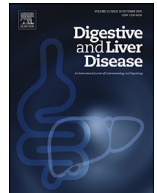




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SIED-GISCOR recommendations for colonoscopy in screening programs: Part I – Diagnostic

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ABSTRACT

The implementation of FIT programs reduces incidence and mortality from CRC in the screened subjects. The ultimate efficacy for CRC morbidity and mortality prevention in a FIT program depends on the colonoscopy in FIT+ subjects that has the task of detecting and removing these advanced lesions. Recently, there has been growing evidence on factors that influence the quality of colonoscopy specifically withing organized FIT programs, prompting to dedicated interventions in order to maximize the benefit/harm ratio of post-FIT colonoscopy. This document focuses on the diagnostic phase of colonoscopy, providing indications on how to standardise colonoscopy in FIT+ subjects, regarding timing of examination, management of antithrombotic therapy, bowel preparation, competence and sedation.

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1. Introduction

Organized screening programs based on biannual Faecal Immunochemical Test (FIT) are widely adopted in European countries, like Italy, France, Spain, and United Kingdom, to reduce the burden of Colorectal Cancer (CRC) in average-risk subjects. There is now clear evidence that implementation of FIT programs reduces incidence and mortality from CRC in the screened subjects [1–4].

FIT is effective in identifying subjects at increased risk of advanced neoplasia, namely already developed CRC (Positive Predictive Value, PPV: 3–5%) and advanced adenomas (PPV: 15–20%) [5], representing a 5-fold enrichment effect as compared with the initial prevalence in average-risk population. However, the ultimate efficacy for CRC morbidity and mortality prevention in a FIT program depends on the colonoscopy in FIT+ subjects that has the task of detecting and removing these advanced lesions, as well as the non-advanced lesions that are nonetheless present in a FIT+ population [6].

Differently from FIT, that is a well standardized test with consistent values in terms of repeatability and generalizability, performance of endoscopists in FIT+ colonoscopy is much more variable due to differences in performance across centres and operators [7]. When assessing the quality of colonoscopy in a sample of 79 centres and 479 endoscopists in the Italian CRC screening program, we noticed a variability in the key quality indicator, namely Adenoma Detection Rate, between 13.5% and 75% [8]. Recently, this difference in performance has been associated with a different level of prevention of CRC in FIT+ subjects. In detail, data from the same Italian screening program showed a significant inverse association between ADR and post-colonoscopy CRC (PCCRC) incidence risk, with a 2.35-fold risk increase (95% CI, 1.63 to 3.38) in the lowest performing endoscopists group compared with the highest. The adjusted HR for PCCRC associated with 1% increase in ADR was 0.96 (CI, 0.95 to 0.98) [1]. Data from the Dutch screening program, adopting a higher positivity cut-off, showed a similar association of the increase in the ADR with a progressive reduction of PCCRC incidence (HR:0.95) also in a population at higher prevalence of neoplasia and a consequential higher ADR (higher PPV) [3].

Recently, there has been growing evidence on the factors that influence the quality of colonoscopy specifically withing organized FIT programs, prompting to dedicated interventions in order to maximize the benefit/harm ratio of post-FIT colonoscopy, both in the diagnostic phase (i.e., inspection of the mucosa) and in the operative phase (i.e., polypectomy and advanced endoscopic resection).

When considering the importance of colonoscopy for an adequate CRC prevention in FIT programs, the Italian Society for Digestive Endoscopy (SIED) and the Italian Group for CRC Screening (GISCOR) decided to prepare this Position Statement in order to provide indications on how to standardize colonoscopy in FIT+

subjects. This first part of the document focuses on the diagnostic phase of colonoscopy.

