

**"CAROL DAVILA" UNIVERSITY OF MEDICINE AND
PHARMACY, BUCHAREST
DOCTORAL SCHOOL
THE FIELD OF GENERAL MEDICINE**

*Clinical and histopathological prognostic factors in left colon
cancer*

PHD THESIS SUMMARY

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2022

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INTRODUCTION

Neoplasia is a major public health problem worldwide both in terms of associated morbidity and mortality and in terms of health policy decisions involving the implementation and monitoring of control and intervention strategies.

Colon cancer has been on the rise in global incidence and prevalence in recent times, both in the proliferation of number of cases in general and in the increasing number of cases of breast cancer in particular. (1) In Romania, colorectal cancer is the second most common localization in patients diagnosed with de novo malignancy.

The incidence of this type of cancer is higher in male patients, and it increases in direct proportion to age. (2) The reported mortality in 2020 was 9.4%, being the second leading cause of cancer death. The combined efforts of researchers, physicians and policy makers to treat and prevent colon cancer have failed to limit mortality rates, which are still on a steady upward trend. (3) At the same time, the increase in life expectancy led to the increase in colorectal cancer cases, leading to almost half of these patients being over the age of 70. (4)

Survival rates in colorectal cancer patients are determined by a number of factors. Among the most important are the stage of the disease and the presence of metastasis. Thus, the 5-year survival rate is 90% for patients diagnosed in the early stages with localized tumor formation, the survival rate decreases by about 70% for tumors with regional invasion, reaching only 10% in case of distant metastasis. (5), (6)

The control of neoplasms is currently the subject of numerous studies, and prevention and prognostic factors are the main gaps in order to increase the survival rate and decrease the number of resources allocated to the treatment of these patients. Colon cancer, due to its frequency in the population and the aggravating nature it has had in recent years, thus becomes a favorite subject in clinical trials. The left colon malignancy, worldwide and especially in Romania is insufficiently encountered as a unique subject in the literature, the relevant works in the field addressing the issue of clinical and histopathological differences between left and right colon cancer.

This paper aims to focus on left colon cancer by exposing the current state of knowledge in the first part and presenting a personal research in the second part, and finally launching discussions by interrelating the two parts.

CURRENT STATE OF KNOWLEDGE

1. LEFT COLON SURGICAL ANATOMY AND PHYSIOLOGY

Surgically, the left colon is located between two conventional landmarks as follows: cranial - the point where the transverse colon is located posterior to the left costal margin, and caudal - anterior to the third sacral vertebra, where the junction with the rectum is located. Anatomically, one of the delimitation criteria is the colonic vascularization - the cranial limit of the left colon being located at the level where the left branch of the middle colic artery is located in the vicinity of the mesenteric margin of the transverse colon; caudal colorectal boundary is the same skeletal landmark as in the case of surgical delimitation. Colon motility contributes to the formation of faeces by changing the pressure that causes water to be absorbed and the contents to move to the rectum. (7)

2. LEFT COLON CANCER

Colon cancer is a major cause of morbidity and mortality worldwide, with major implications for both the medical and socio-economic fields.

Genetic, epidemiological and experimental studies show that colorectal cancers are the result of a complex interaction between environmental factors and genetic susceptibility. (8), (9)

Colon cancer has the appearance of adenocarcinoma in 95% of cases, the remaining 5% are squamous cell carcinomas, melanomas, adenosquamous carcinomas, primitive colonic lymphomas and carcinoid tumors. (10) The macroscopic aspect of left colon cancer includes the following pathological forms: - ulcerative, - vegetative, - annular, - diffuse infiltrative.

For tumors located on the left colon and colorectal junction, the annular, ring-shaped or circumferential stenotic shape is specific. (11) There are multiple reports regarding the histopathological classification of colon cancer, both macroscopically and microscopically, among the most common being: Broders, Grinnell and Dukes, OMS.

OMS classification of colon cancer

Histological type	Definition	Grading 1-4	Grading L / H
Adenocarcinoma	Glandular, tubular epithelium +/- villus	1-3	L / H
Mucinous adenocarcinoma	> 50% extracellular mucin	1-3	L / H
Ring cell carcinoma with seals	> 50% "seal ring" cells	3	H
Squamous cell carcinoma	Squamous differentiated cells	1-3	L / H
Adenosquamous carcinoma	Mixed cellularity	1-3	L / H
Small cell carcinoma	Neuroendocrine differentiation	4	H
Undifferentiated carcinoma	No differentiating elements	4	H

Staging of left colon cancer is also reported in various forms, the most well-known being the modified Dukes classification Astler-Coller and TNM.

