Characteristics of colorectal cancer detected by quantitative faecal hemoglobin test in hospital opportunistic screening

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SUMMARY

Background: Colorectal cancer (CRC) is the second most frequent malignant disease in Europe. Since population-based screening with immunochemical test (FIT) in the Czech Republic has started in January 2014, in this study we describe the characteristics of CRC in relation to the values of quantitative FIT test.
Methods: Between years 2008-2013 we analysed 14,495 samples with FIT OC-Sensor test in our hospital within opportunistic screening. The analytical data-mining tool I-COP (Cancer Care Information Center) was used to link different data sources - Laboratory information system (LIS) and Cancer Registry records (CNCR) for relevant information on CRC characteristics.
Results: Searching LIS with CNCR databases we found CRC for 97 FIT samples. Analysis of 64 fully characterised CRCs revealed the values of Hb (ng/ml, median, 10-90 percentiles) 1656 (421-2154), 960 (453-1639), 848 (37-1554) and 720 (175-1396) for patients with CRC stage I (n=11), II (n=21), III (n=17) and IV (n=15), respectively. Hemoglobin values in CRCs classified according to International Classification of Diseases (ICD-10 codes) C180-1 (n=16), C182-3 (n=11), C184-6 (n=8) and C187-C200 (n=29) were 810 (180-1646), 627 (309-1422), 1322 (695-1580) and 969 (346-1855) ng/ml, respectively. False negativity below 75 ng/ml (the cut-off value recommended by the CRC Commission of the Ministry of Health, Czech Republic) was 15.6% and 84.4% of CRC were correctly detected. Hb values were independent of the CRC stage (p=0.25) and tumour location (p=0.60). The most common type of CRC were adenocarcinoma (ICD-O-3 8140/3; n=33) and tubular adenocarcinoma (ICD-O-3 8211/3; n=22) with Hb values 848 (233-1409) and 1480 (784-2050) (p=0.07).
Conclusions: The analytical data-mining tool I-COP provides a pioneering solution to merge laboratory information data with population-based cancer data. Detailed analyses of colorectal cancers detected in our study suggest that neither CRC stage nor tumour location substantially impact the FIT cut-off value. This could help to optimise FIT cut-off value in population-based CRC screening.

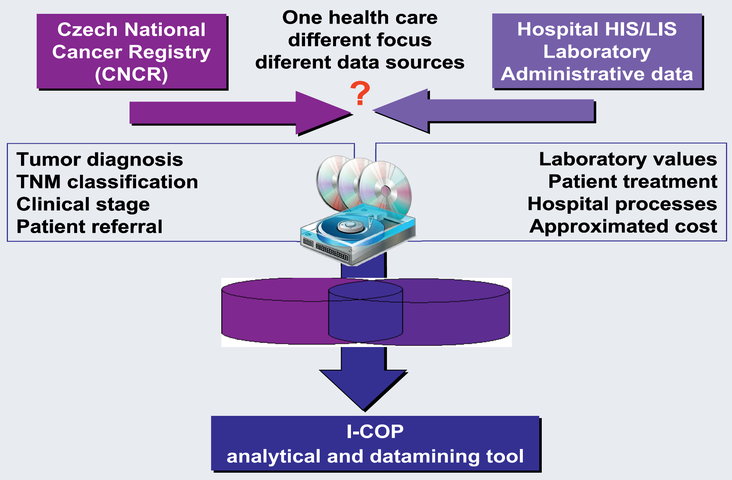
QUANTITATIVE FIT METHOD

Hemoglobin in stool was measured using **quantitative immunochemical method.** Stool sampling was carried out following the instructions of producere.
Stool was picked up by the brushing with the sampling brush on the stool surface and the immersion into the solution in test tube. This tube was kept in the temperature between 4 – 8 ºC till the evaluation.
Samples were analysed continuously during a one week on the **OC Sensor-mikro®** analyzer (Eiken Chemical Co., Tokyo, Japan).

Quantitative assessment of human hemoglobin in stool (qI-FOBT) evaluates the level of human hemoglobin using polyclonal antibody against hemoglobin. The analysis is performed using turbidimetric measurement by 600 nm in interval of measurement 0 - 2000 ng Hb/ml. In this reaction monoclonal antihuman HbA0 antibodies, which had been sentitized to latex, react with hemoglobin in the sample resulting in a latex agglutination reaction. The change in optical density of the reaction solution is analyzed, optical density increases in proportion to higher concentrations of HbA0 in the sample.

DATA-MINING TOOL I-COP

Set of all applied medicaments and performed treatment procedures including laboratory results, date of the application and approximate costs of the treatment can be found in administrative data of the hospital. We are able to follow the patient treatment path during his/her hospitalization. Each newly diagnosed tumour in the Czech Republic must be reported by the treating doctor to the central registry, as stipulated by law. This unique structured data source of clinical information is called the Czech National Cancer Registry (CNCR).



