Preliminary study of correlations between the intratumoral microvessel density and the morphological profile of colorectal carcinoma

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Abstract

Aim: New blood vessel formation (angiogenesis) is a fundamental event in the process of tumor growth and metastatic dissemination. The aim was to evaluate intratumoral vascular density (ITMVD) and to analyze possible correlations between ITMVD and the morphological profile of colorectal carcinoma. Materials and Methods: The studied group consisted of 50 patients that underwent surgery for colorectal tumors, 12 of them receiving preoperative radiotherapy. The analyzed morphological parameters were tumor site, tumor gross aspect, tumor grading, local invasion (pT), regional invasion (pN), distant metastases (pM) and intratumoral microvessel density (ITMVD) expressed as number of capillaries/mm². The malignant tissue samples were included in paraffin blocks and serial tissue sections were cut both for Hematoxylin–Eosin staining and CD34 immunomarking. For each case, five consecutive fields without necrosis were randomly selected with ×10 objective. Quantitative measurements were performed using special software for image analysis. Results: For non-irradiated colorectal tumors, ITMVD was the highest in rectal localization, in infiltrative tumors, in circumferential tumors, in tumors with low longitudinal extension, in moderately differentiated (G2) tumors and in pT4, pN0 and pM1 tumors. Discussion: Correlations showed different trends of ITMVD depending on each parameter. ITMVD was higher when the tumor was closer to the rectum, when it was more infiltrative, more circumferential or with low longitudinal diameter. These trends might be exploited in defining future anti-angiogenic therapeutic strategies. Conclusions: There were some interesting correlations between ITMVD and studied morphological parameters that have to be validated on larger series of cases.

Keywords: colorectal cancer, microvessel density, ITMVD, CD34, angiogenesis, morphological.

Introduction

Colorectal cancer (CRC) is the third prevalent cancer in adults and it is a worldwide health problem [1]. Tumors stimulate the growth of host blood vessels, a process called angiogenesis, which is essential for supplying nutrients for the tumor [2, 3].

Angiogenesis plays an important role in tumor growth and dissemination. Therefore, it has become a new target for oncological therapy [4, 5]. Angiogenesis is evaluated using blood microvessel density (MVD), which is supposed to be predictive for chemotherapy response and to be a significant prognosticator of overall survival in CRC patients [6–8].

The assessment of blood microvessel network in colorectal cancer is controversial in the literature, possibly due to different staining protocols and variations in the methods of analysis as they are described by an important number of articles [6, 9, 10]. In most studies, intratumoral microvessel density (ITMVD) was determined using anti-CD34 immunohistochemical staining [11–15].

The CD34 antigen is a single chain transmembrane glycoprotein with a molecular weight of 110 kD. The CD34 protein is selectively expressed on human lymphoid and myeloid hematopoietic progenitor cells. The CD34 antigen is also expressed on vascular endothelium.

Our study aims to present a protocol that offers a good quantitative evaluation of ITMVD on paraffin embedded specimens and to evaluate if there are any correlations between the ITMVD and the morphological profile of colorectal carcinoma.

Materials and Methods

The study was designed prospectively. We used a total of 50 tissue samples from patients with colorectal adenocarcinomas that underwent surgery at IInd Surgery Clinic, Emergency County Hospital, Craiova, Romania.
from May 2014 to October 2014. All patients were informed about their participation in this study and a written consent was provided by every patient.

Therapeutic approach is quite different for colon carcinoma localization than for rectal localization, meaning colon cancer needs surgery and chemotherapy, without radiotherapy, while for rectal cancer radiotherapy is used as neoadjuvant or adjuvant therapy, together with surgery and chemotherapy.

Therefore, it is clear why we created the following three subgroups of patients:

- 25 patients with colon carcinoma (CC);
- 13 patients with rectal carcinoma that did not receive preoperative radiotherapy (RC-NR);
- 12 patients with rectal carcinoma that benefited from radiotherapy before the surgery (RC-R).

From all surgical specimens, the tissue samples were carefully taken, in such way to contain all layers of the colon or rectum and to include both tumor and normal adjacent tissue.

The samples were processed using the classical histopathological technique (fixation in 10% buffered formalin and embedding in paraffin). Paired, 3 µm thick serial sections were cut from each paraffin block.

