20111906A

別紙１

厚生労働科学研究費補助金

がん臨床研究事業

離島をモデルとした新しい対策型大腸がん検診システムの構築とその実現に向けた研究
－新島STUDY

平成２３年度　総括研究報告書

研究代表者　松田　尚久

平成２４（２０１２）年　３月

別紙２

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研究代表者　松田 尚久（国立がん研究センター中央病院 医長）

研究要旨

わが国では，1992 年より 40 歳以上の成人を対象とした免疫学的便潜血反応（2 日法）による大腸がん検診が行われているが，その受診率は男性：27.5%，女性：22.7%（H19 年：国民生活基礎調査）と低く，都道府県別格差が大きい．とくに離島が抱える大腸がん検診の問題が深刻化している．東京都新島村（人口：3,068 人，1,384 世帯）における大腸がん検診は，平成 18 年：23.9%，平成 21 年：12.8%，平成 22 年：約 12%とその受診率の低下が顕著であり，大腸内視鏡検査施行医がいない現状も相俟って要精検者（便潜血陽性者）に対する精査が十分に施行されていない．本研究では，離島（新島村）をモデルに「内視鏡検査による大腸がん検診受診率 50%以上」を達成目標とし，個人登録下でのアンケート調査及び内視鏡検査結果に基づいた大腸がんリスクの層別化と，目標に向けた適正な個人勧奨のあり方について検証を行う．

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A．研究目的

本研究の目的は，日本における258の指定有人離島（人口42.9万人，関係市町村数：110）における理想的な地域大腸がん検診モデルの確立を目指し，科学的根拠に基づいた検診体制を構築するための臨床研究を策定することにある．本研究では，新島村をモデルに「内視鏡検査による大腸がん検診受診率50%以上」の目標達成として計画する啓発活動（パンフレット作成・講演会）の有効性評価と，検診非受検者に対して行う6か月ごとのリコール（反復受診勧告）による受診率向上効果を明らかにする．実際には，東京都新島村をモデルとし，大腸がん検診対象者中40～79歳の男女約1,600名に対して啓発活動後に検診としての全大腸内視鏡検査の案内を行い，文書による本研究参加の応諾が得られた者に対して，全例大腸内視鏡検査を計画する．

B．研究方法

新島村住民で，平成 23 年度大腸がん検診の対象者中 40～79 歳の男女約 1,600 名に対して，検診としての全大腸内視鏡検査（TCS）の案内状を送付する．この時点で，文書による本研究参加の応諾が得られた者に対して，全例 TCS を計画する（参加同意が得られない住民及び 80 歳以上の方につ

いては，例年通りの免疫学的便潜血検査：FOBT を推奨）．また，上記いずれの検査も受検しなかった対象者に対しては，初回呼びかけ後 6 か月の期間を利用して，大腸がん検診の重要性と TCS 及び FOBT のメリット・デメリット等について，パンフレット送付と地域での講演会を通じて普及啓発活動を行った後に案内状を再送付（リコール）し，検診受診を再度呼びかける．

また，新島村住民すべてを対象としたアンケート調査（大腸がん検診受検・非受検理由および大腸がんリスクに関する食生活等の生活習慣・がん家族歴・既往歴・身体所見：BMI等の調査）を行う．また検診受検者については，検診結果に基づいた個別のフォローアップ方法（推奨される検査間隔およびその方法）についての情報提供を行う．

（倫理面への配慮）

本研究への参加同意が得られた島民のデータについては，新島事務局（新島村さわやか健康センター）にて管理するが，TCS 及び FOBT 検査結果については匿名化した形でデータセンター（メディカルリサーチサポート）が集中管理する．データセンター，新島事務局、中央事務局（国立がん研究センター）の施設責任者は，研究のために作成されたデータセットまたは資料を研究終了後も保管する．いずれの参加者も個人情報保護法を遵守する．

