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DIFFERENTIATED MEDICAL-SURGICAL TACTICS IN PRIMARY COLON NEOFORMATIONS

321.13 – Surgery

Summary of PhD Thesis of Medical Sciences

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CONTENT

1. INTRODUCTION

Actuality and importance of the topic. Colorectal cancer (CRC) continues to be one of the leading causes of cancer morbidity and mortality worldwide, representing a major public health problem, especially in industrialized countries. The terms "primary neoplasm" and "incipient neoplasia" of the colon were formulated in 1983 by the Japanese Society for the Study of Colorectal Cancer, as a tumor of the colon, which is limited to the mucosa and submucosa, without lymph node invasion or local and distant metastases [1, 2]. According to reports prepared by the International Agency for Research on Cancer, CRC ranks fourth in terms of global incidence, surpassed only by lung, prostate and breast neoplasia. In terms of mortality, this pathology ranks third, after lung and breast cancer. Despite important advances in early detection, research into carcinogenesis mechanisms and understanding the natural history of the disease, its prevalence remains significant, affecting between 8% and 33% of patients. [2, 3]. The situation in the Republic of Moldova largely reflects the trends observed in other European countries, with comparable incidence and mortality. Since 2008, when colonic and rectal localizations were integrated into a single nosological entity, CRC has become the main form of cancer in the structure of oncological pathologies in the country, representing 12.9% of all cases. The annual incidence was estimated at 36.0 in men and 23.0 in women, and the mortality rate reached 22.0 among men and 12.6 among women, placing CRC in second place among the causes of death from cancer in the Republic of Moldova [2, 3]. According to the GLOBOCAN 2022 report, 1991 new cases of CRC were estimated in the Republic of Moldova, representing 49.4% of all digestive tumors. Of these, 1203 cases (62.3%) were diagnosed in men, and 788 cases (37.7%) in women. Estimates for the next five years indicate a cumulative prevalence of approximately 4760 cases. In terms of mortality, data for 2020 show a death rate of 29.4%, with a total number of 1187 deaths, of which 718 (37.2%) in men and 469 (22.3%) in women [3].

Overall five-year survival for all stages remains modest, hovering around 45%, despite diagnostic and treatment efforts. Thus, in the case of CRC, the proportion of patients with late diagnosis remains at 77.1%, and for rectal cancer – at 61.1%. [4]. CRC develops through the uncontrolled malignant transformation of the cells of the mucosal epithelium of the colon and rectum. In most cases, colorectal carcinomas arise from pre-existing adenomas. Their evolution follows a pattern known as the *adenoma–carcinoma sequence,* which involves the gradual conversion of adenomatous formations into invasive carcinoma, a process determined by the successive accumulation of genetic alterations. These include both the activation of oncogenes and the inactivation of tumor suppressor genes, mechanisms that ultimately lead to the loss of proliferative control of cells [5, 6, 7]. The transformation of normal colonic epithelium into adenoma and, subsequently, carcinoma is a slow process, which takes place over several years. This gradual evolution provides a favorable time window for the application of diagnostic methods that allow early identification of lesions with malignant potential. [8, 9]. Complete exploration in patients with suspected CRC is essential, but not always feasible in practice. Lesions that remain undetected follow their natural course, and at the time of subsequent discovery may be in advanced stages, sometimes even unresectable. [10]. Early identification of premalignant lesions, through the application of an effective screening program, contributes significantly to reducing the costs associated with the treatment of advanced and untreatable forms of the disease. [11]. Early diagnosis of CRC has a major impact on the chances of long-term survival. According to recent studies, there is a direct correlation between the stage at which the tumor is detected and the 5-year survival rate. Thus, patients diagnosed in stage I have a survival rate of approximately 90%, while in stages II and III this varies between 70-80% and 40-65%, respectively. In contrast, for patients in stage IV, the 5-year survival rate drops below 10%. [4].

Considering the presence of studies in determining patient survival rates, the lack of an effective algorithm for detecting neoplasms, which would reduce CRC mortality by preventing progression to advanced forms of the disease, an effective screening program would allow for a more rational use of medical resources. In this context, it is necessary to continue research aimed at improving early detection and early intervention strategies in CRC [2]. The differentiated management of primary colonic neoformations (PCN) is complex, using multiple therapeutic means, which must be successive and combined – endoscopic resection procedures, classical surgery, adjuvant treatment. The choice of treatment method depends on the TNM staging, the location of the neoplasms, the histological and morphological structure, its invasiveness, the general condition of the patient and the technical and material endowment of the medical institution. [12]. Currently, the "gold standard" is represented by the resection of the colonic portion with R0 margins. Performing this intervention is radical, and the incidence of loco-regional recurrences does not exceed 5% [13]. The term "local excision" includes different technical variants: from resection of the colonic mucosa to partial resection of the lesion. Local excision of NPC is more easily tolerated by patients compared to open surgery methods, reduces the risk of postoperative complications, and reduces the duration of hospitalization [14]. However, the role of local excisions in colonic adenocarcinoma remains questionable, due to the lack of adequate lymphadenectomy, which leads to a high risk of recurrence [15]. Despite the presence of a modern diagnostic arsenal and the implementation of CRC screening programs, differentiated medical-surgical tactics in colon neoformations remain the focus of attention for colorectal surgery and serve as the basis for initiating the present study.

Aim of study. Identification of optimal diagnostic methods and therapeutic procedures for structuring differentiated curative conduct in colon neoformations.

Objectives of study:

1. Correlational analysis of clinical and paraclinical manifestations of colonic neoformations predictive of the malignant process.
2. Studying the morphological and histological aspects of primary colon neoformations.
3. Argumentation and correlation of types of surgical interventions according to clinicopathological data in patients with primary colon neoformations.
4. Structuring a screening algorithm that would improve early detection of colorectal cancer and its preoperative staging.
5. Identification of genomic markers predictive of colorectal cancer.

The novelty and scientific originality of obtained results lies in the complex approach to the evaluation of colonic neoformations, combining clinical-paraclinical, histopathological and molecular data. Following a detailed examination, which included clinical, imaging and biological analysis, the evolutionary particularities of these neoformations were identified in correlation with the age of the patients, the exact topography of the lesions and the histopathological characteristics of the specimens. These results allowed the outline of objective schemes for optimizing diagnostic and therapeutic conduct at all stages of surgical management, thus contributing to personalizing treatment and reducing the risk of complications and relapses. In addition, the study allowed the definition of a set of clinicopathological criteria for the differentiated selection of patients, facilitating the choice of the most appropriate surgical method depending on the individual characteristics and the evolutionary stage of the tumor. Also, the risk factors for malignant transformation of colonic neoplasms were systematized, identifying relevant predictive biomarkers for CRC and highlighting the molecular profile associated with tumor progression. This integrated approach provides not only a better understanding of the pathogenesis and dynamics of CRC, but also a solid scientific foundation for the development of personalized therapeutic protocols, with a direct impact on improving the prognosis and quality of life of patients.

The theoretical and scientific importance of the results obtained and the relevance of the research. The detailed analysis of morphological, endoscopic, histological features and their correlation with clinical evolution in primary colon neoformations allows the assessment of differentiated and personalized tactics in their management. Risk factors for malignant colon neoformations have been systematized with the development of screening programs to ensure periodic follow-up of people detected with positive tests or with increased risk factors. To directly quantify the association between an exposure factor and the occurrence of a clinical outcome, the odds ratio (OR) was calculated. This measure of association expresses the ratio between the odds of an event occurring in an exposed group compared to an unexposed group, and is mainly used in observational studies. In the context of colorectal pathology, determining the OR for variables such as abdominal pain, intestinal transit disorders or the presence of multiple polyps allows the assessment of the strength of the association between these clinical manifestations and the existence of premalignant or neoplastic lesions, highlighting their potential role as predictive clinical markers. Highlighting the molecular profile of CRC can lead to a better understanding of tumor genesis, classifying patients into various risk groups, who can benefit from individualized, more or less aggressive treatment, and the determination and bioinformatic analysis of genomic markers predictive of CRC will contribute to the early diagnosis of neoplasms and the early initiation of their treatment, which will lead to an increase in the survival rate of patients.

The applicative value of study. The research has supplemented the foundation of screening programs that can ensure periodic follow-up of people detected with positive tests or with increased risk factors, diagnostic examination and prompt treatment of colonic neoformations. A consensus has been developed regarding the determinants of the differentiated therapeutic attitude in colonic neoformations.

Implementation of scientific results. The results of this doctoral research were implemented in the diagnosis and treatment of patients with primary colonic neoformations in the surgery and endoscopy departments of the Institute of Emergency Medicine (Chișinău, Republic of Moldova) and in the teaching process at the Department of Surgery No. 1 "Nicolae Anestiadi" of the IP "Nicolae Testemițanu" State University of Medicine and Pharmacy in the Republic of Moldova.

Approval of scientific results. The scientific results obtained in this study were reported and discussed within national and international scientific forums: the 7th, 8th, 9th and 10th International Medical Congress of Students and Young Doctors "MedEspera" (Chișinău, 2018; 2020; 2022; 2024); the National Congresses of Surgery in Romania (editions 29-32, Sinaia, 2018; 2020; 2022; 2024); the National Congresses of the Romanian Society of Coloproctology (Iași, 2019; 2025); the 13th Congress of the "Nicolae Anestiadi" Association of Surgeons and the 3rd Congress of the "V.M.Guțu" Society of Endoscopy, Minimally Invasive Surgery and Ultrasonography of the Republic of Moldova (Chișinău, 2019); XX and XXII European Congress of Trauma and Emergency Surgery (Prague, 2019; Ljubljana, 2023); Congress dedicated to the 75th anniversary of the founding of the "Nicolae Testemiţanu" USMF (Chișinău, 2020); Annual Conferences of the "Nicolae Testemiţanu" USMF (Chișinău, 2018-2024); XIV Congress of the "Nicolae Anestiadi" Association of Surgeons and IV Congress of the "V.M.Guţu" Society of Endoscopy, Minimally Invasive Surgery and Ultrasonography of the Republic of Moldova (Chișinău, 2023); XXXVII Balkan Medical Week "Perspectives of Balkan Medicine in the Post-COVID-19 Era" (Chișinău, 2023); National Surgery Conference (Eforie Nord, 2023).

The results of the study were discussed and approved within: were discussed and approved at the meeting of the Department of Surgery no. 1 "Nicolae Anestiadi", USMF "Nicolae Testemiţanu" (minutes no. 11 of 04.07.2025); meeting of the Profile Scientific Seminar - 321. General Medicine/ specialties: 321.13 Surgery; 321.14 Pediatric Surgery; 321.24 Transplantology, USMF "Nicolae Testemiţanu" (minutes no. 4 of 29.10.2025).

Publications on the thesis topic: 36 scientific papers were published on the topic of the thesis, of

which 3 were articles in international journals listed in ISI and SCOPUS and other international databases, 2 were articles in nationally circulated journals, 10 were materials/theses at international conferences (abroad), 8 were materials/theses at international conferences in the republic, 13 were materials/theses at national conferences, 2 were innovation patents, and one gold medal and 2 were silver medals at invention exhibitions were obtained.

Summary of the thesis contents. The thesis includes a list of abbreviations, introduction, 5 chapters, general conclusions, practical recommendations. Attached is a bibliographic index with 184 sources, annexes, a statement of responsibility, the author's CV, 25 tables, 43 figures.

Key-words: primary colonic neoformations, colorectal cancer, risk factors, colonoscopy, colonography, histopathological examination, biomarkers, endoscopic treatment, surgical treatment, follow-up, prevention.

