

CASE REPORT

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Small invasive colon cancer with systemic metastasis: A case report

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ABSTRACT

Background: Recently, especially in Japan, several researchers have suggested that colorectal cancer can develop not only through an adenoma-carcinoma sequence but also from normal mucosa via a *de novo* pathway, and that these *de novo* cancers have more aggressive malignant potential. We report a case of aggressive colon cancer resulting in systemic metastasis despite small tumour size.

Case Presentation: A 35-year-old woman presented at the referring hospital with swelling of the left cervical lymph node. Biopsy of the lymph node revealed metastatic adenocarcinoma; however, CT scan and mammography were unable to identify the site of the primary lesion. She was diagnosed with unknown primary cancer and referred to our hospital for further examination. Immunohistochemical reevaluation showed the cervical lymph node biopsy specimen to be positive for CDX2 and CK20 and negative for CK7 expression, leading us to suspect the presence of a primary colorectal cancer. We performed a total colonoscopy, and detected a small protruding lesion in the transverse colon. The tumour was only 12 mm in diameter, with a central depressed component and a severely thickened stalk, which suggested direct cancer invasion of the deep submucosa. We concluded that this lesion was the site of origin of the metastasis despite the small tumour size, and performed diagnostic endoscopic mucosal resection. The lesion was found to have an intramucosal cancer component, demonstrating that this lesion represented primary colon cancer. The patient was referred to the gastrointestinal oncology division for systemic chemotherapy.

Conclusions: In this case, immunohistochemical findings strongly suggested the existence of a colorectal cancer. The non-polypoid gross appearance of the tumour suggested that it can originate *de novo*, thus providing a valuable case in support of the aggressive malignant potential of a *de novo* colorectal cancer pathway.

Keywords: Nonpolypoid colorectal cancer, CDX2, CK20, CK7, systemic metastasis

Background

Colorectal cancer is the second leading cause of cancer deaths in men and women in Western countries [1], and its incidence is gradually increasing in Japan as well. The most common pathway of colorectal cancer development is thought to be the adenoma-carcinoma sequence, in which carcinoma develops from an adenomatous polyp [2]. The current practice of removing adenomatous polyps of the colon and rectum is based on the belief that this will prevent colorectal cancer [3]. However, recent

reports have described small depressed [4], leading to the proposal of an alternative pathway of *de novo* colon carcinogenesis, which involves an aggressive growth phenotype and quick infiltration of neighbouring tissue and lymph nodes [5-7]. The most common site of metastasis of these cancers is the liver, followed by the lung. Herein, we report a rare case of a small colon cancer with a depressed component and aggressive malignant potential with systemic metastasis, where the chief complaint was cervical lymph node swelling.

Case Presentation

In September 2009, a 35-year-old woman presented at the referring hospital with left cervical lymph node

