The Joint Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endoscopy (PSDE) Consensus Guidelines on the Management of Colorectal Carcinoma

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Background and Objectives:

Colorectal cancer (CRC) is an increasingly prevalent malignancy in the Philippines. According to the 2010 Philippine Cancer Facts and Estimates it is the most common cancer of the gastrointestinal tract.[1] In the 2012 IARC Globocan Report, CRC ranks fifth among all cancers in both sexes in the Filipinos, even higher than liver cancer. Except for Japan and Singapore, the incidence rates of CRC have been increasing in Asia, including the Philippines.[2-5]

The natural history CRC presents a unique opportunity for early intervention because the colon is accessible to examinations which enable early identification and efficient removal of precursor premalignant and/or early malignant lesions. Many of these examinations are available in the country. CRC has a high survival rate if detected in its early stages. Advances in the understanding of its epidemiology and carcinopathogenetic pathways, as well as, availability of better diagnostic tests and treatment approaches have improved the cure rates, survival and outlook of patients with CRC.

In developed countries, initiatives by their national health care systems directed at increasing public awareness and promoting screening programs have contributed further to these strides.[6-10] In Asia, awareness and knowledge on the symptoms and risk factors of CRC are extremely low, as well as, the need and compliance to undergo CRC screening even when asymptomatic. In addition to physician practices and health insurance status which impact substantially on testing, many perceived health, psychological, and access barriers to testing also exist.[11] In the Philippines, the awareness on CRC is relatively high largely because CRC claimed the life of an iconic, high-profile public figure. Thus, we must take advantage of this important first step in our strategy to control CRC in the country.[12]

Many experts argue that a comprehensive and well-executed program in early detection and appropriate treatment will help prevent deaths and morbidity associated with CRC. A European review opined that it is no longer acceptable that a cancer which can be detected early by widely-available screening methods and can be treated adequately with currently-available surgical/endoscopic procedures should continue to cause so many deaths.[13]

The objective of this clinical practice guideline is to provide evidence-based recommendations on the appropriate approach to the management of CRC, encompassing early detection, proper treatment and efficient follow-up care, as well as, addressing the need for the national healthcare system of the country to adopt a strategy to achieve these ends.

Methods

A core working party composed of nine members (JDS, MDCL, RPR, MAAL, JCB, ECB, TCM, DAP, FTD) was convened to determine the needs and concerns of local medical practitioners, as well as, evaluated the national health policies regarding screening, diagnosis, treatment, and follow-up surveillance for CRC. The members were chosen for their active clinical practice and researches focused on colorectal cancer, expertise in evidence-based medicine and academic affiliations. Review of scientific papers from different accredited training institutions of the Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endosocopy (PSDE) which dealt with CRC was performed. An electronic survey was conducted on 12 training institutions all over the country to gather current information on the clinical presentation of CRC and the attitudes and practices of gastroenterology colleagues regarding screening, colonoscopy, surveillance and use of CRC guidelines in their care of the CRC

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patients and the at-risk population. Several pre-consensus development meetings were held to evaluate the results of the surveys, identify the needs of the local physicians in tackling efficiently the important concerns about CRC, scrutinize appropriate scientific articles and formulate draft recommendations relevant to the scope of this CRC consensus guidelines. Twelve recommendations were drafted utilising the literature retrieved from Medline, Embase, the Cochrane Central Register of Controlled Trials and ISI Web of Knowledge, including manual searches in bibliographies of key articles, proceedings of abstracts of major gastroenterology and endoscopy meetings held in the past five years (Asian Pacific Digestive Week (APDW), Digestive Disease Week (DDW) and United European Gastroenterology Week (UEGW) and articles published in the Philippine Journal of Internal Medicine and Philippine Journal of Gastroenterology, as well as, the outcome of the electronic survey as basis.

Thru a modified Delphi process, the 12 recommendations proposed by the core working party were circulated to all training program directors/chiefs of GI section for electronic voting by email. Voting for every statement was done as follows; (A) Accept completely; (B) Accept with some reservation; (C) Accept with major reservation; (D) Reject with reservation; (E) Reject completely. Additional comments were encouraged for each statement and revisions made accordingly during subsequent deliberations of the core working party. After the electronic voting, a consensus development conference was held and participated in by the training program directors and the core working party (CWP). Each CWP member was assigned to present and defend a statement/recommendation using appropriate studies to support his/her argument. During the conference, a pre-assigned panel composed of the training directors served as resource experts and together with the presenters were required to evaluate appropriate publications, taking special care to include publications from the Philippines and where there were none, studies from Asia were preferred. After a robust discussion and debate, voting on every statement was conducted anonymously using a wireless keypad system. If the pre-determined agreement of 85% was not achieved, the statement was rejected. The level of evidence and the strength for each recommendation were rated by the participants using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process, as follows; a) High — Further research is very unlikely to change our confidence in the estimate of effect b) Moderate — further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate c) Low — further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate d) Very low — any estimate of effect is uncertain. The strength of recommendation was classified as follows; a) strong b) conditional.14 The participants were constantly reminded that care is needed so as to recognize that 'quality of evidence' is not necessarily synonymous with 'strength of recommendation', and vice versa; and that their informed judgment is necessary. An unrestricted educational grant from the PSG and PSDE made possible the preparation and completion of this document. During the entire duration of the consensus process, as well as, in the writing of the manuscript, no interference or representations from any third party were allowed by the consensus development group.

Statement 1

Colorectal cancer (CRC) is an increasingly prevalent malignancy in the Philippines. Currently, it is the most common cancer of the gastrointestinal tract among Filipinos.