2. RESEARCH METHODS

The research in question presents a prospective clinical study, based on the analysis of the results of the treatment of subjects with colonic and rectal neoplasms, admitted to the Surgery Clinic No. 1 "Nicolae Anestiadi", IMSP Institute of Emergency Medicine during the years 2018-2022. To carry out the study, based on the informed consent approved by the Research Ethics Committee of the "Nicolae Testemiţanu" SUMPh (positive opinions no. 52 of 16.03.2018 and no. 7 of 18.05.2022), the subjects' data, operating protocols, endoscopic investigation protocols, histopathological reports were collected and processed. The complex evaluation of the subjects was carried out within an interdisciplinary collaboration, involving clinical examinations, paraclinical investigations, intraoperative evaluations and histopathological analyses, carried out in the Departments of Surgery, Endoscopy, Laboratory Medicine and Pathological Anatomy. The following criteria were analyzed: age, sex, date of diagnosis, anatomical location of the tumor, grade of neoplasia, type of surgery, postoperative length of hospitalization, macroscopic and microscopic anatomopathological examination of surgically resected or biopsy colonic tissue specimens.

The respective research was structured in two studies, based on the analysis of the results of the detection and differentiated treatment in PCN. Study 1 (clinical): **observational, descriptive**, **cross-sectional**, **selective** in which 255 subjects with PCN were included, the representative sample being calculated in the EpiInfo Program 7.2.2.6, "Stat Calc-Sample Size and Power" compartment based on the following parameters: confidence interval for 95% of significance of the results, statistical power – 80%, the presence of colonic neoformations in the environment being 27% [3], design effect (DEFF) = 4 (justified by the sampling scheme, stepwise cluster). The calculated value is 216, with the adjustment for non-response 10%, the minimum sample becomes 240 (216/0.90). Study 2 (molecular): **pilot**, **observational** (without intervention in the management of the subjects), **analytical**, **clinically controlled**, samples were taken from 166 consecutive subjects (positive opinion no. 52 of 16.03.2018 approved by the Research Ethics Committee) enrolled in the research: 89(53.6%) - polyps, 77(46.4%) - neoplasms, as well as 10 subjects from the control group without oncological pathology. Given that some of the samples did not meet the quality criteria required for molecular analysis, only 84 blood samples and 12 pairs of tissue biopsies were eligible in the final stage. This methodological limitation requires the research to be classified as a pilot study, with all the associated constraints, the main one being the low statistical power of the analysis, which must be taken into account when interpreting the results and formulating conclusions.

Criteria for inclusion in the research group:

1. Subjects with polypoid formations of the colon, examined colonoscopically
2. Subjects with primary malignant colonic neoplasms detected (exclusively for objective 5)
3. Persons over 18 years of age

4. Subjects who signed the informed consent to be included in the study
5. Subjects whose mental state allows participation in the study.

The exclusion criteria were represented by:

1. Subjects hospitalized and operated on urgently without endoscopic examination
2. Subjects with neoplasms located in other anatomical regions, with a history of surgical interventions for various types of cancer
3. Subjects with previously treated colorectal cancer (surgery, chemotherapy and radiotherapy)
4. Subjects with immunological pathologies
5. Subjects who refused inclusion in the study

After confirming eligibility, subjects were fully informed about the purpose of the study, the benefits and risks of the investigations, and they signed the informed consent to participate in the research. In order to achieve the purpose and obtain the expected results, we designed the following research design for the base group (figure 1):

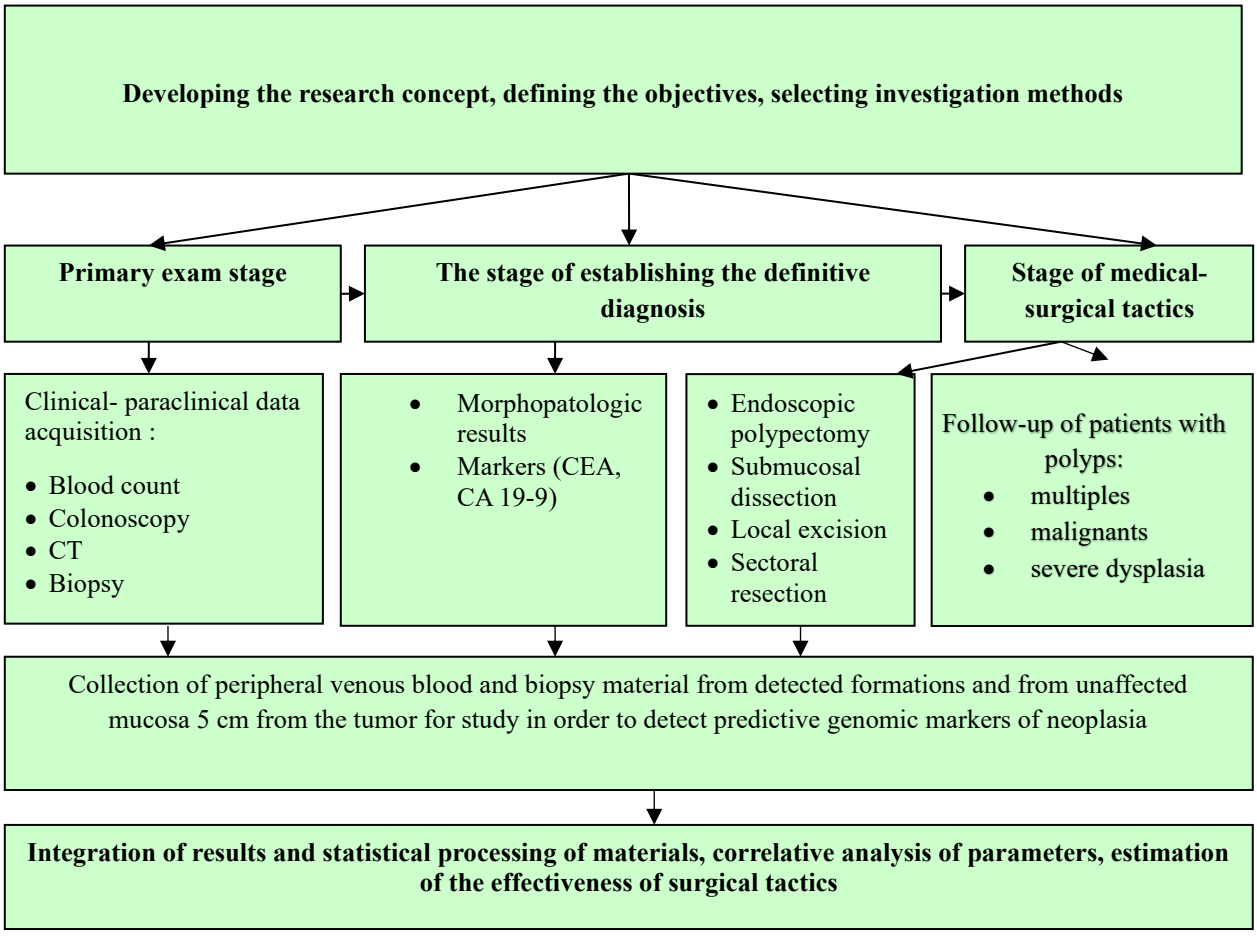

Figure 1. Patient research design from the observational, descriptive, cross-sectional, selective study

All methods of investigation of subjects with colonic neoplasms, along with clinical examinations and biological laboratory samples, included videocolonoscopy, rectosigmoidoscopy, CT, morphological/histopathological examination and statistical analysis.

Method of collecting and processing samples for the molecular study of genomic markers. In accordance with the study's aim to investigate genomic markers in cancer tissue and peripheral blood, the following samples were collected: 1) two tubes of peripheral whole blood in Tempus™ tubes for RNA sequencing; 2) biopsies from the malignant lesion and healthy (unaffected) tissue preserved in RNA Later solution for RNA sequencing; 3) one tube of blood with EDTA anticoagulant for analysis of epigenetic changes in circulating amino acids.

RNA sequencing method. The initial set of samples was sequenced using the direct RNAseq (DRS) method (Ozsolak et al., 2009). This method allows sequencing of RNA molecules in their native state, without the need to convert them into complementary DNA (cDNA) or amplify them by polymerase chain reaction, thus preserving the transcriptomic composition and biological value of the transcription process. In addition to analyzing the expression level of transcripts, DRS allows the evaluation of epigenetic changes of RNA molecules to estimate their functionality.

Statistical analysis methods. The statistical analysis of the results obtained in the study was recorded in Excel format tables. For reproducible statistical analysis, open source tools (Python Software Foundation, version 3.10) were used, using the *NumPy*, *SciPy* and *Matplotlib* packages. The source code used can be presented upon request. For categorical variables (dichotomous and ordinal), absolute and relative frequencies were calculated, as well as 95% confidence intervals, the latter being estimated by the Wilson method in the case of small proportions. The graphical representation of the data was made in the form of bar charts (barplot). Testing the hypothesis of association between categorical variables was performed using the χ^2 test with Monte Carlo simulation, with 10000 iterations/samples, in order to ensure the robustness of the results. The effect size was evaluated by calculating the odds ratio (OR), together with 95% confidence intervals, based on 2×2 contingency tables. In situations where cells with zero frequency were identified, the OR estimate was made by applying the Haldane–Anscombe correction, by adding the value of 0.5 to each cell. For numerical variables, descriptive indicators were calculated, namely the mean and standard deviation, the median and the interquartile range, as well as the minimum and maximum values. The graphic representation was made by boxplot diagrams (box with whiskers). Comparative analysis of numerical variables between groups was performed using the non-parametric Mann–Whitney U test. Analysis of RNA sequenced samples was performed using the RStudio program (Version:2024.12.1+563), available at https://posit.co/download/rstudio-desktop/, using the *DESeq2* packages for differential gene expression analysis, *edgeR* and *limma* for validation of statistical results, ggplot2 and *EnhancedVolcano* for graphical representations (volcano plot, MA-plot), as well as heatmap for generating heat maps and hierarchical clustering analysis. For all statistical tests performed, the statistical significance threshold (type I error) was set at $p<0.05$. In the case of sequencing analyses, data were subjected to corrections for multiple testing, in order to reduce the risk of obtaining false positive results.

3. CLINICAL-ENDOSCOPIC CORRELATIONS OF COLONIC NEOFORMATIONS

3.1. Socio-demographic characteristics of PCN

The 255 patients included in the study were analyzed in detail by gender, so 146 of the patients were male, compared to 109 female. The gender distribution differed significantly from an equal distribution (χ^2=5.38, df=1, p=0.020), highlighting a predominance of male patients. The gender distribution in the colorectal neoplasm group was: 37/77(48.1%) men and 40/77(51.9%) women, with a M:F ratio of 0.93:1. In the case of patients with premalignant colonic lesions, 69/178(38.8%) cases were reported in females and 109/178(61.2%) cases in males, with a M:F ratio of 1.6:1. (Table 1).