From each pair, the first section was stained with Hematoxylin–Eosin (HE), for diagnosis orientation and was revised for the type, grade, and stage (according to pTNM staging system, AJCC-2010).

The second section was placed on SuperFrost slides and immunomarked with monoclonal anti-CD34 antibody (Novocastra Lyophilized Mouse Monoclonal Antibody Endothelial Cell Marker – CD34, dilution 1:70) after previous application of three-stage indirect Steptavidin–Biotin Complex (SaBC)/Horseradish peroxidase (HRP) method. DAB chromogen and Hematoxylin counterstaining were used for visualization of intratumoral vascular structures.

Tissue slides were analyzed using an Olympus CX 31 microscope equipped with a ColorView II camera and AnalySis Pro 5.0 software calibrated for this microscope.

For the assessment of intratumoral vascular density (ITMVD), for each case, five consecutive fields without necrosis were randomly selected with ×10 objective. Quantitative morphometric measurements were performed using the “Measurements” module of the Analysis Pro 5.0 software and mean value of ITMVD was calculated and expressed as number of capillaries/mm² for each case.

The purpose of this paper is to evaluate any possible statistical correlation between ITMVD and the different colon, hepatic flexure and transverse colon); creating defined subgroups.

Data, both numeric and non-numeric, to be filtered by statistical analysis.

Statistical data analysis was done with the help of Kruskal–Wallis correlation test from XLSTAT version 3.02 (p<0.05 indicating statistical significance).

Results

Clinical profile

Gender

Male patients prevailed over female patients in all study groups (31 males and 19 females), and also in subgroups. The number of men was even twice the number of women in RC-R group and was decreasing in percentage in CC group, being almost equal to women in RC-NR group (Figure 1).

Age

Age was ranging from 45 to 85-year-old in study group. For each of the three subgroups, most patients were over 60-year-old (over 80% of patients in RC-R and RC-NR subgroups and respectively over 70% of patients in CC subgroup). More than 50% of the patients with rectal cancer, irradiated and non-irradiated (RC-R and RC-NR), were included in the interval 60–69-year-old, while for the ones diagnosed with colon cancer (CC) more than 50% of patients were over 70-year-old (Figure 2).

Morphological profile

Tumor gross aspect

A common characteristic of tumor gross aspect for each of the three subgroups of patients was the fact that vegetant and ulcerated aspect (VU) were the most frequent...
ones (almost 50% in RC-NR subgroup, almost 60% in RC-R subgroup and almost 70% in CC subgroup) (Figure 3c). Also, pure infiltrative (I) (Figure 3d) and pure vegetant (V) (cauliflower-like) (Figure 3a) tumor aspects had an inverse proportionally distribution in the three subgroups: RC-R subgroup had no pure infiltrative aspect and three pure vegetant ones, while CC subgroup had five pure infiltrative aspects and only one cauliflower-like tumor (Figures 3 and 4).

**Tumor dimensions**

According to tumor longitudinal diameter (Figure 6a), there were some differences in patients’ distribution. Most patients with rectal cancer (both RC-R and RC-NR) had low tumor longitudinal diameter (I class), of up to 5 cm, whereas most colon tumors (CC) had a medium tumor longitudinal diameter (II class) from 5 to 8 cm. The third class (III), tumors with longitudinal diameter of over 8 cm, had a weak representation in all subgroups (Figure 5).

Tumor transverse diameter (Figure 6b) distribution pointed out some interesting characteristics, which may result from different preoperative therapeutic approach. In RC-R subgroup, most patients had low tumor transverse diameter (I – SC class) (Figure 6c) and few patients had circumferential tumors (III – C class) (Figure 6d). This distribution may be explained by the preoperative radio-therapeutic shrinkage effect upon tumor volume, which made possible bowel transit, thus permitting to postpone surgery [as 75% of RC-R cases were non-circumferential (I – SC and II – >SC classes)]. On the contrary, for RC-NR and CC subgroups, most patients (2/3 of them) had circumferential tumors (III – C class) (Figure 6d). This fact had an impact on bowel transit and that was the reason (in many cases) why surgery was performed as the first therapeutic step, as intestinal occlusion or subocclusion occurred (Figure 7).
Figure 4 – Tumor gross aspect distribution in study subgroups.

