

Technological advances: what hope for colorectal cancer?

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Abstract

Introduction: Colorectal cancers rank third in all cancers. Mass screening has proven effectiveness by significantly reducing incidence and mortality. If optical colonoscopy is the reference exam, virtual colonoscopy is an alternative of choice. We evaluate its first-line position in screening, following technological progress.

Methods: We used PubMed's electronic search data from 2010. Among the 100 most consulted articles, have been studied those in English-language and which looked at screening in the population at average risk aged between 50 and 75 years , asymptomatic and dealing with optical and virtual colonoscopy. Studies in the symptomatic, high-risk, or very high-risk population or for diagnostic purposes were excluded.

Results: in the USA, studies confirm the trend towards a decrease in incidence and mortality by colorectal cancers, shifting from 56.7 per 100,000 and 23.6 deaths respectively in 1992 to 36.5 per 100,000 and 14 deaths in 2015, thanks to the means of screening including the endoscopy. Although optical colonoscopy is the standard exam, virtual colonoscopy, with a specificity of 90% and a sensitivity of 85%, is becoming more and more a first-line means of screening for colorectal cancers.

Conclusion: Thus, first-line endoscopic screening has proved its effectiveness in reducing morbidity and mortality by this cancer. However, the virtual endoscopy chosen by the National Comprehensive Cancer Network as a means of screening will undoubtedly constitute a strategy for the future, particularly in developing countries.

Keywords: colorectal cancers; screening; optical colonoscopy; virtual colonoscopy.

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1. INTRODUCTION

With more than 1 million diagnosed cases per year worldwide and a mortality of more than 500,000 [1], colorectal cancers (CRC) are a public health problem [2].

They are sporadic in 70 to 80% of cases, occur in a family context in 20 to 30% [3] of cases and are linked to a genetic predisposition in 5 to 10% of cases [4].

Depending on the risk of developing CRC [5-8], we distinguish the group at:

- Average risk:[9] to which belongs any person over the age of 50, without any other associated risk factor of CRC [10].

- High risk: higher than 5% throughout life and in which we find people with personal or family history of adenoma or CRC [11] as well as people with chronic inflammatory bowel disease [12-15] (chronic inflammatory rectocolitis or Crohn's disease).

- Very high risk: characterized by genetic mutations [8, 16] and in this case it is hereditary cancers which represent 5% of all CRC [17].

While colonoscopy surveillance does not pose an indication problem for high and very high risk groups [6, 7], this is not the case for the average risk group [18].

Advances in technology have enabled the development of numerous means

including high definition endoscopy coupled with virtual chromoendoscopy and virtual colonoscopy, which must be optimized to obtain the best results in terms of lives saved.

2. Methods

We studied the 100 most cited articles and the 20 most cited articles per year [19]. In order to reinforce our study and not to ignore recent publications, which are necessarily less cited and whose results are a reflection of technological progress, we conducted a search using the Pubmed database over the period from 2010 through 31 January 2019, using the keywords: "colorectal screening", "Colonography, Computed Tomo-graphy," "virtual colonoscopy," "optical colonoscopy". We studied the recommendations and their justifications of the learned society NCCN [6, 7] and US Preventive Services Task Force [10, 20].

- **Inclusion criteria**, this study included articles in the English language that deal exclusively with colorectal screening in the general population aged 50 to 75 years, in both sexes, with no family or personal history of CRC or adenoma, or personal history of inflammatory bowel disease. These studies, which may be comparative, must necessarily deal with the so-called direct screening means, structural or endoscopic, namely virtual and optical colonoscopy.

- **Exclusion criteria** were excluded studies that deal with the diagnosis of CRC or symptomatic subjects as well as those concerning subjects under 50 years old, in the case of a contraindication of a means of screening, and in the case where a study does not evaluate a tool as a means of screening. All studies evaluating screening in the high or very high risk population were excluded.

- Studies dealing with the diagnosis of CRC.
- Studies concerning subjects under 50 years old.
- Studies not dealing with the evaluation of a tool as a means of screening.
- Studies evaluating screening in the high or very high risk population.
- In cases of contraindication of a means of screening.

3. MEANS

Endoscopy

Optical colonoscopy (OC) explores the entire colon and rectum.

