

PREDICTIVE IMPORTANCE OF TUMOR BUDDING, LYMPHOVASCULAR AND PERINEURAL INVASION IN COLORECTAL CARCINOMA

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Colorectal cancers comprise a heterogeneous group of malignant intestinal tumors that have various mechanisms of onset, based on different combinations of genetic and epigenetic alterations. Many authors suggest that the TNM staging most accurately determines the prognosis of each case of colorectal cancer, however other parameters that indicate the aggressive behavior of the tumor are required as well. Such parameters involve perineural invasion, lymphovascular invasion, and tumor budding. The aim of this paper was to examine association between perineural invasion, lymphovascular invasion, and tumor budding with the tumor stage in colorectal cancers. The study included histopathology cases of 142 large bowel cancers removed at the Surgical Clinic in Niš during the period of one year (2016). The tumor stages were determined based on the TNM classification recommended by AJCC. Perineural invasion, lymphovascular invasion, and tumor budding were relatively common finding: 20.4, 40.1, 44.4 percent of examined cases, respectively. Univariate logistic regression analysis revealed a statistically significant correlation between high grade tumor budding, lymphovascular and perineural invasion and the advanced stage of tumor disease. The evaluation method, according to the International Tumor Budding Consensus Conference (ITBCC), should be used to evaluate/define biological aggressiveness of a tumor, and may represent the basis of a routinely used staging system in patients with colorectal cancer.

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Key words: colorectal carcinoma, tumor budding, lymphovascular invasion, perineural invasion

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Introduction

Colorectal cancers are one of the commonest causes of disease and death in the world, especially in developed countries (1, 2). They are more frequent in men than in women, developing after the

age of 50, and more than 70% of carcinomas occur after the age of 60. Colorectal carcinomas account for 70% of all malignancies that occur in the gastrointestinal tract (3). They comprise a heterogeneous group of tumors that may develop based on several alternative genetic pathways, each involving different combinations of genetic and epigenetic changes (4). They are a consequence of chromosomal instability, microsatellite instability, and epigenetic mechanisms, and thereby, different responses to applied therapies. The most common histological type is conventional adenocarcinoma more than 90% originating from epithelial cells of the colorectal mucosa, whereas other histological types are infrequent. Most often they are moderately differentiated more than 70% and localized in the rectum and sigmoid colon. Large bowel cancers infiltrate the intestinal wall and spread onto regional lymph nodes, and most commonly, metastasizing hematogenously to the liver (5). Patients diagnosed with stage I of the disease have a 97% probability of five-year survival, whereas in stages II, III and IV the probability decreases to 78%, 64%, and 11%, respectively (6). Due to great advancements in the application of neoadjuvant immunotherapy, chemotherapy, and surgery, patients have a prolonged relapse-free

period, and permanent remission is achieved in some patients (7–9). In addition to the stage, and histopathology differentiation, there are other prognostic factors that indicate the aggressive behavior of the tumor (10), such characteristics involve tumor budding, lymphovascular invasion and perineural invasion.

Lymphovascular invasion indicates the presence of tumor emboli in lymph and blood vessels. Differentiating venous and lymphatic invasion is important as they have different clinical implications. Presence of lymphatic invasion has been shown to correlate well with lymph node metastasis (11–13), while venous invasion is associated with the potential for visceral metastases occurrence (14, 15).

The most widely used definition of PNI is broad, including invasion of tumor cells in, around and through the nerves. Namely, with the presence of tumor cells within any of the 3 layers of the nerve sheath (epineurium, perineurium and endoneurium) or juxtaposition of tumor foci outside of the nerve with involvement of 33% of the nerve's circumference (16). Some authors report PNI only when tumor cells are observed inside the perineurial layer (17).

Tumor buds signify the presence of individual or smaller groups of cancer cells, less than four cells on the invasive tumor front, and represent an independent indicator of poor prognosis (18–20). It has been observed that in two same-stage cancers, the one with tumor budding will exhibit more aggressive behavior (21). It is thought to be a manifestation of epithelial-mesenchymal transition. This transition is characterized by a serial of cell alterations such as loss of cell adhesion molecules, increased production of extracellular matrix components, cytoskeletal alteration and ability to degrade basement membrane resulting in a phenotype with increased migratory capacity and invasive phenotype (22). Routine reporting is now advocated for extension, outlined by the International Tumor Budding Consensus Conference (ITBCC), with recommendations for the assessment and reporting of tumor budding in colorectal carcinoma (20).

