20111907A

別紙１

# 厚生労働科学研究費補助金

# がん臨床研究事業

# ポリープ切除の大腸がん予防に及ぼす効果の評価と内視鏡検査間隔の適正化に関する前向き臨床試験

## 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

# 目　　次

厚生労働科学研究費補助金（がん臨床研究事業）
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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**

本研究“ポリープ切除の大腸がん予防に及ぼす効果の評価と内視鏡検査間隔の適正化に関する前向き臨床試験：Japan Polyp Study（JPS）”は，我が国が誇る内視鏡を基盤とした初めての大規模な多施設共同前向き比較試験であり，平成15年2月より登録を開始した．平成18年12月末日（最終登録者数：3,926名）をもって登録を完了し，現在，割り付け後のフォローアップ全大腸内視鏡検査（TCS）と病理中央判定，割り付け前検査データの解析が進行中である．

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## A．研究目的

大腸がんの高危険群としては，腺腫性ポリープ患者の存在が知られているが，これらに対して内視鏡的な予防介入（内視鏡摘除）を行う場合，1）微小ポリープに対する摘除の必要性，2）全大腸内視鏡検査（TCS）による精検処理能の限界，3）平均的リスク群と高リスク群における適正な検査間隔の設定，4）ポリープ摘除によるがん罹患率抑制効果の有無，など様々な要件が未解決であり，これらに対して医療経済の側面を含めた科学的な回答を得ることが急務となっている．

上記 3），4）については，米国より1993年に報告された National polyp study（NPS）の成績から，平均的リスク群では3cm以下の全ての腺腫を摘除すること（クリーンコロン）で，その後の検査間隔は3年で良いこと，さらに，一般人口や腺腫を摘除しなかった過去のデータとの比較により，76～90%の大腸がん累積罹患率の減少が期待できると結論づけられた．しかし本邦では，内視鏡検査および腸管前処置の質の違いと，本研究開始に際して行った遡及的検討結果から，表面陥凹型がんの存在を無視した NPSの結果に基づくこのガイドラインを完全には容認できないという結論に至った．本研究は，わが国の平均的リスク群に対して NPSと同質の前向き介入試験を行うことで，クリーコロンにおける適正な検査間隔を求めるとともに，欧米とは異なる日本独自の検査体制の要否（表面陥凹型大腸がん診断の意義），内視鏡的ポリープ摘除が大腸がん罹患率減少に及ぼす効果の有無とその程度を明らかにすることを目的に本臨床試験プロトコールを作成し，各研究施設（11施設）の倫理審査委員会の承認を得て，平成15年2

月より登録開始となった.

B．研究方法

【対象】40 歳～69 歳の健常者

【目的】大腸がん罹患の超高危険群（家族性大腸腺腫症・遺伝性非ポリポージス性大腸がん）を除く，全ての腫瘍性ポリープを摘除した対象者に対する全大腸内視鏡(TCS)の至適検査間隔期間について，1年と3年後に行う2回検査群と3年後のみに行う1回検査群とのランダム化比較試験によって評価する.

・Primary endpoint:

クリーンコロン後のIndex lesion（10 mm以上の上皮性腫瘍・高度異型腺腫・がん腫）の発生割合.

・Secondary endpoint:

クリーンコロン後の全大腸腫瘍，陥凹型腫瘍，有害事象の発生割合.

尚，3年後のランダム化比較試験評価後は，浸潤がんの発生頻度，予後に関する長期経過観察から探索的検討を行う.

【除外・中止基準】

I）除外基準

1. 大腸切除の既往(虫垂切除は除く)
2. 大腸上皮性腫瘍に対する内視鏡切除の既往（既往病変について詳細な情報が確認されている場合は除外しない)
3. 炎症性腸疾患の既往，活動性感染性腸炎の現症
4. 家族性大腸腺腫症，遺伝性非ポリポージス性大腸がんの発端者または家系構成員
5. 重篤な合併症(活動性の他臓器がん)あり
6. クリーンコロン化困難例

II）中止基準

1. 1次・2次検査におけるクリーンコロン化不履行
2. 3 cm以上の広基性腫瘍が存在
3. sm以深大腸がんあり
4. 炎症性腸疾患および活動性感染性腸炎
5. Total colonoscopy不可能
6. 他，本研究計画に不適格と判断される大腸疾患あり

【参加施設】：全国11施設（国立がん研究センター中央病院・国立がん研究センター東病院・藤井隆広クリニック・昭和大学横浜市北部病院・昭和大学病院・佐久総合病院・服部胃腸科・栃木県立がんセンター・静岡がんセンター・北里大学東病院・大阪成人病センター)

【サンプルサイズ】

当初，登録期間3年・目標登録者数3,000人と設定したが，1次・2次TCSにて腺腫性ポリープを有さない群が約20%認められたためサンプルサイズの再算出を行い，3,700名を最終目標登録者数に修正するプロトコール変更申請手続きを行った.

