The Endoscopic Characteristics of Advanced Colorectal Adenomas – Colonoscopic Study

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SUMMARY
Both advanced and nonadvanced adenomas are most frequent in male older than 50. According to their endoscopic appearance, advanced adenomas can be recognized even during the colonoscopy, and differed from the nonadvanced ones. The most frequent distal localization of advanced adenomas indicates that they can be initially diagnosed even with rectosigmoidoscopy. However, considering the fact that there is a significant number of patients without distal, but only with proximal tumors, colonoscopy is the method of choice for the diagnosis of all colorectal adenomas. This refers particularly to those patients with nonobstructive CRC who are planned for surgical intervention. Preoperative colonoscopy detects possible synchronous CRC in early postoperative period, prevents the malignant transformation of adenomas and improves long-standing wellbeing of the patients.

Key words: adenomas, colonoscopy, surgery.

1. INTRODUCTION
Colorectal carcinoma (CRC) is one of the most frequent malignant tumors of gastrointestinal tract and the second most frequent cause of death among patients with malignant diseases. Literature data show that more than 95% of CRC develops from a malignant alteration of adenoma, which is not discovered in time and removed. Progression of adenoma to CRC is multistep process, accompanied by alterations of several suppressor genes that result in abnormalities of cell regulation, with a natural history of 10-15 years [1,2,3,4]. The connection between adenoma and CRC was first described in 1928 [5].

The malignant potential of colorectal adenomas depends on their diameter, histological type and degree of dysplasia. Recently literature has adopted the term “advanced colorectal adenoma” to describe colorectal polyps with advanced characteristics (diameter > 10mm and/or villous component and/or severe dysplasia) [6,7,8]. This characteristics are interdependent and predicting an increased likelihood of malignant transformation [9,10,11]. Advanced adenomas are a link in the chain of malignant transformation of benign adenomas, that is a biological–medium stage in the final process of colorectal carcinogenesis. The removal of advanced adenomas directly prevents the development and decreases the expected incidence of CRC to 90% [12].

2. WORK GOAL
The goal of this study is to present the endoscopic characteristics of advanced adenomas. Likewise we will show that these endoscopic characteristics prove “adenoma-carcinoma sequence” theory and that colonoscopy is the chosen method for their adequate diagnosis.

3. MATERIAL AND METHODS
A prospective, four-year research included 184 patients with colorectal adenomas. This study excludes all patients with incomplete colonoscopy, the diagnosis of familiar adenomatosis polyposis (FAP), Lynch syndrome and ulcerous colitis. In the course of colonoscopic examination, we analyzed the localization, the macroscopic shape and the surface of 120 advanced and 120 nonadvanced adenomas (control group). All patients were examined colonoscopy in the endoscopic office. Colonoscopies were performed with Olympus colonoscope types: CF 20HI and CF 30HI. Colorectal polyps were completely removed by standard or “piece meal” polypectomy techniques. Sessile colorectal polyps, diameters up to 4 mm were removed by hot biopsy forceps (FD 1L), but larger polyps by snare ectomy, using Olympus standard diathermic snares: SD-6 and SD 9/11 and Olympus electro-surgical unit PSD 2E. Mucosal lesions suspected on malignant tumors were multiply biopsed (4-6) by standard bioptic forceps FB 23K, FB 24K and FB 25K.

Classic HE (hematoxilin-eozin) staining for confirmation of pathohistologic processes and histochemic’s stainings AB-PAS (Periodic Acid Schiff), HID-AB(pH=2.5) (High Iron Diamine/Alcian blue) for mucins were used too.

For statistical analysis Student’s t test and χ2 test were applied.

4. RESULTS
Statistically, advanced adenomas were significantly more often solitary (78 65.0%) than multiple, synchronous (42 35.0%) (p<0.001) as opposed to the nonadvanced ones, which were more often syn-
The average of advanced synchronous adenomas per patient was 1.2±1.1. The synchronous advanced adenomas were most often combined with the nonadvanced adenomas (22 52.4%) (p<0.001) (Table 1).

There was no statistically significant difference in age between patients with solitary (60.1±11.4%) and patients with synchronous (63.5±5.3) advanced adenomas (p>0.05). We obtained similar results through the analysis of the control group. The analysis of the synchronous adenomas showed that the oldest patients (77 years of age) were those with CRC and those who had two advanced adenomas (p>0.05).

