in vivo *36*: 398-408 (2022)
doi:10.21873/invivo.12717

Associations Between Dynamic Contrast Enhanced Magnetic Resonance Imaging and Clinically Relevant Histopathological Features in Breast Cancer: A Multicenter Analysis

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Abstract. *Background/Aim: To provide data regarding relationships between quantitative dynamic contrast enhanced magnetic resonance imaging (DCE MRI) and prognostic factors in breast cancer (BC). Patients and Methods: Data from 4 Centers (200 female patients, mean age, 51.2±11.5 years) were acquired. The following data were collected: histopathological diagnosis, tumor grade, stage, hormone receptor status, KI 67, and DCE MRI values including K_{trans} (volume transfer constant), V_e (volume of the extravascular extracellular leakage space (EES) and K_{ep} (diffusion of contrast medium from the EES back to the plasma). DCE MRI values between different groups were compared using the Mann-Whitney U-test and by the Kruskal-Wallis H test. The association between DCE MRI and Ki 67 values was calculated by the Spearman's rank correlation coefficient. Results: DCE MRI values of different tumor subtypes overlapped significantly. There were no statistically significant differences of DCE MRI values between different tumor grades. All DCE MRI parameters correlated with KI-67: K_{trans}, r=0.44, p=0.0001; V_e, r=0.34, p=0.0001; K_{ep}, r=0.28, p=0.002. ROC analysis identified a K_{trans} threshold of 0.3 min^{-1} for discrimination of tumors with low KI-67 expression (<25%) and high KI-67 expression (≥25%): sensitivity, 75.5%, specificity, 73.0%, accuracy, 74.0%, AUC, 0.78. DCE MRI values overlapped between tumors with different T and N stages. Conclusion: K_{trans}, K_{ep}, and V_e cannot be used as reliable a surrogate marker for hormone receptor status, tumor stage and grade in BC. K_{trans} may discriminate lesions with high and lower proliferation activity.*

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Key Words: Breast cancer, DCE MRI, KI 67, hormone receptor.

Breast cancer (BC) is the most common non cutaneous malignancy among women, representing 4 in 10 female cancer patients in the United States (1). Radiological imaging plays an essential role in the diagnosis and staging of BC. Moreover, imaging can also predict some clinically important histopathological features like expression of proliferation marker KI-67 (2, 3). So far, it has been shown that rim enhancement on dynamic magnetic resonance imaging (MRI) was associated with high expression of KI-67 and poor prognosis of BC (3). Similarly, numerous studies analyzed the role of diffusion weighted imaging (DWI) in characterization of BC (4-7). Some authors observed statistically significant correlations between apparent diffusion coefficient and expression of KI-67 (6, 7), as well as with hormone receptor status (8). However, multicenter studies showed that ADC cannot reflect KI-67 and hormone receptor expression in BC (9, 10).

Previously, some reports also indicated that dynamic contrast enhanced MRI (DCE MRI) can be used as imaging biomarker in BC (6, 11, 12, 13). According to the literature, quantitative parameters of DCE MRI, namely volume transfer

Table I. *Data regarding patient acquisition and technical details of breast DCE MRI in the involved Centers.*

Center	Data acquisition	Patients, n (%)	MR scanner	DCE sequence	TR/TE, ms	Slice thickness, mm	Field of view, mm	Contrast medium
1	Prospective	80 (40.0%)	3T system (Trio Tim, Siemens Healthcare, Erlangen, Germany)	VIBE	3.5/3.1	2	320×320	gadobutrol (Gadovist; Bayer Schering Pharma, Berlin, Germany)
2	Prospective	42 (21.0%)	3T system (Biograph, Siemens Healthcare, Erlangen, Germany)	VIBE	5.3/1.9	3.6	356×379	Gadopentate dimeglumine (Gd-DTPA; Magnevist, Bayer Pharma AG, Berlin, Germany
3	Prospective	49 (24.5%)	3T system (Trio Tim, Siemens Healthcare, Erlangen, Germany)	TWIST	6.2/2.9	1.4	320×320	ProHance (Bracco Diagnostic Inc.)
4	Retrospective	29 (14.5%)	Philips 3T Achieva MR scanner (Philips Healthcare, Best, The Netherlands)	RF-spoiled 3D gradient echo	7.9/1.3	5	220×220	Gadopentate dimeglumine (Gd-DTPA; Magnevist Wayne, NJ)

