colectomy with lymph node dissection). Among the lesions treated surgically, the incidence of lymph node metastasis was analyzed. Recurrence was recorded as local, distant, and overall. Recurrent lesions were identified by endoscopic examinations, CT scan, or abdominal ultrasound.

Histopathologic evaluation. Resected specimens were immediately fixed in a 10% buffered formalin solution. Paraffin-embedded samples were then sliced into 3-μm sections and were stained by H&E. Experienced gastrointestinal pathologists blinded to each endoscopic diagnosis evaluated all pathological specimens. The histopathological type and lymphovascular (lymphatic and venous) invasion, poor differentiation, and depth of invasion were examined. Histopathological diagnosis was based on the World Health Organization criteria.[10] The upper limit of level 2 according to Haggitt's classification was used as baseline for all lesions and the invasion depth was classified into two groups (head invasion and stalk invasion).

Definition of terms. *Haggitt's line:* The baseline to distinguish between head invasion and stalk invasion. This imaginary line is drawn according to an upper limit of level 2 invasion by Haggitt *et al.* (Fig. 1). *Head invasion:* The deepest portion of cancer invasion is limited to above the baseline (Haggitt's line), as shown in Figure 1(A). *Stalk invasion:* The cancer has invaded into the submucosal layer deeply beyond Haggitt's line (Fig. 1B).

Statistical analysis. Patients' characteristics were summarized using mean and standard deviation for continuous variables, and percentage for discrete variables. Both the chi squared test and Fisher's exact tests were used to examine the difference in incidence (lymph node metastasis and recurrence) between head invasion and stalk invasion. Risk factors for lymph node metastasis were also examined by chi squared or Fisher's exact tests. All statistical tests were two-sided and the significance level was set at 5%. All statistical analysis was carried out using SPSS statistical software (version 16.0J for Windows; SPSS, Tokyo, Japan).

Results

A total of 384 patients with pedunculated type early invasive colorectal cancer (male, 286 [74%]; female, 98 [26%]; mean age, 62.7 years [range, 29–89 years]; follow-up period [median], 44 months) were enrolled in this study. There were 154

(40%), 156 (41%), and 74 (19%) endoscopic resection cases, endoscopic resection followed by surgical operation, and surgical resection cases, respectively. The mean tumor size was 18.2 ± 8.0 mm (range, 5–60 mm), and location was as follows: sigmoid colon, 304 (79%); ascending colon, 25 (7%); rectum, 23 (6%); descending colon, 18 (5%); and transverse colon, 14 (3%). Three-hundred and forty patients (89%) were followed up and available for recurrence rate analysis. Among them, 159 (72%) patients in the head invasion group and 95 (79%) patients in the stalk invasion group were followed up for more than 36 months. In contrast, 21 (6%) patients were followed up for <12 months as shown in Table 1.

Histopathological characteristics. Among 384 pedunculated type early invasive colorectal cancers, 240 (63%) lesions were diagnosed as head invasion, and 144 (37%) were classified as stalk invasion. There were 54 (14%), 53 (14%), and 52 (14%) positive cases of lymphatic invasion, venous invasion, and poorly differentiated component, respectively (Table 2).

Incidence of lymph node metastasis and recurrence rate. The overall incidence of lymph node metastasis and recurrence rate were 3.5% (8/230; 95% confidence interval CI, 1.5–6.7%) and 0.3% (1/340; 95% CI, 0.01–1.6%), respectively (Table 2). Among lesions diagnosed as head invasion, the incidence of lymph node metastasis and recurrence rate were 0% (0/101; 95% CI, 0.0–3.6%) and 0% (0/219; 95% CI, 0.0–1.7%), as compared with 6.2% (8/129; 95% CI, 2.7–11.9%) and 0.8% (1/121; 95% CI, 0.02–4.50%) in patients with stalk invasion. Head versus stalk invasion: lymph node metastasis, *P* = 0.02; recurrence, *P* = 0.72.

Among lesions diagnosed as head invasion, 29 of 101 (29%) were lymphovascular (lymphatic and/or venous) invasion positive, and 72 of 101 (71%) were negative. There were no cases of lymph node metastasis in either group. In contrast, among stalk invasion lesions, 49 of 129 (38%) were lymphovascular invasion positive, whereas 80 of 129 (62%) were negative. There were three of 49 (6.1%) cases of lymph node metastasis in the lymphovascular invasion positive group, and there were five of 80 (6.3%) cases of lymph node metastasis in the lymphovascular invasion negative group, as shown in Table 3. There was no significant difference between lymph node metastasis and lymphovascular invasion.

Risk factors of lymph node metastasis. Clinicopathological factors were compared between lymph node metastasis positive
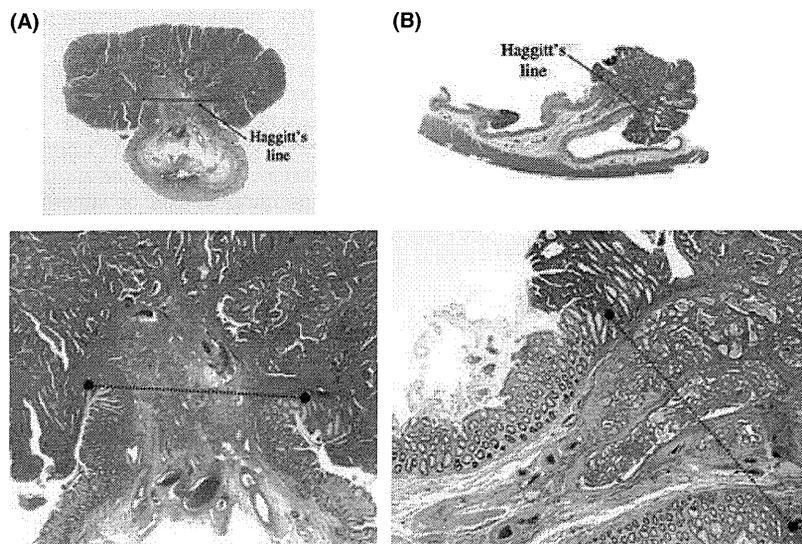

Fig. 1. Definition of head invasion (A) and stalk invasion (B) in pedunculated type early invasive colorectal cancer.

Table 1. Clinical characteristics of 384 patients with pedunculated type early invasive colorectal cancer

	Head invasion	Stalk invasion	Total
Total number, n (%)	240 (63)	144 (37)	384 (100)
Gender (M/F), n (%)	183 (76)/57 (24)	103 (72)/41 (28)	286 (74)/98 (26)
Age (years), mean (range)	62.1 (36–87)	63.6 (29–89)	62.7 (29–89)
Size (mm), mean ± SD† (range)	17.5 ± 7.4 (6–60)	19.4 ± 9.0 (5–57)	18.2 ± 8.0 (5–60)
Location, n (%)			
Rectum	11 (5)	12 (8)	23 (6)
Sigmoid colon	194 (81)	110 (76)	304 (79)
Descending colon	13 (5)	5 (4)	18 (5)
Transverse colon	10 (4)	4 (3)	14 (3)
Ascending colon	12 (5)	13 (9)	25 (7)
Treatment strategy, n (%)			
Endoscopic resection	139 (58)	15 (10)	154 (40)
Endoscopic resection followed by surgical operation	67 (28)	89 (62)	156 (41)
Surgical operation	34 (14)	40 (28)	74 (19)
Follow-up period, median (months)	43	47	44
<12 months, n (%)	17 (8)	4 (3)	21 (6)
12–36 months	43 (20)	22 (18)	65 (19)
>36 months	159 (72)	95 (79)	254 (75)

†Standard deviation.

Table 2. Histopathological characteristics of 384 cases of pedunculated type early invasive colorectal cancer

	Head invasion	Stalk invasion	Total
Lymph node metastasis			
n (%)	0/101 (0)	8/129 (6.2)	8/230 (3.5)
95% CI (%)	0.00–3.60	2.70–11.90	1.50–6.70
		*	
Recurrence			
n (%)	0/219 (0)	1/121 (0.8)	1/340 (0.3)
95% CI (%)	0.00–1.70	0.02–4.50	0.01–1.60
		**	
Lymphovascular invasion†, n (%)	35/240 (15)	55/144 (38)	90/384 (23)
Lymphatic invasion, n (%)	21 (9)	33 (23)	54 (14)
Venous invasion, n (%)	16 (7)	37 (26)	53 (14)
Poorly differentiated component, n (%)	26/240 (11)	26/144 (18)	52/384 (14)

*P = 0.02; **P = 0.72. †Lymphatic and/or venous invasion.
CI, confidence interval.

