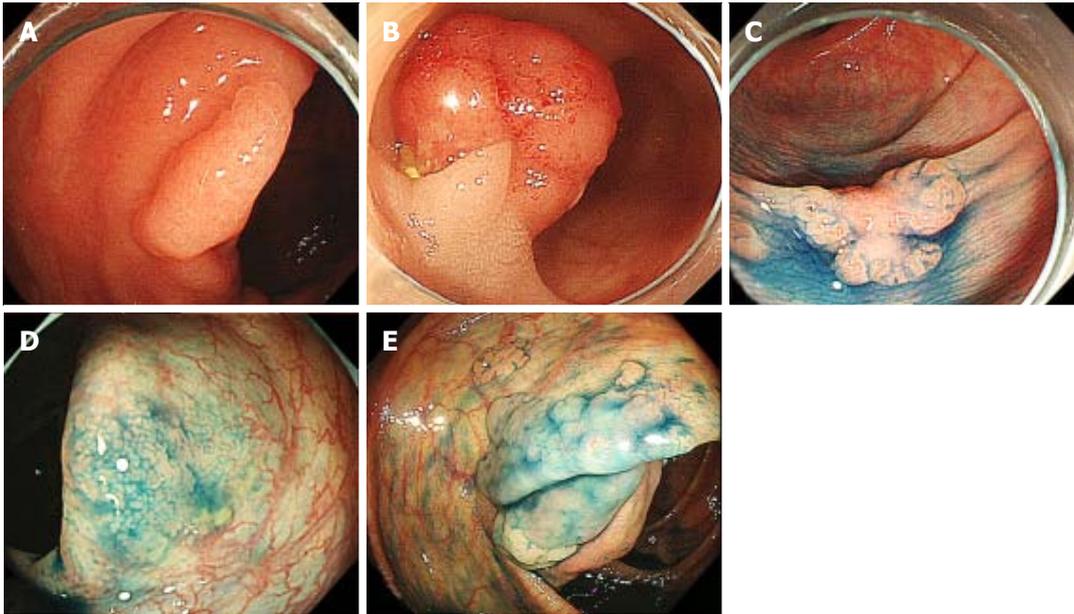


Figure 2 Typical endoscopic pictures of each polyp. A: Low grade adenoma; B: High grade adenoma; C: Cancer; D: Sessile serrated adenoma; E: Sessile serrated adenoma with cytological dysplasia.

