European Journal of Surgical Oncology xxx (2018) 1–3

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Short Report

Triage for selection to colonoscopy?

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ARTICLE INFO

Article history:
Accepted 14 June 2018
Available online xxx

Keywords:
Colorectal cancer
Colonoscopy
Screening
Biomarkers
Triage
Blood test

ABSTRACT

Implementation of population screening for colorectal cancer by direct colonoscopy or follow-up colonoscopy after a positive fecal blood test has challenged the overall capacity of bowel examinations. Certain countries are facing serious colonoscopy capacity constraints, which have led to waiting lists and long-time latency of follow-up examinations. Various options for improvement are considered, including increased cut-off values of the fecal blood tests. Results from major clinical studies of blood-based, cancer-associated biomarkers have led to focus, however, on a triage concept for improved selection to colonoscopy. The triage test may include subject age, concentration of hemoglobin in a feces test and a combination of certain blood-based cancer associated biomarkers. Recent results have indicated that triage may reduce the requirements for colonoscopy by around 30%. Such results may be advantageous for the capacity, the heath budgets and in particular, the subjects, who do not need an unnecessary, unpleasant and risk-associated bowel examination.

For debate

In Denmark screening for colorectal cancer (CRC) was initiated in March 2014 and is currently based on a result of an out-reach test for occult human blood in feces. It was decided that all Danes 50–74 years of age should be offered screening within a four years period. The testing was performed using the fecal immunochemical test (FIT, OC-Sensor, Eiken Pharmaceuticals Inc., Japan). The cut-off level was set to 100 ng/ml; those above were offered subsequent free of charge colonoscopy within 14 days (Danish Health Legislation) and those below were offered new screening at the next screening round, which was initiated by January 2018. At present, results including 2014–2016 are available and indicate that the Danish CRC screening initiative has been a success. During the three years 1,437,836 subjects were invited; they received the FIT testing device including instructions on how to handle the feces collection and the subsequent shipment. In total, 889,441 subjects responded by returning the FIT testing tube to the laboratories for analysis – immediate compliance was 62.6%. FIT testing identified 61,922 subjects, who were offered subsequent colonoscopy, but only 55,202 subjects (89.1%) did however accept the bowel examination. At the first colonoscopy examination 47,522 had a complete colonoscopy; those with incomplete examinations were offered subsequent new colonoscopy and/or CT-colonography.

The screening success is based on the findings at the bowel examination; CRC was diagnosed in 3183 subjects, who were offered subsequent treatment modalities including surgery and if indicated neoadjuvant and/or adjuvant chemo or chemo-radiation therapy. Indeed, it is remarkable that screening identified 1675 subjects (52.6%) with stage I (pT1 and pT2) and only 5% with stage IV tumors; at diagnostic colonoscopy that particular figure is around 20% stage IV. In addition, 17,229 subjects were diagnosed with high-risk or medium-risk adenomas (Table 1) and were referred to adenoma control colonoscopy within one or three years, respectively.

Before the nationwide population screening was initiated the Danish Screening Board estimated that the additional number of colonoscopies would mount 18,000 annually. Indeed, that number might challenge the capacity, and therefore training of additional

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[1] Appendix.

https://doi.org/10.1016/j.ejso.2018.06.013
0748-7983/

Table 1
Criteria for diagnosis of high-risk adenoma (HRA), medium-risk adenoma (MRA) and low-risk adenoma (LRA).

HRA	≥5 lesions or one lesion ≥20 mm or resected by piece-meal technique
MRA	3–4 lesions or one lesion between 10 and 19 mm or high-grade neoplasia or villous elements
LRA	<3 lesions or lesion <10 mm or low-grade neoplasia or tubular lesion

endoscopists including nurses was intensified to balance the requirements and the capacity. Beginning by January 2018 the Danish screening interval has been reduced to two years; at present the Screening Board has estimated that the number of additional colonoscopies would require a capacity of 34,500 annually, plus a yet not estimated number of adenoma control colonoscopies. Those numbers of additional colonoscopies were considered to lead to capacity constraints, which eventually may lead to even higher endoscopist training rates. An alternative would be, however, to reduce the number of required colonoscopies by increasing the cut-off level that decides whether a person has to be offered subsequent colonoscopy. Due to success with CRC screening other European countries have already increased their cut-off levels [1], but that will definitely lead to many subjects, in whom neoplastic lesions including CRC would be missed [1].

Due to the capacity constraints and to improvement of the health budgets it would be urgent to evaluate alternative options of identifying those subjects, who indeed requires colonoscopy, both for screening, adenoma-control and diagnostic purposes. Therefore, focus on the three colonoscopy situations shows that approximately 65% of those subjects offered colonoscopy after a positive FIT test did not have neoplastic or other serious bowel findings that needed subsequent treatment (Danish Screening Report); the similar numbers are >80% at adenoma control colonoscopy even in subjects, who had their primary lesion removed by EMR technique [2] and around 70% in subjects offered diagnostic colonoscopy [3,4]. In conclusion, the major part of those subjects undergoing colonoscopy is offered an unnecessary bowel examination, which is associated with an unpleasant and a far from effective bowel preparation that even may hinder adequate intraluminal examination [5,6]. In addition, colonoscopy is associated with subjects being out of work or daily routines for 1-1½ day [7]. Finally, a plethora of recorded and non-recorded adverse events are associated with colonoscopy and ranges from post-procedure cognitive impairment over cardiopulmonary incidents and bleeding episodes to perforation and ultimately death [8–10].

