

# Adherence to Surveillance Guidelines after the Removal of Colorectal Polyps: A Multinational, Multicenter, Prospective Survey

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\*Current affiliation of Achmad Fauzi is Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. **Background/Aims:** As the number of colonoscopies and polypectomies performed continues to increase in many Asian countries, there is a great demand for surveillance colonoscopy. The aim of this study was to investigate the adherence to postpolypectomy surveillance guidelines among physicians in Asia.

**Methods:** A survey study was performed in seven Asian countries. An email invitation with a link to the survey was sent to participants who were asked to complete the questionnaire consisting of eight clinical scenarios.

**Results:** Of the 137 doctors invited, 123 (89.8%) provided valid responses. Approximately 50% of the participants adhered to the guidelines regardless of the risk of adenoma, except in the case of tubulovillous adenoma  $\geq$ 10 mm combined with high-grade dysplasia, in which 35% of the participants adhered to the guidelines. The participants were stratified according to the number of colonoscopies performed:  $\geq$ 20 colonoscopies per month (high volume group) and <20 colonoscopies per month (low volume group). Higher adherence to the postpolypectomy surveillance guidelines was evident in the high volume group (60%) than in the low volume group (25%). The reasons for nonadherence included concern of missed polyps (59%), the low cost of colonoscopy (26%), concern of incomplete resection (25%), and concern of medical liability (15%).

**Conclusions:** A discrepancy between clinical practice and surveillance guidelines among physicians in Asia was found. Physicians in the low volume group frequently did not adhere to the guidelines, suggesting a need for continuing education and appropriate control. Concerns regarding the quality of colonoscopy and complete polypectomy were the main reasons for nonadherence. (Gut Liver 2021;15:878-886)

Key Words: Colon; Rectum; Polyp; Guideline adherence; Colonoscopy

# INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer, and the fourth second leading cause of cancer-related death worldwide.<sup>1</sup> The incidence of CRC continues to rise in many Asian countries.<sup>2</sup> The number of colonoscopies performed for CRC screening has increased tremendously in many Western countries. Although the use of colonoscopy as a primary screening modality in Asian countries has been limited due to its invasiveness, insufficient colonoscopy resources and low CRC screening uptake, it continues to increase as the incidence of CRC increases.<sup>3</sup> In Korea, the overall volume of colonoscopies increased 8-fold over a 12-year period.<sup>4</sup> Colonoscopy is

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very effective for reducing CRC risk since it can detect and remove precancerous colorectal polyps during colonoscopy.<sup>5,6</sup> Surveillance colonoscopy after polypectomy should be performed at appropriate intervals based on findings from the index colonoscopy. Many academic societies, including those in the United States, Europe, and Asia-Pacific regions, have published recommendations regarding the CRC surveillance interval after index colonoscopy.<sup>7-10</sup> In these guidelines, the surveillance colonoscopy interval is based on risk stratification according to the number, type, and histopathological findings of all resected polyps identified during colonoscopy. However, adherence to surveillance colonoscopy intervals in Western countries is low, with more than 50% of patients undergoing follow-up colonoscopy either too early or too late.<sup>11</sup> While overuse of surveillance colonoscopy is associated with increased financial burden and a risk of complications, underuse can increase the risk of post-colonoscopy cancer and cancerrelated mortality.<sup>12</sup> Although the rate of adherence to surveillance guidelines in Korea is similar to that in Western countries,<sup>13,14</sup> empirical data on the use of surveillance colonoscopy and adherence to surveillance guidelines in many Asian countries are lacking.<sup>3</sup> The aim of this study was to evaluate adherence to postpolypectomy surveillance guidelines among physicians in Asia and identify reasons for nonadherence.

### MATERIALS AND METHODS

### 1. Survey content and participants

This survey was a comprehensive study of primary care and specialty physicians. The study was designed to obtain multinational data on how CRC surveillance is being performed in seven Asian countries. Asian gastroenterologists who attended the 2nd International Meeting on Intestinal Disease in Conjunction with the Annual Congress of the Korean Association for the Study of Intestinal Diseases (April 13-14, 2018, Seoul, Korea) were invited to participate in the study. For domestic physicians, members of the Korean Association for the Study of Intestinal Diseases were invited. Respondents included 40 Korean gastroenterologists and 83 physicians from other Asian countries. The survey study was conducted using SurveyMonkey (SurveyMonkey<sup>®</sup>, San Mateo, CA, USA). An email invitation, which provided a link to the survey, was sent to the physicians, who were asked to complete the survey between July and October 2018. The responses were stored in a password-protected SurveyMonkey database, and exported to Microsoft Excel (Microsoft, Redmond, WA, USA) for analysis.

