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Review Article

New Non-Invasive Genetic Studies in Colorectal Cancer

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Abstract

Colorectal Cancer is the second leading cause of cancer death worldwide second only to lung cancer. Screening modalities have been developed by various medical organizations and that has shown a dip in the mortality rates. As the screening modalities vary from non-invasive fecal occult blood test to Colonoscopy, there is a large variation between the two spectra. Radiological imaging has tried to bridge this gap, but has failed to do so significantly. Recently the Food and Drug Administration of USA has approved for the use of a stool DNA test (Colorgurad®, Exact Science) and blood test (Epi proColon®) for Colorectal Cancer Screening. This article attempts to shows how the two new non-investigations, being non-invasive, can be an integral part of the armament of a patient and his clinician for screening, diagnostic and monitoring for Colorectal Cancer.

Keywords: *Non-Invasive; Colorectal Cancer; Screening*

Introduction

Colorectal Cancer is the second leading cause of cancer death worldwide second only to lung cancer. Varied screening modalities and algorithms developed by many medical associations and that have shown a dip in the mortality rates. As the screening modalities vary from non-invasive fecal occult blood test (FOBT) to Colonoscopy, there is a large variation between the two spectra. Radiological imaging has tried to bridge this gap, but has failed to do so significantly. Recently the Food and Drug Administration of USA (FDA) has approved for the use of a stool DNA test (Cologurad®, Exact Science) and blood test (Epi proColon) for Colorectal Cancer (CRC) Screening. This article would aim to understand the use of these two new modalities.

Discussion

The 2016 guidelines by the US Preventive Services Task Force (USPSTF) strongly recommend screening for colorectal cancer. It lists 7 different screening strategies, stating that "the screening tests are not presented in any preferred or ranked order," implying that the task force considers them to be equivalent. However, the task force presents evidence that some strategies are better than others when tested in representative populations [1,2].

Fecal Occult Blood Test: FOBT

FOBT is the test where the fecus is tested for occult blood. The two common methods for testing are guaiac solution based or immuno-chemical tests.

a) FOBT Guaiac.

b) FIT – Immunochemical (OC FIT-CHEK Polymedco).

Both these tests have very low sensitivity and specificity. Its low negative predictive value and positive predictive value make its use very unreliable in the hand of a clinician. Resorting to use of colonoscopy or virtual colonoscopy to detect CRCs. Its accuracy is even worse for detection of adenomas. Therefore, rending it useless for CRC screening and possibly helpful in detecting CRCs. As most of the reduction

in mortality of the CRC has been mostly been attributed to cancer prevention when compared to treatment. Stool-based tests are generally considered not as good as direct visualization tests, like colonoscopy and flexible sigmoidoscopy, as many cancers or polyps can be missed. They can also yield false-positive results, which may lead to unnecessary colonoscopy [3]. In spite of being a non-invasive, annual screening procedure, there is low adherence to the FOBT [4].

Colonoscopy

It is the gold standard in CRC diagnosis testing [5]. Providing a more thorough view of the inside of the digestive tract, this screening test must be repeated after an interval of 10 years, if all appears to be normal. The direct visualization facilitates screening and diagnostic follow up of positive findings during the same examination [3,6]. Colonoscopy is a highly sensitive and specific screening method. Data suggests that the sensitivity for colonoscopy to detect adenomas ≥ 10mm, ranges from 89% to 98%, and for adenomas ≥ 6 mm, ranges from75% to 93% [6]. Another European study, aiming to demonstrate the sensitivity and Negative Predictive Value of T1 cancer detection, showed that Colonoscopy has low values of 60% and 75% respectively [7].

However, major factors contributing to the lower adherence rates of this screening procedure are:

- Long bowel preparation and examination time: leading to dehydration or electrolyte balances.
- Sedation: resulting in cardiovascular events.

Invasiveness of the procedure: that can result in infection, colonic perforations and bleeding [6].

CT of Virtual Colonoscopy

The American Cancer Society officially recommended this modality for screening test in 2008 [1]. It has good sensitivity even for flat lesions with combing various CT techniques [8]. It also has as high as 90% positive predictive value for polyps 6 mm [9]. In a British screening showed higher accuracy with better detection rates and PPV at busy centres with experienced radiologists and using 3D interpretation [10]. Therefore, even though this is non-invasive test, its accuracy is not up to the mark in screening when it's done at a population level.