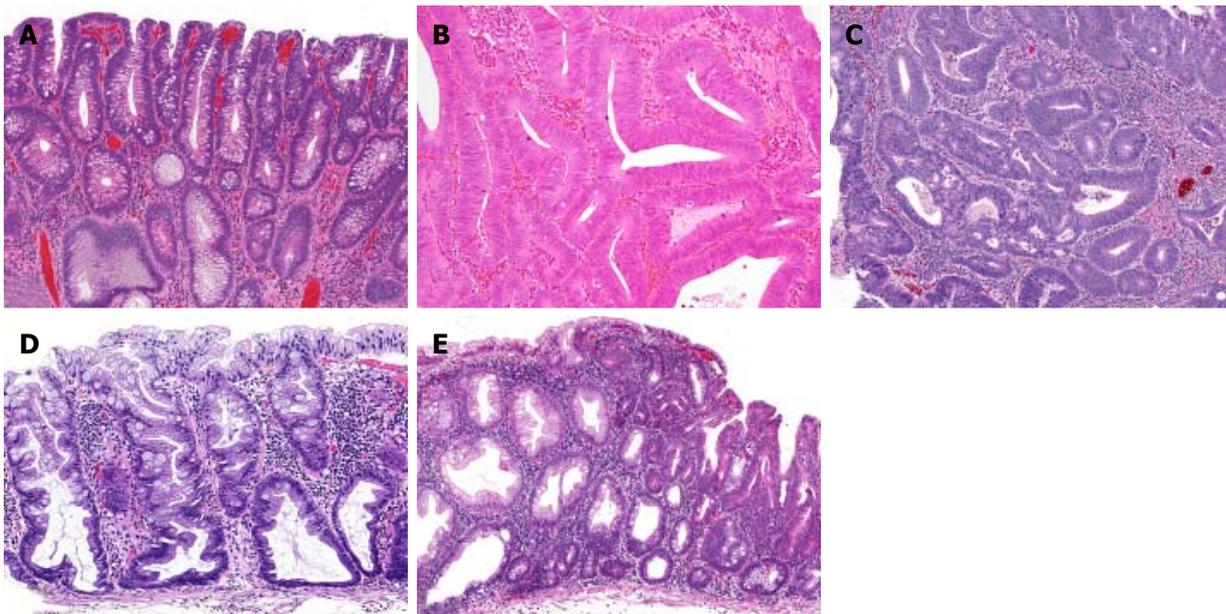


Figure 3 Histopathological pictures of each polyp. A: Low grade adenoma; B: High grade adenoma; C: Cancer; D: Sessile serrated adenoma; E: Sessile serrated adenoma with cytological dysplasia.

of adenoma detection using *t*-test or chi-squared test. Gastroenterologists' experience and their average withdrawal time that was calculated after excluding polypectomy were also summarized. Predictors of ADR were examined using logistic generalized estimating equation models, which explain the adenoma detection probability of each total colonoscopy by patient- and gastroenterologist-level variables. We used robust sandwich variance estimators that specified each gastroenterologist as a cluster to compute 95% confidence intervals (CI) and *P*-values. Predictors of SSADR were similarly examined, but adenoma detection

of corresponding total colonoscopy was added as a predictor. The bivariate association of SSADR and ADR of each gastroenterologist were illustrated by a scatter plot and correlation coefficient that were weighted by the number of performed total colonoscopies. All analyses were conducted using SAS version 9.4 (Cary, NC, United States).

RESULTS

Study group and characteristics of colonoscopies

A total of 4253 colonoscopies were performed by

Table 1 Patient characteristics	
	Total (n = 3691)
Age, mean ± SD (yr)	63.5 ± 13.3
Sex: Male (%)	2224 (60.3)
Adequate bowel cleansing (%)	3585 (97.1)
Cecal intubation rate (%)	3636 (98.5)
Indications for colonoscopy (%)	
Surveillance	1314 (35.6)
Fecal occult blood test	538 (14.6)
Screening for other symptoms	544 (14.7)
Others	1295 (35.1)

Others include screening before surgery or chemotherapy, patients' desire, and so on.

Table 2 Gastroenterologist characteristics	
	n = 35
Sex: Male (%)	25/35 (71.4)
Years of experience in colonoscopy (%)	
5-9	24/35 (68.6)
10-14	6/35 (17.1)
≥ 15	5/35 (14.3)
Number of colonoscopies performed (%)	
≤ 100	19/35 (54.3)
100-200	10/35 (28.6)
≥ 200	6/35 (17.1)
Withdrawal time: Mean (SD), m	10.1 ± 6.9

gastroenterologists during the study period. Overall, 562 colonoscopies were excluded based on the predetermined criteria, and 3691 colonoscopies were included in the analysis (Figure 1). Baseline characteristics of colonoscopies are shown in Table 1. Adequate bowel cleansing and cecal intubation rate were observed in 3585 (97.1%) cases and 3636 (98.5%) cases, respectively.

Characteristics of gastroenterologist

Baseline characteristics of gastroenterologists are shown in Table 2. All gastroenterologists had at least 5 years of colonoscopy experience; 16 (45.7%) gastroenterologists performed more than 100 cases a year.