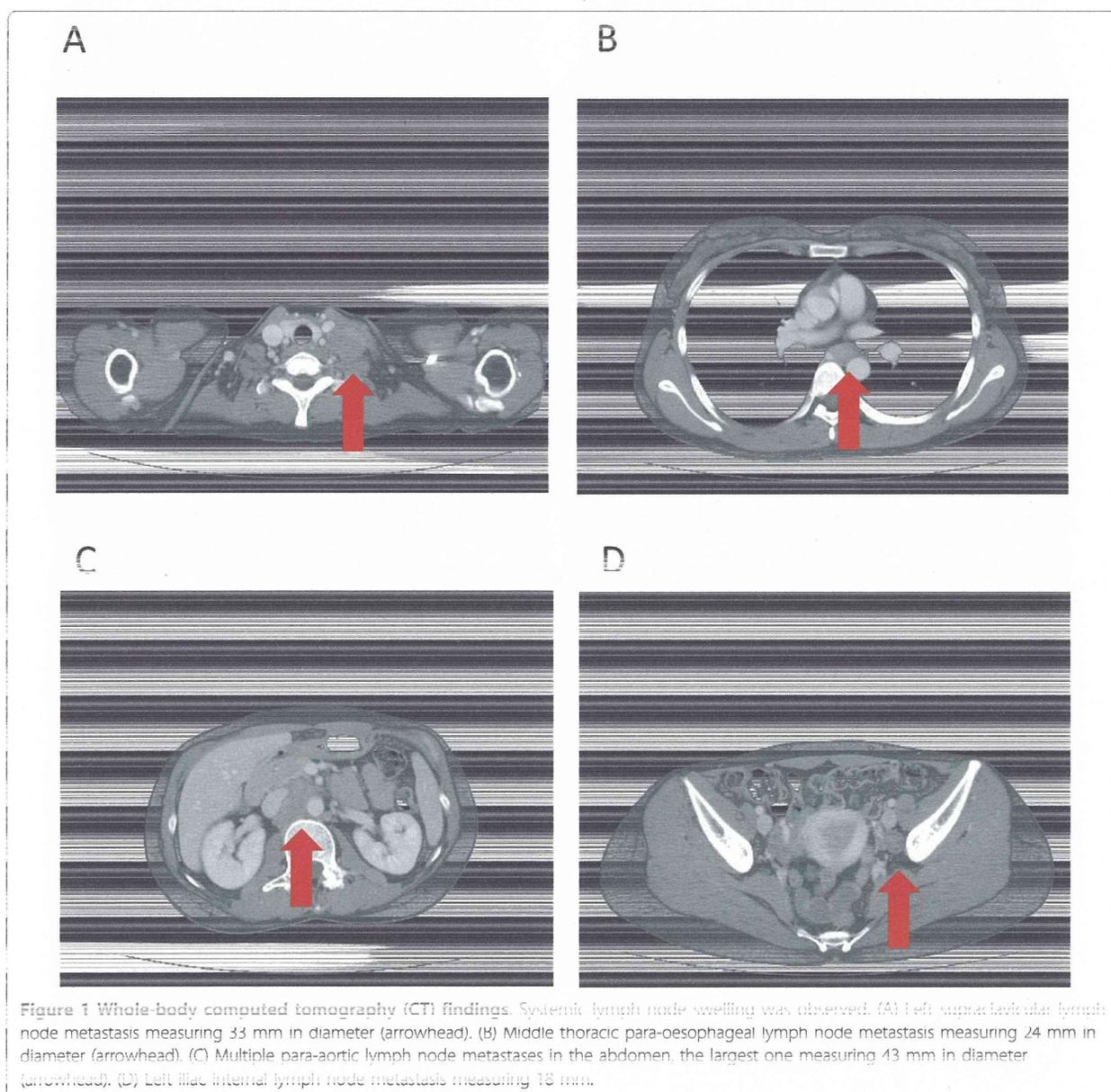
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swelling. Malignant lymphoma (ML) was first suspected, but aspiration cytology and biopsy of the lymph node suggested metastatic adenocarcinoma resulting from breast cancer. However, no evidence of breast cancer was found on ultrasonography and mammography examinations. Whole-body computed tomography (CT) showed systemic lymph node swellings (left supraclavicular and multiple para-aortic lymph nodes) but no primary lesion (Figure 1). Upper Gastrointestinal endoscopy revealed no evidence of malignancy. The patient was diagnosed with unknown primary cancer and referred to our hospital for further examination in November 2009.

We reevaluated the lymph node biopsy specimen obtained by the referring hospital. The tumour cells with oval to round nuclei with prominent nucleoli were found to be showing partial ductal structures, leading us to suspect poorly differentiated adenocarcinoma. Additionally, immunohistochemistry (IHC) studies showed the biopsy specimen to be negative for cytokeratin 7 (CK7), and positive for CDX2, an intestine-specific homeobox transcription factor, and cytokeratin 20 (CK20), a cytoskeletal protein usually found in the colonic epithelium. These IHC results strongly suggested the metastasis from a primary colorectal cancer (Figure 2). We performed a total colonoscopy and detected a small