2. Methods

This Position Statement was commissioned by the Governing Boards of the two societies (SIED, GISCOR) to a commission formed by members of the Scientific Commission of the SIED and the II-level Group of GISCOR. Such commission was responsible for:

- (1) Identification of the main domains to be addressed in the field of post-FIT colonoscopy
- (2) Definition of the Rationale and possible risk and burden for each of these domains
- (3) Search and summary for the available evidence (i.e., PubMed)
- (4) Formulation of the recommendations

The consensus for the proposed statements was assessed through an anonymous and iterative online Delphi process. A maximum of three sequential voting rounds to reach consensus was set beforehand. All statements were graded by using a 5-point Likert scale (1. Strongly disagree [D+], 2. Disagree [D], 3. Neither agree nor disagree [U], 4. Agree [A], 5. Strongly agree [A+]). Consensus was considered to be reached when there was at least 80% agreement (the sum of agree and strongly agree) on each statement. It was agreed that statements would have been deleted or reformulated by the project leaders for the subsequent voting rounds if the agreement was <80%. Changes were to be made to statements after each round of voting to consider the comments and discussions of the previous draft. It was previously agreed that in case of repeated lack of consensus to a reformulated question, the choice would have been made to exclude the statement from the final draft and report the lack of consensus. However, after 1 voting round, all statements were approved with over 80% agreement. A summary of recommendations is available in Table 1.

As this is a Position Statement, no formal grading of the recommendations was performed. This is because only a few articles were expected for each domain, and for the inclusion of variables other than scientific evidence, such as local factors that could affect the feasibility and implementation of the recommended interventions.

3. Timing and adherence to POST-FIT+ colonoscopy

3.1. Timing

3.1.1. Rationale

The need for a colonoscopy in the short term after FIT positivity is driven by the increased risk of advanced neoplasia and colon cancer (positive predictive value 25% and 5%, respectively) [5]. Such high prevalence mainly determines the risk of cancer progression due to diagnostic delay [9,10]. In addition, an excessive delay in the timing of post-FIT colonoscopy may affect the adherence to such

Table 1

Summary of recommendations.

TIMING AND ADHERENCE TO POST-FIT+ COLONOSCOPY

It is recommended that colonoscopies after FIT+ are performed within 60 days of test positivity.

It is recommended that adherence to colonoscopy after FIT+ should be at least 85%, 90% being desirable. Multi-modal interventions that can improve adherence are recommended.

MANAGEMENT OF ANTITHROMBOTIC THERAPY

1) *Aspirin*: continued medication is recommended. This recommendation is given because literature data do not demonstrate an increased risk of bleeding in patients on ASA therapy undergoing colonic polypectomy or advanced resection procedures (mucosectomy or submucosal dissection).

2) *Clopidogrel*: It is suggested that patients on secondary prophylaxis replace the drug with aspirin 7 days before the procedure if the patient is not allergic to aspirin. In aspirin-allergic subjects, a continuation of the drug may be considered if the patient's thrombotic risk is considered high. The recommendation is given because within screening programs, more than 80% of patients with polyps have non-pedunculated lesions of sub-centimeter size (<10 mm), the resection of which is relatively safe even without discontinuation of therapy, especially with the use of "cold" loop and the eventual application of mechanical hemostasis.

3) *Dual antiplatelet therapy (DAPT: aspirin + P2Y12 receptor antagonist)*: in all DAPT patients, cardiology or neurology consultation is recommended before scheduling a colonoscopic examination. In case of suspension, even temporarily, of DAPT (patient at low thrombotic risk), continued aspirin therapy is recommended. In case of impossibility of discontinuation of DAPT, the situation will be evaluated on a case-by-case basis (expected duration of treatment, patient's will) whether to postpone the performance of colonoscopy or to perform the examination with only diagnostic intent.

4) *Direct oral anticoagulants (DOACs; dabigatran, apixaban, edoxaban, rivaroxaban)*: discontinuation of treatment is suggested, with taking the last dose 3 days before the procedure (5 days in patients on dabigatran with impaired renal function, i.e. Cr-Cl 30–50 ml/min).

5) *Vitamin K antagonists (VKA; warfarin, acenocoumarol)*: discontinuation of treatment within 5 days before the examination is suggested, testing INR on the day before the procedure. "Bridging" therapy with low molecular weight heparin (EBPM) is recommended only in patients with high thromboembolic risk.

BOWEL PREPARATION

It is recommended to prepare the patient with a low-volume (2 L) or very low-volume (1 L) split bowel preparation. One day of low-fiber diet is also recommended. The addition of oral instruction to those written, as well as the use of electronic aids is also recommended.

