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Lymphovascular Invasion in the Evolution of Colon Cancer: A Single Center Experience and Analysis of the Specialized Literature

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Rezumat

Invazia limfovasculară în evoluția neoplasmului de colon: experiența unui singur centru și analiza literaturii de specialitate

Introducere: Invazia limfovasculară (LVI) confirmată histopatologic necesită identificarea celulelor tumorale fie în interiorul unui conduct delimitat de endoteliu fie de lamina elastică. Vasele de calibru mic ce nu pot fi încadrate ca limfatice sau venule pot fi identificate drept vase angiolimfatice. Invazia tumorală a vaselor mici nemuscularizate poate fi reprezentată de invazia limfaticelor postcapilare sau a venulelor, ambele variante descrise reprezentând factori de prognostic negativ. Multe studii au evidențiat LVI ca potențial indicator prognostic al evoluției pacientului cu neoplasm de colon, indiferent de stadiul bolii.
Material şi Metodă: S-a realizat un studiu retrospectiv observațional pe o perioadă de 5 ani, desfăşurat în perioada 2015-2019, în cadrul Clinicii de Chirurgie Generală a Spitalului Clinic Colțea din Bucureşti, unde am colectat şi analizat datele pacienților cu diagnosticul de neoplasm de colon.
Rezultate: Au fost decelate 241 cazuri de neoplasm de colon diagnosticate şi operate în cadrul Clinicii de Chirurgie Generală a Spitalului Clinic Colțea din Bucureşti, aflate în faze diferite de evoluție, reprezentate de 116 cazuri (48,13%) pacienți de sex masculin şi 125 cazuri pacienți de sex feminin, reprezentând un procent de 51,86% din totalul lotului studiat.
Concluzii: Cele mai frecvente localizări ale LVI au fost la nivelul ceco-ascendentului şi la nivelul colonului sigmoid, iar gradul

moderat de diferențiere G2 a fost cel mai frecvent întâlnit urmat apoi de adenocarcinomul bine diferențiat G1.

Cuvinte cheie: invazie limfovasculară LVI, cancer de colon, grad de diferențiere tumorală

Abstract

Introduction: Histopathologically confirmed lymphovascular invasion (LVI) requires the identification of tumor cells either within a duct delimited by the endothelium or the elastic lamina. Small-caliber vessels that cannot be classified as lymphatics or venules can be identified as angiolymphatic vessels. Tumor invasion of small non-muscularized vessels can be represented by invasion of postcapillary lymphatics or venules, both variants described as negative prognostic factors. Many studies have established LVI as a potential prognostic indicator for the evolution of the patient with colon cancer, regardless of the stage of the disease.

Material and Method: In the present article,we report a retrospective observational study over a 5-year period, conducted between 2015 and 2019, within the General Surgery Clinic of Colțea Clinical Hospital in Bucharest, where we collected and analyzed data from patients diagnosed with colon cancer.

Results: 241 cases of colon cancer diagnosed and operated on in the General Surgery Clinic of Colțea Clinical Hospital in Bucharest were identified, in different stages of evolution, represented by 116 cases (48.13%) male patients and 125 cases female patients, representing a percentage of 51.86% of the total studied group.

Conclusions: The most frequent localizations of LVI were in the ceco-ascending and sigmoid colon, and the moderate degree of differentiation G2 was the most frequently encountered, followed by well-differentiated adenocarcinoma G1.

Keywords: lymphovascular invasion LVI, colon cancer, degree of tumor differentiation

Introduction

Tumor invasion of peritumoral (locoregional) lymph nodes is undoubtedly one of the most important negative prognostic factors in the evolution of colon cancer (1). Its absence on the resected specimens of a curative surgical intervention can be correlated with a survival prognosis of up to 90% at 5 years, which decreases dramatically if the presence of secondary determinations is confirmed histopathologically in intermediate lymph node stations. Difficult is the invasion of central nodes, an aspect that argues for a possible migration of tumor cells away from the primary tumor (2).

Tumor invasion of small non-muscularized vessels can be represented by the invasion of postcapillary lymphatics or venules, both described variants representing negative prognostic factors (3).

