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Correlation Between K_{trans} and Microvessel Density in Different Tumors: A Meta-analysis

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Abstract. *Background/Aim: Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) is a technique based on the measurement of the signal intensity of the investigated tissue before, during, and after administration of an intravenous contrast agent. DCE MRI parameters can reflect tumor angiogenesis and, therefore, can provide information about tumor behavior. The purpose of this meta-analysis was to analyze the reported data regarding associations between K_{trans} (volume transfer constant) and microvessel density (MVD) in different tumors. Patients and Methods: For this meta-analysis the MEDLINE library was screened for associations between K_{trans} and MVD in different tumors up to July 2017. After thorough reviewing, the present analysis included 16 studies. The following data were extracted from the literature: authors, year of publication, number of patients, tumor type, MR scanners, study design, and correlation coefficients. Results: The identified correlation coefficients ranged from –0.65 to 0.75. The calculated pooled correlation coefficient was 0.23 (95%CI=0.07-0.38). Furthermore, correlation coefficients for every tumor entity were calculated: rectal cancer: ϱ=–0.07 (95%CI=–0.56-0.43); prostatic cancer: ϱ=0.08 (95%CI=–0.06-0.23); glioma: ϱ=0.70 (95%CI=0.64-0.75). Conclusion: Our meta-analysis showed different correlations between K_{trans} and MVD in several tumors.*

Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) technique based on the measurement of signal intensity of the investigated tissue before, during, and after the administration of an intravenous contrast agent (1-4). DCE MRI reflects a composite of tissue perfusion, vessel permeability, and the volume of the extravascular-extracellular space (1-4). Several pharmacokinetic parameters can be retrieved from DCE MRI. Most frequently, the following parameters are used: K_{trans} or volume transfer constant, which estimates the diffusion of contrast medium from the plasma through the vessel wall into the interstitial space, representing vessel permeability, V_e or volume of the extravascular extracellular space, and K_{ep} or parameter for diffusion of contrast medium from the extravascular extracellular space back to the plasma (1-4).

Previously, numerous reports showed the usefulness of DCE MRI in oncology (1-7). According to the literature, DCE MRI parameters can reflect tumor angiogenesis and, therefore, can provide information about tumor behavior (1-3). Especially K_{trans} has been reported to be sensitive (1-3). For example, it has been shown that low pretreatment K_{trans} in regional lymph node metastases in head and neck cancer was associated with a poor response to radiochemotherapy (8). In breast cancer, tumors with high K_{trans} values showed poorer prognosis in comparison to lesions with low K_{trans} values (9).

These effects are based on associations between DCE MRI parameters with several histopathological features, such as microvessel density (MVD). Some reports showed previously strong correlations between K_{trans} and MVD in several malignancies (10-12). However, published data were inconsistent and the reported correlations ranged widely (10, 13, 14). Furthermore, most reports investigated small patient samples (8, 13, 14).

The purpose of this meta-analysis was to analyze the reported data regarding associations between K_{trans} and MVD in different tumors in a first meta-analysis.

Patients and Methods

Data acquisition and proving. For this meta-analysis MEDLINE library was screened for associations between K_{trans} and MVD in different tumors up to July 2017 by using the following search words: "DCE OR Dynamic contrast enhanced AND MVD OR

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Key Words: DCE MRI, K_{trans}, microvessel density, MRI.

micro vessel density OR vessel count OR VEGF". Secondary references were also checked. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research (15).

We identified 95 items. After exclusion of duplicates (n=15), non-English publications (n=1), experimental animals and *in vitro* studies (n=29), papers with other perfusion techniques than DCE (n=19), and publications without correlation coefficients between K_{trans} and MVD (n=15), the present analysis comprised of 16 studies (8-14, 16-24). The following data were extracted from the literature: authors, year of publication, number of patients, tumor type, MR scanners, study design, and correlation coefficients.