C．研究結果

第一期検診結果：平成 23 年 7 月から 9 月の第一期検診にて，全検診対象者 1,671 名中 29.7%にあたる 497 名より検診希望があり，その中の 466 名（93.8%）が大腸がん検診を受検した．これは，昨年度の新島村での検診受診率（12%）を大きく上回る数字である．検査種別内訳は TCS+FOBT：235 名，TCS 単独：111 名，FOBT 単独：120 名であり，男性 26.7%，女性 28.6%の検診受検率であった．FOBT 陽性率は 8.2%（29/355）であり，陽性者に対する TCS 精検が全例完了した．第一期検診として全 11 週（計 41 日間）の TCS 検診を「新島村さわやか健康センター」にて行い 346 名の島民が受検した．第一期 TCS 検診では，96 名（27.7%）に要治療病変（5mm 以上の腫瘍性病変）を，またその中には 54 名（15.6%）の Index lesion（10mm 以上の腫瘍あるいは内視鏡的に癌が疑われる病変）陽性者を認めた．現在，上記要治療者に対する内視鏡治療あるいは外科手術を都内専門施設にて保険診療として継続中であり，約 65 名の治療が完了している．

また，現在も毎月発行される広報「にいじま」と共に全島民に配布する「大腸がん検診啓発活動の一環」としてパンフレットの送付を継続しており，今年 7 月～9 月にかけて実施予定としている第二期検診（第一期未受検者に対する検診）での受検率向上を目指している．

D．考察

本研究は，離島における将来の大腸がん検診体制の在り方を提案するための臨床研究として立案した．内視鏡検査の受検機会が乏しい地域に対して，内視鏡専門医が直接出向き，検診の重要性に関する啓発活動と検診としての大腸内視鏡検査の機会を提供することにより，どの程度の検診受診率向上と大腸がん罹患率の抑制が得られるか，

また非受検者に対するリコール（反復受診勧告）による受診率向上が得られるか否かについての検証が可能である．

E．結論

離島という人口動態の把握が比較的容易なコミュニティを対象とするため，研究データの信憑性は高く，今後長期的な検討（予後調査等）を行う上でも質の高い研究となるものと確信する．また，地域における患者支援という視点で考えた場合，島を離れず一度の内視鏡検査で大腸がん検診を完遂できることは，受検者のみならず関係市町村にとっても将来的に非常に大きなメリットとなると考えられる．本研究のモデルとなる新島村での研究成果に基づき，将来的にはその他の離島関係市町村における内視鏡介入型の新しい対策型大腸がん検診システムの構築が期待できる．

F．健康危険情報

報告すべき事項なし．

G．研究発表

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H．知的財産権の出願・登録状況（予定を含む）

出願・登録なし．今後申請の予定なし．

別紙４

研究成果の刊行に関する一覧表

雑誌

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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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Revised 2 February 2011
Accepted 2 February 2011
Published Online First 14 March 2011

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.

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.

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]

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

Gut 2011;**60**:1236—1241. doi:10.1136/gut.2010.221168

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	–	–	–	–

Gut 2011;**60**:1236–1241. doi:10.1136/gut.2010.221168

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

	Derivation cohort		Validation cohort		
Risk tier (RS)	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)	

Acknowledgements We would like to thank all members of the Asia-Pacific Working Group on Colorectal Cancer and the staff of all participating endoscopy centres for their contribution to the study.

The members of the Asia-Pacific Working Group on Colorectal Cancer are: China—Joseph J Y Sung, James Lau, W K Leung and Francis K L Chan (Hong Kong); M H Chen and C J Li (Guangzhou), Kai Chun Wu (Xi'an); India—R Tandon, Govind Makharia (New Delhi); Indonesia—Murdan Abdullah (Jakarta); Japan—Rikiya Fujita and Takahisa Matsuda (Tokyo); South Korea—Jeong-Sik Byeon Jin Yong Kim, Hyo Jong Kim, Won Ho Kim, Tae Il Kim, Sang-Kil Lee and Suk-Kyun Yang (Seoul); Malaysia—Ida Hilmi and K L Goh (Kuala Lumpur); Philippines—Jose Sollano, Euan Ong and Jose Tan (Manila); Singapore—Khek-Yu Ho and Khay-Guan Yeoh (Singapore); Taiwan—Han-Mo Chiu, Jaw-Town Lin and Cheng-yi Wang (Taipei); Deng-Chyang Wu and Huang-Ming Hu (Kaohsiung); Thailand—Pradermchai Kongkam, Pinit Kullavanijaya and Rungsun Rerknimitr (Bangkok); Australia—Rupert Leong (Sydney). The study is also supported by the Asia-Pacific Society of Digestive Endoscopy, which is an affiliate of Organisation Mondiale d'Endoscopy Digestive (OMED).