In this material, we report a retrospective observational study over a 5-year period, conducted between 2015-2019, within the General Surgery Clinic of Colțea Clinical Hospital in Bucharest, where we collected and analyzed data from patients diagnosed with colon cancer.

Aim and Objectives

The aim of this study is to identify patients at high risk of unfavorable postoperative outcome due to the presence of lymphovascular invasion and to establish whether there is a correlation between the degree of tumor

differentiation and the presence of lymphovascular invasion, in the study group.

The objectives of the study are to identify patients with lymphovascular invasion, establish the incidence of lymphovascular invasion in the examined group, having as variables sex, tumor location and degree of tumor differentiation.

Material and Method

A retrospective, observational study was conducted within the General Surgery Clinic of Colțea Clinical Hospital during the period 2015-2019. Patients with colon cancer admitted and operated on were included in the study, regardless of the stage and the type of approach practiced, classic open or minimally invasive. In order to collect data, the surgical protocols, clinical observation sheets, histopathological results, as well as all other clinical and paraclinical investigations performed were analyzed.

Adult patients diagnosed histopathologically with colon cancer located from the ileocecal valve to the sigmoid inclusive were included in the study. Patients with incomplete data were excluded from the study, as a limiting variable of the study. The variables used are represented by age, sex, type of surgical approach used, postoperative histopathological result of the resected specimen, tumor stage and degree of tumor differentiation, as well as the presence or absence of lymphovascular invasion.

The agreement of the ethics committee of Coltea Clinical Hospital was previously obtained, before initiating the study.

Results

241 cases of colon cancer diagnosed and operated on in the General Surgery Clinic of Colțea Clinical Hospital in Bucharest were identified, in different stages of evolution, represented by 116 cases (48.13%) male patients and 125 cases female patients, representing a percentage of 51.86% of the total studied group. With nonrepresentative variations depending on the year of study, the distribution of patients by gender was relatively similar, data consistent the specialized literature (4,5).

The age of the patients ranged from 34 to 92 years, with a mean age of 69.14 years and a median age of 70 years (*Table 1*).

Staging of the cases was performed postoperatively according to the pTNM classification proposed by the American Joint Committee on Cancer, edition number 8 (6). The majority of cases were represented by adenocarcinomas in various degrees of differentiation, a small number of cases were represented by other types of tumors (*Table 2*).

Discussion

Lymph node invasion is an important parameter and a negative prognostic factor described and quantified in the latest TNM 8th classification, where the presence of tumor cells at this level signifies at least a tumor stage IIIA (6). Currently, it is considered necessary to evaluate histopathologically at least 12 peri-tumoral lymph nodes on the

Table 1. TNM staging distribution in the study group

TNM	0	I	II A	II B	II C	III A	III B	III C	IV A	IV B	IV C
2015	-	10	17	2	-	3	14	3	4	-	3
2016	-	9	14	2	1	1	5	2	3	-	1
2017	2	8	19	4	-	-	13	2	6	-	2
2018	-	9	15	1	1	-	12	-	6	1	-
2019	-	7	11	3	1	4	7	4	5	1	3
Total	2	43	76	12	3	8	51	11	24	2	9

Table 2. Degree of tumor differentiation distribution in the study group

Degree of tumor differentiation	2015	2016	2017	2018	2019	Total
ADK well differentiated	31	16	16	23	21	107
ADK moderately differentiated	24	19	33	20	22	118
ADK poorly differentiated	2	1	3	2	2	10
Other types *	-	1	4	-	1	6

*Signet ring, mixed adenoneuroendocrine, intramucosal, mucinous

resection specimen in order to accurately determine the presence or absence of secondary lymph node determinations (7,8). Examination of a larger number of lymph nodes allows an adequate tumor staging, thus avoiding diagnostic errors and misleading classification of the case in a less advanced stage. The significant difference in survival rates observed in patients with colorectal cancer diagnosed at an advanced stage (at least stage III), led to the need to subclassify lymph node invasion according to the number of invaded nodes out of the total lymph nodes studied, thus, 1-3 invaded lymph nodes represent N1 (category subdivided into 3 subcategories), the involvement of more than 4 lymph nodes representing the N2 category (category subdivided into 2 sub-categories) (9).