It contains a detailed, standardized clinical description of all nearly 2 million diagnosed tumours in the Czech Republic since 1976. The first part of completed registry record involves basic prognostic markers such as the diagnosis, clinical stage, grade, while the second part contains information about the applied therapeutic scheme, such as the date and type of operation, applied chemotherapy, radiotherapy, and other applied modalities. The main idea of I-COP solution is to join these complementary data sources together and to build a new, information-rich data warehouse.

COLORECTAL CANCER - FIT VALUE ng/ml

CRC stage	number	mean	SD	median	10-90% percentile
Stage I	11	1579	1276	1656	421-2154
Stage II	21	1062	676	960	453-1639
Stage III	17	881	805	848	37-1554
Stage IV	15	814	657	720	175-1396

The values of hemoglobin concentration (mean, SD, median, 10-90% percentiles) in the stool (ng/ml) for various stages of colorectal cancer, stage I - stage IV and for individual location of colorectal cancer in the left-right-hand.

CRC location	number	mean	SD	median	10-90% percentile
cecum - appendix	16	942	810	810	180-1646
ascending	11	774	589	627	309-1422
transverse - descending	8	1176	614	1322	695-1580
sigmoid - rectum	29	1168	1013	969	346-1855

ACCURACY OF QUANTITATIVE FIT A HISTORICAL COHORT STUDY

-3807 adult patients with their first FIT performed during 2009-2010
-patients without prior CRC, minimal 1 year follow-up through CNCR records
-mean age 61 years, 60% women
-positivity cut-off 75 ng/mL
-accuracy characteristics according to considered length of surveillance in cancer registry (FUP)

1 year FUP	CRC present	CRC absent	Total
Positive test	22	476	498
Negative test	9	3300	3309
Total	31	3776	3807

1 year FUP	%	95% CI
Sensitivity	71.0	52.0-85.8
Specificity	87.4	86.3-88.4
PPV	4.4	2.8-6.6

2 year FUP	CRC present	CRC absent	Total
Positive test	25	473	498
Negative test	10	3299	3309
Total	35	3772	3807

2 year FUP	%	95% CI
Sensitivity	71.4	53.7-85.4
Specificity	87.5	86.4-88.5
PPV	5.0	3.3-7.3

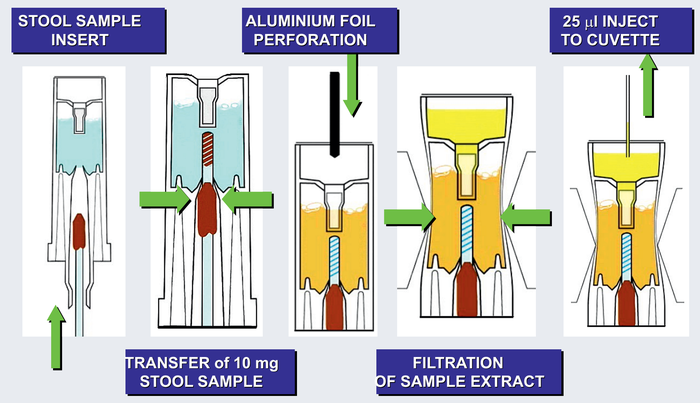
2 year follow-up may be incomplete in patients tested in 2010

COLORECTAL CANCER SCREENING

Colorectal cancer (CRC) is the second most frequent malignant disease in Europe. Every year, 412 000 people are diagnosed with this condition, and 207 000 patients die of it. The introduction of population-wide national screening programs is a priority for the healthcare policies of individual nations, and this is also being addressed at the highest levels by European Union (EU) administrators. A national screening program, of one sort or another, has been implemented in 19 out of 27 European countries. The most frequently applied method is testing the stool for occult bleeding (faecal occult blood test, FOBT). In the Czech Republic we began CRC screening programs in 1994, and population-based screening with FOBT was started in 2014. The involvement of GPs has been found to improve patient compliance with bowel cancer screening.
The first level of FOBTs tested were guaiac based gFOBT methods with sensitivity for colorectal cancer lower than 30%, and therefore this method of FOBT has been changed to immunological FIT. **This second level of FOBTs** tested were qualitative immunochemical based, which uses an antibody against human globin and are more sensitive than the gFOBT methods. These methods have very different accuracies and sensitivities, ranging from 29 - 72%, using different sampling devices and different stabilities of the sampling buffer. **The third level of FOBTs** are now quantitative methods of faecal hemoglobin determination with automated analysers (qiFOBT), increasing the accuracy to 90 - 95%, enabling the setting to country-specific optimal cut-offs, and most importantly to be controlled by the **External Quality Assurance Services (EQAS)** programs. The European Group on Tumour Markers recommends the use of a quantitative iFOBT with an adjustable cut-off point to all new centres undertaking FOBT for colorectal neoplasia; and organized faecal immunochemical test screening has been associated with an increase in annually detected CRC.The pilot study with OC-Sensor qiFOBT recommended 75 ng Hb/ml as the optimal cut-off value for screening in the Czech Republic.