Table 1. Gender distribution of patients in the study sample

Gender	Neoplasms (abs)(%, 95%CI:)	Premalignant lesions (abs)(%, 95%CI:)	Statistical test	OR (95%CI:)
Female	40(36.7%, 28.2-46.1)	69(63.3%, 53.9-71.8)	χ^2=3.86 df=1 p=0.049	1.71 (1.00-2.93)
Male	37(25.3%, 18.9-32.9)	109(74.7%, 67.1-81.1)		
Total	77(30.2%, 24.8-36.1)	178(69.8%, 63.9-75.2)		

The analysis of the association between diagnosis and gender using the Pearson χ^2 test revealed a statistically significant result (χ^2=3.86, df=1, p=0.049), the null hypothesis of lack of association between

the mentioned parameters being rejected. A higher proportion of colorectal neoplasms was recorded among women (36.7%, 95%CI: 28.2-46.1) compared to men (25.3%, 95%CI: 18.9-32.9), the estimated odds ratio was OR=1.71 with 95%CI: 1.00-2.93. These results indicate probable particularities in the colorectal pathological profile depending on gender, the practical significance being uncertain considering that the lower limit of the confidence interval is equal to 1, as well as the wide confidence interval. Regarding the distribution of cases by area of origin, a higher rate was recorded in patients from urban areas compared to rural areas, with a percentage of 59.6% (n=152, 95%CI: 53.5-65.4) of patients coming from urban areas, compared to 40.4% (n=103, 95%CI: 34.6-46.5) from rural areas. This ratio was described in both the group of patients with CRC and in the group with premalignant lesions, with 59.7% (n=46/77, 95%CI: 48.6-70.0) of patients with CRC and 59.6% (n=106/178, 95%CI: 52.1-66.5) of patients with premalignant lesions coming from urban areas compared to 40.3% (n=31/77, 95%CI: 30.0-51.4) and 40.4% (n=72/178, 95%CI: 33.5-47.9), respectively, coming from rural areas. Comparative analysis of the distribution of colorectal lesions according to the area of origin revealed similar results between the two groups. The χ^2 test indicated a value of 0 (df=1, p=1.00), thus no statistically significant differences were revealed. The chances of being diagnosed with colorectal cancer are practically equal between urban and rural patients (OR=1.01, 95%CI: 0.58-1.74). The confidence interval includes the value 1, which confirms the absence of a statistically significant association. The analysis of age distribution by gender revealed statistically significant differences between the two groups (Mann–Whitney U=9395.0, p=0.010). In women, the mean age was 63.2±12.7 years (95%CI: 60.7-65.6), with extreme values ranging from 22 to 87 years. In men, the mean age was 60.2±11 years (95%CI: 58.4-62), with limits between 31 and 82 years. The results obtained indicate that women in the analyzed cohort have an older mean age compared to men.

3.2. Clinical profile of patients with primary colorectal neoformations

The type of hospitalization correlated largely with the severity of symptoms and risks associated with the respective conditions. In patients with premalignant lesions, scheduled hospitalization predominated, being required in 74.2% of cases (132/178, 95%CI: 67.1-80.2), compared with emergency hospitalization in 25.8% of cases (46/178, 95%CI: 19.8-32.9). In contrast, in patients with colorectal neoplasms, emergency hospitalization was more frequent, being reported in 63.6% of cases (49/77, 95%CI: 52.5-73.5), compared with 36.4% scheduled hospitalizations (28/77, 95%CI: 26.5-47.5). The association between the type of hospitalization and colonic diseases was statistically significant (χ^2=36.9, p<0.0001). It is likely that colonic neoplasms are more frequently associated with acute clinical manifestations. The characteristic of the symptomatology in the patient group taking into account the type of colonic neoplasms is presented in figure 2.

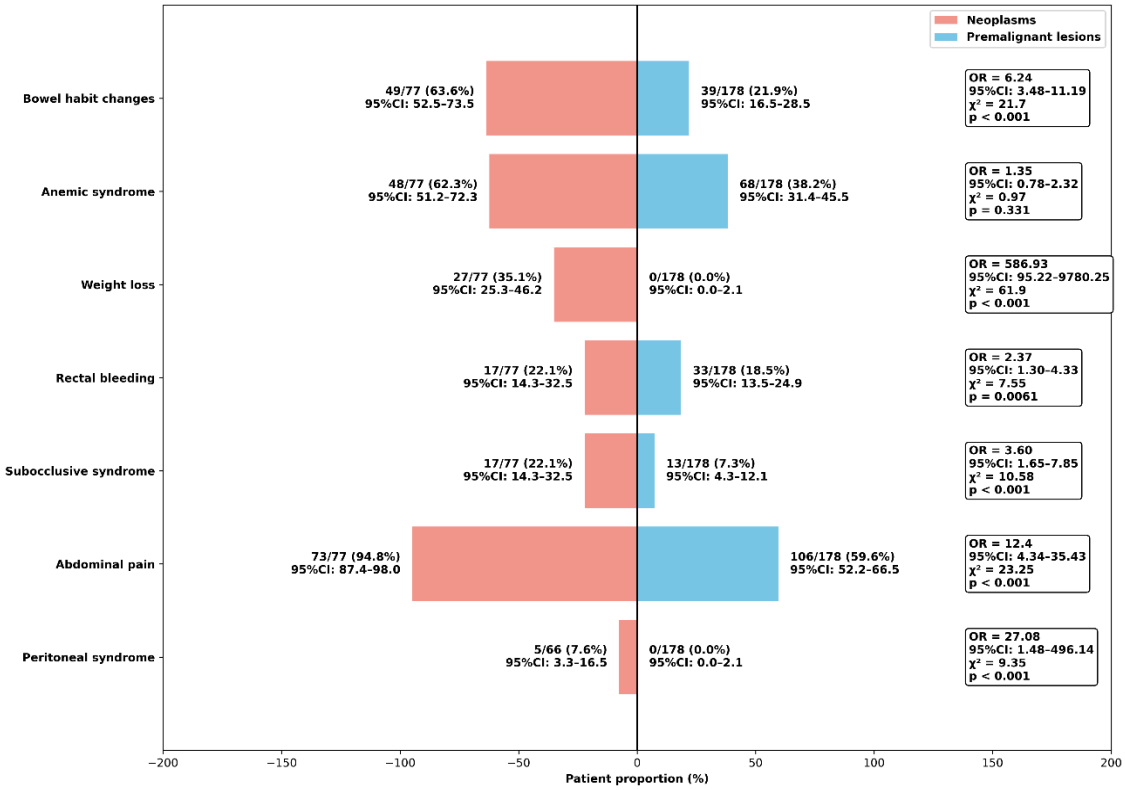

Figure 2. Distribution of subjects according to symptoms at hospitalization, abs(%)

Peritoneal syndrome was absent in premalignant lesions (0/178, 0.0%, 95%CI: 0.0-2.1), but present in neoplasms (5/77, 6.5%, 95%CI: 2.8-14.3), with significant association (OR= 27.08, 95%CI: 1.48-496.14, χ^2=9.35, df=1, p=0.0023). Abdominal pain predominated in neoplasms (73/77, 94.8%, 95%CI: 87.4-98.0) compared to premalignant lesions (106/178, 59.6%, 95%CI: 52.2-66.5), being associated with malignant pathology (OR=12.4, 95%CI: 4.3-35.4, χ^2=23.25, df=1, p<0.001). Subocclusive syndrome (22.1% vs 7.3%, OR=3.60, 95%CI: 1.6-7.8, χ^2=10.58, df=1, p=0.0014) and rectal bleeding (35.1% vs 18.5%, OR=2.37, 95%CI: 1.3-4.3, χ^2=7.55, df=1, p=0.0061) were also significantly more common in neoplasms. Weight loss was exclusively present in the neoplasm group (48/77, 62.3%, 95%CI: 51.2-72.3), absent in premalignant lesions, with a very high OR (OR=586.93, 95%CI: 35.2-9780.2, χ^2=61.9, df=1, p<0.001). Transit disorders were more frequent in the neoplasm group (63.6% vs 21.9%, OR=6.24, 95%CI: 3.5-11.2, χ^2=21.7, df=1, p<0.001). The type of pathology (neoplasms or polyps) was not associated with the anemic syndrome, the rates being 45.5% vs 38.2% (OR=1.35, 95%CI: 0.8-2.3, χ^2=0.97, df=1, p=0.3307). These data highlight a significantly more severe clinical profile in colorectal neoplasms, characterized by increased frequencies of obstructive, painful and systemic symptoms, while the anemic syndrome presents a comparable distribution between the two groups.

In order to evaluate the relationship between hematological status and the type of colonic lesion, a comparative evaluation of hemoglobin levels was performed in patients from the research groups (figure 3).

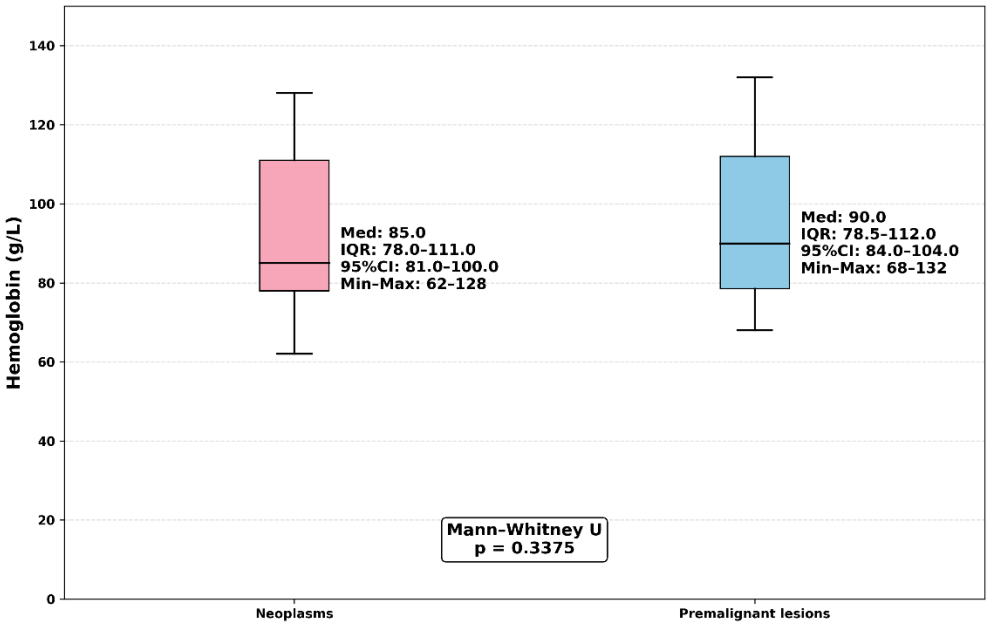

Figure 2. Comparative evaluation of Hb levels in patients from the research groups

Comparison of the two distributions using the Mann–Whitney U test did not reveal a statistically significant difference between the groups (p=0.3375), indicating that we do not have sufficient data to reject the null hypothesis. Although the medians differ slightly numerically, the wide overlap of the interquartile ranges and confidence intervals suggests the absence of a clinically relevant difference in the hemoglobin distribution between the two groups.

Clinical manifestations associated with colorectal pathology, including digestive symptoms and general signs, are presented in table 2. To assess the degree of association between the diagnosis of colorectal neoplasm and the presence of these clinical manifestations, the odds ratio (OR) was estimated. In the context of colorectal pathology, determining the OR for variables such as abdominal pain, intestinal transit disorders, rectal bleeding or other relevant clinical signs allows the assessment of the relationship between these manifestations and the nature of the lesion (premalignant or malignant). Thus, the use of OR in the present study contributes to a more rigorous characterization of clinicopathological associations, providing useful information for risk stratification and optimization of screening and early diagnosis strategies.