The Aim of the Paper

The aim of the paper was to determine preference and degree of the association between high grade tumor budding, lymphovascular and perineural invasion with tumor stage in colorectal carcinomas.

Materials and Methods

The study included histopathology cases of 142 colorectal cancer patients which were undergoing surgical removal of the tumor at the Surgical Clinic of the Clinical Center Niš during the period of one year (2016). Surgically resected samples of large bowel with the tumor were fixed in aqueous 4% formaldehyde solution (10% formalin solution), and routinely processed to the paraffin blocks. Paraffin sections were stained by hematoxylin and

eosin (HE) method. Data used for this research were obtained from the histopathology report archives of the Pathology Center (Clinical Center Niš), included: anatomic localization of the tumor, tumor size, lymph node status, and metastasis stage (TNM), histological type of tumor, histological grade, presence or absence of peritumoral lymphovascular and perineural invasion. Determination of the disease stage as well as histopathology classification of the tumors were performed on the recommendation of AJCC (American Joint Committee on Cancer) (23). The grading system for colorectal cancer is based on the percentage of cancer gland formation. Well differentiated adenocarcinoma exhibits gland formation in more than 95% of the tumor, moderately differentiated in 50% to 95% of the tumor, and poorly differentiated adenocarcinoma exhibits less than 50% gland formation. Poorly differentiated adenocarcinoma accounts for 5% to 10% of all cases and are associated with a greater incidence of adverse outcome. Tumor buddings defined as single tumor cells or cluster of less than four cells at the invasive front of tumor. The quantification of tumor budding at the invasive front of tumor has been assessed on HE stained slides at magnification $\times 100$, thereby identifying fields with the highest density of tumor budding which are then analyzed at magnification $\times 200$. The specimen with the highest number of tumor budding is considered a hotspot (in a field measuring 0.785 mm^2). A two-tier system was used: low grade (0–9 tumor buds); and high grade (≥ 10).

Statistical Analysis

Interrelationships between tumor location and clinicopathological characteristics were analyzed using Chi square (χ^2) test. The univariate Cox proportional hazards regression using to calculate hazard ratios and 95% confidence intervals. Variables found to be statistically significant ($p < 0.05$). Analyses were performed using SPSS software version 24.

Results

The study consisted of 142 patients aged 67.4 ± 10.0 years, with age ranging from 22 to 88 years. Male subjects were predominant (62.7%), and their number was statistically significantly higher than the number of female subjects ($p < 0.05$) (Table 1).

Colorectal cancers were most commonly localized in the rectum (35.2%), which is statistically a more frequent localization compared to the sigmoid colon and other less represented localizations ($p < 0.001$). The most prevalent histological type conventional adenocarcinoma was present in 116 patients (81.7%) and was statistically far more present than other histological types ($p < 0.001$). The histological grade G2 was reported in 111 patients (78.2%) and was statistically more common than the histological grade G3 ($p < 0.01$). The depth of invasion T3 was present in 96 patients (67.6%) and was statistically more frequent than other depth of

invasion categories individually ($p < 0.001$). Metastases to regional lymph nodes were present in just over half of patients – 72 (50.7%), and compared to the total number of patients they averaged 2.6 ± 4.7 , with very high standard deviation given that the number of metastases to regional lymph nodes

ranged from 0 to 27. Stage III was the most common stage and was reported in 72 patients (50.7%), which was statistically more frequent compared to other stages individually. Clinical and pathological features are shown in Table 2.