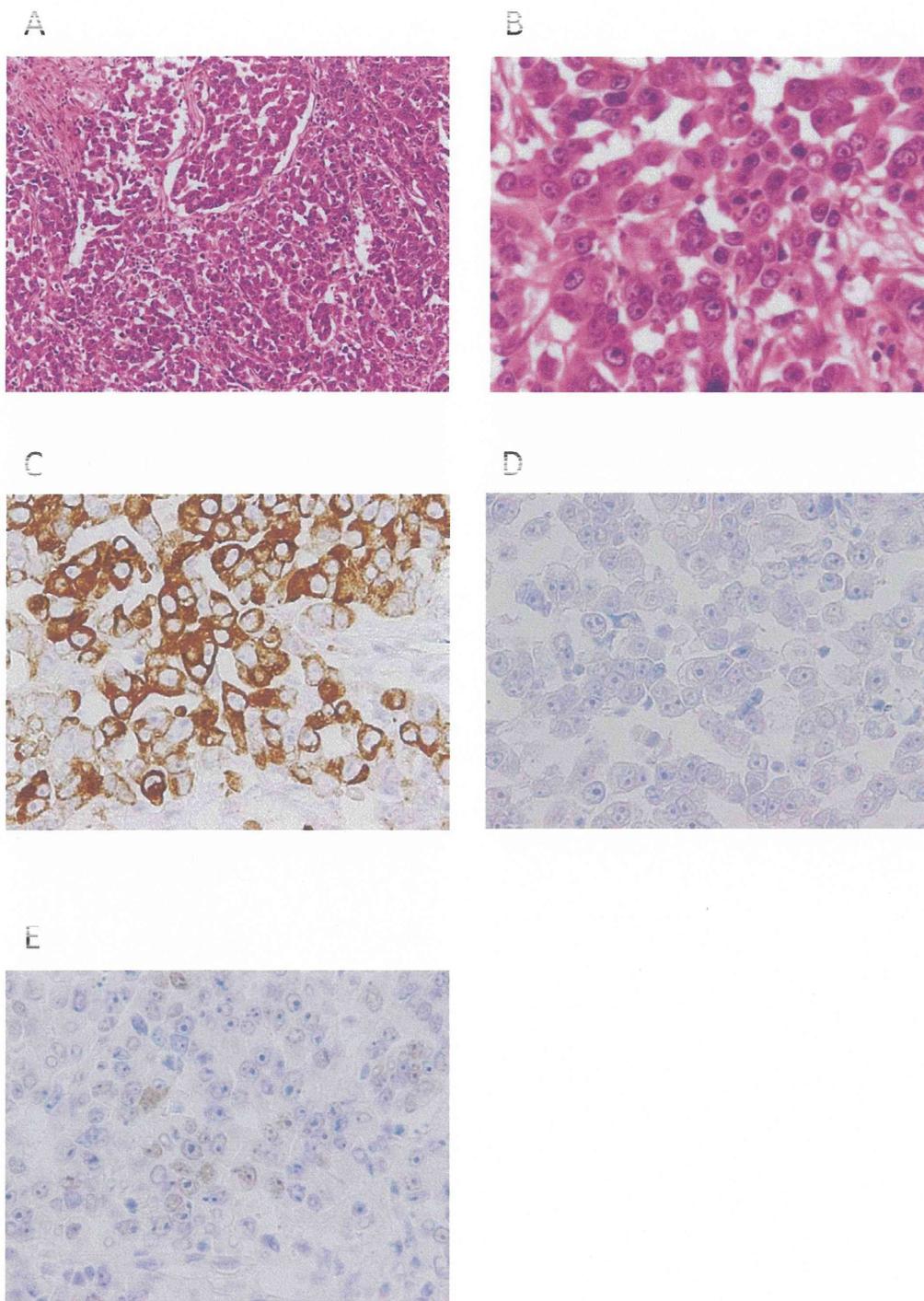


Figure 2 Pathological findings of lymph node metastasis. (A, B) Poorly differentiated adenocarcinoma was observed, with tumour cells spreading into fibrosis stroma in the tumour tissue. Tumour cells contained acidophilic vacuoles and oval nuclear bodies with several clear nucleoluses and partially formed glandular differentiations. (C) Immunohistochemical staining for CK20 was positive. (D) Immunohistochemical staining for CK7 was negative. (E) Immunohistochemical staining for CDX2 was weak but diffusely positive.