Rectosigmoidoscopy allows endoscopic examination of the rectum and left colon (up to the left colic angle), the development site of $\frac{3}{4}$ of CRC. Endoscopy reduces CRC mortality through early diagnosis [21] especially the detection of precancerous lesions that are polyps [11] (by resecting them preventing their progression to cancer). OC has allowed the USA to reduce the incidence of CRC [17] from 76 to 90% [22] in a population with endoscopy. This reduction is significant for left lesions less for right colon cancers [23, 24].

The CO with dual diagnostic and therapeutic advantage [9] must first detect a polyp and, in a second time, characterize it.

The detection of polyps can be difficult because of:

- Their size, they can be hidden by colic folds.

- The appearance of the polyp. A polyp can be pediculated projecting into the light or sessile based implantation more or less wide or even plan aspect and in this case the detection is even more difficult.

Modern endoscopes make it possible to obtain high definition images "HD" (2,000,000 pixels). Some studies have not found a difference in the detection rate of adenomas (DRA) or polyps (DRP) between standard colonoscopy and HD [25, 26].

A multicenter study showed that DRA was higher with HD colonoscopies, especially for flat adenomas and right colon [27]. White light with HD images seems to increase the DRA by 3.5% [28]. In order to increase the detection rate, have been made available to endoscopists:

➤ Colonoscopes with enlarged vision:

- The Full-Spectrum Endoscopy system has the particularity of having 3 cameras which allows a 330 ° angle of view compared to 140 to 170 ° for the other endoscopes and this system seems interesting for the detection of polyps behind the folds and to the internal side of the colic angles with less adenoma missed [29].

- The Extra-Wide-Angle-View Colonoscope with wide field of view thanks to two cameras placed on the sides (144 - 232 °) and one at the end of the endoscope (140 °) and this system seems to improve the DRA by 22 % [30, 31].

- The third eye or Third Eye Retroscope. The retro vision is often used in the rectum to analyze the anal area and not to miss lesion at the bottom caecal [32].

➤ Endoscopes with balloon system.

➤ Colonoscopy assisted by cap.

All polyps do not degenerate [8, 33, 34] and the risk is related to the histological type, namely adenomatous polyps with villous component and serrated polyps (the latter predominate in the right colon and are usually sessile), the presence of severe dysplasia, and size of the polyp [35, 36]. Hyperplastic polyps of small size (less than 1 cm) especially those located in the rectum or sigmoid pose no risk of malignant transformation [7, 37].

Very innovative approaches have been made possible by technological progress. In the age of modern technology and in the case of CRC the purpose of the examinations is to detect polyps at risk and resect them. This supposes that we can recognize them. We can also remove without analyzing the (so no pathologic study) polyps that are certainly safe with a cost saving [38]. This is the so-called DISCARD strategy of "Detect InSpect ChAracterize Resect and Discard Or "Characterize, Resect, and Leave". This strategy is feasible [39] and safe [40] because we can count on modern technology. It is possible to recognize polyps certainly safe, hyperplastic type, small and localized in the rectum or sigmoid and abandon them which allows even more economy. This is the so-called strategy: Characterize and Leave or "Detect-and-leave" or "Detect-and-disregard".

To better analyze the colonic surface and find the polyps we have the indigo carmine vital staining or chromoendoscopy [41] and virtual chromoendoscopy using integrated systems including NBI (Narrow Band Imaging) [42-44]. The principle of virtual chromoendoscopy relies on the exploitation of the physical and optical properties of certain specific bands of the white light spectrum.

The endoscopy of the modern era must characterize the polyps detected hence the notion of optical biopsy [45]. If for the detection of polyps, the expertise of the operator remains the essential element and although the detection rate is improved by HD modern endoscopes including the right, it should be specified that the characterization which consists in predicting the histological diagnosis of polyps has, with the NBI and without Zoom, a diagnostic accuracy of 96 to 98% for polyps less than 1 cm [46, 47].

The high magnification optical Zoom up to X60 or even X400 allows a microscopic scale analysis of the mucosal surface indeed subcellular analysis (X1000) by endo-microscopy by mini probe allowing a histological analysis in real time [48, 49]. In combination with the NBI the diagnostic accuracy approaches the histopathology [49].

The NBI associated with a high optical magnification used by Japanese teams allows a diagnostic accuracy higher than 96% and a negative predictive value (NPV) of 96% [50].