Histopathologically confirmed lymphovascular invasion (LVI) requires the identification of tumor cells either within a duct delimited by the endothelium or the elastic lamina (10). Small-caliber vessels that cannot be classified as lymphatics or venules can be identified as angiolymphatic vessels. Many studies have enlisted LVI as a potential prognostic indicator of the evolution of the patient with colon cancer, regardless of the stage of the disease (11), and the usefulness of LVI is reflected especially in the therapeutic decision regarding adjuvant chemotherapy in patients with stage II cancer to avoid disease progression (12,13).

For colorectal cancer, it is important for the pathologist to specify on the histopathological report the presence or absence of lymphovascular invasion as well as the type of vessel involved (14). For venous invasion, the location of the invasion relative to the structure of the vessel, intramural or extramural, is particularly important with different clinical and prognostic implications (15). Compared to lymphatic invasion, vascular invasion is more frequently associated with recurrence and systemic metastatic disease (16).

We have previously mentioned the need for correct staging and its impact on the evolution of a patient with colon cancer (17). Correct staging can, however, be compromised by the presence of micrometastases not detectable on microscopic examination, which sometimes leads to inadequate therapeutic management, due to the case being classified as having a less advanced tumor stage (18). In practice, microscopically visualized lymph nodes do not show any features suggestive of the presence of secondary tumor determinations, the histopathological diagnosis of the surgical specimen suggesting a "false negative" result.

Micrometastatic lymph node invasion is considered an independent risk factor, difficult to quantify, with a major impact on the evolution of a neoplastic patient, due firstly to the increased risk of distant metastasis through isolated tumor cells not visualized microscopically, and secondly, due to adjuvant oncological treatment inappropriate to the tumor stage (19,20).

Identification of the presence of micrometastases and isolated tumor cells involves significant increases in the costs allocated to the diagnosis and treatment of a neoplastic patient, thus immunohistochemistry and PCR techniques are currently not widely used in routine practice, having elective indications (21). 11 female cases (45.83%) and 13 male cases (54.16%) with lymphovascular invasion (LVI+) were identified on the

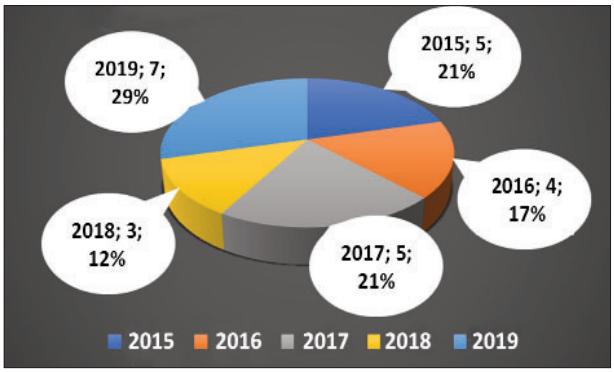

Figure 1. Lymphovascular invasion distribution in the study group

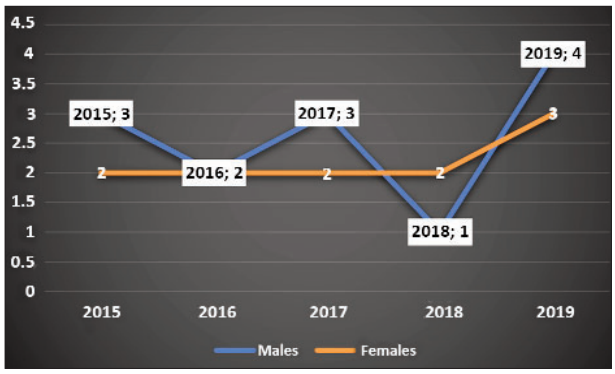

Figure 2. Distribution of LVI by gender in the study group

histopathological reports studied. Their distribution was relatively similar throughout the study (*Figs. 1* , 2) (*Table 3*).

The most frequently detected location of LVI+ cases was in the right colon where 13 cases (54.1%) were identified, followed by the sigmoid colon with 8 cases detected (33.3%). The transverse colon and the left colon were represented by 2 and 1 case of lymphovascular invasion, respectively (*Table 4*).