Level of evidence: high;
Strength of recommendation: strong
A – 95%; B – 5%

In the last three decades, the incidence of colorectal cancer in Asia, the Philippines included, has increased rapidly. Except for Japan and Singapore, CRC-related mortality has increased similarly. This rising trend in CRC incidence appears to be more pronounced in economically-advanced than in poorer societies.[3,15]

From 1988-2002, data from two population-based cancer registries of Metro Manila and Rizal province showed an increasing trend in the age-standardized incidence rates (ASRs) for colorectal and prostate cancers. Interestingly, ASRs significantly above the average, i.e., ASRs 14.0–21.7 were observed among the most urbanized and affluent cities in these two sites in the country.[2, 5, 16, 17] Towards the end of 2002, CRC was more common than liver and gastric cancers. In the Globocan 2012 IARC report, CRC was the most common cancer of the gastrointestinal tract among Filipinos.

Statement 2

Older age, male gender, obesity, cigarette smoking, increased consumption of red meat, alcohol, physical inactivity, or a family history of CRC or advanced adenoma increases the risk of CRC.

Level of evidence: high;
Strength of recommendation: strong
A – 55%; B – 45%

Increasing age is the most significant risk factor for CRC.18, 19 Most cases of CRCs (>90%) are diagnosed

at age 50 years or above.[19,20] Between 2001-2010, data from the US indicate that the while the incidence of CRC has been declining for patients >50 years old, it has been slowly increasing for patients 40-49 years old.[21]

A recent meta-analysis which included 18 large studies from Asia, America and Europe showed strong evidence that men are at greater risk for advanced colorectal neoplasia across all age groups. Relative risk (RR) for advanced neoplasia was 1.83 (95%CI, 1.69-1.97) and CRC was 2.02 (95%CI, 1.53-2.66), respectively.[22]

Obesity has been repeatedly mentioned as a risk factor not only in colon cancer, but also for other malignancies. A meta-analysis of 31 prospective studies revealed an association of obesity with CRC in both men (RR-1.30, 95%CI, 1.25-1.35) and women (RR-1.12, 95%CI, 1.07-1.18). This association was seen to be stronger with males than females (p <0.0001).[23-25] Interestingly, high BMI is associated with an increased rectal cancer risk in males (RR1.12, 1.09-1.16) but not in females (RR-1.03, 95%CI, 0.99-1.08). This observation is corroborated by several other meta-analyses.[23-25]

There is also evidence demonstrating a direct relationship between smoking and CRC risk. Tsoi et al, pooled 28 prospective studies of more than a million subjects from around the world and demonstrated that "ever smokers" have a higher risk CRC than "never smokers" (RR 1.20, 1.10-1.30). This risk is more pronounced with male smokers.[26] Another meta-analysis of 121 articles reported similar results and estimated that this risk is most significant in those who smoked for >30 pack years.[27]

In a meta-analysis of cohort and case-control studies, Norat et al showed an increased risk of CRC with consumption of red meat (RR-1.35, 95%CI, 1.21-1.51) and processed meat (RR-1.31, 95%CI, 1.13- .51).28 An increased risk for CRC is associated with consumption of 120g/day of red meat (RR-1.28, 95%CI, 1.15 - 1.42) and 30g/day of processed meat (RR-1.20, 1.11-1 31).[29, 30]

In 2008, the NIH-AARP Diet Health Study revealed that spending more than nine hours watching TV per day increased the risk for CRC (RR-1.61, 95%CI, 1.14 - 2.27; p<0.001). Inversely, engaging in exercise or sports more than five times a week compared to never or rarely exercising reduced the risk of colon cancer in men (RR- 0.79. 95%CI, 0.68 - 0.91; p<0.001).31 The risk of CRC is increased with longer TV viewing time (RR-1.54, 95%CI,1.19-1.98), longer occupational sitting time (RR-1.24, 95%CI, 1.09-1.41) and general total sitting time (RR-1.24,95%CI, 1.03-1.50).[32] A recent meta-analysis showed sedentary behavior increased the risk of colon cancer (RR-1. 30, 95%CI, 1. 22-1.39) but not for rectal cancer (RR-1.05, 95%CI, 0.98-1.13).[33]

Fedirko et al, reported that moderate (RR-1.21,95%CI, 1.13-1.28) and heavy, i.e., more than four drinks per day or >50g/day (RR-1.52, 95%CI, 1.27-1.81) alcoholic drinking increased the risk of CRC. This association was weaker for females compared to males and stronger for Asians compared to Caucasians.[34] With increasing grams of alcohol consumed per day, there is an exponential increase in CRC mortality.[35]

The risk for CRC is also increased for both men and women with increasing number of CRC affected first degree relatives.[36] There is a two-fold increase in individuals with one affected first degree relative (RR-2.24, 95%CI, 206 - 2.43) and an even higher risk for individuals with two or more affected first degree relatives (RR-3.97, 95%CI, 2.60-6.06).[37] The risk is also higher for siblings or parents of patients with a history of colorectal adenomas (RR 1.78, 95%CI, 1.18 – 2.67). A prospective cohort study involving >5000 participants reported that first-degree relatives of patients with newly diagnosed adenomas, particularly those diagnosed younger than 50 years old, are at increased risk of CRC. The risk increasing to more than four times greater as compared to relatives of CRC patients diagnosed at >60 years old (RR-4.36, 95%CI, 2.24-8.51).[38] Patients with second degree relatives diagnosed with adenomas are also at risk for CRC (RR 1.15, 1.07-1.23).[39]

Statement 3

CRC can be prevented by early detection and removal of precursor colonic polyps. Diagnosis and treatment at an early stage is associated with good survival.