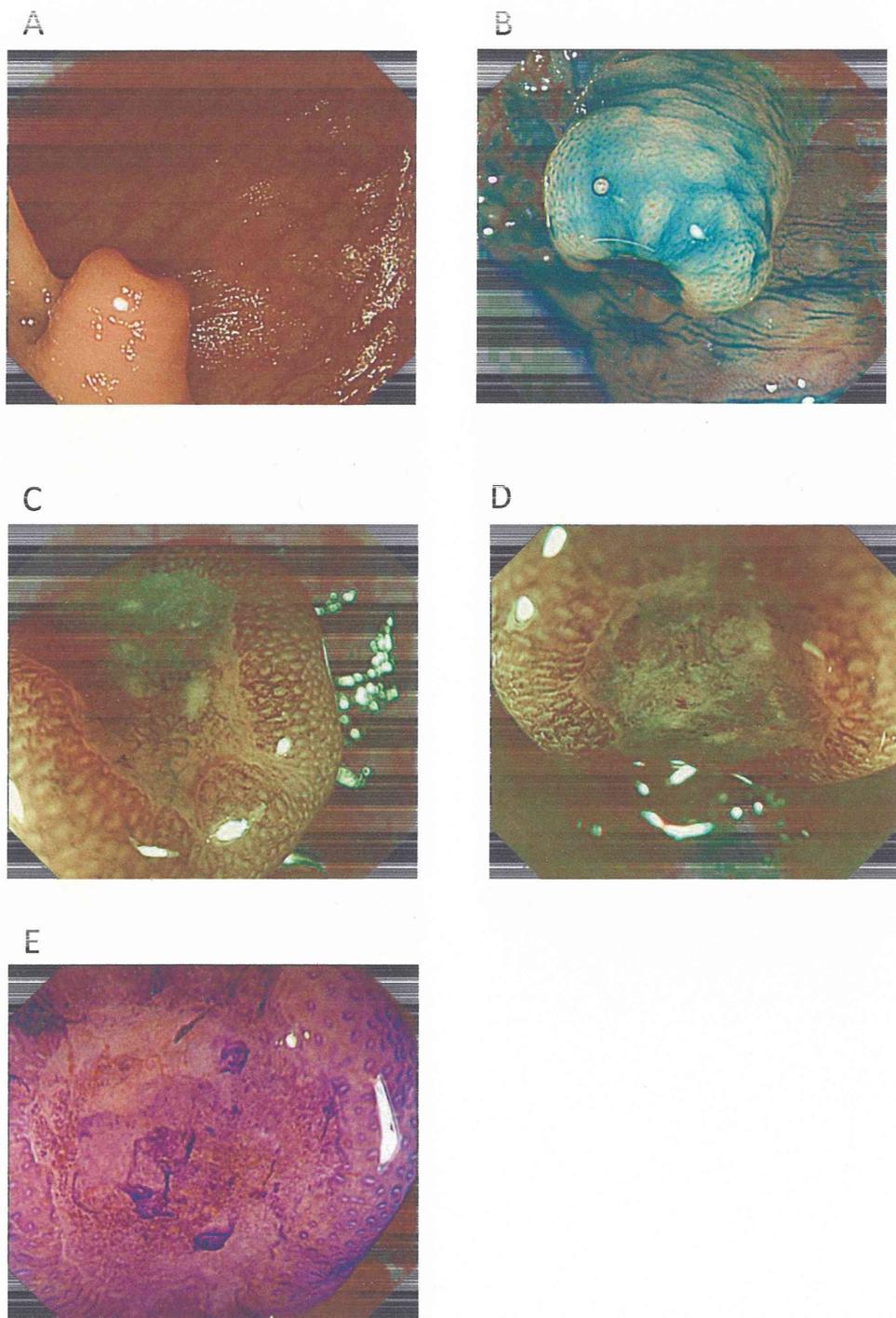


Figure 3 Colonoscopy findings. (A) Conventional colonoscopy showed a protruding lesion with central depression in the transverse colon, 12 mm in diameter. Its stalk was severely thickened, suggesting cancer invasion. (B) Chromoendoscopy with 0.4% indigo-carmin dye clearly showed the depressed area and non-neoplastic mucosa covering the edge of the cancer, suggesting that this tumour followed a non-polypoid growth (NPG)-type pattern. (C, D) Magnified NBI (Narrow Band Imaging) micrograph of the central depressed area, showing loose, irregular capillary vessels. We diagnosed the tumour as type IIIb according to Sano's classification, which suggests the possibility of deep cancer invasion of the submucosal layer. (E) Magnified view with 0.05% crystal violet staining of the surface of the central depression with a severe irregular pit pattern identified in the demarcated area.

protruding lesion in the transverse colon (Figure 3). The tumour was very small, with a diameter of only about 12 mm, and contained a depressed component, leading to a diagnosis of macroscopic type with 0-Is+IIc according to the Paris classification [8]. Furthermore, the severely thickened stalk and irregular pits visible in a magnified image of the depressed area combined to suggest direct invasion of the deep submucosa (Figure 3C) [9]. We concluded that this lesion was the primary site of the metastatic cancer despite its small size.

A diagnostic endoscopic mucosal resection (EMR) was performed and the specimen removed was serially dissected into three sections and examined. The tumour was composed of poorly differentiated adenocarcinoma and signet-ring cell carcinoma (Figure 4). It primarily consisted of solidly proliferated cells, but exhibited some indistinct gland formation. The tumour had a preserved intramucosal component but infiltrated deeply into the submucosal layer, with severe lymphatic and venous invasion detected the submucosal layer. The vertical and horizontal cut ends of the resected tumour were both positive for cancer cells (Figure 4). IHC studies showed strong expression of MUC5AC, and weak expression of MUC2 and CDX2; indicating