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Original contribution

Incidence of extramural venous invasion in colorectal carcinoma as determined at the invasive tumor front and its prognostic impact☆

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Summary Extramural venous invasion (EMVI) is prognostic for colorectal cancer; however, veins are only detected partially by normal perpendicular preparation. Therefore, reported findings are conflicting and standardization is required. A total of 239 resection specimens were examined by tangential preparation of the extramural veins at the invasive tumor front. Average follow-up was 39 months. The relationship of EMVI to metachronous hematogenic metastasis (MHM) was evaluated. With this method, a high prevalence of EMVI beginning in stage II is apparent. In stage I, 66% of patients with EMVI developed MHM; in stage II, 25%; and in stage III, 49%. In stage III, the number of tumor-invaded veins is crucial. In the absence of detection of EMVI, MHM occurred in 1 of 29 patients in stage II and in 2 of 13 patients in early stage III. By tangential sectioning at the invasive tumor front, we found a high incidence of EMVI beginning in stage II, which increases with tumor stage. Especially in stages II and III, the correct determination of absent EMVI has a high negative predictive value for MHM. In stage I, EMVI defines a patient group with increased risk for MHM. The quantification of EMVI is an important issue for standardization.

1. Introduction

The prognostic assessment of extramural venous invasion (EMVI) in colorectal carcinoma has long been discussed as a central risk factor for the onset of metachronous hematogenic metastasis (MHM) [1-5]. However, because of extremely discrepant data regarding the prevalence of the finding of EMVI in colorectal carcinoma, a general recommendation is not given in the literature. The numerous proposals published to resolve this situation have so far only provided partial improvements [6-9]. This has resulted in a merely general and not further specified assessment of EMVI in the literature.

Because only a fraction of the extramural veins are detected by means of the recommended perpendicular preparation method of colorectal carcinoma, the question arises as to whether, with regard to vessel architecture in the mesocolon/

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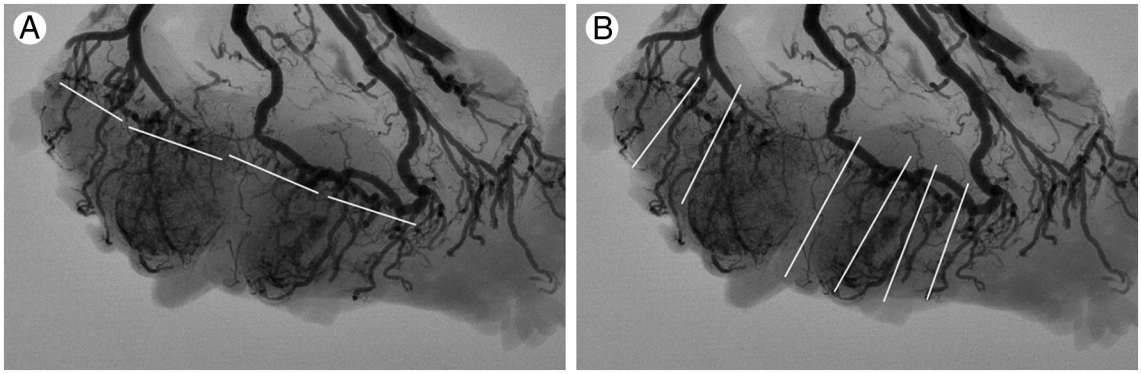

Fig. 1 Radiologic depiction of the veins of the mesocolon (adenocarcinoma of the sigmoid colon). A, By tangential preparation of the physiologically dense venous vessels in the mesenterium at the invasive tumor front, all of the (extramural) veins in the vicinity of the tumor can be detected. B, In contrast to perpendicular preparation) which results in assessing only a portion of these veins.

mesorectum, better results may be obtained by detection of all of the veins in the tumor region, especially by avoiding false-negative findings. Because intravascular growth beyond the invasive tumor front is generally known for carcinomas, an additional, tangential preparation of the mesocolon/mesorectum immediately distal to the invasive tumor front with a section of the veins emerging from the tumor region is an alternative method for the detection of EMVI. At a right angle to the normal, perpendicular section, all veins coming from the tumor region can be detected on cross sections parallel to the invasive tumor front (Fig. 1). For a colorectal carcinoma with a macroscopically well-delineated invasive tumor front, an ideal setting is provided. For stage II colorectal carcinoma, we have already shown that EMVI can be well demonstrated with this additional tangential preparation at the invasive tumor front [10,11].

