EFFECTIVENESS OF THE IMMUNOCHEMICAL FECAL TEST (FIT) FOR DETECTION OF ADVANCED ADENOMAS IN COLORECTAL CARCINOMA SCREENING IN AN ASYMPTOMATIC POPULATION

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EFFECTIVENESS OF THE IMMUNOCHEMICAL FECAL TEST (FIT) FOR DETECTION OF ADVANCED ADENOMAS IN COLORECTAL CARCINOMA SCREENING IN AN ASYMPTOMATIC POPULATION (Abstract): **Aim:** The aim of the study was to evaluate the benefit of the immunochemical fecal blood test (FIT) for detection of advanced adenomas. **Material and methods:** We have conducted a screening study on an average-risk cohort of subjects, aged 50 – 74 years. We used a rapid quantitative FIT to perform the screening. Colonoscopy was recommended in all participants with positive FIT. We assessed the participation rate and analyzed advanced adenomas detected in the screening examinations. **Results:** Our study enrolled 1111 asymptomatic participants. Immunochemical test results were positive in 72 subjects (6.5%). Colonoscopy was performed by 50/72 (69.4%) subjects. The detection rate for advanced adenomas was 2.2%. A total number of 28 advanced adenomas were detected in 24 subjects, meaning 1.2 advanced adenoma/subject. Analyzing the 3 characteristics of advanced adenomas, we observed in our study that 25/28 adenomas (89.3%) had sizes ≥ 10 mm, 11/28 adenomas (39.3%) were tubulovillous/villous and 19/28 adenomas (67.9%) had high dysplasia. The majority of advanced adenomas were found in the left colon as compared to the right colon: 71.4% vs. 28.6%, p=0.0008. **Conclusions:** In our study was obtained a 2.2% detection rate for advanced adenomas, most of them (71.4%) being located in the left colon. The dominant feature of advanced adenomas detected was the size ≥ 10 mm (89.3% of cases). **Keywords:** IMMUNOCHEMICAL FECAL TEST, ADENOMAS, COLORECTAL CARCINOMA, SCREENING.

Colorectal cancer (CCR) is a major cause of mortality in the developed countries, with a 6% risk to develop the disease during life, with an incidence of more than one million new cases per year and with a long term survival of 50% (1).

Detecting the early stages of CCR and adenomas in an apparently healthy population using the screening tests reduces incidence and mortality due to colorectal car-
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cinoma. Noninvasive testing as fecal occult blood tests (FOBT) is now widely accepted as a screening tool for detecting CCR (2). At the beginning the guaiac fecal occult blood tests were used for screening but due to their low sensitivity and specificity (they are not specific for human hemoglobin and they need dietary restrictions) they are less used nowadays (3).

The fecal immunochemical test (FIT) is considered a superior screening test because of its better reproducibility and acceptance. Detection rates for advanced adenomas and cancer are higher compared to guaiac fecal occult blood test (gFOBT) (4). Therefore the American Cancer Society has replaced the guaiac based test with immunochemical tests as a screening tool for CCR (5). A better sensitivity in detecting CCR in early phases when the disease is asymptomatic has been demonstrated by fecal immunochemical test than gFOBT (1). Data from Saito demonstrated a sensitivity of 67-89% in detecting CCR using immunochemical test compared with 33-37% using Hemoccult. A reduction in CCR mortality with 60% was demonstrated with annual screening (6).

The aim of the study was to evaluate the benefit of the FIT for detection of advanced adenomas knowing their malignant potential.

MATERIAL AND METHODS

Our study included a cohort of average risk persons, meaning asymptomatic subjects aged between 50 and 74 years. To limit the percentage of FIT false positives results the following subjects were excluded: subjects with adenoma or colonic carcinoma or with family history of adenoma or colonic carcinoma (first – degree relatives), subjects with inflammatory bowel diseases, people that took part in a screening program and performed one of the screening methods accepted by the international guidelines in the last years (2 years for FOBT, 5 years for virtual colonoscopy/barium enema/flexible sigmoidoscopy and 10 years for colonoscopy). Subjects with a short life expectancy (less than 10 years) were also excluded.

All subjects included in our study signed an informed consent; the study was approved by the local Ethics Committee and was in accordance with the Helsinki Declaration of 1975.

The stool sample was collected in a clean dry screw-top container according to the instructions that they have received. The stool sample was handed to the laboratory on the same day of the collection or within the first 24 hours. The test format of HEM CHECK-1 (VedaLab, France), used in our study, employs the standard antibody/antigen lines of capture, typically with a control line to interpret a positive and negative result. Test results were sent to the participant, physician and medical screening program coordinator.