Table 3. Lymphovascular invasion among 384 cases of pedunculated type early invasive colorectal cancer with lymph node metastasis

	Head invasion	Stalk invasion	Total
Lymph node metastasis, n (%)			
ly (+), v (+)	0/1 (0.0)	0/14 (0.0)	0/15 (0.0)
ly (+), v (−)	0/16 (0.0)	2/17 (11.8)	2/33 (6.1)
ly (−), v (+)	0/12 (0.0)	1/18 (5.6)	1/30 (3.3)
ly (−), v (−)	0/72 (0.0)	5/80 (6.3)	5/152 (3.3)

ly, lymphatic invasion; v, venous invasion.

and negative groups. Regarding the depth of invasion, eight stalk invasion cases were identified in the lymph node metastasis positive group, representing a significant difference compared with the negative group ($P = 0.02$). No significant differences in any other factors were noted between lymph node metastasis positive and negative groups (Table 4).

Discussion

Advances in endoscopic instruments and techniques have allowed increased detection of early stage colorectal cancer, and endoscopic resection is a safe and effective curative treatment for such lesions when there is no risk of lymph node metastasis.

Kudo[11] was the first to classify submucosal invasion of early invasive colorectal cancer as SM1 (upper third of submucosa), SM2 (middle third of submucosa), and SM3 (lower third of submucosa). Since then, Kikuchi et al.[12] have reported lymph node metastasis in 0%, 10%, and 25% of 182 patients with SM1, SM2, and SM3 early invasive colorectal carcinomas, respectively. More recently, Nascimbeni et al.[13] showed that SM3 invasion had a significantly higher risk of lymph node metastasis compared to SM1–2 by multivariate analysis (SM1, 3%; SM2, 8%; SM3, 23%). The overall risk of lymph node metastasis in early invasive colorectal cancer is approximately 10%, suggesting that endoscopic removal of the vast majority of lesions without surgical intervention could ultimately be curative. In contrast, the rate of lymph node metastasis in patients who underwent additional surgical excision of the colorectum following endoscopic treatment has been reported to be 2.1–25.0%.[3,14–17] This suggests that a significant percentage of patients may undergo unnecessary additional surgery following endoscopic treatment, and more stringent criteria are required to prevent this. Protruding colorectal neoplasms and, more specifically, pedunculated lesions may be easier than non-pedunculated lesions to detect and remove endoscopically. However, the risk

Table 4. Comparison of clinicopathological factors between lymph node metastasis positive (+) and negative (−) groups among 384 cases of pedunculated type early invasive colorectal cancer

Variables	Lymph node metastasis	P-value
Depth of invasion (stalk vs head)	(+) 8/0 (−) 121/101	0.02
Lymphovascular invasion (ly and/or v [+] vs [−])	(+) 3/5 (−) 75/147	>0.99
Poorly differentiated component	(+) 1/7 (−) 38/184	>0.99
Tumor size† (≥20 mm vs <20 mm)	(+) 5/3 (−) 101/108	0.67

†Unknown, 13 cases. ly, lymphatic invasion; v, venous invasion.

of lymph node metastasis and the prognostic significance of this specific subtype of early invasive colorectal cancer have not been sufficiently examined. This is the first large-scale multicenter study in Japan to assess the incidence of lymph node metastasis and recurrence of pedunculated type early invasive colorectal cancer.

Conventional measurement of submucosal invasion using SM1–SM3 was originally devised for examination of surgical specimens where the full thickness of the colonic wall was available to the pathologist. Haggitt's level 2 was used as the baseline to differentiate between head and stalk invasion by Kitajima et al.[18] and submucosal invasion depth was measured as the vertical distance from this baseline (Haggitt's line) to the deepest point of invasion. This method of invasion measurement is more appropriate to endoscopically resected specimens where the muscularis propria is not included. According to the data from the Japanese Society for Cancer of the Colon and Rectum, the "so-called 1000 μm rule of submucosal invasion" is applied to not only non-pedunculated type but also pedunculated type early invasive colorectal cancers. In our current study, among lesions diagnosed as "stalk invasion", the incidence of the "<1000 μm group" was under 10%, similar to Kitajima's data.[18] Moreover, all lymph node metastasis positive cases (eight cases) were classified into the "more than 1000 μm group". In this study, however, the number of lymph node metastasis positive cases was limited. Therefore, we concluded that more cases with stalk invasion and more cases with lymph node metastasis are necessary to investigate the feasibility of the present 1000 μm rule.

We devised a straightforward description of cancer invasion to either head (above Haggitt's line) or stalk (below this line) and estimated the risk of lymph node metastasis and recurrence rate for pedunculated type early invasive colorectal cancer according to these groups. In our retrospective study there was no risk of lymph node metastasis in patients with head invasion (0%, 0/101) compared to 6.2% (8/129) of patients with stalk invasion. Furthermore, the recurrence rate during the follow-up period (mean ± SD, 40.7 ± 24.1 months) in patients with head invasion treated by endoscopic resection was also 0% (0/139; 95% CI, 0.0–2.6%).

In the past 20 years investigators have proposed that the presence of submucosal invasion more than 1000 μm, lymphatic invasion, and/or poor differentiation required additional surgery following endoscopic mucosal resection of early invasive colorectal cancer. Conversely, depth of invasion (stalk invasion) was the only predictive factor for lymph node metastasis in our study. Although our results showed that none of the patients in the head invasion group showed lymph node metastasis, lymphovascular invasion was present in 29 cases in this group and these patients underwent additional surgery. Our results are promising and indicate that the risk of lymph node metastasis in these 29 patients is low, however, prospective studies confirming these findings are required before a change in surgical management is implemented.

It is widely recognized that depressed type (0–IIc) lesions invading into the submucosa display a significantly higher rate of lymph node metastasis in comparison to protruded type (0–Ip and 0–Is), superficial elevated (0–IIa), and flat (0–IIb) lesions.[6,18,19] Pan et al.[20] also reported that early invasive colorectal cancers at the fold-top or with a long distance from the muscularis mucosae to the muscularis propria have a lower tendency to metastasize to lymph nodes. These studies indicate that the lower rate of lymph node metastasis in pedunculated type early invasive colorectal cancers could be elucidated by the presence of a greater muscularis mucosae to muscularis propria distance. Our study also showed a low rate of lymph node metastasis in pedunculated type lesions, although this data was only available for patients who underwent surgical resection (n = 230).

Some controversies with regard to pedunculated type lesions exist. Haggitt et al.[9] stipulated that the presence or absence of a stalk is largely irrelevant histopathologically. Moreover, they commented that the surgeon and pathologist may disagree on stalk length or even existence. Certain factors such as traction force used during removal, retraction of the pedicle following division and shrinkage after fixation could explain this. To avoid contention we imposed strict inclusion criteria in our study allowing only endoscopically diagnosed pedunculated type lesions with an obvious stalk to be eligible.

There are some limitations to our study. First, we retrospectively analyzed the clinical records of all patients who underwent endoscopic resection or surgical resection for pedunculated type colorectal cancers at seven institutes in Japan. The number of examined cases was large compared to previous studies, however, we did not re-evaluate lymphovascular invasion using immunohistochemical staining for all cases. Routine use of immunohistochemistry should be considered in future retrospective studies. Second, several authors have indicated that early invasive colorectal cancers in the rectum have a higher incidence of lymph node metastasis and local recurrence.[9,12,21] We were unable to assess this risk in our patients as 79% (304/384) of the pedunculated type lesions were located in the sigmoid colon. Finally, tumor budding, which has also been referred to as sprouting or dedifferentiation[22,23] was not evaluated in this study. We evaluated the presence or absence of any poorly differentiated adenocarcinoma component, including that found at the most invasive submucosal margin. This is similar to the focal dedifferentiation reported by Tominaga et al.,[24] however, Sohn et al.[25] argued that tumor budding should be categorized separately.

