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Is There a Place for Screening Flexible Sigmoidoscopy?

Doron Boltin and Yaron Niv

Department of Gastroenterology, Rabin Medical Center, Tel Aviv University, 39 Jabotinski Street, Petach Tikva 49100, Israel

Abstract

Flexible sigmoidoscopy is a valid screening tool for the early detection of colorectal cancer (CRC). Recently published long-term data from UKFSST, a randomized controlled trial, demonstrate a 33% reduction in colorectal cancer incidence and a 43% decrease in colorectal cancer mortality, with once-in-a-lifetime screening. On the other hand, data from the NORCCAP trial with a similar protocol show no reduction in CRC incidence and only nonsignificant decrease in CRC mortality at 7 years. At best, flexible sigmoidoscopy can detect only 70% of cancers and polyps as it does not detect the 40% of proximal neoplasms which are not associated with a distal lesion. The advantage of flexible sigmoidoscopy over other screening modalities lies in its safety profile, patient tolerance, and overall acceptance. Its technical simplicity, short duration, and cost-effectiveness advance its applicability to mass screening programs.

Keywords

Flexible sigmoidoscopy; Screening; Colorectal cancer; Prevention and early detection

Introduction

With the development of the flexible endoscope in the 1950s and 1960s and its widespread application in the 1980s, flexible sigmoidoscopy (FS) rapidly emerged as an attractive screening test for the early detection of colorectal cancer (CRC). FS is generally performed with a 60-cm flexible endoscope following 1–2 enemas administered the morning of the examination. The procedure may be performed in an ambulatory setting, and usually lasts less than 10 min. As sedation is not required, patients may present alone to the clinic/hospital, and return immediately to work. Patients with a positive screen will be referred for colonoscopy. Accepted guidelines define a positive screen as the presence of advanced (villous histology or high-grade dysplasia), large (>10 mm), or multiple (≥ 3) adenomas [1, 2, 3•, 4]. Recent US guidelines recommend screening with FS every 5–10 years where colonoscopy is not available [4], while others advocate FS a priori as reflected by its endorsement for screening programs in many countries. As will be discussed, FS is limited by the fact that it does not examine the proximal colon where 40% of advanced lesions

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Correspondence to: Yaron Niv.

nivaron80@gmail.com.

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occur, and can at best detect 70% of cancers and polyps [5, 6]. Yet FS remains attractive, owing to its proven effectiveness, acceptability to patients, affordability, accessibility, and safety. Over recent years large population-based randomized controlled trials (RCTs) have thrust FS into the spotlight, affirming its validity as a screening tool.

Development of FS as a Screening Modality

The first RCT addressing FS as a screening tool was the Telemark Polyp Study ($n=799$), which demonstrated that once-only FS could reduce CRC incidence, but not CRC mortality [7, 8].

Over the past decade four landmark RCTs have been published. Long-term data from the British UKFSST [9, 10••] were published in 2010 by Atkin et al. Here, 170,432 men and women aged 55–64 years were randomized to either a single screening FS or no intervention. After a mean follow-up of 11.2 years, FS screening reduced CRC incidence by 33% (NNT 191) and mortality by 43% (NNT 489). The incidence of distal CRC was reduced by 36% and proximal cancer was reduced by 2%. Of the distal cancers diagnosed during the follow-up period, 59% were detected at screening. Seven-year follow-up data from the Norwegian NORCAPP study were reported by Hoff et al. in 2009 [11]. Here, 8,846 55 to 64-year-olds underwent a single FS with or without FOBT. This study showed no reduction in CRC incidence at 7 years. A nonsignificant reduction in CRC mortality was noted (ARR = 27%). Segnan et al. [12] in the Italian trial, SCORE, used a similar study design to UKFSST. A total of 9,911 men and women aged 50–64 years underwent a single screening FS. Baseline results indicate a 10.8% yield for distal adenomas. Colonoscopy was indicated in 8.4%. The yield for proximal adenomas among those without distal cancer who underwent colonoscopy was 15.5%. CRC incidence was 5.4 per 1,000 screened (54% Dukes A, 6.9% proximal). In the North American PLCO trial, Weissfeld et al. [13] screened 64,658 men and women 55–74 years old with FS at baseline and at 3–5 years. Here, 23.4% had a positive screen, which was liberally defined as the detection of any polyp at FS (as opposed to polyp size >0.5–1.0 cm, 3 adenomas, villous features, or high-grade dysplasia in the other RCTs). Distal adenomas were identified in 7.2% of initial FS, with 2.9 CRCs per 1,000 screened (14.8% of CRCs were proximal). Long-term mortality data from SCORE and PLCO have not yet been published.