【方法】

1）文書による同意取得，2）1次TCSにより腫瘍性ポリープ全てを内視鏡摘除，データセンターに登録，3）全例1年後に再検査（2次TCS）を行い，初回検査での見逃しを含めた全ての腺腫性ポリープの摘除を行いクリーンコロンとする．その後，データセンターから2回検査群（1年と3年後の検査）と，1回検査群（3年後に検査）の割り付け情報を入手，4）経過観察中にみられるIndex lesion: IL（10 mm以上の上皮性腫瘍，高度異型腺腫，がん腫）の発見割合を1回検査群と2回検査群間で比較し，クリーンコロン施行後3年間で2回検査が必要か，3年後の1回検査で十分かどうかを検証する.

尚，本研究のPrimary endpointは，ILの発見割合とし，1回検査群の3年後に発見されるIL発生割合と，1年と3年後の合計したIL発生割合の両群間の比較試験を行ない，2%以内を許容範囲とした非劣性試験である．

（倫理面への配慮）

本研究の実施に際しては，各参加施設（全国11施設）における倫理審査委員会での承認取得を前提条件とした．また，各施設にて生じる有害事象に関しては，モニタリング委員会（委員長：四国がんセンター 新海哲医師，他4名の医師より構成）を設置し，早急（72時間以内）に対処できるよう配慮している．

データ管理体制については，本研究に関する全ての試験データおよび参加患者プロファイルを匿名化し，データセンター（メディカル・リサーチ・サポート）による委託管理としている．外部からのデータ参照および抽出の防止には細心の注意を払っている．尚，本研究への参加については，十分な口頭での説明の上，文書による参加の同意を得ることを前提とした．また，患者側から試験中止の希望があった際には，患者意思を尊重し速やかに中止措置をとり，その後の診療においても患者不利益が生じないよう配慮している．

C．研究結果

現時点で，3,926 名の登録と 2,757 名の割り付け作業が完了し，2 回のクリーンコロン化とその後のフォローアップ TCS および病理中央判定が進行中である．割り付け状況は，2 回検査群（1.3 年後検査群）：1,087 名，1 回検査群（3 年後検査群）：1,079 名，腫瘍性ポリープ（-）群：591 名である．尚，平成 23 年 11 月末現在，3 年後の最終 TCS 完了者数は，2 回検査群：739 名，1 回検査群：802 名，腫瘍性ポリープ（-）群：416 名の合計 1,957 名であり，2,000 名近い参加者が順調に本試験を完遂している．

また，本試験に伴う重篤な偶発症および大きな問題は生じておらず，メインの結果（内視鏡的ポリープ摘除後の適正な検査間隔）が得られる平成24年末まで，参加者の脱落をいかに最小限に抑えられるかが最大の課題と考えている．

本年度は，クリーンコロン化1年後に発見されたIndex lesion（IL）の臨床病理学的特徴，1次・2次TCSにおける発見腫瘍性病変の関係についてのデータ集計および解析を開始した．

併せて，平成 23 年度末の班会議において，今後のデータ開示に関するディスカッションを行い，各種専門委員会（学術委員会・診断委員会・データベース作成管理委員会）の役割分担を再確認した．

D．考察

近年の内視鏡機器および診断・治療技術の向上にも関わらず，大腸がん罹患率・年齢調整死亡率は増加傾向にあり，その予防対策についての施策を講ずべき段階にある．わが国の検診システムは，便潜血反応によって集団から抽出された要精密検査群に対して，全大腸内視鏡検査が推奨されているが，その後に繰り返される経過観察例の増加も相まって，検査件数は増大の一途を辿っている．また，内視鏡医の不足，検査処理能力の限界，医療費の増大などが社会問

題ともなっている.

しかし，大腸がんは超高危険群（家族性大腸腺腫症，遺伝性非ポリポージス性大腸がん）を除けば，経過観察中に浸潤性大腸がんが発見されることは極めて少なく，適正な検査間隔指針の確立が求められている．本研究により，不必要な大腸内視鏡検査を減少させることが可能となり，医療経済学的に大きなメリットがあるものと考えられ，「がん対策基本法」の基本的施策に合致するものと思われる.