All advanced adenomas, as well as the nonadvanced ones, were most localized in the distal part of the colon (rectum+sygma) (p<0.001). The nonadvanced adenomas, as opposed to the advanced ones, were most often localized in the proximal part of the colon (32.5%, that is 25.0%) (p>0.05) (Graph 3).

Synchronous tumors may be localized in the same, in different segments and, if there are more than two, in both the same and different segments. Synchronous advanced adenomas, in relation to the nonadvanced ones were less frequently localized in the same segment of the colon, but that was not a statistically significant difference (p>0.05).

The analysis of index (rectal) and proximal tumors verified that the proximal tumors were statistically more often nonadvanced in the cases where there was no index tumor, than when the index tumor was an advanced adenoma (p<0.001) (Table 2).

Patients with an advanced index adenoma had proximally advanced adenoma in 30.8% of the cases, nonadvanced in 15.4%, CRC in 7.7% and negative result in 46.2%. When there was no index tumor (33 patients with synchronous tumors), the prevalence of the proximal synchronous tumors was the greatest (69 57.0%). Proximal tumors were most often nonadvanced (44 63.8%), then advanced (22 31.9%) and least CRC (3 4.3%).

Advanced adenomas in the rectum were statistically more often present in male than in female (Graph 1).

**TABLE 1. Groups of synchronous advanced adenomas**

<table>
<thead>
<tr>
<th>Groups of synchronous tumors</th>
<th>Number of tumors</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>advanced + advanced</td>
<td>14 19.5%</td>
<td>7 20.6%</td>
</tr>
<tr>
<td>advanced (2)+ nonadvanced</td>
<td>3 4.2%</td>
<td>1 2.9%</td>
</tr>
<tr>
<td>advanced + nonadvanced</td>
<td>44 61.1%</td>
<td>22 64.7%</td>
</tr>
<tr>
<td>advanced + nonadvanced (2)</td>
<td>6 8.3%</td>
<td>2 6.0%</td>
</tr>
<tr>
<td>advanced + CRC</td>
<td>2 2.7%</td>
<td>1 2.9%</td>
</tr>
<tr>
<td>nonadvanced + advanced + CRC</td>
<td>3 4.2%</td>
<td>1 2.9%</td>
</tr>
<tr>
<td>Total</td>
<td>72 100.0%</td>
<td>34 100.0%</td>
</tr>
</tbody>
</table>

**GRAPH 1. Advanced and nonadvanced adenomas related with multiplications**

**GRAPH 2. Prevalence of adenomas related with patient's sex**

**GRAPH 3. Localization of advanced and nonadvanced adenomas**
male ($\chi^2=5.45; p<0.05$). We obtained similar results through the analysis of non-advanced adenomas. This difference was of no importance for those patients with adenomas in other segments of the colon ($p>0.05$).

Distaly localized adenomas were more often present in patients older than 40. Statistically, there was no significant difference in age between patients with distal and proximal advanced adenomas ($\chi^2=0.18; p>0.05$). We obtained similar results through the analysis of nonadvanced adenomas.

In relation to size, we grouped all adenomas into adenomas $>10$mm and adenomas $<10$mm. Table 3 shows that there were significantly more adenomas $<10$mm (144 60.0%) ($p<0.05$).

Between patients with adenomas of size $<10$mm and those of size $>10$mm, we verified no significant difference in relation to sex ($p>0.05$), or age ($\chi^2=4.07; p>0.05$). Statistically, there was no significant difference between adenomas of distal and proximal segment of the colon ($\chi^2=0.38; p>0.05$).

Likewise, we verified no statistically significant difference in size between adenomas of specific colon segments ($p>0.05$) (Graph 4).

In relation to the macroscopic form, we analyzed all adenomas as sessile (with wide base) and peduncular adenomas. Statistically, advanced adenomas were significantly more often peduncular (63.3%) than sessile (36.7%) ($p<0.001$). We obtained the same result through the analysis of the control group ($p<0.001$).

Peduncular advanced adenomas were more often of size $>10$mm (86.8%) as opposed to the sessile ones (68.2%) ($\chi^2=6.06; p<0.05$) (Table 4). We obtained the same result through the analysis of the control group.

The analysis of localization of the specific forms of advanced adenomas showed that sessile adenomas were most often localized in the rectum, whereas peduncular adenomas were localized in the sygma ($p<0.001$). We obtained the same result through the analysis of the control group (Graph 5).

There was no statistically significant difference between the forms of advanced adenomas of distal and proximal part of the colon ($\chi^2=0.24; p>0.05$). We obtained the same results through the analysis of the control group.