Meta-analysis. On the next step the methodological quality of the acquired 16 studies was independently checked by two observers (A.S. and H.J.M.) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument (25, 26). The results of QUADAS are shown in Table I.

Correlations between K_{trans} and MVD were analyzed by Spearman's correlation coefficient. The reported Pearson correlation coefficients in some articles were converted into Spearman correlation coefficients according to the previous description (27).

In addition, the meta-analysis was undertaken by using RevMan 5.3 (Computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was calculated by means of the inconsistency index I^2 (28, 29). DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction (30).

Table I. *Methodological quality of the involved 16 studies according to the QUADAS criteria.*

QUADAS criteria	Yes (%)	No (%)	Unclear (%)
Patient spectrum	16 (100)		
Selection criteria	12 (75)		4 (25)
Reference standard	16 (100)		
Disease progression bias	16 (100)		
Partial vertification bias	16 (100)		
Differential vertification bias	16 (100)		
Incorporation bias	16 (100)		
Text details	16 (100)		
References standard details	16 (100)		
Text review details	7 (43.75)	8 (50)	1 (6.25)
Diagnostic review bias	7 (43.75)	8 (50)	1 (6.25)
Clinical review bias	16 (100)		
Uninterpretable results	16 (100)		
Withdrawals explained	16 (100)		

Results

Most studies were retrospective (n=14) and their data were obtained on different 1.5 and 3T scanners (Table II). The included studies comprised 652 patients with several tumors including breast tumors (31.4%), followed by rectal cancer (15.5%), prostate cancer (13.9%), and glioma (12.6%) (Table III). Other tumors were rarer.

Most frequently, MVD was estimated on CD31 or CD34 or CD105 stained specimens (Table II).

The identified correlation coefficients ranged from -0.65 to 0.75 (Figure 1). The calculated pooled correlation coefficient was 0.23, (95%CI=0.07-0.38), heterogeneity τ^2=0.10, (p<0.00001), I^2=100%, test for overall effect Z=2.87 (p<0.004).

Furthermore, correlation coefficients for tumor entities were calculated. For this sub-analysis, only data for primary tumor entities with more than two reports were included. There were 3 entities with 274 patients. The calculated correlation coefficients were as follows (Figure 2): rectal cancer: ϱ=–0.07 (95%CI=–0.56-0.43); prostatic cancer: ϱ=0.08 (95%CI=–0.06-0.23); glioma: ϱ=0.70 (95%CI=0.64-0.75).

Discussion

To the best of our knowledge, this is the first meta-analysis regarding associations between K_{trans} and MVD. As seen, the reported correlation coefficients ranged significantly. Overall, a weak correlation between the analyzed parameters was identified. Thereby, three different situations are possible. First, K_{trans} can well correlate with MVD. This constellation was observed in retinoblastoma, breast cancer, gastric cancer, and different gliomas (10, 11, 18, 20, 21, 24). The correlation coefficients ranged from 0.49 in rectal cancer to 0.76 in gastric cancer (10, 11, 18, 20, 21, 24). This finding seems to be consequential. In fact, K_{trans} reflects the diffusion of contrast medium from the plasma through the vessel wall into the interstitial space. However, as seen, there were different correlation coefficients in several tumors. It may be related to different microvessel features, such as vessel fenestration or perivascular space, in the investigated malignancies (31, 32). Furthermore, different cell densities, relation of tumor parenchyma/stromal area, as well extracellular space may play a role here (31, 32).

Second, some authors did not find a significant correlation between K_{trans} and MVD (14, 17, 19, 22). This phenomenon is difficult to explain. K_{trans} represents vessel permeability. Presumably, vessel permeability can be different in lesions with similar vessel count and does not depend on MVD only (33).

Third, although rarer, K_{trans} correlated inversely with MVD (8, 13, 16). This relationship was detected in rectal cancer (–0.65) (13), pancreatic lesions (–0.19) (16), and in nodal metastases of head and neck squamous cell carcinoma (–0.57) (8). The identified situation is paradoxical and unclear. Some authors hypothesized that this finding may be related to the high level of maturation of vessels within the investigated tumors, in particular, in rectal cancer (13). Typically, mature vessels demonstrate relatively low permeability (13).