It is recommended to repeat colonoscopy in those patients with an inadequate level of bowel cleansing within 6 months from the index colonoscopy.

COMPETENCE (ADR)

It is suggested that the ADR be greater than or equal to 40%, when using a 20 µg positivity cut-off. FIT cutoff level and FIT round must be considered when determining ADR cutoff.

It is recommended to perform post-FIT colonoscopies in dedicated sessions.

It is recommended that screening centres provide periodic feedback to individual endoscopists on their ADR. When ADR levels are suboptimal, it is recommended to undergo retraining sessions and/or other interventions proven to increase ADR.

SEDATION

It is recommended that post-FIT screening colonoscopy is routinely offered under sedation. Performance and type of sedation may vary, depending on local availability, expertise and patient preference.

procedure (see below). On the other hand, an early timing of the colonoscopy may be impossible due to the rigid and limited capacity of colonoscopy. This capacity limitation may in turn affect the extension of FIT invitation to that part of the population that still has not received the invite.

In theory, it may be more practical to calculate the timing to post-FIT colonoscopy by the time of the visit of the patient at the time of FIT positivity. However, this timing may be variable across the different settings, and it may also vary (telephone vs. physical visit). Thus, to measure it by the time of the FIT positivity seems to be a more consistent and homogeneous standard.

3.1.2. Evidence

Recently, some studies have evaluated the effects of diagnostic delay on the progression of colon cancer. An Italian study [11] performed in the Veneto organized program showed that undergoing a colonoscopy more than 9 months after a positive FIT was associated to an increased risk of developing colon cancer, while no excess risk was found for shorter periods. In addition, the proportion of cancers diagnosed at an advanced stage was almost three times higher in patients who performed colonoscopy more than 9 months after FIT.

A U.S. study showed similar results, reporting both an increased generic risk of colon cancer and an increased risk of more advanced cancer [12]. These studies showed an increase in progression risk to a higher CRC stage proportional to the time between positive FIT and colonoscopy.

In addition, a simulation model based on a Dutch screening program [13] estimated that individuals undergoing diagnostic colonoscopy within 2 weeks of a positive FIT had a lifetime risk of CRC incidence of 35.5/1000 persons and mortality of 7.8/1000 persons. For each month the colonoscopy is delayed, the model estimated a 0.1/1000 person increase in risk of cancer incidence and mortality. Among people receiving a colonoscopy 12 months

after a positive FIT, a CRC incidence of 37/1000 (4% increase, compared with 2 weeks) and mortality of 9.1/1000 (16% increase) is estimated.

3.1.3. Health impacts of recommendation and organizational requirements

Regarding to the risk of a progression of the neoplastic disease, such a risk has been consistently shown after 9 months (see above).

The advantages of a more conservative approach towards the time lag between FIT positivity and colonoscopy are related to the limited endoscopic capacity, which may make it problematic to arrange a colonoscopy within a short time. The disadvantages, on the other hand, are related to the anxiety of waiting and a possible detrimental effect on colonoscopy adherence.

It is recommended that colonoscopies after FIT+ are performed within 60 days of test positivity.

Agreement : A+, 76.5%; A, 23.5%; U, 0%; D, 0%; D+, 0%

3.2. Adherence**3.2.1. Rationale**

Adherence to post-FIT colonoscopy is a critical issue. The efficacy of FIT depends on the selection of a group at much higher risk of advanced neoplasia. However, if these subjects do not undergo post-FIT colonoscopy, it will not only prevent any benefit on these high-risk group, but it will decrement the efficacy of FIT testing in the whole population. Adherence to post-FIT colonoscopy is in general much higher in organized than non-organized settings, underlining the value of an organized approach [14–16]. However, even in organized programs, such adherence is far from being 100% and variable according to several factors, such as the geographic area, cultural and personal barriers and beliefs [8,17]. Recently, several

interventions have been described to increase the adherence to post-FIT colonoscopy, such efficacy being counterbalanced by the exploitation of additional resources [18,19].

