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Current status of screening for colorectal cancer

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Background: Colorectal cancer (CRC) is a leading cause of cancer morbidity and mortality. A well-defined precursor lesion (adenoma) and a long preclinical course make CRC a candidate for screening. This paper reviews the current evidence for the most important tests that are widely used or under development for population-based screening.

Material and methods: In this narrative review, we scrutinized all papers we have been aware of, and carried out searches in PubMed and Cochrane library for relevant literature.

Results: Two screening methods have been shown to reduce CRC mortality in randomised trials: repetitive faecal occult blood testing (FOBT) reduces CRC mortality by 16%; once-only flexible sigmoidoscopy (FS) by 28%. FS screening also reduces CRC incidence (by 18%), FOBT does not. Colonoscopy screening has a potentially larger effect on CRC incidence and mortality, but randomised trials are lacking. New screening methods are on the horizon but need to be tested in large clinical trials before implementation in population screening.

Conclusions: FS screening reduces CRC incidence and CRC mortality by removal of adenomas; FOBT reduces CRC mortality by early detection of cancer. Several other tests are available, but none has been evaluated in randomised trials. Screening strategies differ considerably across countries.

Key words: colorectal cancer, screening, prevention, adenoma, colonoscopy

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introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in Europe and the United States [1]. For both genders combined, it is the most frequently diagnosed cancer in Europe, with more than 400 000 new cases and more than 200 000 deaths in 2008 [1]. The lifetime risk of CRC is ∼5% in Western countries. A strong family history of CRC or rare genetic syndromes, such as familial adenomatous polyposis and hereditary nonpolyposis CRC syndrome, increase risk and warrant specialised screening and surveillance. However, only ∼15% of CRC patients belong to defined high-risk groups [2], and the majority of the population is considered to be at average risk.

Epidemiologic evidence suggests that dietary and lifestyle factors including high intake of red and processed meat, low level of physical activity, obesity and smoking increase risk of CRC [3], but the impact of modifying these risk factors is not established. Screening of average risk individuals, on the other hand, has been shown to significantly reduce CRC incidence and/or mortality in high-quality randomised controlled trials (RCTs) [4–10]. Therefore, many health authorities recommend CRC screening. In the United States, several tests are recommended including faecal occult blood testing (FOBT), flexible sigmoidoscopy (FS), colonoscopy and CT colonography [11–13]. While the FOBT is the only test currently recommended by the European Union Commission [14], some European countries recommend other screening methods, including colonoscopy [15].

This review outlines the evidence for the most important CRC screening tests. Challenges with screening implementation, quality measures, emerging strategies and ongoing research are also discussed.

development of colorectal cancer

The vast majority of CRCs is believed to develop from adenomas, benign precursor lesions that can undergo malignant transformation through a series of genetic and epigenetic alterations, the adenoma-carcinoma sequence [16]. Transition from detectable adenomas to cancer may take at least 10 years, leaving an applicable window for endoscopic removal at the premalignant stage (Figure 1). In addition, the time from early invasive cancer to clinically overt disease may span several years (Figure 1). The long premalignant and preclinical course makes CRC a candidate for screening. The FOBT may detect early invasive cancer and thereby improve prognosis. Endoscopy with adenoma removal may additionally prevent CRC and thereby reduce both incidence and mortality. The prevalence of adenomas by far exceeds the incidence of CRC [17–19], and most adenomas will not progress to cancer. Still, adenoma characteristics (number, size, histology and grade of dysplasia) are currently the best means to stratify the anticipated risk of CRC and guide surveillance strategies after screening and polypectomy [20, 21] (Figure 2).

A recent acknowledgement is that up to 30% of CRCs do not develop through the classical adenoma-carcinoma sequence [22]. Accumulating evidence suggests that flat mucosal lesions with a characteristic serrated architecture on histological examination and commonly without cellular dysplasia, may be precursor lesions that can undergo malignant transformation through the serrated neoplasia pathway [22]. These lesions are frequently referred to as sessile serrated adenomas, sessile serrated polyps, or sessile serrated lesions, but to date there has been no general consensus about the nomenclature. Although recommendations for removal and surveillance have been outlined, the evidence to support them is limited [21, 23]. The role of these lesions in CRC screening therefore remains to be clarified.