Another interesting fact is that the amount of proliferative microvessels might be more clinically important than the sole number of microvessels alone and might more

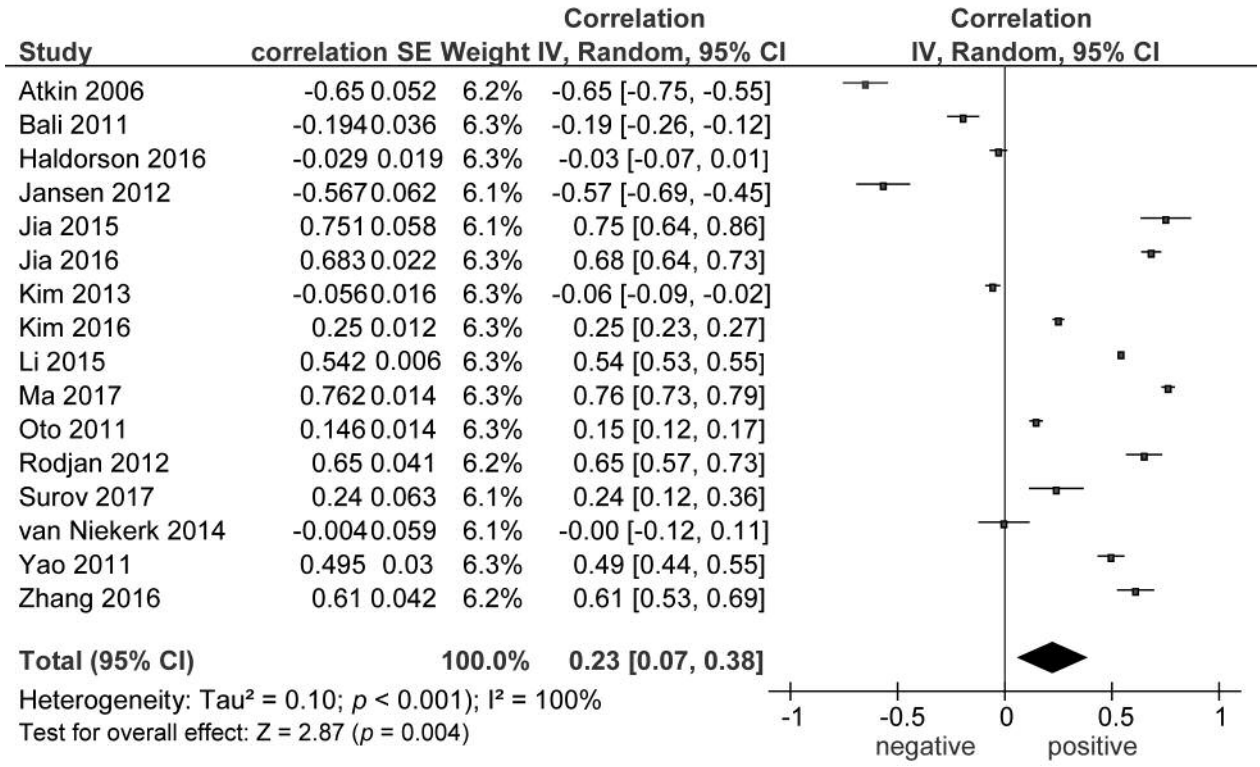

Figure 1. *Forest plots of correlation coefficients between K_{trans} and MVD in all involved studies (n=16).*