The survey included eight hypothetical clinical scenarios based on the findings from a screening colonoscopy in a 55-year-old man in good health (Supplementary Data). The six clinical scenarios were previously developed by Boolchand et al.<sup>15</sup> and have also been used in other studies.13,16,17 Colonoscopic and histological findings varied among the individual questions and included a 6-mm hyperplastic polyp, a 6-mm tubular adenoma, two 6-mm tubular adenomas, a 12-mm tubulovillous adenoma, or a 12-mm tubular adenoma with a focus of high-grade dysplasia. Another scenario included a 55-year-old man with a 12-mm tubular adenoma resected by polypectomy on index colonoscopy and no polyp identified on surveillance colonoscopy after 3 years. Two vignettes added to the clinical scenarios developed by Boolchand et al.<sup>15</sup> included multiple adenomas ( $\geq$ 3) and a 12-mm sessile serrated adenoma (SSA) with dysplasia. The participants were asked to recommend surveillance intervals for each scenario from the following choices: colonoscopy at 6 months, 1 year, 3 years, 5 years, 10 years, or no repeated colonoscopy. We also asked for the reasons for nonadherence to the guidelines. As a reference, the primary standard guidelines for colonoscopy surveillance after screening and polypectomy from the 2012 U.S. Multi-Society Task Force on Colorectal Cancer were used.<sup>7</sup> Instances in which another guideline recommended a longer surveillance interval than that in the U.S. Multi-Society Task Force guidelines were also taken into consideration when determining the reference range for determining the respondents' adherence.<sup>8-10,18</sup> We defined high-risk adenoma as (1) advanced stage, (2) presence of at least three adenomas, and (3) SSA/sessile serrated polyps  $\geq 10$  mm or adenomas with dysplasia. The study was approved by Institutional Review Boards from participating institutions, and informed consent was waived.

### 2. Statistical analysis

For respondents, colonoscopy volume according to the number of colonoscopies performed was categorized into  $\geq$ 20 colonoscopies per month (high volume [HV] group) and <20 colonoscopies per month (low volume [LV] group). All analyses were performed using SPSS for Windows (version 21.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were obtained for all variables, and the frequencies of the responses to scenarios and questions were calculated. The odds ratios for adhering to the guidelines on surveillance intervals were calculated using logistic regression analysis. The multivariate logistic model included age, sex, specialty, practice institution, country, years of clinical practice, number of colonoscopies performed (per month), number of polypectomies performed (per month), and number of outpatients (per week). A pvalue less than 0.05 was considered statistically significant.

# RESULTS

### 1. Characteristics of the survey respondents

The overall survey response rate was 89.8% (123/137 physicians). The characteristics of the respondents, who comprised 40 Korean gastroenterologists and 83 physicians

Table 1. Basel	ine Characteristics	of the Respondents
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from other Asian countries, are shown in Table 1. After stratification by the number of colonoscopies performed, 78 respondents (64%) were classified in the HV group and 45 (36%) in the LV group. The overall mean age was 40.8 $\pm$ 8.0 years, and those in the HV group (41.5 $\pm$ 7.9 years) were slightly older than those in the LV group (37.4 $\pm$ 7.7 years). Sixty-five percent of the respondents were male, and the majority of the respondents were specialists in gastroenterology. The most common type of medical facility