opportunistic versus population-based screening

Opportunistic screening denotes that eligible individuals on self-prompted request, or after consulting their primary physician, are referred for testing [14]. Conversely, population-based screening (also referred to as programmatic screening or organised screening programmes), usually involves publicly funded organisation machinery with systematic invitation procedures to cover the entire eligible population. While opportunistic screening is the most commonly used strategy in the United States, programmatic screening is increasingly popular in Europe [24]. In 2010, the EU Commission issued CRC screening guidelines for member states outlining a

Figure 1. Screening may aim at prevention or early detection of colorectal cancer. Endoscopic screening may prevent cancer through detection and removal of premalignant adenomas. FOBT screening allows early detection of cancer.

Figure 2. Adenoma characteristics influence the risk of colorectal cancer. Adenomas with one or more of the following features are usually referred to as advanced: ≥10 mm in diameter, high-grade dysplasia, ≥20% villous components [14]. Adapted by permission from Macmillan Publishers Ltd: The American Journal of Gastroenterology (Rex DK, Ahnen DJ, Baron JA et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol 2012; 107: 1315–1329, copyright (2012).
preference for publicly funded, population-based screening programmes [14]. Quality assurance (QA) is required at all levels, and RCT-level evidence is a prerequisite for implementation of new screening modalities [14]. Major advantages with population-based screening programmes are that everybody has equal access to the service, allowing systematic monitoring of coverage, outcomes and quality of service.

screening trials versus screening programmes

Trial results are sample specific and may not be generalisable to screening programmes. Some trials investigate the efficacy of a screening intervention by including volunteers likely to comply. These trials show the maximal effect that can be achieved with the screening test in study [25]. Other trials focus on effectiveness, meaning that the study sample is truly population-based to avoid selection of participants and to provide an estimate of effect on the entire population. In screening programmes, however, efficacy and effectiveness are impossible to evaluate if there are no valid comparison groups. Furthermore, because only a small proportion of the target population will truly benefit from CRC screening (Figure 3), but all screening attenders risk potential complications such as bleeding or perforation after polyp removal, the risk–benefit ratio must remain under constant scrutiny. To facilitate outcome evaluation and continuous programme improvement, implementation of RCT methodology in programmatic screening has been recommended [14, 26].

tests for colorectal cancer screening

In practice, two main screening strategies are available: FOBT and endoscopic screening (FS and colonoscopy). Newer modalities are in progress, but the level of evidence to support their use in screening is scarce, and availability and costs are major limiting factors. Table 1 summarises the results of RCTs on CRC screening.

faecal occult blood testing

FOBT is the most widely used screening test for CRC [27] and the only screening test currently recommended by the European Union [14]. FOBTs are based on the premise that CRCs bleed and that this blood can be detected in the stool. FOBTs are non-invasive, cheap, easy to use, and may be carried out by the screenee at home. As CRCs only bleed intermittently [28], FOBTs have to be repeated either each year or every other year to increase sensitivity for cancer. There are principally two test approaches available, the guaiac-based FOBT (gFOBT) and the faecal immunochemical blood test (FIT), of which the older gFOBT has been most extensively studied.

guaiac faecal occult blood test (gFOBT)

There is good evidence from four large RCTs that annual or biennial gFOBT reduces CRC mortality [4–7], and a Cochrane meta-analysis quantified the relative reduction to 16% [29] (Figure 3). These results are supported by one observational study [30]. gFOBT screening has not reduced all-cause mortality [29]. There are several tests available on the market, all carried out similarly: two samples from three consecutive stools are collected at home on test cards with six test windows, and the cards may be mailed for analysis. The gFOBT detects peroxidase activity present in the haeme moiety of the haemoglobin molecule. Because haeme is slowly degraded through the gastrointestinal (GI) tract, any bleeding source in the GI tract may produce a positive test result [31]. In addition, haeme is not specific to human haemoglobin, and the test may detect dietary blood or other sources of peroxidase activity [32]. Dietary restrictions before the test have therefore been applied in the past, but are no longer recommended due to limited clinical significance and possible negative impact on screening adherence [14, 27, 33–35].