## E．結論

【JPS 第 1 期】平成 12 年～平成 14 年：遡及的検討および JPS プロトコール作成.
【JPS 第 2 期】平成 15 年～平成 18 年：試験参加登録者数（3,700 名）の達成.
【JPS 第 3 期】平成 19 年～平成 21 年： 1 次・2 次 TCS と割り付け作業の完了および割り付け後検査・病理中央判定の遂行.

以上の達成目標を設定し，本研究を進めてきた．平成 21 年末時点で，割り付け作業が完了し，フォローアップ TCS をいかに脱落なく遂行していけるかが本研究成功の最大の課題である．平成 23 年度以降は，JPS から得られるデータをさらに国内・外に向けて発信していく.

米国の National Polyp Study (NPS)では，1,400 名程度のサンプルサイズをもって，クリーンコロン後 3 年後のフォローアップの妥当性を論じている．しかし，長年，我が国から報告してきた表面・陥凹型大腸腫瘍の重要性が，ここ数年欧米でも更に注目されるに至り，本研究の臨床的意義が高まっている．一般に内視鏡的に発見することが難しいと言われている表面・陥凹型腫瘍に対しても十分注意を払った本研究結果は，海外研究者からもその結果が期待されている．最終結果が得られる平成 24 年まで，参加 11 施設が一丸となって本研究成功に向けて尽力している.

## F．健康危険情報

報告すべき事項なし.

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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

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Digestive Endoscopy
Journal for Gastroenterologists and Endoscopic Surgeons

*Digestive Endoscopy* (2011) **23**, 118–123 doi:10.1111/j.1443-1661.2010.01049.x

## ORIGINAL ARTICLE

# COMPARISON OF MAGNIFYING CHROMOENDOSCOPY AND NARROW-BAND IMAGING IN ESTIMATION OF EARLY COLORECTAL CANCER INVASION DEPTH: A PILOT STUDY

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**Background:** Several previous studies have identified narrow-band imaging (NBI) with magnification as being useful in evaluating early colorectal cancer invasion depth, but comparative diagnostic accuracy of invasion depth between pit pattern analysis using magnifying chromoendoscopy and NBI remains unclear. The aim of this retrospective study was to compare NBI and pit pattern analysis using magnifying chromoendoscopy in estimating early colorectal cancer invasion depth and to assess interobserver agreement.

**Patients and Methods:** We analyzed a total of 72 early colorectal cancers in 72 patients fulfilling the inclusion criteria. Each lesion image was subsequently reviewed by two experienced colonoscopists (A, B) and then classified clinically based on invasive/non-invasive pattern and Sano's capillary pattern classification with a five-point scale of confidence.

**Results:** In terms of diagnostic accuracy with confidence for A and B, the areas under the receiver operating characteristics curve were 0.84 and 0.81 for pit pattern analysis and 0.82 and 0.79 for NBI, respectively. Interobserver agreement for the diagnosis of submucosal deep (>1000 μm) invasion was evaluated for both modalities and indicated substantial agreement with pit pattern analysis ($\kappa = 0.63$) and moderate agreement with NBI ($\kappa = 0.44$).

**Conclusion:** Estimating invasion depth of early colorectal cancer using NBI appeared to have been comparable to pit pattern analysis, but there was greater interobserver variability using NBI.

**Key words: early colorectal cancer, narrow-band imaging, magnifying chromoendoscopy, invasion depth.**

## INTRODUCTION

Endoscopic therapy represents a major advance in the management of early gastrointestinal cancers. In the colorectum, lymph node metastasis invariably occurs only with submucosal deep invasion (≥1000 μm, SM-d).[1,2] Lesions diagnosed as well-differentiated adenocarcinomas limited to the mucosa (intramucosal, M) or as superficially invading the submucosa (<1000 μm from the muscularis mucosa, SM-s) without lymphovascular invasion or a poorly differentiated component (or both) are generally regarded as not involving lymph node metastasis.[3] Of these factors, however, only invasion depth can be endoscopically estimated before treatment. This characteristic emphasizes the importance of accurate estimation of depth prior to any therapeutic decision-making.

The efficacy of magnifying chromoendoscopy (MCE), not only in differentiating between colorectal neoplastic and non-neoplastic lesions,[4–6] but also in accurately determining invasion depth of early colorectal cancer, has widely been demonstrated.[7–13] Chromoendoscopy is operator-dependent and labor-intensive, however, and requires the use of staining solutions, spraying catheters, and several water rinses. These requirements have hampered its wider acceptance, particularly in Western countries, despite its demonstrated effectiveness.