Table 1. Demographic characteristics of subjects

Gender	n	%	Range
Female	53	37.3	
Male	89	62.7*	
Age	67.4	± 10.0	(22–88)

* $p < 0.05$

Table 2. Clinicopathological characteristics of the tumours

Localization	n	%
Caecum	22	15.5
Ascending colon	15	10.6
Transverse colon	8	5.6
Descending colon	6	4.2
Sigmoid colon	41	28.9
Rectum	50	35.2 ***
Histological type		
Adenocarcinoma Conventional	116	81.7 ***
Mucinous Adenocarcinoma	21	14.8
Mixed Adenoneuroendocrine carcinoma	2	1.4
Signet ring cell carcinoma	3	2.1
Histological grade		
G2	111	78.2 **
G3	31	21.8
Depth of invasion		
T1	1	0.7
T2	24	16.9
T3	96	67.6 ***
T4a	14	9.9
T4b	7	4.9
Metastases to regional lymph nodes	72	50.7
Average number of metastases to regional lymph nodes ^a	2.6	± 4.7
TNM stage		
I	18	12.7
II	45	31.7
III	72	50.7 ***
IV	7	4.9

** $p < 0.01$, *** $p < 0.001$ (χ^2 test)

Lymphovascular invasion is the presence of single tumor cells or small cluster in a space lined by endothelial cells and/or containing erythrocytes surrounding the tumor cells. Vascular and lymphatic invasion in colorectal cancer (Figure 1 and 2).

Perineural invasion was detected in all neural

components of nerve fascicles, usually in form of single cancer glands, or less often as groups or single cancer cells (Figure 3).

Tumor buds were detected as the presence of single cells or small clusters of cancer cells at the invasive front of a tumor (Figure 4).

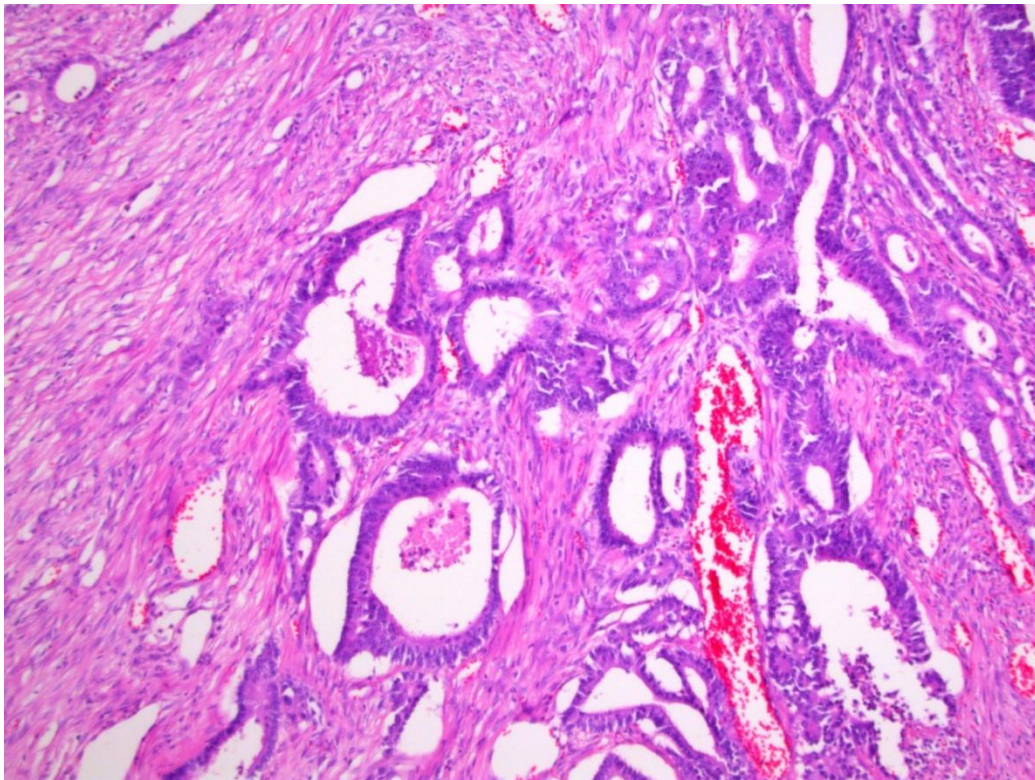


Figure 1. Intravascular invasion. Presence of cancer cell cluster in lumen of small vein. (HE, x200)