A major disadvantage of the gFOBT is the low sensitivity for both CRC (25%–38%) and advanced adenomas (16%–31%) [36]. Failure to detect adenomas may be the reason why the gFOBT does not reduce CRC incidence [29]. Sensitivity may be increased by rehydrating the test windows before development [37], but this reduces specificity significantly and is therefore not advisable [12, 27]. Further, as reading of the test cards cannot be automated, there may be an inter-reader variability; and (as guaiac is developed from the bark of the guaiac tree) there may be a batch-to-batch variation [27]. On the other hand, the tests are cheap, may be easily distributed, are stable at different temperatures [38], and the cut-off (1 to 6 positive test windows) for referring for work-up colonoscopy may be adjusted to available local endoscopy resources and the prevalence of CRC in the test population.

faecal immunochemical tests (FIT)

The FIT utilises antibodies to detect the globin moiety of human haemoglobin. These tests are specific for human blood, and as globin is rapidly degraded through the GI tract, they are less sensitive to bleeding from sources proximal to the colon [14]. There are two different FIT tests, qualitative FIT and quantitative FIT. Qualitative FITs give a binary result (positive or negative), but does not allow for different haemoglobin cut-off levels and reading of the tests cannot be automated. Test performance varies vastly among different manufacturers [39]. Quantitative FITs, however, may be automatically read and return measures of haemoglobin concentration in the stool,

Figure 3. Relative and absolute risk reduction of colorectal cancer mortality and incidence during follow-up reported in screening trials of repetitive FOBT and once only flexible sigmoidoscopy (FS), respectively. Data are derived from meta-analyses [29, 104] and adapted by the authors.
<table>
<thead>
<tr>
<th>Study country</th>
<th>Intervention</th>
<th>Participants (n) intervention group/control group</th>
<th>Age group</th>
<th>Follow-up (years)</th>
<th>Compliance</th>
<th>Relative risk CRC mortality (95% CI)</th>
<th>Relative risk CRC incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK [105]</td>
<td>Biennial 3–6 rounds</td>
<td>76 466/76 384</td>
<td>45–74</td>
<td>20</td>
<td>One round: 59%</td>
<td>0.91 (0.84–0.98)</td>
<td>0.97 (0.91–1.03)</td>
</tr>
<tr>
<td>United States [7, 106]</td>
<td>Annual 11 rounds Biennial 6 rounds</td>
<td>311 57/15 394</td>
<td>50–80</td>
<td>18</td>
<td>Annual: One round: 90%</td>
<td>Annual: 0.67 (0.51–0.83), Biennial: 0.79 (0.62–0.97)</td>
<td>Annual: 0.80 (0.70–0.90), Biennial: 0.83 (0.73–0.94)</td>
</tr>
<tr>
<td>Sweden [6]</td>
<td>Biennial 2–3 rounds</td>
<td>34 144/34 164</td>
<td>60–64</td>
<td>15</td>
<td>One round: 70%</td>
<td>0.84 (0.71–0.99)</td>
<td>0.96 (0.86–1.06)</td>
</tr>
<tr>
<td>Denmark [107]</td>
<td>Biennial 9 rounds</td>
<td>30 967/30 966</td>
<td>45–75</td>
<td>17</td>
<td>First round: 67%, Only compliers invited thereafter</td>
<td>0.89 (0.78–1.01)</td>
<td>1.02 (0.93–1.12)</td>
</tr>
<tr>
<td>United States [9]</td>
<td>At baseline and repeated after 3–5 years</td>
<td>77 445/77 455</td>
<td>55–74</td>
<td>12</td>
<td>One screening: 84% Two screenings: 51%</td>
<td>0.74 (0.63–0.87)</td>
<td>0.79 (0.72–0.85)</td>
</tr>
<tr>
<td>UK [8]</td>
<td>Once only</td>
<td>57 099/112 393</td>
<td>55–64</td>
<td>11</td>
<td>71%</td>
<td>0.69 (0.59–0.82)</td>
<td>0.77 (0.70–0.84)</td>
</tr>
<tr>
<td>Italy [10]</td>
<td>Once only</td>
<td>17 136/17 136</td>
<td>55–64</td>
<td>11</td>
<td>58%</td>
<td>0.78 (0.56–1.08)</td>
<td>0.82 (0.69–0.96)</td>
</tr>
<tr>
<td>Norway [60]</td>
<td>FS once only with or without FIT</td>
<td>13 653/41 092</td>
<td>55–64</td>
<td>7</td>
<td>65%</td>
<td>0.73 (0.47–1.13)</td>
<td>NR</td>
</tr>
<tr>
<td>Norway [67]</td>
<td>Once only</td>
<td>400/399</td>
<td>50–59</td>
<td>13</td>
<td>81%</td>
<td>NR</td>
<td>0.20 (0.03–0.95)</td>
</tr>
</tbody>
</table>