Level of evidence: high;
Strength of recommendation: strong
A – 89.5%; B – 10.5%; C - 0%, D - 0%, E=0%

CRC is a common malignancy with a long asymptomatic phase. Most colon cancers arise in pre-existing colonic polyps thus, it offers an enviable opportunity where early detection and removal of advanced adenomas, i.e., polyps >10 mm or with significant villous features or with high grade dysplasia, can impact on the natural history of CRC. Advanced adenomatous polyps are associated with a higher risk of CRC and are recognized as its non-obligate precursor.[40-46] In a study among 2,602 patients who had adenomas removed and followed for 15.8 years, the standardized incidence-based mortality ratio was 0.47 (95% CI, 0.26 – 0.80) in those who had colonoscopic polypectomy, suggesting that this approach contributed to a 53% reduction in CRC-associated mortality.[47] In the US, recent declines reported by national surveys and microsimulation modelling have attributed the recent consistent decrease in the incidence and mortality of CRC largely to the impact of CRC screening and to a lesser degree, the contributions of improved treatment

and risk factors modification.[48] A large number of patients with adenomas are now being diagnosed as a result of the increased utilization of colorectal cancer screening, particularly the dramatic increase in screening colonoscopy. The preference towards colonoscopy is largely due to its additional ability to remove colonic polyps during the same screening examination. In the Philippines, colonoscopy services are not available outside urban centres and thus, may not be readily available to a) patients who test positive from other screening tests b) symptomatic patients requiring diagnostic colonoscopy and, c) patients who need surveillance colonoscopy after removal of an adenoma or CRC. A national comprehensive program on CRC risk factor reduction, screening, early treatment and surveillance, using a relatively inexpensive, culturally acceptable and widely available examination, is badly needed.

Statement 4

Screening for CRC should start at 50 y/o for average-risk and earlier for high-risk individuals.

Level of evidence: moderate;
Strength of recommendation: strong
A – 60%; B – 35%; C – 5%

Patients who have a personal history of inflammatory bowel disease, polyps or colorectal cancer, or a family history of polyposis syndromes have an increased risk of CRC. Patients who have none of the mentioned risk factors are considered average-risk individuals.[49]

The US Preventive Services Task Force found that among average-risk individuals, starting screening at age 50 resulted in the best balance between life-years gained and risks associated with colonoscopy. The evidence supporting screening at an earlier age is weak.[50,51] The incidence of CRC rises dramatically from approximately six to seven per 100,000 among individuals 0-49 years old to approximately 60-80 per 100,000 among individuals 50-64 years old.[52] Ninety-three percent of CRC deaths also occur at age 50 and older.[53]

In a prospective multinational survey in 2007, the Asia Pacific Working Group on Colorectal Cancer found that the prevalence of colorectal neoplasm was 11.2% among those <50 years old and 23.9% among those >50 years old.[54] The prevalence of advanced neoplasm was 2.0% versus 5.8% in the younger and older group, respectively. This significant observation led to age as being a criterion included in the Asia Pacific Colorectal Cancer Score to stratify the risk of CRC in Asian individuals.[20]

In multiple unpublished retrospective and prospective studies in the Philippines, adenomas are found in only 4-6% of patients <50 years old. CRC is diagnosed in 4.0% of all patients who underwent a lower GI endoscopy. The mean age at CRC diagnosis is 59 and most are in Stage III.

Statement 5

Routine CRC screening for patients >75 y/o should be individualized depending on life expectancy and associated risks.

Level of evidence: moderate;
Strength of recommendation: strong
A – 78.9%; B – 21.1%

Screening beyond 75 years after consecutive negative screenings from age 50 adds very little benefit because the chance of having a missed adenoma or developing a new lesion that can progress to cancer is very small.[51] The survival benefit of routine CRC screening may be observed not earlier than five years after its performance thus, limiting its value among the elderly with short life expectancy. In a retrospective cohort study, age and the validated Charlson comorbidity index[55] co-dependently predicted overall mortality. The median survival was less than five years regardless of comorbidity among the subjects 80 years and older, and over five years among patients aged 75-79 with fewer comorbidities, i.e., Charlson score <4.56 Likewise, among patients diagnosed with CRC, increasing comorbidities resulted in significant reduction in life-expectancy across all stages of the disease.[57]

Using evidence-informed statistical models, Lin et al, showed the estimated extension of life expectancy after removal of an adenoma during a screening colonoscopy is significantly higher among younger subjects, i.e., 50-54 years old, compared to subjects >75 years old.58 The number needed to screen and number needed to prevent one CRC death increase as a function of age and is inversely related to the life expectancy.[59, 60]

Aside from shorter life expectancy, screening elderly patients entails a higher risk for complications, mostly related to unnecessary colonoscopic examinations. In a systematic review of 12 studies, the rate of total serious complications, including perforations, hemorrhage, cardiovascular events and death, is 2.8 per 1000 procedures.[8] The odds of developing these complications in the elderly is 1.66 compared to younger individuals.[61]

Statement 6

Fecal occult blood tests, preferably using fecal immunochemical test (FIT), flexible sigmoidoscopy and colonoscopy are recommended screening examinations for CRC.

Level of evidence: high;
Strength of recommendation: strong
A – 78.9%; B –21.1%

Statement 6A

Annual fecal based occult blood testing (FOBT), preferably fecal immunochemical testing (FIT), is the recommended first line screening test for CRC in average risk individuals 50 years old and above.