In the present material, we determined a number of 13 cases, representing 54.1% of the total cases studied, that are identified with moderately differentiated adeno2carcinoma G2, followed by well-differentiated adeno-carcinoma G1 with a total of 6 cases representing 25% (*Table 5*).

Lymphovascular invasion was most frequently identified in stage III B in 25% of all LVI+ cases. In the second place, stages II A, IV A, and IV C were identified in 20.8%. No patients were detected in stages 0, I, II C, III A, and IV B, respectively (*Tables 6,7*).

Table 3. LVI distribution by year and histological differentiation

LVI	ADK well differentiated G1	ADK moderately differentiated G2	ADK poorly differentiated G3	Mixed adenoneuroendocrine
2015	2	3	-	-
2016	1	2	-	1
2017	-	3	-	-
2018	2	1	-	-
2019	1	4	2	-
Total	6 (25%)	13 (54.1%)	2 (8.3%)	1 (4.1%)

Table 4. LVI localization distribution by year of diagnosis in the study group

LVI location	2015	2016	2017	2018	2019	Total
Right colon neoplasm	1	4	2	2	4	13 (54.1%)
Transverse colon neoplasm	-	-	1	-	1	2 (8.3%)
Left colon neoplasm	-	-	1	-	-	1 (4.1%)
Sigmoid colon neoplasm	4	-	1	1	2	8 (33.3%)

Table 5. LVI distribution according to tumoral localization and histological differentiation

LVI+	G1	G2	G3	Mixed adenoneuroendocrine	Total
Right colon neoplasm	3	7	2	1	13 (54.1%)
Transverse colon neoplasm	-	2	-	-	2 (8.3%)
Left colon neoplasm	-	1	-	-	1 (4.1%)
Sigmoid colon neoplasm	3	5	-	-	8 (33.3%)

Table 6. LVI distribution according to TNM classification and year of diagnosis

TNM LVI+	0	I	II A	II B	II C	III A	III B	III C	IV A	IV B	IV C
2015	-	-	1	-	-	-	1	-	1	-	2
2016	-	-	1	1	-	-	2	-	-	-	-
2017	-	-	2	-	-	-	1	1	-	-	1
2018	-	-	1	-	-	-	-	-	2	-	-
2019	-	-	-	-	-	-	2	1	2	-	2
Total	-	-	5 20.8%	1 4.1%	-	-	6 25%	2 8.3%	5 20.8%	-	5 20.8%

Table 7. Percentage of LVI diagnosis according to TNM staging in the study group

TNM	0	I	II A	II B	II C	III A	III B	III C	IV A	IV B	IV C
Total cases	2	43	76	12	3	8	51	11	24	2	9
LVI+	-	-	5	1	-	-	6	2	5	-	2
%	0%	0%	6,5%	8,3%	0%	0%	11,7%	18,1%	20,8%	0%	22,2%

Conclusions

The presented material identified 24 cases of lymphovascular invasion out of a total of 241 cases studied, representing a percentage of 9.95%. The most frequent localizations of LVI were in the ceco-ascending and sigmoid colon, and the moderate degree of differentiation G2 was the most frequently encountered, followed by well-differentiated adenocarcinoma G1. Lymphovascular invasion was identified most frequently in stage III B in a percentage of 25% of all LVI+ cases. Only one patient was identified in stage II B. No patients were detected in stages 0, I, II C, III A and IV B, respectively.

Conflicts of Interests

The authors declared no potential conflicts of interest.

Ethical Statement

This study was approved by the Ethics Committee of Colțea Clinical Hospital.

References

1. Zhang MR, Xie TH, Chi JL, Li Y, Yang L, Yu YY, et al. Prognostic role of the lymph node ratio in node positive colorectal cancer: a meta-analysis. Oncotarget. 2016;7(45):72898-72907.
2. American Cancer Society. American Cancer Society. https://www.cancer.org/cancer/types/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html.
3. Santos C, López-Doriga A, Navarro M, Mateo J, Biondo S, Martínez Villacampa M, et al. Clinicopathological risk factors of Stage II colon cancer: results of a prospective study. Colorectal Dis. 2013;15(4):414-22.
4. Martinez A, Grosclaude P, Lamy S, Delpierre C. Influence of Sex and/or Gender on the Occurrence of Colorectal Cancer in the General Population in Developed Countries: A Scoping Review. Int J Public Health. 2024; 69:1606736.
5. Wu Z, Huang Y, Zhang R, Chuan Z, Fengming Y, Min W, et al. Sex differences in colorectal cancer: with a focus on sex hormone–gut microbiome axis. Cell Commun Signal. 2024; 22(1):167.
6. Weiser MR. AJCC 8th Edition: Colorectal Cancer. Ann Surg Oncol. 2018; 25(6):1454-1455.
7. Compton CC, Greene FL. The staging of colorectal cancer: 2004 and