The classification Nice [51] (NBI International Colorectal Endoscopic) is widely used [52]. It is based on NBI analysis without zooming the color of the polyp, the presence of vessels (and their diameter) and the pattern of the mucosa. It makes it possible to distinguish the polyps hyperplastic (type 1), adenomas (type 2) and infiltrating cancers (type 3).

Virtual colonoscopy or Computed tomography colonography (CTC) :

It is a colon scan with CO₂ insufflation that can be performed without intravenous injection. This examination whose performance improves in parallel with technological advances has shown since few years 90% of polyps larger than 1 cm found by optical colonoscopy (OC), discovered some lesions not perceived by CO, for a total a sensitivity and a specificity of 90% for polyps larger than 1 cm [53-55]. The CTC is very specific even for small polyps [56] but the sensitivity varies widely according to the studies [20]. These differences could be explained by the types of scanners, detectors, the thickness of the cuts [57], the terms of acquisition and are based on readers [58] and their expertise [59, 60]. Overall, the CTC has excellent sensitivity and specificity for polyps > 10 mm in particular adenomatous and early cancers, hence its place in screening [53-55, 61-65] even if the sensitivity decreases with the size of the polyp [66-69]. The detection of polyps is enhanced with computer assistance (Computer-Aided polyp Detection (CAD) program) [70] especially for small polyps [71]. Interpretation time is reduced [72, 73] and detection seems comparable to that of OC according to some studies for adenomatous polyps > or = 8 mm [74]. However flat polyps are difficult to detect [75] but this should not be an obstacle for the CTC as a means of screening including first-line [76]. This assistance does not replace the expertise that the radiologist must have [59] whose experience in gastrointestinal radiology is an undeniable advantage that can not be bridged by the single learning curve [77]. The interpretation is done by a radiologist who has the required expertise [9] the consequences of inadequate interpretation can be severe. CTC screening adherence [78] is significantly higher compared to OC, which probably identifies more polyps per 100 people. The diagnostic performance of advanced neoplasia per 100 participants is equivalent, which justifies the use of

the both means of screening in the average-risk population [79]. Indeed OC remains the reference exam and the most used in the USA [80] and whose sensitivity and specificity are higher compared to the CTC [81]. Higher CTC participation rate [82] fills this difference globally leading to a similar detection of advanced neoplasias [83, 84].

The CTC is sensitive, especially after colon preparation even at minima [85] and ingestion of contrast product (gastrographine) which can be sufficient in itself for colonic preparation [86]. Currently even in low doses that do not alter its sensitivity [87] CTC does not require rigorous preparation of the colon [88]. As the prevalence of CRC is low (3.5 to 4.5%), a first-line CTC is desirable to avoid the complications of negative or white OC [89].

The detection rate by CTC for first-line screening is equivalent to the one of optical colonoscopy but the rate of complications and polypectomy is lower, which justifies the use of CTC as a means of screening and OC as a therapeutic means [90]. The complications of CTC are rare, especially the perforations that must be feared in elderly people with concomitant colic diseases [91].

The good negative predictive value of the CTC must reduce the indications of OC thus reducing the inconvenience of OC screening and cost [61, 92, 93]. It has a good concordance with the OC [92], is an effective option, safe, affordable, available, repeatable, fast and cost effective for colorectal cancer screening [94], that is why it was proposed in 2018 as a means of first-line screening [7, 83, 95].

It should be kept in mind that the detection rate of serrated polyps at risk is significantly higher for OC (facilitated by chromoendoscopy) compared with CTC (facilitated by contrast labeling) [96, 97].

Extra colic discoveries can be important [98, 99], beneficial but cause additional costs [100] that can be amortized by the management of serious illnesses [101].

It could cost up to 50% cheaper than the OC if its indications became broader to meet demand [102] and currently, compared to colonoscopy, its cost seems competitive [102, 103].

CTC allows better localization of lesions, which is important for surgery [104]. It has been an important part of colorectal exploration for more than ten years [105, 106]. There are currently wider indications for screening and first-line prevention of CRC [7, 106].

If for polyps of more than 1 cm discovered in CTC the indication of colonoscopy is certain, it will be more mitigated for polyps of 6 to 9 mm. Exploration and polypectomy are required for many polyps but for one or two polyps 6 to 9 mm, CTC control is possible because 38% of these polyps remain stable, 27% regress and only 35% become advanced [107]. In comparison with other screening techniques, virtual colonoscopy offers a safe option especially useful when colonoscopy is contraindicated [108].