Table 2. Comparative analysis of clinical characteristics according to the type of lesions

	Premalignant lesions (abs)(%, 95%CI:)	**Neoplasms (abs)(%, 95%CI:)**	**Statistical test χ^2 Monte Carlo**	**OR (95%CI:)**
Abdominal pain	106/178(59.6%, 52.2-66.5)	73/77(94.8%, 87.4-98.0)	χ^2=31.9, df=1 p<0.001	12.4(4.3-35.5)
Transit disorders	39/178(21.9%, 16.5-28.5)	49/77(63.6%, 52.5-73.5)	χ^2=41.4, df=1 p<0.001	6.2(3.5-11.2)
Anemic syndrome	68/178(38.2%, 31.4-45.5)	35/77(45.5%, 34.8-56.5)	χ^2=1.17, df=1 p=0.331	1.3(0.8-2.3)
Mucus filled-stool	71/178(39.9%, 32.9-47.3)	14/77(18.2%, 10.-28.5)	χ^2=11.4, df=1 p=0.001	0.3(0.2-0.6)
Anal itching	7/178(3.9%, 1.9-7.9)	14/77(18.2%, 10.9-28.5)	χ^2=14.4, df=1 p=0.001	5.4(2.0-14.5)
Incomplete defecation	9/178(5.1%, 2.7-9.4)	33/77(42.9%, 32.2-54.3)	χ^2=55.8, df=1 p<0.001	14.1(6.3-31.5)
Rectal bleeding	33/178(18.5%, 13.5-24.9)	27/77(35.1%, 25.3-46.2)	χ^2=8.16, df=1 p=0.006	2.4(1.3-4.3)

The presence of abdominal pain was significantly more frequent in patients with neoplasms (n=73, 94.8%, 95%CI: 87.4-98.0) compared to those with premalignant lesions (n=106, 59.6%, 95%CI: 52.2-66.5). The difference was confirmed by the χ^2 test with Monte Carlo simulation (χ^2=31.9, df=1, p<0.0001), with patients with neoplasms presenting an approximately 12-fold higher probability of experiencing abdominal pain (OR=12.4, 95%CI: 4.3-35.5) in the studied population. Also, changes in bowel transit were reported in 63.6% (95%CI: 52.5-73.5) of patients with colorectal neoplasms, compared to 21.9% (95%CI: 16.5-28.5) of those with premalignant lesions. The difference was statistically significant, according to the χ^2 test with Monte Carlo simulation (χ^2=31.1, df=1, p<0.001), with patients with neoplasms presenting a probability of more than 6 times higher to accuse disorders of bowel transit (OR=6.2, 95%CI: 3.5-11.2). Regarding the anemic syndrome, although the frequency was slightly higher in the neoplasm group (45.5% vs 38.2%), the difference did not reach statistical significance (χ^2=1.17, p=0.331), and the OR of 1.3 (95%CI: 0.8-2.3) indicates a weak and insignificant association. The presence of mucus-filled stool was significantly more frequent in the group with premalignant lesions (39.9% *vs* 18.2%), the difference being statistically significant (χ^2=11.4, p=0.001). The subunit OR of 0.3 (95%CI: 0.2-0.6) suggests a relative protective effect of this manifestation against malignant pathology.

3.3. Morphological and histopathological study of malignant and premalignant colorectal lesions

In the 255 patients included in the study group, colonic neoformations were identified by imaging methods, videocolonoscopy and intraoperatively. Analyzing the data of these subjects, 77(30.2%) patients were diagnosed with malignant neoplasm of the colon or rectum with various histological types, and in 178(69.8%) patients, precursor lesions of malignancy were detected. The location of the colonic neoformations is represented in table 3.

Table 3. Distribution of patients according to the location of colorectal neoformations

Localisation	Right colon (abs,%)(95%CI:)	Left colon (abs,%)(95%CI:)	Rectum (abs,%)(95%CI:)	Statistical test χ^2 Monte Carlo
Premalignant lesions	52/178(29.2%, 22.8-36.4)	78/178(43.8%, 36.7-51.1)	48/178(27.0%, 21.0-33.9)	χ^2=8.87, df=2 p=0.012
Neoplasms	35/77(45.5%, 34.8-56.5)	26/77(33.8%, 24.1-45.1)	16/77(20.8%, 13.1-31.6)	
Total	87/255(34.1%, 28.4-40.3)	104/255(40.8%, 34.9-46.9)	64/255(25.1%, 20.2-30.6)	
OR (95%CI:)	2.02 (1.2-3.4)* p=0.009	0.64 (0.4-1.1)** p=0.091	0.71 (0.4-1.3)*** p=0.280	
*right colon *vs* other localisations; **left colon *vs* other localisations; ***rectum *vs* other localisations				

The distribution of anatomical locations (table 3) was correlated between patients with colorectal neoplasm and those with premalignant lesions (χ^2 with Monte Carlo simulation=8.87, df=2, p=0.012). Neoplasms were more frequently located in the right colon (45.5%, 95%CI: 34.8-56.5) compared to premalignant lesions (29.2%, 95%CI: 22.8-36.4), this location being associated with an approximately twofold higher probability of neoplastic diagnosis (OR=2.02, 95%CI: 1.2-3.4, p=0.009) compared to other locations. These data support the existence of topographical differences between premalignant lesions and colorectal neoplasms, with clinical relevance in diagnostic and curative strategies. Regarding the endoscopic appearance, colorectal neoplasm had the following forms of presentation: vegetative formations occupied 54.5% (n=42, 95%CI: 43.5-65.2) of the total of 77 patients, vegetative-ulcerative tumor formations were recorded in 24.7% (n=19, 95%CI: 16.4-35.4), infiltrative formations with ulceration areas were described endoscopically in 10.4% (n=8, 95%CI: 5.4-19.2) of the cases, while the classic infiltrative appearance of the tumor was detected in 8 patients (10.4%, 95%CI: 5.4-19.2). In the study conducted, the conventional form of adenocarcinoma was the most frequently encountered, representing 87.1% (n=67, 95%CI: 77.7-93.1) of all cases examined histologically. Table 4 presents the histological typology of colonic neoplasias.

Table 4. Histological typology of colonic neoplasms in patients included in the study

Histological type of tumor	Cases (abs, %)	(95%CI:)	Statistical test	OR *vs* conventional ADK (95%CI:)
Conventional adenocarcinoma (ADK) NOS (*not otherwise specified*)	67(87.1%)	77.7-93.1	χ^2=91.6 df=2 p<0.0001	reference
Mucinous adenocarcinoma subtype	6(7.8%)	3.6-15.9		0.09 (0.04–0.2)
Medularry carcinoma	4(5.1%)	2.0-12.4		0.06 (0.02–0.2)
Total	77(100%)	-		-

The data in Table 4 show that the histological typology of colorectal neoplasms is dominated by conventional adenocarcinoma (87.1%). Thus, mucinous adenocarcinoma presented an OR of 0.09 (95%CI: 0.04-0.2), and adenocarcinoma with a medullary component an OR of 0.06 (95%CI: 0.02-0.2), indicating a significantly lower frequency compared to conventional adenocarcinoma. The present study concluded that out of a total of 77 patients with colorectal neoplasms – 9(11.7%, 95%CI: 6.2-21.0), presented high degree of differentiation (G1), 59(76.6%, 95%CI: 65.8-84.8) – moderate degree of differentiation (G2), and 9(11.7%, 95%CI: 6.2-21.0) – poor degree of differentiation (G3). The analysis of the distribution of proportions revealed statistically significant differences between the degrees of differentiation (χ^2=68.7, df=2, p<0.0001), which led to the rejection of the null hypothesis, according to which the degrees of differentiation would be uniformly distributed in the studied population. In the present study, depending on the number of polyps, solitary polyps were detected in 146 (82.0%, 95%CI: 75.7-87.0) patients, compared to the other situations, 2 polyps – in 14 (7.9%, 95%CI: 4.7-12.8), three and more polyps – in 18 (10.1%, 95%CI: 6.5-15.4%) patients, with a total number of excised polypoid formations of 243. Within the study, the analysis of the distribution of patients according to the number of polypoid formations revealed a clear predominance of solitary polyps. The comparative assessment of polyp size in relation to number and type is shown in *f*igure 4. Comparison of the two groups using the Mann–Whitney U test revealed a statistically significant difference between the sizes of solitary and multiple polyps ($p=2.8\times10^{-5}$), confirming that solitary polyps tend to be significantly larger than multiple ones.

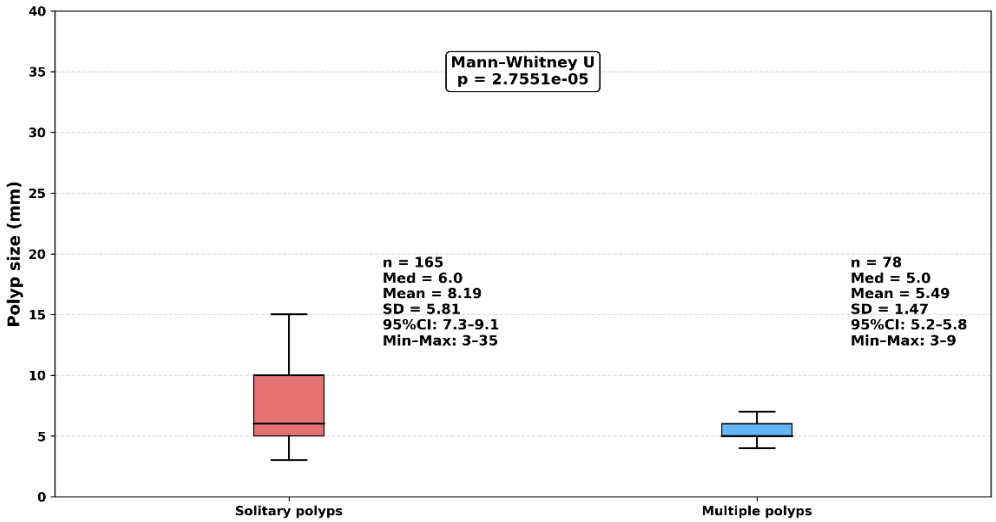

Figure 4. Comparative evaluation of polyp sizes in relation to their number and type in the study group

The distribution of primary colonic lesions varied statistically significantly (p<0.001) in relation to the size and location of the polyps, with the maximum size being determined at the recto-sigmoid level (table 5). The largest polyps (10.2±0.5 mm) were located at the level of the left hemicolon.

Table 5. Associative distribution of polyps in relation to their size and location

Location	Size (abs)(%, 95%CI:)			Statistical test χ^2 Monte Carlo	OR (large in segment *vs* rest of colon (95%CI:)
	very small	small	large (reference)		
cecoascending	23(51.1%, 36.6-65.5)	21(46.7%, 32.5-61.4)	1(2.2%, 0.1-11.8)	χ^2=39.2 df=8 p <0.001	0.1 (0.02-0.9) p=0.041
transvers	5(23.8%, 10.6-45.1)	14(66.7%, 45.4-82.8)	2(9.5%, 2.6-28.9)		0.5 (0.1-2.4) p=0.39
descending	9(50%, 29.0-71.0)	4(22.2%, 9.0-45.2)	5(27.8%, 12.5-50.9)		2.9 (0.9-9.2) p=0.058
sigmoid	31(46.3%, 34.8-58.2)	27(40.3%, 29.3-52.4)	9(13.4%, 7.1-23.7)		0.9 (0.4-2.0) p=0.76
rectum	6(22.2%, 10.6-40.8)	7(25.9%, 13.2-44.7)	14(51.9%, 34.0-69.4)		8.6 (3.5-21.3) p <0.001

The analysis revealed significant differences between colon segments (χ^2=39.2, df=8, p<0.001). Thus, the rectum had the highest probability of large polyps (OR=8.6, 95%CI: 3.5-21.3, p<0.001), suggesting a strong association between this location and increased polypoid dimensions. In contrast, the ceco-ascending location was associated with a significantly lower probability of large polyps (OR=0.1, 95%CI: 0.02-0.9, p=0.041). For the transverse, descending and sigmoid segments, no statistically significant associations were found (p=0.39, p=0.058, p=0.76), although a trend towards association was observed in the descending colon (OR=2.9, p=0.058). Regarding histological type, the majority were neoplastic, with tubular adenomatous polyps predominating – 162 (91%, 95%CI: 86.0-94.5), followed by hyperplastic ones – 12 (6.75%, 95%CI: 3.5-11.9) and tubulo-villous ones – 4 (2.25%, 95%CI: 0.6-5.6) (figure 5). The distribution of histological types highlights a clear predominance of tubular adenomas, which represented 91% of the total lesions analyzed (n=162, 95%CI: 86-94.5). Hyperplastic polyps were identified in a significantly lower proportion, 6.7% (n=12, 95%CI: 3.5-11.9), and tubulo-villous formations constituted only 2.2% of cases (n=4, 95%CI: 0.6-5.6).

