A Multicenter Prospective Study of Immunochemical Fecal Occult Blood Testing for Colorectal Cancer Detection

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Background: *Colorectal cancer (CRC) screening by guaiac fecal occult blood test (gFOBT) can reduce the mortality of CRC. The new immunochemical fecal occult blood test (iFOBT) has possibly improved sensitivity and specificity without any dietary restriction.*
Objective: *The present study aimed to evaluate the sensitivity, specificity, positive and negative predictive values of iFOBT for CRC detection compared to the colonoscopic and pathologic findings in known CRC cases.*
Material and Method: *A multicenter prospective study was conducted in three university hospitals in Bangkok, Thailand, between May and August 2006. Stool samples from 100 histologically-proven CRC patients and 64 control cases with normal colonoscopic findings were collected for iFOBT (OC-Light, Nagase, Singapore) without dietary restriction.*
Results: *The results showed the sensitivity, specificity, positive and negative predictive values of iFOBT for CRC detection to be 91.0% (95% CI: 83.8-95.2), 93.8% (95% CI: 85.0-97.5), 95.8% (95% CI: 89.7-98.4) and 87.0% (95% CI: 77.0-93.0) respectively. The sensitivity for CRC according to Dukes' stage was 71.4% (Dukes' A), 88.0% (Dukes' B), and 96.7% (Dukes' C or D). The sensitivity was 84.2% for proximal colon and 92.6% for distal colon and rectum.*
Conclusion: *The iFOBT revealed high sensitivity, specificity, positive and negative predictive values for CRC detection without dietary restriction. It should be considered as a noninvasive tool for CRC detection.*

Keywords: *Immunochemical fecal occult blood test, FOBT, Colorectal cancer, Sensitivity, Specificity, Accuracy*

J Med Assoc Thai 2007; 90 (11): 2291-5
Full text. e-Journal: *http://www.medassocthai.org/journal*

Colorectal cancer (CRC) is one of the leading causes of cancer death in Thailand. CRC screening was shown to decrease CRC incidence by 20% and mortality by 33%[1]. Fecal occult blood testing (FOBT) has been used as a screening test for more than three decades because it is inexpensive and noninvasive. Based on the detection of peroxidase activity in the stool sample, traditional guaiac FOBT (gFOBT) has poor sensitivity and specificity for CRC and requires dietary restrictions before testing[1,2]. New immunochemical FOBT (iFOBT) has possibly improved the sensitivity and specificity requiring no dietary restriction[3]. However, the results of iFOBT remain controversial and no CRC screening by iFOBT in Thai people has ever been reported.

The aim of the present study was to determine the sensitivity, specificity, positive predictive value, and negative predictive value of iFOBT for CRC detection and to compare the results with the colonoscopic and pathologic findings.

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Material and Method

A multicenter prospective study was conducted in the departments of Surgery, Faculty of Medicine Siriraj Hospital, Pramongkutklao Hospital and Rajavithi

Hospital, Bangkok, Thailand, between May 2006 and August 2006. A series of patients with histologically-proven CRC who were scheduled for elective oncological resection, and control cases with normal colonoscopic findings were enrolled. Ethics committee approval was obtained at each center prior to the study commencement, and each patient provided written informed consent to participate in the present study.

Patients with CRC would be excluded from the present study for one of the following reasons: age below 18 years, time interval between colonoscopic biopsy and operation less than two weeks, recurrent colorectal cancer, preoperative chemoradiation, active or gross gastrointestinal bleeding, menstruation, aspirin or non-steroidal anti-inflammatory drug usage, administration of heparin or anticoagulant, unresectable locally advanced tumors considered by surgeons in the operative field, and consent refusal. Distant metastasis was not an exclusion criterion as the authors studied only locoregional disease in this paper.

In the CRC patients, one sample of spontaneously passed stool from the day before mechanical bowel preparation (two days prior to operating date) was examined.

Control cases were asymptomatic subjects who showed normal colonoscopic findings on their routine check-up program. They collected stool samples in collection kit by themselves in the morning on the day of the colonoscopy.

All the stool samples were examined without rehydration. They were subjected to iFOBT (OC-Light, Nagase, Singapore) by well-trained investigators in each institute. A small portion of fecal material was transferred to a plastic spiral rod attached to the lid of the iFOBT kit. A chromatography strip would be placed in the resulting suspension and allowed to develop, approximately three minutes. A single, distal transverse line indicates a negative result, whereas two lines indicate a positive result. A positive result on any specimen was considered as iFOBT positive. Consequently, patients would be categorized as iFOBT positive or negative.

