MALIGNANCY AND MORTALITY OF COLORECTAL POLYPS

Marilena Stoian\textsuperscript{1,2}, Nicoleta State\textsuperscript{2}, Emilia Rusu\textsuperscript{1,3}, V. Stoica\textsuperscript{1,2}, R.S. Gavril\textsuperscript{4}, Andreea Gherasim\textsuperscript{4}, Gabriela Radulian\textsuperscript{1,3}

1. Carol Davila University of Medicine Bucharest, Romania
2. Dr. Ion Cantacuzino Hospital, Bucharest, Romania
3. „Prof. Nicolae Paulescu” National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest, Romania
University of Medicine and Pharmacy ”Grigore T. Popa”- Iasi
Faculty of Medicine
4. Ph.D. student

MALIGNANCY AND MORTALITY OF COLORECTAL POLYPS (Abstract) **Objectives:**
To evaluate the rate of morbidity and mortality associated with colorectal polyps after the next 8-years period of endoscopic polypectomy, in a high risk managed care population. **Material and method:**
Cohorts of 77 subjects with benign neoplasms were identified with a colonoscopy in 1999. Three groups of subjects: benign neoplasms with polypectomy, benign neoplasms without polypectomy, and no neoplasms were evaluated. Five years recurrence rates (1999-2004) of benign or new malignant colorectal neoplasms were identified: for the benign determined for the baseline benign neoplasms with polypectomy and no neoplasm groups neoplasm without polypectomy, only rates for malignancy were observed. Malignancy was evaluated with immunohistochemical p53 (tumor protein 53) and PCNA (Proliferating Cell Nuclear Antigen) staining pattern. Over the next 8 years 2004-2012 were evaluated the mortality and the recurrence rate of the benign polyps. **Results:**
77 subjects were enrolled in our study; 71.4% were diagnosed with benign and 2.5% with malignant neoplasms. The 5-years cumulative incidence rates of malignant colorectal neoplasms in the no neoplasm (n=20) and benign neoplasm groups (n=55) were (n=1) 5% and (n=10) 18.1%, respectively (p < 0.005). A lower 5-years malignancy rate was observed in benign neoplasms group with polypectomy (12%) compared to the benign neoplasm group without polypectomy (33.3%) (p < 0.05). The 8-years mortality rate was compared into benign recurrent polyps group and into malign group: the lower 8-years mortality rate was observed into benign polyp no neoplasm group (0%) and into benign recurrent polyps group (40%); the highest rate was observed into neoplasm group (100%). **Conclusions:**
The high recurrence rate of benign colorectal neoplasms and a higher incidence of colorectal cancer in subjects at high risk-history of benign colorectal neoplasm-highlight a healthcare opportunity for surveillance and/or interventions to reduce the morbidity associated with colorectal neoplasms. **Keywords:** COLORECTAL POLYPS, POSTPOLYPECTOMY RECURRENT, BENIGN POLYPS, PCNA, p53.

Over one million new cases of colorectal cancer (CRC) are diagnosed worldwide each year, and incidence seems set to rise with the progressive westernization of lifestyles in Asian and African populations.
Many colorectal cancers are thought to arise from adenomatous polyps in the co-
lon, defined as circumscribed lumps of epithelial dysplasia with uncontrolled crypt cell division. Single transformed cells may generate clones through new mutations, with the possibility of an enhanced growth rate. The present study was specifically designed to determine the recurrence rate of benign colorectal neoplasms in a managed care population over a 5-years period of follow-up. By using this defined population, the study also provided us the opportunity to estimate and compare the rate of development of malignant neoplasms in subjects’ postpolypectomy and in subjects without polypectomy over 8 years following period postpolypectomy.

