



A retrospective study of immunochemical fecal occult blood testing for colorectal cancer detection

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ABSTRACT

Background: Colonoscopic examination is the common pathway for positive screening tests detecting colorectal lesions. We evaluated a specific, quantitative high-throughput automatic immunochemical fecal occult blood test (Auto iFOBT) method for colorectal cancer (CRC) screening and to determine its concordance with physician assessments informed by complete colonoscopy, the gold-standard technique for evaluation of the colonic mucosa.

Methods: 1200 CRC symptomatic patients were recruited for a retrospective investigation. Colorectal neoplasia were localized by colonoscopy and cancer outcomes were enumerated according to severity. In addition, stool samples were collected and analyzed by Auto iFOBT to derive sensitivity, specificity, and positive predictive value. Qualitative colonoscopy and Auto iFOBT results were correlated, as were cancer severities and quantitative hemoglobin concentrations.

Results: Ninety-one patients were found positive for CRC; 50 mucosal, 20 submucosal, and 21 advanced. At standard cutoff, sensitivity was 60%, 90%, and 95%, respectively. Specificity and positive predictive value for all neoplasia and cancers were 89.6% and 86.4%, and 60.9% and 33.7%, respectively. Cancer severities could be approximated roughly according to hemoglobin concentrations.

Conclusions: Specific qualitative 2-day Auto iFOBT is an accurate tool for the detection of colorectal cancer and therefore provides the basis for a large-scale screening program.

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1. Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer death in all industrialized countries. In Japan, CRC has increased steadily both in its incidence and in mortality [1]. Effective screening methods have been shown to decrease CRC incidence by 20% and mortality by 33% [2]. Fecal occult blood testing (FOBT) is known to be the simplest and least expensive noninvasive

approach to CRC screening available yet has several disadvantages. Traditional guaiac FOBT (gFOBT), based on the detection of peroxidase activity in the stool sample, exhibits poor sensitivity and inadequate specificity. Consequently, reagents bind to non-human hemoglobin-like substances in feces, such as animal myoglobin and plant peroxidases. As the presence of these substances in the colon and rectum are the likely result of common eating patterns, curtailing hemoglobin mimicry requires dietary restriction and makes patient compliance a potential confounding variable [2,3]. The newer approach, immunochemical FOBT (iFOBT), exhibits improved sensitivity and specificity and involves no dietary restriction, resulting in fewer abnormalities due to interfering substances [4]. In the current study, we perform a 2 day diagnostic regimen evaluating a specific qualitative iFOBT high-throughput automatic analyzer (Auto iFOBT) as compared to total colonoscopy, and analyze the method for assay sensitivity, specificity, positive predictive value and usefulness in approximate localization of CRC.

Abbreviations: CRC, colorectal cancer; FOBT, fecal occult blood test; gFOBT, guaiac fecal occult blood test; iFOBT, immunochemical fecal occult blood test; Auto iFOBT, specific, quantitative high-throughput automatic immunochemical fecal occult blood test.

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2. Materials and methods

From June 2007 to June 2008, 1200 patients thought to be symptomatic for a range of colorectal disorders following either point-of-care rapid test or physician examination were referred to the Tokyo Metropolitan Cancer Detection Center and scheduled for colonoscopy. Patients recruited for this study, after being fully briefed and providing written informed consent, were asked to obtain two fecal samples at home on 2 separate days within the 5 days prior to colonoscopy using a hygienic sample collection kit. The collection kit is comprised of two specimen collection containers, 2 sheets of specimen collection paper, and an instruction page in a sanitary resealable plastic bag provided by the manufacturer (Nescauto®Hemo Plus: Alfresa Pharma Corp., Osaka, Japan). Samples were then sent to a central testing center for qualitative analysis and quantification by means of a high-throughput diagnostic automatic analyzer (Hemo Techt NS-Plus® C, Alfresa Pharma). According to the manufacturer's instructions, the test is considered positive when at least one of the two samples contains at least 100 ng/ml of hemoglobin.

Patient colonoscopy was performed to the cecum or up to an obstructing carcinoma if present. If a colonoscopy was incomplete because of obstructing tumors, or if an incomplete colonoscopy was completed by another manner of colonic examination (i.e., double-contrast barium enema) that failed to reveal any lesion, the results were included in the analysis. The location and size histologies of colorectal neoplasias were recorded according to standard protocols. In this study, adenomas are classified as with non-malignant, benign polyps rather than pre-phase cancers; hyperplastic polyps were not included as carcinomas. Cancers are divided histological invasion depth into three representative bands, mucosal, submucosal, or advanced, according to standard protocols. As such, cancers falling into the mucosal band are deemed early phase curable carcinomas and both submucosal and advanced cancers are judged to be invasive cancers. If a subject had more than one lesion, subject was classified according to the most advanced pathological lesion and included in the analysis. Endoscopic resection or surgery was performed for patients diagnosed with either adenoma or CRC.

