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Opportunistic Colorectal Cancer Screening using Colonoscopy. Comparative Results between two Historical Cohorts in Bucharest, Romania

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ABSTRACT

Background & Aims: Even though Romania has one of the highest incidence and mortality in colorectal cancer (CRC) in Europe, there is currently no organized screening program. We aimed to assess the results of our opportunistic CRC screening using colonoscopy.

Methods: A single center retrospective study to include all opportunistic screening colonoscopies performed in two 18 month periods (2007-2008 and 2012-2013) was designed. All asymptomatic individuals without a personal or family history of adenoma or CRC and with complete colonoscopy performed in these two time periods were included.

Results: We included 1,807 individuals, 882 in the first period, 925 in the second period. There were 389 individuals aged below 50, 1,351 between 50 and 75 and 67 older than 75 years. There were 956 women (52.9%), with a mean age of 58.5 (median 59, range 23-97). The detection rates were 12.6% for adenomas (6.1% for advanced adenoma) and 3.4% for adenocarcinoma. Adenoma incidence (4.9% in subjects under 50, 14.7% in those aged 50 to 75, and 16.4% in those older than 75, $p<0.0001$) and size (6.3mm in subjects younger than 50, 9.2mm in those 50 to 75 and 10.8mm in those older than 75, $p=0.015$) significantly increased with age. Adenoma incidence increased in the second period (14.8% vs. 10.3%, $p=0.005$), while adenoma size decreased in the second period (8.4mm vs. 10mm, $p=0.006$). There were no procedure related complications.

Conclusions: The neoplasia detection rate was 16% (12.6% adenoma, 3.4% adenocarcinoma). Adenoma incidence and size increased with age in both cohorts. In the second screening period significantly more and smaller adenomas were detected.

Key words: colorectal cancer – screening – adenoma detection rate – advanced neoplasia detection rate.

Abbreviations: ACS: American Cancer Society; CRC: colorectal cancer; FIT: fecal immunochemical test; FOBT: fecal occult blood test; PEG: polyethylene glycol; WHO: World Health Organization.

INTRODUCTION

Colorectal cancer (CRC) has the second leading incidence and mortality rates in both sexes in the European Union (EU): 432,000 new cases were diagnosed in 2008 and approximately half of them died of the disease [1-3]. Romania has one of the highest rates of incidence and mortality in the EU: 29.2/100,000 incidence and 14.7/100,000 mortality for women and 50.3/100,000 incidence and 27.5/100,000 mortality for men, in 2012 [4].

The 5 year survival rate is 90% if the tumor is limited to the bowel wall, 35-60% if it is extended to regional lymph nodes and about 10% for metastatic disease [5]. Most CRCs are sporadic, only 10 to 30% occur in subjects with a positive family history of CRC [6]. More than 90% of cases are diagnosed above the age of 50.

Colorectal cancer meets the criteria for a disease amenable to screening as stated in 1968 by the World Health Organization (WHO) [7]: it has a large prevalence; most cases develop on precursor benign lesions (adenomas) within a long latent period. Colorectal cancer screening is recommended

in asymptomatic individuals aged 50 to 74 (medium risk population). In 2003, the EU recommended each member state to develop and implement national CRC screening programs [1]. By the year 2007, 12 member states have organized CRC screening programs, and some other countries are initiating them [2]. In Romania, a screening program has still not been implemented.

Currently used CRC screening tests are: 1) fecal occult blood test (FOBT) detection either guaiac based or by fecal immunochemical test (FIT), or 2) sigmoidoscopy, both with colonoscopy as the confirmatory test. Another variant is the use of colonoscopy directly as screening test. In the USA, in the year 2000, one third of the screening tests for CRC were colonoscopies, and the American Cancer Society (ACS) currently recommends colonoscopy repeated every 10 years as a screening test [8, 9]. Every screening strategy has different advantages, risks, accessibility, acceptability and costs, and no particular screening methodology has been clearly identified as more cost-effective than any other [10].

