

Increasing Prevalence of Right-Sided Colonic Adenomas in a High-Volume Endoscopy Department in Romania: Implications for Colorectal Cancer Screening

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ABSTRACT

Background & Aims: A gradual shift of colorectal adenoma and carcinoma location toward the proximal colon has been recently observed both in the United States and Europe. We aimed to study the polyp and adenoma detection rate in a major endoscopy center of northwestern Romania over a 16-year period, and to characterize the distribution and the pathological features of the removed polyps according to age and sex, in order to assess the trend of proximal adenoma prevalence in our population.

Methods: We retrospectively analyzed 9,230 consecutive colonoscopies performed between 1996 and 2011 in a high-volume outpatient clinic in Cluj-Napoca, Romania. We analyzed 2,436 complete colonoscopies that detected 3,642 polyps in two time periods: 1996 to 2003 and 2004 to 2011. We compared the number, size and histopathological features of the polyps removed from the right-sided colon and the left sided-colon in the two periods.

Results: An increasing trend of polyp detection rate in the right-sided colon was observed, from 9.36% in the first period to 12.17% in the second period ($p < 0.001$). The prevalence of right-sided colon adenomas also presented an increased trend (OR 1.45; CI95% 1.02-2.05; $p = 0.03$). High-grade dysplasia (HGD) was found in 8.6% of the adenomas and in 4.1% of the diminutive polyps. Advanced neoplasia was detected in 1.5% of persons younger than 50 years. Multivariate logistic regression analysis evidenced that the right-sided polyps were significantly associated with the last time period (OR 1.3; $p = 0.001$; CI95% 1.12-1.56), male gender (OR 1.3; $p = 0.001$; CI95% 1.1-1.5) and age above 48 years (OR 1.3; $p = 0.006$; CI95% 1-1.6).

Conclusion: An increasing trend of polyp detection rate in the right-sided colon was documented, with an increasing prevalence of right-sided adenomas. The evaluation of the proximal colon is particularly important in males aged over 48. A clear-cut risk of HGD in the diminutive polyps and in the middle age subjects has been also observed.

Key words: colorectal cancer screening – colonoscopy – polypectomy - right-sided adenoma.

INTRODUCTION

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world [1, 2]. Adenomas are the main precursor lesions of CRC [3-5]. An accumulating amount of evidence demonstrates that endoscopic polypectomy reduces the incidence and disease-specific mortality of CRC [6, 7]. Colonoscopy is considered the gold-standard screening tool for colon cancer prevention by removing precancerous

adenomas, thus interrupting the adenoma-carcinoma sequence.

Most reported data regarding CRC screening and adenomatous polyps come from North America and Western European countries; data from Eastern Europe are relatively scarce [8, 9]. As adenoma and CRC features might differ between populations [10], the screening procedures should rely as much as possible on local data. Another important aspect for planning the screening procedure is the distribution of polyps throughout the colon. A gradual shift of colorectal adenomas and carcinomas location toward the proximal colon has been observed both in the United States and Europe [10, 11].

In this study we aimed to evaluate the polyp and adenoma detection rate in a major endoscopy center of northwestern Romania, and to characterize the distribution and pathological

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features of removed polyps during a 16-year period in order to assess the trends of proximal adenomas in our population.

METHODS

We retrospectively analyzed 9,230 consecutive colonoscopies performed in our outpatient center of gastroenterology between 1996 and 2011. The patients included in this study are representative for the northwestern part of Romania, being addressed for colonoscopy to our private high-volume center of endoscopy in Cluj-Napoca. The patients were examined with video-colonoscopy (Pentax, Olympus series: CL 160, CL 180, Exera II) by experienced gastroenterologists.

For a proper assessment of polyp detection rate in the right-sided colon we included in our analysis only the complete colonoscopies (photo-documented cecal intubation). We thus selected 2,436 consecutive total colonoscopies that detected 3,642 polyps. All polyps found during colonoscopy were removed by standard biopsy forceps or snare catheter (hot or cold) and those recovered were referred for histopathological examination.