Level of Evidence : High
Strength of Recommendation: Strong

Fecal occult blood test (FOBT) is known to detect cancer more than adenomas. It is a non-invasive and simple test, however, needs to be repeated annually or at least every two years to increase its sensitivity and specificity. Multiple studies have proven that FOBT decreases CRC and CRC-related mortality.[62-64] FOBT is further differentiated as gFOBT (guaiac-based fecal occult blood test) or iFOBT/FIT (fecal immunochemical test). Several Australian and Asian cost analysis studies consistently showed that FOBT is the most cost-effective CRC screening test.[65] iFOBT/FIT does not need the dietary restrictions imposed by gFOBT thus, improving patient compliance. It is also better than gFOBT in detecting adenomas.[66-73]

A cohort study of 1,041 asymptomatic high-risk patients who underwent FIT prior to elective colonoscopy showed that CRC detection rates were comparable between FIT and colonoscopy.[74] An interim analysis of an ongoing study comparing FIT with colonoscopy in average risk patients also showed no significant difference in detecting CRC.[75]

Many countries consider FOBT as the best screening approach to CRC because of its wide acceptance. In resource-limited countries, FOBT is the most affordable test and may be used to direct higher-risk individuals for colonoscopy. FOBT, preferably iFOBT/FIT, is the screening test of choice for CRC detection.[20]

Statement 6B

Flexible sigmoidoscopy every five years and colonoscopy every 10 years are recommended screening examinations for CRC.

Level of Evidence: High
Strength of Recommendation: Strong

Using flexible sigmoidoscopy (FS) as the CRC screening tool, the Norwegian Colorectal Cancer Prevention Trial (NORCCAP), the US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial 9US PLCO), the UK Flexible Sigmoidoscopy (UKFS) screening trial, and the Italian once-only sigmoidoscopy (SCORE) trial reported reductions in CRC incidence by 18-23% and, in CRC mortality by 22-31%.[76-80] Five-yearly FS is cost effective compared with FOBT and colonoscopy, although no studies have been performed to verify its cost-effectiveness in the Philippine setting.[65]

Currently, colonoscopy is the gold standard to detect and treat CRC precursor lesions, i.e., adenomas. Simple white light colonoscopy (WLE) can detect adenomas in asymptomatic individuals above 50 years by at least 30% and CRC around 0.1-1%.[20,81] In a head-to-head comparison of detection rates of adenomas, polyps, and flat lesions using advanced high-resolution scopes, i.e., HD-NBI and HD-WLE, no significant difference in the performance of either models of high-definition (HD) colonoscopes was found.[82]

Large studies, although most indirect and observational, have shown that both colonoscopy and proctosigmoidoscopy significantly reduce the risk of and deaths due to CRC.[83] Nishihara et al, have shown that CRC mortality after screening colonoscopy can be reduced by up to 68%.[84] The added advantage of being able to remove precursor lesions have been shown by the US National Polyp Study to drastically prevent up to 53% of colorectal cancers. In the Philippines, given the limited availability, expense and expertise associated with colonoscopy, its utility may be best prioritized to those populations who may have an increased risk for CRC or those who test positive on the other less-invasive, less-expensive screening tests.

Statement 6C

Colonoscopy should be performed for patients with an increased risk for CRC or have positive findings on sigmoidoscopy, FOBT, CTC, or DCBE.

Level of Evidence: Moderate
Strength of Recommendation: Moderate

Colonoscopy is the gold standard for detecting and treating colonic neoplasms but is still a relatively expensive and invasive procedure and, requires availability of well-trained endoscopists. In resource-limited countries like the Philippines, colonoscopy may not be feasible as a population-based screening test for CRC. However, when

there is a positive finding with other modalities, such as, FS, double-contrast barium enema (DCBE), FOBT, CT colonography (CTC), Stool DNA (SDNA, not yet available locally), and Capsule Endoscopy (CE), colonoscopy provides the patients that enviable opportunity for a non-operative removal of adenomas and/or early CRC.[46, 47, 85]

Statement 6D

Stool DNA, DCBE, and CTC are not recommended screening tests for CRC

Level of Evidence: Moderate
Strength of Recommendation: Moderate

Due to its unavailability, higher cost compared to FIT, uncertainties of screening intervals and unknown approach to patients with a positive stool DNA (SDNA) but negative colonoscopy, this guideline does not recommended SDNA as a screening test for CRC .

The sensitivity of DCBE is lower than that of CTC, FS and colonoscopy and is solely diagnostic.[86] In addition to associated radiation risks and the decline in its use in the country, DCBE is not recommended as a screening option for CRC. It can be reserved as an alternative screening tool in patients who cannot undergo the other recommended screening tests or in centres without endoscopy facilities.

Unlike DCBE, there is increasing evidence that CTC may be an accurate screening method in asymptomatic average-risk adults.[87] A review of several CTC studies in a screening setting reported a sensitivity of 83% in detecting polyps >10 mm in size and 68% for polyps measuring 6-9mm. The specificity of CTC for polyp detection was above 95%.[88-90] The use of multidetector scanner equipped with 3-D colonoscopy simulators may increase the sensitivity of CT colonography, however, they are not available yet even in urban centres in the Philippines.

In addition, the disadvantages of CTC are numerous, i.e., risks of radiation, under-reporting of polyps <6mm, need for expensive equipment and expertise.[20,89,91] Patients also found that CTC was more burdensome, more painful and caused more embarrassment than conventional colonoscopy.[92,93] Most importantly, CTC is only a diagnostic procedure. Currently, CT colonography, if available, may be used as an alternative screening tool for patients who cannot undergo colonoscopy or have had an incomplete colonoscopy.

Statement 7A

Currently, colonoscopy is the preferred modality in the detection and treatment of premalignant colonic lesions.

