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

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Rezumat

Invazia perineurală în evoluția neoplasmului de colon - experiența unui singur centru și analiza literaturii de specialitate

Introducere: Intens mediatizată în ultimul deceniu, dinamica răspândirii tumorale de-a lungul traiectelor nervoase nu este pe deplin cunoscută, existând numeroase mecanisme moleculare ce intervin şi favorizează invazia perineurală. În prezent, această entitate patologică nu beneficiază de existentă unui tratament specific.
Material şi Metodă: S-a realizat un studiu retrospectiv observațional desfăşurat pe o perioadă de 5 ani. Pe toată durata studiului au fost colectate şi analizate datele pacienților cu neoplasm de colon, internați şi operați în cadrul Clinicii de Chirurgie Generală a Spitalului Clinic Colțea din Bucureşti. Studiul a presupus analiza atentă a protocoalelor operatorii, a foilor de observație clinică, a investigațiilor clinice şi paraclinice efectuate pe parcursul internării în spital şi în special a buletinelor histopatologice ale pieselor de exereză.
Rezultate: Studiul de față a identificat un număr de 34 (14,1%) cazuri cu rezultat histopatologic pozitiv pentru invazie perineurală dintr-un total de 241 de cazuri.
Concluzii: Cele mai frecvente localizări ale neoplasmului PNI pozitiv au fost la nivelul colonului drept şi la nivelul colonului sigmoid având gradele de diferențiere histopatologică G1 (52,9%) respectiv G2 (38,2%). Cele mai multe cazuri au fost identificate în stadiu III B (9 cazuri), acestea reprezentând 26,4% din total lotului PNI pozitiv.

Cuvinte cheie: invazie perineurală (PNI), neoplasm de colon, grad de diferențiere tumorală

Abstract

Introduction: Intensely published in the last decade, the dynamics of tumor spread along nerve pathways is not fully known, there are numerous molecular mechanisms that intervene and favor perineural invasion. Currently, this pathological entity does not benefit from the existence of a specific treatment.

Material and Method: The present material represents a retrospective observational study conducted over a period of 5 years. Throughout the study, data were collected and analyzed on patients with colon cancer, hospitalized and operated on within the General Surgery Clinic of Colțea Clinical Hospital in Bucharest. The study involved careful analysis of surgical protocols, clinical observation sheets, clinical and paraclinical investigations performed during hospitalization and especially the histopathological reports of the resected specimens.

Results: The present study identified 34 (14,1%) cases of perineural invasion out of 241 enrolled patients.

Conclusions: PNI prevalence was highest in histopathological differentiation grades G1 (52.9%) and G2 (38.2%). Most cases were identified in stage III B (9 cases), representing 26.4% of the total positive PNI group.

Keywords: perineural invasion (PNI), colon neoplasm, degree of tumor differentiation

Introduction

Described in the literature since the early 1800s, the perineural dissemination pathway (PNI) has received little attention until recently. Its importance is highlighted in neoplastic processes of the pancreas, colorectal neoplastic processes, prostate, stomach and biliary tract. Its association undoubtedly represents an unfavorable prognostic element, perineural invasion being recognized as a negative prognostic factor independent of other dissemination pathways (1,2). Intensely publishd in the last decade, the dynamics of tumor spread along nerve pathways is not fully known, there are numerous molecular mechanisms that intervene and favor perineural invasion (3). Currently, this pathological entity does not benefit from the existence of a specific treatment.

The present material represents a retrospective observational study carried out over a period of 5 years. Throughout the study, data from patients with colon cancer, hospitalized and operated on at the General Surgery Clinic of Colțea Clinical Hospital in Bucharest, were collected and analyzed.

Aim and Objectives

The aim of this study is to identify patients at high risk of unfavorable postoperative outcome due to the presence of perineural invasion and to establish whether there is a correlation between the degree of tumor differentiation, the tumor localization and the presence of perineural invasion, in the study group. The objectives of the study are to identify patients with perineural invasion, establish the incidence of perineural invasion in the examined group, having as variables sex, tumor location and degree of tumor differentiation.