In conclusion, all cases with lymph node metastasis or recurrence were categorized into the stalk invasion group in this retrospective multicenter study. Our data suggest that pedunculated type early invasive colorectal cancer diagnosed as head invasion could be managed by endoscopic treatment alone.

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Disclosure Statement

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Neoplastic lesions with "superficial" morphology in pedunculated type early invasive colorectal cancer.

Fig. S2. Haggitt's classification of pedunculated type early invasive colorectal cancer.

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Colon

The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects

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ABSTRACT

Objective To develop and validate a clinical risk score predictive of risk for colorectal advanced neoplasia for Asia. **Methods** A prospective, cross-sectional and multicentre study was carried out in tertiary hospitals in 11 Asian cities. The subjects comprise 2752 asymptomatic patients undergoing screening colonoscopy. From a development set of 860 asymptomatic subjects undergoing screening colonoscopy, multiple logistic regression was applied to identify significant risk factors for advanced colorectal neoplasia defined as invasive carcinoma or advanced adenoma. The ORs for significant risk factors were utilised to develop a risk score ranging from 0 to 7 (Asia-Pacific Colorectal Screening (APCS) score). Three tiers of risk were arbitrarily defined: 0—1 'average risk' (AR); 2—3 'moderate risk' (MR); and 4—7 'high risk' (HR). Subjects undergoing screening colonoscopy between July 2006 and December 2007 were prospectively enrolled to form an independent validation group. Each subject had a personal APCS score calculated by summing the points attributed from the presence of risk factors in the individuals. The performance of the APCS score in predicting risk of advanced neoplasia was evaluated.
Results There were 860 subjects in the derivation set and 1892 subjects in the validation set, with a baseline prevalence of advanced neoplasia of 4.5% and 3%, respectively. Applying the APCS stratification in the validation set, 559 subjects (29.5%) were in the AR tier, 966 subjects (51.1%) in the MR tier and 367 (19.4%) subjects in the HR tier. The prevalence of advanced neoplasia in the AR, MR and HR groups was 1.3, 3.2 and 5.2%, respectively. The subjects in the MR and HR tiers had 2.6-fold (95% CI 1.1 to 6.0) and 4.3-fold (95% CI 1.8 to 10.3) increased prevalence of advanced neoplasia, respectively, than those in the AR tier.
Conclusions The APCS score based on age, gender, family history and smoking is useful in selecting asymptomatic Asian subjects for priority of colorectal screening.

INTRODUCTION

Colorectal cancer is the fourth most common cancer in the world.[1] While it is the second most common cancer in most Western countries, there has also been a rapid rise in incidence in recent decades in many countries in Asia.[2]

Significance of this study

What is already known about this subject?
▸ Consensus guidelines recommend screening for colorectal cancer at age 50 years and above in an average risk population.
▸ The recent US Multi-Society Task Force on Colorectal Cancer guidelines recommend that colon cancer prevention should be the primary goal of screening, and that tests (such as colonoscopy) that both detect early cancer and prevent cancers through the detection and removal of adenomas are preferred.
▸ Despite widespread adoption of guidelines by professional bodies, the actual uptake and implementation of screening remains low in many countries, in part due to resource limitations.

What are the new findings?
▸ The new proposed Asia-Pacific Colorectal Screening (APCS) score enables risk stratification using elementary clinical information on age, gender, family history and smoking. This is simple and can be used by general practitioners or nurse-educators.
▸ The APCS score successfully predicts the risk of colorectal advanced neoplasia in asymptomatic Asian subjects. High risk groups have fourfold higher risk compared with the average risk group.

How might it impact on clinical practice in the foreseeable future?
▸ Risk stratification may help to optimise the efficiency of resources for screening.
▸ Risk stratification offers an option of prioritising high-risk subjects for colonoscopy screening (as is already the case for a strong family history) and average-risk subjects for faecal occult blood screening.
▸ The risk score tool may also enhance awareness of risk and encourage people to be screened.

There is strong evidence that screening for colorectal cancer improves survival.[3-5] Current international practice guidelines and expert consensus

statements[6] recommend colorectal cancer screening for people over 50 years. In reality the risk for colorectal cancer is uneven in the population and varies significantly with age,[7–9] gender,[7 9] smoking,[8 10–13] family history,[7] obesity,[14] ethnicity,[2 15] dietary[10–13] and other factors. This suggests the possibility that knowledge of risk factors could be used to risk stratify the population.

Since resource limitations hinder the implementation of colorectal cancer screening in many countries,[16–18] a risk stratification system may also help to make screening more cost-effective.

The aim of this prospective study was to develop and validate a simple clinical risk score for colorectal advanced neoplasia for Asian subjects.

PATIENTS AND METHODS

Study population for development of the risk score (derivation cohort)

We have previously described a colonoscopy survey of 860 asymptomatic subjects enrolled between July and December 2004 in 17 endoscopy centres in 11 Asian cities (Bangkok, Guangzhou, Hong Kong, Jakarta, Kuala Lumpur, Manila, New Delhi, Seoul, Singapore, Taipei and Tokyo).[19] Briefly these were asymptomatic adults undergoing screening colonoscopy with a mean age of 54.4 years (SD ±11.6 years) of which 471 were men (54.8%). There were nine ethnic groups (Chinese, Indian, Indonesian, Japanese, Korean, Malay, Filipino, Thai and Caucasian). The characteristics of the study population have been described in detail[19] and are summarised in table 1. Subjects who had undergone colorectal imaging including colonoscopy, sigmoidoscopy or barium enema within the past 5 years, or who had previous colorectal surgery were excluded from the study. Colorectal advanced neoplasia was defined as colorectal carcinoma or advanced adenoma. Advanced adenoma was defined as any adenoma at least 10 mm in diameter, or with villous histological features or high-grade dysplasia.[20] A study questionnaire administered at the time of colonoscopy captured clinical and lifestyle information, and this were entered into a database. Institutional ethics board approvals were obtained by the respective centres.

Table 1 Characteristics of patients in the derivation and validation populations

	Derivation cohort n = 860	Validation cohort n = 1892	p Value
Age (years), mean±SD	54±11.6	51±11.2	<0.01
Gender (%)			
Male	471 (55)	1032 (54)	0.63
Female	389 (45)	860 (46)	
Smoking (%)			<0.01
Current*	132 (15.6)	269 (15.5)	
Ex-smoker	263 (31.0)	122 (7.0)	
Non-smoker	452 (53.4)	1342 (77.5)	
Alcohol consumption (%)	157 (18.6)	412 (23.9)	<0.01
Diabetes mellitus (%)	48 (5.6)	113 (6.3)	0.48
Family history present for a first-degree relative (%)	109 (12.7)	286 (15.4)	0.06
Colon neoplasia (%)	168 (18.5)	353 (18.7)	
Cancer (%)	9 (1.0)	8 (0.4)	
Advanced neoplasia (%)	39 (4.5)	57 (3.0)	
Proximal neoplasia (%)	66 (7.7)	204 (10.8)	
Proximal advanced neoplasia (%)	17 (2.0)	24 (1.3)	

*Current smoking denotes ≥1 pack of cigarettes/week.

Development of risk score

Univariate analysis was carried out on the derivation set using the Pearson χ^2 method to examine the association between clinical risk factors, neoplasia and advanced neoplasia. Variables associated with neoplasia or advanced neoplasia in univariate analyses ($p<0.15$) were entered in multivariate logistic regression models. Risk factors (variables) which retained significance in multivariate analyses were selected for incorporation into the risk score. For each risk factor, we assigned weight in the risk score by using the respective adjusted ORs yielded by the logistic regression. The latter was halved and then rounded to the nearest whole number, in the interests of simplicity and to keep the total score under 10. The risk score for an individual was the summation of their individual risk factors. The validity of the score was assessed by receiver operating characteristic (ROC) analysis.