Narrow-band imaging (NBI) is an innovative optical technology that uses interference filters to spectrally narrow the bandwidth used in conventional white light medical videoscopy. NBI allows more detailed visualization of the mucosal architecture and capillary pattern without the need for dye spraying. Although the usefulness of the NBI system in differentiating colorectal neoplastic from non-neoplastic lesions, as well as in estimating invasion depth, has been reported,[14–23] few studies have compared the usefulness of pit pattern analysis using MCE and NBI to estimate invasion depth of early carcinoma.

Here, we evaluated the use of NBI to estimate invasion depth in early colorectal cancer with diagnostic confidence in comparison with MCE using the invasive/non-invasive pattern classification of Matsuda and colleagues.[13] Additionally, we also assessed interobserver agreement for the two endoscopic modalities.

## METHODS

### Subjects

Seventy-two patients with 72 early colorectal cancers fulfilling the inclusion criteria were enrolled in this retrospective study (Table 1). A total of 3520 cases were present on our database and inclusion criteria were applied to these cases. These included all lesions observed with MCE using crystal

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Received 22 February 2010; accepted 10 May 2010.

violet staining and the NBI system; and all lesions diagnosed endoscopically as early colorectal cancer that underwent subsequent endoscopic or surgical resection. Images were taken of all lesions in the same condition using both MCE and NBI. Lesions diagnosed histopathologically as adenoma or advanced colorectal cancer as well as lesions with images judged to be of poor quality were excluded (Fig. 1). Images were taken by experienced colonoscopists, who were not reviewers, and analyzed by another experienced colonoscopist, who was also not a reviewer. The study protocol was approved by the ethics committee of the National Cancer Center Hospital, and written informed consent was obtained from all patients.

**Table 1.** Inclusion and exclusion criteria

| |
|---|
| Inclusion criteria |
| 1) All lesions observed by magnifying chromoendoscopy using crystal violet staining and NBI with magnification between April 2007 and March 2008 |
| 2) All lesions endoscopically diagnosed as early colorectal cancer that were subsequently treated by endoscopic or surgical resection |
| 3) Images taken of lesions in the same area |
| Exclusion criteria |
| 1) Lesions diagnosed histopathologically as adenoma or advanced colorectal cancer |
| 2) Images judged to be of poor quality |

NBI, narrow-band imaging.

### Endoscopic examination

All patients were prepared for colonoscopy with 2–3 L of polyethylene glycol-electrolyte solution administered on the morning of the examination. Scopolamine butylbromide (10 mg) or Glucagon (0.5 mg) was administered i.v. in patients without contraindications beforehand to minimize bowel movement. All procedures were performed by colonoscopists who had each performed more than 500 colonoscopies per year using magnifying colonoscopes (CF-H260AZI or PCF240ZI; Olympus, Tokyo, Japan), which enhance images up to 80–100 times using a one-touch operation power magnification system. A standard videoendoscopic system (EVIS LUCERA system; Olympus Optical, Tokyo, Japan) with two light sources was used, one for the standard optical broadband filter and the second for the NBI system.

Whenever a lesion was detected by standard colonoscopy, the system was switched to NBI by a single touch of the control section button to allow examination of the microvascular architecture. Indigo-carmine (0.4%) was then sprayed directly on the mucosal surface for pit pattern analysis after washing with proteinase to remove any overlying mucous. When high magnification observation with indigo-carmine spraying revealed an irregular pit pattern suspected of being type V, 0.05% crystal violet was applied for staining purposes.[9] In this study, all lesions were observed by MCE using crystal violet staining. After detailed observation, including imaging, all lesions were resected endoscopically or surgically.

### Histopathological examination

Resected specimens were fixed in 10% buffered formalin and cut into serial 5 mm slices for surgical specimens and 2 mm