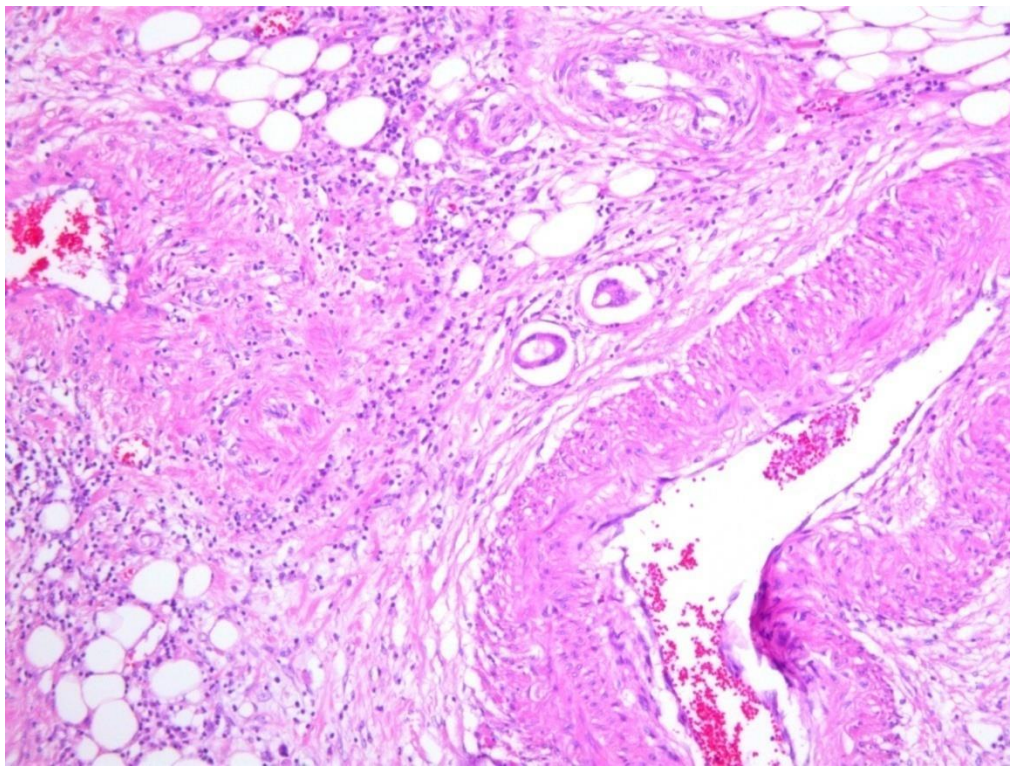


Figure 2. Cancer invasion of lymph vessels. Lumina of small lymphatic vessels occupied with cancer cell clusters. (HE, x200)