In the following study, the prognostic value of EMVI with this modified preparation method will be discussed for all stages of colorectal carcinoma. This issue will also be discussed in light of the repeatedly required standardization of EMVI [12,13].

2. Materials and methods

With our method of tangential preparation at the invasive tumor front, 315 consecutive colorectal carcinoma resection specimens were examined over a period of 2.5 years (January 31, 1994 to June 19,1996). After exclusion of 76 patients (death within 3 months postoperatively, second malignancy, metastasizing tumor, absence of disease data, excessive stapling of the intestine in the tumor area, anastomotic tumor recurrence), 198 patients in Union for International Cancer Control (UICC) stages I-III were analyzed. The remaining 41 patients were in stage IV. The patients were predominantly in their seventh decade (between 62 and 71 years of age) with a slight predominance of female patients. The average follow-up time was 39 months (between 4 and 89 months) (Table 1).

In the case of macroscopically unambiguous infiltration of the mesocolon/mesorectum, first, 5-mm–thick sections were prepared from the entire tumor. Afterward, the tissue sections were prepared for determination of EMVI by tangential (perpendicular) cutting beginning in the adipose tissue and then including the whole tumor extension; the boundary zone between the tumor and mesocolon and the tumor and periproctal connective tissue, respectively, in Dukes B, C, and D (beyond UICC stage I) tumors of the colon and rectum (Fig. 2); and the boundary between the bowel wall and surrounding fatty tissue at the level of Dukes A (UICC stage I) cancers [10]. In the case of intramural tumors, the border zone between the tunica muscularis propria and the mesocolon/mesorectum was sectioned parallel to the longitudinal axis of the intestine. The histological sections were stained with hematoxylin and eosin and Weigert-Elastica. *EMVI* was defined as intraluminal tumor growth or complete infiltration of the venous wall (Fig. 3). Depending on the tumor size, an average of 6 blocks (minimum 4, maximum 10 blocks, especially in the usually larger circumferential tumors) is required for this additional preparation.

The diagnosis of metachronous hematogenous metastases was based on imaging techniques including sonography and

Table 1 Clinical characteristics according to stage

Stadium (n/%)	Sex (male/female)	Average age at diagnosis (y)	Average follow-up (mo)
I (39/16%)	19/20	68	45
II (79/33%)	41/38	68	43
III (80/34%)	36/44	66	35
IV (41/17%)	18/23	64	

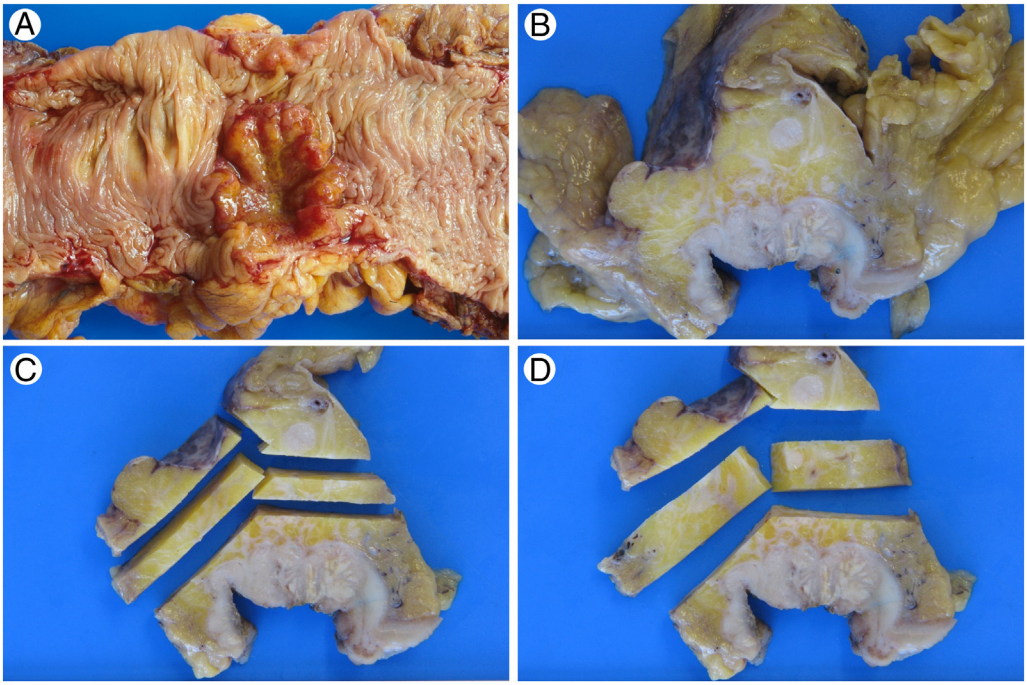

Fig. 2 Macroscopic dissection of a colorectal carcinoma specimen. A, Overview of an insular colorectal carcinoma. B, Initially, the tumor is dissected perpendicularly; a lymph node is seen in the periphery. C, Thereafter, tangential sections are prepared at the invasive tumor front. D, Before embedding, the tangential sections are rotated by 90°. The tissue of the main tumor mass and the surface of the peritoneum are embedded conventionally.