Prior to the publication of these RCTs, evidence for sigmoidoscopy as a screening tool consisted largely of retrospective case control studies [14–18]. The Californian Kaiser Permanente study [14] compared 261 cases of CRC death with matched controls. Screening with rigid sigmoidoscopy within 10 years of diagnosis was associated with a 59% reduction in mortality (OR 0.41). There was no significant reduction in mortality from proximal CRC. In a cohort of 4411 US veterans, the incidence of both distal and proximal CRC was reduced by 59% following FS or colonoscopy, with a retained efficacy after 5 years [15]. Kavanagh et al. [16] reported a 42% reduction in the incidence of all CRC, in a cohort of 24,744 men exposed to screening FS or colonoscopy.

There have been several uncontrolled prospective studies as well as retrospective studies which have similarly reported yields for adenoma and CRC detection rates for FS screening. Although providing insights in specific clinical settings and demographics, the relevance of these small observational studies is limited now that long-term data from multicenter RCTs are available.

Technical Problems

Safety in FS

Screening FS has been proven to be a safe procedure with rare adverse events. The publication of administrative data by Kaiser Permanente reveals serious complications in only 1/16,000 procedures. Colonic perforations, bleeding, and diverticulitis requiring surgery each occurred less often than 1 in 50,000 examinations [19]. The risk of myocardial infarction is not increased following the procedure [20].

Compliance

The uptake of FS in trials is highly variable, ranging from 20.9% to 81% [9, 12, 21•, 22]. Women have a reported lower uptake for a first FS screening exam [10••, 11, 12]. In an Australian screening program although 94% of those undergoing an initial FS agreed to have the procedure again, the actual return rate was 45% [23].

Tolerance

The efficacy of FS as a screening tool is contingent upon patient tolerance. In a Dutch population-based study, FS was reported as burdensome by 12.9% of screenees, more commonly amongst women [24]. In a large prospective series women were twice as likely as men to have a limited FS, with a shorter insertion depth and a significantly lower adenoma detection rate (ADR) [25]. Up to 18% of FS examinations are incomplete, more commonly in women and in older patients, as reported by Walter in a large cross-sectional study [26].

Regarding dropout from a screening program, some 65% cite pain or unpleasantness/embarrassment as the primary reason for lack of compliance with follow-up FS. Lack of interest and lack of time were less commonly cited [27]. Nevertheless, severe pain is rarely encountered (2.7%) and up to 80% experience no pain [28].

Various strategies have been studied to address these perceived barriers in an attempt to improve FS compliance. Highest compliance rates (81%) were achieved when restricting bowel preparation to an enema at the screening center [22]. Giving women the choice of a male or female endoscopist may improve compliance in this sector [29].

Different caliber endoscopes [30], pain reduction techniques such as distraction [31], and medications such as inhaled nitrous oxide [32], sublingual hyoscine [33], and oral midazolam [34] have been examined. However, there is concern that over-complicating the procedure would limit its applicability for large-scale screening compared to colonoscopy.

Variability

Atkin et al. [35] found wide variability in ADR among 13 endoscopists with similar levels of experience at 13 different centers throughout the United Kingdom. These differences were independent of medical specialty (gastroenterologist or surgeon), cancer incidence, previous experience, or patient characteristics. The miss rate was estimated at 50% by comparing the ADR (per 100 people screened) of the highest and lowest ranking endoscopists (21.7 vs. 10.4). This may not necessarily be an accurate calculation of the miss rate, as data from the PLCO Trial associated higher ADRs with higher false-positive rates [36]. In PLCO the overall false-positive rate was 35.5% with a coefficient of variation 23%.