CI: confidence interval; NR: not reported.
most often as nanograms of haemoglobin per millilitre buffer added. The threshold concentration for referral to work-up may be adapted to endoscopy resources and the prevalence of CRC and advanced adenomas in the target population.

There are no RCTs of the effect of FIT on CRC mortality. The evidence of benefit is indirect by comparison with the gFOBT. In recent years, a number of trials compared test accuracy of the gFOBT versus FIT [40–49]. However, because the accuracy of the FIT depends on the number of test samples and the threshold used to define positivity [40, 43, 44, 50], the trials are difficult to compare. Overall, the FIT has higher sensitivity for both CRC (61%–91%) and advanced adenomas (27%–67%) compared with the gFOBT, but slightly lower specificity (FIT 91%–98% versus gFOBT 98%–99%) [36]. The optimal number of stool samples for FIT testing and the concentration of haemoglobin in the stool that should be used as threshold for referral to colonoscopy are not clear; as reflected by the different guidelines for FIT screening in different countries [45, 46, 51–54].

Cumbersome stool handling may have a negative effect on compliance. Thus, it may be better to choose a lower stool haemoglobin threshold than multiple testing as the latter may reduce compliance with screening [55, 56]. In two Dutch studies, the participation rate for a 1-day FIT was 60%–62%, compared with 47%–50% with a 3-day gFOBT [40, 46]. Several trials have indicated that a single FIT with cut-off of 75 ng/ml may represent a good trade-off between test sensitivity and specificity [48, 57–59].

flexible sigmoidoscopy

FS allows inspection of the mucosa as well as tissue biopsies and polyp removal in the distal part of the colon. RCTs show that screening with FS reduces CRC mortality by 22%–31% and incidence by 18%–23% [8–10] (Figure 3). It should be noted, however, that all these trials recruited participants among volunteers, and the generalisability to a screening programme is uncertain. A population-based trial from Norway conversely showed no reduction in CRC mortality or incidence; this might be due to short follow-up (6–7 years, compared with 10–12 years for the aforementioned trials) [60].

A major concern with FS screening is that both CRCs and advanced adenomas proximal to the sigmoid colon are missed. According to a recent meta-analysis, 58% of individuals with proximal advanced adenomas do not have a distal lesion which could trigger a full colonoscopy [61]. This distribution of adenomas seems to be especially common in women [62]. Combining FOBT and FS to overcome the problem of missed proximal lesions is not superior to screening with FS alone [60, 63], however, and may increase the burden of screening and reduce compliance [60, 64, 65].

Adherence to screening with FS is highly variable, ranging from 14% to 81% in published studies [66, 67]. Importantly though, even if adherence to FS screening may be lower than for stool testing, the detection rate of adenomas is higher [68–70]. In a Dutch trial, 15,000 people were randomised to receive an invitation for a 1-day FIT, a 3-day gFOBT or FS. Compliance was 62%, 50% and 32%, respectively. Despite considerably lower compliance, the number of advanced adenomas and cancer detected by screening was higher for FS (2.4/100 invitees) compared with both gFOBT (0.6/100 invitees) and FIT (1.5/100 invitees) [40].

Risk of complications after screening with FS seems to be modest. In a large survey of 109,534 screening flexible sigmoidoscopies, 24 individuals were hospitalised due to GI complications, of which 7 were regarded as serious (perforations, bleeding requiring transfusion, diverticulitis requiring surgery) [71].

colonoscopy

Colonoscopy allows direct inspection of the entire colonic mucosa, tissue biopsies and polyp removal throughout the colorectum in one session. These qualities suggest that colonoscopy is an ideal test for both early detection and prevention of CRC. In experienced hands, the sensitivity and specificity of screening colonoscopy to detect advanced adenomas and cancer approaches 100%, and it is the final conclusive examination following any other positive screening test [11, 12, 14]. However, in contrast to the gFOBT and FS, screening colonoscopy has not been evaluated in RCTs with CRC incidence or mortality as primary endpoints. Recommendations of colonoscopy screening are thus merely based on indirect evidence of benefit and the logical reasoning that a test with performance characteristics outdoing the less invasive, albeit proven effective, alternatives will yield more favourable long-term results.