Material and Method

This material is based on a retrospective,

observational study conducted within the General Surgery Clinic of Colțea Clinical Hospital. It includes all patients admitted, diagnosed, operated on and treated between 2015 and 2019 with colon cancer, regardless of stage and type of approach used, classic open or minimally invasive.

The study involved careful analysis of the surgical protocols, clinical observation sheets, clinical and paraclinical investigations performed during hospitalization and especially the histopathological reports of the resected specimens.

Results

The study includes the analysis of 241 patients with colon cancer at different stages of the neoplastic disease, who underwent surgery at the Surgery Clinic of Colțea Clinical Hospital over a period of 5 years.

Inclusion and Exclusion Criteria

The inclusion criteria in the study were represented by adult patients, a positive histopathological diagnosis for malignancy in patients with colon cancer from the ileocecal valve to the sigmoid level inclusive, and the variables used were represented by age, sex, type of surgical approach used, postoperative histopathological result, tumor stage and degree of tumor differentiation, as well as the presence or absence of lymph node and/or perineural invasion (PNI). The exclusion criteria were represented by patients with incomplete data collection.

The total gender distribution of all cases was represented by 125 female patients representing a percentage of 51.86% and 116 male patients, respectively 48.13%. The gender distribution was relatively similar in the studied group, and the data obtained were comparable with the data found in the specialized literature (4,5).

The age of the patients analyzed in the study ranged from 34 to 92 years. The average age for the entire studied group is 69.14 years, with a median of 70 years (*Table 1*).

Staging of the cases in the study group was performed postoperatively according to the TNM classification proposed by the American Joint Committee on Cancer, 8th edition (pTNM) (6) (*Table 2*).

Discussion

Heavily published in the last decade, perineural invasion is represented by the dynamics of tumor spread along nerve

Table 1. TNM staging distribution by year of diagnosis

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. Tumoral differentiation distribution by year of diagnosis

Tumoral 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
ADK other types*	-	1	4	-	1	6

* Signet ring, mixed adenoneuroendocrine, intramucosal, mucinous

pathways, with numerous molecular mechanisms intervening, favoring its occurrence. Currently, this pathological entity does not yet benefit from the existence of a specific treatment. A more detailed knowledge of the entire process can improve therapeutic management in the treatment of oncological patients, can reduce tumor recurrence and can improve prognosis and survival rate (7).

Understanding the mechanism of perineural invasion requires knowledge of the basic structure of the peripheral nerve sheath and their composition. The sheath is consistent of 3 layers of connective tissue, from the outside to the inside being represented by the epinerve, perinerve and endonerve (8). The epinerve is represented by the structure that connects one or more fascicles into a single nerve. It containes 2 distinct layers: an external layer of areolar connective tissue and an internal layer represented by elastic fibers and collagen fibrils. At the level of the areolar connective tissue of the epinerve, the epineural component of the vasa nervorum and lymphatic channels that do not penetrate the epinerve are located. Akert et al, using electron microscopy, described the organizational structure of the perinerve as a multilamellar structure, formed by concentrically arranged endothelial cells, each cell layer of the perinerve being flanked on each side by a basement membrane (9,10). The endonerve is formed by a matrix arranged individually around the nerve fibers, including Schwann cells and individual axons, the endoneurial blood vessels being relatively impermeable (the blood-neural barrier).

In 1985, the first definition of perineural invasion (PNI) was developed, where Batsakis refers to the invasion of the connective structures that envelop the nerve and considers them to be the structures with the least resistance (11). A less frequent mechanism also mentioned by him is tumor dissemination at the endolymphatic level. Currently, the criteria on the basis of which we can make the diagnosis of perineural invasion refer to the finding of tumor invasion in any of the 3 layers that make up the nerve sheath (12).