the tumour having a mixed gastric and intestinal character, with the gastric phenotype being predominant. Patients with advanced colorectal cancer with gastric phenotypes have been reported to frequently exhibit lymphatic permeation and lymph node metastasis [10]. Additionally, the tumour was positive for CK20 and slightly positive for CK7. There was no evidence of differentiation to endocrine tumour or hepatoid adenocarcinoma (Figure 5).

These pathological results suggested that colon cancer was the origin of lymph node metastasis. The patient was referred to the Gastrointestinal Oncology Division, where she underwent combination chemotherapy using capecitabine (Xeloda[®]) plus oxaliplatin (Eloplatin[®]) and bevacizumab (Avastin[®]), which is one of the standard therapy of metastatic colon cancer. After 4 courses, CT scan showed a significant reduction of tumour volume, but after 10 courses, the tumour marker rapidly increased and peritoneal metastasis progressed. The genomic analysis of KRAS status revealed wild type, so we started the second-line combination chemotherapy using cetuximab (Erbiximab[®]) plus irinotecan hydrochloride (Topotecin[®]). After the 4 times administration of cetuximab, tumor marker was decreased significantly. Her age, i.e. 35-years, is in accordance with the Guideline, which are used as recommendation criteria for MSI testing. However, she did not agree to undergo MSI testing, because she would like to give top priority to receive the chemotherapy.

Conclusions

In patients with an unknown primary carcinoma, the site remains unidentified in 15–25% of the cases even after autopsy [11,12], although recent advances in clinical examination and diagnostic work-up have decreased this frequency. The median survival of high-risk patients with cancer of unknown primary origin ranges from 3 to 11 months, making prompt diagnosis and treatment very important [13–15]. In this case, 2 months elapsed between the initial consultation at the referring institution and the patient's presentation at our hospital. Pathological and IHC reviews of cervical lymph node tissue were the main tools used to determine the primary site of cancer origin.