DCE MRI, Dynamic contrast enhanced magnetic resonance imaging; VIBE, volumetric interpolated breath-hold examination; TWIST, time-resolved angiography with stochastic trajectories; RF, radio frequency.

constant (K_{trans}), volume of the extravascular extracellular leakage space (V_e), and diffusion of contrast medium from the EES back to the plasma (K_{ep}) reflect different histopathological features in BC (6, 12, 13). For example, Kang *et al*. showed that triple-negative BC exhibited higher K_{trans} and K_{ep} in comparison to luminal cancers (p<0.05) (12). Furthermore, estrogen receptor (ER) negative tumors had higher K_{trans} than ER-positive tumors (p<0.05) and progesterone receptor (PR)-negative tumors presented higher V_e than PR-positive tumors (p<0.05) (12). Finally, tumors with higher KI-67 showed higher K_{ep} than tumors with lower Ki-67 (p<0.05) (12). Nagasaka *et al*. reported that the mean of V_e was lower in cancers with a high KI-67 index than in cancers with low KI-67 (p=0.002) (13). However, other authors did not find any significant association between V_e, K_{ep} and expression of KI-67 in BC (14).

The purpose of the present study was to provide evident data on relationships between DCE MRI parameters and clinically relevant histopathological features in BC.

Patients and Methods

Data acquisition and patients. The present analysis was approved by the institutional review board (Number: 36/20, Otto-von-Guericke University, Magdeburg).

For analysis of associations between imaging and histopathology in BC a multicenter work group was established (9, 10). For this study, the partners of our work group were contacted *via* email with the request to provide the data regarding DCE MRI in BC. There were the following Centers:

- Medical Research Institute, Pusan National University School of Medicine, Busan, Republic of Korea and Department of Radiology, Pusan National University Hospital, Busan, Republic of Korea (center 1);
- RCCS SDN, Istituto di Ricerca, Naples, Italy (center 2);
- Advanced Imaging Research Center, Oregon Health & Science University, Portland, OR, USA (center 3);

Table II. *Tumor subtypes.*

Subtype	n (%)
Invasive ductal carcinoma	167 (83.5)
Invasive lobular carcinoma	6 (3.0)
Mucinous breast cancer	3 (1.5)
No special type	24 (12.0)
Receptor status	
Luminal A	49 (24.5)
Luminal B	84 (42.0)
HER 2+	32 (16.0)
Triple negative	19 (9.5)
Not available	16 (8.0)
Tumor grade	
1	25 (12.5)
2	96 (48.0)
3	79 (39.5)
T stage	
1	73 (36.5)
2	78 (39.0)
3	22 (11.0)
4	27 (13.5)
N stage	
0	104 (52.0)
1	51 (25.5)
2	22 (11.0)
3	23 (11.5)
M stage	
0	186 (93.0)
1	14 (7.0)

HER, Human epidermal growth factor receptor.

Table III. *DCE MRI values in BC with different hormone receptor status.*

	Luminal A cancer	Luminal B cancer	HER 2+ cancer	Triple negative cancer	*p*-Value
K_{trans}, min^{-1}	0.24±0.27	0.44±0.44	0.22±0.50	0.53±1.71	0.161
V_e, %	0.50±0.43	0.61±0.43	0.30±0.23	0.44±0.44	0.003
K_{ep}, min^{-1}	0.47±0.31	0.72±0.53	0.56±0.58	0.62±1.33	0.159

DCE MRI, Dynamic contrast enhanced magnetic resonance imaging; BC, breast cancer; HER, human epidermal growth factor receptor.

- Departments of Biomedical Engineering, Diagnostic Medicine, and Oncology, Livestrong Cancer Institutes, Oden Institute of Computational and Engineering Sciences, The University of Texas at Austin, USA (center 4).

