Small Bowel Evaluation in Asymptomatic Fecal Immunochemical Test-Positive Patients with a Negative Colonoscopy: Is It Necessary?

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Screening for colorectal cancer (CRC) and its precursors by fecal occult blood test (FOBT) is widely recommended and is being applied more than ever [1–3]. Although annual or biennial guaiac fecal occult blood test (gFOBT) screening has been proved to reduce the mortality of CRC [4], the gFOBT has been faulted for its low sensitivity [5, 6]. More recently, the fecal immunochemical test (FIT) has been introduced as an alternative to the gFOBT. The FIT is currently preferred over the gFOBT due to its higher sensitivity and improved detection rate for advanced neoplasia [5, 7–10]. Besides its diagnostic performance, the FIT has several advantages over the gFOBT including no need for dietary restriction, easier stool collection method, and automated analysis [11]. Furthermore, quantitative FIT allows for the adjustment of the cutoff value for an abnormal result based on population characteristics and available colonoscopy resources. Due to these characteristics, quantitative FIT is more favored as a screening tool than qualitative FIT [11].

The FIT selectively reacts with the globin moiety of human hemoglobin [12]. Because globin is rapidly degraded by proteases in the upper gastrointestinal (GI) tract, the FIT does not detect small amounts of blood in the upper GI tract and selectively recognizes occult bleeding of colorectal origin [12]. With regard to small bowel lesions,

although there is a possibility that some small bowel occult bleeding could be identified by FIT, no data are currently available regarding this issue.

In the current issue of *Digestive Diseases and Sciences*, Chiba et al. [13] present the results of their prospective study on small bowel evaluation in asymptomatic FIT-positive subjects with a negative colonoscopy. In this, the first study to evaluate the small bowel with capsule endoscopy (CE) in asymptomatic FIT-positive patients with a negative colonoscopy, 53 asymptomatic patients with FIT-positivity and a negative total colonoscopy and esophagogastroduodenoscopy underwent CE. The CE findings were classified into three categories: P0, no abnormalities or findings without potential for bleeding; P1, findings with uncertain potential for bleeding; and P2, findings with high potential for bleeding. The cecal completion rate was 92.5%. There were no cases of P2, 19 cases of P1, and 34 cases of P0. Moreover, no abnormalities were identified in five patients who underwent additional diagnostic evaluations that were considered necessary based on the individual clinical results. No clinically significant small bowel lesions were found in the asymptomatic FIT-positive patients with negative bidirectional endoscopy.

Although FIT has been widely accepted as a CRC screening tool, 40–60% of subjects with a positive FIT are found to have no lesions in their colon or rectum to explain their positive status [5, 14, 15]. How then do we explain the discrepancy between the results of FIT and colonoscopy? There are several possible explanations for this discrepancy. First, this may reflect true false-positive results of FIT for advanced neoplasia. Quantitative FIT results are subjected to predetermined cut-off values for fecal hemoglobin; this methodology could inevitably yield some true false positives. Additionally, medications that can increase the likelihood of GI bleeding may cause false-positive FIT

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results. However, recent data, although not sufficient, demonstrated that low-dose aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticoagulant use have no or marginal effects on the specificity of FIT, rather they increase the sensitivity of FIT [16, 17]. At this time, concomitant use of those drugs does not seem to be the culprit behind FIT false-positive results. More studies are needed to elucidate this issue. Beyond this, sample contamination by menstruation may also lead to false-positive FIT results. Second, there may be significant lesions that are missed during endoscopic examinations. According to tandem colonoscopy data, the adenoma miss rate of lesions ≥ 10 mm size is 1–8% [18]. Moreover, in cases of suboptimal bowel preparation, the miss rate increases considerably, up to 36% [19]. With this in mind, clinicians should verify the quality of the colonoscopy when they are faced with unexplained colonoscopy results in FIT-positive subjects. Additionally, significant small bowel lesions may be missed by CE. The potential miss rate of CE has been reported to be approximately 20% [20]. The observation that the rebleeding rate for patients with obscure GI bleeding and a negative CE is considerable also reflects this significant miss rate [21]. Third, FIT may yield positive results for small adenomas. Morikawa et al. [22] reported that FIT detects small adenomas (≤ 9 mm) in men with a level of sensitivity significantly higher than serendipity, although the sensitivity is low. In contrast to asymptomatic subjects, it is noteworthy that, in cases of overt obscure GI bleeding or iron deficiency anemia, a substantial portion of cases had significant small bowel lesions, as demonstrated by data presented by Chiba et al. [13] and shown in their Table 2.

In clinical practice, patients with a false-positive FIT can embarrass physicians. Is additional small bowel exploration needed? What kind of clinical management should be provided? As shown by the work of Chiba et al. [13], the role of CE is limited in asymptomatic patients with a positive FIT; these findings partly relieve concern for the need for small bowel evaluation in these patients. At present, a regular follow-up with repeated FITs and consideration of repeated or earlier follow-up colonoscopy according to the quality of the initial endoscopy may be an appropriate management strategy.

In order to determine the sensitivity of FIT for detecting any type of small bowel bleeding, additional studies of FIT in patients who are undergoing CE or deep enteroscopy examination for suspected small bowel lesions are needed. These future studies may reveal the true performance of FIT in detecting small bowel lesions with respect to the detectable degree of bleeding and the exact locations of these lesions in the small bowel. Moreover, long-term follow-up studies for FIT positive patients with a non-explanatory colonoscopy are also warranted.

In summary, additional small bowel evaluation is not recommended in asymptomatic FIT-positive patients with a negative colonoscopy. However, further small bowel evaluation should be considered in patients with clinical symptoms, iron deficiency anemia, or gross bleeding after negative conventional endoscopic examinations.

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