Sample size for the validation cohort

The sample size estimation was based on published data on the prevalence of colorectal advanced neoplasia in populations being screened in Asia, which was reported to be between 3% and 12%.[21–23] In the derivation set in the current study, the prevalence of advanced neoplasia was 4.5%.[19] We used the latter as the point prevalence of advanced neoplasia for the validation set and assumed an estimated prevalence of individual risk factors to be ~25%. Based on these assumptions, a minimum of 1800 asymptomatic subjects was required for a power of 80% to detect a risk factor with OR of 2 at $p<0.05$ level of significance based on the prevalence of advanced neoplasia of 4.5% in the derivation set.

Study population for validation of the risk score (validation cohort)

A separate and independent cohort of asymptomatic subjects were prospectively enrolled for the validation of this risk score from consecutive asymptomatic subjects undergoing screening colonoscopy at the various participating centres. The colonoscopy and study protocols for these subjects were identical to those used in the development phase.

Calculation and validation of the risk score

Each subject in the validation group had a personal risk score calculated by software that summed the points attributed from the presence of risk factors in the individual. This was performed by software in a double-blind fashion independent of colonoscopy findings and the colonoscopist was unaware of the score. The calculation of the score was performed by software at the data centre after data were sent from individual clinical study sites. The performance of the Asia-Pacific Colorectal Screening (APCS) in predicting risk of advanced neoplasia was evaluated by comparing the RR of the latter in the high-risk (HR) and moderate-risk (MR) group versus the average-risk (AR) group.

Statistical analysis

Statistical analysis was performed with SPSS software (version 16.0); a two-tailed p value of <0.05 was considered statistically significant. The Pearson χ^2 test was used for categorical data to compare proportions of each candidate risk factor—age, gender, smoking, alcohol consumption, diabetes and family history of colorectal cancer in a first-degree relative. Multiple logistic regression models were used to analyse the risk factors for colorectal neoplasia and advanced neoplasia. The Hosmer–Lemeshow goodness-of-fit statistic was used to test the reliability of the model; a large p value (>0.05) indicates a good match of predicted

Table 2 Prevalence of colorectal neoplasia and advanced neoplasia in the derivation cohort by risk factors

	All subjects Prevalence (%)	Neoplasia, n=168		Advanced neoplasia, n=39	
		Prevalence (%)	p Value	Prevalence (%)	p Value
Gender					
Male	471 (55)	106 (22.5)	0.016	28 (5.9)	0.029
Female	389 (45)	62 (15.9)		11 (2.8)	
Age					
<50 years	295 (34.3)	33 (11.2)	<0.001	6 (2.0)	0.001
≥50 years	565 (65.7)	135 (23.9)		33 (5.8)	
Family history of colorectal cancer in a first-degree relative					
Present	109 (12.7)	27 (24.8)	0.140	8 (7.3)	0.139
Absent	751 (87.3)	141 (18.8)		31 (4.1)	
Smoking					
Never	452 (53.4)	76 (16.8)		15 (3.3)	
Current or ex	395 (46.6)	91 (23.0)	0.025	24 (6.1)	0.070
Alcohol					
No	688 (81.4)	130 (18.9)		29 (4.2)	
Yes	157 (18.6)	35 (22.3)	0.33	8 (5.1)	0.63
Diabetes					
No	812 (94.4)	155 (19.1)		35 (4.3)	
Yes	48 (5.6)	13 (27.1)	0.18	4 (8.3)	0.19

risk over observed risk. The ability of the APCS score to predict the risk of developing colorectal advanced neoplasia was assessed with the c-statistic and area under the ROC curve. A model with a c-statistic near 1 demonstrates excellent predictive ability, while a c-statistic near 0.5 demonstrates poor predictive ability.

RESULTS
Characteristics of patients in the derivation and validation cohorts
Among the 860 asymptomatic subjects in the derivation cohort, 168 (18.5%) were found to have colorectal neoplasia, of which 39 patients (4.5%) had advanced neoplasia and 9 patients (1.0%) had invasive cancers (table 1). The detailed results have been published.[19] The prevalence of colorectal neoplasia and advanced neoplasia in the derivation cohort stratified by risk factors is shown in table 2.

A total of 1892 asymptomatic subjects were enrolled in the validation cohort. The mean age was 51 years (SD ±11.2 years), 1032 were male (54%), 19% were smokers and 15.1% had a family history of a first-degree relative with colorectal cancer. Three hundred and fifty-three (18.7%) were found to have colorectal neoplasia, of which 57 patients (3.0%) had advanced neoplasia and 8 patients (0.4%) had invasive cancers (table 1).

Univariate and multivariate predictors of colorectal neoplasia and advanced neoplasia in the derivation cohort
Univariate and multivariate analyses were performed for each risk factor. Multivariate logistic regression showed that age >50 years, male gender, a positive family history in a first-degree relative and smoking were significant risk factors for colorectal neoplasia, with ORs (95% CI) of 2.6 (1.7 to 4.0), 1.6 (1.1 to 2.3), 2.1 (1.3 to 3.5) and 1.4 (1.01 to 2.0) (table 3). Age >50 years, male gender and a positive family history in a first-degree relative were also significant risk factors for advanced colorectal neoplasia, with ORs (95% CI) of 3.2 (1.3 to 8.1), 2.4 (1.2 to 5.0) and 3.1 (1.3 to 7.4), while smoking with an OR of 1.8 (0.9 to 3.4) did not reach significance in this group due to the small number of advanced lesions (table 4). The Hosmer—Lemeshow goodness-of-fit statistic was p=0.29 for the derivation cohort.

Development of the risk score
Points were assigned to each risk factor for advanced neoplasia as follows: age <50 years (0), 50—69 years inclusive (2), ≥70 years (3), male gender (1), female gender (0), family history of colorectal cancer in a first-degree relative present (2) or absent (0), non-smoking (0) and smoking (1). The points attributed to each risk factor were weighted according to the respective adjusted OR in the multiple logistic regression. The respective adjusted

Table 3 Univariate and multivariate predictors of colorectal neoplasia in the derivation cohort

	Unadjusted		Adjusted			
Risk factors	OR (95% CI)	p Value	β coefficient	SE	OR (95% CI)	p Value
Gender, male	1.5 (1.1 to2.2)	0.016	0.484	0.184	1.6 (1.1 to 2.3)	0.008
Age (years)						
50—69	2.3 (1.5 to 3.5)	<0.001	0.956	0.221	2.6 (1.7 to 4.0)	<0.001
≥70	3.6 (2.0 to 6.5)	<0.001	1.396	0.317	4.0 (2.2 to 7.5)	0.002
Family history of colorectal cancer	1.4 (0.9 to 2.3)	0.140	0.756	0.259	2.1 (1.3 to 3.5)	0.003
Smoking	1.5 (1.1 to 2.1)	0.024	0.354	0.178	1.4 (1.01 to 2.0)	0.047
Alcohol	1.2 (0.8 to 1.9)	0.333	—	—	—	—
Diabetes	1.6 (0.8 to 3.0)	0.18	—	—	—	—

Table 4 Univariate and multivariate predictors of colorectal advanced neoplasia in the derivation cohort

Unadjusted			Adjusted			
Risk factors	OR (95% CI)	p Value	β coefficient	SE	OR (95% CI)	p Value
Gender, male	2.2 (1.1 to 4.4)	0.029	0.871	0.373	2.4 (1.2 to 5.0)	0.019
Age (years)						
50–69	2.7 (1.1 to 6.7)	0.029	1.167	0.470	3.2 (1.3 to 8.1)	0.013
≥70	4.6 (1.5 to 14.2)	0.007	1.820	0.597	6.2 (1.9 to19.9)	0.002
Family history of colorectal cancer	1.8 (0.8 to 4.1)	0.139	1.142	0.440	3.1 (1.3 to 7.4)	0.009
Smoking	1.9 (0.97 to 3.6)	0.070	1.142	0.440	1.8 (0.9 to 3.4)	0.099
Alcohol	1.2 (0.5 to 2.7)	0.63	–	–	–	–
Diabetes	2.0 (0.7 to 5.9)	0.20	–	–	–	–

OR was halved and then rounded to the nearest whole number, in order to keep the score simple. One point was accorded to positive smoking history as it was a significant risk factor for colorectal neoplasia although it did not reach significance for advanced neoplasia (tables 4 and 5).