The exclusion criteria were incomplete colonoscopies or poor bowel preparation, patients with CRC, familial adenomatous polyposis or inflammatory bowel diseases.

The indications for colonoscopy in selected cases included: rectal bleeding, abdominal pain, weight loss, anemia, CRC screening or surveillance after polypectomy.

Bowel preparation was performed using polyethylene glycol solution in a split manner. The endoscopists assessed the quality of bowel preparation as "good" (almost 100% mucosal visualization after aspiration of liquid residue), "fair" (greater than 90% mucosal visualization) or "poor" (less than 90% mucosal visualization).

The following data were registered for each patient: gender, age, polyp number, size, location and histology for each polyp. The location of the polyps in the colon was defined as right-sided or left-sided. Right-sided colon location was defined as starting at the cecum and ending at the splenic flexure. If the patients had more than one polyp in the same location, only one location was given. Patients with synchronous polyps (including those who had both left-sided and right-sided polyps) were evaluated and every polyp was analyzed separately. In patients with more polypectomies, the polyp with the highest degree of dysplasia and largest size was used for per-patient analysis.

During the study period, serrated adenomas were inconsistently reported and, therefore, we decided not to list them as a separate category but rather to include them in the adenoma group.

Dysplasia in the adenoma was graded as low or high according to the World Health Organization Classification [13]. The intramucosal carcinoma and carcinoma in situ were noted within the high-grade dysplasia (HGD) category. Invasive carcinoma was considered when malignant cells were found in the submucosa or in the deeper tissues. Advanced neoplasia was defined as cancer or adenoma that was at least 10 mm in diameter, had villous or tubulovillous histologic characteristics and presented high-grade dysplasia (HGD) [14, 15].

We divided the patients in two groups corresponding to two consecutive periods of 8 years: the first group comprised cases investigated between 1996 and 2003 and the second group cases between 2004 and 2011. We compared the number, the size and the histopathology of the polyps from the right-sided colon and the left-sided colon, respectively, between the two groups.

Statistical analysis

Statistical analysis was carried out using Medcalc software 12.5. Normality of distribution for quantitative variables was tested by the Kolmogorov-Smirnov test. The quantitative data with a non-normal distribution was characterized by using median and 25th and 75th percentiles. Nominal variables were described by frequency and percentage. The difference between the two groups regarding a quantitative variable was assessed by a Mann-Whitney test. Chi-square test was used for testing differences in proportions between nominal data. Spearman correlation was used to investigate the relationship between quantitative data. ROC curves were used in order to calculate the specificity and sensitivity of a certain quantitative variables regarding a certain outcome. Logistic regressions were used in order to determine the factors independently associated with a dependent variable. The level of statistical significance was set at $p < 0.05$.

RESULTS

Most of the 9,230 consecutive colonoscopies performed between 1996 and 2011 were total colonoscopies: the cecal intubation rate was 98% in the first period and 98.8% in the second period. After exclusion from our analysis of patients with incomplete colonoscopies, 2,436 patients with total colonoscopies were analyzed, in whom 3,642 polyps were detected. The polyp detection rate was 33.41% in the first time period and 35.39% in the second period.

The patients' age and gender for the two periods are shown in Table I. The median age of patients was higher in the second group (59 vs 57, $p < 0.001$). No differences were noted regarding the sex distribution between the two groups.

The quality of bowel preparation was good in 85% and fair in 15% of cases in the first period, and good in 82% and fair in 18% in the second period, respectively.

A number of 3,206 polyps (88% of all removed polyps) were recovered and sent for pathological examination. The polyps' features in the two periods are described in Table 1. The size of polyps varied between 1 and 50 mm, with a median of 8 mm. The polyp size was directly correlated with the patients' age ($r = 0.11$; $p < 0.001$), being significantly larger in males (9 mm vs. 8 mm $p < 0.001$) and in the left-sided colon (9 mm vs. 8 mm $p < 0.001$).