Peduncular advanced adenomas were more often of size $>10$mm (86.8%) as opposed to the sessile ones (68.2%), ($\chi^2=6.06; p<0.05$) (Table 4). We obtained the same result through the analysis of the control group.

### Table 2. Prevalence of proximal tumors related with index tumor type

<table>
<thead>
<tr>
<th>Index tumor</th>
<th>Number of proximal tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>advanced adenomas</td>
<td></td>
</tr>
<tr>
<td>nonadvanced adenomas</td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td></td>
</tr>
<tr>
<td>without tumors</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Prevalence of all adenomas related with size

<table>
<thead>
<tr>
<th>Size of adenomas</th>
<th>Number of adenomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;10$mm</td>
<td>144 60.0%</td>
</tr>
<tr>
<td>$10$mm – $20$mm</td>
<td>67 27.9%</td>
</tr>
<tr>
<td>$&gt;20$mm</td>
<td>29 12.1%</td>
</tr>
<tr>
<td>Total</td>
<td>240 100.0%</td>
</tr>
</tbody>
</table>

### Graph 4. Localization of all adenomas related with size

### Graph 5. Localization of advanced adenomas related with macroscopic form
TABLE 4. Diameter of advanced adenomas related with macroscopic form

<table>
<thead>
<tr>
<th>Size of adenomas</th>
<th>Sessile</th>
<th>Peduncular</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10mm</td>
<td>14 31.8%</td>
<td>10 13.2%</td>
</tr>
<tr>
<td>&gt; 10mm</td>
<td>30 68.2%</td>
<td>66 86.8%</td>
</tr>
<tr>
<td>Total</td>
<td>44 100.0%</td>
<td>76 100.0%</td>
</tr>
</tbody>
</table>

In relation to the appearance of the surface, we analysed all adenomas as intact, red, rough or eroded. Statistically, advanced adenomas were not significantly different in surface from the nonadvanced ones ($\chi^2=5.77; p>0.05$). There was no statistically significant difference in the appearance of the surface of the advanced adenomas in relation to the sex ($\chi^2=1.12; p>0.05$) and the age ($\chi^2=2.47; p>0.05$) of the patients. We verified no statistically significant difference in the appearance of the surface of the advanced adenomas of different localization ($\chi^2; p>0.05$).

We obtained similar results through the analysis of the control group ($\chi^2=2.47; p>0.05$).

Adenomas of size > 10mm most often had a rough surface whereas those of size < 10mm most often had an intact surface ($\chi^2=10.62; p<0.001$) (Table 5).

We obtained similar results through the analysis of the nonadvanced adenomas ($\chi^2=47.86; p<0.001$).

Sessile advanced adenomas most often had an intact surface (52.0%), whereas peduncular adenomas most often had rough surface ($\chi^2 =9.81; p<0.05$) (Table 6).

We obtained similar results through the analyses of the nonadvanced adenomas.

5. DISCUSSION

Adenomas make 66.5% of all removed colorectal polyps [9]. Considering that adenomas do not generally have clinical manifestations, in more than 30% of the patients they are discovered during the endoscopic examination of the colon, indicative of some other disease, or as an accidental lesion during autopsy [13].

Colonoscopy is the most sensitive method for the diagnosis of colorectal adenomas. A complete colonoscopic examination provides the identification of all possible solitary or multiple adenomas. Synchronous colorectal tumors are a usual result in the course of colonoscopic evaluation of the colon. Patients with synchronous tumors have a bigger risk of later adenoma development or CRC [5,14-16]. Some authors claim that synchronous tumors spread intracolically from one primary position. Allegedly, during the colonoscopy, there is a possibility of transport of neoplastic cells into more proximal segments of the colon. These authors suggest early postoperative colonoscopy for the purpose of exclusion of any danger of such disease spread [5,16,17,18].

In our study, the advanced adenomas were more often solitary as opposed to the nonadvanced ones, which has no statistical significance. In the group of synchronous advanced adenomas, the average number of adenomas per patient was 1.2±1.1. The results that we had obtained were compatible with the results of other studies [5, 9,16,19,20,21,22).