MATERIAL AND METHODS

77 subjects diagnosed with colonoscopy were categorized into three groups: benign neoplasms, malignant neoplasms, and no neoplasms. Subjects with a malignant neoplasm at baseline were excluded from the study. Thus, the remaining subjects had either benign neoplasms or no neoplasms detected based on the baseline colonoscopy. We further divided subjects with benign neoplasms at baseline into two groups: colonoscopy with polypectomy and colonoscopy without polypectomy (fig. 1). The subjects in the three diagnostic groups: no neoplasm, benign neoplasm with polypectomy, and benign neoplasm without polypectomy, were subsequently evaluated for up to 5 years. If at any time during the follow-up period a malignant neoplasm diagnosis was recorded, then that subject was excluded from subsequent follow-up. If at any time during the follow-up period a benign neoplasm was detected, then the subject was only evaluated further for estimating the rate of subsequent malignant neoplasm development.

For subjects who had no baseline neoplasms, we evaluated the subsequent incidence of benign and malignant neoplasms over the 5 years follow-up period. For subjects who had benign neoplasms at baseline and underwent polypectomy, we assessed the recurrence rates of benign neoplasms and the incidence of malignant neoplasms. For subjects who had benign neoplasms at baseline and did not undergo polypectomy, we evaluated the incidence of malignant neoplasms only; for this group the recurrence rate of malignant neoplasms was not estimated. The 8 years malignancy rate was observed into benign recurrent neoplasm group vs. malign group. Malignancy was evaluated with immunohistochemical staining pattern of p53 and Proliferating Cell Nuclear Antigen (PCNA).

Chi-square analysis was conducted to check for differences in rates of benign and malignant colorectal neoplasms based on age and gender, malignancy in benign neoplasm subjects (with and without polypectomy) and, recurrence and incidence of benign neoplasms in subjects with benign neoplasm diagnosis and no neoplasm diagnosis at baseline, respectively. EpiInfo and Statgraphics Plus 6.0 programs were used for statistical analyses; qualitative variables were compared by $\chi^2$ test and Fischer’s Exact Test (2-tailed, p-level < 0.05).

RESULTS

The percentage of subjects with benign and malignant neoplasms at baseline were 71.4 (n=55) and 2.5 (n=2), respectively. Males appeared to have a higher rate of benign (46% vs. 33%) (p<0.001) and malignant neoplasms (5.7% vs. 5.2%) (p > 0.05) than females. In general and as expected (7, 8) the rate of benign or malignant neoplasms increased with increasing
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Age (p < 0.001). Subjects without neoplasms (n=20) and benign neoplasms (n=55) at baseline colonoscopy were included in subsequent analyses.

Fig. 1. Follow-up of Subject Cohort

Five-year diagnostic outcomes of these subjects are presented in table I. Among 20 subjects without neoplasm at baseline, the incidence rate of benign neoplasms ranged from 0 to 10% for each year with a 5-year cumulative rate of 20%. In the same cohort, the incidence rate of malignant neoplasm ranged from 0 to 5% for each year with a cumulative rate of 5%. It is interesting to note that of the 55 subjects with benign neoplasms at baseline (with and without baseline polypectomy), 10 subjects (18.1%) develop malignant neoplasms over the subsequent five years, which was significantly higher (p<0.05) than the rate observed in the subjects without neoplasms at baseline (5%). The highest rates of malignant neoplasm follow-up from no neoplasm at baseline were observed during the 4th year of study (5%); in the 4th year of study was observed the maximum of benign neoplasm at follow-up from no neoplasm at baseline.
(10%). The adenomatous polypoidal character and carcinomatous polypoidal character were established by immunohistochemical staining for p53 and PCNA.