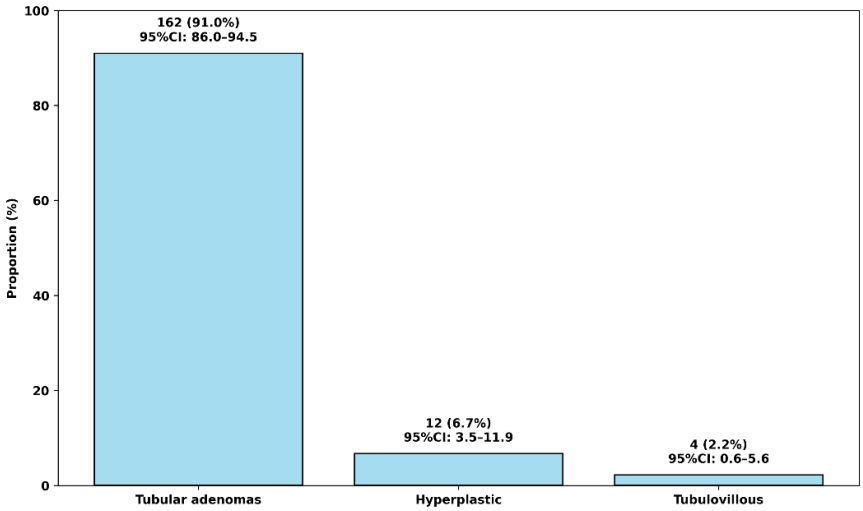

Figure 5. Histological type of premalignant colonic lesions in patients included in the study

Of the total polypoid formations detected during colonoscopy, it was possible to perform histopathological examination in 178 (73.2%) cases, and in 65 (26.8%) cases with multiple polyps - the excised formations were very small and their extraction from the colonic lumen was not successful. Compared to the total of 243 excised polyps, mild dysplasia was identified in 43.6% cases (n=106, 95%CI: 37.5-49.9), moderate dysplasia in 19.8% (n=48, 95%CI: 15.3-25.1), and high-grade dysplasia in 9.9% cases (n=24, 95%CI: 6.7-14.4). According to the WHO (2019) regrouping, low-grade dysplasia

predominated, being present in 63.4% of cases (n=154, 95%CI: 57.1-69.3), compared to high-grade dysplasia – 9.9% (95%CI: 6.7-14.4) (figure 6).

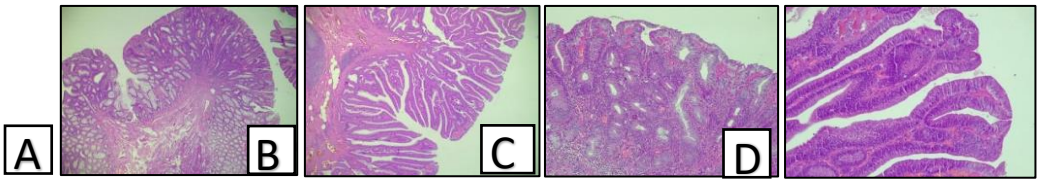

Figure 6. Morphological subtypes of conventional adenomas according to the WHO classification (2019):
A – tubular adenoma with moderate epithelial dysplasia (HE stain, ×100; x200); B – villous adenoma with moderate epithelial dysplasia (HE stain, x200); C – tubular adenoma with high epithelial dysplasia (HE stain, x200); D – tubulo-villous adenoma with high epithelial dysplasia (HE stain, x200);

In the group of polyps with mild dysplasia (n=154), the size distribution revealed a predominance of very small polyps (55.8%, 95%CI: 46.5-64.7) and small polyps (39%, 95%CI: 30.1-48.6), while large polyps were rare (5.2%, 95%CI: 2.3-10.7). In contrast, in the group of polyps with severe dysplasia (n=24), almost all lesions were large (95.8%, 95%CI: 82.7-99.2), with a minimal representation of small polyps (4.2%, 95%CI: 0.7-21.1) and a complete absence of very small polyps. Statistical analysis revealed a significant association between polyp size and degree of dysplasia, confirmed by the χ^2 test, demonstrating that increased polyp size is closely correlated with severe dysplasia (figure 7).

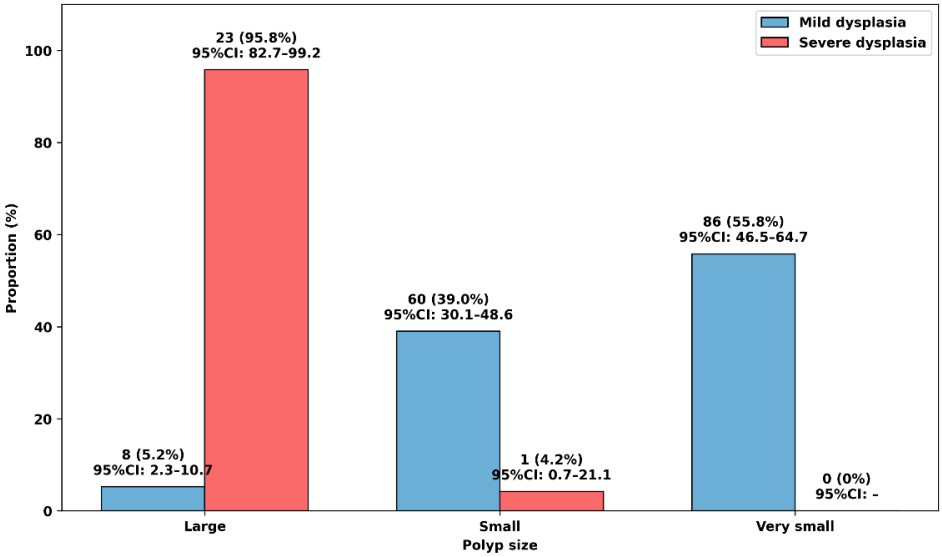

Figure 7. Distribution of polyps according to size and degree of dysplasia, abs(%)

The analysis according to the histological result of the polyps and their degree of malignancy reveals that for all histological types, polyps with low-grade dysplasia were recorded, and only for tubulo-adenomatous and tubulo-villous polyps, respectively, were polyps with high-grade dysplasia recorded (table 6).

Table 6. Associative distribution of polyps according to histological type and dysplasia type

Type of dysplasia	**Histological type (abs)(%, 95%CI:)**			**Total (abs,%)**	**Statistical test χ^2 Monte Carlo**
	Tubular adenomatous*	Tubulo-villous**	Hyperplastic***		
Low grade	140(90.9%, 85.3-94.6)	2(1.3%, 0.4-4.6)	12(7.8%, 4.5-13.2)	154(86.5%)	χ^2=8.21 df=2 p=0.12
High-grade	22(91.7%, 74.2-97.7)	2(8.3%, 2.3-25.9)	- (0.0-13.8)	24(13.5%)	
OR(95%CI:)**	0.8 (0.3-2.2)	7.1 (0.9-54.1)	0.14 (0.008-2.4)	-	
Total (abs,%)	162(91%, 85.9-94.4)	4(2.2%, 0.9-5.6)	12(6.8%, 3.9-11.4)	178(100%)	
* tubular adenomatous polyps *vs* the rest; ** tubulo-villous *vs* the rest; *** hyperplastic *vs* the rest;**** calculated with Haldane–Anscombe correction, due to the "0" cell which makes the classical OR estimation impossible					

The evaluation of the relationship between the histological type of polyps and the degree of dysplasia revealed a clear predominance of tubular adenomatous polyps, representing 91% of the total lesions analyzed. The overall statistical analysis did not reveal a significant association between the histological type and the degree of dysplasia (χ^2 Monte Carlo=8.21, df=2, p=0.12).

4. DIFFERENTIATED CURATIVE ATTITUDE IN COLONIC NEOFORMATIONS

4.1. Principles and characteristics of treatment methods

Preventing the progression of premalignant lesions to colorectal cancer involves the application of various therapeutic methods, aimed at the excision or destruction of polypoid formations. In this study, the selection of the treatment technique was individualized for each patient. The evolution of polypectomy methods went in parallel with the technological advance of endoscopic imaging and the diversification of the instruments used. Among the essential criteria that formed the basis of the therapeutic decision were the location and size of polyps with neoplastic potential, as well as the possibility of endoscopic delimitation of the lesion edges. In the current study, two different treatment methods were used in patients: endoscopic – polypectomy (n=170/66.7%, 95%CI: 60.7-72.2), endoscopic submucosal dissection (n=5/1.9%, 95%CI: 0.6-4.5) and resection procedures (n=79/31%, 95%CI: 25.0-37.3) with/without primary anastomosis. The structure of surgical interventions for the entire group of patients is presented in table 7.

Table 7. The extent and type of surgical interventions performed on patients in the research group

Type of surgery	Solitary polyps (abs)(%, 95%CI:)	Multiple polyps (abs)(%, 95%CI:)	Neoplasms (abs)(%, 95%CI:)	Full lot (abs)(%, 95%CI:)
Endoscopic polypectomy	140(95.9%, 91.2-98.2)	30(93.8%, 79.2-98.9	-	170(66.7, 60.7-72.2)
Endoscopic submucosal dissection	5(3.4%, 1.5-7.7)	-	-	5(1.9%, 0.8-4.5)
Anterior rectal resection (Dixon)	1(0.7%, 0.1-3.8)	1(3.1%, 0.5-15.7)	15(19.5%, 12.3-29.4)	17(6.6%, 4.2-10.4)
Sectoral resection of the sigmoid colon	-	1(3.1%, 0.5-15.7)	11(14.3%, 8.1-23.9)	12(4.7%, 2.7-8.1)
Transverse colon sectoral resection	-	-	1(1.3%, 0.2-6.9)	1(0.4%, 0.1-2.2)
Subtotal colectomy	-	-	4(5.2%, 2.0-12.6)	4(1.6%, 0.8-4.0)
Left hemicolectomy	-	-	14(18.2%, 11.3-28.1)	14(5.5%, 3.4-8.9)
Left hemicolectomy + STEC	-	-	2(2.6%, 0.7-9)	2(0.8%, 0.2-2.8)
Right hemicolectomy	-	-	24(31.2%, 22.1-41.9)	24(9.4%, 6.4-13.6)
Operation Chiricuță	-	-	3(3.9%, 1.3-10.8)	3(1.2%, 0.4-3.4)
Operation Hartmann	-	-	2(2.6%, 0.7-9)	2(0.8%, 0.2-2.8)
Refuse surgery	-	-	1(1.3%, 0.2-6.9)	1(0.4%, 0.1-2.2)

The association between the type of surgery and the lesion category was assessed by the χ^2 test with Monte Carlo simulation (χ^2=244.6, df=22, p<0.001), an appropriate method in the presence of low frequencies and a non-uniform distribution of the data. The absence of a uniform distribution of the types of surgery between the groups, together with the non-overlapping confidence intervals between endoscopic and major surgical procedures, support the existence of a clear association between the severity of the pathology and the degree of complexity of the surgical treatment applied. It is noteworthy that, in the 170 patients who benefited from polypectomy, a number of 243 polypoid formations of different sizes, histological type, degree of dysplasia were found, and there were 140 solitary and 103 multiple, synchronous. In the doctoral study, very small polyps predominated in frequency in 128 (52.7%, 95%CI: 46.4-58.9) cases, small in 84 (34.6%, 95%CI: 28.8-40.9) cases, and large polyps represented 12.8% (n=31, 95%CI: 9.1-17.6). All 128 (52.7%) of very small polyps and 63 (25.9%) of the small ones were excised by cold loop polypectomy. In other clinical situations, 28 (11.5%) small polyps and 24

(13.5%) large polyps were removed with a hot loop for prophylaxis of immediate or late postpolypectomy bleeding, followed by en bloc retrieval of the excised polyp for the purpose of evaluating the resection margins. Open surgical interventions were performed in cases when polyp malignancy was evident or confirmed histopathologically.