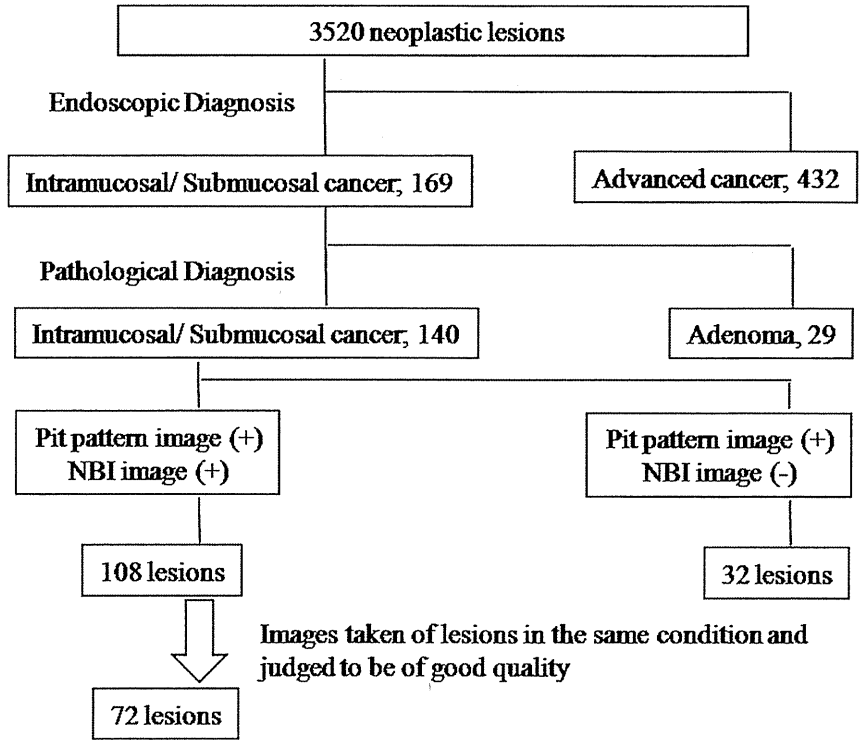


**Fig. 1.** Subject selection process in this study. NBI, narrow-band imaging.

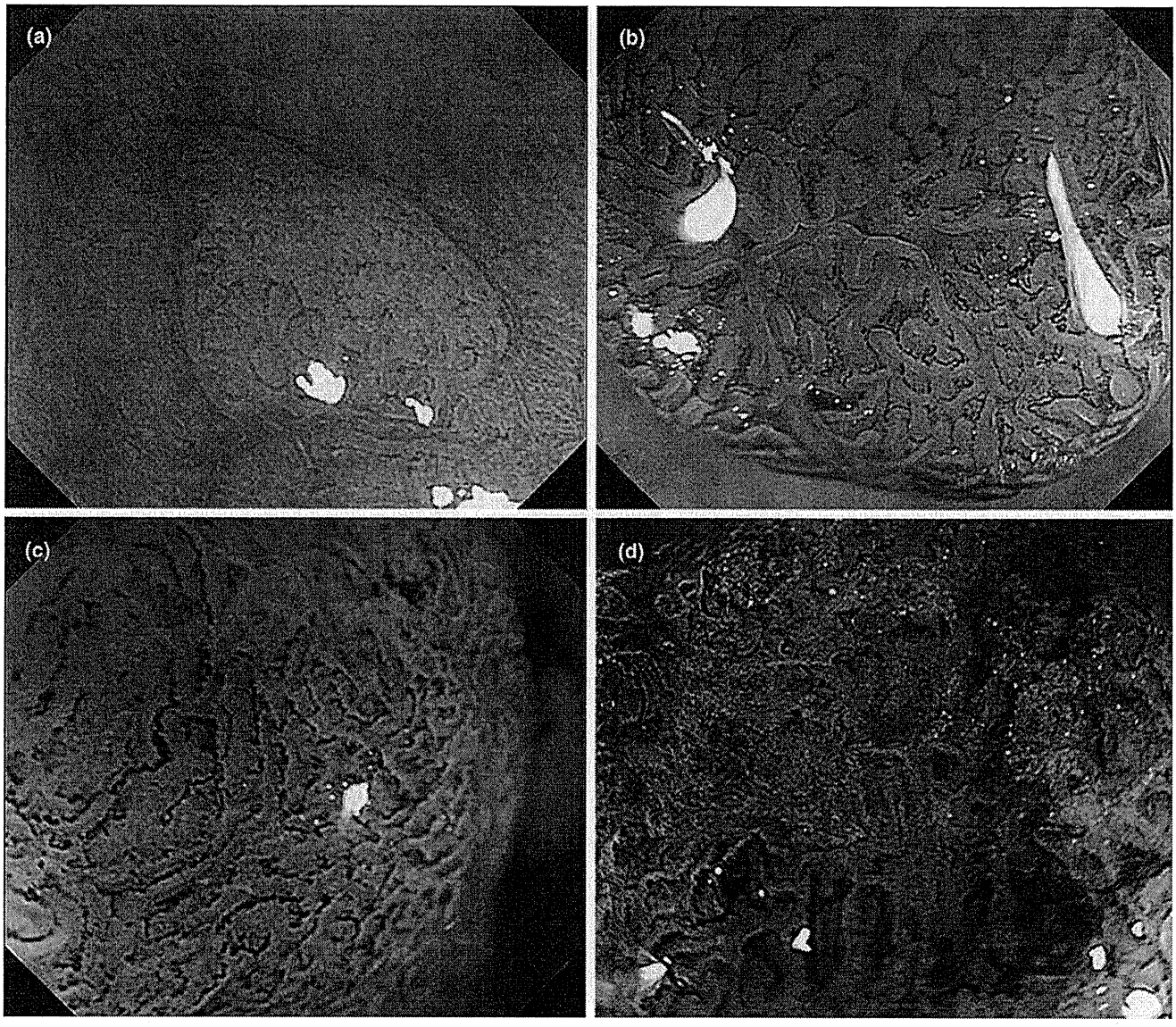


**Fig. 2.** Illustration of Sano's narrow-band imaging capillary pattern classification. (a) Faintly visible micro-vessels surrounding the pits (type I). (b) Elongated and increased thicker vessels surrounding the pits (type II). (c) Increased thick vessels unevenly sized with branching and curtailed irregularity (type IIIA). (d) Nearly avascular or loose vessels with fragmentation (type IIIB).

slices for endoscopic resection specimens. The slices were embedded in paraffin, cut into 3 μm sections and stained with hematoxylin–eosin, and microscopically examined for histological type by pathologists who specialized in gastrointestinal pathology. Histological diagnosis was based on the Japanese Research Society for Cancer of the Colon and Rectum and the Vienna classification.[24,25]

### Image evaluation

A total of 246 images of 72 lesions, excluding conventional images, were selected and grouped into two diagnostic modalities (i.e. MCE with crystal violet, 123 images; NBI with magnification, 123 images) in random order. The images were independently reviewed by two other senior colonoscopists (A and B), each with experience in more than 5000 cases of chromoendoscopy and NBI. Invasion depth was evaluated separately for each modality group without knowledge of lesion histopathology. Interobserver agreement in estimating invasion depth in early colorectal cancer was also assessed.

After review of mucosal crypt patterns observed with MCE, the lesions were classified using the clinical classification of Matsuda and colleagues.[13] All neoplastic lesions were classified into two categories: a non-invasive pattern predicting adenoma or carcinoma with M/SM-s invasion and an invasive pattern predicting carcinoma with SM-d invasion.