Competing interests None.

Ethical approval The domain-specific Review Board of the National Healthcare Group, Singapore approved 'Colorectal Neoplasm Risk Stratification in Asia Population'.

Contributors KGY, JJYS, KYH, HMC, DCW, TM, JSB, SKL, KLG, JS, RR, RL, JTL participated in the design and performance of the study, review of results, analysis and discussion. KGY, KYH, HMC, DCW, JSB, SKL, KLG, JS, RR, JTL, JJYS enrolled subjects for the study and contributed clinical data. FZ, JYLC, KFT managed and analysed the data and FZ performed statistical analysis. The manuscript was drafted by KGY and reviewed by all authors. All authors read and approved the final manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

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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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Gut 2011 60: 1236-1241 originally published online March 14, 2011
doi: 10.1136/gut.2010.221168

Cancer Science
The official journal of the Japanese Cancer Association JCA

Risk of lymph node metastasis in patients with pedunculated type early invasive colorectal cancer: A retrospective multicenter study

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(Received November 11, 2010/Revised February 14, 2011; May 20, 2011/Accepted May 25, 2011/Accepted manuscript online May 31, 2011/Article first published online July 21, 2011)

Depth of invasion in early invasive colorectal cancer is considered an important predictive factor for lymph node metastasis. However, no large-scale reports have established the relationship between invasion depth of pedunculated type early invasive colorectal cancers and risk of lymph node metastasis. The aim of this retrospective cohort study was to clarify the risk of lymph node metastasis in pedunculated type early invasive colorectal cancers in a large series. Patients with pedunculated type early invasive colorectal cancer who underwent endoscopic or surgical resection at seven referral hospitals in Japan were enrolled. Haggitt's line was used as baseline and the invasion depth was classified into two groups, head invasion and stalk invasion. The incidence of lymph node metastasis was investigated between patients with head and stalk invasion. We analyzed 384 pedunculated type early invasive colorectal cancers in 384 patients. There were 154, 156, and 74 endoscopic resection cases, endoscopic resection followed by surgical operation, and surgical resection cases, respectively. There were 240 head invasion and 144 stalk invasion lesions. Among the lesions treated surgically, the overall incidence of lymph node metastasis was 3.5% (8/230). The incidence of lymph node metastasis was 0.0% (0/101) in patients with head invasion, as compared with 6.2% (8/129) in patients with stalk invasion. Pedunculated type early invasive colorectal cancers pathologically diagnosed as head invasion can be managed by endoscopic treatment alone. (*Cancer Sci* 2011; 102: 1693–1697)

It has been reported that intramucosal colorectal cancers show no lymph node metastasis and are good candidates for endoscopic resection.[1,2] In contrast, 6–12% of early invasive colorectal cancers (i.e. cancer cells invade through the muscularis mucosae into the submucosal layer but do not extend into the muscularis propria) are associated with lymph node metastasis requiring surgical resection including lymph node dissection for curative treatment.[3–7] Recently, increasing evidence suggests that lesions with submucosal invasion limited to <1000 μm without lymphovascular invasion and/or poorly differentiated components do not metastasize to lymph nodes.[8] Endoscopic resection is an appropriate treatment for early stage colorectal cancers, however, the resected specimen must be examined to determine whether there is a clinically significant risk of lymph node metastasis that would warrant additional surgery. Colorectal lesions can be subdivided according to endoscopic appearance using the Paris classification (Fig. S1), whereas Haggitt's classification is frequently used to define the depth of invasion of pedunculated lesions.[9] Haggitt and colleagues stratified the level of cancer invasion according to the following criteria: level 0, carcinoma *in situ* (i.e. has not extended below the muscularis mucosae); level 1, carcinoma invading through the muscularis mucosae but limited to the head of the polyp (i.e. above the junction between the adenoma and its stalk); level 2, carcinoma invading the level of the neck (i.e. the junction between adenoma and its stalk); level 3, carcinoma invading any part of the stalk; and level 4, carcinoma invading into the submucosa of the bowel wall below the stalk (Fig. S2). The authors concluded a low risk of metastasis or local recurrence when the level is <4. Pedunculated lesions can easily be treated endoscopically, however, there are no large-scale reports establishing the risk of lymph node metastasis in this lesion type stratified by depth of invasion. We report the incidence of lymph node metastasis in pedunculated type early invasive colorectal cancers in a large series.