Level of evidence: moderate;
Strength of recommendation: strong
A – 94.7%; B – 5.3%

The joint guideline of the American Cancer Society, USMTFCC and the American College of Radiology differentiates the screening test(s) which can detect adenomatous polyps from test(s) which detect primarily colorectal cancer.[1] Screening tests that detect primarily colon cancer include FOBT, FIT and stool DNA. Tests which detect both adenomatous polyp and cancer include DCBE, CTC, FS and colonoscopy (Table I).[49,94]

Polypectomy, usually performed when polyps are found during a diagnostic colonoscopy, has contributed to a significant reduction in the incidence of colorectal carcinoma by 43-90%.[46,84,95] Based on a comparison with expected mortality in the general population Zauber et al. calculated a reduction in mortality from 25.4 to 12 deaths in 20 years for patients who have had endoscopic polypectomy.[47] An Asian study reported that the proportion of colorectal neoplasms prevented by FS is 37.1% and for colonoscopy, 54.1%, respectively.[65] In this context, colonoscopy is usually performed after a non-invasive screening test have shown positive results. Among the screening examinations available for CRC, only endoscopic modalities allow the removal of premalignant colorectal lesions. The choice between flexible sigmoidoscopy and colonoscopy may be influenced by the frequency of right-sided colonic (proximal) lesion in the population being screened. Sung et al, compared the frequency of advance colorectal neoplasm (ACRN) in the proximal colon between western and eastern studies and showed a comparable distribution, i.e., 23.7-45% and 19.6-43.6% respectively.[96] The Asia Pacific Working Group on Colorectal Cancer found that colonoscopy performed among symptomatic patients yielded 512 ACRN out of 5464 patients (9.4%), 136 of them (3.0%) have proximal lesions. Advanced age was also identified as a risk factor for proximal colonic lesions.[97] A recent review showed that even though population-based case-control and cohort studies have indicated that colonoscopy with polypectomy reduces CRC incidence by 67-77% and mortality by 31-65%, these are observational studies and results may have biases in adherence, sampling and design. Hence, the magnitude of effectiveness of colonoscopy remains unclear.[98] The benefits of colonoscopy, however, made it the preferred and recommended CRC prevention test by the American College of Gastroenterology.[18]

Table I. Advantages and disadvantages of different tests to detect and treat premalignant colonic lesions

Tests	Advantages	Limitations
Double contrast Barium enema	Non-invasive, almost always evaluates the entire colon, useful when colonoscopy is incomplete	Lack of RCTs to reduce incidence or mortality from CRC in average risk adults, requires bowel preparation, expertise, exposure to radiation, no opportunity for polypectomy, findings of polyp >6mm requires colonoscopy; perforation rate: 1 in 25,000
CT colonography	Less invasive, high sensitivity for the detection of lesions >10mm	No evidence of reduction in CRC incidence, requires bowel preparation, special resources and expertise, treatment of patients with <6mm polyps uncertain, detection of flat polyp uncertain, repeat testing unknown
Flexible sigmoidoscopy	Office-based, sedation not necessary, pre-malignant colonic lesions can be removed, case control studies showed 60% reduction in mortality from distal colon cancers	Does not detect proximal lesions, less effective in elderly and in women, sensitivity and specificity in clinical practice unknown
Colonoscopy	90% sensitivity for lesions >10mm, case-control studies show a 53-72% reduction in incidence of CRC and 31% reduction in mortality, premalignant colonic lesions can be removed and is the recommended test to evaluate the colon when other screening tests show positive result	Lack of RCTs showing reduced incidence or mortality from colorectal carcinoma. Requires bowel preparation, special resources and expertise, Expensive, invasive, 3-5 adverse events per 1000 examinations and sensitivity and specificity in clinical practice unknown

Statement 7B

Colonic polyps should be removed, preferably with a well-performed endoscopy-based polypectomy.

Level of evidence: high;
Strength of recommendation: strong
A – 85%; B – 15%

Colonoscopic polypectomy reduces the incidence of CRC compared with that expected in the general population.[46, 84, 95, 99] Nishihara et al, demonstrated that when comparing groups who underwent endoscopy and no endoscopy, the multivariate hazard ratios for CRC were 0.57 after polypectomy, 0.60 after negative sigmoidoscopy, and 0.44 after negative colonoscopy.[84]

All visible polypoid lesions of the colon should be removed. Although most are diminutive (<0.5cm) and small (0.6-0.9cm) polyps, majority of these warrant attention because 40-50% of these diminutive polyps may be neoplastic.[100-103] A recent Asian study reported that a substantial proportion of high-grade dysplasia was seen in diminutive polyps (18.7%) and small polyps (37.6%). The proportion of polyps containing villous histology in diminutive and small polyps were 3.0% and 12.5%, respectively.[104] An unpublished study from the Philippines by Peña et al. showed congruent results, i.e., 24% of diminutive polyps have neoplastic histology.[105]

Techniques in polyp removal vary but the best options are those which can achieve complete removal with very minimal associated risks. Cold forceps polypectomy is suitable for polyps less than three mm because they can be completely removed with a single bite, the entire sample is retrieved for histopathological examination and the associated risks are exceptionally low. Hot biopsy applies diathermy through the forceps to ablate residual polyp tissue. It is suitable for polyps up to 5.0 mm in size, however, this technique has fallen out of favor due to the risk of post-polypectomy bleeding and perforation. Cold snare polypectomy is fast, effective, and safe and is currently the preferred technique for small sessile polyps up to 7.0 mm in size while hot snare is recommended for sessile lesions >7–8mm. Pedunculated lesions are better snared and cut with diathermy when larger than a few millimeters to avoid bleeding risk.[106, 107] Endoscopic mucosal resection (EMR) may be performed for removal of small (<2 cm), sessile or flat neoplasms confined to the superficial layers (mucosa and submucosa). EMR may be utilized also for piecemeal removal of larger lesions. Endoscopic submucosal dissection (ESD) has been developed for en bloc removal of large, >2 cm, flat GI tract lesions. EMR and ESD may be used for definitive therapy of premalignant and early stage (T1M0N0) malignant lesions.[108]

The polyp must be completely excised and submitted in toto for pathological examination – to properly classify the polyp, determine presence or absence of malignancy; evaluate grade, vascular and lymphatic involvement and proximity to the margin of resection if malignant.[41] Invasion of the stalk of pedunculated polyps, by itself, is not an unfavorable finding, for as long as the cancer does not extend to the margin of resection. In addition, there must

be no vascular or lymphatic involvement. The estimated risk of residual cancer or nodal metastases from endoscopically-resected pedunculated and sessile malignant polyps with favorable criteria is 0.3% and 1.5%, respectively.[109] Endoscopically-resected malignant polyps associated with poor prognosis include polyps which have a poorly differentiated histology, positive resection margin, or with lymphatic or vascular invasion. The reported residual cancer is 8.5% and 14.4% in pedunculated and sessile malignant polyps, respectively.