The sum of points for risk factors present in an individual formed the APCS score (table 5). The APCS score has a range of 0–7 points based on the sum of the score in an individual subject according to the presence or absence of risk factors. The APCS score was arbitrarily divided into three tiers of risk: score 0–1 'average risk', AR; score 2–3 'moderate risk', MR; and score 4–7 'high risk', HR. The frequency distribution of subjects by score is shown in table 6. Using this stratification, 165 subjects (19.2%) were in the AR tier, 454 subjects (52.8%) in the MR tier and 241 subjects (28%) in the HR tier. This grouping was chosen to allow flexibility in the future application of the risk score. For example, the risk score tool could be used to identify the subjects in the cohort with higher risk than average by selecting HR + MR versus 'AR', or alternatively to identify just subjects with the highest risk (HR). We included the 2-point score under the MR risk tier because it includes positive family history in a first-degree relative which we regard as a strong risk feature and therefore felt it inappropriate to classify that under 'AR'. Another rationale was that the 0–1 point scores were associated with absence of advanced neoplasia in the derivation cohort (table 6), which lended additional justification to categorising them as 'AR'.

The prevalence of colorectal advanced neoplasia in the three tiers (AR, MR and HR) was 0%, 4.4% (95% CI 2.78% to 6.83%) and 7.9% (95% CI 4.95% to 12.25%), respectively. By ROC analysis, the c-statistic for the risk score in the derivation cohort was 0.66±0.04, indicating good discrimination.

Risk stratification of the validation group using the the APCS score

Using the APCS stratification, 559 subjects (29.5%) were in the AR tier (score 0–1), 966 subjects (51.1%) in the MR tier (score 2–3) and 367 subjects (19.4%) in the HR tier (score 4–7).

Table 5 Asia-Pacific Colorectal Screening score for prediction of risk for colorectal advanced neoplasia

Risk factor	Criteria	Points
Age	<50	0
	50–69	2
	≥70 years	3
Gender	Female	0
	Male	1
Family history of colorectal cancer in a first-degree relative	Absent	0
	Present	2
Smoking	Never	0
	Current or past	1

The prevalence of colorectal advanced neoplasia in the AR, MR and HR categories was 1.3% (95% CI 0.58% to 2.74%), 3.2% (95% CI 2.22% to 4.57%) and 5.2% (95% CI 3.25% to 8.13%), respectively (p=0.003). The c-statistic for the risk score in the validation cohort was 0.64±0.04. Subjects in the MR and HR tiers had 2.6-fold (95% CI 1.1 to 6.0) and 4.3-fold (95% CI 1.8 to 10.3) increased rates of advanced neoplasia, respectively, compared with those in the AR tier. Within the AR group, out of 559 subjects, seven had advanced neoplasia (two proximal, five distal) at initial colonoscopy, of which two were carcinomas (both distal) and five were advanced adenomas. Of the latter five persons, one has had subsequent follow-up colonoscopy with no abnormal findings(table 7)

The Hosmer–Lemeshow goodness-of-fit statistic was used to test the reliability of the model in the validation cohort, and a p value of 0.49 indicated a good match of predicted risk over observed risk.

DISCUSSION

Although there is level one evidence that screening for colorectal cancer improves survival[3–5] and is widely advocated by professional[6] and health authorities,[24] the implementation and uptake of screening is hampered by resource limitations, lack of awareness in the target population, insufficient advocacy by healthcare professionals and poor compliance.[25–30]

Risk stratification of the target populations to be screened may bring potential advantages. Those identified at higher risk may be particularly motivated to come forward for screening. Colorectal cancer screening is considered to be cost-effective,[31–34] and the impact of risk stratification on cost-effectiveness deserves further study. In countries with limited resources in the healthcare system, prioritised screening may enhance the feasibility of a screening programme.

There have been previous efforts describing risk stratification approaches. Imperiale et al proposed an index to stratify risk for advanced proximal neoplasia based on age, sex and distal findings.[9] This approach requires an initial sigmoidoscopy to determine the presence of distal neoplasia before the index can be calculated. Driver et al described a scoring system to identify men with increased RR for colorectal cancer based on age, alcohol, smoking and obesity, using data from the large Physician Health Study.[8] As the latter comprised an entirely male cohort, the risk score did not include gender in its constitution. Lin et al proposed an index comprising age, sex and family history to stratify a high-risk group for colonoscopy screening.[7] This score did not include modifiable risk factors such as smoking or alcohol which are well-studied risk factors for colorectal cancer.[10–13] A study by Betes et al proposed a score based on age, sex and body mass index (BMI), which were independent predictors of advanced adenoma;[35] however, this

Table 6 Distribution of number of subjects for each score category in the derivation cohort

Score	No. of subject (%)	No. of subjects with advanced neoplasia (%)
0	57 (6.6)	0
1	108 (12.6)	0
2	205 (23.8)	3 (1.5)
3	249 (29)	17 (6.8)
4	186 (21.6)	13 (7.0)
5	45 (5.2)	4 (8.9)
6	10 (1.2)	2 (20)
7	0	0
Total	860 (100)	39 (4.5)

score system did not include smoking and family history. Our study attempted to identify important risk factors in an Asian population and to derive a risk score tool which was then validated in an independent cohort. Our proposed tool incorporates demographic and personal risk factors which were statistically significant in our population, and since age,[7–9] gender,[7 9] smoking[8 10–13] and family history[7] have been corroborated in previous studies, the further contribution added by the present study is in the combination of multiple risk factors in a simple scoring system and its validation in an independent cohort. A limitation of our study was the absence of data on weight, and therefore obesity and BMI could not be evaluated.

In our study, the validation cohort was slightly younger than the derivation cohort, with a lower proportion of smokers and a higher consumption of alcohol. The study participants were recruited from all-comers at the study sites and the mix of participants was different between the two cohorts. For both cohorts, we performed the Hosmer–Lemeshow goodness-of-fit statistic (derivation cohort p=0.29, validation cohort p=0.49) and ROC analysis; the c-statistic for the risk score was 0.66±0.04 for the derivation cohort and 0.64±0.04 in the validation cohort. In practice some variation may be expected in the risks of different populations in which the risk score tool may be applied.

The APCS score is a simple risk stratification index for colorectal advanced neoplasm that uses elementary clinical information on age, gender, family history and smoking to stratify the risk of colorectal advanced neoplasm in asymptomatic Asian subjects. It is simple enough to be used by family physicians and healthcare providers. We designed the APCS score to risk stratify for colorectal advanced neoplasia as we believe this should be the target lesion for screening. Identification of advanced neoplasia allows secondary prevention by polypectomy, interrupting the progression to carcinoma.[36–38] As advocated and emphasised in a recent expert consensus statement,[6] this aim of preventing carcinoma confers a higher level of prevention and greater benefit to the screened population compared with case-finding

for early cancers. Despite its attractiveness as a target for screening, advanced adenomas are a surrogate end point, and more needs to be understood about its natural history.

While risk stratification utilises RR as a means of prioritisation, absolute risks are important to clinical decisions on screening. In our study the absolute prevalence of advanced neoplasia in the derivation and validation cohorts was 4.5% and 3.0%, respectively, which is lower than might be expected in a high-prevalence Western population. This is not surprising as the cohort comprised subjects from various Asian countries, some of which have a low prevalence of colorectal cancer. In the validation cohort, a high risk score was associated with a prevalence of 5.2% of advanced neoplasia compared with a 1.3% prevalence in the AR group. In clinical practice, a risk score tool which differentiates a 1 in 20 likelihood of finding advanced lesions in a high-risk group versus a 1 in 100 likelihood in an average-risk group might be considered helpful in making decisions on screening. In order not to overstate this, it should be understood that the difference in absolute risk is 3.9%—that is, it would make a difference in 4 people out of 100.

There is substantial variation in the spectrum of risk in different populations in Asia, together with differences in health resources available for screening. This was recognised in the Asia-Pacific consensus recommendations for colorectal cancer screening published in 2008. The risk score tool offers the option of risk stratification to optimise the cost-effectiveness of screening. In a high-prevalence country, people with a high risk score could potentially be offered colonoscopy, while those at average risk could be screened using stool tests. This already has an analogy in current practice where people with a strong family history are offered screening by colonoscopy. In a low-prevalence country, stratification of risk could be applied to selectively offer screening to high-risk subjects. This might be expected to make screening more cost-effective, and this approach should be tested in a future study.