When attempting to trace the primary site of a metastatic tumour of unknown origin, clarification of the histological type is indispensable in selecting appropriate treatment. Microscopic features and cell morphologies can be identified with hematoxylin and eosin (HE) staining, and this information can be used to identify the primary site. However, in the evaluation of undifferentiated or poorly differentiated cancers, IHC evaluation is a useful addition to HE staining in locating the tumour site. In particular, a pattern of positive CDX2 or CK20 expression and negative CK7 expression is indicative of primary colorectal cancer [16,17].

In this case, IHC investigation of a lymph node biopsy strongly suggested primary colorectal cancer. In a total colonoscopy examination, we detected one colorectal lesion with the gross appearance of a submucosal tumour. This appearance is relatively rare in primary colon cancer, and thus we should exclude metastatic colon cancer as a possible diagnosis. EMR is more useful than simple biopsy in confirming the existence of a mucosal component, which would lead to a primary cancer diagnosis, but it carries a high risk of bleeding and perforation in cases where deep submucosal invasion is suspected. We performed diagnostic EMR after obtaining proper consent and agreement.

The adenoma-carcinoma sequence hypothesis proposes that colorectal cancers arise from adenomatous polyps. Alternately, several researchers, especially in Japan, have suggested that colorectal cancer can also develop from normal mucosa, in a *de novo* process involving morphological changes from a small superficial-type carcinoma to depressed-type carcinoma. *De novo* cancers are thought to have an aggressive growth phenotype, despite small tumour size, and to quickly infiltrate neighbouring tissue and lymph nodes. In this case, the tumour exhibited a severely thickened stalk, which suggested direct cancer invasion of the deep submucosa, and a clearly demarcated depressed area in the centre of the lesion, suggesting that it can originate *de*