The decision to proceed with surgical resection needs to be individualized, taking into account the age of and comorbidities present in the patient.

Statement 8

A proper bowel preparation prior to colonoscopy is essential for an optimal assessment of the entire colonic mucosa.

Level of evidence: moderate;
Strength of recommendation: strong
A – 95%; B – 5%

The Asia Pacific guidelines on colorectal screening emphasize that the effectiveness of colonoscopy in the detection of colonic neoplasms is dependent on the quality of the colonoscopic examination.[96]

Thus, adequate pre-endoscopic preparation of the large bowel to ensure a complete visual examination of the colonic lumen and mucosa is mandatory. The importance of the quality of bowel preparation is reflected in the diagnostic yields, polyp missed rates, difficulty, speed and completeness of colonoscopies, CRC rates after screening colonoscopy and the adenoma detection rate (ADR) of individual endoscopists.[110-114] Most missed polyps, blamed as an important reason of post-polypectomy CRCs, occur not uncommonly on inadequately prepared colons.[115-117]

In both Western and recent Asian studies, poor bowel preparation also reduced cecal intubation rates, prolonged colonoscopy time, lowered diagnostic yields and contributed to frequent repeat colonoscopies outside the recommended interval with more patients experiencing discomfort.[111, 118]

Several patient and procedure-related factors that may influence adequacy of bowel preparation prior to colonoscopy have been described, namely; calcium channel blocker use, age, male gender, constipation, diabetes, low educational background, history of appendectomy, colorectal resection and hysterectomy, previous poor preparation and lag time >16 weeks from scheduling to actual performance of the colonoscopy.[119] Recognition of these factors prior to colonoscopy and adequate manipulation of the bowel preparation will help reduce poor quality colonoscopy.

The quality of preparation must be included in the endoscopy report. This will serve as a quality indicator of colonoscopy and it is recommended that a 93% reporting rate should be achieved.[113] Quality of preparation is usually reported as excellent, when there is no or minimal solids with minimal fluid requiring suctioning; good, when there is more fluid that require suctioning; fair, when there is semisolid material that are difficult to clear; and poor, when there are solid/semisolid materials which cannot be cleared.[119]

There are three validated bowel preparations scales often used in clinical trials, namely; Aronchik, Ottawa and Boston Bowel Preparation Scales (BBPS),[119-121] For uniformity in reporting for bowel preparation in endoscopy units in the country, we recommended the BBPS be adopted. The BBPS rates the three segments of the colon only after cleansing is done as one withdraws the scope. This is more important clinically since follow up recommendation is based upon how much colon was visualized adequately.

Meanwhile, the American Society of Anesthesia recommends that clear liquids may be taken up to two hours before the procedure.

There are several bowel cleansing formulas available in the Philippines thus, a good knowledge of their safety and side-effect profiles, drug-drug interaction, dosing and administration scheme is highly recommended. One of the ultimate goals of this guideline is to narrow the gaps in bowel preparation in order to achieve consistently a high quality colonoscopy.

Statement 9

Surveillance colonoscopy is recommended in asymptomatic individuals with previously-identified precancerous lesions. The interval of surveillance colonoscopy depends on the adenoma risk level after baseline examination.

Level of evidence: moderate;
Strength of recommendation: strong
A – 94.1% B – 5.9%

Colonoscopic surveillance is performed to "identify recurrent or metachronous neoplasia in an asymptomatic individual with previously identified precancerous lesions."[122] The surveillance interval depends on the findings on baseline or previous colonoscopy and on the assumption that the procedure adequately visualized all segments of the colon and all identified polyps were adequately removed.

This guideline adapted the 2006 US Multi-Specialty Task Force (USMSTF) classification of adenoma risk based on size and histologic characteristics, as follows; low risk adenomas are defined as 1–2 tubular adenomas, <10mm in size; high risk or advanced adenomas are adenomatous polyps with any of the following features: multiple (≥ 3 adenomas), ≥10 mm in size, presence of villous component or with high grade dysplasia.[123] These feature have also been identified as predictors for metachronous advanced neoplasia and cancer, particularly the number of adenomas identified, i.e., HR-2.44, 95% CI, 1.11-5.35124 to 3.06, 95% CI, 1.51-6.57)125 and OR - 2.52, 95% CI,1.07-5.97,126 (Table II).

Table II. Predictors for metachronous advance neoplasia and cancer on surveillance colonoscopy

STUDY	No of adenoma OR for ≥3	Size of adenoma ≥10mm	Villous component	High grade dysplasia
Winawer (NEJM 1993)[46] RCT	2.4 (1.7,3.5)	not significantly associated	not significantly associated	not significantly associated
Saini (Gastroint Endosc 2006)[127] SR/Metaanalysis 5 studies	2.52(1.07,5.97)	1.39	1.26	1.84 (1.06,3.19)
Martinez (Gastroenterology 2009)[128] SR/pooled analyses, 8 studies	p<0.0001	p<0.0001	1.28	-not independently associated
Huang (J Gastroenterol 2012)[129] Retrospective cohort (N=1356)	p<0.05	p<0.05	HR 2.57 (1.24,5.32)	HR 1.61 (1.07, 2.42)
de Jonge (Endoscopy 2011)[126] SR - 27 studies	1.64	1.66		
Chung (Gut 2011)[125] Prospective (N=2452)	HR 3.06 (1.51,6.57)	HR 3.02 (1.80, 5.06)		
Ji 2009[124] (correcting for miss rates) Miss rate: 21.2% Prospective (N=120	HR 2.44 (1.11-5.35)	not independently associated	not independently associated	not independently associated