All the CRC patients underwent standard oncological resection. All specimens were sent for histopathological examination. Tumor and lymph node status were reported by using TNM classification as well as modified Dukes' clinicopathologic classification of CRC[4].

Sensitivity, specificity, positive predictive value, and negative predictive value were analyzed with 95% Confidence Interval (95% CI) Analysis for Windows (Statistics with Confidence, 2nd Edition, BMJ Books, London 2000).

Results

One hundred patients with histologically proven CRC (CRC group) and sixty-four subjects with normal colonoscopic findings (control group) were enrolled. In the CRC group, there were forty-nine males (49%) with a mean age of 63 (range, 23-82) years and a mean tumor size of 4.9 (range, 1-12) cm.

Of the histologically proven CRC patients, iFOBT was positive in ninety-one cases (91%) as shown in Table 1. Of the control group, iFOBT was positive in four cases (6.3%). Therefore, the overall sensitivity, specificity, positive predictive value, and negative predictive value of iFOBT for CRC detection were 91.0% (95% CI: 83.8 to 95.2), 93.8% (95% CI: 85.0 to 97.5), 95.8% (95% CI: 89.7 to 98.4), and 87.0% (95% CI: 77.0 to 93.0) respectively.

The sensitivity for invasive cancer according to Dukes' stage showed 71.4% for Dukes' stage A, 88.0% for Dukes' stage B, and 96.7% for Dukes' stages C or D. In addition, the sensitivity for invasive cancer according to location of the tumor revealed 84.2% for proximal colon (proximal to splenic flexure) and 92.6% for distal colon and rectum.

Discussion

In 2002, the American Cancer Society (ACS) Colorectal Cancer Advisory Group concluded the iFOBT had some advantages that merited revision of their guideline statement for FOBT to include iFOBT[5]. In this study, the authors evaluated the diagnostic

Table 1. Results of iFOBT in CRC and control groups

Cases	CRC group	Control group	Total cases
Number of Positive iFOBT	91	4	95
Number of Negative iFOBT	9	60	69
Total cases	100	64	164

validity of iFOBT (OC-Light) for CRC in Thai patients. This iFOBT uses immunochromatography technique to detect human hemoglobin's intact globin protein and results in a positive test result. Occult blood detection using this system is sensitive to a level of 50 ng Hb/ml of buffer in accordance with the product brochure.

In this present study, the sensitivity of iFOBT for CRC was slightly higher than that of iFOBT previously reported (69-88%)[6,7]. This may be due to differences in the population studied (previous studies included only asymptomatic patients), advanced staging of the tumors and probable previous biopsy two weeks prior to the test.

Similar to the large study of iFOBT by Morikaya[8], the present study found that iFOBT was slightly less sensitive for proximal colon than distal colon or rectal tumors. One possible explanation is that stool in the distal colon is more solid and easily causes occult bleeding of the tumors during bowel movement or defecation.

The specificity of this iFOBT for CRC was comparable to the values quoted by other studies (88-99%)[9,10] which had higher specificity than gFOBT. In the recent publication by Fraser et al[11], iFOBT also substantially decreased the number of false positives in a screening program for CRC by gFOBT. The reason is that iFOBTs generally use monoclonal or polyclonal antibodies to detect human hemoglobin's intact globin protein. Labeled antibody attaches to the intact globin antigen and results in a positive test result. The globin protein does not remain intact after passage through the upper gastrointestinal tract. A positive iFOBT is, therefore, specific for bleeding in the lower gastrointestinal tract and not affected by diet or medications[12]. Contrary to iFOBT, the result of gFOBT is based on the detection of nonspecific peroxidase activity in the stool sample. However, positive iFOBT may result from other causes of lower gastrointestinal bleeding such as angiodysplasia, colitis, diverticulitis and bleeding hemorrhoid.