4.2. Differentiated management of colonic neoformations depending on staging

Colorectal neoplasias classified as **stage 0** (in situ) are characterized by the presence of the tumor process strictly limited to the mucosa or, at most, to the submucosa of the colonic wall, without invasion of the muscularis propria and without evidence of lymph node metastases (N0). Colorectal neoplasias classified in **stage I** (T1–T2, N0, M0) being considered localized forms of the disease, were characterized by limited extension of the tumor to the submucosal layer (T1) or to the musculature of the colonic wall (T2), without evidence of regional lymph node metastases and without distant dissemination [20]. In the doctoral study, 32 (12.5%, 95%CI: 9.0-17.2) patients with multiple polyps were registered: in 14 (43.8%, 95%CI: 28.2-60.7) subjects, 2 polyps were detected during colonoscopy, and in 18 (56.3%, 95%CI: 39.3-71.8) subjects – three or more polyps. The therapeutic approach to these clinical situations included: cold loop polypectomy in 23 cases, hot loop in 7 cases. Only in 2 patients was polypectomy not possible (pediculated type with large dimensions and high-grade dysplasia) and the surgical method was decided, performing sectoral resection of the sigmoid and recto-sigmoid resection. At the same time, in the study, 24 (13.5%, 95%CI: 9.2-19.3) polypoid formations with high-grade dysplasia were identified, of which 3 (12.5%, 95%CI: 4.3-31.0) had a pedunculated morphology, and 21 (87.5%, 95%CI: 69.0-95.7) were sessile, with a wide implantation base. All formations had centimeter dimensions (1.7±0.4 cm). Sessile polyps were excised using the hot loop technique, while the three pediculated polyps required polypectomy, a technique with a high degree of difficulty, due to the thick pedicle, with a diameter of approximately 1 cm – a size at the limit of the opening capacity of the polypectomy loop and which prevented stable fixation of the formation due to sliding movements. This determined, in these three cases, surgical intervention: for the polyp located in the sigmoid colon, a sectoral resection of the sigmoid was performed with the application of end-to-end colo-colic anastomosis, and for the polyps located at the recto-sigmoid junction – the Dixon operation. In **stage II** of CRC, the study group representing 12 patients (15.6%), the tumor penetrated beyond the muscularis propria, invading the colonic wall, and in some cases, even the neighboring structures. In the subcategory IIA (T3), the tumor formation was limited to the colonic wall, without exceeding the serosa. In contrast, in stages IIB and IIC, the tumor had extension beyond the colonic wall, either by reaching the visceral peritoneum (T4a) or by direct invasion of adjacent organs or structures (T4b). In this latter situation, the adhesion of the tumor to a neighboring organ was considered real invasion, requiring multivisceral en bloc resection. In stage II of CRC, the main therapeutic approach consisted of surgical resection of the affected colonic segment, associated with the excision of regional lymph nodes [22, 23]. The main feature of **stage III** CRC (n=23 patients, 29.9%) was regional lymph node involvement, with the presence of metastases in 1-3 lymph nodes (substage N1) or in more than 3 nodes (substage N2). In fact, this lymphatic extension signals an increased risk of recurrence and requires the application of a systemic approach to treatment, combining curative surgery with the administration of adjuvant chemotherapy [24]. These patients were operated on for complications, and subsequently treated and monitored at the Oncological Institute. The standard therapeutic approach for stage III CRC involves surgical resection of the affected colonic segment together with excision of regional lymph nodes, with the sampling of at least 12 nodes being recommended for adequate oncological staging. Surgical intervention tended to follow the principles of complete excision of the mesocolon and to include central ligation of the corresponding vascular pedicles, to ensure radical resection [22, 25]. **Stage IV** CRC is defined by the presence of distant metastases, indicating a systemically advanced disease. The study group included 40 patients with grade IV CRC.

The most common locations of metastases were the liver – n=21 (27.3%), as well as the lungs (n=3 cases). Although the management of patients with stage IV CRC involves an integrated therapeutic strategy, established within a multidisciplinary team, these patients were operated on for complications with absolute indications (occlusion, hemorrhage, peritonitis). These lesions being considered resectable, the objective of the treatment was curative, aiming at complete removal of the tumor. Only in one case, an elderly patient (90 years old) refused surgical intervention and was discharged on her own responsibility.

Most patients with neoplasms included in the study benefited from scheduled surgical interventions 64 (84.4%), 12 (15.6%, 95%CI: 9.0-25.4) were operated on urgently, having as indications tumor perforation with peritoneal syndrome in 5 (6.5%, 95%CI: 2.8-14.3) cases and intestinal occlusion in 7 (9.1%, 95%CI: 4.5-17.6) of the cases. The distribution of patients according to the type of surgical resection is represented in figure 8.

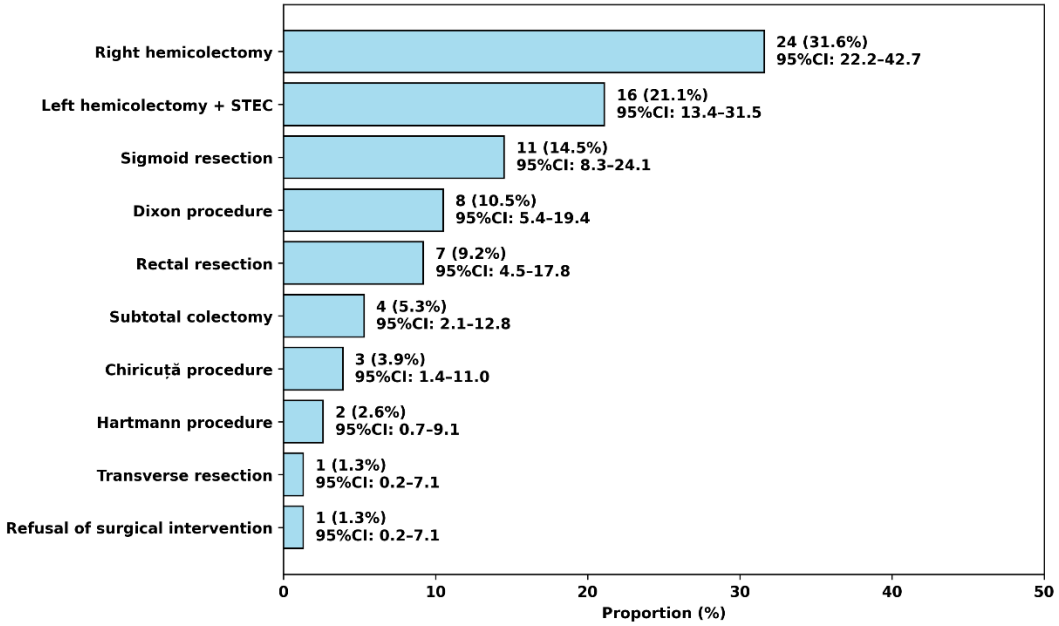

Figure 8. Distribution of patients with neoplasms included in the study according to the type of surgical resection

The most common intervention was right hemicolectomy (31.6%, 95%CI: 22.1-43.3), followed by left hemicolectomy (18.4%, 95%CI: 11.5-27.9) and sigmoid colon resection (14.5%, 95%CI: 8.3-24.1) with primary anastomosis. Less common interventions included rectal resection, Dixon operation and other procedures, each with weights below 11%, and only one patient refused surgery (1.3%, 95%CI: 0.2-7.0). The uneven distribution of the types of interventions reflects both the topographic peculiarities of the lesions and the need to individualize the surgical management depending on the extent of the disease and the clinical status of the patient, confirming the predominance of radical interventions in cases with right colonic location. The distribution of postoperative complications revealed a variation in relative frequencies between the different types of events analyzed. The highest proportions were recorded for respiratory failure associated with COVID-19 infection (21.7%, 95%CI: 9.3-42.8), followed by *E. coli* infection and dynamic occlusion, each with a relative frequency of 17.4% (95%CI: 7-36). Anastomotic fistula and wound suppuration showed intermediate frequencies, of 13% (95%CI: 4.5-31.2) each, while eviscerations and encephalopathy were identified less frequently, with a relative frequency of 8.7% each (95%CI: 2-25.6). Overall, the observed variations in relative frequencies between types of complications can be attributed mainly to random variability, with no statistically significant predominance of a particular type of complication being demonstrated within the analyzed group.

4.3. Results of performing *cold* and *hot loop* polypectomies

According to the current research data, 170 (66.7%) of the patients included in the study underwent endoscopic polypectomy with total excision of 243 polypoid formations. Of these, 140 (54.9%) subjects had solitary polyps, and 30 (11.8%) subjects had multiple polyps. Cold loop polypectomy was performed on 191 (78.6%) polyps, and hot loop polypectomy on 52 (21.4%) polyps. The mean size (M±SD) of polyps among those excised with cold loop was 5±2 mm (Med (IQR): 6 (5–7) mm, SD=6.1 mm), while in the group of polyps excised with hot loop – 7±2 mm (Med (IQR): 8 (6–9) mm, SD=7.3 mm), with a statistical difference (t=6.39, df ≈79, p<0.0001). The analysis of postpolypectomy complications, reported in comparison between cold loop polypectomy (n=191 polyps) and hot loop polypectomy (n=52 polyps), revealed their occurrence exclusively in the hot loop group. Postpolypectomy syndrome was recorded in 3 patients (5.8%, 95%CI: 2-15.4), hemorrhage was encountered in 2 cases (3.9%, 95%CI: 1.0-12.9), and the most severe complication was represented in one case (1.92%, 95%CI: 0.3-10.1), of perforation of the sigmoid wall, without peritonitis, which was resolved by laparotomy and suturing of the sigmoid parietal defect. The χ^2 test with Monte Carlo simulation demonstrated a statistically significant association between surgical technique and the distribution of complications (χ^2=23.2, df=1, p<0.001).

4.4. Follow-up of patients after endoscopic or surgical polypectomy with multiple polyps

Surveillance of patients after endoscopic polypectomy or surgery is an essential step in the management of colonic lesions, especially in patients with multiple polyps, who are at increased risk of recurrence and neoplastic progression. Post-interventional monitoring aims to detect early the appearance of new lesions, to evaluate the effectiveness of the applied treatment and to prevent the development of CRC. Patients diagnosed with confirmed colonic neoplasms were not integrated into the long-term follow-up cohort, they were included in specialized oncology circuits and continuously monitored by oncologists, within the multidisciplinary committees (tumor board). All patients with premalignant polypoid lesions were explained the postpolypectomy follow-up and control measures. However, we considered it important to monitor patients with multiple polyps and those with high-grade dysplasia earlier. Thus, this group included 32 patients, which constituted 12.5% (95%CI: 8.9-17.3) of the total group of patients with polypoid formations, 24 of whom were detected with high-grade dysplasia upon histological examination (75.0%, 95%CI: 57.8-86.8). These patients were monitored in dynamics with control colonoscopy performed 6 and 12 months after primary polypectomy. Of the 32 subjects with multiple polyps, 30(93.7%, 95%CI: 79.9-98.3) underwent colonoscopy or colonography at a 6-month interval, 2(6.3%, 95%CI: 1.7-20.2) patients could not be contacted by telephone for follow-up or information about outpatient endoscopic investigations. In 15(46.9%, 95%CI: 30.9-63.6) cases, a polypoid formation (different colonic level) was diagnosed, subsequently endoscopic cold loop polypectomy was performed, the histopathological results showing adenomas with low-grade dysplasia. Another 15(46.9%, 95%CI: 30.9-63.6) patients did not present any colonic mucosal lesions or residual polypoid tissue following colonoscopic/colonographic examination. At 12 months, 27(84.4%, 95%CI: 68.2-93.1) subjects presented for colonoscopy or reported having a follow-up outpatient examination. Of these, 23(71.9%, 95%CI: 54.6-84.4) subjects had no colonic mucosal lesions, and 4(12.5%, 95%CI: 5.0-28.1) cases had a colonic polyp that was excised endoscopically, with histological findings showing adenomas with low-grade dysplasia, and 5 (15.6%, 95%CI: 6.0-34.1) elderly patients did not present for a follow-up colonoscopy.