computerized tomography, as well as histological and/or cytological sampling of the lesions. All patients were discussed in a weekly multidisciplinary tumor board and only analyzed here if unequivocal metastatic disease was present. Fluorouracil combination therapy was given to some of the patients in stage II and all of the patients in stage III. No patient received adjuvant chemotherapy.

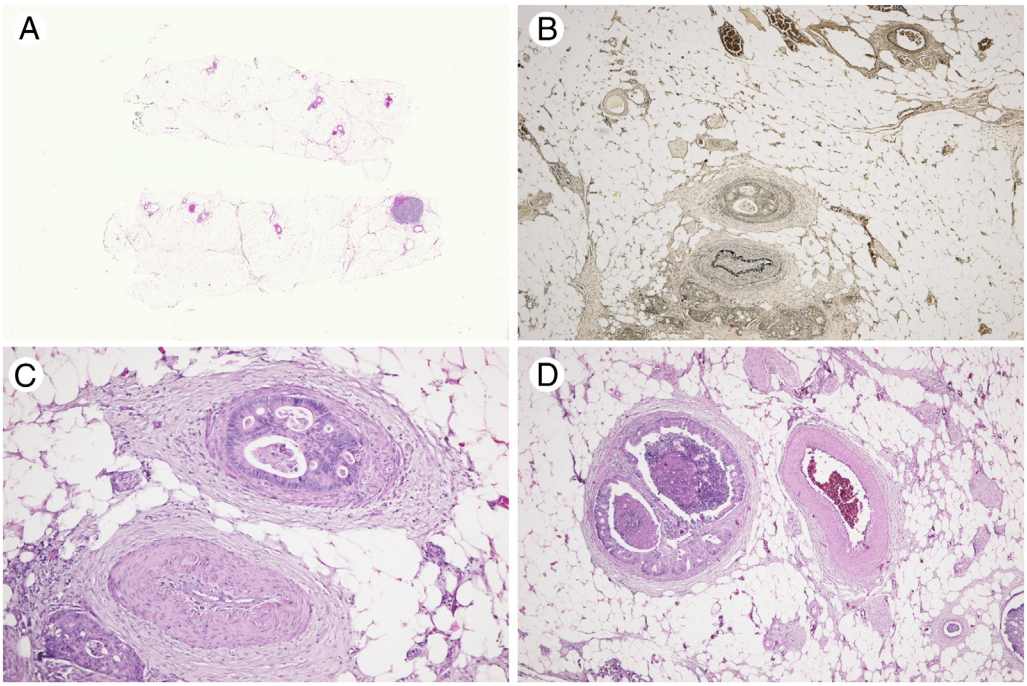

Fig. 3 Histologic evaluation of extramural venous invasion in tangential tissue at the tumor invasion front. Overview of a tangential section of a colorectal carcinoma without extramural venous invasion. A, Multiple vessels cut transversely are easily discerned. B, Elastic stains support in the visualization of arteries and accompanying veins, and extramural venous invasion is detected at low power in the center of the field. C, High-power resolution shows a retained muscle layer of the infiltrated vein. D, In more advanced tumors, occasionally, extramural venous invasion was seen in multiple veins.

Table 2 Characteristics of extramural venous invasion for colorectal carcinoma according to tumor stage

		Tumor stage			
		I	II	III	IV
Number of invaded veins according to type of tumor growth	Insular	1	2	3	3.4
	Circumferential	0	2.8	5.5	4.1
	Average	1	2.5	3.5	3.9
Extramural venous invasion (V) and metachronous hematogenic metastasis (M)	V1/M1	2	13	27	35
	V1/M0	1	37	28	0
	V0/M1	1	1	8	6
	V0/M0	35	28	17	0
Characterization of extramural venous invasion in respect to metachronous hematogenic metastasis	Sensitivity	0.66	0.92	0.77	
	Specificity	0.97	0.96	0.37	
	Positive predictive value	0.66	0.26	0.49	
	Negative predictive value	0.97	0.96	0.68	

For the nomenclature of the plane of section, the following is added: *Perpendicular* (vertical) corresponds to the longitudinal axis of the intestine. The term *tangential* is given by Talbot for the circumferential tumor margin and corresponds to a perpendicular (vertical) direction of the section [1]. The term *tangential* used by us is a right angle to the perpendicular direction or parallel to the surface of the invasive tumor front.