The first study to demonstrate a reduction in CRC incidence by colonoscopy with polypectomy was the US National Polyp Study (NPS) published in 1993 [72]. In this study, a cohort of patients (not screening) undergoing colonoscopy with adenoma removal reduced their CRC incidence by 76–90% after an average follow-up of 5.9 years compared with the expected incidences in three reference groups. A subsequent retrospective study of patients with adenomas undergoing polypectomy in routine clinical practice in Italy showed a 66% reduction in CRC incidence compared with the general population [73].

Studies of screening colonoscopy cohorts were carried out in the 1990s. They demonstrated a substantial prevalence of advanced neoplasia (advanced adenomas and CRCs) in asymptomatic, gFOBT negative individuals [74] and in the proximal colon beyond the range of FS, even without concurrent distal pathology [75, 76]. These findings, fuelled by an unequivocal editorial in the New England Journal of Medicine in 2000 [77], led major health insurers in the United States to cover colonoscopy as a primary screening test. Colonoscopy screening programmes have also been launched in some European countries [15]. Population-based case–control studies from Canada and Germany [78, 79], a cohort study of average-risk patients in the United States [80], and a recent follow-up study of the NPS cohort [81] have later indicated that colonoscopy reduces CRC incidence by 67%–77% and CRC mortality by 31%–65%. However, derived from observational studies, these results cannot be directly translated into effectiveness in population screening due to possible biases in design, sampling and adherence. Thus, the magnitude of the effectiveness of colonoscopy in reducing CRC incidence and
mortality is currently unclear. Three large RCTs are underway to address this issue [19, 82, 83].

Colonoscopy is usually considered the gold standard to detect colonic pathology, but high operator variability implies that in real life there is no such gold standard. The adenoma detection rate (ADR) varies among endoscopists, and low ADR is associated with persistent risk of CRC after screening colonoscopy [84]. Moreover, recent retrospective reports have questioned the ability of colonoscopy to reduce right-sided CRC incidence [85, 86] and mortality [78, 87] in community settings. Although rare, severe complications such as major bleeding and perforation probably occur more often than with FS [36]. Thus, proper training of endoscopists and continuous quality assurance are decisive for the success of any screening colonoscopy programme, and performance quality indicators have been outlined [88].

Colonoscopy is invasive, time-consuming, expensive and associated with possible pain. It also requires rigorous peroral bowel cleansing. All these factors may negatively affect acceptability of screening colonoscopy. In contrast to a substantial and increasing uptake of screening colonoscopy in the United States [89], participation in European programmes is disappointingly low [90]. Therefore, results of both efficacy and effectiveness from ongoing RCTs are eagerly awaited.

virtual colonoscopy
The term virtual colonoscopy includes both computed tomographic colonography (CTC) and magnetic resonance colonography (MRC). These techniques, used to create computerized two- and three-dimensional images of the colorectum, have been developed to overcome some of the invasive features of endoscopy and potentially improve the acceptability of CRC screening. Nevertheless, any positive virtual colonoscopy test has to be followed by endoscopy to confirm and treat pathologic findings. Both the techniques may also uncover extracolonic findings that warrant further investigations, which remain controversial when considering mass screening [36]. The main drawback with CTC compared with MRC is the potential harm associated with ionizing radiation. However, higher costs, limited availability, higher operator dependency, longer examination times, and more imaging artefacts severely limit the usability of MRC as a screening test compared with CTC [91]. Virtual colonoscopy screening protocols require some degree of bowel preparation and colonic distension by means of gas insufflation or fluid infusion during procedures. Some protocols also necessitate administration of intravenous contrast agents. Both modalities are therefore invasive and may be associated with considerable discomfort and other complications. Neither technique has been documented to reduce CRC incidence or mortality.