beyond. CA Cancer J Clin. 2004;54(6):295-308.
8. Hwang J, Lee D, Shin JK, Jang JH, Huh JW, Park YA, et al. Is a cutoff value of 12 still useful in stage II right-sided colon cancer without risk factors? Korean J Clin Oncol. 2022;18(1):27-35.
9. Arrichiello G, Pirozzi M, Facchini BA, Facchini S, Paragliola F, Nacca V, et al. Beyond N staging in colorectal cancer: current approaches and future perspectives. Front Oncol. 2022;12:937114.
10. Zhong JW, Yang SX, Chen RP, Zhou YH, Ye MS, Miao L, et al. Prognostic Value of Lymphovascular Invasion in Patients with Stage III Colorectal Cancer: A Retrospective Study. Med Sci Monit. 2019;25:6043-6050.
11. Harris EI, Lewin DN, Wang HL, Lauwers GY, Srivastava A, Shyr Y, et al. Lymphovascular invasion in colorectal cancer: an interobserver variability study. Am J Surg Pathol. 2008;32(12):1816-21.
12. Yuan H, Dong Q, Zheng B, Hu X, Xu JB, Tu S. Lymphovascular invasion is a high risk factor for stage I/II colorectal cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(28):46565-46579.
13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). NCCN Clinical Practice Guidelines in Oncology. [Interactiv] 7 February 2025. [Citat: 9 2 2025.] https://www.nccn.org/professionals/physician_ gls/pdf/colon.pdf.
14. Zarbaliyev E, Turhan N, Çelik S, Çaglıkülekçi M. Lymphovascular invasion in colorectal cancers: can we predict it preoperatively? Ann Coloproctol. 2024;40(3):245-252.
15. Lymphatic and venous invasion (Core). International Colaboration on Cancer Reporting. [Interactiv] [Citat: 09 02 2025.] https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.iccr-cancer.org%2Fdatasets%2Fdocs%2Ficcr-poly-lvi%2F&psig=AOvVaw3Z9YB-JXAcamsaKhI8G2eC&ust=1739198477456000&source=images&cd=vfe&opi=89978449&ved=0CAQQn5wMahcKEwjYyrTXjbeLAxUAAAAAHQAAAAAQBA.
16. Fujii T, Sutoh T, Morita H, Yajima R, Yamaguchi S, Tsutsumi S, et al. Vascular invasion, but not lymphatic invasion, of the primary tumor is a strong prognostic factor in patients with colorectal cancer. Anticancer Res. 2014;34(6):3147-51.
17. Jestin P, Pţhlman L, Glimelius B, Gunnarsson U. Cancer staging and survival in colon cancer is dependent on the quality of the pathologists' specimen examination. Eur J Cancer. 2005;41(14):2071-8.
18. Yamamoto H. Micrometastasis in lymph nodes of colorectal cancer. Ann Gastroenterol Surg. 2022;6(4):466-473.
19. Park SJ, Lee KY, Kim SY. Clinical significance of lymph node micrometastasis in stage I and II colon cancer. Cancer Res Treat. 2008;40(2):75-80.
20. Chuang WY, Chen CC, Yu WH, Yeh CJ, Chang SH, Ueng SH, et al. Identification of nodal micrometastasis in colorectal cancer using deep learning on annotation-free whole-slide images. Mod Pathol. 2021, (34): 1901–1911.
21. Taliano RJ, LeGolvan M, Resnick MB. Immunohistochemistry of colorectal carcinoma: current practice and evolving applications. Hum Pathol. 2013; 44(2):151-63.