3.2.2. Evidence

A recent Italian cohort study performed in the Veneto regional screening program showed that among the more than 23,000 patients who did not perform a colonoscopy after a positive FIT, CRC death risk was increased by two-fold as compared to patients undergoing post FIT+ colonoscopy [20]. The overall risk of CRC incidence was also significantly increased. A meta-analysis performed in Israel including data on more than 500,000 patients with positive FIT recorded a total adherence of 72.5%, showing that there is a significant proportion of the population who refuse any test after positive FIT [21]. This result underscores how there is still a need for interventions aimed at increasing adherence to post FIT+ colonoscopy.

A recent meta-analysis summarized possible interventions to increase screening adherence in the United States, and showed that the widespread distribution of FITs, guiding (or “navigating”) the individual patient through the screening program, educational interventions, and reminders sent by different modalities all significantly increased screening adherence [19]. Another metanalysis of 73 RCTs strengthened these findings and found that navigation and spreading FIT outreach locally are the interventions that have the strongest evidence base and each have shown to increase screening adherence rate by approximately 20% [18].

Another meta-analysis of studies assessing barriers and facilitators of colonoscopy uptake identified five main analytical themes: perceptions of the procedure, previous personal experience, concern, social influences, physician-patient relationship, and the health care system. Sharing personal experiences of health care personnel, involvement of patients' families in recommendations for colonoscopy, and dissemination of positive narratives from patients who have already received the examination were all identified as factors favoring compliance with endoscopic examination. Ethnic and cultural factors were identified as potential barriers to compliance and should be specifically addressed according to different needs [22].

3.2.3. Health impacts of recommendation and organizational requirements

Two-fold increase in the risk of death among FIT+ subjects who do not undergo colonoscopy.

The main burden is represented by the cost of personnel involved in interventions aimed at improving patient adherence to colonoscopy.

It is recommended that adherence to colonoscopy after FIT+ should be at least 85%, 90% being desirable. Multi-modal interventions that can improve adherence are recommended.

Agreement : A+, 88.2%; A, 11.8%; U, 0%; D, 0%; D+, 0%

4. Management of antithrombotic therapy

4.1. Rationale

FIT based screening programs is targeting an age group in which cardiovascular comorbidities are frequent. Therefore, the proportion of invitees on antithrombotic therapy, whether primary or secondary prophylaxis, is significant. In detail, 12–14% of FIT-positive subjects invited to perform colonoscopy as part of screening programs are on antithrombotic therapy, and about 4% are taking oral anticoagulants [23,24]. This may affect the risk of bleeding at the timing of polypectomy. On the other hand, their interruption may generate a thrombotic risk that may affect the safety

of post-FIT+ colonoscopy. This sometimes crucial decision making is usually in the hands of the endoscopist, either first-hand or by standardised Unit procedures. This is the main reason why we decided to anticipate this chapter here rather than in the next Position Statement on operative endoscopy in FIT+ subjects. In addition, patients on antithrombotic therapy have shown reduced adherence to follow up colonoscopy [25].

4.2. Evidence

It is known that antithrombotic drugs increase the risk of gastrointestinal bleeding, and this could affect the specificity of the screening test (increase in false positives) and negatively impact its performance. Although literature data in this regard are conflicting, a recent meta-analysis (13 studies, 27,518 patients) [23] and a large Danish cohort study (77,007 FIT+ subjects undergoing colonoscopy) [25] have shown that both antiplatelet drugs and oral anticoagulants significantly reduce the positive predictive value (PPV) of the test, an effect that is particularly evident for patients on direct oral anticoagulants (DOACs).

Nonetheless, both European [26] and American [27] guidelines do not recommend temporary withdrawal of antithrombotic therapy before performing FIT, considering the theoretical increase in potentially serious cardiovascular events and a reduction in test performance that is nonetheless small.

Evidence regarding the safety of resection of sub-centimeter polyps in patients in double anti platelet therapy (DAPT) is scarce. Moreover, it is imperative in this setting to minimize the risk of procedure-related complications, which may require the complete discontinuation of antithrombotic therapy and a consequent risk of serious cardiovascular complications.