Detection of each polyp

Low- and high-grade adenomas, and cancers were found in 978 (26.5%) cases, 84 (2.2%) cases and 81 (2.2%) cases, respectively. Overall ADR was 29.5% (men 33.2%, women 23.8%). SSAs and SSAs with cytological dysplasia were found in 66 (1.8%) cases and 2 (0.1%) cases, respectively. Overall SSADR was 1.8% (men 1.7%, women 2.1%).

The location of each polyp was also investigated. Altogether, 672 low-grade adenomas (68.8% of all the detected low-grade adenomas), 58 (69.9%) high-grade adenomas, 29 (34.5%) cancers, 52 (78.8%) SSAs, and 2 (100%) SSAs with cytological dysplasia were found in the proximal colon.

Predictors for adenoma detection

Univariable and multivariable analyses were performed

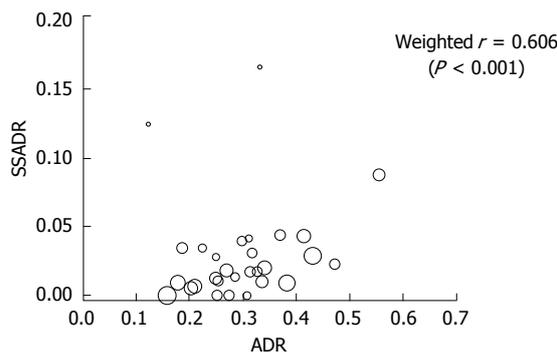


Figure 4 Weighted scatter plot and correlation coefficient for detection rates of sessile serrated adenomas and adenomas of each gastroenterologist. The area of the circle is proportional to the number of colonoscopies performed. SSADR: Sessile serrated adenomas; ADR: Adenomas.

to evaluate factors associated with adenoma detection (Table 3). In our institution, the cecal intubation rate was almost 100%, but could not be used in the analyses. Mean withdrawal time was 10 min, and there were only 2 gastroenterologists whose withdrawal time was less than 6 min. According to the scatter diagram plotting each endoscopist's ADR against their mean withdrawal time, as previously reported^[7], the recommended ADR level of 25%^[6] corresponded to a withdrawal time of 8 min. All factors, except for years of colonoscopy experience, were significantly associated with adenoma detection in both analyses with a 5% significance level. Being a woman (adjusted OR: 0.61, 95%CI: 0.54-0.70; *P* < 0.001) and those with non-adequate bowel cleansing (adjusted OR: 0.32, 95%CI: 0.19-0.52; *P* < 0.001) had a statistically inverse relationship with adenoma detection. Mean withdrawal time ≥ 8 min had statistically significant correlation with adenoma detection (adjusted OR: 1.77, 95%CI: 1.28-2.46; *P* < 0.001).

Predictors for sessile serrated adenoma detection

Univariable and multivariable analyses were performed to evaluate factors associated with SSA detection (Table 4). Both analyses revealed that adenoma detection was the only significant predictor for SSA detection (adjusted OR: 2.53, 95%CI: 1.53-4.20; *P* < 0.001). Mean withdrawal time ≥ 8 min tended to be associated with SSA detection, but was not statistically significant (adjusted OR 1.53; 95%CI: 0.62-3.75; *P* = 0.35).

Correlation between ADR and SSADR

As for the correlation between ADR and SSADR, a scatter diagram of ADR and SSADR is shown in Figure 4. The correlation coefficient between ADR and SSADR weighted by the number of each gastroenterologist's examinations was 0.606 (*P* < 0.001).