TNM staging

Primary tumor - Tx Primary tumor cannot be evaluated

- T0 The primary tumor does not appear
- Tis Carcinom in situ
- T1 The tumor invades the submucosa
- T2 The tumor invades its own muscle
- T3 The tumor protrudes beyond the muscle and invades the subserosal or perirectal tissues of the subperitoneal rectum
- T4 The tumor invades nearby organs

Regional lymph nodes - Nx Regional lymph nodes cannot be evaluated

- N0 No metastases in the regional lymph nodes
- N1 Metastases present in 1 to 3 regional lymph nodes
- N2 Metastases present in 4 or more regional lymph nodes
- N3 Metastases in each lymph node along a vascular axis

Distant metastasis - Mx The presence of distant metastasis cannot be assessed

- M0 No distant metastasis
- M1 Distant metastasis present

Colon cancer staging groups

Stage 0 Tis N0 M0

Stage I T1 N0 M0

T2 N0 M0

Stage II T3 N0 M0

T4 N0 M0

Stage III Tis - 4 N1 M0

Tis - 4 N2, N3 M0

Stage IV Tis - 4 N0-3 M1

The most commonly used methods in colon cancer screening are: fecal occult blood test and colonoscopy.

The left colon cancer prognosis includes a multitude of factors. These factors can be grouped into several categories: tumor-related factors, clinical factors, histopathological factors, and biological factors (eg, oncogenetic and molecular factors). Currently, the expression of p53, k-ras and bcl-2, TGF- α , EGF, proliferation index and aneuploidy are evaluated as potential prognostic factors along with known factors. One of the major problems of the left colon cancer evolution is the disease recurrence (local recurrence and / or distant metastasis) after surgery is a major problem. The disease recurrence is very often the final cause of death. Among the proteins known to play important roles at the cellular level, the present research aimed to study the MMR, p53 and Bcl-2 proteins that exist in tumor tissue. MMR proteins are known to be responsible for DNA repair, p53 protein is a tumor suppressor protein, and Bcl-2 is a protein with a role in regulating cell survival and death.

Clinical factors of prognostic importance:

1-Age - young patients seem to have a poor prognosis due to the association with the more frequent presence of poorly differentiated tumors with a high degree of malignancy;

2-Gender- women with colon cancer have a better prognosis;

3-Obstruction and perforation worsen survival in the colon neoplasm; Under conditions of emergency surgery as in the case of obstructive tumors with bowel obstruction, it is estimated that only 50% of patients are candidates for curative deeds, postoperative morbidity and mortality being obviously higher than scheduled operations. In the case of colonic tumors perforated in the peritoneal cavity, it is seeded with tumor cells, which makes the surgical

therapeutic deed can no longer be considered curative and thus the hope of survival is greatly diminished;

4-Location of the primary tumor

It seems that the locations on the right colon would have a more pessimistic prognosis than those on the left colon, probably by the more technically difficult dissection of the central lymphatic station at the level of the origin of the superior mesenteric artery;

5- Symptomatology

Colon tumors diagnosed in asymptomatic patients are less advanced and have a better prognosis. When complications are present and / or the cancer is detected in the advanced stage, both the immediate postoperative prognosis and the distant survival are affected.

6-Rectorage associated with colon cancer is correlated with a good prognosis, possibly due to the fact that it leads to alarming the patient with early diagnosis and treatment. (12)

3. THERAPEUTIC OPTIONS IN LEFT COLON CANCER

Treatment of left colon cancer is a multimodal treatment.

Surgical intervention is mandatory. It is carried out in the first time; it depends on the evolutionary stage of the neoplasm, existing complications and other associated chronic diseases.

Even patients with metastases benefit from surgical treatment because by removing the tumor decreases the risk of complications.

Adjuvant-chemotherapy treatment is associated with surgical treatment depending on the staging of the neoplasm.

Preoperative preparation includes: **1-general preparation** -refers to organic deficiencies, hydro-electrolyte imbalances, acid-base, anemia, hypoproteinemia.

2-local preparation - colon preparation is carried out by mechanical preparation and bacteriological preparation. (10, 20, 178)

Treatment of precancerous lesions

Well-visualized pediculate polyps are resected endoscopically.

Sessile polyps (sessile lesions) are resected endoscopically together with a mucosa corelet.

Solitary polyps with malignancy in situ are excised endoscopically.

Sessile polyps or malignancies that go beyond the mucosa lend themselves to surgical treatment of colon cancer.

If a polyp is too large in size (villous polyps more than 2 cm in diameter) or caused an invagination, colic resection is practiced.

Endoscopic removal of polyps in difficult situations may be associated with laparotomy or laparoscopy.

The basic principles in the treatment of familial adenomatous polyposis are:

- Application of surgical treatment before malignancy;
- Detection of the disease in other family members.

The most commonly used surgical procedure is total colectomy with terminal ileo-rectal anastomosis plus excision of rectal polyps. This process gave the best results.

Other surgical procedures applied are:

- proctocolectomy with ileo-anal anastomosis and ileal reservoir;
- panproctocolectomy with definitive ileostomy rarely used in this disease. (14, 183)

The recommended treatment is prophylactic total colectomy.

Proper surgical treatment of left colon cancer includes:

- curative, palliative and undefined procedures

Each of these procedures are performed in an emergency or scheduled.

Palliative surgery is practiced in the following cases:

- 1-distant metastases are present;
- 2-the primary tumor is inoperable;
- 3-the presence of postoperative residual local tumor tissue.

Indefinite surgeries are those in which we do not have the certainty of removing the tumor and/or regional lymph nodes in full.

Curative surgical procedures with oncological radicality visa are part of a multimodal treatment.

