Fecal Occult Blood Test and Colonoscopy in Screening for Colorectal Cancer

RECOMMENDATION

Among asymptomatic apparently healthy adults aged at least 50, we recommend to screen for colorectal cancer using annual FOBT or FIT, followed by colonoscopy, when indicated. ***(strong recommendation, high certainty evidence)*****.**

Considerations

The consensus panel considered the following when formulating this recommendation:

- Colorectal cancer (CRC) screening was deemed in the periodic health examination. Screening for colorectal cancer had net benefits and uses accurate tests. However, the high cost of colonoscopy included in the screening pathway was raised as a concern. The consensus panel perceived the certainty of evidence to be high.
- Individuals age 50 years were considered because of the prevalence of colorectal cancer in the age group.
- Panelists recognized that only fecal occult blood test (FOBT) has more direct evidence compared with the fecal immunochemical test (FIT).
- Panel members also have taken into account the challenge in FOBT procedures that need three tests. Utilizing a single test may result in a high false-positive rate because of its interaction with the patient's diet.
- Panelists agreed that FOBT, FIT, and colonoscopy are acceptable and feasible. Inequity issues arise in using colonoscopy. Although it is widely available in the country, practitioners trained to use colonoscopy may be limited, particularly in remote areas. They also considered the cost of performing colonoscopy.
- Aside from its feasibility, FIT was also perceived to be more accurate than FOBT based on the evidence presented.

3.8.1 Burden of disease

Disease Frequency

In the Philippines, colorectal cancer (CRC) is the third leading malignancy for both sexes, with rapid increases in incident cases from 5,787 in 2010, 9,625 in 2015, and 17,634 in 2020.(1) It is now the second most common cancer in Filipino men and the third most common cancer in Filipino women. Age-standardized incidence rates per sex are 23.7 per 100,000 and 15.1 per 100,000 for men and women, respectively.(2)

Severity of Disease

Mortality from CRC is on the rise in the country, with an average annual percentage change of 5.7 (95% 4.7-6.7).(3) In 2020, CRC was the third-leading cause of cancer-related deaths for both Filipino men and women with an age-standardized mortality rate of 10.1 per

100,000.(2) The five-year relative survival rate of CRC patients in Metro Manila was 40.2% using data from 1993 to 2002, which is significantly lower compared to Filipino-Americans (62.3%) and Caucasians (64%) in the United States.(4, 5) Moreover, decreased survival rate may be attributed to late stage in the diagnosis caused by delays in consultation, diagnosis, and intervention.(4, 6)

Natural course of the disease

CRC is hypothesized to develop from adenomas which are benign tumors that may become malignant. It is presumed that the time for a polyp to grow into a malignant tumor is ten years, during which a patient with a differentiating tumor may be asymptomatic.(7, 8) There is a paucity of symptoms in early CRC. The symptoms may manifest over time depending on tumor location, size, and presence of metastasis. They may include occult to overt bleeding, non-specific abdominal pain, alternating constipation and diarrhea, abdominal distention, weight loss, and anorexia.(9) Prognosis is related to stage at initial diagnosis, with the American Joint Committee on Cancer (AJCC) Tumor Node Metastases (TNM) staging as the most commonly used staging algorithm. The five-year overall survival (OS) ranges from 92% in stage I to 11% in stage IV.(10) Patients with stage II and III disease have a wider range of prognosis, particularly in those who receive adjuvant chemotherapy, with a five-year OS between 50% to 90%, with OS affected by age, sex, primary tumor location, tumor grade, number of positive lymph node, lymphovascular and perineural invasion, presence of bowel obstruction or perforation and adjuvant treatment.(11)

Management of the disease

Further management depends on the results of confirmatory tests. When polyps are detected, these can be characterized, removed, and sent to histopathology. The type of polyp, size, and number determine the frequency of colonoscopies to be recommended. On the other hand, tumors can be managed according to size and depth of tumor invasion, either endoscopically or surgically. Finally, a patient may undergo chemotherapy or combination chemoradiation therapy, depending on final staging.

Economic impact of the disease

CRC is costly. In 2015, the Association of Southeast Asian Nations Costs in Oncology (ACTION) reported that 48% of families with a member with newly diagnosed cancer face financial catastrophe within the first year of treatment. In a similar study using the Philippine data set, it was reported that 40.6% of Filipino households struggle financially after a cancer diagnosis.(1) Cost of cancer treatment worldwide in 2009 amounted to approximately Php 10.446 trillion (USD217 billion) with Php 1.877 trillion (USD39 billion) colorectal treatment expenditure. The cost per patient increased with the stage of CRC ranging from Php 160,957.65 (RM13,672) for stage I to Php 329,308.62 (RM 27,972) for stage IV.(12)

Social impact of the disease

Patients with CRC experience poor social involvement that has an impact on the patients and their families. For patients diagnosed with stage IV disease, their scores for emotional functioning were significantly lower. Patients and their caregivers may also experience fear, anxiety, depression, and anger. Patients with low scores on health-related quality-of-life

scales were more often recommended to receive special attention from healthcare providers and their families as supportive care strategies.(13)