CT colonography
CTC is an accurate test to detect CRC and large adenomas, but sensitivity drops markedly for lesions 6 mm or smaller [36]. In an ongoing RCT comparing screening colonoscopy with CTC in the Netherlands, participation was higher in the CTC group, but advanced neoplasia was found more frequently in the colonoscopy group. The researchers concluded that both tests can be used for population-based screening [92]. Participants anticipated colonoscopy to be more burdensome than CTC, whilst the perceived burden was actually higher with CTC [93]. Although recommended as one of several tests in some US guidelines, the US Centers for Medicare and Medicaid Services recently decided to deny coverage of CTC screening due to inadequate evidence of effect [94].

MR colonography
In a recent systematic review of 13 prospective studies, MRC was found to be an accurate test to detect CRC and large adenomas [95]. However, MRC has no current place in CRC screening due to numerous limitations (listed above).

colon capsule endoscopy
Capsule endoscopy was first developed in 1997 for examination of the small bowel. By means of an ingestible camera, images could be wirelessly transmitted to an external receiver. Technical advancements including a wide angle camera on both sides of the capsule and a sophisticated external data recorder, have resulted in a minimally invasive, painless technique suitable for visualisation of the colonic mucosa with a prospect for increased screening participation [96]. The sensitivity and specificity of colon capsule endoscopy (CCE) to detect advanced lesions have been evaluated in numerous studies with varying results [97]. Although CCE may be suitable in cases were colonoscopy is either undesirable or contraindicated, there is currently a lack of studies to establish the role of CCE in CRC screening. Limitations include the need for vigorous bowel cleansing and high cost.

molecular markers
As all aforementioned screening tests are either invasive or only have modest effectiveness, genetic and epigenetic markers (in faeces or blood) for the detection of adenomas or early invasive CRC is a rapidly emerging field, with large numbers of scientific studies and great interest of the biomedical industry.

Detection of tumour DNA or epigenetic changes is possible because mucosal cells are shed continuously from the surface of the GI tract. These cells can be detected in faeces and analysed for changes indicative of tumour growth, such as DNA mutations or epigenetic changes associated with dysplasia and cancer. Blood-based markers may be advantageous compared with faeces because many patients would probably favour a blood sample over a stool sample. However, biologically, it seems more challenging to be able to detect remnants of tumour-associated changes in blood compared with faeces.

Markers that have been associated with cancer or adenomas include the well-known K-RAS, APC and p-53; methylation markers such as vimentin and septin-9; and proteins such as CEA or M2-PK [98]. So far, no marker or marker panel has been effective in the screening of average-risk individuals. Most tests are still evaluated only in high-risk populations or in case–control studies, and therefore, their performance in a screening setting is currently unknown. Presently, molecular markers do not play a role in CRC screening and should not be used outside clinical trials.
quality assurance in a screening programme

QA that maximizes benefit and minimizes harm should be an integral part of screening programmes [14, 99]. Prevention of interval cancer, defined as cancer diagnosed between screening rounds or between screening and post-screening surveillance, is a fundamental goal. Because colonoscopy, often with polypectomy, is the ultimate intervention following any positive CRC screening test, endoscopists’ performance play a pivotal role in the quality of CRC screening. A study in the Polish colonoscopy screening programme found the risk of interval cancers to be related to the endoscopists’ adenoma detection rate [84]. The caecal intubation rate, a measure of the endoscopists’ ability to reach the caecum, has also been linked to the risk of interval cancer [100]. Furthermore, a recent US study showed a significant difference in the rate of incomplete adenoma resection among endoscopists [101]. These studies illustrate the importance of appropriate training of endoscopists and continuous surveillance of key quality indicators to identify suboptimal performance.

compliance with screening recommendations and how to improve it

A failure to reach at least some of the ~5% who would eventually develop CRC will render any screening programme ineffective. Compliance was higher with FOBTs than with endoscopic screening in several RCTs [19, 40, 92]. FOBTs must, however, be repeated frequently, and compliance may drop over time (Table 1). Endoscopic screening entails higher yield of advanced neoplasia than FOBT [102], but the comparative impact of either modality on CRC mortality remains unknown. Preferences may differ across ethnic groups, and a possibility to choose between screening modalities may lead to better overall compliance [103]. In most countries where screening programmes are launched, the availability of tests will be limited by costs and endoscopy resources. Nevertheless, continuous tailoring of the best local strategy may be feasible by introducing different elements of a screening programme such as invitational procedures and public awareness initiatives with a randomised, comparative effectiveness approach [26].