3. Results

In stage I, 3 patients (10.3%) with pT2 tumors showed EMVI, each with 1 invaded vein. Two of these patients developed MHM. Additionally, in this patient group, there was 1 patient with MHM without EMVI.

The prevalence of EMVI in 63% of the patients in stage II is a strong increase compared to stage I, with an average of 2.5 tumor-infiltrated veins (Table 2). Approximately 25% of the patients with EMVI also developed MHM. On the other hand, in the absence of EMVI detection, only 1 of 29 patients showed MHM. In patients with EMVI and MHM, the number of veins infiltrated by the tumor is approximately the same. The difference in the number of infiltrated veins in circumferential versus insular tumors is between 2 and 3. The number of risk factors for stage II and EMVI with or without MHM is 53% and 37%, respectively, each with predominantly only 1 of these factors.

In stage III, the prevalence of EMVI was 70%. On average, these patients had 3.5 tumor infiltrated veins, with MHM found in 44% of the patients. In "early" stage III (pN1a, pT3, G1-2), in the case of absent EMVI or a maximum of 2 tumor-infiltrated extramural veins, 21 of 30 (70%) patients were without MHM (Table 3). In those patients with insular tumors (independent of MHM), between 2.7 and 3.1 infiltrated veins were detected, the frequency of MHM here being 70%. In the case of circumferential tumor growth, the number of tumor-infiltrated veins is higher, especially in the rectum, with 4.7 invaded veins in patients without MHM and 5.3 in patients with MHM, which occurred in 34% (Table 2).

Table 3 Relation of EMVI to MHM in "early" stage III (pT3, PN1a, G1-2, EMVI 0–2)

	MHM positive	MHM negative
EMVI positive	7	10
EMVI negative	2	11

Abbreviation: CRC, colorectal carcinoma.

In stage IV, 85% of patients were with EMVI, with an average of 3.8 tumor-infiltrated veins.

The correlation of EMVI status to the frequency of MHM depending on UICC stage is shown in Table 2.

The average number of detected lymph nodes was 9 in stage I and between 13 and 15 in stages II-III.

Statistically, the sensitivity of EMVI with respect to MHM is generally high for stage I to stage III: 0.66-0.77. The specificity for stages II and III is 0.96 and 0.37, respectively (Table 2).

The negative predictive value is nearly 1 in stages I and II and 0.68 in stage III. The positive predictive value for stages I-III varies between 0.66 and 0.26. These predictive values are the same for colon and stage II rectum (Table 2). Histologically, the intravenous tumor parts are covered by thromboses in the tip area; otherwise, they are endothelialized to a variable extent. These tumors frequently show necrosis and also extensive recent and older bleeding with siderophages.

4. Discussion

When analyzing the individual stages of colorectal carcinoma, our study for EMVI at the invasive tumor front shows a continuous trend. A high prevalence beginning in stage II is a central characteristic of EMVI, although in this stage, only singular veins are invaded. In correlation to the UICC stages, the number of the few extramural veins invaded corresponds to tumor progression with a moderate increase (Table 2). In correlation to the UICC stages, EMVI at the invasive tumor

front shows that the risk of MHM increases with an increasing number of tumor-infiltrated, extramural veins (Table 2). EMVI can therefore be interpreted as an indicator of the progression of colorectal carcinoma.

In clinical practice, the decision of adjuvant chemotherapy for colorectal carcinoma can be determined by patient-related factors such as comorbidity and life expectancy, or complications during the surgical procedure or patient preference by means of clinical and pathological-morphological criteria [14,15]. However, a prospective evaluation of these factors is not available. New or improved parameters for optimal risk assessment are therefore urgently required. In our view, an improvement can be made here by correct detection of EMVI at the invasive tumor front, especially with the correct determination of absent EMVI. The criterion of missing EMVI has not been specifically considered in the literature for this risk assessment. However, with our preparation method, this can be discussed for the first time. Therefore, clinically, it is possible to determine the central issue of risk for the patient with colorectal carcinoma.