Figure 5 – Tumor longitudinal diameter distribution in study subgroups.

Figure 6 – Tumor diameters: (a) Tumor longitudinal diameter measurement; (b) Tumor transverse diameter measurement; (c) Semi-circumferential tumor; (d) Circumferential tumor.

Figure 7 – Tumor transverse diameter distribution in study subgroups.

Figure 8 – Tumor grading distribution in study subgroups.
**Tumor grading**

Regarding tumor-grading distribution, there were some specific features. On one hand, moderately (G2) differentiated tumors (Figure 9b) prevailed, representing over 50% in each study subgroup. On the other hand, well (G1) differentiated tumors (Figure 9a) were under-represented in rectal cancer, whereas in colon cancer they occupied the second place with almost 30%.

Poorly (G3) differentiated rectal tumors (Figure 9c) were very close to G2 ones, with nearly 40% (Figure 8).

**Tumor staging (pT)**

RC-R subgroup included the only two cases with pT1 stage (Figure 10a) in all study groups and only one case of pT4 stage. Thus, it was obvious the beneficial influence of preoperative neoadjuvant radiotherapy with its downsizing capacity for rectal tumors (pT1 and pT2 represented over 40% in RC-R subgroup).

Tumors with pT3 stage (Figure 10c) were most frequent in RC-R and CC subgroups, whereas in RC-NR subgroup pT2 tumors (Figure 10b) represented the majority (Figure 11).

**Lymph node invasion (pN)**

There was a similarity in the distribution of lymph node invasion (Figure 13) in all subgroups, meaning most cases had pN0 stage, followed by pN1 and respectively by pN2 stages. However, we must admit that those figures cannot represent a statistical analysis base, since a lot of specimens had just a few lymph nodes examined, significantly affecting the correct pN staging (Figure 11).

**Distant metastases (M)**

Most patients (78%) had no metastases in the moment of surgery (Figure 14). The only case with metastases in RC-R subgroup was considered an intraoperative discovery, as previous imagistic investigations showed no distant invasion.
Intratumoral microvessel density

It was remarked a decreasing trend of the mean value (AV) of ITMVD in the following order: RC-NR, CC and RC-R, with mean values of 80.54, 72.28 and respectively 69.29 microvessels/mm² of tumor.

The ITMVD values dispersion varied within wide ranges and had almost the same patterns of distribution in the three subgroups. For each of them, the interval comprising the majority of ITMVD values had almost the same size, due to close standard deviations (STDEV).

The intervals comprising most ITMVD values for both rectal cancer subgroups (RC-NR and RC-R) were placed in the middle of the whole range of values, as AV was almost equal with HRV (half range value).

However, for colon tumors, the interval comprising the majority of ITMVD values was displaced towards the lower limit of the range because of an AV value smaller than the corresponding HRV (Figure 15).

Correlations ITMVD – tumor morphological parameters

ITMVD – tumor site

Tumors on the right colon (I – RC) had the lowest mean value (AV) of ITMVD (68.81 microvessels/mm² of tumor) and rectal or recto-sigmoid junction tumors (III – R/RS) had the highest AV (80.54 microvessels/mm² of tumor). The standard deviation of ITMVD for tumors on the left colon (II – LC) was higher than the standard deviations of the other two localizations by almost 10 microvessels/mm² of tumor, meaning most of ITMVD values for left colon tumors were included in a higher segment of distribution. The whole range of values had no significant differences between the three subgroups. The intervals comprising the majority of values were extended around an AV, which was smaller than the corresponding HRV for both colon tumor localizations, thus displacing these intervals towards the inferior limit of the range. On the contrary, rectal tumors (III – R/RS) had a symmetrical distribution of ITMVD values around HRV, as AV and HRV were almost equal (Figure 17a).