If DAPT can be discontinued, a colonoscopy should be scheduled at least 7 days after discontinuing the P2Y12 receptor antagonist (clopidogrel, prasugrel, or ticagrelor).

If immediate discontinuation of DAPT is not possible, the interval between FIT positivity and the date of possible discontinuation of dual antiplatelet should be evaluated. If the interval is less than six months, a period within which both prevalence of invasive cancer and stage progression [11] remain stable in screening programs, it is suggested to defer the performance of colonoscopy. Conversely, if the interval is greater than 6 months, scheduling an examination with only diagnostic intent is advisable.

Although there is growing evidence of the relative safety of cold loop resection of polyps <10 mm without discontinuation of anticoagulant therapy [28,29], current guidelines recommend anticoagulant discontinuation before polypectomy, regardless of polyp size and type of anticoagulant (DOACs or vitamin K antagonists [VKA]).

The recommendation also considers the fact that the thromboembolic risk associated with temporary discontinuation of DOACs is very low, both because of the pharmacokinetic characteristics of these drugs, which are favorable due to their periprocedural management (rapid off-set and on-set of action), and because patients at higher thromboembolic risk (patients with mechanical heart valves) are excluded from DOACs treatment.

In the subgroup of patients on DOAC at particularly high thromboembolic risk (e.g., for a recent arterial or venous thromboembolic event), it is reasonable to consider postponing colonoscopy until 3 months after the event to reduce the potential risks associated with periprocedural anticoagulant discontinuation.

The pre-procedural discontinuation interval of VKAs is longer than those of DOACs and the mode of discontinuation is more complex, especially in patients at high thromboembolic risk who require bridging therapy with low weight molecular heparin (LWMH) (mechanical valve prostheses, atrial fibrillation (AF) associated with mitral stenosis, AF with a previous ischemic event and/or other associated risk factors). These considerations, associ-

ated with the low prevalence of patients undergoing VKAs, would suggest performing a colonoscopy without VKA suspension, and possibly rescheduling the examination if polypectomy is needed.

Nevertheless, in settings with a prevalence of polyps greater than 35%, VKAs suspension strategy appears to have a more favorable cost-effectiveness ratio and as such would be preferred [30].

If “bridging” therapy with LWMH (100 IU/Kg bid) is needed, it should be introduced 3 days before the procedure, with the last administration on the morning of the day before the examination (24 h).

As with patients on DOACs, in patients with a recent arterial or venous thromboembolic event, it is reasonable to consider postponing the colonoscopic examination 3 months after the event.

4.3. Health impacts of recommendation and organizational requirements

The decision regarding temporary withdrawal or continuation of antithrombotic therapy before the performance of colonoscopy in this setting is complex and endoscopists must consider:

- the high prevalence of colonic adenomas in FIT-positive individuals
- the individual patient's thrombotic risk
- the hemorrhagic risk related to different antithrombotic agents
- the implications of the possible need to repeat the examination (cost, organizational difficulties, patient discomfort, risks)
- the possibility of deferring the performance of colonoscopy in favor of temporary treatments (e.g., double anti-aggregation) or in case of situations of particular risk (e.g., recent thrombotic events)
- the indications of the European guidelines (ESGE) on the management of antithrombotic therapy in patients undergoing digestive endoscopy⁶
- the patient must be taken care of for the management of complex therapeutic choices (investment by the program)
- option of virtual CT to select patients who have a greater risk (presence of polyps) and therefore a more favorable cost-benefit ratio for undergoing operative colonoscopy

Based on these considerations, the following recommendations are provided:

- (1) Aspirin: *continued medication is recommended*. This recommendation is given because literature data do not demonstrate an increased risk of bleeding in patients on ASA therapy undergoing colonic polypectomy or advanced resection procedures (mucosectomy or submucosal dissection).