The Asia-Pacific Consensus Recommendations for Colorectal Cancer Screening report recognised that healthcare resources are limited in certain countries in Asia.[39] The APCS can be flexibly applied to local conditions according to the epidemiology of colorectal cancer in each country. Screening based on risk stratification deserves to be explored further for its potential benefits, although its social, political and practical implications need careful consideration.

CONCLUSION

We have developed and validated a clinical risk score for colorectal neoplasm using age, gender, family history and smoking, that predicts the risk of colorectal advanced neoplasm in asymptomatic Asian subjects. Future studies should test this scoring system in Asian countries with variable prevalence of colorectal cancer and evaluate the cost-effectiveness of this approach.

Table 7 Prevalence of colorectal advanced neoplasia by risk tier and risk score

Risk tier (RS)	Derivation cohort		Validation cohort		
	No. of subjects (%)	Colorectal advanced neoplasm (%) (95% CI)	No. of subjects (%)	Colorectal advanced neoplasm (%) (95% CI)	RR (95% CI)
Average risk (0–1)	165 (19.2)	0	559 (29.5)	7 (1.3) (0.58 to 2.74)	Reference
Moderate risk (2–3)	454 (52.8)	20 (4.4) (2.78 to 6.83)	966 (51.1)	31 (3.2) (2.22 to 4.57)	2.6 (1.1 to 6.0)
High risk (4–7)	241 (28.0)	19 (7.9) (4.95 to 12.25)	367 (19.4)	19 (5.2) (3.25 to 8.13)	4.3 (1.8 to 10.3)
Total	860 (100)	39 (4.5) (3.26 to 6.17)	1892 (100)	57 (3.0) (2.3 to 3.9)	

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ORIGINAL ARTICLE

Use of Gascon and Pronase either as a pre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: A prospective, randomized, controlled, blinded trial

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Abstract

Objective. To assess whether endoscopic flushes of the bubble-bursting agent Gascon and the mucolytic agent Pronase are as effective in terms of improving endoscopic mucosal visibility as a pre-endoscopic drink of the same agents. *Material and methods.* A total of 112 patients attending a Japanese tertiary referral centre for upper gastrointestinal endoscopy were randomized to receive either the standard Japanese procedure of a pre-endoscopic drink of water containing Gascon and Pronase with endoscopic flushes of 20-ml aliquots of water, or no pre-endoscopic therapy but endoscopic flushes of 20-ml aliquots of water containing Gascon, with or without Pronase as necessary. *Results.* Visibility scores were significantly better in the pre-endoscopic drink group than in either of the endoscopic flush groups. The group receiving a pre-endoscopic drink required fewer flushes during the procedure and there was no difference in the endoscopic time between the three groups. *Conclusions.* Our results suggest that endoscopic spraying of these bubble-bursting and mucolytic agents is not able to offer equivalent improvements in endoscopic mucosal visibility when compared with the standard Japanese therapy of a pre-endoscopic drink of these agents. The addition of Pronase to the spray solution had no measurable benefit over Gascon alone. We therefore cannot recommend endoscopic spraying of mucous clearing agents over their use as a pre-endoscopic drink.

Key Words: *Endoscopy, gascon, mucolytic, pronase, simethicone, visibility*

Introduction

Since the advent of gastrointestinal endoscopy, practitioners have been frustrated by foam and mucous obscuring the field of view. Mucosal toileting techniques with bubble-bursting agents such as Gascon (simethicone) have been used since the 1950s [1–3] and more recent studies have shown that the addition of a mucolytic such as Pronase further improves mucosal visualization [4,5]. These mucosal toileting techniques have become standard practice in Japan [6,7], where cancers tend to be detected earlier than in the West. Patients there are routinely asked to drink 100 ml of water containing 2 ml of Gascon and 20,000 units of Pronase 10 min prior to the endoscopy. These medications are freely available in Europe but it is not

usual practice for them to be used. One explanation for this is concern amongst Western endoscopists of an increased risk of aspiration during the procedure if a drink is taken beforehand.

Minimally invasive techniques such as photodynamic therapy and endoscopic mucosal resection (EMR) are now able to offer excellent results for cancers detected at early stages. EMR often offers complete cure but can only be considered for tumours that are well characterized at endoscopy. Detection and characterization of early changes can be achieved through a variety of diagnostic techniques, including chromoendoscopy, high-magnification endoscopy, confocal endoscopy and narrow-band imaging, but all depend upon optimized mucosal views. In addition, chromoendoscopy requires a clear field in order

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that the dye binds to the intended cells rather than the overlying mucous [8,9]. Effective and acceptable mucosal toileting techniques are therefore increasingly vital as advanced endoscopic techniques become used more frequently.

In an attempt to provide the proven benefits of Gascon and Pronase [9–12] without the theoretical increased risk of pulmonary aspiration associated with a pre-endoscopic drink, this study was designed to compare the effectiveness and practicality of spraying Gascon, with or without Pronase, directly onto the mucosa as intermittent flushes through the biopsy channel of the endoscope during the procedure, compared with identical treatment given as a drink prior to endoscopy (conventional Japanese mucosal toileting).

Material and methods

Patients

The Japanese national screening programme for gastric cancer involves the majority of people over the age of 40 years undergoing an annual barium swallow. The tertiary referral centre in which this trial was set accepts patients for gastroscopy either directly (patients with abnormal results on these tests or with appropriate symptoms), or as referrals from other hospitals where early cancers have been detected that are thought to be suitable for EMR. This study was restricted to the screening population because there are differences in the endoscopy technique for those requiring a therapeutic procedure (e.g. the use of zoom scopes and special dyes requiring additional time). A total of 148 of these patients were recruited into this study over a 2-week period. Patients were excluded from the study if they had previously undergone oesophagectomy or gastrectomy, if the endoscopy revealed a lesion requiring a therapeutic procedure such as EMR or if there was active gastrointestinal bleeding or strictures in the upper gastrointestinal tract. The results from 112 patients were therefore available for analysis (Figure 1).

Pre-medication and endoscopic procedure

The study gained ethical approval and informed consent was obtained from all participants. Sealed envelopes were used to randomly allocate patients to one of three groups, as follows. Group S: standard Japanese procedure comprising a pre-endoscopic drink of 100 ml of water, 2 ml of Gascon and 20,000 units of Pronase. During the endoscopy, flushes of 20-ml
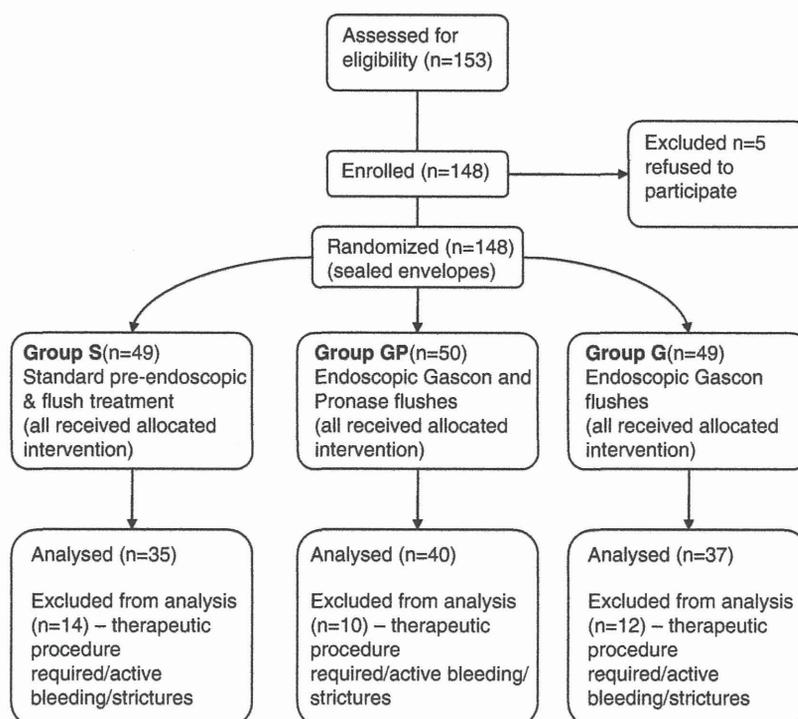

Figure 1. Flowchart showing the disposition of the study patients.

aliquots of water were used as required. Group G: no pre-endoscopic preparation. During the endoscopy, flushes of 20-ml aliquots of pre-mixed solution containing 100 ml of water and 2 ml of Gascon were used as required. Group GP: no pre-endoscopic preparation was given. During the endoscopy, flushes of 20-ml aliquots of pre-mixed solution containing 100 ml of water, 2 ml of Gascon and 20,000 units of Pronase were used as required.