Out of the 3,206 polyps, 2,000 (62.4%) were adenomas: 704 (21.9%) were detected in the first period (9.95% on the right-sided colon) and 1,296 (40.4%) in the second period (21.55% on the right-sided colon). Among all patients that presented adenomas (1,431), right-sided colon adenomas were found in 227 (15.8%) patients, left-sided colon adenomas in 1,048 (73.2%) patients, and both left and right-sided colon polyps in 156 (10.9%) patients. The number of adenomas per patient

Table I. Patients' demographic data and polyp features divided between the two periods.

| Variable | First period 1996-2003 | Second period 2004-2011 | p |
|---|---------------------------|----------------------------|--------|
| Age (median; percentile 25%; 75%) | 57 (49; 65) | 59 (52; 67) | <0.001 |
| Females (n; %) | 333 (13.6%) | 640 (26.2%) | 1 |
| Males (n; %) | 501 (20.5%) | 962 (39.4%) | |
| Polyp size (median; 25%;75%) | 9 (6;13) | 8 (5; 10) | <0.001 |
| Polyps on the right-sided colon (n; %) | 288 (8.98%) | 749 (23.34%) | <0.001 |
| Polyps on the left-sided colon (n; %) | 740 (23.08%) | 1429 (44.57%) | |
| Polyps histology | | | |
| adenomatous (n; %) | 704 (21.9%) | 1296 (40.4%) | |
| hyperplastic (n; %) | 244 (7.6%) | 643 (20%) | <0.001 |
| inflammatory (n; %) | 34 (1%) | 170 (5.3%) | |
| adenocarcinoma (n; %) | 46 (1.4%) | 69 (2.1%) | |
| Adenomas on the right-sided colon | 199 (9.95%) | 431 (21.55%) | |
| Adenomas on the left-sided colon | 505 (25.5%) | 865 (43.25%) | |

was 1.39. The pathological classification of the adenomas was the following: 76.8% tubular, 17.2% tubulo-villous and 4% villous. The size of polyps was different according to their histology; adenocarcinomas were larger than adenomatous polyps (13 mm vs. 9 mm, $p<0.001$), and these were larger than hyperplastic polyps (9mm vs. 6mm, $p<0.001$).

Right-sided versus left-sided adenomas

The polyp and the adenoma detection rates are shown in Table II, separately for the left and right-sided colon and for the two periods of time. The prevalence of adenomas increased in the right-sided colon (OR 1.45; CI95% 1.02-2.05; $p=0.03$), while it decreased in the left-sided colon (OR 0.59; CI95% 0.49-0.71; $p<0.001$). The detection rate of concomitant right and left-sided polyps also increased, but this was not statistically significant (OR 1.36; CI95% 0.91-2.05; $p=0.1$).

The patients aged 50 to 70 years and those older than 70 had a higher frequency of right-sided colon polyps (OR 2.1; CI 95% 1.31-3.34; $p<0.001$, and OR 1.54; CI 95% 1.05-2.27; $p=0.02$, respectively) as compared to patients under the age of

Table II. The polyp and the adenoma detection rate, separately on the left and right sided colon, in the two periods.

| | First period 1996-2003 | Second period 2004-2011 | p |
|-----------------------------------|---------------------------|----------------------------|--------|
| Left-sided colon | | | |
| Polyp detection rate | 24.05 % | 23.22 % | 0.3 |
| Adenoma detection rate | 16.41 % | 14.05 % | 0.001 |
| Hyperplastic polyp detection rate | 5.62 % | 6.59 % | 0.07 |
| Right-sided colon | | | |
| Polyp detection rate | 9.36 % | 12.17 % | <0.001 |
| Adenoma detection rate | 6.46 % | 7 % | 0.03 |
| Hyperplastic polyp detection rate | 2.3 % | 3.85 % | <0.001 |

50, but HGD adenomas were less frequent at this level (OR 1.7; $p<0.001$). There was no gender difference regarding right-sided adenoma detection rate (6.6% vs.6.7% $p=0.8$). A cut-off value of 48 years was determined over which a patient was more likely to present right-sided colon polyps (AUC – 0.551; Se 84.7%, CI95% 82.2-87.1; Sp 23.1%, CI95% 21-25.4; LR+ 1.1, CI95% 1.1-1.1; LR- 0.66, CI95% 0.5-0.8).