We established that all adenomas were statistically more significantly present in male than in female. Other authors have also confirmed the sex predilection of adenomas [19,21]. Akarca et al. proved the connection between a bigger prevalence of adenocarcinomas and advanced adenomas of colorectum in male, in relation to female [5]. The existence of the same sex and age predilection, as well as the localisation for colorectal adenomas, especially advanced adenomas, and colorectal carcinoma give one more proof in favour of “adenoma-carcinoma sequence” hypothesis. There are studies that show that male and female differ in terms of the time of intestinal transit feces volume and the production of bile acids and fat acid of short chain. These data indicate the differences between the sexes in intestinal metabolism, the bacterial population of the colon, the degree of fermentation and the general state of the colon, which may be responsible for the sex predilection of colorectal adenomas and carcinomas. It is believed that these differences are conditioned by hormones [23].

Colorectal adenomas can develop at any age. We have concluded that the prevalence of both advanced and nonadvanced adenomas increases with the age of the patients especially after 50, reaching the maximum at the age of 60-69. Of all the patients with advanced adenomas, 86.9% was older than 50. The oldest patients had several advanced adenomas at the same time or adenomas combined with CRC, which indicates that we should always insist on to-

![Table 4](image-url)

TABLE 5. Surface of advanced adenomas related with size

<table>
<thead>
<tr>
<th>Size of adenomas</th>
<th>Surface of adenomas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intact</td>
<td>red</td>
</tr>
<tr>
<td>&lt; 10mm</td>
<td>15 62.5%</td>
<td>5 20.9%</td>
</tr>
<tr>
<td>&gt; 10mm</td>
<td>33 34.4%</td>
<td>12 12.5%</td>
</tr>
</tbody>
</table>

![Table 5](image-url)

TABLE 6. Surface of advanced adenomas related with macroscopic form

<table>
<thead>
<tr>
<th>Macroscopic form of adenomas</th>
<th>Surface of adenomas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intact</td>
<td>red</td>
</tr>
<tr>
<td>Sessile</td>
<td>23 52.0%</td>
<td>4 9.1%</td>
</tr>
<tr>
<td>Peduncular</td>
<td>25 32.9%</td>
<td>13 17.1%</td>
</tr>
</tbody>
</table>
The Endoscopic Characteristics of Advanced Colorectal Adenomas – Colonoscopic Study

In early detection of CRC is timely detection of all colorectal tumors. In our study, both advanced and nonadvanced adenomas, solitary and multiple, were most often localized in the distal part of the colon, more precisely in the sigma (46.7%), and least often in the ascending (3.3%). The prevalence of colorectal adenomas evidently decreases from distal segments to proximal, both in our study and those of other authors [16,24,25,26,27,28,29]. One explanation for the bigger prevalence of distal adenomas is their earlier clinical manifestation. An increased adenoma incidence in the distal part of colorectum suggests that, even in smaller endoscopic centres, where the rigid rectosigmoidoscopy is a routine procedure, we can do the following diagnose the majority of colon tumors, short the time needed to diagnose adenomas and CRC, and manage to diagnose CRC at an earlier stage and without complications. However, there are clinical and autopsy studies which show that approximately half of colorectal adenomas appear in the proximal part of the colon. This can be explained by real limitations in the diagnosis of colon adenomas. Some authors claim that, in the past few years, there has been a trend of decreased incidence of adenomas and CRC in the proximal part of the colon that is, a decrease in the distal part [16,30]. This can be explained by biological differences in the development of the tumor and it is believed that distal and proximal colons behave as two different entities. A proximal colon is characterised by retrograde propulsion, along with longer intramucosal exposure to intraluminal carcinogens [31]. There are different genetic mechanisms of the development of carcinoma of the right and left colon and the rectum [5,16,31]. However, the increase of the frequency of CRC of the right colon may also be the consequence of the frequent use of colonoscopy in CRC detection, which is a far more sensitive method than other methods.

The analysis of adenoma localization, in relation to the sex of the patients, proved that both male and female most often had distal adenomas (advanced and nonadvanced). All proximal adenomas were more often localized in female than in male. There are studies to prove that female more often had a carcinoma of the right half of the colon, while male had a carcinoma of the left half, irrespective of age [16,32].

Numerous studies have show that adenoma localization is connected with the age of the patients, that is, age indicates adenoma localization in the proximal part of the colon [16,22]. It is a belief that the transit through the colon becomes shower with age and prolongs the time of exposure to intraluminal carcinogens, especially in the right colon. By analysing patients of the average age of 67.4. Nagorni et al. established that over 50% of adenomas were localized proximally from sigma. The authors concluded that, with screening sigmoidoscopy of this age, one could overlook a significant number of adenomas; however, that could be acceptable because a huge majority of proximal adenomas do not advance into CRC within the life expectancy of this age group [16].