All patients underwent routine gastroscopy, including chromoendoscopy, by one of 14 experienced unblinded endoscopists. The endoscopist was free to use as many flushes as deemed necessary to produce a satisfactory view. Once all flushes had been given, one extra photograph was taken from each of four predefined areas: the oesophagogastric junction, the antrum, the lower body and the upper body of the stomach. A record was kept of the total time taken to perform the procedure (from intubation to extubation) and the number of flushes required.

A single, blinded investigator who was experienced in endoscopy but had played no part in the endoscopic procedure then reviewed all of the pictures and assigned each of them a score between one and three for mucosal visibility: 1 = no adherent mucus and clear view of the mucosa; 2 = a thin coating of mucus but not obscuring vision; and 3 = adherent mucus obscuring vision.

The individual scores for each of the four photographs taken were then totalled for each patient to give an overall visibility score ranging from four to 12.

A second blinded investigator separately reviewed and scored the pictures from 20 patients and the results were compared with the original assigned scores.
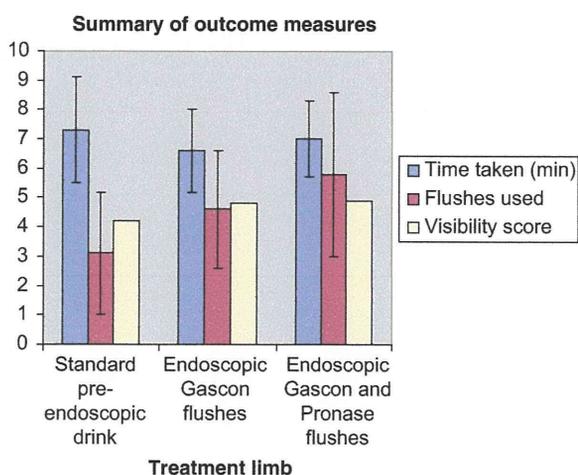
Statistical analysis

The sample-size calculations showed that 35 participants were required in each treatment group (105 patients overall) to detect a 20% improvement in visibility scores, from 7 to 5.6, assuming a standard deviation of 2 for each group and a power of 90%. Allowing for a 30% attrition rate, we aimed to recruit 150 participants.

Differences between the number of flushes and the time taken were analysed using ANOVA and Fisher's least significant difference. As visibility scores were non-normally distributed, the Kruskal–Wallis and Dwass–Steel–Chritchlow–Fligner tests were used for these results. All analyses used SPSS software (SPSS Inc, Chicago, IL). A *P*-value of 0.05 was taken to be significant throughout.

Results

A total of 112 patients were evaluable in the study, with a mean age of 61 years. The study population comprised 51 males (46%) and 61 females (54%). There were no significant differences between treatment groups (Table I) for a summary of outcome measures please see Figure 2.

Visibility

Visibility scores allocated by the two independent visibility score assessors correlated well (Cohen's weighted kappa 0.604, standard error 0.187, 95% CI 0.237–0.971).

There were significant differences in the visibility scores assigned between groups (H = 17.8, P = 0.0001). The photographs taken from the premedicated Group S scored significantly better for visibility than either of the endoscopic therapy groups GP and G (P = 0.0002 and P = 0.0008, respectively). There was no significant difference in visibility scores between Groups GP and G (P = 0.999).

Figure 2. Outcomes.

Table I. Patient characteristics.

Characteristic	Group		
	S (*n* = 35)	G (*n* = 37)	GP (*n* = 40)
Gender; *n* (%)			
Male	18 (51)	14 (38)	19 (48)
Female	17 (49)	23 (62)	21 (52)
Age (years); mean (SD)	63 (1.9)	61 (1.6)	61 (2.1)

Number of flushes needed

There were significant differences in the mean number of flushes used between groups ($F = 12$, $P = 0.0001$). Significantly fewer flushes were used during the procedure in those patients receiving conventional Japanese pre-medication (Group S) than either of the other groups (Group GP, $P = 0.008$; Group G, $P < 0.001$). In the groups receiving endoscopic flush therapy only, significantly fewer flushes were used in the group with Pronase added to the Gascon mixture ($P = 0.023$).

Time taken for procedure

There was no significant difference in the time taken to complete the procedure between any of the three groups ($F = 2.23$, $P = 0.112$).

Safety

There were no complications in any of the groups. In particular, there were no clinically detectable cases of pulmonary aspiration.

Discussion

Optimal mucosal visualization is vital for thorough endoscopic inspection, particularly when using newer methods such as chromoendoscopy [13–16]. The use of bubble-bursting agents and mucolytics has been shown to improve mucosal visibility in previous trials [17–20], but safety concerns have discouraged generalized use in the West.

We assessed a potentially more acceptable technique of spraying these agents endoscopically. Gascon (simethicone or dimethicone) is silicone-based and non-absorbable, with an excellent safety record. It causes gas bubbles to burst by reducing their surface tension and is marketed for the relief of abdominal bloating. Pronase is a mixture of proteases isolated from *Streptomyces griseus*. These agents were chosen for the study as they both have proven efficacy and have been adopted as standard treatment at the trial centre.

Our results showed that spraying the anti-foam and mucolytic agents endoscopically was not as effective in terms of improved mucosal visibility as pre-endoscopic treatment with the same combination, despite the endoscopist using a greater number of flushes to attempt to clear the mucous. We would ideally have compared the endoscopic flushes with Western standard practice, which in the UK would be

to give no pre-endoscopic preparation and to use water endoscopic flushes, but were unable to do this in Japan as using mucous-clearing medication has become so accepted that it was considered unethical not to do so. Adding Pronase to the basic endoscopic flush mixture did not add any advantage in terms of mucosal visibility. The apparent superiority of a pre-endoscopic drink of mucous-clearing solution as compared to endoscopic flush therapy may reflect the more diffuse application of the solution or the 10-min delay between the drink and endoscopy.

No technique resulted in clinically detectable pulmonary aspiration but rates of aspiration during a standard gastroscopy are less than one in a thousand [21] and a larger trial would therefore be needed to properly evaluate this risk.

We conclude that the standard Japanese practice of administering a pre-endoscopic drink containing a mucolytic and anti-bubble agent is superior in terms of endoscopic mucosal visibility to endoscopic application of either both agents or an anti-bubble agent alone. We cannot recommend applying these agents as an endoscopic spray.

Whether improved mucosal visibility results in a higher detection rate of early cancers or improved clinical outcomes remains unknown and well-designed large clinical trials will be needed in the future to evaluate this.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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The Natural History of Non-Polypoid Colorectal Neoplasms

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The importance of non-polypoid colorectal neoplasms (NP-CRN) is now recognized throughout the world.[1–9] There is little information, however, known about the natural history of NP-CRN, perhaps because the initial reports of NP-CRN suggested that it had high risk of invasion and lymph node metastasis as compared with polypoid lesions of similar size.[10,11] Long-term follow-up of NP-CRN without resection was therefore not an accepted treatment strategy, and had been reported only based on analysis of interval neoplasms or sporadic case reports. In addition, outside Japan, many endoscopists viewed NP-CRN, especially the depressed lesion, as a uniquely Japanese phenomenon and thus, paid little attention to such lesions, limiting the data even more. This article will summarize the available data to gain some estimates of the natural history of NP-CRN.