Table II. *Characteristics of the involved studies.*

Autor	Patients, n	Tumors	Studies design	Scanner	MVD staining
Atkin *et al*.	12	Rectal Cancer	Retrospective	1.5 T, Siemens	CD31
Bali *et al*.	28	Pancreatic Cancer	Retrospective	1.5T, Philips	CD34
Haldorson *et al*.	54	Endometrial cancer	Prospective	1.5T, Siemens	Faktor VIII
Jansen *et al*.	12	Head and neck lymph node metastases	Prospective	1.5T, GE	VEGF
Jia *et al*.	33	High Grade Glioma	Retrospective	3 T, Siemens	CD105
Jia *et al*.	25	Glioma	Retrospective	3 T, Siemens	CD105
Kim *et al*.	63	Rectal cancer	Retrospective	3 T, Siemens	CD34
Kim *et al*.	81	Breast cancer	Retrospective	3 T, Siemens	CD34
Li *et al*.	124	Breast tumors	Retrospective	3 T, Philips	CD31 and CD105
Ma *et al*.	32	Gastric cancer	Prospective	3 T, Siemens	VEGF
Oto *et al*.	73	Prostatic cancer	Retrospective	1.5 T, GE	CD31 and D34
Rodjan *et al*.	15	Retinoblastoma	Retrospective	1.5 T, Siemens	CD31
Surov *et al*.	16	Head and neck cancer	Retrospective	3 T, Philips	CD31
van Niekerk *et al*.	18	Prostatic cancer	Retrospective	3 T, Siemens	CD31
Yao *et al*.	26	Rectal cancer	Retrospective	1.5 T, GE	CD34
Zhang *et al*.	16	Renal cell carcinoma	Retrospective	3 T, Philips	CD31 and CD34

accurately reflect the state of angiogenesis (34). Moreover, MVD might not be correlated with the number of proliferative microvessels, indicating that these parameters might be independent of each other (34). However, no study has investigated, whether DCE-MRI might be also associated with the amount of proliferative microvessels.

Overall, our meta-analysis shows that several tumors seem to have different associations between K_{trans} and MVD. Therefore, a previously reported suggestion that DCE MRI parameters can be used as a noninvasive tool for tumor angiogenesis, should be relativized. At least, this postulate does not apply for every tumor entity.