Surgical intervention is performed in the first time, according to the staging of the neoplasm; then chemotherapy treatment follows.

Curative operations are practiced in the following situations:

1-the tumor is localized at the level of the colic wall, without invading the lymph nodes;

2-the tumor penetrates the colic wall, without invading the lymph nodes;

3-the tumor penetrates the colic wall or not, with the invasion of lymph nodes.

The objectives of surgical treatment are:

1 - resection of the tumor along with segmental interested colic, within oncological boundaries;

2 - removal of nodes from the drainage area;

3- restoration of digestive continuity. (178)

Emergency surgery

The purpose of emergency surgical interventions is to resolve complications of colon neoplasm.

The most common complications are: occlusion, perforation and hemorrhage.

In neoplastic occlusion of the left colon are several therapeutic options:

1-the tumor is located on the proximal left colon, after resection the two segments externalize; the proximal one as a colostoma, and the distal one as a mucous fistula;

2-the tumor is located on the distal left colon; after resection, the proximal segment is externalized in the form of a terminal colostomy, and the distal one is closed and abandoned – the Hartmann operation;

3-tumor resection followed by anastomosis, associated with clearance colostomy;

4-segmental colic resection in oncological boundaries or subtotal colectomy with anastomosis in one time is risky.

PERFORATION occurs at tumor level or remote – diastase.

Treatment includes 1-for peritonitis-spectrum antibiotics; lavage and drainage of peritoneal cavity;

2 - the perforation will be solved as follows: - the one at the tumor level:

- a) either removal of the lesion when possible followed by a Hartmann procedure or terminal colostomy with mucous fistula;
- b) if the local situation does not allow resection of the tumor will be performed colostomy or ileostomy.

Diastatic perforation of the cecum in left colon cancer is sanctioned with subtotal colectomy with ileostomy.

Hemorrhage is a rare complication of left colon cancer. Treatment requires resection of the tumor.

Liver metastases are maximum 4 resected at the same time as the tumor. When they are in greater numbers, disseminated in both lobes their annihilation is done by: chemotherapy, cryotherapy, alcoholization. (21)

Chemotherapy in left colon cancer

In left colon cancer chemotherapy is used as adjuvant therapy. Mandatory in stages III and IV, according to the recommendations of the European Society of Medical Oncology (ESMO).

There are currently several protocols on the recommendation of ESMO used in colon neoplasm. The standard protocol consists of treatment with 5 fluorouracil+folinic acid administered on days 1-5 of the week in 6 cycles, which is repeated every 4 weeks. (158)

PERSONAL RESEARCH

4. RESEARCH PURPOSE, OBJECTIVES AND HYPOTHESES

Research purpose

The aim of this paper is to identify the main clinical, histopathological and immunohistochemical prognostic factors involved in left colon cancer.

Research objectives

1. identifying the socio-demographic profile of patients with left colon cancer
2. description of the profile of patients with left colon cancer according to the main clinical features present at admission
3. analysis of paraclinical investigation results in patients with left colon cancer
4. identification of the main anatomical, histopathological, immunohistochemical features and staging of patients with left colon cancer
5. evaluation of the main methods of surgical treatment of patients with left colon cancer
6. identification of the main postoperative complications of patients with left colon cancer

Research hypotheses

- do elderly patients have an unfavorable prognosis compared to other categories of patients?
- are patients from rural environment at a disadvantage in the prognosis of left colon cancer?
- is the advanced age of patients associated with an increased risk of intra- and postoperative complications?
- is the risk of postoperative complications associated with advanced stages of colon cancer?

- is the age of the patients positively correlated with the number of days of hospitalization?
- is the histopathological type of the tumor different depending on its location?

5. GENERAL RESEARCH METHODOLOGY

Type of study and population studied

This research is built in the form of a retrospective, descriptive, cross-sectional study, conducted in a cross-sectional manner conducted over two calendar years between January 1st, 2015 – December 31, 2016 at the Bucharest Emergency Clinical Hospital, Surgery Clinic.

The study population includes 171 patients and is made up of well-defined inclusion and exclusion criteria:

Inclusion criteria:

- Age over 18
- Left colon cancer diagnosis, with or without surgery. Left colon cancer has been defined as the presence of a malignant tumor located in the splenic flexion, descending colon, sigmoid colon and / or rectosigmoid junction)
- Patients undergoing surgery after previous surgery with a left colon cancer diagnosis
- Acceptance to participate in the study and signing of informed consent

Exclusion criteria:

- Minors (under 18)
- Post-operative invalidate of the initial diagnosis of left colon cancer
- Refusal to participate in the study

Data collection and statistical analysis

The data necessary for the implementation of the current study were obtained from the observation sheets of the patients admitted to the SCUB Surgery Clinic, from the histopathological examination reports and from the electronic files included in the SCUB integrated computer system.