Inter-endoscopist variability was similarly observed amongst the eight Norwegian endoscopists in the NORCCAP study, where ADR varied from 12.7% to 21.2% [37]. Statistically significant differences were similarly found in mean procedure time and depth

of insertion, not biased by other variables. There was no difference in detection rates of advanced lesions.

In an earlier analysis, withdrawal time was identified as a factor explaining inter-endoscopist differences [38].

Maslekar et al. [39••], in a recent study, placed endomucosal clips at FS with subsequent X-ray, and found that the endoscopist accurately predicted scope location in only 75%. There was no correlation between scope insertion depth and its position in the colon.

In an attempt to grapple with the reality of inter-endoscopist variability some have suggested systems for monitoring endoscopy performance or setting a standard for recertification. However, the substantial variability may not necessarily reflect poor quality. Examiners operate at different points of a receiver-operator characteristic curve in terms of their threshold for false-positive versus false-negative results, as seen in PLCO.

Training

In a community-based Canadian screening program performed by nurses, cancer detection rates were on par with those in the aforementioned RCTs [40]. Non-physicians and gastroenterologists have similar detection rates for advanced lesions, although the former are more likely to identify small lesions [36]. Average depth of insertion, procedure time, complication rates, and patient satisfaction are similar for non-physicians, non-gastroenterologist physicians, and gastroenterologists [41–43]. These data suggest that experience is the most important factor for safe and effective FS.

Lesions of the Left Colon as a Marker for Significant Lesion of the Right Colon

The rationale for FS as a screening tool to decrease CRC incidence is predicated on the assumption that distal colonic lesions are predictive of proximal neoplasia. In the PLCO database subjects with distal non-advanced adenomas (single or multiple tubular adenomas <10 mm) had rates of advanced proximal neoplasia similar to subjects with hyperplastic polyps or other benign lesions. The presence of an advanced distal lesion conferred a 1.9–2.7 fold risk for a synchronous proximal lesion [44]. Overall, advanced proximal neoplasia (carcinoma, HGD, villous or large tubular adenoma) can be found in 8.8%–11.7% of subjects with advanced distal adenomas, 4.3%–7.1% with non-advanced distal adenomas, and 2.8%–5.3% with hyperplastic polyps [5, 6, 44, 45].

Nevertheless, it is clear that right-sided neoplasia may occur in the absence of a distal lesion. In the PLCO trial, only 37% of advanced proximal neoplasia was associated with advanced distal neoplasia. In other studies this figure is closer to 60%. That is, approximately 40% of advanced proximal lesions occur in the absence of distal lesions, with an overall prevalence of 1.3%–3.2% [46, 47]. Increasing age, smoking, and a family history of CRC may be predictors of isolated proximal adenomas [46].

Comparison with Other Modalities

Several RCTs have shown the efficacy of gFOBT screening in reducing CRC mortality, with risk reduction ranging from 13% to 33% [48]. This is somewhat less than the 43% reduction in CRC mortality with once-only FS as reported in UKFSST [10••]. FIT is probably more accurate than gFOBT and has been adopted by many countries for population screening [49]; however, long-term mortality data are lacking.

In a randomized trial directly comparing FS, FIT, and gFOBT, detection rates of advanced neoplasia were 8%, 2.4%, and 1.1%, respectively, indicating the higher sensitivity of FS. So

too, FS had a higher diagnostic yield compared to FIT or gFOBT [50•]. Another population-based screening program compared biennial FIT, once-only FS, and once-only colonoscopy [51]. Here, detection rates for advanced neoplasia were highest with colonoscopy. FS would have detected 70%–75% of people with advanced neoplasia but only a quarter of the proximal advanced neoplasms found at colonoscopy [51–53]. However, 48 colonoscopies would be necessary to detect one additional advanced neoplasm missed by FS. This must be taken into account when considering the relative advantages of FS over colonoscopy; although colonoscopy has a higher sensitivity, participation is lower and the procedure is less well tolerated [51].