Patients with positive FIT were sent to the Gastroenterology Department of Arad County Hospital to set an appointment for the colonoscopy. The Gastroenterologist explained to the subjects the benefits and the risks of performing a colonoscopy and if needed, a polypectomy. Preparation for colonoscopy was done with polyethylene glycol. All colonoscopies were performed under sedo-analgesia. Anesthesia, colonoscopy and polypectomy were performed only after obtaining the written consent from the patient. Administration of anticoagulant therapy, non-steroidal anti-inflammatory drugs or clopidogrel was stopped in the last 5-7 days prior to the
endoscopic procedure. The colonoscopy result includes the number of polyps, their size (≤ 5 mm, from 5-9 mm, and ≥ 10 mm) and their location. The histopathology result of the biopsy mentions besides the size (≥ 10 mm), the tubulovillous or villous structure and the high grade mucosal dysplasia of the adenoma to confirm the diagnosis of advanced adenoma.

We used the term advanced adenomas for adenomas with at least one of these characteristics: size ≥ 10 mm and / or high-grade mucosal dysplasia and / or with a villous structure of ≥ 20% (tubulovillous, villous).

Statistical analysis was performed using the MedCalc Software, version 12.4.0 (MedCalc, Belgium). The distribution of the numerical variables was first tested by the Kolmogrov-Smirnov test. In case of numerical variables with normal distribution mean value and standard deviation were calculated, while in case of non-normal distribution median values and range interval were presented. Qualitative variables were presented as numbers and percentages. The Fisher’s exact test was used for the comparison of two proportions expressed as a percentage. 95% confidence intervals were calculated for each predictive test. A p-value less than 0.05 were regarded as significant for each statistical test.

RESULTS
Our study enrolled 1111 asymptomatic participants with mean age 61.4 ± 12.8 years, 461 (41.5%) men and 650 (58.5 %) women. FIT results were positive in 72 (6.5%) persons with mean age 62.1±11.9 years, 34 (47.2%) men and 38 (52.8%) women. The mean age of women with positive FIT was similar with the mean age of men with positive FIT: 62.3±12.1 years vs. 61.9±12.1 years, p=0.76.

Among the 72 participants with positive FIT, 50 (69.4.%) accepted to perform a colonoscopy. The others refused colonoscopy or delayed this investigation. Advanced adenomas were detected in 24 subjects (2.2%), 16/24 subjects (66.7%) were men and 8/24 subjects (33.3%) were women. The mean age of men with advanced adenomas was similar with that of women detected with advanced adenoma: 63.5±11.4 years vs. 62.6±12.1 years, p=0.85. A total of 28 advanced adenomas were detected in these subjects, meaning 1.2 advanced adenoma/subject. Association of advanced adenomas with colorectal cancer was met in 5 patients (20.8%) (tab. 1).

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Total investigations</th>
<th>Advanced adenomas</th>
<th>Number of advanced adenomas</th>
<th>Number of advanced adenomas /subject</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of subjects</td>
<td>%</td>
<td>number of subjects</td>
<td>%</td>
</tr>
<tr>
<td>50-54</td>
<td>225</td>
<td>20.3</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>55-59</td>
<td>256</td>
<td>23.0</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>60-64</td>
<td>254</td>
<td>22.9</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>65-69</td>
<td>178</td>
<td>16</td>
<td>6</td>
<td>3.4</td>
</tr>
<tr>
<td>70-74</td>
<td>198</td>
<td>17.8</td>
<td>6</td>
<td>3.0</td>
</tr>
<tr>
<td>Total</td>
<td>1111</td>
<td>100</td>
<td>24</td>
<td>2.2</td>
</tr>
</tbody>
</table>

TABLE I
The distribution of advanced adenomas according to the age
Effectiveness of the immunochemical fecal test (FIT) for detection of advanced adenomas

Analyzing the 3 characteristics of advanced adenomas, we observed that 25/28 adenomas (89.3%) had sizes ≥ 10 mm, 11/28 adenomas (39.3%) were tubulovillous/villous and 19/28 adenomas (67.9%) had high dysplasia.

In our study 7/28 (25%) advanced adenomas showed a single characteristic: 5 adenomas had size ≥ 10 mm, one adenoma had tubulovillous/villous structure and one adenoma was with high grade dysplasia. Two characteristics were found in 15/28 (53.6%) adenomas: 11 adenomas had size ≥ 10 mm and high grade dysplasia, 3 adenomas had size ≥ 10 mm and had tubulovillous/villous structure and one adenoma had tubulovillous/villous structure and high grade dysplasia. All 3 characteristics were found in 6/28 (21.4%) adenomas.