Although colonoscopy identifies the vast majority of bowel neoplasia the number of unnecessary examinations has to be reduced by a significant improved selection procedure. It is well-accepted that the risk of colorectal neoplasia is associated with age – the higher the age of the subjects the higher the risk of bowel neoplasia [11,12], and is associated with the concentration of fecal occult blood [12] and certainly with blood-based cancer-associated biomarkers, such as proteins, nucleosomes and DNA mutations and methylations [13–16]. These facts have been combined to show the efficiency of a triage test, which may be valuable in future colonoscopy selections; subject age + fecal occult blood concentration + combined blood-based cancer-associated biomarkers may be used to select specific subjects, who need subsequent colonoscopy [[1], Fig. 1].

At present, that suggestion has to be evaluated and subsequently validated before introduction into the daily routine of colorectal cancer screening. Currently, results of one major study of 13,600 subjects with positive and negative FIT screening results are under analysis, and a subsequent study that includes data from 90,000 subjects with FIT results below the present cut-off is ongoing [17]. Furthermore, recent results underline that fecal hemoglobin concentration and age may be of help in colorectal cancer prediction in diagnostic colonoscopy [18]. These results are currently validated in a prospective protocol that includes 5000 subjects referred to diagnostic colonoscopy [19]. Finally, a protocol on adenoma-control colonoscopy is currently under review by the Ethics Committee. In conclusion, results of present and future research may validate the triage concept in screening, adenoma-control and diagnostic colonoscopy.

Within shortly, the triage concept may be even more relevant, because current discussions and considerations have focus on extending the screening age interval. In Europe, screening for colorectal neoplasia is mostly, with a few exceptions however, offered to subjects between 50 and 74 years of age. The United States Preventive Services Task Force (USPSTF) has recommended that screening may also be offered to subjects between 75 and 85 years of age, specifically to subjects, who have health conditions that are needed to undergo treatment due to diagnosis of bowel neoplasia [20]. In addition, the USPSTF is currently considering lowering the age and including subjects from 45 years of age due to an explosive increase specifically of young-onset rectal cancer [21], personal communication at World Endoscopy Organization Annual Meeting. Transferred to Europe such recommendations may significantly increase the requirements for colonoscopy and thereby challenge the capacity. Therefore, amongst others, the triage concept has to be developed clinically and finally validated.

Introduction of improved selection criteria for colonoscopy may also be of benefit for the health institutions in specific countries. In Europe most countries have recommendations for early follow-up colonoscopy after a positive fecal blood test; in Denmark legislation dictates colonoscopy within 14 days, which is almost fulfilled. In many US states the actual time from a positive fecal blood test to

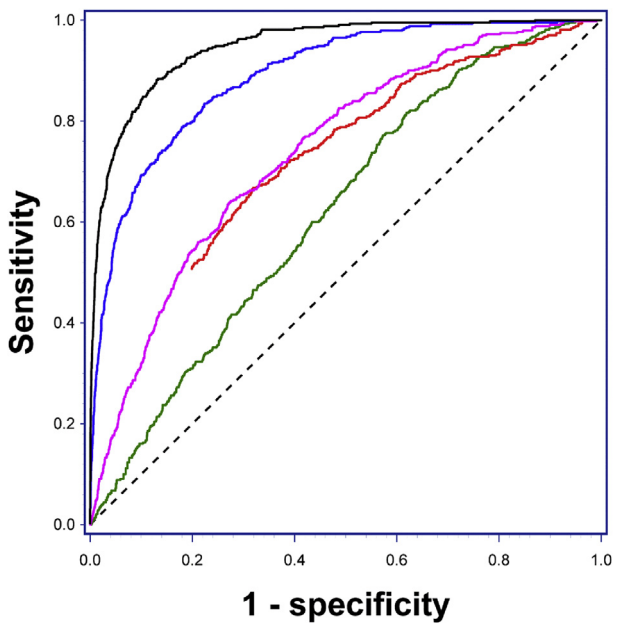

Fig. 1. ROC curves based on results of age and positive FIT tests from 8415 subjects. The dotted line shows the diagonal, the solid green line shows the effect of age, the solid red line shows the effect of the concentration of occult blood in the FIT test, the solid purple line shows combination of age of the subjects and their corresponding FIT results. The blue line shows the effect of addition of fictitious, independent protein biomarkers to the solid purple line, and the black solid line shows the effect of addition of fictitious, independent DNA methylations to the results illustrated by the solid blue line. The solid red line is cut at 1000 ng/ml of occult blood to show that the risk of cancer with that concentration is 52% (extrapolation into the y-axis).

Please cite this article in press as: Mertz-Petersen M, et al., Triage for selection to colonoscopy?, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2018.06.013

follow-up colonoscopy varies from 8 days to more than a year [22]. Such latency to colonoscopy appears to increase the risk of colorectal cancer and even higher stages at final diagnosis [23]. Therefore, improved selection criteria for colonoscopy may be a significant advantage.

In conclusion, the triage concept − age of the subject + the fecal blood concentration + combinations of various blood-based biomarkers including proteins and DNA methylations and/or mutations [24] - may be of benefit for future screening for neoplastic bowel lesions, and thereby for the health budgets and specifically for those subjects, who don't need to undergo an unnecessary and unpleasant bowel examination, which is not even free from side effects. Hopefully, such improved selection criteria may also increase the number of subjects, who adhere to subsequent follow-up colonoscopy. In the Danish screening concept almost 11% of those with a positive FIT result resist to undergo colonoscopy. The results of the current major collaborative international studies are awaited with interest.

Appendix

The following researchers are members of the Danish Collaborative Group on Early Detection of Colorectal Neoplasia.

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