No head-to-head data exist regarding detection rates for FS, barium enema, and CT colonography. Patient acceptance of FS is greater than for barium enema [54, 55]. However, compared to CT colonography, FS is more painful and less accepted by patients [54].

Interval

Current recommendations are to repeat FS after 5 years, following a negative examination. This is based on results from case control studies which indicate an apparent protective effect of 6–10 years [14, 15]. Preliminary data from the PLCO database indicate that the incidence of an advanced distal lesion 3 years after a negative FS is 0.8% (cancer incidence is less than 0.1%) [56]. Similar figures were obtained when screening those entering the SCORE trial [57]. A retrospective cohort study found no difference in the incidence of advanced lesions or cancer between those undergoing FS surveillance at 3-year or 5-year intervals [58]. The 33% reduction in CRC incidence and 43% mortality reduction seen in UKFSST with a once-only FS may justify further debate regarding the optimal screening interval.

Cost Effectiveness

Direct costs of FS include fees for endoscopists and nursing staff, equipment cleaning, and histopathology services. Indirect costs include management overheads, administration and office expenses, and servicing. Cost estimates per procedure vary between center and country, and range from approximately \$63–\$450 (based on 2000 prices) [59, 60]. In UKFSST the unit cost of FS entailed approximately 60% of the total cost of screening to the NHS.

In a recent review of 12 different analyses of FS cost effectiveness, 11 found five yearly FS to be cost effective compared to no screening. Incremental cost per life-year gained ranged from \$1,300 to \$56,600 [61•]. The commonly quoted willingness-to-pay threshold is \$50,000 per life-year gained. All screening modalities, including five yearly FS, 10 yearly colonoscopy, five yearly FS with annual gFOBT, annual gFOBT, and biennial gFOBT, are cost effective compared to no screening. No single strategy was consistently found to be the most cost effective or preferred.

Compliance with Colonoscopy for Positive FS

Following a positive FS, compliance with colonoscopy is extremely high as demonstrated in UKFSST (96.2%) [10••], NORCCAP (97%) [11], SCORE (93.1%) [12], and Wintzenheim trials (96.9%) [21•].

Combination FS and FOBT

Fecal occult blood testing (FOBT), as a high compliance–low yield test, has been proposed as being complementary to FS, which has lower compliance but a higher yield. In theory

these two tests are additive—FOBT should be able to detect some advanced proximal lesions which would be missed by FS. Three RCTs show that the yield for advanced neoplasia is significantly higher (fourfold to fivefold) with combination FS and FOBT than with FOBT alone [62–64]. The effectiveness of the combined strategy was examined in a French population-based study comparing once-only FS and biennial FOBT with each test alone [21•]. The number of positive tests with the combined strategy was twofold higher than those with gFOBT alone. The detection rate for advanced neoplasia was 3.5 times higher with the combined strategy than with gFOBT. The number of colonoscopies needed to detect one advanced neoplasia was 4.6 for gFOBT screening, 1.8 for FS screening, and 2.6 for the combined screening strategy. So while FS increases the efficacy of gFOBT as a screening tool, the reverse may not be true [65].

Data to support combination testing are equivocal, and derive from a nonrandomized study by Winawer et al. [66] in which subjects underwent rigid sigmoidoscopy alone or with gFOBT. Adherence in both groups was poor. After 5–11 years of follow-up, CRC mortality was lower in the combined group (0.36 vs. 0.63 per 1,000 per year, $P=0.053$). Robust data in support of combined FS and FOBT are lacking.

Conclusions

FS remains a valid screening tool with proven efficacy in decreasing CRC incidence and mortality. To be sure, FS will detect fewer advanced lesions than colonoscopy, but the analogy with a “one-sided mammogram” is not entirely precise. The attraction of FS lies in its simplicity, safety, and ability to be applied on a large scale. Future controversies involve the role of non-physician endoscopists, reimbursement issues, and screening intervals. Further studies are required to examine the role of FS in the face of emerging technologies for CRC detection, including FIT and CT colonography.

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