Materials and Methods

Patients. Patients with pedunculated type early invasive colorectal cancers that had been treated by endoscopic resection or surgical resection at seven institutions in Japan (National Cancer Center Hospitals [Tokyo, Kashiwa], Tokyo Medical University Hospital, Okayama University Hospital, Shizuoka Cancer Center, Tochigi Cancer Center, and Okayama Saisei-kai General Hospital) between January 1992 and December 2007 were examined retrospectively. Patients eligible for this study had pathologically proven adenocarcinoma invading through the muscularis mucosae into the submucosal layer but not extending deeply into the muscularis propria. Eligibility also required the lesion to be endoscopically diagnosed as pedunculated type suitable for one-piece resection. Patients with synchronous advanced colorectal cancer, multiple early invasive colorectal cancers, inflammatory bowel disease, hereditary non-polyposis colorectal cancer, and familial adenomatous polyposis were excluded from this study. This study was carried out with the approval of each institution's ethics review board.

Treatment strategy. *Endoscopic resection:* All lesions diagnosed as intramucosal or superficial submucosal invasive cancers at colonoscopy were removed by polypectomy or endoscopic mucosal resection. If the histopathological result did not meet the criteria for complete endoscopic resection, additional surgery was recommended. *Surgical operation:* Patients with endoscopic features suggestive of submucosal invasion into the stalk were referred directly for surgical operation (i.e.

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doi: 10.1111/j.1349-7006.2011.01997.x

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

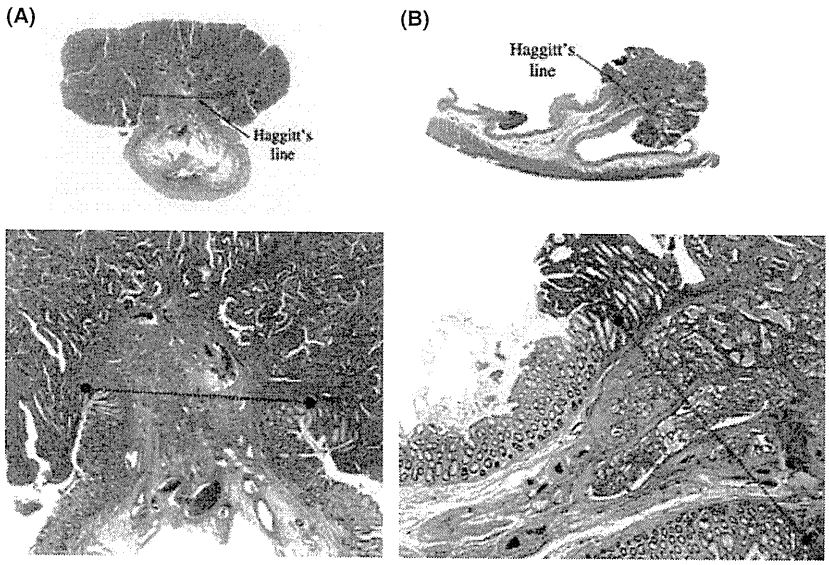

Fig. 1. Definition of head invasion (A) and stalk invasion (B) in pedunculated type early invasive colorectal cancer.

doi: 10.1111/j.1349-7006.2011.01997.x

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.

Acknowledgments

We would like to express our appreciation to Drs Abby Conlin (Department of Gastroenterology, Manchester Royal Infirmary, Manchester, UK) and Tonya Kaltenbach (Division of Gastroenterology, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA) for their assistance in editing this manuscript.

Disclosure Statement

None of the authors had any financial relationships relevant to this publication.