4.5. Management algorithm for premalignant colonic lesions and repeated polypectomies

The results of the doctoral study demonstrated a significant correlation between the size of the polyps and the presence of high-grade dysplasia. Based on this, essential criteria were defined for the

development of the polypectomy algorithm, having as criteria the location, size, shape and histological type of the polyps. However, it is important to emphasize that this algorithm requires further validation through prospective research, including within the surgical clinic of the Emergency Hospital, to confirm its efficiency, safety and reproducibility in current practice. The order and priority of excision were established as follows: (1) **location** – polyp excision is performed from the left to the right of the colon, starting with the rectum; (2) **size** – the intervention is performed progressively, from larger to smaller polyps; (3) **shape** – in the case of polyps of similar size, priority is given to the excision of sessile formations, followed by pediculated ones; (4) **histological type** – when there are previous histopathological results, villous polyps are excised with priority, followed by the other histological types. The algorithm for serial polypectomies in patients with multiple polyps is represented in figure 9. After the excision of the first large polyp "PM1", it will continue with "PM2" and the following ones, up to "PMx", its effectiveness being also reported in the studies of Septimiu and coauthors (2018) [26].

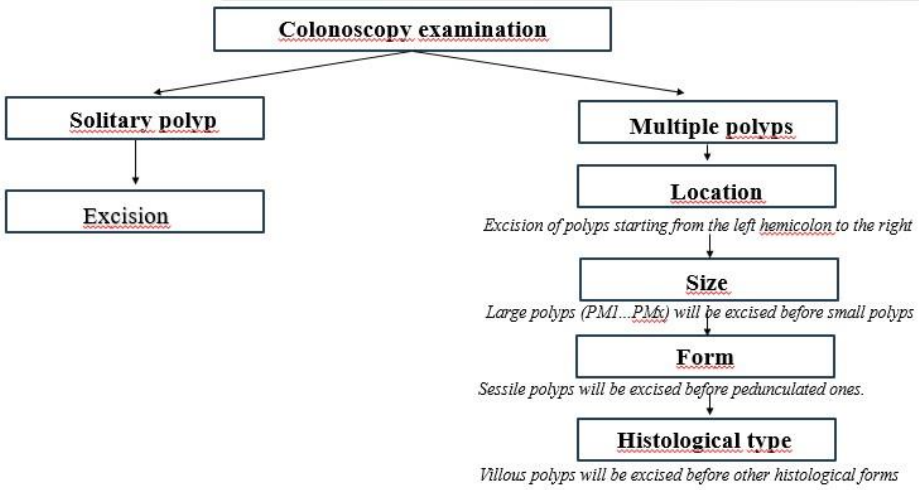

Figure 9. Curative algorithm for serial polypectomies in multiple colonic polyps

5. EVALUATION OF GENOMIC MARKERS IN THE EVOLUTION OF COLORECTAL NEOPLASIAS: PILOT STUDY

5.1. Genetic epidemiology of primary colonic neoformations

In the present study, we attempted to identify genomic markers associated with susceptibility to colonic neoplasia, using a genome-wide association study and evaluation of the identified genomic markers. The study cohort consisted of 176 (69.1%) subjects, most of whom were hospitalized patients, as follows: 89 (53.6%, 95%CI: 43.2-57.9) – polyps, 77 (46.4%, 95%CI: 36.6-51.1) – neoplasms and 10 control cases, constituting the group of non-oncological patients. Given that some of the samples did not meet the quality criteria required for molecular analysis, in the final stage only 84 blood samples and 12 pairs of tissue biopsies were eligible. This methodological limitation requires the research to be classified as a pilot study, with all the associated constraints. Using the R Studio statistical program, a total of 63242 markers were generated for each patient included in the study cohort through imputation procedures. The quality check of the obtained data involved the exclusion of markers with a minor allele frequency below 1% and a determination rate lower than 0.95. Following filtering, only 7000 markers met the selection criteria. Subsequently, an association test was performed between the imputed markers (n=63242) and the phenotype represented by the positive biopsy for CRC. For the transcriptomic analysis, the R language was used within the R Studio integrated development environment, which provided a modular and reproducible framework for organizing the entire bioinformatics workflow. The entire set of analyses was structured in a central file, used for managing scripts and graphical results.

5.2. Selection and comparative analysis of gene expression markers obtained to reproduce the results reported in the literature

To validate the presence of biopsy-identified markers in the patients included in this study, a comparative analysis was performed using the NHGRI (National Human Genome Research Institute Home) catalog of published genome-wide association studies [27, 28], along with a systematic review of the literature on genetic variants associated with CRC. After excluding duplications, 20 distinct markers were identified, of which 10 did not provide information on the tested allele and did not fall within the 95% confidence interval. Of the remaining 10 common markers detected and mentioned in the literature as predictors of colorectal cancer, we identified 6 markers in the samples taken from the patients in the present study (table 8).

Table 8. Sequenced markers with the most important significant values

Marker name	Chromosome*	Position*	Base Mean	log2 Fold Change	p value	p-adj (FDR)
ABHD16B	**Chr 20**	**63.861.498-63.862.988**	**73.1157**	**9.13489**	**0.000314516**	**0.001048**
BACH1-IT	Chr 21	29.496.046-29.500.387	125.2627	10.55968	0.000528852	0.001058
ARPP19P1	Chr 5	180.982.174-180.987.560	123.243	10.34907	0.0004356	0.001089
BNIP3P20	Chr 19	20.351.502-20.352.079	98.0814	9.71834	0.0014285	0.002041
C15orf32	Chr 15	92.471.653-92.501.119	90.0937	8.95804	0.00319374	0.003194
VWA3B	**Chr 2**	**98.087.116-98.330.616**	**647.0456**	**9.10061**	**0.00224577**	**0.002495**
WDPCP	**Chr 2**	**63.119.559-63.840.826**	**101.5674**	**11.33582**	**0.000198945**	**0.000995**
ZNF738	**Chr 19**	**21.358.930-21.388.582**	**64.2895**	**10.44028**	**0.000611559**	**0.001019**
ZNF74	**Chr 22**	**20.394.115-20.408.461**	**133.177**	**8.46168**	**0.0014731**	**0.001841**
ZNFX1	**Chr 20**	**47.862.437-47.894.594**	**370.7101**	**13.36414**	**0.00000971976**	0.000097

* according to **GeneCards** – The Human Gene Database

In this study, six genes (table 8) with the most relevant differential expression values were identified and analyzed. Their characteristics, including biological functions, tissue distribution, molecular interactions and their importance in colon neoplastic pathology, were investigated using the GeneCards database. The results highlighted the involvement of these genes in essential processes, such as cell proliferation, apoptosis regulation and inflammatory mechanisms associated with tumorigenesis. The integration of the data obtained with the information from GeneCards allowed to outline a detailed perspective on the potential role of these genes as molecular biomarkers or as possible therapeutic targets in colonic neoplasias. Although in the present study the **ABHD16B** gene showed a high expression value in the analyzed samples, there are currently insufficient data in the specialized literature to support its role as a predictive or diagnostic marker in CRC. Available sources, including The Human Protein Atlas and GeneCards, do not indicate a significant association between the expression of this gene and colorectal carcinogenesis, and **ABHD16B** is not mentioned in current guidelines or scientific papers as a validated biomarker for this pathology. According to data from The Human Protein Atlas, **VWA3B** expression in CRC tissues is low, and survival analysis of CRC patients does not indicate a significant association between the expression level of **VWA3B** and the prognosis of patients with this type of cancer. Although

the other 4 genes **WDPCP, ZNF738, ZNF74** and **ZNFX1** are not specific markers for colorectal cancer according to the available data, other zinc-arm proteins may have oncogenic or tumor suppressor roles in this disease. A detailed understanding of the mechanisms of action of these proteins could facilitate the identification of new diagnostic and prognostic markers, as well as the development of targeted therapeutic strategies in CRC. However, in the context of the bioinformatic analysis performed in the pilot study, these genes should be considered as preliminary results, requiring further validation. This highlights the importance of conducting further research to clarify their biological relevance and clinical potential.

5.3. Analysis of differential gene expression according to tumor stage

In the present study, a transcriptomic analysis was performed on 84 peripheral blood biological samples collected from patients with colonic neoplasias (polyps and neoplasms), using RNA-seq technology and bioinformatics packages from the R/Bioconductor ecosystem. The main goal was to identify genes with differential expression during various stages of tumor progression (I–IV), compared to the non-malignant reference stage (stage 0). Based on the RNA-seq transcriptomic analysis, on the selection of genes that was performed based on the log2FoldChange value and statistical significance ($p<0.05$), we present a comparative diagram of the most significant 5 differentially expressed genes for each stage of CRC (stages I–IV), compared to stage 0 (considered the biological reference) (figure 10).

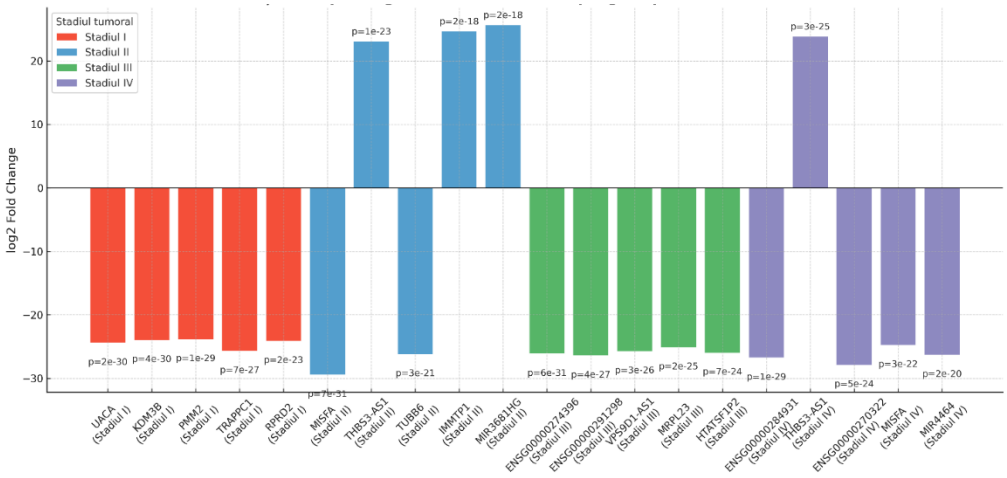

Figure 10. Comparative diagram of the most significant 5 differentially expressed genes for CRC stages

The graph shows gene expression variations expressed by log2 Fold Change (vertical axis), for a total of 20 genes (5 per stage), compared to stage 0: positive values (upward-facing bars) indicate overexpression of the respective gene at the respective stage compared to stage 0. Negative values (downward-facing bars) reflect significant underexpression.

For each tumor stage compared to the reference stage, MA (Mean-Average) plots were generated from the R Studio program, indicating the relative variations in gene expression (Figures 11-12). These revealed a consistent number of up- and downregulated genes in advanced stages (III–IV), signaling the progressive activation of molecular pathways associated with invasion and metastasis. Following the differential gene expression analysis between different stages of colorectal cancer (I, II, III and IV) compared to stage 0, out of a total of approximately 5000 genes, 1867 genes per group with statistically significant differential expression ($p\text{-adj}<0.05$) were identified. The selection of these priority genes was based on high log2FoldChange values and an adjusted significance level ($p\text{-adj}<0.05$), highlighting those transcripts with potential direct involvement in colon carcinogenesis and differentiation between clinical stages of the disease. This approach allows for a focused interpretation on the most representative biomarkers for the evolution of CRC.