### TABLE I

<table>
<thead>
<tr>
<th>Diagnosis at Colonoscopy</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>Cumulative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neoplasm at baseline</td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Benign neoplasm at follow-up FROM No neoplasm at baseline</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>malignant neoplasm at follow-up FROM No neoplasm at baseline</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table II presents results for subjects entering the study with a baseline benign neoplasm (n=55 patients). For those subjects who had a baseline polypectomy (40 patients) the rates of recurrent benign neoplasms and the incidence of malignant neoplasms are reported. For subjects without baseline polypectomy (15 patients) only the rate of malignant neoplasms is reported. As can be seen, the yearly rates of benign neoplasm recurrence for the post-polypectomy group ranged widely from 5% to 12.5%; the highest rates were observed during the last two years. To assess the effect of polypectomy on the rate of subsequent malignancies, the rates of malignant neoplasms at follow-up were compared for the two groups: with and without polypectomy. As expected polypectomy was associated with a lower five year cumulative rate (20%) as compared to no polypectomy (73.3%) (p < 0.05). The 5-years cumulative incidence rates of malignant colorectal neoplasms in the no neoplasm (n=20) and benign neoplasm groups (n=55) were (n=1) 5% and (n=10) 18%, respectively (p < 0.005). A lower 5-years malignancy rate was observed in benign neoplasms group with polypectomy (12%) compared to the benign neoplasm group without polypectomy (33.3%) (p < 0.05).

In patients without polypectomy, the malignancy was evaluated by immunohistochemical staining pattern of p53 and PCNA: to patients with initial polypectomy (1999) immunohistochemical pattern of p53 and PCNA confirmed the malignant neoplastic lesions.

Comparing the five year cumulative incidence of benign neoplasms in subjects without a baseline neoplasm (n=4; tab. I) to those with a baseline benign neoplasm with...
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Polypectomy (n=15; tab. II) it is obvious that the 5-years cumulative recurrence rate of 40% was significantly greater (p < 0.005) than the 5% rate in subjects without baseline neoplasm. These data demonstrate the risk associated with a past history of benign tumors (high risk).

The 8 years (2004-2012) mortality rate was compared into benign recurrent polyps group, into benign group and into malign group: the lower 8-years mortality rate was observed into benign polyp no neoplasm group (0%) and into benign recurrent polyps group (40%); as expected the highest rate was observed into neoplasm group (100%) (p < 0.005) (fig. 2).

TABLE II
Five-year diagnostic outcomes of patients undergoing colonoscopy and with the diagnosis of benign neoplasms at baseline (with v. without polypectomy)

<table>
<thead>
<tr>
<th>Benign Neoplasm at Baseline</th>
<th>Years</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy with polypectomy</td>
<td>1st</td>
<td>40</td>
<td>100</td>
<td>40</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Recurrent benign neoplasm:</td>
<td>2nd</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3rd</td>
<td>5</td>
<td>12.5</td>
<td>5</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy with polypectomy</td>
<td>4th</td>
<td>15</td>
<td>100</td>
<td>15</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Malign neoplasm:</td>
<td>5th</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
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<td></td>
<td></td>
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<td></td>
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<td>3</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

DISCUSSION AND CONCLUSIONS

In present, there are reported several studies with estimated rate of benign polyp recurrence with widely varying results. So, National Polyp Study (9), a prospective clinical trial, the reported cumulative rate of adenomatous polyp recurrence was 41.7% when subjects were examined with colonoscopy at one and three years and 32% when examined at only three years. Our results indicate a similar polyp recurrence rate (40%) (tab. II) over a 5 years’ time frame; the estimate of the three-year polyp recurrence rate (15%) in our study was Whereas our results are numerically similar, it must be noted that the study populations and conditions for follow-up varied greatly between our study and the National Polyp Study. In National Polyp Study were included the subjects with adenomatous polyps only. Additionally, the National Polyp Study was a prospective trial with scheduled colonoscopies. In contrast, no such procedures were required in our analysis. Despite these very significant differences, our naturalistic retrospective study still was numerically similar in its findings. Our study did not explore the reasons for performing colonoscopy. Different reasons for colonoscopy (for "cause" vs. surveillance vs. screening) could influence and lead to different rates of colorectal neoplasm detection. In light of this limitation, the conclusions of this study are
limited to recurrence rates in subjects with a baseline neoplasm, without consideration to the clinical indication associated with the baseline colonoscopy.