Basic characteristics responders	Total (n=123)	High volume group (n=78)	Low volume group (n=45)
Age, yr	40.8±8.0	41.5±7.9	37.4±7.7
Male sex	80 (65.0)	61 (78.2)	19 (42.2)
Specialty certification			
Gastroenterologists	96 (78.1)	67 (85.9)	29 (64.4)
Internal medicine	8 (6.5)	1 (1.3)	7 (15.6)
General surgeon	7 (5.7)	1 (1.3)	6 (13.3)
Gastroenterology trainee	11 (8.9)	9 (11.5)	2 (4.4)
Family medicine	0	0	0
Other	1 (0.8)	0	1 (2.2)
Practice hospital			
Tertiary referral	92 (74.8)	54 (69.2)	38 (84.4)
Secondary referral	26 (21.1)	19 (24.4)	7 (15.6)
Primary	5 (4.1)	5 (6.4)	0
Nations			
South Korea	40 (32.5)	40 (51.3)	0
Mongolia	24 (19.5)	0	24 (53.3)
Thailand	18 (14.6)	9 (11.5)	9 (20.0)
Myanmar	5 (4.1)	2 (2.6)	3 (6.7)
Malaysia	14 (11.4)	12 (15.4)	2 (4.4)
Indonesia	12 (9.8)	7 (9.0)	5 (11.1)
Vietnam	10 (8.1)	8 (10.3)	2 (4.4)
Years in clinical practice			
<10	53 (43.1)	28 (35.9)	25 (55.6)
10–19	47 (38.2)	35 (44.9)	12 (26.7)
20–29	20 (16.3)	12 (15.4)	8 (17.8)
≥30	3 (2.4)	3 (3.8)	0
No. of colonoscopies performed/month			
None	25 (20.3)	-	25 (55.6)
<10	4 (3.3)	-	4 (8.9)
10–19	16 (13.0)	-	16 (35.6)
20–39	26 (21.1)	26 (33.3)	-
40–59	13 (11.0)	13 (16.7)	-
≥60	39 (31.7)	39 (50.0)	-
No. of polypectomies performed/month			
None	26 (21.1)	0	26 (57.8)
<5	17 (13.8)	7 (9.0)	10 (22.2)
5-9	15 (12.2)	10 (12.8)	5 (11.1)
10–19	21 (17.1)	17 (21.8)	4 (8.9)
20–39	24 (19.5)	24 (30.8)	0
≥40	20 (16.3)	20 (25.6)	0
No. of patient/week		,	-
<25	10 (8.1)	1 (1.3)	9 (20.0)
25-49	24 (19.5)	11 (14.1)	13 (28.9)
50-99	38 (30.9)	22 (28.2)	16 (35.6)
≥100	51 (41.5)	44 (56.4)	7 (15.6)

Data are presented as mean±SD or number (%).

	Recommendation in U.S. Multi-Society			Response	Responses on surveillance intervals	e intervals		Repeat colonoscopy
Utilitical scenario	Task Force guidelines 2012, yr	- dnoio	6 Months	1 Year	3 Years	5 Years	10 Years	not indicated
6-mm TA	5-10	Total	4 [3.3]	19 [15.4]	33 (26.8)	56 (45.5)	11 [8.9]	0
		ЪЧ	1 (1.3)	5 (6.4)	19 (24.4)	48 (61.5)	5 (6.4)	0
		L<	3 (6.7)	14 (31.1)	14 (31.1)	8 (17.8)	6 [13.3]	0
6-mm Hyperplastic polyp	10	Total	2 [1.6]	9 (7.3)	22 (17.9)	56 (45.5)	25 (20.3)	9 (7.3)
		Η	0	1 [1.3]	8 (10.3)	44 (56.4)	17 (21.8)	8 (10.3)
		۲۷	2 (4.4)	8 (17.8)	14 (31.1)	12 (26.7)	8 (17.8)	1 (2.2)
12-mm SSA with dysplasia	ε	Total	26 (21.1)	32 (26.0)	61 (49.6)	3 (2.4)	0	1 (0.8)
		Ν	8 (10.3)	18 (23.1)	48 (61.5)	3 (3.8)	0	1 [1.3]
		LV	18 (40.0)	14 (31.1)	13 (28.9)	0	0	0
12-mm TA with focal HD	с	Total	44 (35.8)	32 (26.0)	43 (35.0)	3 (2.4)	0	1 (0.8)
		ЪН	19 (24.4)	20 (25.6)	35 (44.9)	3 (3.8)	0	1 [1.3]
		LV	25 (55.6)	12 (26.7)	8 (17.8)	0	0	0
12-mm TVA	m	Total	21 (17.1)	34 (27.6)	64 (52.0)	3 (2.4)	1 (0.8)	0
		Η	8 (10.3)	18 (23.1)	50 (64.1)	2 (2.6)	0	0
		LV	13 (28.9)	16 (35.6)	14 (31.1)	1 (2.2)	1 (2.2)	0
Two 6-mm TAs	5-10	Total	6 (4.9)	22 (17.9)	37 (30.1)	52 (42.3)	6 (4.9)	0
		Η	2 (2.6)	7 (9.0)	23 (29.5)	44 (56.4)	2 (2.6)	0
		LV	4 (8.9)	15 (33.3)	14 (31.1)	8 (17.8)	4 (8.9)	0
Six <10-mm TAs	ε	Total	15 (12.2)	46 (37.4)	60 (48.8)	1 (0.8)	0	1 (0.8)
		Ρ	8 (10.3)	24 (30.8)	46 [59.0]	0	0	0
		L<	7 [15.6]	22 (48.9)	14 (31.1)	1 (2.2)	0	1 (2.2)
No polyps in a patient with a 12-mm TA 3 yr earlier	ß	Total	5 [4.1]	8 (6.5)	29 (23.6)	67 (54.5)	13 (10.6)	1 (0.8)
		Ν	0	1 [1.3]	13 [16.7]	56 [71.8]	7 (9.0)	1 [1.3]
		۲۷	5 (11.1)	7 [15.6]	16 (35.6)	11 [24.4]	6 [13.3]	0