QUANTITATIVE FIT METHOD - PREANALYTICS

Pre-analytical process, the processing of samples for quantitative analysis of hemoglobin in stool, covers semi-quantitative sampling of feces, extraction in a stabilizing buffer, filtering of a heterogeneous mixture of feces with buffer and direct sampling to reaction cell.



FIT POSITIVITY & CUT-OFF VALUE

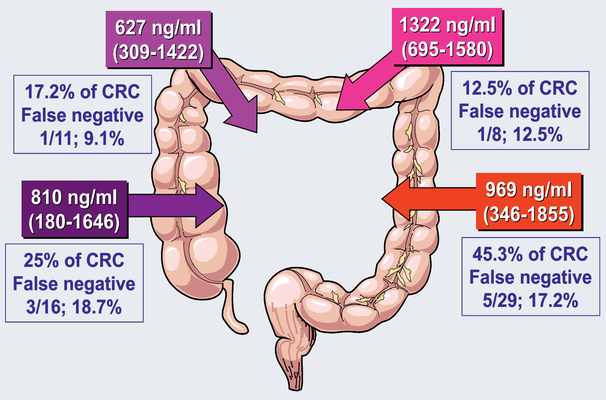
Determination of hemoglobin in stool is carried out as a routine diagnostic test for outpatient and inpatient specialist clinics in the General Faculty Hospital, Prague, for practical and occupational physicians as well as for pediatric clinics, where the concentration of hemoglobin in the stool serves as a marker of intestinal enteropathy.

subjects (50-90 years)	4151	FIT + (%)	6514	FIT + (%)
cut-off Hb ng/ml	Primary care, GPs		Specialized clinics	
> 50	392	9.44	1527	23.44
> 75	294	7.08	1285	19.73
> 100	228	5.49	1114	17.10
> 1000	47	1.13	311	4.77
detected CRC	11	0,26	53	0,81

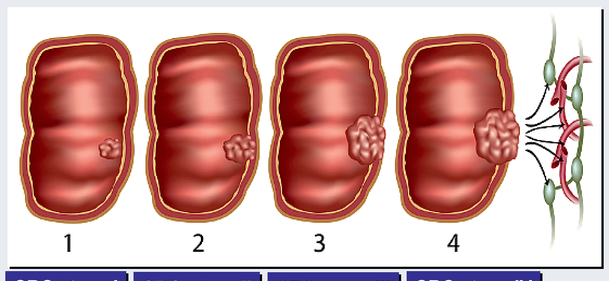
Data analysis of laboratory information system (LIS - OpenLIMS, Stapro) provides clinically relevant information about the degree of positivity FIT tests. This table compare two groups of subjects, patients for primary care, GPs, and outpatient or inpatients of specialized hospital clinics. The FIT positivity were calculated for different cut-off values. Finally, there are also mentioned number of detected colorectal cancer, in these groups, CRC detection rate - 2.65/1000 and 8.08/1000, and average time interval between FIT test and CRC surgery 5.34 months and 2.95 months.

COLORECTAL CANCER LEFT-RIGHT POSITION

Clinically, it is very important that not significantly different values of Hb ng/ml in various CRC locations. Our study shows 45.3% of cancers in the rectosigmoid localization, consistent with published data, and the values of Hb ng/ml during left-right-sided gradient did not differ significantly (p = 0.60). This demonstrates that the test OC-Sensor can be reliably used for left tumors, which is discussed in the literature repeatedly due to the possible degradation of the hemoglobin protein in the passage, and some studies show a lower reliability of immunochemical tests in the leftward localization.



COLORECTAL CANCER - TUMOUR STAGES



CRC stage I (n=11) 1656 ng/ml (421-2154)
CRC stage II (n=21) 960 ng/ml (453-1639)
CRC stage III (n=17) 848 ng/ml (37-1554)
CRC stage IV (n=15) 720 ng/ml (175-1396)

In our study, we do not identified the dependence on Hb values ng/ml to CRC stage (p = 0.25), but it is necessary to consider the potential bias of the wide range between the implementation of FIT test and CRC diagnosis (0.1 to 35.7 months) in this study. False negativity of OC-Sensor FIT test with cut-off value 75 ng/ml was in this study 15.62 % corresponding to the sensitivity for CRC - is 84.38 %. False negativity for individual CRC stages are 1/11; 9.1% for stage-I, 2/21; 9.5% for stage-II, 5/17; 29.4% for stage-III and 2/15; 13.3% for stage-IV.

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