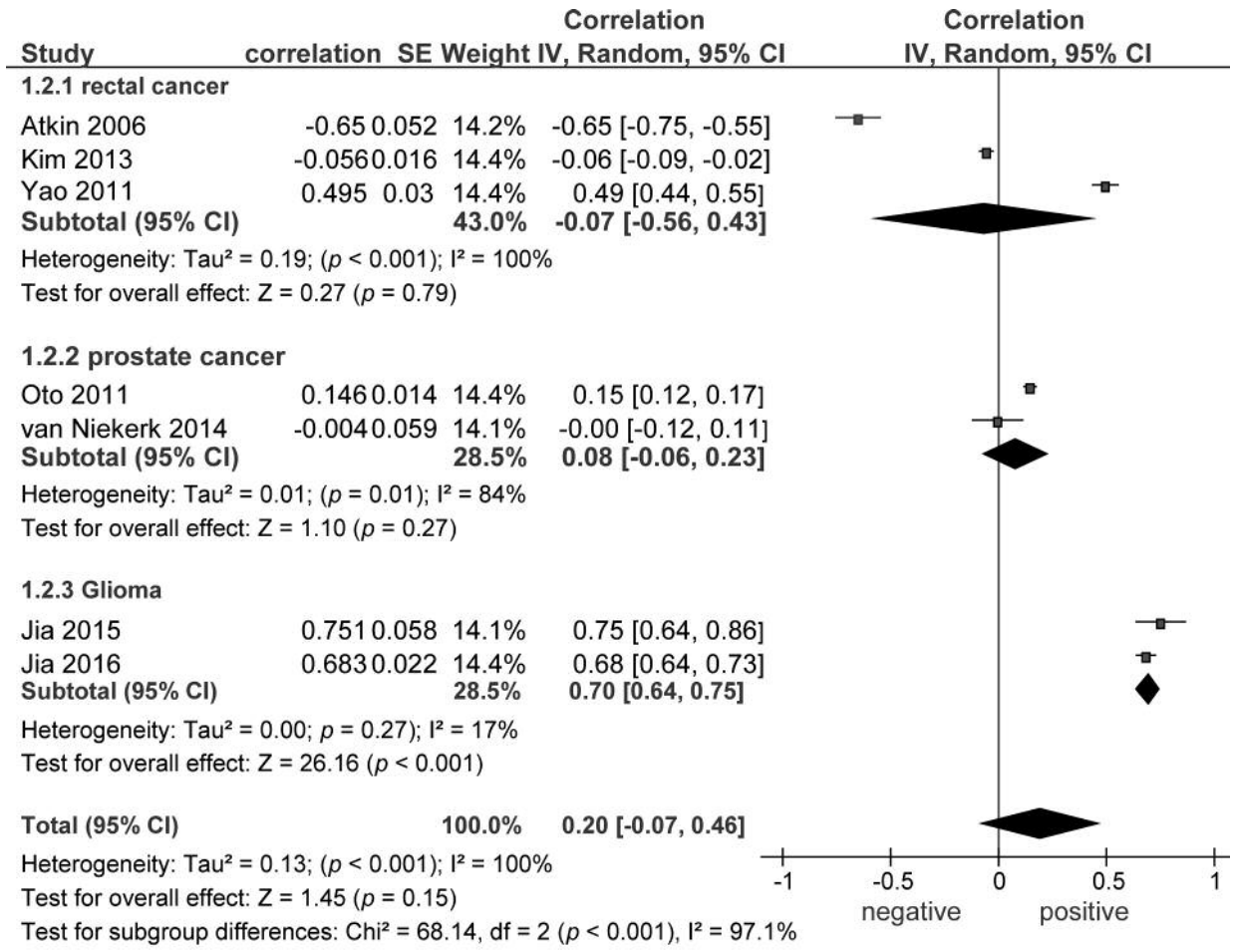

Figure 2. *Forest plots of correlation coefficients between between K_{trans} and MVD in different primary tumors.*

The present meta-analysis identified several problems. Although DCE MRI is widely used in cancer diagnosis and treatment response control, only 16 reports analyzed associations between DCE MRI parameters and histological findings like MVD. Furthermore, only three tumor entities could be acquired for separate calculation of correlation coefficients between K_{trans} and MVD. For other identified tumors, only one report was published, respectively, and these entities could not be included into the subgroups analysis. There are no reports regarding correlation between DCE MRI parameters and MVD for frequent gastrointestinal tumors like esophageal cancer, hepatocellular carcinoma, lung cancer, and for lymphomas and different sarcomas.

Another problem is the fact that the MVD was estimated using different stainings. Most authors used CD31 or CD34 expression. However, there were studies that analyzed MVD by means of CD105 staining. In addition, some reports defined MVD using VEGF expression (8, 21). There were also different MRI scanners like 1.5 or 3 T with also different sequence parameter for estimation of K_{trans}. These facts limited our results.

Table III. *Overview of all involved tumor types.*

Diagnosis	n	%
Different breast tumors and tumor like lesions	205	31.4
Rectal cancer	101	15.5
Prostatic cancer	91	13.9
Glioma	82	12.6
Endometrial cancer	54	8.3
Gastric cancer	32	4.9
Pancreatic cancer	28	4.3
Renal cell carcinoma	16	2.5
Head and neck cancer	16	2.5
Retinoblastoma	15	2.3
Lymph node metastases	12	1.8
Total	652	100

Clearly, the question regarding the relationships between DCE MRI parameters and MVD is open and needs further research. Also, associations between DCE MRI parameters and other histopathological features, for instance, proliferation potential or cellularity, should be analyzed. Isolated reports indicated such associations. For instance, it has been shown that K_{trans} inversely correlated with proliferation marker KI67 (8, 23).

In conclusion, our meta-analysis showed different correlations between K_{trans} and MVD in several tumors.

Conflicts of Interest

None.

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