Multivariate logistic regression analysis demonstrated that right-sided polyps were significantly associated with the last period of time (OR 1.3; $p=0.001$; CI95% 1.12-1.56), male gender (OR 1.3; $p=0.001$; CI95% 1.1-1.5) and age above 48 years (OR 1.3; $p=0.006$; CI95% 1-1.6).

Advanced neoplasia and associated factors

High grade dysplasia was found in 172 (8.6%) adenomas and an invasive adenocarcinoma in 115 (3.6 %) from the total number of adenomas. In the first period 71.7% of adenomas with HGD were located in the left-sided colon and 28.3% in the right-sided colon. In the second period, 66.7% were located in the left-sided colon, and 33.3% in the right-sided colon, respectively.

The frequency of HGD increased with the size of polyps (Table III). In the last period, HGD was found more frequently in the left-sided large adenomas ($p=0.03$). Patients with HGD adenomas were significantly older than those with low grade dysplasia (61 years vs 59 years; $p=0.001$). Sex ratio was not different in these categories ($p=0.1$). The grade of dysplasia was not influenced by sex ($p=0.8$). In diminutive polyps, HGD was reported in 4.1% of patients (1.13% in the right colon).

Advanced neoplasia was detected in 1.5% (30 out of 2,000) adenomas in patients younger than 50 years (Table IV).

Table III. High grade dysplasia frequency related to the size of polyps.

| | First period 1996-2003 | | Second period 2004-2011 | |
|--------------------------|------------------------|-------------------|-------------------------|-------------------|
| Adenoma size (number) | Right-sided HGD | Left-sided HGD | Right-sided HGD | Left-sided HGD |
| ≤0.5 cm (439) | 0 (0%) | 1 (0.22%) | 5 (1.13%) | 12 (2.73%) |
| 0.6-1 cm (864) | 5 (0.57%) | 13 (1.5%) | 17 (1.96%) | 21 (2.43%) |
| 1.1-2 cm (562) | 7 (1.24%) | 19 (3.38%) | 8 (1.42%) | 32 (5.69%) |
| > 2 cm (135) | 2 (3.29%) | 15 (11.1%) | 2 (1.48) | 13 (9.62%) |
| P | 0.5 | | 0.03 | |

Table IV. The distribution of adenomas and advanced neoplasia in relation to age.

| Age (years) | Adenomas | Advanced neoplasia | Right-sided advanced neoplasia | Left-sided advanced neoplasia |
|----------------|--------------|-----------------------|--------------------------------------|-------------------------------------|
| < 50 | 357 (17.8%) | 30 (1.5%) | 7 (0.35%) | 23 (1.15%) |
| 50-69 | 1267 (63.4%) | 186 (9.3%) | 50 (2.5%) | 136 (6.8%) |
| > 70 | 376 (18.8%) | 71 (3.55%) | 20 (1%) | 51 (2.55%) |
| Total | 2000 (100%) | 287 (14.35%) | 77 (3.85%) | 210 (10.5%) |

DISCUSSION

The prevalence of adenomas in our patients was 62.4%, similar to that found in other large series published. In the National Polyp Study, conducted by Winawer et al [16] in the United States, adenomas represented 68% of all polyps

removed by colonoscopy. In a more recent study, Rex et al found a prevalence of adenomas of about 65% in patients older than 50 years [17].

In our study, the colorectal adenomas were more frequently (63.4%) detected in patients aged between 50 and 70 years, without significant difference in terms of gender distribution. In reported CRC screening studies, the prevalence of adenomas was higher in males, occurring a few years earlier than in females [18, 19]. In a meta-analysis that included 17 studies, adenomas with advanced histology and CRCs were more frequently found in males [21]. Although some authors suggested an earlier start for CRC screening in males [18, 20], current guidelines recommend the start of screening at the same age for both sexes. We found no statistically significant differences in the prevalence of adenomas or HGD lesions between males and females, suggesting that gender specific indication might not be necessary for screening procedures in our population.