To assess the effect of polypectomy on the rate of subsequent malignancies, the rates of malignant neoplasms at follow-up were compared for the two groups: with and without polypectomy. In our study (tab. II), as expected, polypectomy was associated with a lower five year cumulative rate (20%) as compared to no polypectomy (73.3%) (p < 0.05). Most of colorectal cancers that occur within 5 years after colonoscopic polypectomy develop because of failure to identify or completely remove high-risk neoplasms (advanced adenomas or cancers) at the time of the initial colonoscopy (10, 11). The adequacy of a polypectomy is assessed according to the endoscopic appearance of the polypectomy site and by a review of the pathological specimen to determine whether its margins are free of neoplastic tissue. The adenoma “miss rate” which can vary by a factor of 2 to 3 among examiners, is about 6 to 12% for adenomas that are 1 cm or larger and up to 25% for smaller adenomas (12, 13, 14). Thus, missed adenomas or cancers may contribute to the occurrence of colorectal cancer despite colonoscopic surveillance and may underlie many instances of “metachronous” neoplasia reported during surveillance. To be most effective, colonoscopy should be performed by well-trained, certified endoscopists who meticulously examine the entire colon during withdrawal of the instrument.

There is a higher rate of recurrence of benign and malignant neoplasm detected in our study population in the last two years. This may reflect early recurrence of symptoms, repeated examinations and the detection of neoplasms that may have been missed on the baseline evaluation. Additionally, and despite national guidelines to the contrary, these examinations may have been scheduled early for subjects thought to be at high risk. With increased surveillance a higher rate of recurrences may have been estimated in these shorter time frames.

Our study (fig. 2) indicated a higher rate of lesional prevalence to men of benign (46% vs. 33%) (p < 0.001) and malignant neoplasms (5.7% vs. 5.2%) (p > 0.05) than females. In general and as expected (7, 8) the rate of benign or malignant neoplasms increased with increasing age (p < 0.001). Similar results were reported from Jemal, Siegel and Ward that appreciated colonic adenomas, the precursors of almost all sporadic colorectal cancers, are found in up to 40% of persons by 60 years of age (1).

Although controlled trials have not compared surveillance intervals that are longer than 3 to 4 years, the low rate of colorectal cancer after 5 to 6 years of follow-up in patients with only one or two small, tubular adenomas on initial colonoscopy (15, 16, and 17) suggests that a follow-up interval of 5 or more years is safe for these patients.

The adenoma–carcinoma sequence the progression from normal colonic mucosa to small tubular adenomas to larger adenomas and those with more advanced histological features (villous features, high-grade dysplasia, or both) to cancer is a central tenet of our understanding and management of colonic adenomas. Although not all colonic polyps are adenomas (hyperplasic polyps account for about half of small, recto-sigmoidian polyps) and more than 90% of adenomas do not progress to cancer, it is currently not possible to reliably identify those that will progress. Thus, colonic polyps identified at colonoscopy should be
removed if it is technically feasible to do so. Complete removal of a colonic adenoma eliminates the risk of cancer from that adenoma, but the finding of a colonic adenoma may indicate an increased risk of metachronous adenomas and colorectal cancer for both the patient and his or her first-degree relatives (i.e., parents, siblings, and children). Colonic adenomas are typically asymptomatic and are most commonly found by means of colonoscopic or radiological imaging studies performed because of unrelated symptoms or for colorectal cancer screening. Since at least 25% of men and 15% of women who undergo colonoscopic screening by experienced endoscopists are found to have one or more adenomas, the cumulative burden of subsequent surveillance colonoscopy on the health care system is substantial.

**Fig. 2.** 8-Year Follow-up of Subject Cohort

The high recurrence rate of benign colorectal neoplasms and a higher incidence of colorectal cancer in subjects at high risk—history of benign colorectal neoplasm—highlight a healthcare opportunity for surveillance and/or interventions to reduce the morbidity associated with colorectal neoplasms. The active interventions for health
care providers can include adherence to colonoscopic guidelines for surveillance in high-risk populations and possibility the use of secondary chemoprevention to prevent the morbidity and mortality associated with colorectal neoplasms.

REFERENCES