DISCUSSION

In the present study, a relatively strong association between ADR and SSADR was observed. Some reports

Table 3 Odds ratio estimates from logistic generalized estimating equations for adenoma detection

Variable	Univariable model		Multivariable model	
	OR (95%CI)	P	OR (95%CI)	P
Patient-level variable				
Age (yr)	1.02 (1.02, 1.03)	< 0.001	1.02 (1.02, 1.03)	< 0.001
Female	0.63 (0.55, 0.71)	< 0.001	0.61 (0.54, 0.70)	< 0.001
Non-adequate bowel cleansing	0.36 (0.22, 0.57)	< 0.001	0.32 (0.19, 0.52)	< 0.001
Endoscopist-level variable				
Endoscopist's experiment (yr)	0.98 (0.94, 1.02)	0.36	0.99 (0.96, 1.02)	0.55
Mean withdrawal time \geq 8 min (<i>vs</i> < 8 min)	1.72 (1.23, 2.41)	0.0015	1.77 (1.28, 2.46)	< 0.001

Multivariable model simultaneously adjusted for listed variables. Confidence intervals and *P*-values were calculated by robust variance specifying a gastroenterologist as a cluster.

Table 4 Odds ratio estimates from logistic generalized estimating equations for sessile serrated adenoma detection

Variable	Univariable model		Multivariable model	
	OR (95%CI)	P	OR (95%CI)	P
Patient-level variable				
Adenoma detection (<i>vs</i> none)	2.44 (1.45, 4.09)	< 0.001	2.53 (1.53, 4.20)	< 0.001
Age (yr)	0.99 (0.98, 1.01)	0.27	0.99 (0.98, 1.00)	0.07
Female	1.28 (0.77, 2.11)	0.34	1.40 (0.85, 2.29)	0.19
Non-adequate bowel cleansing	0.50 (0.07, 3.47)	0.48	0.60 (0.08, 4.28)	0.61
Endoscopist-level variable				
Endoscopist's experiment (yr)	0.99 (0.89, 1.10)	0.86	1.00 (0.91, 1.09)	0.96
Mean withdrawal time \geq 8 min (<i>vs</i> < 8 min)	1.74 (0.70, 4.29)	0.23	1.53 (0.62, 3.75)	0.35

Multivariable model simultaneously adjusted for listed variables.

have described the correlation of ADR and SSADR in Western countries patients^[17,18]; however, to our knowledge, the prevalence of SSAs or SSADR in Asian populations has not yet been fully investigated and appropriate SSADR has not been determined. Therefore, our study holds importance, as it is the first report to demonstrate the correlation between SSADR and ADR in Asian populations.

There is controversy regarding the prevalence of SSAs, which differs among previously published studies, varying from 2%-10%^[13,17,18,23,24]. In our institution, the prevalence of SSAs was approximately 2%, which is lower than previously reported results in Western populations. Each endoscopist's cognitive capability to detect SSAs may differ in degree. Payne *et al*^[25] reported that the prevalence of SSAs varied among endoscopy centers. In addition, Abdeljawad K *et al*^[26] reported that a review of pathology slides by an experienced gastrointestinal pathologist increased the prevalence of SSAs, and the prevalence of SSAs increased over the study period, suggesting that each endoscopist improved his detection skills over time. However, the gastroenterologist's ADR in this study was approximately 30%, which is within the standard of quality indicators for colonoscopy specified by ASGE^[6]. Therefore, the quality of the present study is assured. The quality of the pathological evaluation was also high, because the experienced gastrointestinal pathologist (U.T.), who was acquainted with the definition of the Japanese Society for Cancer of the Colon and Rectum, reassessed the pathology slides. As previously mentioned, the prevalence of SSAs

in Asian populations has not been determined, as there may be a difference between races. It is mandatory to investigate the true prevalence of SSAs in Asian populations in the future.

The factors associated with SSA detection were investigated, and our study demonstrated that adenoma detection at the patient level was the only independent significant factor associated with SSA detection. Previous reports have shown that when a patient presented with serrated lesions, especially SSAs, he/she was also more likely to have advanced neoplasia^[23,27-29]. These results were compatible with previous reports and suggested that ADR is correlated with SSADR.

A withdrawal time of \geq 8 min was not a statistically significant factor for SSA detection, although it was significantly related to adenoma detection. However, considering that ADR and SSADR are correlated, a longer duration of inspection seems to improve ADR and SSADR. In this study, the total number of SSAs was quite small. This may be a reason why a significant association between withdrawal time and SSA detection was not found.