For every case of the investigated patients/tumors the following data were collected: age, precise histopathological diagnosis, tumor grade, tumor stage, hormone receptor status, KI-67 index, and DCE MRI values including K_{trans} or volume transfer constant, V_e or volume of the extravascular extracellular leakage space (EES) and K_{ep} or diffusion of contrast medium from the EES back to the plasma.

The acquired sample comprises 200 patients (Table I). In every case, breast MRI was performed on a clinical scanner with dedicated breast radiofrequency coil. MR scanners and imaging protocols varied across the centers.

Statistical analysis. Continuous variables were described by mean value and standard deviation. Categorical variables were given as relative frequencies. The comparison of DCE MRI values in groups was performed by Mann-Whitney *U*-tests where the *p*-values are adjusted for multiple testing (Bonferroni correction). The association between DCE MRI values and KI-67 values was calculated by Spearman's rank correlation coefficient. Sensitivity, specificity, negative and positive predictive values, accuracy, and area under the receiver operating characteristic curve (AUC) value were calculated for the diagnostic procedures. Thresholds are chosen to maximize the Youden index.

Results

Patients and tumors. A total of 200 female patients, mean age, 51.2±11.5 years were included in this study. The patients had a variety of different breast tumor histologic types (Table II). The majority of tumors were invasive ductal carcinoma (IDC, 81.95%) with a limited number of other histopathological subypes. The DCE MRI values (M±SD) of the tumors were as follows: K_{trans}, 0.33±0.65 min^{-1}; V_e, 0.48±0.41%; K_{ep}, 0.60±0.60 min^{-1}.

DCE MRI and hormone receptor status. Hormone receptor status was available for 184 cases. Most frequently, luminal B cancers were diagnosed (Table III). DCE MRI values in different BC subtypes are given in Table IV. Triple-negative cancers had highest K_{trans} values, luminal B cancers had highest K_{ep} and V_e values, and HER 2+ BC had lowest K_{trans} and V_e values. There were no significant differences between K_{trans} and K_{ep} values in the BC subtypes. V_e values were different among the tumors with several receptor expressions (p=0.003). However, all DCE MRI values of different tumor subtypes overlapped significantly (Figure 1).

Table IV. *DCE MRI values in BC with different tumor grades.*

	Grade 1	Grade 2	Grade 3	*p*-Value
K_{trans}, min^{-1}	0.12±0.10	0.32±0.44	0.42±0.90	0.135
V_e, %	0.35±0.29	0.49±0.39	0.52±0.46	0.225
K_{ep}, min^{-1}	0.34±0.16	0.60±0.54	0.67±0.75	0.064

DCE MRI, Dynamic contrast enhanced magnetic resonance imaging; BC, breast cancer.

DCE MRI and tumor grade. DCE MRI values in different tumor grades are given in Table IV. All DCE MRI values increased with tumor grade. However, there were no significant differences of DCE MRI values between several tumor grades and all DCE MRI values of different tumor types overlapped significantly (Figure 2).

DCE MRI and KI-67. The level of proliferation index KI-67 was available for 123 tumors. The mean value was 27.4±23.6%, median value=20%, range=1%-90%. All DCE MRI parameters correlated with KI-67. The correlation coefficients were as follows: K_{trans}, r=0.44, p=0.0001; V_e, r=0.34, p=0.0001; K_{ep}, r=0.28, p=0.002. On the next step, ROC analysis was performed for distinguishing tumors with high proliferative potential from tumors with low proliferation rate using DCE MRI values. A KI-67 value of 25% was used as the threshold for discrimination between tumors with low KI-67 expression (<25%) and high KI 67 expression (≥25%). The Youden index identified threshold values of K_{trans}, V_e, and K_{ep} (Table V). K_{trans} cut-off value of 0.3 min^{-1} showed best results (Figure 3). Furthermore, other threshold values of KI 67 ranging from 10% to 50% were also analyzed (Table VI). DCE MRI values had low area under the curve for every KI-67 threshold.