Several ways of contact of tumor cells with nerve structures have been described, from simple tangential contact to their circumferential invasion, pathognomonic microscopic aspects easily recognized by the anatomopathologist, if the perineural invasion is distant from the primary tumor and much more difficult if the tumor site is within the primary tumor. In order to make a definitive diagnosis, perineural invasion (PNI) is considered if at least 33% of the nerve circumference is affected by tumor (10), any value less than 33% representing focal tumor infiltration and cannot certify the presence of perineural invasion (13). Multiple theories supporting perineural invasion by migration of tumor cells along lymphatic pathways have been described in the literature, but these have been abandoned, studies demonstrating the lack of lymphatic vessels inside the nerve sheath (14,15).

Colorectal cancer, being among the main causes of cancer mortality worldwide, requires early identification of patients who associate unfavorable prognosis and high risk of relapse. Among the biomarkers currently used, the cost-effective ones stand out: neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, lymphocyte-C-reactive protein ratio, systemic inflammation score, Glasgow prognostic score and nutritional prognostic index (20). Fibrinogen also correlates with negative prognosis in multiple studies, being associated with tumor size, depth of tumor invasion and TNM staging, its increased value preoperatively being in close connection with the risk of distant metastases (21).

In colorectal cancer, an increased rate of locoregional tumor recurrence was found, associated with a negative prognosis at 5 years, in the presence of PNI (7). Studies have reported its presence in almost 33% of cases (22), with histopathologically confirmed metastatic disease in these patients being much more frequent.

Based on the analysis of the studied group, 34 cases (14.1%) of perineural invasion of a total of 241 was detected. Their distribution by the years of study was represented (*Figs. 1, 2*).

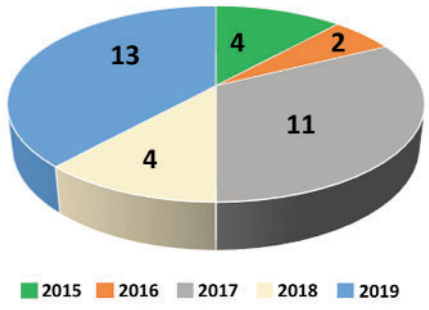

Figure 1. Distribution of PNI cases identified in the study group by year

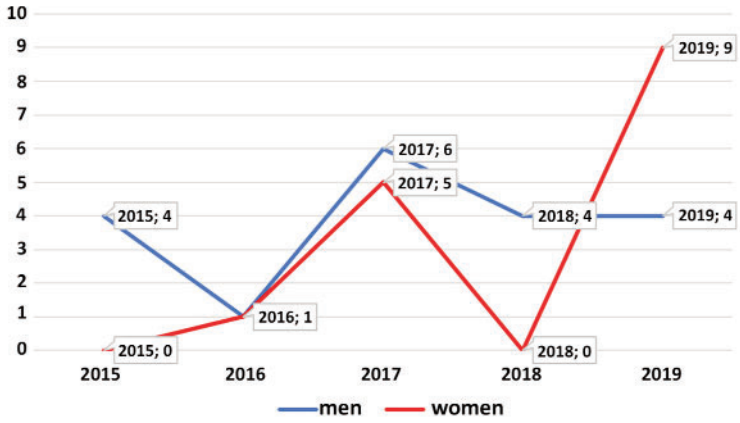

Figure 2. Gender distribution of PNI cases by year of diagnosis

Perineural invasion was more frequently identified in cancer location involving the ascending colon and sigmoid colon. The transverse colon and the left colon are represented by a similar number of cases in the studied group. Similar data have been found in the specialized literature (1,23) (*Table 3*).