Stool Tests - Stool-Based Tests

These tests are exclusively reserved for screening in the so-called average risk asymptomatic population. They consist of looking for occult blood in the stool by guaiac test or by immunological test and looking for alterations of the abnormal exfoliated DNA. These tests are not invasive and does not require any preparation.

Tests for occult blood tests in the stool

Two tests are available namely to find the occult blood in the stool by guaiac test and by immunological test.

The guaiac test (Hemoccult II® test and Hemoccult II Sensa test)

This gFOBT test "Fecal Occult Blood Test", detects the heme via a peroxidase reaction.

The Hemoccult II® and Hemoccult II Sensa tests are simple, inexpensive, painless, reproducible, reliable and validated, thus meeting the criteria necessary for a mass screening test.

In France the Hemoccult II test would detect only 20% of advanced polyps, 1 out of 2 cancers, decrease mortality by 16 to 18% at 10 years with a national observance of only 30% [109].

The Hemoccult-SENSA test is based on the Hemoccult II test on the detection of heme via a peroxidase reaction. It has a sensitivity of 64 to 80% for CRC but lower for adenomas [110].

These tests have the disadvantage of not detecting tumors that bleed very little, intermittently or not at all. The false positives are due to the positive reaction with the nonhuman heme (food) and the blood of gastrointestinal origin thus upper tract [7].

The immunological test "Fecal immunochemical tests (FITs)"

This test (iFOBT) detects the presence of human globin through the use of anti-globin monoclonal or polyclonal antibodies [9]. It has advantages over the Guaiac test [111] and is superior to it in terms of participation rate, positivity rate and detection rate [112-114]. It is specific for blood of colic origin, ruling out false positives for bleeding from the upper digestive tract [110], globin is rapidly digested in the stomach and the small intestine. This test allows an automated and reproducible reading.

Screening combining a positive FITs (iFOBT) test and colonoscopy allows the detection of 2 to 2.5 times more cancers and 3 to 4 times more advanced adenomas than the combination of a positive Guaiac test and colonoscopy [18]. The detection of cancer in-situ and stages I and II would be 71% whereas it is 55% for the Guaiac test; A test (FIT) is significantly superior to the guaiac test as a screening test in the average-risk population [115, 116] and should replace the gFOBT [110]. Screening by (FIT) leads to a reduction in mortality and the incidence of CRC [117, 118].

The gFOBT and iFOBT tests should not be used individually and certainly not in symptomatic people.

The abnormal DNA analysis test in the stool

The identification of abnormal DNA in the stool is a method of early diagnosis of colorectal cancer through searching for the APC gene mutation [6, 7, 18]. These are molecular tests. This method, certainly very promising in the future, is not considered to date as a well codified screening method [7].

Non invasive screening by the *Septin-9* test

The *SEPT9* gene codes for the SEPT9 protein. These proteins control cell growth and prevent uncontrolled divisions. The *SEPT9* gene is considered a tumor suppressor [119]. Hypermethylation can occur in the promising gene and

silencing it [119]. Epi pro Colon® 2.0 (Second Generation Test) allows the detection at the plasma level of methylated septin9[120]. The presence in the plasma of methylated septin9 is a bio-marker of the risk of neoplastic colic [121-124]. A positive test indicates a risk of CRC and an optical colonoscopy is recommended [125]. The sensitivity of the SEPT9 test would be equivalent to that of FIT but its specificity would be lower [126]. The sensitivity of SEPT9 for advanced adenomas would be lower compared to FIT [127]. The combination of tests is increasingly used in CRC screening. The FIT test associated with SEPT9 increases sensitivity and specificity [125]. This test was approved in 2016 by the FDA for CRC screening and the NCCN estimates that its sensitivity and specificity are lower than those of other tests [7].

MR Colonography

Studies on colo-MRI for screening are limited. One study showed a sensitivity and specificity greater than 75% for adenomas and cancers but which remain lower than those of colonoscopy [128]. Lack of equipment and cost would be unhelpful factors for this technique in screening and prevention [18].