The main focus of further prognostic assessment for stages II and III with our method of dissection lies in the verification of absent EMVI. Our patient data show an essential association of absent of EMVI and absence of MHM in stage II with the constellation of high values for sensitivity and negative predictive value (Table 2). Additionally, a comparatively very favorable prognosis is seen in patients with "early" stage III in the absence of EMVI. In contrast, the rarely discussed detection of EMVI in the mesocolon/mesorectum adjacent to the tumor is the main focus of our preparation method in stage I (Table 3).

The decision on whether patients should receive therapy in stage II is difficult because of the heterogeneity of this patient group. The establishment of prognostic and predictive factors for patient selection is therefore urgently necessary and, especially due to little data, an eminent challenge [16]. In UICC stage II, only 2%-5% of patients benefit from adjuvant therapy [17-19]. A recent Cochran meta-analysis has shown an improvement in disease-free survival [20]. These data have recently been updated, and fluorouracil has also shown a survival benefit for unselected patients [21]. Several leading medical associations (such as the American Society of Clinical Oncology, European Society for Medical Oncology, and National Cancer Institute) recommend the use of adjuvant chemotherapy for patients with risk factors in stages II and III. These are patients with tumor obstruction or tumor perforation, less than 12 removed lymph nodes, invasion depth pT4, and undifferentiated carcinomas. The invasion of extramural veins as a risk factor is interpreted contrarily and only partially recognized as a true risk factor [14,22,23].

In UICC stage III, adjuvant chemotherapy has so far undoubtedly improved median overall survival and also median disease-free survival [24]. Regarding the inhomogeneity of stage III colorectal carcinoma, which has been debated for quite some time [25,26], 3 prognostically different groups are to be discussed in our study in connection with EMVI. In addition to the already mentioned "early" stage III, for the "advanced" colorectal carcinoma, circumferential growth must be separated from the insular growing tumor. The number of extramural veins invaded by the circumferential tumor is high; however, the percentage of MHM in the "advanced" insular tumors was significantly higher compared with the circumferential tumor.

The effect of neoadjuvant therapy of the intravenous tumor portion has also been discussed, especially if it is possible for a tumor plug to become detached by intensifying/expanding preexisting necrosis and thus causing consecutive MHM. By means of magnetic resonance imaging, the radiological depiction of EMVI has been established in the rectum for some time and is also discussed as an indication for neoadjuvant therapy [27,28]. In clinical trials, no disadvantage of neoadjuvant therapy compared to single adjuvant therapy has been reported [29]. At the most, the pathologist is challenged by these findings in the magnetic resonance imaging, and the assessment of EMVI in the setting of neoradiotherapy is much more difficult because of therapy-related regression of the tumor [30]. In our patient population—without neoadjuvant therapy—EMVI shows similar behavior in the colon and rectum, whereas the incidence of EMVI in the rectum is somewhat higher when comparing the UICC stages. For a definitive statement, however, our patient groups are too small, and there is no comparison to the radiological findings. This will have to be investigated on a larger cohort.

The complete examination of the veins in the tumor vicinity is the prerequisite for the correct (comparative) diagnosis of absence of EMVI or the avoidance of false-negative findings in addition to the detection of venous invasion. Furthermore, with the numerical specification of venous invasion, an ideal requirement for the integration into the most recently published prognosis schemes is given [31-33]. Also, the data in our study on the prevalence of EMVI are significantly higher than in the representative literature, where the perpendicular preparation technique is used throughout. An additional advantage of our method is the histologically reliable identification of the type and localization of extramural vessels in contrast to intramural vessels.

Our study shows that it is essential that the prognostic assessment of detection of EMVI is not a general but a differentiated issue, depending on the UICC stage. Apart from the additional possibility of a local recurrence, the objective of this evaluation of EMVI is based solely on the emergence or absence of MHM; therefore, a strict orientation of this risk assessment is given for treatment. The focus of the assessment of the parameter EMVI is given by the correct, so far not assessed, diagnosis of absent EMVI, thus enabling a differentiated prognostic subdivision into individual colorectal carcinoma patient groups.

Research of colorectal carcinoma is dominated by the detection of cellular parameters; with EMVI, however, one is dealing with an already advanced stage of the metastatic cascade, which is a significant gain for a comprehensive risk assessment. Whether additional immunohistochemical,

molecular-pathological, hematological, or genetic investigations on selected parts of these intravenous tumor plugs can lead to a further improvement of the prognostic assessment regarding MHM may be evaluated by future studies.

In conclusion, tangential sectioning at the invasive tumor front reveals a high incidence of EMVI beginning in stage II and increasing with stage. Especially in stages II and III, the correct determination of absent EMVI has a high negative predictive value for MHM. On the other hand, in stage I, EMVI defines a patient group with increased risk for MHM.

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