We acknowledge that there were several limitations in our study. First, this study was a retrospective single center study, and the number of SSA cases was small. Second, there were many cases of total colonoscopy surveillance in the present study in addition to total colonoscopy screening. As previously stated, the target ADR should be changed according to patient risk^[30]. However, factors associated with adenoma detection in this study were similar to those in previous reports.

Moreover, Anderson JC reported that the serrated polyp detection rate was similar for screening or surveillance indications, suggesting that both indications could be used to derive the serrated polyp detection rate in practice^[31].

Rex *et al*^[32] has also recently reported that using overall ADR to calculate ADR from screening, surveillance, and diagnostic colonoscopies would be just as effective as a screening-only ADR. Taking this into account, the current findings can be applied to clinical practice to some extent. Finally, the ratio of adequate bowel cleansing in this study was much higher than in previous studies. The ASGE guidelines recommend that the quality of bowel cleansing should be evaluated after retained fluid or stool has been suctioned^[6]. In our institution, if fluid and stool were retained, gastroenterologists suctioned as much as possible to identify polyps ≥ 5 mm in size. Such cases were considered adequate in our study, and therefore, the ratio of the "adequate" level was high.

In conclusion, our study suggests that ADR is correlated with SSADR. In addition, patients with adenomas may have a higher prevalence of SSAs than those without adenomas. A large-scale prospective study will be needed to validate these findings.

ARTICLE HIGHLIGHTS

Research background

Sessile serrated adenomas (SSAa) are difficult to detect and strongly associated with interval colorectal cancer (CRC). It is necessary to investigate the factors which influence SSA detection and to evaluate the SSA detection rate (SSADR).

Research motivation

In Western countries, some reports have described the correlation of ADR and SSADR. However, to the best of our knowledge, there has been no report in Asian countries showing a correlation between ADR and SSADR. In this context, we investigated the association between ADR and SSADR with significant predictors for SSA detection in total colonoscopy screening or surveillance in the Japanese population.

Research objectives

The main objectives were as follows; the prevalence of each polyp (low-grade or high-grade adenoma, cancer, SSA, or SSA with cytological dysplasia), each gastroenterologist's ADR and SSADR, the association between ADR and SSADR for each gastroenterologist and predictors of adenoma and SSA detection.

Research methods

Total colonoscopies performed by the gastroenterologists at the University of Tokyo Hospital between January and December 2014 were retrospectively identified. The prevalence of each type of polyp was investigated. Predictors of adenoma and SSA detection were examined using logistic generalized estimating equation models. The association between ADR and SSADR for each gastroenterologist was investigated by calculating a correlation coefficient weighted by the number of each gastroenterologist's examination.

Research results

A total of 3691 colonoscopies by 35 gastroenterologists were assessed. 978 low grade adenomas (26.5%), 84 high grade adenomas (2.2%), 81 cancers (2.2%), 66 SSAs (1.8%) and 2 SSAs with cytological dysplasia (0.1%) were

detected. Adenoma detection was the only significant predictor of SSA detection (adjusted OR: 2.53, 95%CI: 1.53-4.20; $P < 0.001$). The correlation coefficient between ADR and SSADR weighted by the number of each gastroenterologist's examinations was 0.606 ($P < 0.001$).

Research conclusions

Our study suggests that ADR is correlated with SSADR. Some reports have described the correlation of ADR and SSADR in Western countries patients; however, to our knowledge, the prevalence of SSAs or SSADR in Asian populations has not yet been fully investigated and appropriate SSADR has not been determined. Therefore, our study holds importance, as it is the first report to demonstrate the correlation between SSADR and ADR in Asian populations. In addition, patients with adenomas may have a higher prevalence of SSAs than those without adenomas.

Research perspectives

This study was a retrospective single center study, and the number of SSA cases was small. Therefore, a large-scale prospective study will be needed to validate these findings.

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