The number of patients diagnosed is rising, but survival rates are also improving. These numbers have implications for health services, patients and their families, and society.(14) However, studies show inequalities among socioeconomic groups, with the marginalized sector having a significantly worse prognosis after diagnosis.(15)

3.8.2 Benefits and Harms of Screening Tests

Based on five RCTs (n=404,396) that used intention-to-treat analyses, screening with FOBT (Hemoccult II) resulted in a reduction of CRC-specific mortality compared to no screening, with a pooled relative risk (RR) of 0.82 (95% CI 0.76 to 0.89) for both annual and biennial screening and relative risk of 0.87 (95% CI 0.82 to 0.91) for biennial screening alone. The single study involving annual FOBT showed a marked reduction of CRC-related mortality (RR 0.67; 95% CI 0.56 to 0.80). These studies involved 2 to 9 rounds of screening with a range of 11 to 30 years follow-up. (16-20)

There were no randomized trials involving screening with FIT compared to no screening on the outcome of mortality. One fair quality prospective cohort in Taiwan with 5,417,699 participants aged 50 to 69 years showed that screening biennial FIT was associated with lower CRC mortality than no screening with RR 0.9 (95% CI 0.84 to 0.95) when adjusted for self-selection bias and increasing CRC incidence over time.(21)

There were no harms directly related to testing for fecal occult blood. However, several studies presented complications arising from diagnostic colonoscopies following an abnormal stool test. Based on 11 studies of colonoscopy conducted after abnormal FOBT/FIT (n=78,793), the pooled estimate was 17.5 serious bleeding per 10,000 (95% CI 7.6 to 27.5; I^2=89.3%). The pooled estimate of perforations following abnormal FOBT or FIT was 5.7 per 10,000 procedures (95% CI 2.8 to 9.7; I^2=47.8%).(22)

3.8.3 Diagnostic Performance of Screening Tests

Diagnostic Accuracy of FOBT in detecting CRC

In resource-limited countries, FOBT is the first choice for screening.(23) The guaiac-based test detects the pseudo-peroxidase activity of hemoglobin. Dietary restrictions before the test are recommended to the detriment of decreased compliance and adherence. Moreover, since sensitivity is increased by repeated testing, a complete FOBT is comprised of three separate bowel movement samples, with two samples from each stool.(24) FIT is a newer type of FOBT that uses antibodies to detect the globin portion of human hemoglobin. It avoids the limitations encountered with FOBT with the added benefit of increased sensitivity and specificity. (25-27) Both tests, upon yielding positive results, require further testing, often in the form of direct visualization tests such as colonoscopy or flexible sigmoidoscopy.

Based on five prospective, fair quality studies, two of which used colonoscopy as a reference standard (n=3,503) and three with cancer registry as a reference standard (n=15,969), the sensitivity of guaiac-based FOBT ranged from 0.50 to 0.79 (95% CI 0.01 to 0.99) (28) and specificity ranged from 0.87 to 0.98 (95% CI 0.86 to 0.99) for detecting colorectal carcinoma. (27, 29-31) All five studies involved average-risk individuals with ages ranging from 50 to 80 years. No subgroups by age, sex, race, or ethnicity were reported. (22)

Diagnostic Accuracy of FIT in detecting CRC

The studies on FIT are largely heterogeneous, owing not only to the wide variety of manufacturers, test cutoffs, analysis methods, and test kits available but also to the type of study and settings. Forty-five studies were reviewed in the updated evidence synthesis of the USPSTF. Twenty-eight studies were cross-sectional using one-time FIT with sample sizes ranging from 307 to 21,805. Seventeen studies were conducted under a screening program, and their population ranged from 2,235 to 956,005 individuals. Most studies recruited participants 40 or older and were average-risk, excluding those with the first-degree relative with CRC. The most commonly used FITs were part of the OC-Sensor family (Polymedco in the US or Eiken Chemical outside the US). The studies on the OC Sensor family were pooled and presented. In 26 studies, FIT was followed by a colonoscopy for all participants regardless of the FIT results. Nineteen studies used a combination of cancer registries for all participants and direct visualization for participants with abnormal FIT results. Nine studies were rated as good quality, with the rest of the studies at higher risk of bias in terms of differential verification, unclear or absence of blinding of the FIT results for those performing the colonoscopy, unclear methods of patient selection, and patient attrition (unreadable screening tests).