On reviewing microvascular architecture with NBI, four different patterns were identified according to Sano's classification.[19–22] In this classification, capillary pattern type III suggests 'carcinoma', and invasion depth was subsequently classified by examining the lesion's microvessel pattern with NBI as either M/SM-s (high-density vessels

showing unevenly sized thicker capillaries with branching and curtailed irregularity; capillary pattern IIIA) or SM-d (nearly avascular or loose microvessel diameters; capillary pattern IIIB) (Fig. 2). Diagnostic accuracy of the two endoscopic modalities was determined by reference to the histopathological findings.

### Statistical analysis

Reviewers graded the estimated invasion depth using a five-point scale of diagnostic confidence: 1, definite adenoma or M/SM-s; 2, probable adenoma or M/SM-s; 3, indeterminate; 4, probable SM-d; and 5, definite SM-d. Diagnostic accuracy was evaluated using receiver operating characteristic (ROC) analysis based on calculation of the area under the ROC curve (Az). In addition, the sensitivity, specificity and overall accuracy of diagnosis of invasion depth were evaluated for each modality by comparing endoscopic and final histopathological diagnoses. Kappa (κ) statistics with 95% confidence intervals (CI) were used to test for interobserver agreement using the arbitrary interpretation of Landis and Koch (0, 'poor' agreement; 0.00–0.20, 'slight' agreement; 0.21–0.40, 'fair' agreement; 0.41–0.60, 'moderate' agreement; 0.61–0.80, 'substantial' agreement; and 0.80–1.00, 'almost perfect' agreement).[26]

**Table 2.** Clinicopathological features of colorectal lesions

| | |
|---|---|
| No. of lesions | 72 |
| Macroscopic type | |
| Polypoid | 14 |
| Flat elevated | 34 |
| Depressed† | 24 |
| Mean size of lesions (range) (mm) | 20 (10–120) |
| Location | |
| Right colon† | 25 |
| Left colon‡ | 23 |
| Rectum | 24 |
| Invasion depth | |
| M/SM-s | 49 |
| SM-d | 23 |
| Histopathology | |
| W/D | 65 |
| W/D + M/D | 6 |
| M/D | 1 |

†Cecum-transverse colon; ‡Descending-sigmoid colon.
M, mucosal invasion; M/D, moderately differentiated adenocarcinoma; SM-d, submucosal deep invasion; SM-s, submucosal superficial invasion; W/D, well-differentiated adenocarcinoma.