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employing the participants was a tertiary hospital, followed by a secondary teaching hospital.

# 2. Recommendations based on clinical scenarios and comparison with the guidelines

The surveillance intervals recommended by all respondents and by physicians in the HV and LV groups for the various scenarios identified on the index colonoscopy are shown in Table 2. More than 50% of the respondents adhered to the guidelines regardless of the adenoma type, except in the case of a single tubulovillous adenoma with a focus of high-grade dysplasia, in which 35% of respondents adhered to the guidelines.

# 1) Surveillance recommendations for low-risk lesions

More than half of the respondents stated that they would perform surveillance colonoscopy every 5 years or more for low-risk lesions, except in the case of two 6-mm adenomas. The response of "follow-up in 3 years or less" was selected by 27% of respondents for a single 6-mm hyperplastic polyp, 46% for a single 6-mm adenoma, 53% for two 6-mm adenomas, and 34% for no polyp with a previous high-risk tubular adenoma.

### 2) Surveillance recommendations for high-risk lesions

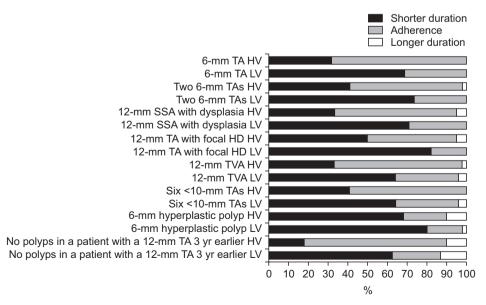
More than 95% of respondents recommended surveillance colonoscopy at a frequency of at least every 3 years. The response of "follow-up in 1 year or less" was recommended by 45% of respondents for a 12-mm tubulovillous adenoma, 62% for a 12-mm tubular adenoma with a focus of high-grade dysplasia, 50% for multiple adenomas ( $\geq$ 3), and 57% for a SSA with dysplasia.

# 3. Physician characteristics associated with surveillance recommendations

More than 60% of physicians in the HV group, but only 25% of physicians in the LV group, responded that they would adhere to the guidelines. The rates of adherence to the guidelines for each clinical scenario according to the physician's colonoscopy volume are shown in Fig. 1. Higher rates of adherence to the guidelines were seen in the HV group (21.8% to 71.8%) than in the LV group (17.8% to 31.1%). For all clinical scenarios, a shorter interval was recommended by more physicians in the LV group (52.3% to 82.3%) than HV group (18% to 68%). Table 3 presents the characteristics of the physicians associated with guideline adherence to surveillance colonoscopy intervals. In the multivariate analysis, the HV group showed significantly higher rate of guideline adherence. In addition, when adherence rate of Korean gastroenterologists was defined as a reference, respondents from other countries except Thailand showed significantly lower adherence rates. The reasons for nonadherence to the guidelines are shown in Fig. 2. The most common reason was concern of missed polyps (59%), followed by the low cost of colonoscopy (26%), concern of incomplete resection (25%), and concern of medical liability (15%).

# DISCUSSION

Using a multinational survey conducted in Asian countries, our results showed a discrepancy between the surveillance interval recommended by physicians and by published guidelines. Approximately half of the respondents recommended a surveillance interval according to



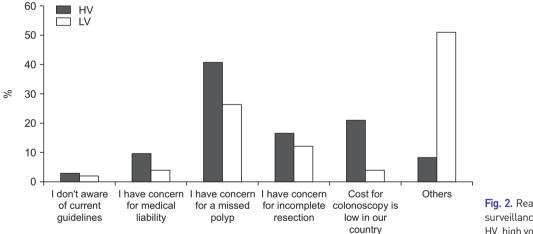
**Fig. 1.** Comparisons of the HV and LV groups regarding the postpolypectomy follow-up surveillance responses.

