Histopathological Characteristics – Immediate Prognostic Factors for Left Colon Cancer
Madi MARINCA¹, Mircea BEURAN²

Abstract

Introduction: Colorectal cancer represents the second leading cause of cancer mortality in our country, the survival rates being determined by the stage of the disease and the presence of metastases, being of 90% for early stages at 5 years, of 70% for the tumors with local invasion and of 10% in case of distal metastases. The aim of our study is to evaluate the prognosis of left colon cancer according to its histopathological characteristics. Material and methods: A number of 171 patients with left colon cancer (splenic flexure, descending colon, sigmoid colon and rectosigmoidian junction) were included in the study. The patients were admitted to the Surgical Unit of the Emergency Clinical Hospital of Bucharest between January 1st 2015 – December 31st 2016. The histopathological analysis followed the norms of the American College of Pathologists, and the determination of tumor staging was done based on the TNM classification. Results: Most patients are in the 3rd stage (65.5%) and in the 4th stage (19.3%) of cancer, only 2.3% being diagnosed in the 1st stage. A number of 36 patients present distal metastases, the most frequent location being in the liver (21 patients). 24% of the patients presented postoperative complications, while 2.3% died, without any differences determined by the presence of lymph nodes or distal metastases. Distal metastases are associated with the resistance environment (p=0.048), while the invasion of lymph nodes is significantly higher (p=0.049) in patients with tubulovillous adenoma. The degree of differentiation of tumors differs significantly from a statistical point of view (p=0.002), according to the histopathological type. Conclusions: The incidence of lymphatic metastases differs according to the histopathological type of the tumor, the tubulovillous adenoma being more frequently associated with lymphatic metastases; distal metastases are more frequently seen in patients in the rural areas, based on the low addressability and accessibility to medical services. The frequency of postoperative complications and nosocomial death is determined by the advanced stage of the disease (stages 3 and 4), as well as by the late arrival of the patient to the emergency room, especially patients with intestinal occlusion.

Keywords: left colon cancer, lymph node metastasis, distal metastasis, histopathological characteristics, prognostic factors.
INTRODUCTION

Colorectal cancer represents the second leading cause of cancer mortality in Romania, the increasing mortality being constant and thus, constituting an important public health problem. In Romania, colorectal cancer represents the second most frequent location of new cases of cancer registered in 2018, the number of new cases being 6,500 in men and 4,576 in women. The incidence is higher among males, increasing with age in both sexes. The survival rates for colorectal cancer are determined by the stage of the disease and the presence of metastases, so that the survival rate at 5 years is of 90% for the early stages of localized tumors, of 70% for the tumors with local invasion and of only 10% for the cases of distal metastases.

From an anatomical point of view, a distinction can be made between colon cancer and rectal cancer, colon cancer being subdivided into right colon cancer and left colon cancer, the latter including the descending colon and the sigmoid colon. The clinical and histopathological characteristics are significantly different depending on the location of the colorectal tumor. The most common histopathological types of left colon tumors are tubular, villous and adenocarcinoma. The frequently seen polyoid morphology makes these tumors detectable from early stages during colonoscopy, thus leading to a better prognosis.

The aim of the present study is to evaluate the prognosis of left colon cancer according to its main histopathological characteristics.

MATERIAL AND METHODS

Patients with tumors located at the level of the left colon (splenic flexure, descending colon, sigmoid colon and rectosigmoid junction) were included in the study. The patients were admitted to the Surgical Unit of the Emergency Clinical Hospital in Bucharest between January 1st 2015 – December 31st 2016. The data were collected retrospectively, including all the patients diagnosed with left colon cancer in this period, irrespective of whether they had undergone surgery or not. The most relevant demographic data were collected (sex, age, residence area), all postoperative complications were recorded, as well as the postoperative evolution. The histopathological analysis was performed according to the norms of the American College of Pathologists, and the determination of tumor staging was done based on the TNM classification (American Joint Committee on Cancer - AJCC).