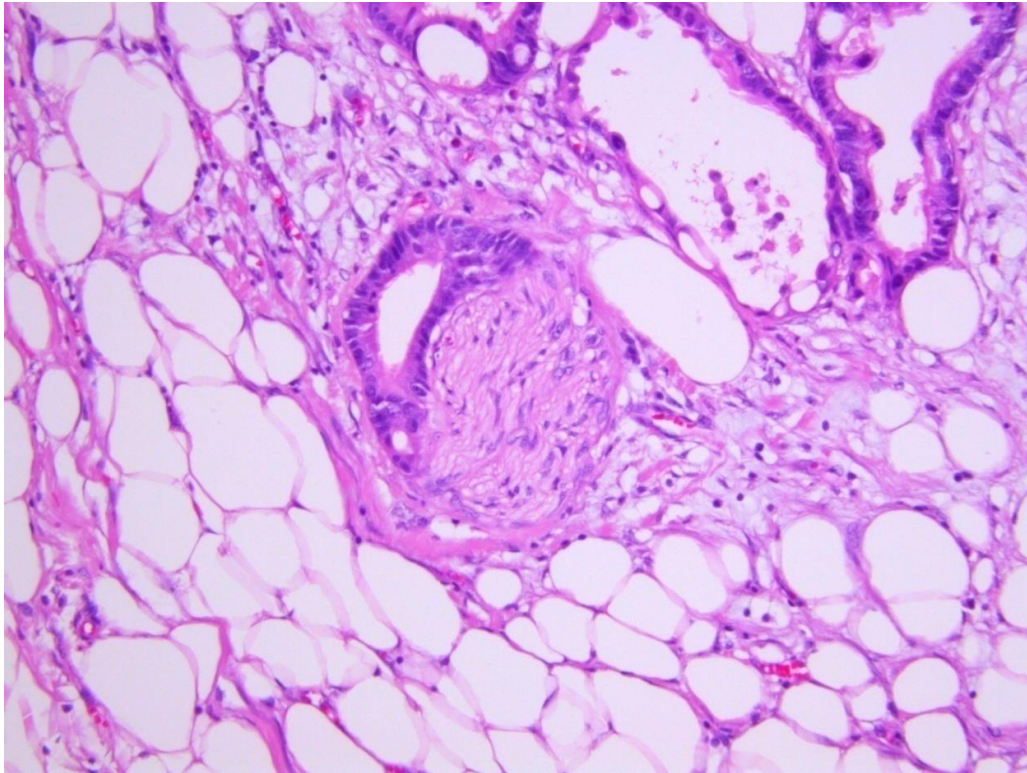


Figure 3. The most usually finding of PN was the juxtapposition of cancer glands to perineurium of nerve fascicles. (HE, x200)

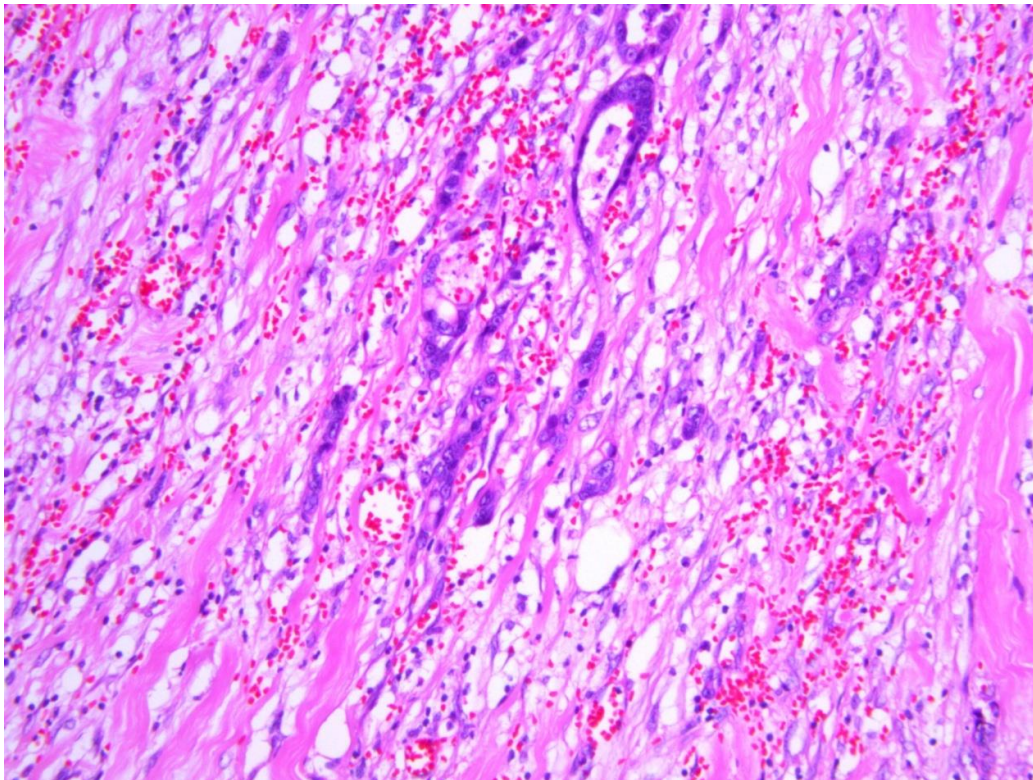


Figure 4. High grade tumor budding. Cancer cell strands, small clusters or single cells, extending from tumor periphery toward inflammatory reactive surrounding. (HE, x200).

Perineural invasion was found in 29 patients (20.4%). It was statistically considerably less common compared to lymphovascular invasion, reported in 57 patients (40.2%), or high grade tumor budding, reported in 63 patients ($p < 0.001$). The presence of lymphovascular invasion, perineural invasion and high grade tumour budding are shown in Table 3.

The univariate logistic regression analysis found that the odds ratio for the presence and absence of lymphovascular invasion showed a 13.8-fold increase in stage III or higher (5.6 to 34.2; $p < 0.001$). The relationship between lymphovascular invasion and TNM advanced stage are shown in Table 4.