Cologurad

The FDA has approved it for screening for CRCs in average risk patients above the age of 50, with a Negative Predictive Value of 99%. Colorectal cancer arises from accumulated genetic and epigenetic alterations, which provide a basis for the analysis of stool to identify tumor specific changes [11]. This test involves a molecular assay to detect DNA mutations involved in biomarkers of CRCs i.e. KRAS mutation, NDRG4 and BMP3 methylation. It also detects occult fecal hemoglobin by immunochemistry like the FIT method. B-actin is also detected and measured. It is used as an internal control to measure the amount of DNA in the fecus [11]. It should be performed at an interval of 1 - 3 years, depending upon the individual cases, taking their prior history and examination findings into account [6]. Published in the New England Journal of Medicine, the study by Imperiale., *et al*. [11] assesses the test characteristics of the only FIT-DNA test available in the United States (Cologuard; Exact Sciences). Its sensitivity and specificity to detect colorectal cancer was 92% and 84%, respectively. Its sensitivity to detect advanced precancerous lesions (advanced adenomas and sessile serrated polyps measuring ≥ 1 cm) was 42%, and its specificity to detect "all none advanced findings" (including non-neoplastic findings and negative colonoscopy findings) was 87%, thereby being exceeding the performance of the FIT overall. The multitarget stool DNA testing, thus, has been shown to have higher single-application sensitivity than a commercial FIT, for both colorectal cancer and advanced precancerous lesions, although with lower specificity [11].

Epi proColon

Approved by the FDA in April 2016, the assay (Epi proColon) relies on qualitative detection of the methylated septin9 gene (SEPT9) [4]. A Case-control study by Warren., *et al.* [12] reported an estimated sensitivity of 90% at 88% specificity for cancer detection, in 50 untreated CRC patients, while in a clinical trial, the assays were reported to have sensitivity and specificity of 68%and 79%, respectively. Comparing to FIT, another clinical trial showed that SEPT9 testing significantly improved sensitivity (68% vs. 73%) but markedly de-

creased specificity (97% vs. 81%). However, the USPSTF guidelines have mentioned SEPT9 to have a low sensitivity of 48% [4,6,12]. Another study comparing Plasma SEPT9 with FIT, found that at a sensitivity of 72%, the Epi proColon test is non- inferior to FIT for CRC detection, although at a lower specificity. With negative predictive values (NPV) of 99.8%, both methods were identical in confirming the absence of CRC [13]. Evidence suggests that some patients who are reluctant to undergo screening would be receptive to a blood test. As shown by one survey, 97% who refused colonoscopy accepted a non-invasive screening test, and 83% of those preferred a blood test. Despite increasing the compliance, the ambiguity regarding the actual clinical application of this newly approved test, suggests the need for more evidence supporting the use of SEPT9 as a screening procedure, and the continuation of efforts to detect new tumor biomarkers, that will overcome the barriers of the present screening techniques. Although the sensitivity, specificity and adherence rates are important factors to consider while adopting a screening method into practice, one major factor that doesn't have enough supporting data, is the impact of all the above screening rates on the mortality and morbidity data. However, there is evidence from RCTs demonstrating that an annual or biennial screening with gFOBT as well as 1-time and every 3 to 5-year flexible sigmoidoscopy reduces colorectal cancer deaths [14]. There is a need for trials showing long-term findings of direct comparisons of the various screening methods.

Conclusion

Colorectal cancer is the most frequently diagnosed among adults aged 65 to 74 years; the median age at death from colorectal cancer is 68 years. Currently, the USPSTF suggests to offer or provide screening, starting at age 50 years and continuing until age 75 years, while that for 76 to 85 years, should be for selected patients, depending on individual circumstances (Recommendation). In view of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program data, the incidence of colorectal cancer may be increasing among adults younger than 50 years. With the availability of non-invasive screening options, like Cologurad and Epi proColon, the screening is likely to be implemented in adults aged 45 – 75 years, thereby ensuring that the increase in screening rates materializes into detection of the cancer at an early and curable stage. This article, thus, shows how the two new tests, being non-invasive, can be an integral part of the armament of a patient and his clinician for screening, diagnostic and monitoring for Colorectal Cancer.

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