ITMVD – tumor gross aspect

There was a decreasing trend of the mean value (AV) of ITMVD from the pure infiltrative tumor aspect (I) to the pure vegetant (cauliflower like) tumor aspect (V), passing through intermediate values for mixed tumor aspects (UI and VU). The STDEV of ITMVD values was
also decreasing in the same range, from near 40 microvessels/mm² of tumor for pure infiltrative tumors to 13 microvessels/mm² of tumor for pure vegetant tumors, therefore the intervals comprising the majority of ITMVD values became smaller and smaller in the following sequence of tumor gross aspect: infiltrative (I) – ulceroinfiltrative (UI) – vegetant and ulcerated (VU) – vegetant (V). AV was almost equal to HRV for three tumor gross aspects: I, UI and V, thus the intervals comprising most ITMVD values were close to the middle of the whole range of values, in opposition to VU tumor aspect, which had an AV smaller than HRV, dislocating beneath this interval. For V tumor gross aspect, both the whole range of values and the interval comprising the majority of ITMVD values were smaller, the latter due to a smaller STDEV, and AV almost equaled HRV, thus defining a more compact group (Figure 17b).

**ITMVD – tumor longitudinal diameter**

The mean values (AV) of ITMVD were decreasing with the length of the tumor, having a relation of inverse proportionality between them. The longer the tumor, the smaller the mean value of ITMVD: for I class (shortest tumors – less than 5 cm) the mean value is 84.97 microvessels/mm² of tumor, for II class (medium tumors – from 5 to 8 cm) – 70.86 microvessels/mm² of tumor, respectively for III class (longest tumors – more than 8 cm) – 63.62 microvessels/mm² of tumor. Another important remark was the fact that STDEV of ITMVD values for tumors with longitudinal diameter less than 5 cm (I class) almost equaled the ones for tumors having 5 to 8 cm (II class) and each of them was almost three times higher than STDEV for tumors with longitudinal diameter more than 8 cm (III class). Therefore, the interval comprising the majority of ITMVD values for longest tumors was three times smaller than the same interval for shortest and medium tumors (the latter ones being almost equal) and together with the whole range of ITMVD values, which was also smaller, defined III class as a more compact group. For I and II classes, the intervals comprising the majority of ITMVD values were displaced towards the lower limit of the ranges because of an AV smaller than the corresponding HRV (Figure 17c).

**ITMVD – tumor transversal diameter**

As opposed to the former distribution of ITMVD mean values depending on tumor longitudinal diameter, there was a relation of direct proportionality between tumor transverse diameter and ITMVD mean values (AV), with an increasing trend: tumors less than semi-circumferential (I – SC) have a mean value for ITMVD of 68.04 microvessels/mm² of tumor, tumors between semi-circumferential and almost circumferential (II – >SC) – 71.35 microvessels/mm² of tumor and circumferential tumors (III – C) – 77.85 microvessels/mm² of tumor. Therefore, the larger the tumor transverse diameter, the higher the density of microvessels/mm² of tumor. The intervals comprising the majority of ITMVD values enlarged in the following order: II – >SC, I – SC and respectively III – C, due to a similar increasing trend of STDEV in the same range. For each class, this interval comprising most ITMVD values was a little displaced towards the lower limit of the range because of an AV smaller than the corresponding HRV (Figure 17d).

**ITMVD – tumor grading**

The highest AV of ITMVD values was registered for moderately differentiated (G2) tumors (79.51 microvessels/mm² of tumor) and the lowest AV for pure vegetant tumors (71.35 microvessels/mm² of tumor), AV for well differentiated (G1) tumors having an intermediate value (74.09 microvessels/mm² of tumor). STDEV was almost two times smaller for G1 tumors than for the other two tumor grading types. Therefore, the interval comprising the majority of ITMVD values for G1 tumors was almost two times smaller than the same interval for G2 and G3 tumors (the latter ones being almost equal) and all these intervals were displaced towards the lower limit of the range because of an AV smaller than the corresponding HRV for each tumor grading type. For well differentiated (G1) tumors, the whole range of values and the interval comprising most ITMVD values were smaller, thus defining this class as a more compact group (Figure 18a).