Numerous studies have show that multiple colorectal adenomas tend to group in every segment of the colon. This grouping can be explained by a possible local response of the colon to the growth of individual tumor, or by the fact that the grouping of tumors is the consequence of the production of oncogen agent, perhaps a virus with local, intraluminal spread, so that polypectomy of the solitary polyp could eliminate the cause of grouping. However, on the basis of our results, we consider, as well as the other authors, that synchronous advanced adenomas, as opposed to the nonadvanced ones, tend to group less within the same segment of the colon [5,14,16,23].

In our study the patients with advanced adenomas in the rectum (index tumor) were most often without proximal tumors or less frequently had advanced proximal, synchronous adenomas. In case of tumor non-existence, in the rectum, we verified the biggest number of proximal synchronous adenomas. The results show that a complete examination of the colon is always necessary and that a rectosigmoidoscopy would overlook a significant number of proximal tumors. Along with the other authors, we believe that in case of colonoscopy only in patients with distal tumors, around 50% of proximal advanced adenomas or CRC will remain undiagnosed [16]. David et al. claim that the clinical significance of rectal colorectal adenomas depends on whether they are advanced proximal tumors [33].

We verified 40% adenomas of size > 10mm, which are therefore defined as advanced. Our results are in accordance with those of other studies [5,30,34]. The numerous studies confirm that adenomas diameter > 10mm have a significantly greater malignant potential in relation to smaller adenomas [5,28]. Several studies have proven that
K-RAS mutation is most frequently found in larger adenomas [5,26].

Based on our results, we concluded that adenomas diameter > 10mm are more frequent in male. However, there are studies which established that large adenomas are more frequent in female, which can be explained by the influence of their hormones on the growth of adenoma and adenoma-carcinoma sequence [5,28,30,35]. We analysed our results, and those of other authors, and concluded that the size of adenomas is positive correlation with the age of the patients [5,16,35].

While analysing adenoma localization, we established that all adenomas, regardless of size, were most often localized in the sygma. There were somewhat more adenomas of size <10mm (68.1%) in the proximal part of the colon, which led us, as well as other authors, to conclude that, with an increase of the size of adenomas, there is a trend of their localization in the distal part of the colon [5,36]. Funnen et al. analysed 1600 patients and concluded that small adenomas were equally distributed in the colon, whereas the large ones tended to localize distally. Adenomas of size 30-39mm were exclusively localized in the rectum, sygmond and descending colon [22]. In the study of Way et al. 71.4%, all CRC were in the rectum and sigmoid colon, where large adenomas are generally detected [37]. The correspondence of the distribution of large (advanced) adenomas with CRC, as opposed to small adenomas, is yet another proof to confirm bigger malignant potential of adenomas > 10mm.

Proximal adenomas of size >10mm have a higher rate of recurrence in ratio to adenomas <10mm. No connection between the recurrence rate and the number of histological structure of adenomas has been established [5,16,22]. We have established that the advanced adenomas were more often peduncular. There are studies where sessile advanced adenomas are dominant in relation to peduncular. Similar to other authors, we have not verified a significant difference in the shape of both advanced and nonadvanced adenomas [5,16,22]. All sessile and peduncular adenomas were more frequent in male than in female. We have not verified the connection between the shape of adenoma and the age of the patients. Peduncular shapes are in 86.8% adenoma diameter >10mm.

The most frequent endoscopic appearance of advanced adenomas (diameter >10mm, peduncular and rough surface) indicates that, in relation to the nonadvanced ones, they are more subject to irritant effect of intestinal are contents and possible cancerogens which may accelerate their malignant alteration. These results were in accordance with the results of other authors [5,8,16,22,37]

6. CONCLUSION

Both advanced and nonadvanced adenomas are most frequent in male older than 50. According to their endoscopic appearance, advanced adenomas can be recognized even during the colonoscopy, and differed from the nonadvanced ones. The most frequent distal localization of advanced adenomas indicates that they can be initially diagnosed even with rectosigmoidoscopy. However, considering the fact that there is a significant number of patients without distal, but only with proximal tumors, colonoscopy is the method of choice for the diagnosis of all colorectal adenomas. This refers particularly to those patients with nonobstructive CRC who are planned for surgical intervention.

Preoperative colonoscopy detects possible synchronous CRC in early postoperative period, prevents the malignant transformation of adenomas and improves long-standing wellbeing of the patients.

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