Agreement : A+, 82.4%; A, 23.5%; U, 0%; D, 0%; D+, 0%

- (2) Clopidogrel: *It is suggested that patients on secondary prophylaxis replace the drug with aspirin 7 days before the procedure if the patient is not allergic to aspirin. In aspirin-allergic subjects, a continuation of the drug may be considered if the patient's thrombotic risk is considered high*. The recommendation is given because within screening programs, more than 80% of patients with polyps have non-pedunculated lesions of sub-centimeter size (<10 mm), the resection of which is relatively safe even without discontinuation of therapy, especially with the use of “cold” loop and the eventual application of mechanical hemostasis.

Agreement : A+, 52.9%; A, 35.3%; U, 5.9%; D, 5.9%; D+, 0%

- (3) Dual antiplatelet therapy (DAPT: aspirin + P2Y12 receptor antagonist): *in all DAPT patients, cardiology or neurology consultation is recommended before scheduling a colonoscopic examination. In case of suspension, even temporarily, of DAPT (patient at*

low thrombotic risk), continued aspirin therapy is recommended. In case of impossibility of discontinuation of DAPT, the situation will be evaluated on a case-by-case basis (expected duration of treatment, patient's will) whether to postpone the performance of colonoscopy or to perform the examination with only diagnostic intent.

Agreement : A+, 58.8%; A, 29.4%; U, 5.9%; D, 5.9%; D+, 0%

- (4) Direct oral anticoagulants (DOACs; dabigatran, apixaban, edoxaban, rivaroxaban): *discontinuation of treatment is suggested, with taking the last dose 3 days before the procedure (5 days in patients on dabigatran with impaired renal function, i.e. Cr-Cl 30–50 ml/min).*

Agreement : A+, 58.8%; A, 29.4%; U, 5.9%; D, 5.9%; D+, 0%

- (5) Vitamin K antagonists (VKA; warfarin, acenocoumarol): *discontinuation of treatment within 5 days before the examination is suggested, testing INR on the day before the procedure. “Bridging” therapy with low molecular weight heparin (EBPM) is recommended only in patients with high thromboembolic risk.*

Agreement : A+, 47.1%; A, 35.3%; U, 11.8%; D, 5.9%; D+, 0%

5. Bowel preparation

5.1. Rationale

The role of cleansing in post-FIT colonoscopy is critical for an adequate inspection of colorectal mucosa and the detection of both advanced and non-advanced neoplasia. In addition, the failure of bowel preparation in post-FIT colonoscopy requires the repetition of colonoscopy that further stresses the limited capacity of endoscopy and inflates procedure related costs. Such failure also depends on the meticulousness of adherence to the recommended regimen of bowel preparation. Thus, the organized setting of post-FIT colonoscopy should improve the level of cleansing by the provision of oral and/or dedicated information. The diet restriction and the tolerability of the laxative agents also affect the patient experience of post-FIT colonoscopy.

5.2. Evidence

The latest updated 2019 ESGE guidelines for bowel preparation before colonoscopy recommend both the use of a low-volume preparation (2 L) and a classic high-volume preparation (4 L) [31].

Before preparation, one day low-fiber diet is advised. Randomized trials have tested the need for an extended period (3 days) of low fiber diet without finding any significant incremental yield of adequate preparation, but a reduced tolerability of patients [32]. No increase in adequate bowel prep was also found in a meta-analysis comparing a one day low fiber diet with a clear liquid diet on the day preceding the colonoscopy, but a much higher willingness to repeat the procedure and better tolerability was found in the low fiber group [33].

Traditionally, although with a lower tolerability, high volume laxatives are associated with a higher efficacy in colon cleansing. Recently however, a meta-analysis [34] of 17 randomized controlled trials comprising 7'528 patients (36 arms of treatment) has subverted this conception, showing that low-volume laxatives are equal in terms of efficacy to high-volume laxatives, with a higher tolerability. In detail, low-volume split bowel regimens (comprising both PEG and non-PEG low volume laxatives), had an equivalent

proportion of patients with an adequate bowel preparation compared with split-dose high-volume PEG [86.1% (95%CI 82.6–90%) vs. 87.4% (95%CI 84.1–90.7%)]. The pooled RR was 1.00 (95% CI 0.98–1.02; I²= 17%; $p = 0.2$) showing no statistically significant difference with a low heterogeneity.