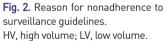
HV, high volume; LV, low volume; TA, tubular adenoma; SSA, sessile serrated adenoma; TVA, tubulovillous adenoma; HD, high-grade dysplasia.

Basic characteristics responders	Univariate OR (95% CI)	Multivariate OR (95% CI)
Sex		
Male	Reference	Reference
Female	0.615 (0.471-0.804)	0.280 (0.506-1.070)
Nations		
South Korea	Reference	Reference
Mongolia	0.027 (0.013–0.056)	0.042 (0.016–0.111)
Thailand	1.719 (1.114–2.652)	2.370 (1.370-4.102)
Myanmar	1.438 (0.705–2.933)	2.020 (0.866-4.710)
Malaysia	0.574 (0.372-0.885)	0.539 (0.322-0.901)
Indonesia	0.440 (0.277–0.700)	0.436 (0.238-0.798)
Vietnam	0.098 (0.050-0.193)	0.099 (0.050-0.198)
No. of colonoscopies performed/month		
<20	Reference	Reference
≥20	3.638 (2.740-4.830)	1.760 (1.068–2.901)
No. of polypectomies performed/month		
<10	Reference	Reference
≥10	2.844 (2.190-3.693)	0.779 (0.497–1.219)
No. of patient/week		
<25	Reference	Reference
25–49	4.481 (2.229–9.005)	0.946 (0.380-2.356)
50–99	5.571 (2.837–10.942)	1.350 (0.562–3.244)
≥100	6.719 (3.454–13.068)	1.112 (0.456–2.712)

Table 3. Odds Ratios for Adherence to Current Surveillance Colonoscopy G	Guidelines
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OR, odds ratio; CI, confidence interval.





the guidelines. Physicians with less experience tended to recommend shorter surveillance interval. Nonadherence to the guidelines was associated mainly with physicians' concerns regarding missed polyps and incomplete resection. A number of studies including survey studies have been performed to assess the rate of adherence to surveil-lance guidelines in Western countries.<sup>11,19</sup> Mysliwiec *et al.*<sup>19</sup> reported that 24% of gastroenterologists and 54% of surgeons recommend surveillance colonoscopy within 5 years for hyperplastic polyps, and more than half of physicians recommend surveillance colonoscopy at least every 3 years for small adenomas. A recent meta-analysis of 16 studies reported a mean rate of surveillance interval adherence of

48.8%, suggesting that more than half of patients underwent a surveillance colonoscopy either too early for lowrisk lesions or too late for high-risk lesions.<sup>11</sup> Taken together, these studies demonstrate that surveillance colonoscopy is overperformed in low-risk patients and underperformed in high-risk patients.

In contrast, there are few studies on adherence to surveillance guidelines in Asian countries other than Korea and Japan. In 2006, a survey of 131 Korean physicians reported that more than 90% of respondents recommended a shorter surveillance interval.<sup>20</sup> A recent Korean survey showed that more than 90% of primary physicians recommended shorter surveillance intervals for both low- and

high-risk lesions. In this survey, the guideline adherence rate was higher among physicians who were young, gastroenterologists, and working at a tertiary hospital and who had an appropriate patient volume.<sup>13</sup> In a Japanese survey, the recommended surveillance interval for low-risk lesions was shorter than that in Korea, but that for high-risk lesions was similar between Korea and Japan.<sup>16,17</sup> These findings suggest that physicians from Korea and Japan recommend shorter surveillance intervals than do Western physicians. However, the results from our study showed better adherence rates compared with previous studies in Korea and Japan, and were comparable with those of Western studies. In our study, guideline adherence was strong among physicians in the HV group. The adherence rate was 2.4-fold higher in the HV than LV group. Physicians with less experience might recommend shorter intervals because they are not as confident in their diagnostic technique. The reasons for the differences in adherence rate among nations need to be further investigated due to the limited sample size in this study.

In our study, a new vignette that described a 12-mm SSA with dysplasia was added to the previously developed clinical scenarios. The World Health Organization classification recommends the use of the term sessile serrated lesion (SSL) rather than other terms including SSA and sessile serrated polyp.<sup>21</sup> For SSLs and other potentially precancerous serrated lesions, guidelines from the U.S. Multi-Society Task Force,<sup>7</sup> an international consensus panel,<sup>22</sup> and Korea<sup>18</sup> recommend surveillance intervals similar to those for conventional adenoma. In our study, approximately 50% and 47% of physicians recommended a surveillance interval of 1 year and within 1 year, respectively. In addition, the adherence rate tended to be higher in the HV than LV group. However, there is debate over the surveillance strategies used for SSLs because the risk of metachronous neoplasia after removal of these lesions is not clear.<sup>23</sup> Therefore, additional longitudinal follow-up studies are necessary.