Nine studies (n=34,352) of the OC-Sensor FIT family with a colonoscopy as the reference standard for all participants and using the manufacturer-recommended cut-off of 20ug Hb/g feces showed a pooled sensitivity of 74% (95% CI 64% to 83%; I^2=31.6%) and specificity of 94% (95% CI 93% to 96%; I^2=96.6%) in detecting CRC. (10, 21, 24, 26, 28, 31-35). Seven studies (n=2,468,638) using OC-Sensor tests at a cutoff of 20ug Hb/g feces to detect CRC with cancer registry follow-up to identify CRC yielded a pooled sensitivity of 81% (95% CI 74% to 88%, I^2=98.6%) and a specificity of 95% (95% CI 94 to 96%, I^2=98.5%).(36-42) Nine other FIT brands were assessed in 11 studies with colonoscopy as the reference standard.(25, 26, 29, 31-33, 43-48) Pooling results for OC Light among these from three studies showed that this test has a sensitivity of 81% (95% CI 70% to 91%; I^2=0) and a specificity of 0.93 (95% CI 0.91-0.96; I^2=99%). (33, 37, 44) The sensitivity range for other FITs was 50% to 97% (95% CI ranges, 90 to 100%) with specificity ranging from 83% to 97% (95% CI ranges, 82% to 97%). There were no clear patterns identified for differential accuracies by tumor location or stage, age, sex, race, ethnicity, or family history.

3.8.4 Cost Implication

Cost-effectiveness studies(49-56) from different countries showed that screening strategies for colorectal cancer (i.e., annual FOBT, FOBT followed by colonoscopy, FOBT and HRFQ, annual FIT, colonoscopy, annual FIT, and colonoscopy) were cost-effective compared with

no screening. Table 22 shows an estimated annual screening cost per patient in Php using FOBT or FIT.

Table 22. Estimated annual cost of screening for CRC using FOBT/FIT

Parameter	Screening intervention		
	FOBT yearly	**FIT yearly**	**Colonoscopy every 10 years**
(A) Unit cost of screening intervention in Philippine Peso (Php)	Php 570 (3 samples at 190/sample)	Php 405	Php 8817
(B) Other direct costs associated with the implementation of the proposed screening intervention in Philippine Peso	Php 30 (3 stool containers at 10/piece	Php 10	Php 6720 (PhilHealth professional fee)
(C) Annual screening cost per patient in Philippine Peso	Php 600	Php 415	Php 15,537

Values based on the 2018 cost-utility study conducted in the Philippines. (291)

3.8.5 Ethical, Social, and Health Systems Impact (Equity, Acceptability, and Feasibility)

Ethical

A study in colorectal cancer screening shows inequities in access to cancer care and screening in general. Factors such as income, education, level, age, location of residence, and immigration status affect screening intervention. Low income has been associated with poorer survival rates for several cancers, including CRC.(57) Access to healthcare has a substantial impact on screening behavior. Patients who have health insurance and regular access to care were more likely to have received CRC screening.(58) Differential availability of screening resources has also limited the uptake of screening programs. The success of a nationwide screening program relies on the availability of facilities for both the initial screening test and the subsequent tests and treatment.

Social

Many factors influence participation in CRC screening, and these range from personal health beliefs, familial contributions to decision making, educational attainment, low household income, and cultural and social stigma.(39, 59-61) Since an FOBT or FIT is non-invasive, patients may be more amenable to comply with this procedure. However, access to the secondary visualization tests must be made available for patients who tested positive. Geographic factors and the maldistribution of specialist care may hinder the adoption of these initial screening tools for CRC. These socio-cultural and geographic factors must be considered in implementing a national CRC program.

Health Systems

To improve CRC screening implementation and rates, improving access to health care through systematic interventions must be done. Strategies may include increasing health insurance coverage and ensuring patients' consistent follow-up with their primary care providers.(58) Facilities should be constructed to provide access and availability of the screening test, proper referral system for the confirmatory testing and procedures, and continuing management for detected cancers. Evidence-based interventions such as patient education regarding the screening and distribution of free FOBT kits can significantly increase screening rates. However, it can only be achieved if intervention is widely implemented.(62) Health care providers play a crucial role in the acceptability of the screening intervention. Increasing awareness of the benefits of screening and reducing the perceived barriers would increase screening uptake.(39)

3.8.6 Recommendations from Other Groups

Multiple organizations worldwide agree on the importance and benefit of CRC screening. Guidelines, however, differ in terms of recommended screening strategies and optimal age to initiate and terminate screening. In 2017, the Philippine Society of Gastroenterology and the Philippine Society of Digestive Endoscopy consensus guidelines recommended screening for CRC in average-risk individuals using a fecal occult blood test (FOBT), preferably fecal immunochemical test (FIT), flexible sigmoidoscopy (FS), and colonoscopy. It begins at the age of 50 up to 75; older patients are individualized by predicted life expectancy and risk factors. They also recommended the performance of colonoscopy for patients with abnormal findings on screening.(63)

In the US, multiple organizations, including the American Cancer Society (ACS), USPSTF, US Multi-Society Task Force of Colorectal Cancer, and the American College of Gastroenterology, agree that the recommended options for screening for CRC include colonoscopy every ten years, annual high-sensitivity guaiac FOBT or FIT, and FS every 5 to 10 years. Notable differences in international guidelines include: 1) an earlier onset of screening at 45 years as a conditional recommendation by the ACS, 2) modalities for screening, and 3) age to stop screening, spans from 75 to 85 years of age. (22, 64)

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