When looking at compliance, tolerability and safety, the meta-analysis found that patients receiving low-volume PEG and non-PEG regimens were more likely to complete the preparation than those receiving high-volume preparation [92.8% (95%CI 89.6–96.1%) vs. 86.8% (95%CI 82.1–91.4%)] with a RR of 1.06 (95% CI: 1.02–1.10; I²= 85%; $p < 0.01$), and that the low-volume PEG and non-PEG group demonstrated statistically significantly higher tolerability as compared with the high-volume group [72.5% (95%CI 56.4–88.7%) vs. 49.6% (95%CI 28.8–70.5%)] with a RR of 1.39 [95% CI: 1.12–1.74; I²= 98%; $p < 0.001$]. In addition, in the studies that reported this outcome, patients undergoing a low-volume regimen were more willing to repeat the preparation compared to patients undergoing a high-volume regimen.

Very low volume (1 L) preparations have been recently introduced to the market, and have been shown to be at least as safe and effective as low volume preparations, with a possible higher degree of patient tolerance [35,36].

Thus, the characteristics of the patient undergoing screening colonoscopy make low- and very low-volume preparations more recommendable than high-volume preparations.

Several studies have shown that the “split” mode of intake, i.e., taking the preparation the night before and the morning of the exam, or all of it the morning of the exam itself (“same day” preparation) with completion at least 2 h before colonoscopy, brings better bowel cleansing and improves patient adherence to taking the preparation, ADR, and willingness in repeating the exam [37,38]. This mode of intake, recommended by guidelines for colonoscopy in general, seems even more desirable in screening colonoscopy.

A recent meta-analysis [39] showed that patients receiving “enhanced instructions” before colonoscopy had increased probability of good bowel cleanliness, higher cecal intubation rate, more willingness to repeat bowel prep. Enhanced instructions consisted of visual aid, social media app, telephone/short message service (SMS) and smartphone applications.

5.3. Health impacts of recommendation and organizational requirements

The main drawback of an inadequate bowel cleansing is represented by the increased miss rate of advanced neoplasia. For this reason, an early repetition of the procedure is recommended. Despite a 1-year interval is generally recommended, it may appear reasonable to restrict it to 6 months for post-FIT colonoscopy due to the expected high prevalence of advanced neoplasia in these patients. The burden of bowel preparation is also related with the poor tolerability of the laxatives and the extent of diet restrictions prior to the exams. Thus, low-volume regimens seem a better choice for patient experience, also resulting in a higher compliance with the required volume. Regarding diet, to minimize the intervention to one-day of low-fiber diet should also improve the acceptability and compliance of patients.

It is recommended to prepare the patient with a low-volume (2 L) or very low-volume (1 L) split bowel preparation. One day of low-fiber diet is also recommended. The addition of oral instruction to those written, as well as the use of electronic aids is also recommended.

Agreement : A+, 70.6%; A, 17.6%; U, 5.9%; D, 5.9%; D+, 0%

It is recommended to repeat colonoscopy in those patients with an inadequate level of bowel cleansing within 6 months

from the index colonoscopy.

Agreement : A+, 70.6%; A, 23.5%; U, 5.9%; D, 0%; D+, 0%

6. Competence (ADR)

6.1. Rationale

The effectiveness of a screening program depends largely on the endoscopist's ability to identify precancerous lesions at endoscopy in FIT-positive individuals. Adenoma detection rate (ADR) is one of the most well-established parameters for evaluating the endoscopist's competence [40–42]. Therefore, to ensure quality standards of screening, monitoring ADR is of critical importance.

6.2. Evidence

Studies conducted in the Netherlands and the United States, in FIT-based population screening and opportunistic settings, respectively, have shown that as ADR increases, the risk of PCCRC occurrence decreases linearly, with rates ranging from 3 to 5% risk reduction for each percentage increase in ADR [3,43].