Several studies from Western countries have reported possible reasons for physician nonadherence to the guidelines, including non-awareness of the current guidelines or disagreement with the guidelines, concerns regarding missed polyps or incomplete resection, inadequate bowel preparation, and reimbursement or monetary reasons.<sup>11</sup> In a recent prospective trial, the rate of recommending a shorter interval (3 years) for removing low-risk adenomas was 38%, and factors associated with a shorter interval included African American or Asia-Pacific island ethnicity, presence of two adenomas versus one at index colonoscopy, more than three serrated polyps, and poor bowel preparation. Interestingly, there were no significant differ-

ences in the incidence of metachronous neoplasia at surveillance colonoscopy between the shorter interval group and the adherent group.<sup>24</sup> In a Korean prospective study involving trainee endoscopists, the rate of nonadherence to the guidelines was 64%, and the endoscopist's concern regarding missed polyps was the only independent factor associated with nonadherence, similar to the results in our study.<sup>14</sup> However, surveys that use fictitious clinical cases to determine the surveillance interval usually focus on awareness of guidelines or agreement with guidelines rather than bowel preparation or concern of missed polyps for nonadherence to the guidelines.<sup>13,15,17,19,20,25-30</sup> In our study, the reasons for nonadherence to the guidelines included concerns regarding missed polyps or incomplete polyp removal, medical liability, colonoscopy cost, and the physician's knowledge. The most common reason for guideline nonadherence was concern of missed polyps since physicians may believe that a shorter interval reduces the incidence of interval CRC or adenoma. However, a recent study reported that the shorter surveillance interval does not reduce interval CRC incidence,<sup>31</sup> suggesting that shortening the surveillance interval in subjects with low-risk adenomas may be an inappropriate surveillance strategy. Furthermore, European Society of Gastrointestinal Endoscopy guideline published in 2020 suggested that patients with complete removal of one to four <10 mm adenomas with low grade dysplasia, any SSL <10 mm without dysplasia, or regardless of villous components, do not require endoscopic surveillance and should be returned to screening.<sup>32</sup>

We found that national healthcare systems in Asian countries participating in this study covered a large proportion of the cost for colonoscopy and polypectomy. Standard conscious sedation with midazolam or pethidine is more often being performed than monitored anesthesia care with assistance of anesthesiologists in Asian countries participating in our study. We think the relatively low cost and ease of sedation might affect the surveillance interval in Asian countries.

Our study has several limitations. First, the results are based only on survey data from fictitious clinical cases and not on clinical details such as technical endoscopic issues, patient characteristics, and interest in follow-up. Second, our study had limited power to detect differences among respondents from different nations, because the number of participants from some countries was relatively small. Third, although our survey asked physicians to explain the reasons for their nonadherence to the guidelines, the responses were limited to close-ended, multiple-choice responses. Finally, most of the participants were from second and tertiary medical centers; therefore, the survey may not reflect actual clinical practice in primary care. Despite these limitations, this is the first survey to include multiple Asian countries. In Asia, the CRC incidence is increasing tremendously, but data on surveillance colonoscopy are lacking. Therefore, the development of surveillance guidelines and guideline adherence are very important because the resources for screening and surveillance colonoscopy are inadequate in many Asian countries.

In summary, this study shows that there is a discrepancy between physicians' recommendations and the current surveillance colonoscopy guidelines in Asian countries. We found that physicians in the LV group frequently did not adhere to the guidelines, suggesting a need for continuing education and appropriate control. Concerns regarding the quality of colonoscopy and issues with the polypectomy technique were common barriers to adherence to surveillance colonoscopy guidelines. It is necessary to develop methods to optimize surveillance, such as checklists, and integrate them into electronic medical systems.

# **CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

# **AUTHOR CONTRIBUTIONS**

Study concept and design: C.K.O., Y.S.C. Data acquisition: C.K.O., S.A., P.P., Z.W., T.S., B.L., Q.T.T., A.F., J.S.B., Y.S.C. Data analysis and interpretation: C.K.O., Y.S.C. Drafting of the manuscript: C.K.O., Y.S.C. Study supervision: Y.S.C. Approval of final manuscript: all authors.

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