The information thus obtained was processed in qualitative and quantitative variables:

The qualitative variables are shown in the following table:

<i>Nominal variables</i>	<i>Ordinal variables</i>
<ul style="list-style-type: none"> - rural / urban area of residence, - male / female, - admission symptoms, - personal history of pathology, - hereditary collateral history, - the basic medication used, - presence of pre- and post-operative anemia, treatment of anemia (pre- and post-operative iron treatment, pre-, intra- and post-operative transfusion), - data on the tumor histopathological characteristics (histopathological type, tumor type, presence of vascular invasion and perineural extension, microscopic invasion of the resection piece, degree of tumor extension, tumor extension to the lymph nodes, distant tumor extension and metastasis location), staging TNM, - time of surgery (scheduled / emergency), - data on surgical technique (description of type of resection, type of anastomosis, drainage and other surgical maneuvers used), - postoperative complications, - the need for reintervention. 	<ul style="list-style-type: none"> - age groups, - data on paraclinical parameters at admission and discharge (proteinemia, leukocytes, erythrocytes, hemoglobin, hematocrit, platelets, cholesterol, blood glucose, etc.) - low / normal / high, - degree of tumor differentiation, - postoperative outcomes (favorable outcome, postoperative

	complications, death)
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Quantitative variables used:

<i>Continuous quantitative variables</i>	<i>Discrete quantitative variables</i>
<ul style="list-style-type: none"> – age – the duration from the onset of symptoms to the presentation to the doctor – the interval between surgery and resumption of intestinal transit – duration of hospitalization 	<ul style="list-style-type: none"> – the number of metastatic lymph nodes

Statistical analysis involved on the one hand the calculation of frequencies, the determination of the normality of the studied population (Kolmogorov Smirnov test), the mean calculation, median and standard deviation and on the other hand the identification of statistically significant correlations, for which the Pearson and Spearman test were applied, bivariate logistic regression, contingency tables. The subpopulations of the study were compared using: chi square test / Fisher test, student test T / Mann-Whitney and ANOVA / Kruskal-Wallis.

In order to interpret the results obtained, the statistical significance threshold was set at 0.05. The p values below this threshold were considered to be of statistical significance.

The data was collected using Microsoft Office Excel. Thereafter, these data were recoded using SPSS. Statistical data analysis was performed using SPSS version 23.0.

RESULTS AND DISCUSSIONS

6. IDENTIFYING THE SOCIODEMOGRAPHIC PROFILE OF PATIENTS WITH LEFT COLON CANCER

The average age of the 171 patients that make up the study group was 67.24 +/- 10.95 years, their distribution being a Gaussian one ($p = 0.140$). The included population has 58.48% male patients and 41.52% female patients. 72.51% of the patients included in the study come from urban areas and the rest from rural environment. Most male patients come from urban areas, and female patients from rural environment. The average age of patients in urban environment is higher than in rural environment, but this is not statistically significant according to the chi-square test.

7. DESCRIPTION OF THE PATIENTS PROFILE WITH LEFT COLON CANCER ACCORDING TO MAIN CLINICAL FEATURES AT THE TIME OF ADMISSION

The most common diagnosis at the time of admission is tumor formation - 54.4% ($n = 93$), followed by subocclusive syndrome - 27.5% ($n = 47$), rectoria / HDI - 15.8% ($n = 27$), abdominal colic - 12.9% ($n = 22$), bowel obstruction - 11.1% ($n = 19$) and anemia - 9.4% ($n = 16$). The stratification according to gender and environment of origin does not reveal significant differences. The frequency of anemia and bowel obstruction as reasons for admission increases with the age of patients.

The main diagnoses at admission according to the age group of the patients

Admission diagnosis	<50 years old	50-59 years old	60-69 years old	70-79 years old	80 years old and over	p value
Abdominal colic	27,3%	6,9%	18,2%	7,5%	13%	0,224
Tumor	27,3%	48,3%	56,4%	56,6%	65,2%	0,290

Anemia	0%	6,9%	5,5%	9,4%	26,1%	0,042
Rectorage / HDI	9,1%	13,8%	18,2%	15,1%	17,4%	0,944
Subocclusive syndrome	27,3%	24,1%	27,3%	26,4%	34,8%	0,937
Bowel obstruction	0%	10,3%	9,1%	7,5%	30,4%	0,027

Clinical manifestations of left colon cancer in the study population and the duration from the onset of symptoms to the presentation to the doctor, stratified according to age group:

Clinic	All patients N (%)	Age <70 years N (%)	Age 70 and over N (%)	p value
Secondary anemia	43 (25.1)	15 (15.8)	28 (36.8)	0.002
Subocclusive syndrome	47 (27.5)	25 (26.3)	22 (28.9)	0.702
Bowel obstruction	19 (11.1)	8 (8.4)	11 (14.5)	0.211
Abdominal pain	99 (57.9)	55 (57.9)	44 (57.9)	1.000
Weight loss	61 (35.7)	26 (27.4)	35 (46.1)	0.011
Rectors / HDI	54 (31.6)	34 (35.8)	20 (26.3)	0.185
Intestinal transit disorders	95 (55.6)	49 (51.6)	46 (60.5)	0.242
Nausea, vomiting	19 (11.1)	10 (10.5)	9 (11.8)	0.786
Duration of onset of symptoms - presentation to the doctor (days) (mean ± SD)	69.6±111.4	61.3±91.8	78.6±130.4	0.525

The mean duration from onset of symptoms to the presentation at the hospital is 74.51 ± 114.25 days.