**ITMVD – local invasion (pT)**

There was an increasing trend of AV from pT2 to pT4 tumors, pT3 tumors having an intermediate value: (71.05 – 76.62 – 77.47 microvessels/mm² of tumor). STDEV was quite similar for pT3 and pT4 stages, but smaller than STDEV for pT2 stage, thus the interval comprising the majority of ITMVD values for pT2 tumors was larger than the same interval for pT3 and pT4 tumors (the latter ones being almost equal). AV almost equaled HRV for pT3 stage, thus the interval comprising most ITMVD values was close to the middle of the whole range of values, in opposition to the other two stages (pT2 and pT4) which had AV smaller than HRV, dislocating beneath these intervals (Figure 18b).

**ITMVD – regional invasion (pN)**

Tumors with no lymph node (regional) invasion (pN0 stage) had the highest AV for ITMVD values: 81.9 microvessels/mm² of tumor. Tumors with metastases in 1–3 regional lymph nodes (pN1 stage) had the lowest AV for ITMVD values: 64.51 microvessels/mm² of tumor, while tumors with metastases in four or more lymph nodes (pN2 stage) had an intermediate value for AV: 67.87 microvessels/mm² of tumor. The interval comprising the majority of ITMVD values for pN0 tumors was almost two times larger than the same interval for pN1 and pN2 tumors (the latter ones being almost equal), due to the fact that STDEV for pN0 stage was also double compared to the other corresponding ones. For pN1 and pN2 tumors, the whole range of values and the interval comprising most ITMVD values were smaller, thus defining these stages as more compact groups, in contrast to the dispersion of ITMVD values for pN0 tumors, which varied within wide ranges (Figure 18c).

**ITMVD – distant metastases (pM)**

Tumors with distant metastases (pM1 stage) had a higher AV of ITMVD values than tumors with no
metastases (pM0 stage): 78.4 compared to 73.93 microvessels/mm² of tumor. There were no important differences between the widths of the intervals that comprise the majority of ITMVD values for both tumor stages, as STDEV were almost equal. Also, a common characteristic was the fact that these intervals are displaced towards the lower limit of the range because of an AV smaller than the corresponding HRV for each class (Figure 18d).

Kruskal–Wallis test was used for statistical evaluation of ITMVD depending on each of the eight studied parameters, p-values being the following (Table 1).

Table 1 – P-values using Kruskal–Wallis test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor site</td>
<td>0.56 (&gt;0.05)</td>
</tr>
<tr>
<td>Tumor gross aspect</td>
<td>0.27 (&gt;0.05)</td>
</tr>
<tr>
<td>Longitudinal diameter</td>
<td>0.42 (&gt;0.05)</td>
</tr>
<tr>
<td>Transverse diameter</td>
<td>0.88 (&gt;0.05)</td>
</tr>
<tr>
<td>Grading</td>
<td>0.41 (&gt;0.05)</td>
</tr>
<tr>
<td>pT</td>
<td>0.29 (&gt;0.05)</td>
</tr>
<tr>
<td>pN</td>
<td>0.17 (&gt;0.05)</td>
</tr>
<tr>
<td>pM</td>
<td>0.67 (&gt;0.05)</td>
</tr>
</tbody>
</table>

**Figure 16** – Variability of intratumoral microvascular density – low level in a poorly differentiated tumor (a) and high level in a moderately differentiated colon adenocarcinoma (b). CD34 immunomarking, ×200.

**Figure 17** – ITMVD distribution depending on macroscopic morphological characteristics of tumors.


**Discussion**

Analyzing clinical and morphological profile of studied colorectal tumors, it can be imagined a specific pattern (which is statistically most frequent) for each of the three subgroups. Therefore, patients with colon cancer were most likely to be males over 70-year-old, with vegetant and ulcerated (VU) tumor aspect, medium longitudinal diameter (5–8 cm) and circumferential tumor, having moderately differentiation (G2), pT3N0M0 stage and medium intratumoral microvessel density (ITMVD). Concerning rectal tumors, there were some common characteristics in patients profiling with colon tumors, meaning: patients were also men, with VU tumor gross aspect, G2 grading and pN0M0 stage. The differences consisted in the fact that most patients with rectal tumors were 60 to 69-year-old and tumors had short longitudinal diameter (<5 cm). Most tumors that received neoadjuvant radiotherapy had low transverse diameter (under semi-circumferential), pT3 stage and the lowest ITMVD of the three subgroups of patients, while non-irradiated rectal tumors were most likely to be circumferential, with pT2 stage and with the highest ITMVD.