RADIOGRAPHIC ANALYSIS

Matsui and colleagues[12] reported a retrospective analysis of a series of colorectal cancers that were missed by double-contrast barium enema examinations. They found six depressed and seven flat lesions (41%) could be retrospectively identified as antecedent lesions that gave rise to 32 advanced cancers. The authors found that all depressed lesions developed into nonprotuberant-type advanced colorectal cancers, whereas flat or polypoid lesions had a possibility to develop into either protuberant or nonprotuberant-type advanced colorectal cancers.

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Umetani and colleagues[13] reported 11 cases of colorectal cancers that had more than two barium enema examinations that were at least 6 months apart. Five non-polypoid submucosal invasive cancers were studied; three developed from non-polypoid and two from polypoid lesions. The authors estimated tumor doubling time to evaluate the growth rate of each tumor, and suggested that NP-CRN grew slowly compared with polypoid lesion and maintained their macroscopic morphology. The data, however, are limited.

COLONOSCOPIC ANALYSIS

Matsui and colleagues[14] reported eight early colorectal cancers that were incidentally followed by colonoscopy. Thirty-five cases, including 14 NP-CRN as initial lesions, were reviewed. They found that NP-CRN progressed to submucosally invasive cancer, retaining its non-polypoid configuration, and some flat lesions developed depressed areas during their progression. Although the authors also estimated the speed of growth compared with polypoid and non-polypoid lesions, they could not conclude which type grew more rapidly.

Sato and colleagues[15] prospectively followed 12 small flat adenomas. The size of the lesions ranged from 2 to 6 mm (median 4 mm), and the observation period ranged from 11 to 26 months (median 19 months). Although eight lesions showed various changes in their shape, only two lesions demonstrated an increase in diameter of the tumor. All of the flat lesions were subsequently removed endoscopically and found to be adenomas. The authors concluded small flat adenoma did not rapidly progress, and configuration change did not indicate tumor progression or invasion.

Watari and colleagues[16] conducted prospective colonoscopic study to elucidate the natural history of NP-CRN. The authors observed 75 colorectal tumors measuring less than 1 cm in diameter in 50 patients. The average follow-up period was 22 months, and 62 lesions (83%) were NP-CRN. They concluded similar observations as those of Sato and colleagues, although they found that 40% of small non-polypoid lesions had exophytic growth with time. This finding suggested some small non-polypoid lesions follow the adenoma–carcinoma sequence the same as polypoid lesions.

THE IMPORTANCE OF THE DEPRESSED-TYPE NP-CRN

Matsuda and colleagues[17] analyzed 6638 colorectal neoplasms, excluding advanced cancers, treated in National Cancer Center Hospital, Tokyo, Japan. There were 4471 (67%) and 2167 (33%), polypoid and non-polypoid colorectal neoplasms, respectively. Among all non-polypoid lesions, there were 178 (2.7%) depressed lesions, 109 (61%) of which were diagnosed as high-grade dysplasia or submucosally invasive cancer. Among 5538 (83%) lesions that were identified as low- or high-grade dysplasia, the proportion of depressed lesions was 1.3%. On the other hand, depressed type was identified in 39% (**Table 1**) of submucosal cancers. This discrepancy may indicate of a rapid progression rate of depressed lesions into invasive cancers.

Sano and colleagues[18] described the incidence of depressed lesions among all of colorectal neoplasms, again excluding advanced cancers. Their multicenter retrospective study conducted in eight Japanese referral institutes revealed that the incidence of depressed lesions was 1.94% (1291 depressed lesions out of 66,670 neoplasms), and, in particular, 51.2% of intramucosal depressed lesions were diagnosed as high-grade dysplasia. These data also suggested that intramucosal depressed lesions showed more aggressive behavior and were perhaps more likely

Table 1
Relationship between macroscopic type and histopathological findings

	LGD	HGD	SM-Ca
Polypoid	3781 (68.3)	578 (67.9)	112 (45.0)
Flat	1688 (30.5)	260 (30.6)	41 (16.5)
Depressed	69 (1.2)	13 (1.5)	96 (38.6)
Total	5538 (83.4)	851 (12.8)	249 (3.8)

Abbreviations: HGD, high-grade dysplasia; LGD, low-grade dysplasia; SM-Ca, submucosal invasive cancer.

Data from Matsuda T, Saito Y, Hotta K, et al. Prevalence and clinicopathological features of non-polypoid colorectal neoplasms: should we pay more attention to identifying flat and depressed lesions? Dig Endosc 2010;22(Suppl 1):S57–62.

to develop into invasive cancers as compared with the polypoid lesions. The depressed type of NP-CRN appears to be pathologically and molecular biologically distinct that other types of NP-CRN.

Several authors reported that depressed-type colorectal cancer does not arise from an adenomatous polyp. This theory was called de novo carcinogenesis, and lack of K-ras mutation was thought to be a distinctive genetic feature.[10,11,19,20] Goto and colleagues[21] reported the proportion of de novo cancers among all colorectal cancers in a cohort of 14,817 Japanese populations. The authors defined de novo cancers according to both criteria: (1) the absence of adenomatous components and (2) all lateral margins of the tumor covered with normal mucosa and non-polypoid growth pattern. They concluded that 22.9% of early colorectal cancers were de novo cancers. Chen and colleagues,[22] from Taiwan, also assessed the proportion of de novo carcinomas using the Markov model, and demonstrated about 30% of colorectal cancers arising from de novo sequence.

Table 2
Description of 13 interval cancers diagnosed within 3 years of a initial colonoscopy

Number	Macroscopic Type	Size (mm)	Location	Depth of Lesion
1	Isp (semipedunculated)	13	Sigmoid	SM
2	Isp (semipedunculated)	15	Sigmoid	SM
3	Is (sessile)	8	Rectum	SM
4	Is (sessile)	10	Sigmoid	SM
5	Is (sessile)	20	Rectum	MP
6	Is (sessile)	6	Transverse	SM
7	IIa (flat)	15	Transverse	SM
8	IIa (flat)	20	Sigmoid	SM
9	IIa + IIc (depressed)	20	Cecum	SM
10	IIa + IIc (depressed)	20	Transverse	SM
11	IIa + IIc (depressed)	10	Rectum	MP
12	IIa + IIc (depressed)	6	Ascending	SM
13	IIa + IIc (depressed)	20	Sigmoid	SS

Abbreviations: MP, muscularis; SM, submucosa; SS, subserosa.

Data from Matsuda T, Fujii T, Sano Y, et al. Five-year incidence of advanced neoplasia after initial colonoscopy in Japan: a multicenter retrospective cohort study. Jpn J Clin Oncol 2009;39:435–42.

THE JAPAN POLYP STUDY

To clarify the natural history of NP-CRN, a large cohort study focused on the detection of NP-CRN is required. Matsuda and colleagues[23] reported the results of multicenter retrospective cohort study to evaluate 5-year incidence of advanced neoplasia after initial colonoscopy. The authors studied 5309 patients with a median follow-up period of 5.1 years. Endoscopists diagnosed 13 invasive cancers on follow-up within 3 years. The initial colonoscopies were performed by Japanese endoscopists who had proficient technique with chromoendoscopy to diagnose NP-CRN, and the patients had good preparation quality, taking polyethylene glycol (PEG) solution in the morning on the day of colonoscopy, Out of the 13 incident cancer cases, seven were NP-CRN, and the mean size of these lesions was less than 15 mm in diameter (Table 2). These data suggested that NP-CRN is responsible for interval cancers, defined as colorectal cancers diagnosed within several years of a complete colonoscopy. Much prospective data, however, are necessary to elucidate the natural history and epidemiology of these lesions. The Japan Polyp Study (JPS) is a multicenter randomized controlled trial prospectively evaluating follow-up surveillance strategy for Japanese patients after removal of all polypoid and non-polypoid neoplasms.[24] This study is intended to continue until 2011 and hopefully will provide new information on the detection and progression of NP-CRN.

SUMMARY

The natural history of NP-CRN is mostly unknown. The results of small observational studies suggest that NP-CRN lesions develop into invasive cancer with minimal size expansion. Among NP-CRN lesions, depressed lesions show more aggressive behavior and frequently develop into invasive cancers compared with polypoid lesions, regardless of their low incidence. A large prospective cohort study focused on the detection of NP-CRN is currently ongoing.

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