The mean duration from the onset of symptoms to the presentation at the hospital does not differ significantly depending on age ($p = 0.978$) or postoperative evolution ($p = 0.520$).

The most common hereditary antecedents in the study group were colon cancer (6.4%), hypertension (4.7%), diabetes mellitus (2.3%), liver cirrhosis, and gastric cancer. 1.8%).

59.6% of the patients included in the study had hypertension and 14% had diabetes.

Characteristics of patients at the time of admission stratified according to age groups:

Patient characteristic	Lot N (%)	age <70 years N (%)	Age 70 and over N (%)	p value
Gender				0.425
Male	100 (58.5)	53 (55.8)	47 (61.8)	
Female	71 (41.5)	42 (44.2)	29 (38.2)	

Residence environment	124 (72.5)	69 (72.6)	55 (72.4)	0.969
Urban	47 (27.5)	26 (27.4)	21 (27.6)	
Rural				
Comorbidities				
Depressive syndrome	8 (4.7)	2 (2.1)	6 (7.9)	0.141
HTA	102 (59.6)	50 (52.6)	52 (68.4)	0.037
Diabetes	24 (14.0)	14 (14.7)	10 (13.2)	0.768
Stroke	9 (5.3)	0 (0.0)	9 (11.8)	0.001
Colon cancer	11 (6.4)	7 (7.4)	4 (5.3)	0.757
Surgery				
Cholecystectomy	19 (11.1)	8 (8.4)	11 (14.5)	0.211
Appendectomy	37 (21.6)	20 (21.1)	17 (22.4)	0.836
Hysterectomy	14 (8.2)	12 (12.6)	2 (2.6)	0.023

The main types of chronic treatment prior to diagnosis stratified according to the patients age group:

Chronic treatment	<50 years old	50-59 years old	60-69 years old	70-79 years old	80 years old and over	p value
Hypotension	9,9%	37,9%	50,9%	58,5%	73,9%	0,003
Diuretics	9,1%	31%	34,5%	37,7 %	56,5%	0,089
Oral antidiabetics	0%	13,8%	14,5%	13,2%	4,3%	0,504
NSAIDs	0%	0%	5,5%	5,7%	8,7%	0,560
Insulin	0%	3,4%	1,8%	1,9%	0%	0,895

Management of associated anemia divided by patient gender:

Anemia treatment	male	female	P value
Preoperative iron treatment	6%	2,8%	0,331
Postoperative iron treatment	5%	5,6%	0,855
Preoperative transfusion	3%	9,9%	0,060
Intraoperative transfusion	19%	15,5%	0,552
Postoperative transfusion	6%	7%	0,471

8. ANALYSIS OF THE PARACLINICAL INVESTIGATION RESULTS IN PATIENTS WITH LEFT COLON CANCER

Following the analysis of the variables about the paraclinical data of the patients included in the study, the following were observed:

- A small percentage of patients had hypoproteinemia at the time of admission, and this percentage increased at the time of discharge.
- Leukocytosis decreased in frequency at the time of discharge compared with admission
- Anemia is present in 40.9% of subjects at the time of admission, later reaching 26.3% postoperatively, respectively 25.7% on discharge
- Thrombocytosis decreases from 25.7% on admission to 8.2% on discharge
- Variations in blood glucose were also included in the study: a small number of patients had hypoglycemia at admission, and the number slightly increased on discharge, while hyperglycemia was present in 35.1% of patients on admission, then decreased to 4.7 % on discharge
- Hypercholesterolemia is also present in 28.7% of patients on admission and then decreases to 2.9% on discharge

A key factor in the statistical analysis of paraclinical investigations is the presence of liver metastasis at the time of admission detected by imaging examinations:

Prevalence of liver metastasis by gender, area of residence and age group

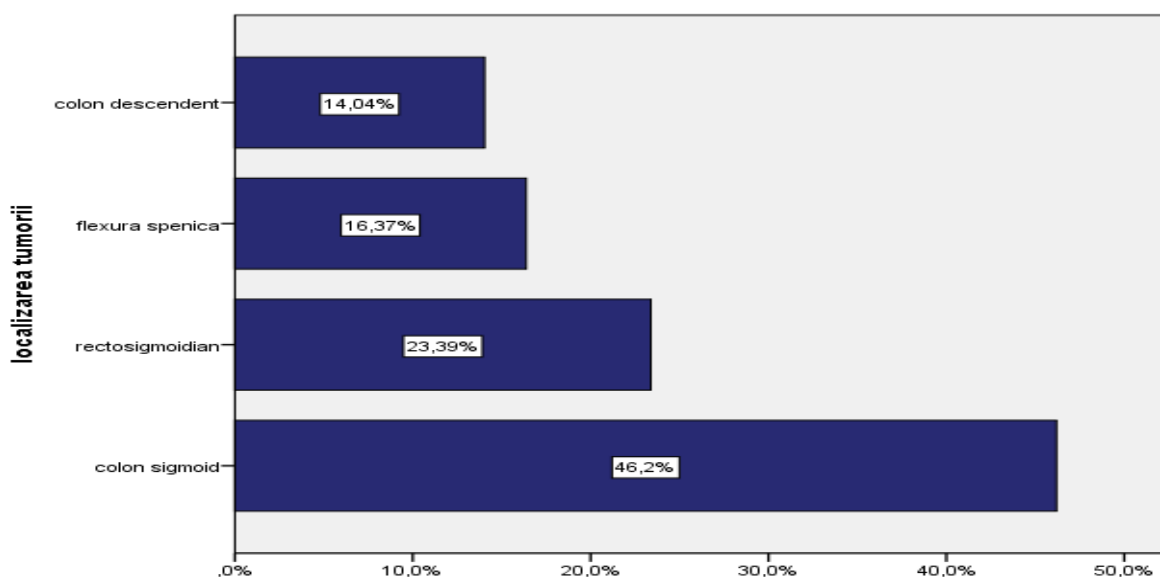
Characteristic	Prevalence of liver metastasis
Gender	
Male	11%
Female	12,7%
Residence environment	
Urban	8,9%
Rural	19,1%