3. Results

The Auto iFOBT tests and colonoscopy were performed successfully in 1073 patients participating in the study. Demographic data and endoscopic findings for these patients were tabulated (Table 1). The mean patient age was 65.0 years. Fifty-two percent of patients were male, and all were ethnically Japanese. Colonoscopies were normal for 743 patients. Two-hundred twenty-four patients were found to have adenomatous polyps, and 91 were positive for CRC. Of the CRC positive group, 50 patients had mucosal cancer, 20 patients had submucosal cancer, and 21 patients had advanced cancer. Auto iFOBT was positive in 202 patients (18.8%), and negative in 871 patients (81.2%). We

calculated the sensitivity, specificity and positive predictive value of Auto iFOBT according to colonoscopic findings (Table 2). At the standard hemoglobin concentration cutoff, 100 ng/ml, the sensitivity for detection of mucosal, submucosal, and advanced cancers were 60%, 90%, and 95%, respectively, while detection rate for adenoma was 25%. At the standard cutoff, Auto iFOBT sensitivity, specificity and positive predictive value for detection of cancer were 74.7%, 86.4%, and 33.7%, respectively. When sensitivities were calculated for different cutoff concentrations, the detection rate of advanced cancer remained at 95%, even when increased to 1000 ng/ml. However, the detection rate for submucosal cancer, mucosal cancer and adenoma diminished inversely to increased cutoff levels (Table 3). The number of clinically confirmed CRC positive patients were then segmented into their representative bands and specified along hemoglobin concentration levels, as measured by Auto iFOBT (Fig. 1). The proportion of mucosal cancer observations was found to be inversely related to increased hemoglobin concentration. The proportion of submucosal cancer observations was greatest within the 200 to 500 ng/ml hemoglobin concentration range. The proportion of advanced cancer observations occurred at greater than 1000 ng/ml hemoglobin concentration, except for one outlier. Auto iFOBT positive rates according to CRC location (cecum and ascending colon, transverse colon, descending and sigmoid colon, rectum) were also recorded (Table 4). There were 3 cases of invasive cancer undetected at the standard cutoff due to false negative results, all of them in ascending colon.

4. Discussion

Rectal bleeding, or hematochezia, is most commonly related to constipation and hemorrhoids but may occur for many reasons, including intestinal disorder and irritation, colonic polyps, and CRC. Such bleeding may originate from anywhere along the digestive tract, as "hidden" or occult blood, undetectable by gross examination. Occult blood in stool is often the first—and sometimes the only—warning sign for colorectal disease, including CRC. For this reason, diagnosing the potential source and the cause of rectal bleeding as accurately as possible before directing further examination, such as full colonoscopy, is important. And, as occult blood cannot be observed with the eye, testing, the FOBT in particular, is employed to detect occult blood in the stool.

Fecal occult blood may be elicited by colorectal neoplasia, including some precursors to cancer such as polyps, before the appearance of symptoms indicating CRC. The FOBT, therefore, is used for early polyp and cancer detection in people without intestinal symptoms, and often forms the basis for CRC vigilance and prevention programs. Tannous et al. demonstrated considerable differences in the analytical sensitivity among various FOBT methods, however. Their work indicated that the fecal occult blood positive rate varied by method, from 8.5% to 42.2%. Therefore, selection of a validated technique with appropriate specificity and sensitivity is essential when choosing an FOBT method for colorectal cancer screening [5].

In traditional gFOBT, interaction between guaiac, an oxidizing agent, and the heme portion of the blood-borne hemoglobin molecule causes the guaiac to turn visibly blue, signaling occult blood in the stool of a patient and to the potential for CRC. Guaiac FOBT is inexpensive and easy, but has several disadvantages, chief among them being that reagents also react with non-human hemoglobin-like substances in feces, animal myoglobin and plant peroxidases in particular. While these substances may confound gFOBT by resulting in a pointlessly high number of false positive outcomes, their presence in the colon and rectum are the likely result of a common and healthy diet. In addition, vitamin C and other drugs may also return abnormal gFOBT results, false negative in these cases. In response, typical gFOBT protocols require strict food intake restriction of patients prior to sample collection, making dietary non-compliance a potential issue. Too, tests are often carried out to be purposefully insensitive in order

Table 1
Patient demographic data and endoscopic findings.

Demographic data	
Male/female	562/511 (52%/48%)
Mean age +/- SD (range)	65.0 +/- 10.6 y (26–89 y)
FOBT	
Positive	202 (18.8%)
Negative	871 (81.2%)
Findings at colonoscopy	
Normal	743 (69.2%)
Inflammatory polyps	3 (0.3%)
Colitis	12 (1.1%)
Adenoma	224 (20.9%)
Cancer	91 (8.5%)

SD: standard deviation.

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