Of the total cases with identified perineural invasion, 18 cases (52.9%) were associated with well-differentiated G1 tumors, counter-

Table 3. PNI cases distribution according to tumoral localization and year of diagnosis

PNI location	2015	2016	2017	2018	2019	Total
Right colon neoplasm	2	1	5	1	9	18
Transverse colon neoplasm	-	-	2	-	1	3
Left colon neoplasm	-	-	1	1	1	3
Sigmoid neoplasm	2	1	4	2	3	12

Table 4. PNI cases distribution according to histological differentiation and year of diagnosis

PNI+	ADK well differentiated G1	ADK moderately differentiated G2	ADK poorly differentiated G3
2015	3	-	1
2016	1	1	-
2017	3	8	-
2018	4	-	-
2019	7	4	2
Total	18 (52.9%)	13 (38.2%)	3 (8.8%)

Table 5. PNI cases distribution according to histological differentiation and tumoral localization

PNI+	G1	G2	G3	Total
Right colon neoplasm	8	7	3	18 (52,9%)
Transverse colon neoplasm	1	1	-	2 (5,8%)
Left colon neoplasm	2	1	-	3 (8,8%)
Sigmoid neoplasm	7	4	-	11 (32,3%)

Table 6. PNI cases distribution according to TNM staging and year of diagnosis

TNM PNI+	0	I	II A	II B	II C	III A	III B	III C	IV A	IV B	IV C
2015	-	-	1	-	-	-	1	1	-	-	1
2016	-	-	1	-	-	-	-	-	1	-	-
2017	-	-	-	2	-	-	5	1	1	-	2
2018	-	-	1	-	-	-	2	-	-	1	-
2019	-	1	3	2	1	-	1	1	2	1	1
Total	-	1	6	4	1	-	9	3	4	2	4
		2.9%	17.6%	11.7%	2.9%		26.4%	8.8%	11.7%	5.8%	11.7%

Table 7. PNI cases according to TNM staging distribution

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
PNI+	-	1	6	4	1	-	9	3	4	2	4
%	0%	2.3%	7.8%	33.3%	33.3%	0%	17.6%	27.2%	16.6%	100%	44.4%

Table 8. Patients with PNI and metastatic disease

Patients with PNI and metastatic disease	Liver metastasis	Lung metastasis	Kidney metastasis	Peritoneal carcinomatosis	Total cases per year
2015	-	-	-	1	1 case
2016	1	-	-	-	1 case
2017	1	1	-	3	3 cases
2018	1	-	1	-	1 case
2019	3	1	-	1	4 cases
Total cases by location	6 cases	2 cases	1 case	5 cases	

balanced by the identification of only 3 cases, representing 8.8%, with poorly differentiated histopathological G3 tumors (*Tables 4, 5*).

Also, perineural invasion is predominantly found in patients with colon cancer located in the ceco-ascending and sigmoid colon, respectively, in G1 and G2 degrees of differentiation (*Table 6*).

The distribution of cases with positive perineural invasion in the patients included in the study had a high degree of variability reported to the staging performed using the TNM classification proposed by the AJCC in 2018 (6). Most positive PNI cases were detected in stage III B, representing 26.4% of the total group, followed by stage II A with 17.6%. Stages II B and IV A, respectively IV C, presented a similar percentage of 11.7% (*Table 7*).

During the 5 years of study, 10 cases with distant metastases and perineural invasion were identified. The most frequent location of metastases was the liver, followed by the peritoneal location (*Table 8*).

Conclusions

The most frequent locations of positive PNI cancer were in the right colon and in the sigmoid colon.

PNI prevalence was highest in histopathological differentiation grades G1 (52.9%) and G2 (38.2%). Most cases were identified in stage III B (9 cases), representing 26.4% of the total positive PNI group, followed by stage II A (6 cases) with a percentage of 17.6%.

Both cases detected in stage IV B presented perineural invasion on histopathological examination of the resected tissue, and no PNI positive patient was identified in stages 0 and III A.

One third of PNI positive cases had metastatic disease with most frequent location being represented by the liver, followed by peritoneum.

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.

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