The degrees of differentiation were defined according to the World Health Organization criteria, using the following categories: undifferentiated, weak, medium and well-differentiated. The perineural invasion (PNI) was defined based on the Betsakis criteria as the presence of tumor cells in any layer of the nervous sheath or groups of tumor cells which occupy more than 33% of the perineural space. Lymphovascular invasion (LVI) was defined based on Sato and Washington criteria as the presence of tumor cells in the vascular space or the presence of erythrocytes or elastic lamina around the tumors.

STATISTICAL ANALYSIS

The results are presented as ranges, averages and standard deviations for the quantitative variables and as absolute frequencies for the qualitative variables. The comparison of averages for the continuous quantitative variables was performed using the parametric t test. According to the comparison between the data regarding patients with versus patients without lymph node metastasis, distal metastases respectively, the difference between proportions was tested using the chi-square test. In order to assess the correlations between tumor grades, staging and grading of tumors and socio-demographic characteristics, the Pearson or Spearman correlation coefficients were used. The statistical analysis was performed using SPSS 23.0, p values lower than 0.05 were considered to be significant.

RESULTS

A number of 171 patients was included in the study, patients with left colon cancer with a mean age of 67.2±10.9 years. 58.5% of the patients included in the study are males, and 72.5% of the come from urban areas. The presence of lymph node and distal metastases does not significantly differ according to the age or sex of the patients, not according to the anatomical location of the primary tumor. However, distal metastases are associated with the residence area of the patients (p=0.048).

The most common histological type seen in patients with left colon cancer is adenocarcinoma, followed by mucinous adenocarcinoma. There are also the tubulovillous adenoma and adenomatous polyps. 31 patients (18.1%) present perineural invasion, while 37 patients (21.6%) present lymphovascular invasion. Lymph node invasion is significantly higher (p=0.049) in patients with tubulovillous adenoma.
DISCUSSIONS

Colon cancers are more frequently present in its distal part (from the splenic flexure to the sigmoid colon) than in its proximal part, and that is why the study of the tumors located at the level of the left colon are of particular importance. In our study, the sigmoid colon (46.2%) represents the most common anatomical location of the tumor, similar to other studies.¹⁵

Most of the patients included in the study are elderly, without any significant differences regarding the age of the patients with lymphatic or distal metastases. A study conducted in 2018 by Murphy and all on a group from 10 European countries states that the advanced age is a good prognostic sign for colorectal cancer.¹⁶ Although in the literature distal colon cancer is more frequently seen among males,¹⁷ in our study there are no significant differences regarding the sex of the patients included in the study. The significantly higher prevalence of distal metastases in rural area patients can be determined by the low addressability and accessibility of these patients to hospitals.

Most studies do not confirm the existence of an association between the histopathological type of the tumor and the presence of lymph node metastases or distal metastases (Table 2). The degree of tumor differentiation differs significantly from a statistical point of view (p=0.002) depending on the histopathological type. All adenomatous polyps are poorly differentiated. The conventional adenocarcinoma is moderately differentiated in 81.8% of the cases and well-differentiated in 13.6% of the cases. Mucinous adenocarcinoma is moderately differentiated in 60% of the cases and strongly differentiated in 40% of the cases (Figure 1).

Table 1. Characteristics of patients

| Patient’s characteristics | All patients (N=171) n (%) | Lymph node metastases (N=119) n (%) | Distal metastases (N=36) n (%) |
|---------------------------|---------------------------|------------------------------------|--------------------------------|
| Age (mean±SD) >70 years-old | 67.2±10.9 76 (44.4) | 68.4±10.5 57 (47.9) | 68.3±11.5 18 (50.0) |
| Sex                       | Male 100 (58.5) Female 71 (41.5) | 73 (61.3) 46 (38.7) | 22 (61.1) 14 (38.8) |
| Residence area            | Urban 124 (72.5) Rural 47 (27.5) | 93 (78.2) 26 (21.8) | 21 (58.3) 15 (41.7) |
| Tumor location            | Splenic flexure 28 (16.4) Descending colon 24 (14.0) Sigmoid colon 79 (46.2) Rectosigmoidian junction 40 (23.4) | 24 (20.2) 12 (10.1) 62 (52.1) 21 (17.6) | 6 (16.7) 5 (13.9) 19 (52.8) 6 (16.6) |