A recent study conducted in the Veneto region confirmed this finding and provided guidance on threshold values of ADR [1]. Unlike previous studies, ADR was calculated in the context of an established screening program, in a population selected based on FIT, employing the positivity cut-off in use in Italy ($\geq 20 \mu\text{g}$ of hemoglobin per gram of stool, corresponding to 100 ng/ml), thus providing ADR values applicable to other screening programs with similar characteristics. With a 10-year follow-up, the study observed that compared to endoscopists with ADRs of 55–70%, there was more than a two-fold increase in risk of developing colorectal cancer among patients screened by endoscopists with ADRs $< 40\%$; the risk was also significantly increased for ADRs of 40–44.9%.

Although there is a lack of studies including an assessment of the clinical and economic impact associated with ADR, from the perspective of reducing the risk of colorectal cancer occurrence, it seems desirable for ADR to remain above 40% in programs using a 20 μg cut-off. It should be kept in mind that higher ADR thresholds might be considered when using higher FIT positivity cut-off levels [3].

An additional parameter that could contribute to the evaluation of the endoscopist's competence is the Advanced Adenoma Detection Rate (AADR). Although the increased risk of colorectal cancer associated with lower AADR values is lower than that found for ADR, the risk of post-colonoscopy colorectal cancer in patients examined by endoscopists with AADR $< 26\%$, compared with those with AADR of 32–46% is significantly increased. The increase again is linear, with a 3–4% reduction in colorectal cancer risk for each percentage increase in AADR. Although studies on the clinical and economic impact associated with AADR are lacking, an AADR $\geq 26\%$ seems to be a desirable value in the context of reducing the risk of colorectal cancer occurrence.

An Italian study in 2014 consistently showed that screening-dedicated sessions as opposed to mixed indication sessions were an independent predictor of a higher colonoscopy quality, namely a 35% increase in ADR and a 2-fold increase in caecal intubation rate [8].

Providing regular ADR feedback to individual endoscopists has been shown to increase and maintain optimal ADR levels. Other interventions have shown to increase ADR of single endoscopists, namely auditing and feedback, educational activities and hands-on training [44,45].

It is suggested that the ADR be greater than or equal to 40%, when using a 20 μg positivity cut-off. FIT cutoff level and FIT

round must be considered when determining ADR cutoff.

Agreement : A+, 52.9%; A, 47.1%; U, 0%; D, 0%; D+, 0%

It is recommended to perform post-FIT colonoscopies in dedicated sessions.

Agreement : A+, 52.9%; A, 35.3%; U, 11.8%; D, 0%; D+, 0%

It is recommended that screening centres provide periodic feedback to individual endoscopists on their ADR. When ADR levels are suboptimal, it is recommended to undergo retraining sessions and/or other interventions proven to increase ADR.

Agreement : A+, 64.7%; A, 35.3%; U, 0%; D, 0%; D+, 0%

7. Sedation**7.1. Rationale**

The role of sedation is multi-dimensional, as it affects the performance of colonoscopy, both in terms of caecal intubation and mucosa inspection, and patient experience, also influencing acceptability and perception of colonoscopy. Sedation for diagnostic colonoscopy is usually based on a combination of short-acting benzodiazepine and opioids that may be directly administered by the endoscopist in a proper setting. However, a minority of centres in our country may also offer a deeper degree of sedation with propofol under supervision of an anaesthesiologist.

7.2. Evidence

The EQUIPE Study performed among 79 Italian screening centers showed that the routine use (more than 2/3 of cases) of sedation was associated with an increase in colonoscopy quality parameter both at an endoscopist level and at a center level as compared to centers not using sedation. In detail, the use of sedation increased ADR by 20% and caecal intubation rate by 50% [8].

Regarding the kind of sedation used, a recent metanalysis [46] of randomised controlled trials comparing sedation with propofol versus midazolam plus short acting opioids found that both sedative groups showed a high rate of patient satisfaction and were safe and effective, with a low rate of cardiorespiratory outcomes (hypotension, hypoxia, bradycardia). Most patients reported willingness to undergo colonoscopy with the same sedation regimen.

It is recommended that post-FIT screening colonoscopy is routinely offered under sedation. Performance and type of sedation may vary, depending on local availability, expertise and patient preference.

Agreement : A+, 100%; A, 0%; U, 0%; D, 0%; D+, 0%

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Conflict of Interest

None.

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