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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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Endoscopic management of colonoscopic perforations (with videos)

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INTRODUCTION

Colonoscopic perforation is a potentially life-threatening complication. Visual recognition of perforation or sites that are high risk to perforate at the time of the colonoscopy and its immediate closure offer the best potential for preventing any sequelae and for reducing its morbidity and mortality. Significant progress in endoscopic closure has been made since its first report by Yoshikane et al[1] over a decade ago. Herein, we summarize the literature on the prevalence, mechanisms, and diagnosis of perforations; review the results of experimental and clinical studies; and offer practical tips on the endoscopic closure of colonoscopic perforations (Fig. 1).

INCIDENCE

The incidence rates of colonoscopic perforations range from 0.07% to 0.1% in diagnostic and therapeutic colonoscopies, respectively (Table 1).[2-10] Most perforations occur in the rectosigmoid colon (53%), followed by the cecum (24%), the ascending and transverse colon (9% each), and the descending colon (5%).[9]

Risk factors for colonoscopic perforations include older age, female sex, increased comorbidity, diverticulosis, bowel obstruction, and biopsy or polypectomy.[7,8,10] The risk of colonoscopic perforation is lower for gastroenterologists as compared with surgeons and family physicians and further reduced for gastroenterologists with high procedure volumes.[10-12]

MECHANISMS

Colonoscopic perforation can result from a number of mechanisms including blunt trauma from the endoscope, unintended resection or dissection of the muscularis propria and serosa, and coagulation necrosis of the muscularis propria (Fig. 1) and serosa. Characteristics of perforations include:

(1) Blunt trauma (direct trauma, torque from the colonoscope, or retroflexion injury) accounts for the majority of colonoscopic perforations. Most are large (mean diameter 2 cm) and are located in the rectosigmoid colon.

(2) Unintended endoscopic resection or dissection (electrocoagulation biopsy, snare resection, EMR, or endoscopic submucosal dissection [ESD]) are the second most common reported cause of perforations. Most are small (mean diameter 1.4 cm) and are located in the cecum and right side of the colon.

- Electrocoagulation biopsy: The degree and duration of electrocautery used determine the risk of colon perforation.[13]
- Snare polypectomy: In a prospective study of 3976 snare polypectomies among 2257 patients from 13 German institutions, perforations occurred in 26 patients (1.2%). Polyps larger than 1 cm in the right side of the

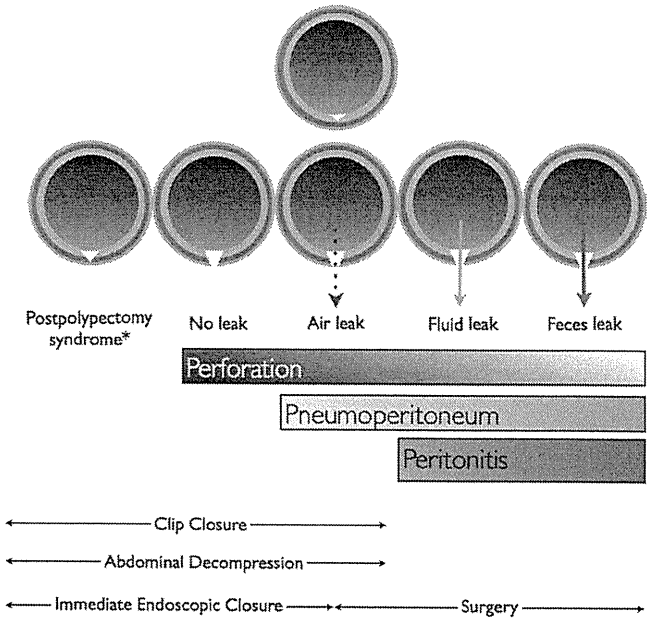

Figure 1. Perforation after colonoscopic resection can begin as postpolypectomy syndrome (serositis from transmural burn) that could evolve into a perforation or as a free perforation with air and fluid leakage, resulting in pneumoperitoneum and peritonitis. Immediate endoscopic closure could be useful before peritonitis develops. Prevention of postpolypectomy syndrome and its potential sequalae is most important.