* with versus without lymph node metastases; ** with versus without distal metastases.
does not show any association between the histological type of cancer and the presence of lymphatic and distal metastases, but this study excluded the mucinous and the signet ring adenocarcinoma from the analysis. In our study, the incidence of lymphatic metastases is significantly different depending on the histopathological type of the tumor, the tubulovillous adenoma being more frequently associated with lymphatic metastases. The 3rd stage tumors are present in 65.5% of the patients included in the study, while 19.3% present 4th stage tumors. The increased percentage of patients in advanced stages of the disease can be explained through the symptoms that are not perceived as alarming by the patients at first, so that most of them consult a physician when the emergency intervention becomes necessary, the main complication seen being intestinal occlusion. Because the tumors diagnosed in asympto-

Table 2. Histopathological characteristics and outcome analysis

| Histopathological characteristics | All patients (N=171) n (%) | Lymph node metastases (N=119) n (%) | Distal metastases (N=36) p value |
|----------------------------------|---------------------------|------------------------------------|---------------------------------|
| Histological type               |                           |                                    |                                 |
| Classical adenocarcinoma        | 118 (69.0)                | 88 (73.9)                          | 0.049                           |
| Mucinous adenocarcinoma         | 21 (12.3)                 | 12 (10.1)                          | 4 (11.1)                        |
| Tubulovillous adenoma           | 15 (8.8)                  | 12 (10.1)                          | 3 (8.3)                         |
| Adenomatous polyp               | 12 (7.0)                  | 4 (3.4)                            | 0 (0.0)                         |
| Cribriform adenocarcinoma       | 5 (2.9)                   | 3 (2.5)                            | 0 (0.0)                         |
| Tumor grade                     |                           |                                    |                                 |
| I                                | 4 (2.3)                   | 0 (0.0)                            | <0.001                          |
| II                               | 22 (12.9)                 | 5 (4.2)                            | 0 (0.0)                         |
| III                              | 112 (65.5)                | 81 (68.1)                          | 0 (0.0)                         |
| IV                               | 33 (19.3)                 | 33 (27.7)                          | 36 (100)                        |
| Staging (pT)                    |                           |                                    |                                 |
| T1                               | 3 (1.8)                   | 0 (0.0)                            | 0 (0.0)                         |
| T2                               | 18 (10.5)                 | 9 (7.6)                            | 0 (0.0)                         |
| T3                               | 82 (47.9)                 | 62 (52.1)                          | 16 (44.4)                       |
| T4                               | 68 (39.8)                 | 48 (40.3)                          | 20 (55.6)                       |
| Staging (pN)                    |                           |                                    |                                 |
| N0                               | 28 (16.4)                 | 0 (0.0)                            | 2 (5.6)                         |
| N1                               | 74 (43.3)                 | 73 (61.3)                          | 7 (19.4)                        |
| N2                               | 45 (26.3)                 | 46 (38.7)                          | 22 (61.1)                       |
| Nx                               | 24 (14.0)                 | 0 (0.0)                            | 5 (13.9)                        |
| Staging (M)                      |                           |                                    |                                 |
| M0                               | 123 (71.9)                | 93 (78.2)                          | 0 (0.0)                         |
| M1                               | 36 (21.1)                 | 25 (21.0)                          | 36 (100)                        |
| Mx                               | 12 (7.0)                  | 1 (0.8)                            | 0 (0.0)                         |
| Grading                          |                           |                                    |                                 |
| G1                               | 22 (12.9)                 | 6 (5.1)                            | 0.255                           |
| G2                               | 116 (67.8)                | 88 (73.9)                          | 30 (83.3)                       |
| G3                               | 33 (19.3)                 | 25 (21.0)                          | 6 (16.7)                        |
| Complication                     | 41 (24.0)                 | 40 (33.6)                          | 0.803                           |
| Hospital mortality              | 4 (2.3)                   | 2 (1.7)                            | 0.709                           |

* with versus without lymph node metastases; ** with versus without distal metastases.
mative patients have a significantly better prognosis, it
would be ideal if elderly patients and those with a fa-
mily history of colon cancer underwent some regular
check-ups. The presence of rectalgia is associated with
a good prognosis because it alarms the patient and
determines an early diagnosis and thus, an adequate
treatment in the early stages of the disease.