Age group	
<50 years old	27,3%
50-59 years old	6,9%
60-69 years old	10,9%
70-79 years old	7,5%
80 years old and over	21,7%

Both anemia and thrombocytosis have been observed predominantly in elderly patients.

9. IDENTIFYING THE MAIN ANATOMICAL, HISTOPATHOLOGICAL FEATURES AND STAGING OF PATIENTS WITH LEFT COLON CANCER

Distribution of patients according to tumor location:



No statistically significant differences were observed between the location of the tumor and the gender, residence environment, or age group of the patients.

The postoperative results were studied from a descriptive point of view and were stratified according to the location of the tumor formation:

Distribution of patients according to tumor location and postoperative outcomes

			postoperative results			Total
			favorable evolution	complications	death	
tumor location	splenic angle	N	9	5	0	14
		%	7,6%	12,2%	0,0%	8,6%
	rectosigmoid junction	N	8	1	0	9
		%	6,8%	2,4%	0,0%	5,5%
	sigmoid colon	N	50	24	2	76
		%	42,4%	58,5%	50,0%	46,6%
	rectosigmoid	N	21	8	1	22
		%	17,8%	19,5%	25,0%	13,5%
	descendant colon	N	21	1	1	23
		%	17,8%	2,4%	25,0%	14,1%
	transverse colon	N	9	2	0	11
		%	7,6%	4,9%	0,0%	6,7%
	Total	N	118	41	4	163
		%	100,0%	100,0%	100,0%	100,0%

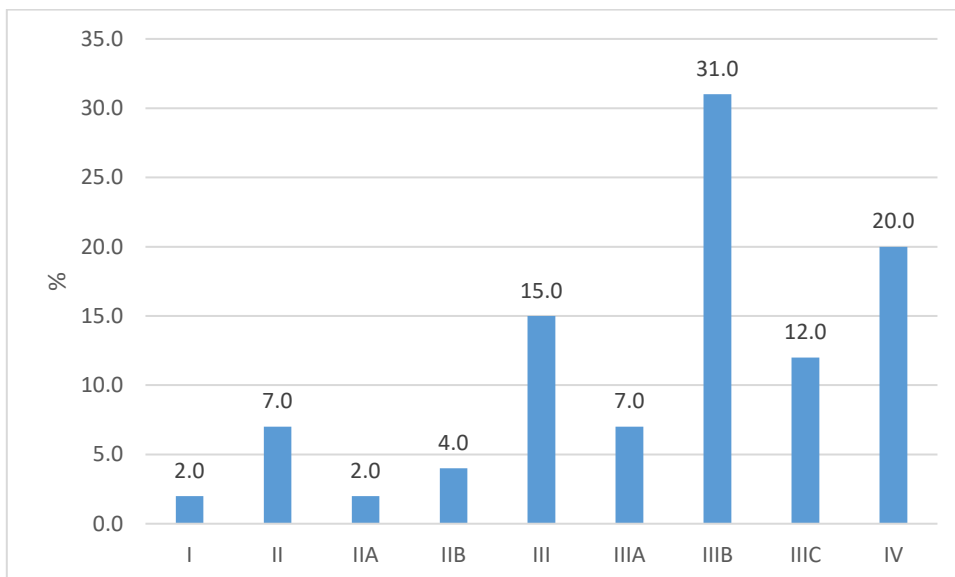
67.92% of the patients included in the study have conventional adenocarcinoma, 13.21% tubulovillous adenoma and 9.43% mucinous adenoma. The histopathological type of the tumor does not differ statistically significantly depending on age group, gender or residence environment, however, according to the present analysis, cribriform alveolar adenocarcinoma occurs only in females (6.67%) and mucinous adenocarcinomas only in males. (13.16%). Although the literature does not support the association between the histopathological type of left colon tumor and the presence of lymphatic metastasis or distant metastasis, this study found significant differences, with tubulovillous adenoma being more frequently associated with lymphatic metastasis.