In this study we detected 28 advanced adenomas. Dominant characteristics of advanced adenomas were size ≥ 10 mm (89.3%) and high-grade dysplasia (67.9%). 39.3% of advanced adenomas contained tubulovillous/villous. Large size, high-grade dysplasia and villous pattern are pathological characteristics that are known to increase the probability of malignant

<table>
<thead>
<tr>
<th>Location</th>
<th>Adenomas</th>
<th>%</th>
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<tbody>
<tr>
<td>Rectum</td>
<td>6</td>
<td>21.4</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>12</td>
<td>42.9</td>
</tr>
<tr>
<td>Descending colon</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>Transvers colon</td>
<td>5</td>
<td>17.9</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>3</td>
<td>10.7</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The purpose of screening for CCR is to reduce the morbidity and mortality because the prolonged evolution of the adenoma to carcinoma (10-15 years) is well known (7). Colonoscopy is the first choice screening option recommended by the international guidelines because of its high sensitivity/specificity and therapeutic utility for advanced adenomas, but it is costly and it requires specialized personnel and corroborated with the risks that are involved (like perforation) (8) make this method a difficult one to be implemented in a national screening program in our country.

The aim of the present paper was to evaluate the effectiveness of FIT in detecting advanced adenomas as the removal of these lesions could be considered a warrant of invasive cancer prevention. We chose the FIT because among the other non-invasive test, such as the guaiac based fecal test, it proved better sensitivity, specificity and a higher compliance (9). We studied an average-risk population cohort, aged 50-74 years, using a rapid qualitative FIT, Hem Check 1, produced in France by VedaLab.

In our study the detection rate of advanced adenomas was 2.2%, similar values being obtained in other studies (9,11) and remained considerably higher compared to the guaiac-based fecal test detection rate (10,11).

In this study we detected 28 advanced adenomas. Dominant characteristics of advanced adenomas were size ≥ 10 mm (89.3%) and high-grade dysplasia (67.9%). 39.3% of advanced adenomas contained tubulovillous/villous. Large size, high-grade dysplasia and villous pattern are pathological characteristics that are known to increase the probability of malignant
transformation (12). It is known that polyps ≥ 10 mm have a 1% malignancy rate per year and they turn into cancer in 24% of cases. Adenomas less than 10 mm may develop invasive cancer in less than 5 years extremely rare (13). Some studies (14, 15) proved that greater size of the adenomas determined higher rate for detection of advanced adenomas or cancer in follow–up colonoscopies and a villous pattern of more than 20% is not a constant risk factor for detecting advanced adenoma during follow–up colonoscopy (1). We obtained similar values compared to the data published by Yang et al evaluating the effectiveness of the FIT in a 5919 cohort study in 2011 when they analyzed the characteristics of the advanced adenomas (16).

Our data analysis supports the hypothesis that FIT is more efficient for detecting left-sided advanced adenomas than right-sided advanced adenomas. The location of advanced adenomas in our study was mainly in the left colon 71.4% vs 28.6% the right colon (p<0.0008). The differences in detecting advanced adenomas in left and right colon are similar to the findings reported by Morikawa et al (2005) regarding immunochemical FOBT (17) and is also supported by other studies, one of them conducted by Haug et al. in 2011 using FIT (18), and another one reporting a test performance of a guaiac-based FOBT (19). Most studies proved a better efficiency in detecting left sided lesions (rectum, sigmoid, descending colon, splin flexure) than in the right colon (transverse, ascending colon, caecum) probably because of the stool consistency and because the blood is more homogeneous distributed in the right sided colon and is more superficial in the left colon (18).

Authors of the “European guidelines for quality assurance in colorectal cancer screening and diagnosis guidelines” (1) gathered information from several studies stating that older age comes with increased risk of detecting advanced adenomas (15, 20). Our study cohort showed a greater rate of advanced adenoma in the group age ≥ 60 years old, but should be specified that a relatively small number of FIT positive subjects were included in each group. Although the majority of the studies (1) analyzing the detection rate of advanced adenomas in older age showed the same conclusions, advanced age is not an indication for more intense surveillance because of the slow progression of advanced adenomas to cancer (1). In our study we detected a greater number of advanced adenomas in men; similar values were obtained in some studies (15) but not in all (20).

**CONCLUSIONS**

In this study we obtained a 2.2% detection rate for advanced adenomas, most of them (71.4%) being located in the left colon. The dominant feature of advanced adenomas detected was the size ≥ 10 mm (89.3% of cases). Knowing that, positive FOBT and, more useful – FIT combined with cut – off hemoglobin levels, are recommended as methods which are correlated with colonic diseases – especially polyps and cancer.

**REFERENCES**

Effectiveness of the immunochemical fecal test (FIT) for detection of advanced adenomas