Regarding the degree of differentiation, 12.9% of
the tumors are poorly differentiated (G1), 67.8% are
moderately differentiated (G2) and 19.3% are well dif-
ferentiated (G3). We noticed lymph node metastases
in 33.3% of the patients with tumors with a G3 degree
of differentiation. Distal metastases were seen in 33.3%
of the tumors with a G1 differentiation degree and in
31.2% of those with a G2 differentiation degree. None
of the patients with a G3 differentiation degree tu-
more presented distant detectable metastases. Although
of these differences was statistically significant,
this thing might result from a too small number of pa-
tients with G1 and G3 differentiation degree tumors.

Ueno and co. used the same cellular pleomorphism
scale to analyze the incidence of lymph node metastases
in patients with colorectal cancer. The study they con-
ducted revealed the presence of lymph node metastases
in 3.7% and 37% of the patients with G1/G2 and G3
differentiation degree, respectively. In 2017, Kamocki
noticed the presence of lymph node metastases in 51%
of the G2 tumors and in 53% of G3 tumors. He also
reported hepatic metastases in 45% of G2 tumors and
33% of G3 tumors.

Because of the low number of poorly differentiated
tumors (G1) and well differentiated tumors (G3), the
results did not reveal statistically significant differences
and the aggressiveness of the tumor could not be deter-
mined depending on the degree of differentiation, nor
the metastatic potential. However, according to most
authors, the G1 tumor differentiation degree is a favo-
rible prognostic factor in cancer patients.

An important part of the patients (69.9%) presents
lymphatic metastases and 21.1% present distal metastas-
tases, thus having an unfavorable prognosis. The exten-
sion to the lymph nodes correlates significantly with
the degree of the tumor extension (p<0.001) and with
the distal extension of the tumor (p=0.014).

Regarding the localization of metastasis, 79.2% of
the 36 patients with metastases present hepatic meta-
stases, 29.1% present peritoneal metastases, 12.5% pul-
monary metastases and 4.2% cerebral metastases. The
distal extension of the tumor correlates with the resi-
dence environment, being more frequent in rural area
patients (p=0.014).

Most of the patients (73%) had a favorable evolu-
tion. None of the 171 patients included in the current
research presented intraoperative complications. The
average hospitalization period was 11.5±6.53 days.

A part of the patients included in the research
(24.0%) presented postoperative complications, while
2.3% of them died. The most common postopera-
tive complications were the infection with E. coli and
Clostridium difficile, followed by hypochromic anemia,
postoperative evisceration, hypokalemia, anastomotic
fistula and wound suppuration. 3.2% of the patients
who underwent surgery needed another re-interven-
tion. The frequency of postoperative complications and
nosocomial deaths are determined by the advanced sta-
ge of the disease (stages 3 and 4), but also by the late
coming of the patients to the emergency room, especi-
ally with intestinal occlusion.

The main limits of the current study are the lack of
data regarding the molecular phenotype of the tumors,
which might have permitted the study of the impact
of molecular profile on the characteristics of left colon
tumors.

The current study is conducted retrospectively in one
center, so the conclusions drawn could be limited to it.
However, the study is well documented and it included
all the patients diagnosed with left colon cancer in the
studied period, the patients being studied homogeno-
usly.

The study of left colon cancer prognosis presents
numerous advantages, the main one being a new re-
search on Romanian patients. The homogeneity of the
data that were the basis of the current study and the
wide range of cases represent an advantage, along with
the evaluation of the histopathological characteristics
according to the international norms and those of a
well-documented study.