Table III. 2012 Recommendations for Surveillance and Screening Intervals in individuals with Baseline Average Risk according to the USMSTF

Baseline colonoscopy: most advanced finding(s)	Recommended surveillance interval (*y*)
No polyps	10
Small (<10 mm) hyperplastic polyps in rectum or sigmoid	10
1–2 small (<10 mm) tubular adenomas	5–10
3–10 tubular adenomas	3
>10 adenomas	<3
One or more tubular adenomas ≥10 mm	3
One or more villous adenomas	3
Adenoma with HGD	3
Serrated lesions	
Sessile serrated polyp(s) <10 mm with no dysplasia	5
Sessile serrated polyp(s) ≥10 mm	3
OR	
Sessile serrated polyp with dysplasia	
OR	
Traditional serrated adenoma	
Serrated polyposis syndrome[a]	1

IMPORTANT.
These recommendations presume that the baseline colonoscopy was of high quality and complete ate and that all polyps seen were removed completely.

[a]Based on the World Health Organization definition of serrated polyposis syndrome (SPS), with one of the following criteria: (1) at least 5 serrated polyps proximal to sigmoid, with 2 or more _10 mm; (2) any serrated polyps proximal to sigmoid with family history of serrated polyposis syndrome; and (3) >20 serrated polyps of any size throughout the colon.

Depending on the lesion identified and removed during the prior colonoscopy, the recommended interval of surveillance colonoscopy according to the 2012 USMSTF is enumerated in Table III. An every ten year-interval for continued screening of patients with negative colonoscopy on baseline examination is based on prospective and retrospective cohort studies which showed the protective effect extends ≥10 years after a negative prior colonoscopy.[130, 131]

Surveillance is also recommended for serrated polyps. Serrated polyps are classified into hyperplastic polyp, traditional serrated adenoma (TSA) and sessile serrated adenoma (SSA). Hyperplastic polyps are small, <0.5 cm, sessile or slightly raised and mostly seen at the left colon. Majority of serrated polyps are hyperplastic. TSAs may be pedunculated or broad based large polyps, usually seen in the left colon. SSAs are smaller polyps, which are difficult to differentiate endoscopically from adenoma or other serrated types, and seen usually at the right colon and on crests of mucosal folds. Annual surveillance is recommended for patients with serrated adenomatous polyposis or serrated polyposis syndrome (SPS) due to the aggressive nature of the disease. In one cohort, 61-83% of patients with SPS have SSA, with development of recurrent SSA on retained colorectum within a median of two years after colon resection.[132] After a clearing colonoscopy of patients with SPS, the cumulative risks after three consecutive colonoscopies for cancer, advance adenoma or adenoma >10mm are 0%, 9% and 34% respectively.[133]

Statement 10

Surveillance is recommended after resection of colorectal cancer.

Level of evidence: high;
Strength of recommendation: strong
A – 94.7%; B – 5.3%

Recommendations about the timing of colonoscopy after colorectal cancer (CRC) resection should be directed towards the early detection and timely polypectomy of metachronous adenomas while meeting the general objectives of CRC surveillance. In 23 studies (1983-2003) involving more than 9000 patients, 57 of 137 patients developed metachronous cancers within 24 months of surgery. Such a rate of cancer detection is comparable to the rate of prevalent cancer detection in the setting of screening colonoscopy.[134] The weight of evidence from the literature support performing the initial post-operative surveillance colonoscopy at one year. If this examination does not reveal a metachronous neoplasia, the intervals between subsequent colonoscopies should be three and five years, depending on the number, size and histologic type of polyps (if any) removed.

A systematic review of eight RCTs of 2,923 patients with CRC undergoing curative resection revealed that overall mortality rate improved significantly for patients who had more intensive surveillance (21.8%) versus less intensive surveillance (25.7%) (OR = 0.74; P = 0.01).[135] Trials utilizing serum CEA demonstrated that an intensive surveillance schedule, three monthly for first two years, has a significant impact on overall mortality (P=0.03). In six studies, the incidence of asymptomatic recurrence was significantly higher in patients who had more intensive follow-up (OR, 3.42; P<0.00001). Another six studies reported that a more intensive follow-up detected the first recurrence 5.91 months earlier (P<0.0001) and significantly increased reoperation rate with curative intent for recurrent disease, irrespective of the diagnostic strategy adopted, P<0.05. This improvement in curative reoperation rates was demonstrated also with more frequent application of individual tests, i.e., serum CEA level, P = 0.0006; colonoscopy, P = 0.01; liver US, P = 0.0006; CT scan, P = 0.01.[135]

We recommend to perform colonoscopy one year after the resection of a sporadic CRC. If the colonoscopy at one year reveals advanced adenoma, the interval of the next colonoscopy should be three years. If the colonoscopy at one year is normal, the interval of the next colonoscopy should be five years. Colonoscopy should be performed three to six months after resection of an obstructing CRC, especially if a complete perioperative colonoscopy was not done. After CRC resection, CEA, and CT scan of the abdomen and chest, should be done every six months and annually, respectively, for five years.

Statement 11

Primary care physicians and other specialists should be engaged to promote public awareness on CRC screening and prevention.