Staging of colon cancer was also analyzed in this study and it was observed that 15.15% of tumors are poorly differentiated, 63.64% moderately differentiated and 21.21% are well

differentiated. The differentiation does not differ statistically significantly with the location of the tumor or the demographic data of the patients, it differs depending on the histopathological type. Depending on the degree of differentiation, it is observed that 12.9% of tumors are poorly differentiated (G1), 67.8% moderately differentiated (G2) and 19.3% are well differentiated (G3). We observed lymph node metastasis in 33.3% of patients with G1 differentiation tumors, in 77.8% of those with G2 differentiation tumors and in 80% of G3 differentiation tumors. Distant metastasis were found in 33.3% of tumors with G1 differentiation and in 31.2% of those with G2 differentiation. None of the patients with G3 differentiation tumor showed distant detectable metastasis. Although none of these differences were statistically significant, this could result from too few patients with G1 and G3 differentiation tumors.

In 15.6% of patients the lymph nodes were not invaded and in 13.76% they could not be evaluated. Among the patients in whom the tumor invaded the lymph nodes, 43.12% had a maximum of 3 invaded regional lymph nodes, 24.77% had a minimum of 4 invaded regional lymph nodes and 2.75% had invasion of the lymph nodes located along an important vascular axis. 79.17% of patients with metastasis have liver metastasis, 29.15% peritoneal metastasis, 12.5% lung metastasis and 4.16% brain metastasis.

Tumor distribution according to TNM classification



Distant tumor extension correlates with the residence environment, being more common in patients from rural environment ($p = 0.014$).

10. IDENTIFYING THE MAIN IMMUNOHISTOCHEMICAL FEATURES IN PATIENTS WITH LEFT COLON CANCER

Among the patients included in the research, 44 patients with left colon neoplasms were included in the study on immunohistochemistry, identifying the prognostic influence of MMR, Bcl-2 and p53 proteins on patients admitted and operated in the Bucharest Emergency Clinical Hospital, between January 1st, 2015 – December 31, 2016.

A positive MMR was identified in 9 of these patients, and their mean age is significantly lower than that of those with a negative MMR. The distribution of patients with positive MMR is statistically significantly different ($p < 0.001$) depending on the family history of colon cancer, the prevalence of positive MMR being higher among patients with hereditary colon cancer. Anemia present at the time of admission correlates statistically significantly with MMR status ($p = 0.041$).

29.5% of patients tested positive for Bcl-2. No statistically significant correlations were identified between the presence of Bcl-2 and the age, history or values of laboratory tests, but these patients were found to have lower postoperative blood glucose levels ($p = 0.043$) and more frequent vascular invasion ($p = 0.047$).

More than half of the studied subpopulation tested positive for p53. A significant association between p53 positive and postoperative anemia and leukocytosis was identified. Vascular invasion is more common in these patients ($p = 0.043$).

The data provided by the literature on the impact of immunohistochemicals on the prognosis of patients with left colon cancer in particular are very few, and are usually included in studies of colon cancer in general. This paper aims to focus on this location in particular by providing important data for future assessment of the prognosis.

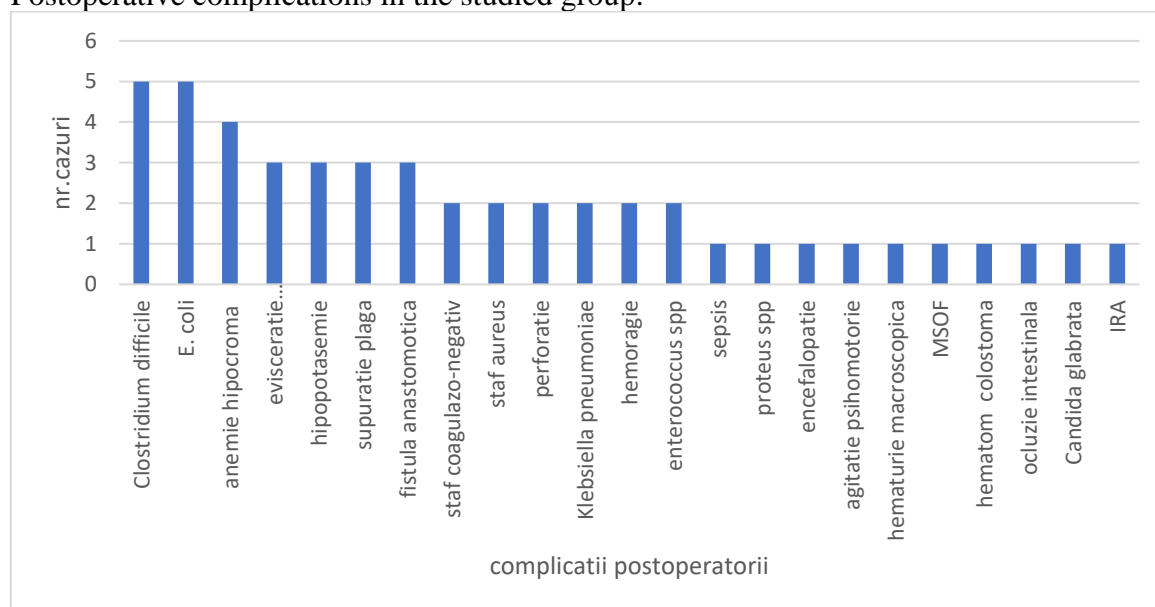
11. EVALUATION OF THE MAIN METHODS OF SURGICAL TREATMENT OF PATIENTS WITH LEFT COLON CANCER