Published papers on screening colonoscopy have documented an adenoma and CRC detection rate of 14.9-37.5%, an advanced adenoma detection rate of 5-8.5%, an advanced neoplasia detection rate of 5-10.5% and a complication rate between 0 to 0.3% [11-13]. A prospective observational study has shown a decreased CRC incidence rate by 67% and a decreased mortality rate by 65% in a population where individuals underwent screening colonoscopy when compared to the general population [14].

There is no "gold standard" for screening, as colonoscopy has a 6-12% adenoma miss rate and a CRC miss rate of 5% [15-17].

Besides the organized screening programs, there is also opportunistic screening. This includes individuals who undergo screening either by their own will, or as indicated by a physician seen by the individual for an unrelated condition, who appreciates that this individual has a certain risk for developing CRC. Opportunistic CRC screening is generally considered more costly and less effective for a population, therefore it is not formally recommended. However, it may be an alternative when organized screening programs are not available. Colorectal cancer screening in Taiwan using the FIT test [18] and in Germany or Iran using colonoscopy [19, 20] has been reported. Recently, it has been advocated in Romania, considering the lack of such an organized program [21].

The aim of our study was to comparatively assess the results of opportunistic CRC screening by colonoscopy in a medium risk population in Bucharest and Ilfov County (2,264,865 inhabitants, about 10% of the Romanian population in 2012) [22] in two distinct time periods, 2007-2008 and 2012-2013.

METHODS

A single center retrospective study was designed. The population study consisted of all individuals who had had one colonoscopy performed for opportunistic screening purposes in the Gastroenterology Department, Elias Emergency Hospital in Bucharest, Romania. We included only colonoscopies performed during two specific 18 month periods, 5 years apart: the first between January 1, 2007 and June 30, 2008 and the second between January 1, 2012 and June 30, 2013.

We included colonoscopies performed in medium risk for CRC individuals from Bucharest and the surrounding county (Ilfov), who were addressed to our department by their family physician or who came by themselves for a screening colonoscopy. We only included asymptomatic individuals aged between 50 and 75 with no personal or family history of colorectal adenomas or CRC, no previous colonoscopy or colorectal surgery.

For comparison, we also included in our retrospective analysis individuals with screening colonoscopy aged less than 50 for both periods and aged above 75 for the first period only (no screening colonoscopy was offered to patients above 75 years in the last period and since then).

The lesions found during colonoscopy were recorded. If multiple lesions were found, the lesion with the worst probable prognosis was recorded as the outcome of screening (adenocarcinoma first, then advanced adenoma, then adenoma and then hyperplastic polyp). If the decision of which was the lesion with the worst probable prognosis was not possible, then the lesion chosen as the outcome of screening was the one necessitating the most invasive therapeutic procedure.

Adenomas were classified according to the WHO criteria: tubular, villous and tubular-villous [23]. Dysplasia was graded by Vienna classification [24]. Advanced adenomas are those ≥10 mm, with high grade dysplasia or a minimum 25% of villous component [25].

Eight fully trained gastroenterology specialists performed the colonoscopies. All colonoscopies were performed during the morning. Patients underwent a 4 liter polyethylene glycol (PEG) based lavage (either the whole dose in the evening before or as a split regimen with a quarter or half dose in the morning). We only included in the analysis individuals with a complete colonoscopy and a level of satisfactory bowel preparation (this was only subjectively assessed on the colonoscopy report). We also recorded all procedure related complications, during the procedure and in the following 30 days.

The study was undertaken with the hospital Ethics Committee approval.

Data were expressed as absolute number and percentages for qualitative variables and mean, median and range for quantitative variables. Comparisons between categorical variables were done using the Fisher exact test for 2 x 2 contingency tables (comparisons between the two periods) and Pearson chi-square test for 3 x 2 contingency tables (comparisons between the three age groups). Comparisons between quantitative variables were done using non-parametric tests for skewed data, U Mann-Whitney test for two groups (comparisons between the two periods) and Kruskal-Wallis test for multiple groups (comparisons between the three age groups). A two-tailed p probability of error of less than 5% was accepted. SPSS 16.0 software was used for statistical analysis.