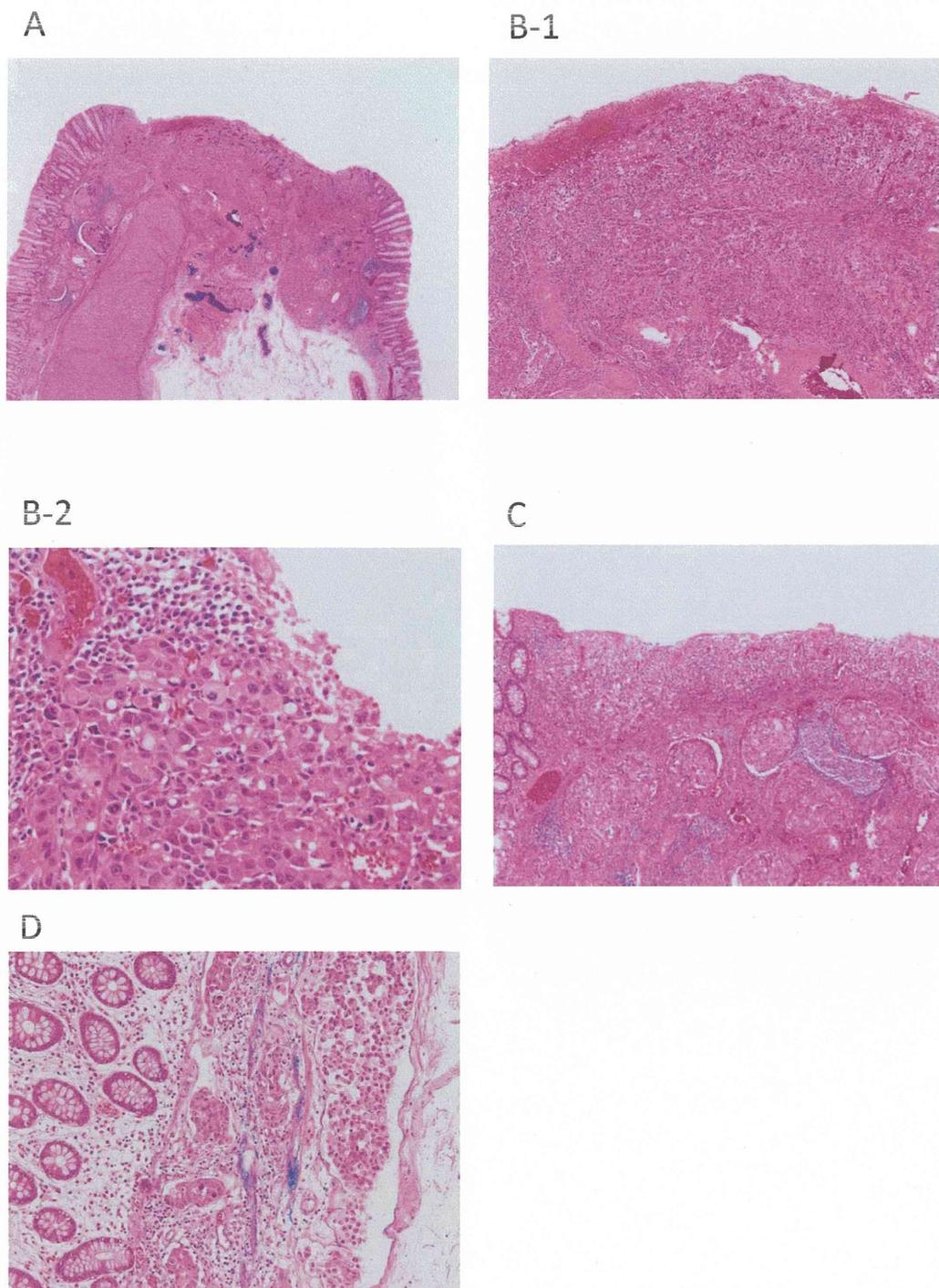


Figure 4 Pathological results of endoscopic mucosal resection. (A) An intramucosal component corresponding to the depressed lesion was observed. The tumour formed a massive invasion below the muscularis propria. (B-1,2) The tumour was composed of poorly differentiated adenocarcinoma and signet-ring cell carcinoma, mostly formed by solidly proliferating cells but with some indistinct gland formation. (C) The tumour had an intramucosal component, but infiltrated deeply into the submucosal layer with severe lymphatic and venous invasion. (D) Extensive lymphatic and venous invasion was detected mainly under the muscularis propria.