The prevalence of adenomas increased significantly in the second time period (40.4% vs. 21.9% in the first period). The median age of the second group was also higher (59 years vs. 57 years), but this difference might not entirely account for the important rise of adenoma frequency in the second period. Similar results were reported by Chan et al [11], who analyzed more than 5,000 colonoscopies performed in Hong-Kong during two different periods of time.

Right-sided adenomas were more frequently detected in the second period of our study, similarly to previous studies [12, 22]. Changes in the anatomical distribution of adenomas and CRCs could be explained by the improved detection of adenomas in the right colon; however, a true increase in the incidence of cancer of the ascending colon and cecum has been demonstrated [23]. Although some studies detected an increasing location of adenomas in the right-sided colon in females, in our patients this location was more common in males. In 2000, Lieberman et al [14] stressed that recto-sigmoidoscopy may omit a significant percentage of lesions located in the proximal colon. Therefore, flexible sigmoidoscopy seems not to be an appropriate method for screening in our population, especially aged over 48, as it might miss about one third of colorectal adenomas.

In the general population, screening by colonoscopy is recommended starting with the age of 50. Previously published necropsy studies have shown an increased incidence of colorectal polyps with the increasing age of the subjects [24, 25], data supported by our findings.

Interestingly, in our study 17.8% of the adenomas were found in patients younger than 50, which is a higher percentage than that reported in the literature, i.e. of 8-9% of adenomas in the age group of 40-49 years [26]. As our patients had a median age of 57 years, it might be possible that in the Romanian population adenomas occur at younger ages. Adenomas with advanced neoplasia were present at a rate of 1.5% in patients under 50 years (all in the range of 45-50 years). Further studies are required to focus on this category of age for screening recommendation purposes.

The prevalence of adenomas with HGD was similar in the two time periods. Thus, the increased number of adenomas in the second period could be due to the small size of detected

polyps, possibly as a consequence of an increased awareness of the endoscopists and the use of high-resolution endoscopes.

High grade dysplasia rate and its risk factors differ in the published studies. The analysis of the database used for the National Polyp Study in USA which included 3,371 adenomas removed from 1,867 patients demonstrated that the size of adenomas, the villous histology, distal location, multiple adenomas and age were independent risk factors for HGD, which was detected in 6.2% of cases [27]. In Europe, an Austrian study with a similar methodology including 7,590 adenomas removed from 4,216 patients reported a HGD rate in 13% [28]. The HGD rate in our study was 8.6%.

The size of the polyps was correlated with their histology. Atkin et al [29] stated that polyps ≥ 1 cm have an increased risk for developing into CRC, while polyps < 1 cm do not present this risk. Under special conditions (comorbidities and advanced age), polypectomy may thus not be performed, reducing costs and possible complications as mentioned by Hofstad et al [30], who highlighted the need for an annual colonoscopy with biopsies for their monitoring. In current practice, all detected polyps are removed. We found in our patients that HGD was present in polyps < 1 cm: 4.1% in the polyps < 0.5 cm and 6.5% in the polyps ranging between 0.6-1 cm, subsequently indicating the need for the removal of all polyps. The presence of HGD in small polyps has been already documented in the literature [31, 32]. Computed tomography (CT) colonography has been evaluated as an option for CCR screening [33]. Because this procedure has a low sensitivity (78%) for the detection of polyps between 0.6-1 cm and even lower for polyps less than 0.5 cm [34], it is not advisable for CRC screening in our population.

Our study has some limitations. First, it is a retrospective study, making it possible for the data to be prone to some degree of bias. Personal and family history of CRC could not be properly assessed. The environmental and metabolic risk factors for polyp development in the two periods could also not be assessed. But although we did not intend to perform a screening study by excluding patients with CRC, familial adenomatous polyposis and inflammatory bowel diseases, we could consider our evaluated population to be similar to a population subjected to screening.

CONCLUSION

Our study revealed an increased prevalence of adenomas in the right-sided colon over the latter years. Performing total colonoscopy is important in people aged over 48 years and particularly in men. The presence of HGD in 6.5% of the polyps smaller than 1 cm indicates that all detected polyps, regardless of size, should be excised.

Conflicts of interest: Nothing to declare.

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