RESULTS

We included in the sudy 1,807 individuals who had undergone complete colonoscopies. There were 956 women (52.9%), with a mean age of 58.5 (median 59, range 23-97).

Table I. Outcome of screening: overall results and results by age groups.

	Overall	< 50 years	50-75 years	>75 years	P
Number	1,807	389	1,351	67	-
Age, years (mean, range)	58.5 (23-97)	40.5 (23-49)	62.5 (50-75)	79.9 (76-97)	-
Female sex (n, %)	956 (52.9)	189 (48.5)	745 (55.1)	22 (32.8)	$<10^{-3}$
Adenoma					
- nr. (median, range)	228 (12.6)	19 (4.9)	198 (14.7)	11 (16.4)	$<10^{-3}$
- size, mm (mean, range)	1 (1-9)	1 (1-4)	1 (1-9)	1 (1-5)	0.462
- right side (n, %)	9 (2-50) 8	6.3 (2-12)	9.2 (2-50)	10.8 (7-20)	0.015
- advanced (n, %)	4 of 228 (36.8)	5 of 19 (26.3)	76 of 198 (38.4)	3 of 11 (27.3)	0.463
Of all adenomas	110 of 228 (48.2)	8 of 19 (42.1)	95 of 198 (48)	7 of 11 (63.6)	0.513
Of all patients	110 of 1807 (6.1)	8 of 389 (2.1)	95 of 1351 (7)	7 of 67 (10.4)	$<10^{-3}$
Colorectal cancer (n, %)	61 (3.4)	5 (1.3)	54 (4)	2 (3)	0.033*
- right side (n, %)	12 of 61 (19.7)	1 of 5 (20)	10 of 54 (18.5)	1 of 2 (50)	0.546*

* Statistical result should be regarded with caution as contingency tables contained cells with less than 5 cases so Pearson chi square test might not be accurate.

There were no procedure related complications. The outcome of the screening is shown in Table I.

Two-hundred and twenty-eight individuals had adenomas: (12.6%): of these, 110 were advanced adenomas (6.1% of all patients); 61 patients (3.4%) had an adenocarcinoma (CRC). Considering both advanced adenomas and adenocarcinomas, 171 patients (9.5%) had advanced neoplasia. One hundred and twenty-nine (7.1%) of the subjects had only non-neoplastic polyps, mostly hyperplastic.

Of the 228 patients with adenomas, 110 (48.2%) had more than one adenoma. Adenoma location was predominantly on the left colon and rectum (144 patients, 63.2%), with only 84 patients (36.8%) on the right colon (Table I). Thirty-five of the 228 patients had adenomas with high grade dysplasia (15.4%) and in 53 of the 228 patients (23.2%) the adenomas were predominantly villous.

In the 61 patients with an adenocarcinoma, 49 of the carcinomas (80.3%) were located at the left colon and 12 (19.7%) at the right colon; 32 were intramucosal or in situ carcinomas that were further curatively treated by endoscopic excision, while 29 patients had invasive carcinomas necessitating curative intent surgery. No patient had distant metastasis at the time of colonoscopy.

Comparison between age groups

There were significant differences among the age groups regarding sex ratio (more males in the extreme age groups), adenoma incidence and size (increasing with age), advanced adenoma (equal proportion in each age group, but with incidence increasing with age as for all adenomas) and CRC incidence (maximum in the 50-75 age group).

Comparison between periods

The proportion of women was significantly higher in the second period (Table II). Adenomas as the outcome of screening were significantly more frequent in the second period. The size of the adenomas detected during screening were significantly smaller when compared with the first period. There was a trend of increased frequency of the adenomas located at the right colon in the second period (not significant).

DISCUSSION

Colorectal cancer has a high prevalence and mortality in Romania. Although efforts have been made by the National Health Service authorities, there is still no implemented organized screening program. As opportunistic screening was the second best alternative, we aimed to comparatively assess its results in our department in two cohorts, 5 years apart.

There were approximately 900 patients in each 18 month cohort, corresponding to roughly 12 individuals per week (2 per day). We perform approximately 16 colonoscopies per day, which results in about 12.5% colonoscopies for screening as daily workload.