## RESULTS

Clinicopathological features of the lesions are summarized in Table 2. Morphologically, there were 14 polypoid, 34 flat elevated, and 24 depressed lesions. Mean size of the lesions was 20 mm (range 10–120 mm). Twenty-five were right-sided colon lesions, 23 were left-sided colon lesions, and 24 were rectal lesions. Histopathological analysis revealed carcinoma with M/SM-s in 49 lesions (68%) and carcinoma with SM-d in 23 (32%). Sixty-five (90%) lesions were well-differentiated adenocarcinomas, six (8%) were well- and moderately differentiated adenocarcinomas and one (2%) was a moderately differentiated adenocarcinoma.

Table 3 shows the results of each modality by reviewer. For reviewer A, visualization of lesions by the pit pattern analysis with MCE and NBI with magnification revealed sensitivity of 60.9% and 60.9%, specificity of 93.6% and 93.9%, and diagnostic accuracy of 82.9% and 83.3%, respectively, for SM-d invasion; while reviewer B achieved a sensitivity of 82.6% and 78.3%, specificity of 73.5% and 77.6%, and diagnostic accuracy of 76.4% and 77.8%, respectively.

Az was 0.84 for pit pattern analysis with MCE versus 0.82 with NBI for reviewer A and 0.81 versus 0.79 for reader B, respectively (Fig. 3).

Interobserver agreement for diagnosis of SM-d invasion for each modality indicated substantial interobserver agreement for pit pattern analysis with MCE ($\kappa = 0.63$) and moderate agreement for NBI with magnification ($\kappa = 0.44$) (Table 4).

## DISCUSSION

To our knowledge, this is the first report to compare the diagnostic performance of NBI with magnification and magnifying chromoendoscopy (i.e. pit pattern analysis) in evaluating the depth of invasion of colorectal neoplasms, based on diagnostic confidence and interobserver agreement. Conventional images were excluded because they would have been a major bias in the course of this study. Results showed that NBI had comparable accuracy to pit pattern analysis using MCE, which has been reported to be one of the most reliable methods for this assessment.[13,27,28]

**Table 3.** Performance of endoscopic modalities in estimation of invasion depth

| Reviewer A | | | |
|---|---|---|---|
| | Sensitivity (95%CI) | Specificity (95%CI) | Accuracy (95%CI) |
| Pit pattern | 60.9 (46.6–69.0) | 93.6 (86.7–97.6) | 82.9 (73.5–88.2) |
| NBI | 60.9 (46.6–69.0) | 93.9 (87.2–97.7) | 83.3 (74.2–88.5) |
| **Reviewer B** | | | |
| | Sensitivity (95%CI) | Specificity (95%CI) | Accuracy (95%CI) |
| Pit pattern | 82.6 (66.7–92.5) | 73.5 (66.0–78.1) | 76.4 (66.2–82.7) |
| NBI | 78.3 (62.2–89.3) | 77.6 (70.0–82.7) | 77.8 (67.5–84.8) |

CI, confidence interval; NBI, narrow-band imaging.