Most patients underwent scheduled surgery (62.57%). 10% of patients underwent emergency surgery. 26.32% of the patients included in the study did not have surgery. The most common types of resection were left colectomy (39.2%), segmental rectosigmoid resection (32.8%) and sigmoid resection (20%). In 49.58% of the operated patients, the colorectal anastomosis was performed, in 26.05% the colo-colo-anastomosis and in 12.61% the colostomy was performed. None of the 171 patients included in the current research had intraoperative complications. The patients included in the study were admitted for an average of 11.5 ± 6.53 days.

12. IDENTIFYING THE MAIN POSTOPERATIVE COMPLICATIONS OF PATIENTS WITH LEFT COLON CANCER

72.93% of patients had a favorable evolution, 25.15% had complications, and 2.45% died.

Postoperative complications in the studied group:



3.17% of patients who underwent surgery needed reoperation

CONCLUSIONS AND PERSONAL CONTRIBUTION

The mean age of the patients included in the study was 67.24 ± 10.95 years, with a minimum age of 38 years and a maximum age of 90 years. The frequency of left colon cancer increases with age, with a median age of 68.00 years.

The frequency of anemia in the patients included in the study increases significantly with the age of the patients ($p = 0.042$). Also, the frequency of bowel obstruction increases significantly with the age of patients ($p = 0.027$), reaching over 30% in patients aged 80 years and over.

Low values of hemoglobin and hematocrit are found in 55.3%, respectively 53.9% of elderly patients versus 29.5%, respectively 23.2% in patients under 70 years old ($p = 0.001$, respectively $p < 0.001$). The frequency of thrombocytosis in elderly patients (13.2%) is significantly higher ($p = 0.048$) compared to the other patients included in the study (4.2%). Liver metastasis were detected imaging in 11% of women in the study and in 12.7% of men, with no statistically significant differences. Liver metastasis occur in 27.3% of patients under 50 years old and in 21.7% of those over 80 years old. Patients from rural environment have liver metastasis in a proportion of 19.1%, compared to 8.9% in urban environment.

The most common location of the tumor in patients included in the study is in the sigmoid colon (46.2%), followed by rectosigmoid location (23.39%) and splenic flexure (16.37%). 15.15% of tumors are poorly differentiated, 63.64% are moderately differentiated and 21.21% are well differentiated.

Patients with MMR positive had a significantly younger age ($p < 0.001$), a significantly more common hereditary history of colon cancer ($p < 0.001$) and a significantly lower hemoglobin at admission. Patients with Bcl-2 positive have significantly lower postoperative blood glucose levels ($p = 0.043$) and significantly more frequent vascular invasion ($p = 0.047$). Patients with p53 positive had a significantly higher frequency of postoperative leukocytosis ($p = 0.049$) and significantly lower postoperative hemoglobin ($p = 0.046$). Also, the frequency of vascular invasion is significantly more common among patients with p53 positive ($p = 0.043$). The most common stages, according to the TNM classification, are grade III (65%) and grade IV (20%); only 2% of patients included in the study had grade I and 15% grade II. Most patients underwent scheduled surgery (62.57%); 10% of patients underwent emergency surgery, and

26.32% had no surgery. None of the 171 patients included in the current research had intraoperative complications, and the average duration of admission was 11.5 ± 6.53 days. 72.93% of patients had a favorable evolution, 25.15% had complications, and 2.45% died.

The efficiency of the immunohistochemical diagnosis, studied in the present research by evaluating MMR, p53 and Bcl-2, was evaluated by the association between the immunohistochemical results and multiple clinico-pathological variables of the subjects included in the research.

MMR proteins could not be associated as important in the prognosis of left colon cancer. However, the presence of MMR proteins correlates with a lower age of the subjects included in the research, as well as with lower hemoglobin values. There is also an association between the presence of MMR proteins and the hereditary history of colon cancer.

The presence of Bcl-2 is correlated with the clinical condition of patients (eg low blood sugar levels). Also, the Bcl-2 study revealed its prognostic value, being associated with vascular invasion.

P53 positive is correlated with inflammation and anemia, but also with the prognosis of left colon cancer, as it is associated with vascular invasion.

The management of colon cancer is not yet standardized in Romania, so the study of adjuvant methods of molecular diagnosis may contribute to a more accurate assessment of the prognosis of colorectal neoplasms and, implicitly, better management of the patient with left colon neoplasm.

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LIST OF PUBLISHED WORKS

1. The elderly patient - clinical-pathological particularities of left colon cancer. Marinca Madi, Mircea Beuran. <http://www.amsibiu.ro/Arhiva/2020/Nr1-en/Marinca.pdf>
2. Histopathological Characteristics - Immediate Prognostic Factors for Left Colon Cancer. Madi Marinca, Mircea Beuran. <https://medicinamoderna.ro/histopathological-characteristics-immediate-prognostic-factors-for-left-colon-cancer/>