Table II. Outcome of screening: overall results and results by period of screening.

	Overall	2007-2008	2012-2013	P
Number	1807	882	925	-
Age, years (mean, range)	58.5 (23-97)	59.7 (23-97)	57.2 (25-75)	-
Female sex (n, %)	956 (52.9)	436 (49.4)	520 (56.2)	0.004
Adenoma				
- nr. (median, range)	228 (12.6)	91 (10.3)	137 (14.8)	0.005
- size, mm (mean, range)	1 (1-9)	1 (1-9)	1 (1-8)	0.911
- right side (n, %)	9 (2-50)	10 (3-30)	8.4 (2-50)	0.006
- advanced (n, %)	84 of 228 (36.8)	29 of 91 (31.9)	55 of 137 (40.1)	0.211
Of all adenomas	110 of 228 (48.2)	51 of 91 (56)	59 of 137 (43.1)	0.059
Of all patients	110 of 1807 (6.1)	51 of 882 (5.8)	59 of 925 (6.4)	0.624
Colorectal cancer (n, %)	61 (3.4)	33 (3.7)	28 (3)	0.436
- right side (n, %)	12 of 61 (19.7)	7 of 33 (21.2)	5 of 28 (17.9)	1.000

The literature data suggests that the optimal age interval for starting CRC screening is 55 to 64 years [1, 14, 26-29]. The lesion prevalence for individuals below 50 is too low to justify screening, whereas for individuals above 75 it seems that risks outweigh the benefits.

The above 75-year age group was minute and it belonged to the 2007-2008 period as we abandoned screening for age above 75 since then. Nevertheless, the 16.4% adenoma rate and 13.4% advanced neoplasia rate, without any complications induced by colonoscopy, are quite significant. It would have been interesting for these patients to assess their survival benefit, but this may be the subject for another study.

We debatably performed screening colonoscopies for patients younger than 50 years. Their number was one quarter of those in the 50 to 75 age group and were mostly above 40, with few cases with ages as low as 23 or 25 years. These young individuals are clearly in a low risk group and one could argue that this was probably not a screening colonoscopy. Although judged by the physician as asymptomatic and for screening purposes, these cases were retrospectively seen as mostly related to psychological reasons, fear of cancer or mild functional abdominal symptoms. Colonoscopy in this setting is arguably a waste of health resources, but as the results show, colonoscopies in these young patients were not useless (4.9% adenoma detection rate and 3.4% advanced neoplasia rate) or dangerous after all. We could have chosen not to present their results and include only cases above 50 years old, but we decided to present facts as they were in the real practice, mainly for comparative reasons. The reader may well choose to regard only the 50 to 75 age group numbers and disregard the extreme age groups results.

We found a 16% "any neoplasia detection rate" in our study (12.6% adenomas and 3.4% adenocarcinomas). We found a 6.1% advanced adenoma rate with a 9.5% advanced neoplasia rate.

Our results compare favorably with those reported from organized colonoscopy screening. Rundle et al. [26], in a cohort of 50-59 years old individuals, reported a 17.7% "any neoplasia detection rate" (14% adenoma detection rate and 3.7% adenocarcinoma detection rate), similar to our results. Regula et al. [12] found a 14.9% "any neoplasia detection rate", similar to our results, but with a lower advanced neoplasia detection rate (6.8%). Finally, Lieberman et al. [13] reported a much higher "any neoplasia detection rate" (37.5%), with a 10.5% advanced neoplasia detection rate.