ongoing research

There are three ongoing large, randomised, controlled trials of CRC screening using colonoscopy as a primary screening tool. In the Spanish COLONPREV study, 53,302 individuals aged 50–69 were randomly assigned 1:1 to either colonoscopy or biennial FIT. Compliance was 24.6% with colonoscopy and 34.3% with the first FIT screening round [19]. Planned follow-up is 10 years, and the results are expected in 2021. The NordICC trial (Nordic-European Initiative on CRC) aims at including 69,000 individuals aged 55–64 years and randomly assigned 1:2 to colonoscopy or care as usual (no screening) in Norway, Poland, Sweden and the Netherlands. An interim analysis is planned after 10 years, and final follow-up after 15 years [82]. In the United States, 50,000 veterans (50–75 years, 95% male) will be invited to participate in the CONFIRM study (Colonoscopy versus Fecal Immunochemical Test in Reducing Mortality from CRC) [83]. Participants will be randomly assigned 1:1 to annual FIT screening for 10 years or once only colonoscopy. Planned follow-up is 10 years (2025).

conclusion

We conclude that screening may reduce CRC burden. We also emphasise that endoscopic techniques that allow detection and removal of precursor lesions may convey a greater benefit than testing for asymptomatic cancer. However, the necessary evidence that allows quantification of benefit and harm with endoscopic examination cannot be derived from opportunistic screening, or from population-based programmes. Randomised trials of colonoscopy - and emerging techniques allowing detection of polyps—are therefore urgently needed. While each country or region should strive to deliver the most suitable screening regimen, individuals should be offered balanced information regarding risks and benefits with both absolute and relative numbers of the effect of screening.

disclosure

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references


Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials

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Background: There is currently no standard of care for the second-line treatment of advanced pancreatic cancer. The aim of this analysis was to compare the different therapeutic approaches in this setting.

Methods: We carried out a systematic analysis of second-line studies in advanced pancreatic cancer that have progressed on or following gemcitabine and published or presented from 2000 to 2012.

Results: Forty-four clinical trials (t) were identified; of which 34 met the inclusion criteria treating an aggregate total of 1503 patients (n). Patients who received treatments (t: 33; n: 1269) had a median overall survival (OS) of 6 months compared with 2.8 months for patients who received best supportive care only (t: 2; n: 234) (P = 0.013). The gemcitabine and platinum-based combination (t: 5; n: 154) provided a median progression-free survival and OS of 4 and 6 months compared with 1.6 and 5.3 for the rest of the regimens (t: 29; n: 1349) (P = 0.059 and 0.10, respectively) and 2.9 and 5.7 for the combination of 5-fluorouracil and platinum agents (t: 12; n: 450) (P = 0.60 and 0.22, respectively).

Conclusion(s): Although not conclusive, these data showed that the advantage of second-line chemotherapy in pancreatic cancer is very limited and there is a need for more studies.

Key words: analysis, cancer, pancreatic, review, second-line, treatment

Introduction

Pancreatic cancer has an estimated 5-year survival rate of 5%–6% and the majority of patients present with unresectable disease [1, 2]. For the past 10–15 years, gemcitabine has been considered the front-line chemotherapy in both locally advanced and metastatic disease due to its positive effect on quality of life and—to a lesser extent—overall survival [3]. While gemcitabine-based combinations have not been shown to be unequivocally more effective compared with gemcitabine alone, several analyses have suggested benefit in defined subpopulations such as patients with good performance status (PS) and metastatic disease [4–6]. Recently, FOLFIRINOX has emerged as an alternative to gemcitabine in the first-line setting after demonstrating superior survival outcome (median OS 11.1 versus 6.8 months, P < 0.001) [7]. However, this regimen is not suitable for patients with poor performance status (PS) and for these patients, gemcitabine-based therapy will remain a favorable first-line option [7, 8]. In the second-line setting, there is no consensus on the optimal treatment. This is due, in part, to the paucity of trials in this patient population. In addition, only ≤50% of patients who fail first-line treatment are still physically fit enough to be offered second-line treatment [4, 7]. It has also been unequivocally established that chemotherapy provides better efficacy compared with best supportive care (BSC), since studies that...