The univariate logistic regression analysis found that the odds ratio for the presence and absence of perineural invasion showed a 6.8-fold increase in stage III or higher (2.2 to 20.9; $p < 0.001$). The relationship between perineural invasion and TNM advanced stage are shown in Table 5.

The univariate logistic regression analysis found that the odds ratio for low and high-grade tumor budding showed a 2.3-fold increase in stage III or higher (1.1 to 4.5; $p < 0.05$). The relationship between tumor budding and TNM advanced stage are shown in Table 6.

Table 3. The presence of lymphovascular invasion, perineural invasion, and high grade tumor budding

Lymphovascular invasion	57	40.2%	***
Perineural invasion	29	20.4%	
High grade tumor budding	63	44.4%	***

*** $p < 0.001$ (χ^2 test)

Table 4. The assessment of the stage on the presence of lymphovascular invasion – results of the univariate logistic regression analysis

Factor	OR	Limits 95%		p
		Lower	Upper	
Stage \geq III	13.8	5.6	34.2	< 0.001

Table 5. The assessment of the stage on the presence of perineural invasion – results of the univariate logistic regression analysis

Factor	OR	Limits 95%		p
		Lower	Upper	
Stage \geq III	6.8	2.2	20.9	0.0008

Table 6. The assessment of the stage on the presence of tumor budding – results of the univariate logistic regression analysis

Factor	OR	Limits 95%		p
		Lower	Upper	
Stage \geq III	2.3	1.1	4.5	0.019

Discussion

Colorectal carcinoma is one of the leading health problems in the world (1, 2). It occurs in elderly people after the age of 60 and is more common in men than in women. In our study, the mean age of patients was 67.4 ± 10.0 years, with age ranging from 22 to 88 years. The overall specimen is dominated by male patients (62.7%), who statistically significantly outnumbered female patients ($p < 0.05$). The largest number of these cancers was developed in the wall of the rectum, which is consistent with literature data (3).

Conventional adenocarcinomas were diagnosed in 81.7% of patients, whereas mucinous adenocarcinoma was reported in about 14.8% of patients, which is in accordance with the literature data (24, 25). Mucinous adenocarcinoma is a distinct subtype and is characterized by abundant mucinous components that comprise at least 50% of the tumor volume (26). In our study, 78.2% of colorectal carcinomas were of histology grade G2, and 21.8% of histology grade G3. The largest number of colorectal carcinomas was in stage III and II, 50.7% and 31.7%, respectively, whereas 4.9% of carcinomas were in stage IV. Stage I carcinomas amounted to only 12.7%, indicating that early diagnosis and screening for colorectal carcinoma were inadequate.

Tumor budding has been found to be an independent adverse prognostic factor in CRC and is a strong predictor of lymph node involvement, venous and lymphatic invasion, local recurrence, metastases and poor disease free survival (27), and in addition to lymphovascular and perineural invasion, it is a factor indicating more aggressive tumor behavior (21, 28, 29, 30). It has been observed that in two same-stage carcinomas, the one with tumor budding will exhibit more aggressive behavior (30). After the examination of our research material, high grade tumor budding was found in 63 patients (44.4%). Furthermore, a statistically significant correlation was discovered between high grade tumor budding and higher stages of colorectal carcinoma (31). However, recognition of tumor budding on H&E may occasionally present some challenges because of the presence of reactive stromal cells or histiocytes surrounding the invasive front of tumor and cytokeratin immunostaining can be performed to confirm the impression of tumor buds (32).

Lymphovascular invasion is defined as the presence of single cancer cells or cancer cell clusters within an endothelial lined channel surrounding smooth muscle or elastic lamina (33). The reporting of vascular invasion is highly variable and underreported, due to the interobserver variability (34), with the incidence of venous invasion reported between 11% and 89.5% (15). Lymphovascular invasion is one of the significant factors indicating the biological aggressiveness of tumors (11–13, 33, 35, 36). In our study, lymphovascular invasion was present in 57 patients (40.1%) and showed statistical

significance in relation to the advanced stage of the disease.