**CONCLUSIONS**

The incidence of lymphatic metastases differs ac-
cording to the histopathological type of the tumor, the tu-
bolovillous adenoma being more frequently associated
with lymphatic metastases; distal metastases are more
frequently seen in patients in the rural areas, based
on the low addressability and accessibility to medical
services. The frequency of postoperative complications
and nosocomial death is determined by the advanced
stage of the disease (stages 3 and 4), as well as by the
late arrival of the patient to the emergency room, especially patients with intestinal occlusion.

In conclusion, our research confirms that there are certain differences in the prognosis of left colon cancer according to the histopathological characteristics of the tumor. These differences will have to be taken into consideration especially in the advanced stages of the disease, i.e. stages 3 and 4, associated with high incidence of immediate complication. In addition, the advance stages of left colon cancer are correlated with unfavorable immediate prognostic.

**Compliance with ethics requirements:** The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

**References**

1. World Health Organization. International Agency for Research on Cancer. Romania Fact sheets. Accessed at https://gco.iarc.fr/today/data/factsheets/populations/642-romania-fact-sheets.pdf
2. Thelin C, Sikka S. Epidemiology of colorectal cancer - incidence, lifetime risk factors statistics and temporal trends. In: Ettarh R(ed). Screening for Colorectal Cancer with Colonoscopy. Interch Open. 2015;1-18.
3. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383 (9927):1490-1502.
4. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med 1990;113:779–788.
5. Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer 2002; 101: 403–408.
6. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H; Colon/Rectum Carcinomas (Primary Tumor) Study Group: Comparison of 17,641 patients with right- and leftsided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 2010; 53: 57–64.
7. Price TJ, Beeke C, Ullah S, Padbury R, Maddern G, Roder D, Townsend AR, Moore J, Roy A, Tomita Y, Karapetis C: Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? Cancer 2015; 121: 830–835.
8. Marzouk O, Schofield J. Review of histopathological and molecular prognostic features in colorectal cancer. Cancers (Basel). 2011;3(2):2767-2810.
9. Baran B, Ozupek NM, Tetik NY, Acar E, Bekcioğlu O, Baskın Y. Gastroenterol Res. 2018; 11(4):264-273
10. Washington MK, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. Arch Pathol Lab Med 2009; 133:1539-51.
11. American Joint Committee on Cancer. Colon and rectum. In: AJCC Cancer Staging Manual. 7th ed. New York: AJCC; 2010. pp. 145-66.
12. Hamilton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: FT B, Carneiro F, Hruban R, ND T, eds. WHO classification of tumours of the digestive system. Lyon: International Agency for Research on Cancer; 2010. pp. 134-46.
13. Batsakis JG. Nerves and neurotropic carcinomas. Ann Otol Rhinol Laryngol 1985;94(Pt 1):426-7.
14. Sato T, Ueno H, Mochizuki H, et al. Objective criteria for the grading of venous invasion in colorectal cancer. Am J Surg Pathol 2010; 34:454-62.
15. Kamocki ZK, Wodynska NA, Zurawska JL, Zareba KP. Significance of selected morphological and histopathological parameters of colon tumors as prognostic factors of cancer spread. Turk J Gastroenterol 2017; 28:248-53
16. Murphy N, Ward HA, Jenab M, et al. Heterogeneity of Colorectal Cancer Risk Factors by Anatomical Subsite in 10 European Countries: A Multinational Cohort Study. Clin Gastroenterol Hepatol 2018
17. Carethers JM. Risk factors for colon location of cancer. Transl Gastroenterol Hepatol. 2018; 3:76.
18. Newland RC, Dent OF, Lyttle MN, Chapuis PH, Bokey EL. Pathologic determinants of survival associated with colorectal cancer with lymph node metastases. A multivariate analysis of 579 patients. Cancer 1994; 73: 2076-82.
19. Heys SD, Sherif A, Bagley JS, Brittenden J, Smart C, Eremim O. Prognostic factors and survival of patients aged less than 45 years with colorectal cancer. Br J Surg Pathol 1994; 81: 685-8.
20. Ueno H, Hashiguchi Y, Kajiwara Y, et al. Proposed objective criteria for «grade 3» in early invasive colorectal cancer. Am J Clin Pathol 2010; 134: 312-22.