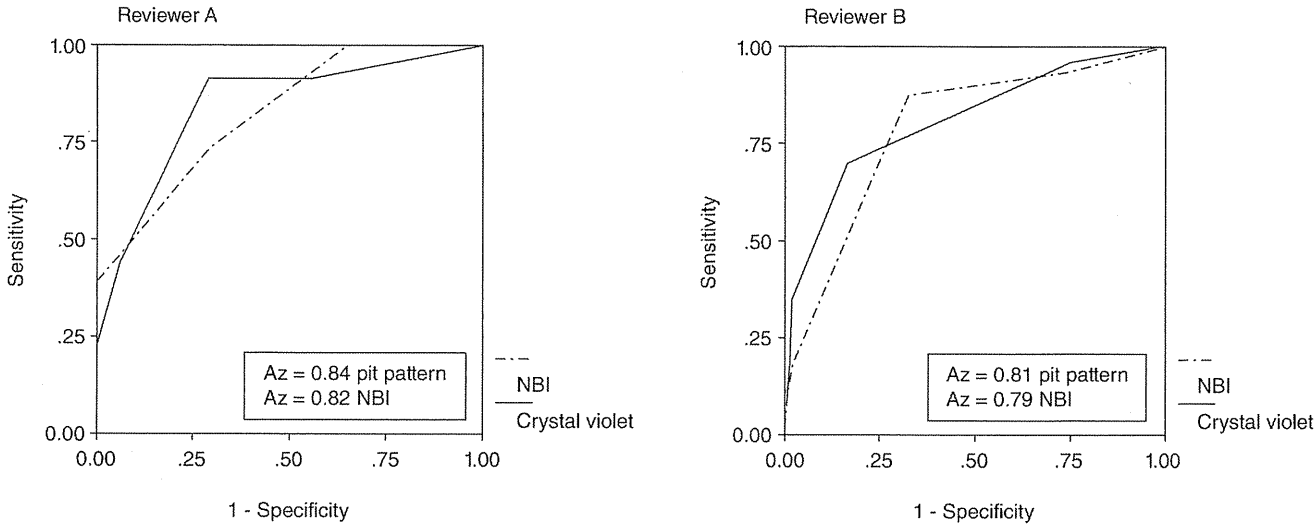


**Fig. 3.** Receiver operating curves of two reviewers. NBI, narrow-band imaging.

**Table 4.** Agreement between colonoscopists for each modality

| Modality | Value of κ (95%CI) | Strength of agreement |
|---|---|---|
| Pit pattern | 0.63 (0.44–0.82) | Substantial |
| NBI | 0.44 (0.22–0.67) | Moderate |

CI, confidence interval; NBI, narrow-band imaging.

Although sensitivity and specificity are generally accepted methods for quantifying morphological diagnostic ability, no study has reported diagnostic ability based on relative levels of confidence. In this study, the estimated depth of invasion of all lesions was scored on a five-point confidence scale. The data were analyzed by ROC analysis, which has been widely used in medical radiology imaging studies to investigate the effects of individual parameters on an imaging system or to compare the performance of different systems.[29,30] ROC analysis is considered optimal with regard to sensitivity if the Az is between 0.75 and 0.80.[31] Our ROC curves were therefore close to optimal. Based on the plotted ROC curves, the NBI system is also comparable to pit pattern analysis with MCE in terms of estimating invasion depth.

We also assessed interobserver agreement in estimating depth invasion for each modality and found 'substantial' agreement for pit pattern analysis with MCE and 'moderate' agreement for NBI with magnification. This moderate result indicates some variation in the reviewers' interpretation of irregularity in the microvascular architecture observed by the NBI system with magnification. As for such lower interobserver agreement in the interpretation of the NBI findings, we should remember that the NBI system is still a relatively new diagnostic method with an unknown learning curve and several different classifications for the evaluation of mucosal morphology in colorectal neoplasms have been proposed recently in Japan, further complicating the matter. As for consensus on microvascular architecture and the classification of findings, there has not yet been enough discussion worldwide as to how use of NBI can become a reality.

Chromoendoscopy with magnification requires considerable time for removing mucous and dye spraying. In contrast, the advantages of NBI include its convenience without the need and additional cost of dye spraying, and the ability to alternate between conventional and NBI images with a single touch of a button on the handle of the scope. If interobserver agreement appreciably improves and a consensus can be reached with regard to microvascular architecture and the classification of findings, it is conceivable that NBI could replace MCE for the diagnosis of invasion depth.

Several limitations of our study warrant mention. First, as this was a pilot study, all images were taken and evaluated by only two colonoscopists experienced in magnification endoscopy. Second, all evaluations were based on the retrospective analysis of still images, which can differ considerably from live endoscopic assessment of specific areas because it does not permit examination of a lesion from different angles and distances. Third, subjects were limited to those with intramucosal and submucosal carcinoma diagnosed pathologically. In this study, we focused on the relevance of diagnostic performance in estimating the depth of invasion in early colorectal cancer, based on our consideration that this is one of the most important clinical purposes of magnifying endoscopy. Moreover, we considered that investigation of the endoscopic differentiation and histopathological characteristics of adenoma and carcinoma was outside the scope of this study. Comprehensive evaluation of the effectiveness of conventional colonoscopy, MCE and NBI with magnification will require prospective multi-center trials involving endoscopists with varying backgrounds and degrees of experience.

In conclusion, our results suggest that the accuracy of the NBI system with magnification in estimating the invasion depth of colorectal neoplasms is comparable to that of pit pattern analysis with MCE. However, NBI showed greater variability in the interpretation of irregularities in microvascular architecture. These findings indicate that further evaluation of pit pattern analysis with MCE in estimating the

invasion depth of early colorectal cancer should be undertaken as a matter of priority.

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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

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 $\chi^2$ 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 $\chi^2$ 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 | Neoplasia, n=168 | | Advanced neoplasia, n=39 | |
|---|---|---|---|---|---|
| | Prevalence (%) | 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) | |