Of the 64 patients with macroscopically normal colonoscopic finding, four patients (6.25%) had a false positive result of iFOBT, whereas the other investigators reported 3.4-6.0%[13,14]. The possible explanation is that mechanical bowel preparation may lead to vigorous peristalsis and occult bleeding from microscopic colonic lesion, or there is an undiagnosed lesion of the small bowel or upper gastrointestinal bleeding[15]. On the other hand, 9% false negative result can be explained by the nature of the tumors in which intermittent bleeding is more common than continuous bleeding, and the rate of bleeding may be less than hemoglobin threshold of the iFOBT test, especially in the early stage or small tumors. Two or three consecutive sample FOBT testing is therefore recommended for colorectal cancer screening and should be repeated annually[16].

Although the iFOBT can identify patients with CRC to a certain extent, the sensitivity of CRC detection is relatively poor in proximal colon cancer and early staging of CRC. Therefore, further investigations including colonoscopy may be necessary to perform in highly suspected CRC patients.

In conclusion, the iFOBT showed high sensitivity, specificity, positive predictive value, and negative predictive value for CRC detection without dietary restriction. It should be considered as a noninvasive tool for CRC detection.

Acknowledgement

This study was supported by the Society of Colon and Rectal Surgeons Thailand.

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การศึกษาผลการตรวจหาเลือดในอุจจาระโดยวิธีเคมีอิมมูโน

วรุตม์ โล่ห์สิริวัฒน์, ปริญญา ทวีชัยการ, บุรินทร์ อาวพิทยา

การตรวจหาเลือดในอุจจาระเป็นวิธีตรวจกรองโรคมะเร็งลำไส้ใหญ่และลำไส้ตรงที่ช่วยลดอัตราตายจากมะเร็งนี้ได้ การตรวจหาเลือดในอุจจาระโดยวิธีเคมีอิมมูโน (iFOBT) ได้รับการพัฒนาขึ้นมาใช้ให้มีความไวมากขึ้น จำเพาะมากขึ้น โดยไม่ต้องจำกัดอาหารก่อนตรวจ การศึกษาครั้งนี้มีจุดประสงค์เพื่อประเมินความไว ความจำเพาะ ค่าทำนายเชิงบวกและค่าทำนายเชิงลบ ของ iFOBT ในการตรวจหามะเร็งลำไส้ใหญ่และลำไส้ตรง โดยเปรียบเทียบกับผลการตรวจด้วยการส่องกล้องและผลการตรวจทางพยาธิวิทยาในผู้ป่วยโรคมะเร็งดังกล่าวที่พิสูจน์ทราบแน่แล้ว ศึกษาในโรงพยาบาลที่เป็นโรงเรียนแพทย์ 3 แห่งในกรุงเทพมหานคร ในช่วงเดือนพฤษภาคม ถึง สิงหาคม พ.ศ. 2549 เก็บอุจจาระจากผู้ป่วยมะเร็งลำไส้ใหญ่และลำไส้ตรงที่มีผลยืนยันทางพยาธิวิทยาแล้ว 100 ราย และกลุ่มควบคุมที่ได้รับการส่องกล้องตรวจลำไส้ใหญ่แล้วไม่พบความผิดปกติ 64 ราย ตรวจอุจจาระด้วยชุดตรวจ iFOBT (OC-light, Nagase, สิงคโปร์) โดยไม่ต้องจำกัดอาหาร การตรวจโดย iFOBT ได้ผลดังนี้ ความไว 91.0% (95% CI: 83.8-95.2), ความจำเพาะ 93.8% (95% CI:85.0-97.5) ค่าทำนายเชิงบวก 95.8% (95% CI:89.7-98.4) และค่าทำนายเชิงลบ 87.0% (95% CI:77.0-93.0) เมื่อแบ่งกลุ่มผู้ป่วยตามความรุนแรงแบบ Dukes พบว่าการทดสอบนี้มีความไว 71.4% สำหรับ Dukes' A, 88.0% สำหรับ Dukes' B, และ 96.7% สำหรับ Dukes' C และ D ถ้าแบ่งตามตำแหน่งของก้อนมะเร็ง iFOBT มีความไว 84.2% สำหรับมะเร็งส่วนต้นของลำไส้ใหญ่ และ 92.6% สำหรับมะเร็งส่วนปลายของลำไส้ใหญ่ สรุปว่า iFOBT มีความไวสูง ความจำเพาะสูง ค่าทำนายเชิงบวกและเชิงลบสูง ในการตรวจหามะเร็งลำไส้ใหญ่และลำไส้ตรง โดยไม่ต้องจำกัดอาหารเป็นเครื่องมือที่ใช้ได้ดีโดยไม่รบกวนผู้ถูกตรวจ