Concerning tumor site, it can be remarked that the closer to the rectum the tumor is, the higher ITMVD is. This result is not statistically significant (Table 1), being concordant to former studies that found no correlation between ITMVD and tumor site [16].

Analyzing distribution of ITMVD depending on tumor gross aspect, an interesting trend can be observed: the more infiltrative a tumor is, the higher ITMVD it has; in opposition, the more vegetant a tumor is, the lower ITMVD it has. Although this observation did not reach statistical significance (Table 1), it would be interesting to investigate this trend in future study, as literature found no relation between tumor gross aspect and ITMVD [16].

In our paper, tumor size is evaluated by longitudinal and transverse diameters, each of the two parameters having a different relation with ITMVD, which was not statistically validated (Table 1): the higher the longitudinal diameter, the lower the ITMVD, unlike the higher the transverse diameter, the higher the ITMVD. Some papers argue the relation between tumor size and ITMVD [16], others disaffirm any correlation [17].

Our preliminary study points out that moderately differentiated (G2) tumors have a higher ITMVD than the others, but this remark needs to be further investigated, as it has no statistical significance (Table 1). Literature has recorded significant correlation between tumor grading and ITMVD [16, 18, 19], some claiming that poorly differentiated tumors have the highest ITMVD [17], others that moderately and poorly differentiated ones have most microvessels [20].

By far, the most investigated correlation in published studies is the one between ITMVD and tumor stage [including local invasion (pT), regional invasion (pN) and distant metastases (pM)] as these results may be used in future anti-angiogenic therapeutic approaches. The number of microvessels increases with the degree of local invasion (pT) in a directly proportional relation, meaning pT4 tumors (that infiltrates other organs) have...
the highest ITMVD. Another remark, also sustained by former papers [16, 19, 21–25], is about the correlation between ITMVD on one hand and lymph node invasion and ability to produce metastasis on the other hand. Tumors with no lymph node infiltration and with at least one distant metastasis had, in our study, the highest ITMVD, matching the results from other studies [26]. It seems that ITMVD can describe the affinity of tumors for lymphatic versus venous metastases but the data should be correlated with the number of resected and examined lymph nodes. In that respect, a promising parameter seems to be log odds ratio – LODDS = log [(harvested nodes - invaded nodes + 0.5) / (invaded nodes - harvest nodes + 0.5)] –, which was reported to better predict the presence of lymph node metastases [27].

Our study lacks correlation between ITMVD and recurrences and survival because the interval of study was too short (for evaluating survival it is needed at least two years). This evaluation is very important for the outcome of CRC patients and to establish the role of anti-angiogenic treatment [7, 10, 28–30]. Further investigations might suggest that microvessel density determined by immunostaining for CD34 in the inner portion of the tumor represent a prognostically relevant parameter in colorectal cancer. We should also not neglect the potential role of other immunohistochemical parameters like E-cadherin or p53 expression that together with ITMVD may help in better characterizing colorectal cancers behavior [31].

Correlations between ITMVD and the eight studied morphological parameters pointed out some interesting trends that might be useful in assessing the need for anti-angiogenic treatment, an already approved therapy for colorectal cancer but without well-defined indications [32]. For example, a higher ITMVD was obtained in infiltrative tumors when compared to vegetant tumors and in rectal tumors compared to right colon tumors. It is also interesting to remark the relation between transversal and longitudinal development of the tumors in relation to ITMVD, the first being directly proportional, while the second was found in an inverse relation. For now, we can only speculate that the MVD influences the pattern of tumor growth by tumoral microenvironment changes. In a future study, it will be interesting to assess the area of the micro vessels. Another therapeutic perspective of ITMVD use is linked to the selection of candidates for local excision in early stage colorectal cancer, but the subject needs further study. Also, moderately differentiated tumors (G2) and pT4, pN0 and pM1 tumors had the highest ITMVD in our study group, being a possible candidate for first line anti-angiogenic therapy.

★ Conclusions

There were some interesting correlations between ITMVD and the eight studied morphological parameters that might influence future oncoligical approach in CRC. However, these results have to be validated on larger series of cases.

Conflict of interests

The authors declare that they have no conflict of interests.

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