4. Discussion :

Colorectal cancers mainly develop in subjects over 50 years of age who have no known risk factors [9, 10, 20]. Mass screening is aimed at this population aged 50 to 75 years [5-7, 10, 20, 80]. Fecal occult blood testing (Hemoccult II, Hemoccult SENSE or FIT) reduced CRC mortality [17, 129].

People screened in the US, where endoscopy is the primary means of screening and prevention, have a reduction in CRC estimated between 76 and 90% [22, 130].

Mass screening is a public health action, not an individual one. People at high or very high risk are excluded from mass screening and must be individually screened by optical colonoscopy according to the recommendations of learned societies [6, 7, 10, 20].

In the USA, screening is done in different ways. Flexible Sigmoidoscopy [23, 131] and OC have both reduced CRC mortality [132]. Virtual colonoscopy was introduced in 2018 as a means of first-line screening [7]. Overall CTC is not as sensitive and specific as CO but can be used for screening in the average risk population [133] because effective enough.

American recommendations include colonoscopy every 10 years, fecal occult blood test by annual immunohistochemical test (FIT), a 10-year Sigmoidoscopy coupled with annual FIT and virtual colonoscopy (CTC) every 5 years in subjects aged 50 to 75 years [6, 7, 20, 134]. These processes offer the same survival benefit in a years and a benefit ratio - equivalent risk [7, 134] in the case of screening. The CTC is better accepted by those screened and found to be less painful [135]. Both CTC and flexible Sigmoidoscopy are well accepted for CRC screening, but reduced discomfort associated with colonic preparation may improve participation in CTC screening [136, 137]. Indeed, the inconvenience of the examination and the disadvantages of the preparation are cited as the main

reasons for refusal of screening [138]. The preference of the CTC is related to the absence of sedation, the speed of the procedure and the least physical constraint [78]. Unfortunately, this examination remains underutilized while it represents an ideal balance between the minimum invasiveness and the performance [139]. The CTC can be an excellent exam that filters the persons with a good health economy avoiding negative colonoscopies and their complications although rare and by systematizing small diminutive polyps (< 6mm) without even taking them on the record [140, 141]. Regarding cost, CTC like other means is more cost effective than lack of screening [142, 143] and in the USA, with 75% compliance OC and CTC may reduce the incidence of CCR 46 to 54% [144] which represents an immense health economy. In addition, the CTC screening every 5 years is, according to a study, more effective than the OC every ten years [143]. The CTC is a relevant test that continues to develop to provide a high diagnostic accuracy that will make the examination cost-competitive with respect to OC [143]. Indeed, the more the subjects are referred to the OC after CTC and the more the advantage is to the OC and even to equal sensitivity the advantage remains for the OC [144]. Given these data, regarding the difficulty of proposing blood tests in the stool in developing countries and given the problems of sensitivity and specificity of these tests, which, in case of false positive, lead to white OC. Having regarding to the impossibility to offer out hand a screening by OC, if only by lack of endoscopists and dedicated blocks, it would be reasonable to propose a screening with virtual colonoscopy. Its sensitivity and specificity for polyps of more than 1 cm may degenerate are excellent. In addition, this examination is easier to practice provided that radiologists with specific training are available. CTC has the dual advantage of being more sensitive and specific than stool tests and has better acceptability than optical colonoscopy. Indeed the latter is more invasive, with several negative examinations and causes a work stoppage at least on the day of the examination.

5. Conclusion :

Although easily preventable, CRC ranks second to lung cancer in terms of overall mortality. However, this situation could be reversed if screening tests to effectively detect advanced adenomas and early cancers were widely applied. In developing countries screening and diagnosis of CRC would be significantly improved by paying particular attention to the mastery of virtual colonoscopy coupled with excellent expertise of endoscopists.

The aging of the population, population growth and exposure to additional risk factors (westernization of our way of life) explain the likely increase in the incidence of CRCs. Training of virtual colonoscopy radiologists must be considered to meet this challenge. Virtual colonoscopy is fast and without contraindications or major complications. It must select subjects with abnormalities under a colonoscopy. It goes without saying that this strategy will only achieve its objectives if expert endoscopists and appropriate equipment are available.

6. Conflict of intereststatement

We certify that there is no conflict of interest with any financial organization in the subject matter or materials discussed in this manuscript.

7. Authors' biography

No Biography

8. References

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