Perineural invasion (PNI) is a continuous and multistep process of interaction developing between nerve structures and cancer cells (37, 38). Nerve cells and tumor cells can interact directly or through the opening and closing of the signal transduction pathways and/or the recognition and response of the ligands and receptors. Schwann cells mediate perineural invasion. Dedifferentiated Schwann cells come into direct contact with cancer cells. This direct contact results in the extension of protrusions from the cancer cells. Schwann cells intercalate between cancer cells, thereby promoting cancer dispersal from the tumor and migration toward the neural fascicles. Perineural invasion is an indicator of poor prognosis (39, 40). A recent large meta-analysis has shown that perineural invasion represents an independent prognostic factor and that stage II tumor patients with perineural invasion have poorer survival than stage III tumor patients without perineural invasion (24). PNI is associated with other pathological markers of poor prognosis such as lymphovascular invasion, poor differentiation and tumor budding (41). Our study confirmed perineural invasion in 29 patients (20.4%) and a statistically significant association with higher stages of the disease (16, 42).

Authors suggest that the TNM staging most accurately determines the prognosis of colorectal carcinoma (43), we find that additional diagnostic parameters, such as tumor budding, lymphovascular and perineural invasion are in strong correlation with advanced tumor stages. Tumor budding should be included in routine diagnostics, for a more accurate therapy and better patient follow-up.

Conclusion

In evaluated histopathology cases of colorectal cancers, lymphovascular invasion and tumor budding were statistically significantly often findings, than perineural invasion. The univariate logistic regression analysis revealed a statistically significant correlation between tumor budding, lymphovascular and perineural invasion and higher tumor stages in colorectal carcinoma. The ITBCC evaluation method should be used to assess tumor budding and may form the basis of a new staging system in patient with colorectal cancer.

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Conflict of Interests

The authors declare that they have no conflict of interests.

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doi:10.5633/amm.2020.0204**PREDIKTIVNI ZNAČAJ TUMORSKOG PUPLJENJA, LIMFOVASKULARNE I PERINEURALNE INVAZIJE KOD KOLOREKTALNOG KARCINOMA***Tijana Denčić^{1,5}, Maja Jovičić-Milentijević^{1,5}, Aleksandar Petrović², Goran Radenković², Marko Jović², Sonja Šalinger-Martinović^{3,6}, Simona Stojanović⁴*¹Univerzitet u Nišu, Medicinski fakultet, Katedra za patologiju, Niš, Srbija²Univerzitet u Nišu, Medicinski fakultet, Katedra za histologiju i embriologiju, Niš, Srbija³Univerzitet u Nišu, Medicinski fakultet, Katedra za internu medicinu i zdravstvenu negu, Niš, Srbija⁴Univerzitet u Nišu, Medicinski fakultet, Katedra za oralnu hirurgiju, Niš, Srbija⁵Klinički centar Niš, Centar za patologiju i patološku anatomiju, Niš, Srbija⁶Klinički centar Niš, Klinika za kardiovaskularne bolesti, Niš, Srbija*Kontakt:* Tijana V. Denčić

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Kolorektalni karcinomi predstavljaju jedan od čestih uzroka oboljevanja i smrtnog ishoda u svetu. Na globalnom nivou, nalazi se na šestom mestu kod muškaraca i na četvrtom mestu kod žena. Kolorektalni karcinomi predstavljaju heterogenu grupu tumora, koji mogu da nastanu na osnovu nekoliko alternativnih genetskih puteva, od kojih svaki uključuje različite kombinacije genetskih i epigenetskih promena. Mnogi autori navode to da TNM stadijum najpreciznije određuje prognozu kolorektalnog karcinoma, međutim, potrebni su i drugi parametri. Osim TNM stadijuma, postoje i drugi prognostički faktori koji ukazuju na agresivno ponašanje tumora. Takvi parametri su limfovaskularna invazija, perineuralna invazija i tumorsko pupljenje. Obrađena su 142 bolesnika sa kolorektalnim karcinomom, koja su operisana na Hirurškoj klinici u Nišu. Cilj rada je da se utvrdi da li postoji povezanost tumorskog pupljenja, limfovaskularne invazije i perineuralne invazije, u odnosu na stadijum tumorske bolesti kod kolorektalnih karcinoma. Stadijum tumorske bolesti određen je na osnovu TNM klasifikacije preporučene od strane WHO i AJCC. U ovom radu, univarijantnom logističkom regresionom analizom, nađena je statistički značajna povezanost tumorskog pupljenja, limfovaskularne i perineuralne invazije sa uznapredovalim stadijumom tumorske bolesti.

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