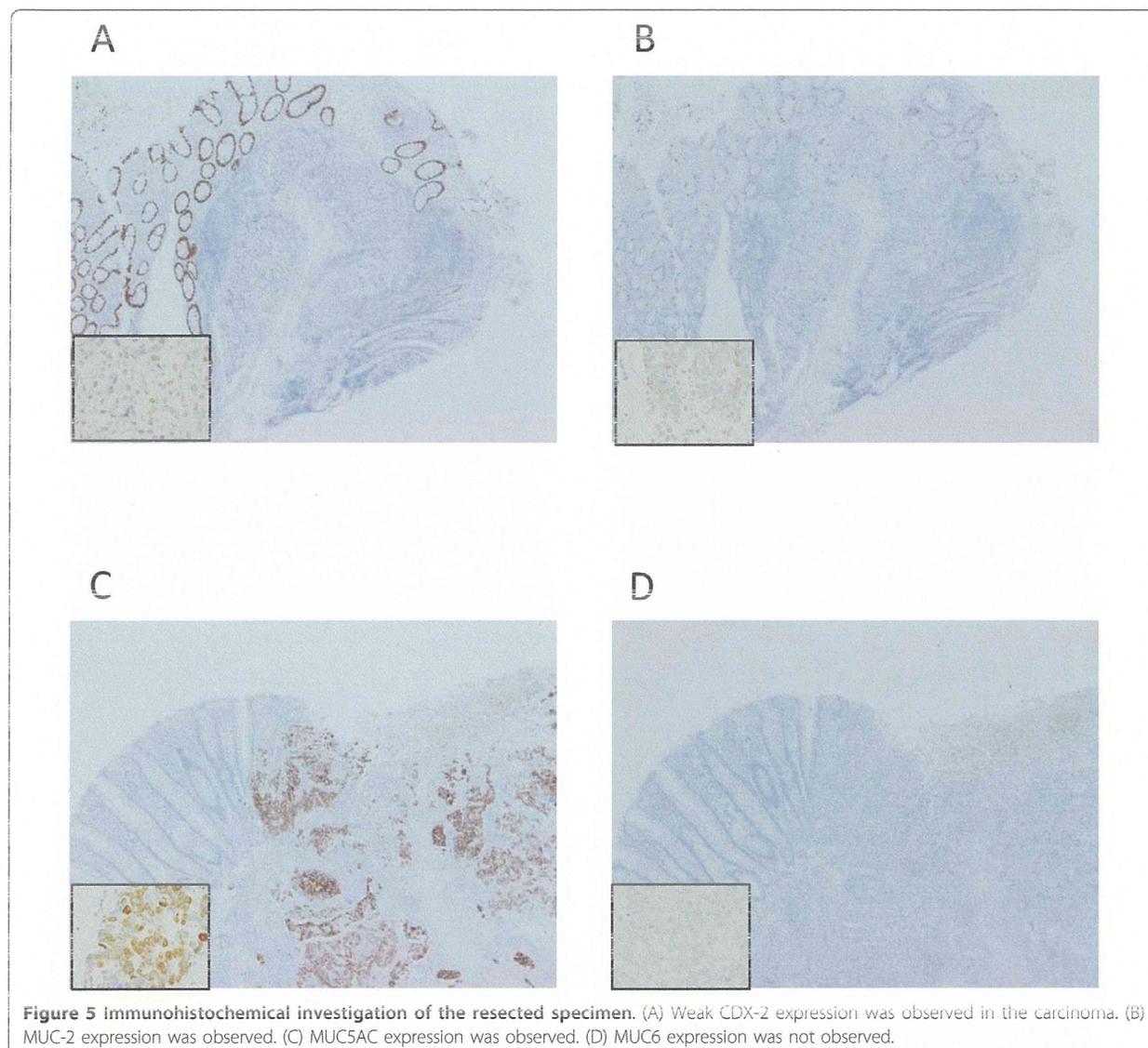


Figure 5 Immunohistochemical investigation of the resected specimen. (A) Weak CDX-2 expression was observed in the carcinoma. (B) MUC-2 expression was observed. (C) MUC5AC expression was observed. (D) MUC6 expression was not observed.

novus simply due to its morphology and clinical behaviour. This case of small primary colon cancer with systemic metastasis provides valuable support for the aggressive malignant potential of the *de novo* pathway in colorectal carcinogenesis.

In conclusion, we have reported a rare case of small primary colon cancer with systemic metastasis

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Abbreviations

CK: cytokeratin, CT: computed tomography, EMR: endoscopic mucosal resection, IHC: immunohistochemistry

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Authors' contributions

MM collected the data and wrote the report, and was involved in drafting the manuscript. TN revised the manuscript critically for important intellectual content. All authors read and approved of the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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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

statements⁶ 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 \pm 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 detail¹⁹ 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 \pm SD	54 \pm 11.6	51 \pm 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 \geq 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 \sim 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

Risk factors	Unadjusted		Adjusted			
	OR (95% CI)	p Value	β coefficient	SE	OR (95% CI)	p Value
Gender, male	1.5 (1.1 to 2.2)	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

Risk factors	Unadjusted		Adjusted			
	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 to 19.9)	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 professional⁶ 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

Colon

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 history⁷ 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 neoplasia (%) (95% CI)	No. of subjects (%)	Colorectal advanced neoplasia (%) (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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The Asia-Pacific Colorectal Screening score: a validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects

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