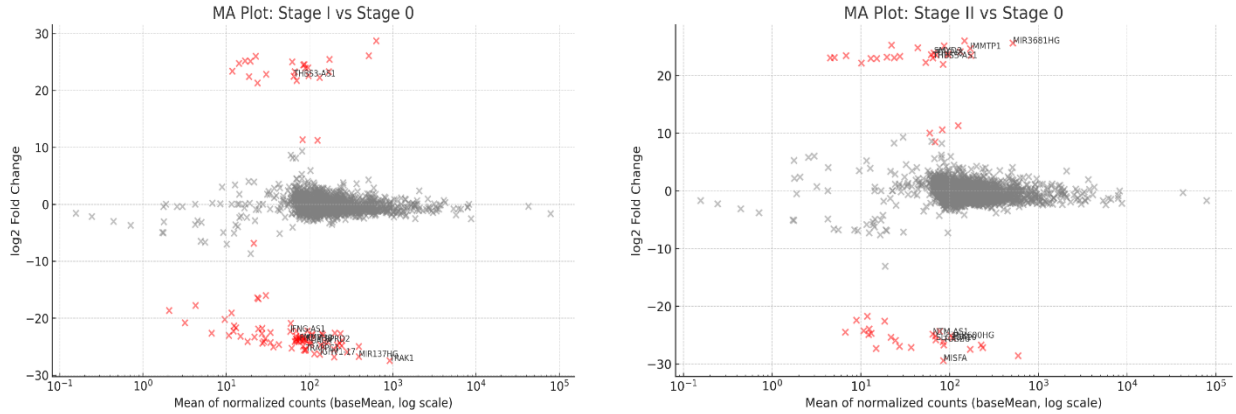

Figure 11. *Mean-Average* diagram of differentially expressed genes in patients with stage I and II neoplasia *vs* stage 0

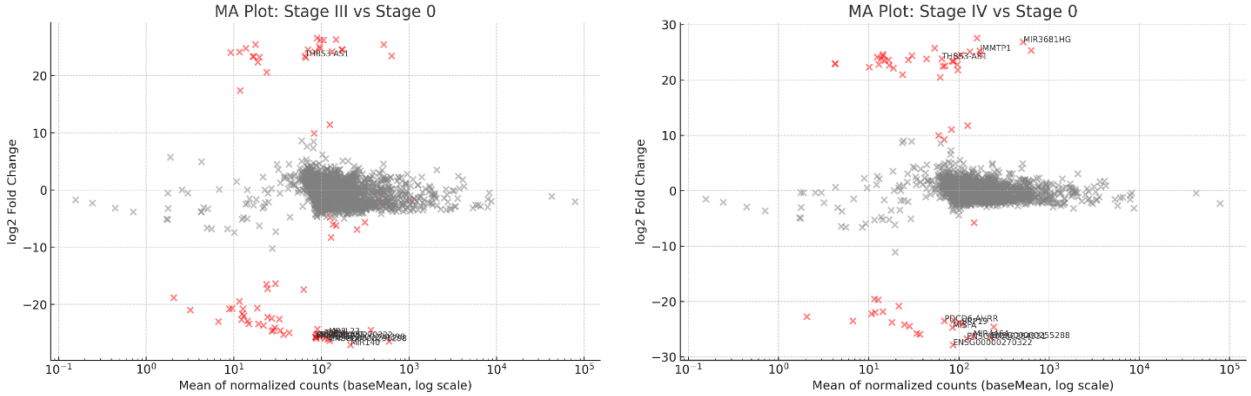

Figure 12. *Mean-Average* diagram of differentially expressed genes in patients with stage III and IV neoplasia *vs* stage 0

For each comparison, the gene with the lowest p-value (corrected for multiple testing) was extracted and visualized using the plotCounts function – expression of the most significant gene. These graphs clearly demonstrate the expression differences between groups and confirm the biological relevance of the findings. Thus, the results obtained indicate a progressive profile of gene expression dysregulation, with emphasis in advanced stages of the disease. Some of the identified genes may constitute potential biomarkers, with clinical value in the evaluation of early diagnosis or prognosis. Subsequently, genes that are differentially expressed with statistical significance (P-adj<0.05) in all stages of CRC (I, II, III, IV) compared to stage 0 were extracted. These common genes are: IMMTP1, JRK, KRTAP19-4, MKI67, MIR302CHG. According to The Human Protein Atlas, we describe their functional significance in the oncological context and the evidence existing in the specialized literature regarding its association with the evolution of CRC.

The **MKI67** gene encodes a nuclear protein expressed exclusively in the active phases of the cell cycle, being absent in resting cells (G0). It is widely used as a marker of cell proliferation, having an important role in the diagnosis and prognosis of CRC. IMMTP1 is a poorly characterized gene in the literature, described as a transcript expressed in immature T cells, without conclusive data regarding its direct involvement in colorectal carcinogenesis. Although not validated as a specific marker for CRC, the differential expression observed in transcriptomic analysis could suggest an indirect role in the immunological regulation of the tumor microenvironment. **JRK** is a homolog of a gene associated with epilepsy (especially juvenile myoclonic forms), but has also recently been implicated in the control of transcription and the maintenance of genomic stability, with possible functions in the regulation of the expression of genes related to the cell cycle. **KRTAP19-4,** a gene belonging to the keratin-associated protein family and structurally involved in the constitution of the hair shaft, has no evidence in the

medical literature to directly correlate it with CRC. In contrast, **MIR302CHG** functions as a long non-coding RNA, harboring the microRNA-302 cluster, involved in the regulation of pluripotency and the cell cycle by inhibiting the expression of the **CDK2** gene and other proliferation factors. This transcript has been associated with cellular regeneration and reprogramming processes and, according to some studies, with the modulation of the tumor microenvironment. In CRC, its role is still being elucidated, but its identification in the DESeq2 analysis suggests the existence of possible mechanisms of epigenetic dysregulation. [29].

GENERAL CONCLUSIONS

1. Correlational analysis of clinical and laboratory manifestations associated with colonic neoplasia revealed statistically significant relationships between certain clinical symptoms (rectorrhea, changes in bowel rhythm, weight loss) and laboratory parameters (tumor markers, imaging and endoscopic data). The results obtained suggest that these indicators may constitute potentially relevant factors for differentiating the type of NPC, highlighting the need for an integrative approach in the diagnosis and management of patients with suspected neoplastic colonic lesions.
2. Studying the morphological and histological aspects of primary colonic neoplasms has revealed a diversity of lesion types, from benign adenomatous formations to invasive carcinomas, with significant variations in their location, glandular architecture, degree of dysplasia and tissue infiltration. Identification of these histopathological features is essential for estimating prognosis and guiding therapeutic decisions.
3. The findings demonstrate that the choice of surgical intervention type in primary colon neoformations must be individualized, depending on the clinical-morphological characteristics of the lesion, highlighting the importance of a rigorous preoperative evaluation. The differences recorded between cold loop and hot loop polypectomy emphasize the need for optimal selection of the endoscopic technique with a direct impact on procedural safety and oncological control.
4. The results obtained favored the development of an integrated screening algorithm for CRC, based on the correlation of potentially relevant risk factors, suggestive symptomatology and standardized paraclinical investigation data, which significantly contributes to correct preoperative staging. The implementation of the algorithm optimizes the selection of patients for invasive evaluation, reduces diagnostic delays and allows the initiation of rational treatment conduct, with a favorable impact on prognosis and long-term survival.
5. Evaluation of genomic markers in different evolutionary stages of colonic neoplasias revealed a significant correlation between tumor molecular profile and disease progression, highlighting their role both in early diagnosis and in prognostic stratification and the choice of targeted therapy. The presence of differential expression of genes involved in carcinogenesis reflects the dynamics of the tumor process and can guide personalized therapeutic decisions, supporting the integration of genomic testing into the PCN management algorithm.

PRACTICAL RECOMMENDATIONS

1. The use of morphological and histological aspects in guiding the therapeutic conduct of patients with colonic neoplasms determines the systematic performance of the histopathological examination of identified colonic lesions, using standardized criteria (WHO, TNM). These data are essential for tumor staging, estimation of the risk of recurrence and therapeutic orientation.
2. The therapeutic approach in the case of colonic neoplasms must be personalized according to the clinical-morphological characteristics of the lesion (size, location, degree of invasion) and the general condition of the patient. It is recommended to establish multidisciplinary teams to establish the optimal therapeutic conduct.

3. As a heterogeneous pathology, colon neoplasia requires the systematic introduction of genomic marker testing. Molecular marker testing (e.g. KRAS, NRAS, BRAF mutations and microsatellite instability – MSI) is indicated in all cases of confirmed colorectal cancer. The results of these analyses contribute to the estimation of prognosis and the selection of targeted therapies, in accordance with the principles of personalized medicine.
4. Careful evaluation of colonic polyps in terms of size, shape, location, and endoscopic appearance (including using the *Paris* classifications) is recommended to choose the optimal resection method. For pedunculated polyps <10 mm in diameter, *cold loop* polypectomy is indicated. For those >10 mm, *hot loop* polypectomy with prophylactic pedicle clip is preferable to prevent postprocedural hemorrhage.
5. In the case of sessile or flat polyps, for lesions <10 mm: cold loop resection is recommended with a low risk of complications. For lesions between 10–20 mm: endoscopic mucosal resection (EMR) is the standard technique. For lesions >20 mm or with a high risk of submucosal invasion: endoscopic en bloc resection (EMR or, in selected cases, endoscopic submucosal dissection – ESD) is indicated.
6. In the case of lesions with high potential for malignancy or those not completely resected, it is recommended to mark the site (*endoscopic tattooing*) with a special pigment injected into the submucosa (e.g., Indian ink), to facilitate subsequent identification for diagnostic or therapeutic purposes.
7. Patients with multiple colonic polyps are at increased risk of adenomatous recurrence and development of colorectal neoplasms. In these cases, careful endoscopic surveillance is essential for early detection of residual lesions or new formations. The recommended interval between follow-up colonoscopies varies depending on the number, size, and histological type of polyps.
8. For patients with ≥3 adenomas or polyps ≥10 mm in size, surveillance colonoscopy is indicated every 3 years. In the case of ≥10 adenomas discovered during a single colonoscopy, evaluation is recommended every ≤1 year, with suspicion of polyposis syndrome. If the polyps are hyperplastic and distally located, without signs of dysplasia, the interval can be extended to 10 years, if no other risks coexist.
9. Compliance with *follow-up* recommendations is crucial for reducing the risk of colorectal cancer. It is recommended to inform patients about the importance of monitoring and include them in an automated reminder and scheduling system.
10. All endoscopically resected colonic polyps should be sent for detailed histopathological analysis, regardless of their macroscopic appearance, because the definitive diagnosis regarding the nature of the lesion (adenomatous, hyperplastic, serrated, etc.) cannot be established endoscopically alone.
11. Determining the degree of dysplasia (mild or severe) is essential for oncological risk stratification. The presence of high-grade dysplasia requires more frequent follow-up and may be an indication for surgical intervention if endoscopic resection is incomplete or the margins are uncertainly negative.
12. Histological examination provides critical information for early identification of invasive carcinoma in the polyp, in which case further imaging and surgical treatment may be necessary, especially if the resection margins are involved or vascular invasion is present. It is recommended that histological results be carefully recorded and archived in the patient record to ensure adequate continuity of surveillance and to avoid incomplete or erroneous interpretations during future follow-ups.
13. Differential gene expression analysis provides essential information for identifying specific molecular profiles associated with the progression from premalignant lesions to invasive neoplasia. This allows for a more precise stratification of oncological risk and contributes to the individualization of therapeutic management. The differentially expressed genes in the studied cohort may be candidates

for the development of early molecular diagnostic panels, useful in high-risk populations, even before the appearance of obvious endoscopic signs.

14. It is necessary to strengthen continuous medical education and correct information of the population in order to signal early clinical signs of colon neoplasia.
15. It is recommended to organize continuing education programs for medical personnel involved in cancer screening, diagnosis and treatment. At the same time, it is necessary to conduct health education campaigns for the population, in order to increase adherence to screening programs and early presentation to the doctor.
16. Given that patients with colonic neoplasms may present for investigation and treatment at different medical institutions, with a high risk of losing important information, it is recommended to create national computerized registries for colorectal cancer, which would include clinical-paraclinical, histological, molecular and treatment data. Such databases allow monitoring of patient progress, evaluation of the effectiveness of interventions and facilitation of multicenter clinical research.

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