Abbreviations:: ESD, endoscopic submucosal dissection.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

0016-5107/$36.00
doi:10.1016/j.gie.2011.08.007

TABLE 1. Summary of perforation rate in studies reporting over 10,000 colonoscopies

Study	Study period, (no. of colonoscopies)	Origin	Perforation rate (mortality)
1	1989-1999 (n= 23,508)	Australia[2] (Teaching hospitals)	1/1000 (0.04/1000)
2	1987-1996 (n= 10,486)	United States[3] (Mayo Clinic, Scottsdale)	0.019/1000 (0.0019/1000)
3	2002-2004 (n= 12,407)	United States[4] (Community GI group practice)	0.002/1000 (no deaths)
4	2000-2004 (n= 50,138)	Poland[5] (40 centers)	0.1/1000 (no deaths)
5	1991-1998 (n= 39,286)	United States[6] (Medicare beneficiaries ≥65 y)	2/1000
6	1994-2002 (n= 16,318)	United States[7] (Kaiser Permanente ≥40 y)	0.9/1000 (0.06/1000)
7	2002-2003 (n= 97,091)	Canada[8] (British Columbia, Alberta, Ontario, and Nova Scotia)	0.85/1000 (0.074/1000)
8	1980-2006 (n=258,248)	United States[9] (Mayo Clinic, Rochester)	0.7/1000
9	2004-2006 (n= 24,509)	Canada[10] (Winnipeg hospitals)	1.0/1000, colonoscopy alone 0.8/1000, sigmoidoscopy alone 0.5/1000, colonoscopy + biopsy 1.8/1000, colonoscopy + polypectomy 59.8/1000, colonoscopy + dilation (0.04/1000)

colon or 2 cm in the left side of the colon and multiple polyps carry an increased complication risk.[14]

- EMR: The risk of perforation after EMR is about 1 in 500 from pooled analysis of 17 reports.[15-31] The low perforation rate (0.7%) may be related to submucosal injection before snaring and electrocautery and routine use of clips to approximate the mucosal defect.[32]
- ESD: The risk of perforation after ESD can be as high as 1 in 20 (5%), although most were small and successfully treated by clips.[33-40] Thus, perforation during ESD rarely requires surgical closure. Inaccurate identification of the cutting line and underestimation of the depth of the submucosal layer may result in perforation. Endoscopist's experience of less than 50 ESDs, tumors larger than 5 cm, and underlying submucosal fibrosis (recurrent tumors and lateral spreading tumors of the nongranular type with converging folds) increase the risk of perforation.[41,42] Tumor location and morphology and the type of resection knives have no effect on the risk of ESD perforation.[40]

(3) Thermal injury (argon beam coagulation or electrocautery to ablate tissue or control bleeding) accounts for 18% of cases. Most of these perforations are small (0.9 cm) and are located in the cecum.

DIAGNOSIS

Recognition of perforation at the time of colonoscopy or high-risk sites for delayed perforation is important to prevent the dreadful complication of colonoscopy. About a third of perforations are diagnosed during the procedure and the remaining within 1 to 2 days after the procedure; a few cases present as late as 14 days.[2-4,10,14,43] Thus, the 14-day reporting period is important to capture all colonoscopic perforations.[43]

Diagnosis of perforation at the time of colonoscopy

Examination of the resection site is essential to ensure that perforation has not occurred. Routine injection of diluted indigo carmine into the submucosa can be helpful in determining the plane of resection—a blue resection base indicates intact submucosa; a white resection base indicates deeper resection into the muscularis propria. This has been described as a "target sign"—white center (muscularis propria), with surrounding blue area (indigo carmine stained submucosa).[44,45] A more subtle perforation may be recognized as shiny serosa seen through the defect (Fig. 2). Perforation also may appear as a rent in the muscularis propria during ESD or as an obvious tear in the sigmoid colon or rectum after blunt trauma.[40,46-51]

Another important physical sign is the development of tension pneumoperitoneum.[52] Thus, periodic assessment of the anterior abdominal wall tone is important.

Diagnosis of perforation after completion of the procedure

Perforation should be considered and appropriate workup performed when a patient complains of abdominal pain. A CT scan of the abdomen and pelvis are most sensitive in the detection of retroperitoneal air, even in the absence of free air under the diaphragm on plain abdominal radiographs.[53]