Level of evidence: moderate;
Strength of recommendation: strong
A – 86.7% B – 13.3%

Physician recommendation increases the likelihood of a patient undergoing CRC screening.[11,12,136-140] People in the Asia Pacific countries with a low CRC screening test uptake have also the least knowledge of CRC symptoms, risk factors and screening tests. These countries have also the lowest physician recommendation rates for CRC screening. Japan and the Philippines have high physician recommendation rates and consequently had the highest participation rate.[12] Sung reported that physician recommendation increased the likelihood of undergoing a CRC screening test by 23 times in a randomly surveyed population of Chinese residents in Hong Kong.[11]

Fenton showed that physician counselling is associated with increased perceived CRC susceptibility and greater intention to undergo CRC screening. Within six months, 17 of 38 patients (45%) who discussed CRC screening with their physician underwent a test compared with 0 of 12 who did not discuss screening (P=0.01).[136] The US Preventive Services Task Force recommends using the 5 As (Assess, Advise, Agree, Assist and Arrange) when counselling. Patients whose visit contained more than one to two steps are more likely to undergo screening. A CRC screening recommendation (Advise) that also describes patient eligibility (Assess) and provides help to

obtain a screening exam (Assist and Arrange) will lead to improved adherence to CRC screening.[137]

Despite the crucial role doctors play in increasing the CRC screening uptake, why are doctors not recommending CRC screening to eligible patients? Factors identified as barriers to physicians offering CRC screening include lack of knowledge and training, lack of time and opportunity, forgetfulness and, an assessment that cost could be prohibitive to the patient. Likewise, inconsistencies in guideline recommendations may make doctors reluctant to give advice to their patients.[138, 141]

Given their pivotal role in a successful CRC screening strategy and in order for the Philippines to reach an uptake of 65-70%, every physician, primary care or otherwise, is therefore enjoined to grab every opportunity to promote colon cancer prevention and early cancer detection among their patients.

Statement 12

Primary care physicians and other specialists should be engaged to promote public awareness on CRC screening and prevention.

Level of evidence: moderate;
Strength of recommendation: strong
A – 84.2%; B – 15.8%

The primary aim of CRC screening as a tool for cancer control is to lower the burden of cancer in the population thru discovery and effective treatment of early and latent disease. CRC screening is more cost saving compared to multi-drug intensive chemotherapy for advanced colorectal cancer.[142]

The secondary aim of CRC screening is to reduce cancer mortality and, in some instances, cancer incidence across the population. In England, results from the phased implementation of the United Kingdom Bowel Cancer Screening Programme (BCSP) launched in 2006, using gFOBT as screening strategy, showed participation of up to 52% after the first 1.08 million tests. If maintained, they project a decrease in overall CRC mortality by 16%.[143]

The Consensus Group advocate that CRC screening should be part of the national health program of the Philippines. Studies show that almost all standard options of CRC screening is more cost effective compared to no screening.[142,144-146] To reduce cancer mortality and cancer incidence there must be adequate uptake and participation by the target population.[147] From experiences in the European Union, it takes a minimum of 10 years to plan, pilot and implement an organized population-based CRC screening program.[148] For the Philippines, this consensus guideline may be a good start going forward.

We recognize that several important issues need to be addressed. First, what will be the screening strategy: iFOBT/FIT or colonoscopy? We await results of three ongoing randomized controlled trials (2 European studies and 1 US study) evaluating colonoscopy as a primary screening tool.[75,149,150] The Asia Pacific Guidelines state that iFOBT/FIT is the preferred screening test for resource-limited countries.[3] We recommend further that a cost-effective analysis study for CRC screening program in the Philippine setting be done.

Second, where will the funding for the screening program come? Funding has to be established and perhaps legislated. In Europe, most organized programs are subsidized fully or partially by the government.[148] In the US, the Affordable Care Act requires that all private health plans cover CRC screening tests without any out-of-pocket costs to patients. Cost for screening tests, including colonoscopy, is waived for Medicare beneficiaries, as well. An incentive is given to states that offer CRC screening to Medicaid beneficiaries.[151] For the Philippines, the Consensus Group recommends that the national health policy must require the Philippine Health Insurance Corporation and/or health maintenance organizations (HMOs) to cover CRC screening costs.

Third, are there enough qualified gastroenterologist to perform colonoscopy and polypectomy in patients who test positive for iFOBT/FIT? It is recommended that the Philippine Societies of Gastroenterology and Digestive Endoscopy to create colonoscopy hubs and craft programs to ensure that qualified gastroenterologists are distributed equitably in all areas of the country.

An opportunistic screening scheme is the current approach to CRC screening in the country. Only patients who are advised by their physicians or who have knowledge about CRC screening from elsewhere and desire to undergo the screening test are examined. Increasing public awareness on CRC and the value of screening and early intervention must be waged relentlessly by multi-sectoral groups.

The planning and implementation of an organized CRC screening program will be difficult. The support from the government, various professional and patient advocacy groups will be essential. The screening strategy chosen will arguably be dependent on medical evidence, availability of resources and funding and the cultural acceptance of the Filipinos to this program.

As we move forward, we put in mind the words of Sydney Winawer, Co-chair of IDCA (international Digestive Cancer Alliance): "The best screening test is the one that gets done…and gets done well. Do what you can with what you have."

Conclusion

In the Philippines, colorectal cancer is currently the most common cancer of the gastrointestinal tract and its incidence and associated mortality are still rising. This common cancer, however, can be prevented by early detection and removal of precursor colonic adenomas. CRC has a high survival rate if detected and removed in its early stages. Due to our better understanding of its

natural history and pathogenesis, there is a well-described at-risk population for whom a screening and surveillance strategy can be directed.

Most importantly, the ability of currently-available, relatively cheap, reliable, and simple tests for early diagnosis and the increased survival of patients wherefrom precursor polyps or early staged CRC have been removed make the case why we must adopt a national program to promote CRC awareness, implement a fully-funded CRC screening and surveillance strategy, as well as, increasing the availability of experts and qualified centres for minimally-invasive CRC treatments.

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