Comparing with opportunistic colonoscopy screening results, Stork et al. [19], who analyzed the follow-up after an index opportunistic screening colonoscopy in the 2007 to 2009 period in a German population aged above 55, found an adenocarcinoma detection rate of 1.4%, significantly lower than our 3.4% percentage. However, these were probably advanced cancers as they all needed surgery for treatment, while in our cohort we counted in the adenocarcinoma group the endoscopically removed superficial cancers. In a similar study to our study, regarding opportunistic CRC screening in Iran by colonoscopy in individuals above 50, Delavari et al. [20] obtained an adenoma detection rate of 33%, an advanced adenoma detection rate of 13.18% and an adenocarcinoma rate of 0.84%. In Romania, in Timis and Mures County, Sporea et al. [30] reported a much higher adenoma detection rate of 32.1%, but with an almost identical 9.2% advanced neoplasia detection rate (2,433 colonoscopies from three centers in a 5-year interval, 2008-2013). These numbers are close to those of Lieberman et al. [13], although with a lower adenocarcinoma rate.

Adenoma detection rate significantly increased with age in our study (4.9% in less than 50 age group, 14.7% in the 50 to 75 age group and 16.4% in the above 75 age group). Also, absolute advanced adenoma rate significantly increased with age, though the relative frequency to adenoma population was comparable among groups. One explanation might be that the mean size of adenoma significantly increased with age (6.3mm in less than 50 age group, 9.2mm in 50 to 75 age group and 10.8mm in the above 75 age group) and surpassed the 10mm cut-off point. It has been reported that the advanced adenoma detection rate increases with age and is independent of non-advanced adenoma detection rate (although here their evolution in groups was parallel) [31].

When comparing the two time periods, one may see that in the second period there were significantly more females (56.2%), with significantly smaller mean size adenomas (8.4mm vs. 10mm). One explanation for this is the bias of including patients above 75 exclusively in the first period. These 67 elderly patients with male predominance and larger adenomas included in the first group will make the second group appear to have more females and smaller adenomas. However, even including these 67 elderly patients with a high proportion of adenomas in the first group, the second group had still significantly more adenomas than the first group (14.8% vs. 10.3%). The differences between the two study groups may be accounted for by the real differences between these two historical cohorts of patients with probably slightly different risk factors and CRC neoplasia incidence. Another possible explanation is that we used better scopes with better resolution which may account for the larger number of significantly smaller adenomas detected in the second period as compared with the first one.

Comparing the outcome of screening for the two time periods, the relative percentage of patients who had their adenoma located at the right colon increased from 31.9% to 40.1%, even though the increase was not statistically significant. This has been recently described in a Romanian population by Visovan et al. [32], who noticed the increase in right sided adenomas from 9.36% in 1996-2003 to 12.17% in the 2004-2011 time period.

Although initial studies have shown a significant increase in the CRC risk for 1st degree relatives of CRC family members [33-40], a recent analysis has shown that this is not the case [41]. If Amsterdam criteria are not fulfilled [42], these individuals can be safely treated as any medium risk case. Screening colonoscopy should be started not sooner than 45 and repeated every 5 years [37, 41]. However, given this debate, we chose to exclude patients with a family history of CRC from this retrospective analysis. Moreover, a recent Romanian report by Maxim et al. [43] on screening colonoscopy of asymptomatic individuals (with a mean age 51.7 ± 11.5 years, range 24-77 years) having a first degree relative with CRC showed a much higher rate of "any neoplasia detection rate" (28.8%) than the reported 16% percentage.

Finally, we did not experience any screening related major complications. Larger similar studies have reported frequencies between 0 to 0.3% [12, 44-46].

CONCLUSIONS

We reported here the results of our tertiary center in performing opportunistic screening colonoscopies in patients from Bucharest and Ilfov County in Romania, results that are similar to previously reported data. The adenoma detection rate significantly increased with age and significantly increased over a 5-year period. Although this study adds to the knowledge of current colorectal screening initiatives in Romania, and hundreds of patients individually benefitted from the opportunistic screening, the impact of this single center retrospective study on the implementing of colon cancer screening in Romania cannot yet be assessed.

Conflicts of interest: No conflict to declare.

Authors' contribution: E.M.I. designed the work, verified and centralized the data, wrote the paper and revised it. E.M.I., T.N., S.I., C.D., T.A., A.S., A.T., and M.A. performed colonoscopies; E.M.I., S.I.G. and A.M. collected data. M.D. designed and supervised the work, revised the paper. M.C. designed the work, analyzed data, wrote and revised the paper.

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