DCE MRI and T stage. DCE MRI values differed significantly among the tumors with different T stages

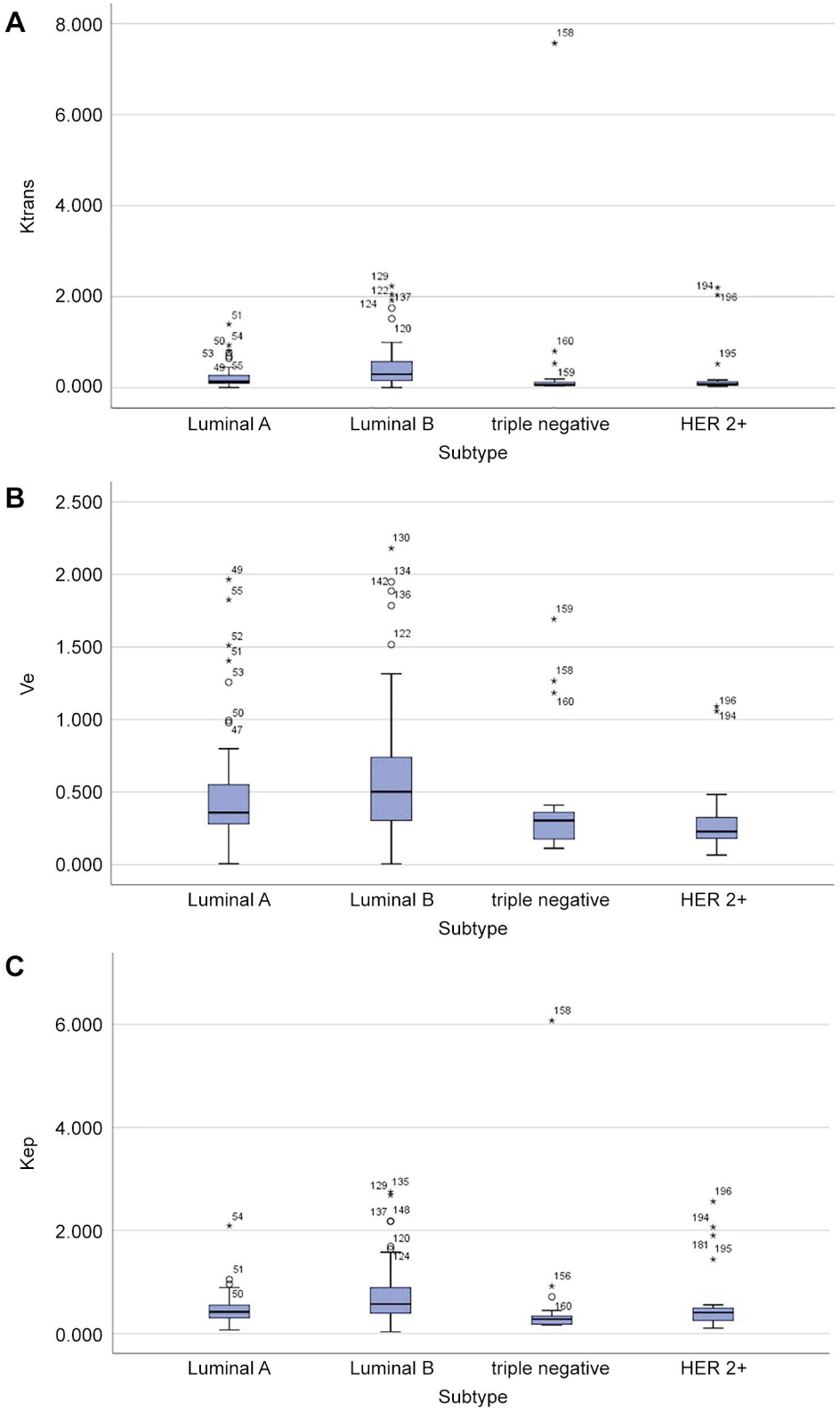

Figure 1. *Box plots of DCE MRI values in tumors with different molecular subtypes. (A) K_{trans}. No significant differences between K_{trans} values in the BC subtypes were found. (B) Overlapping of the V_e values between the tumor subtypes. (C) K_{ep}. No significant differences between K_{ep} values in the BC subtypes were identified.*

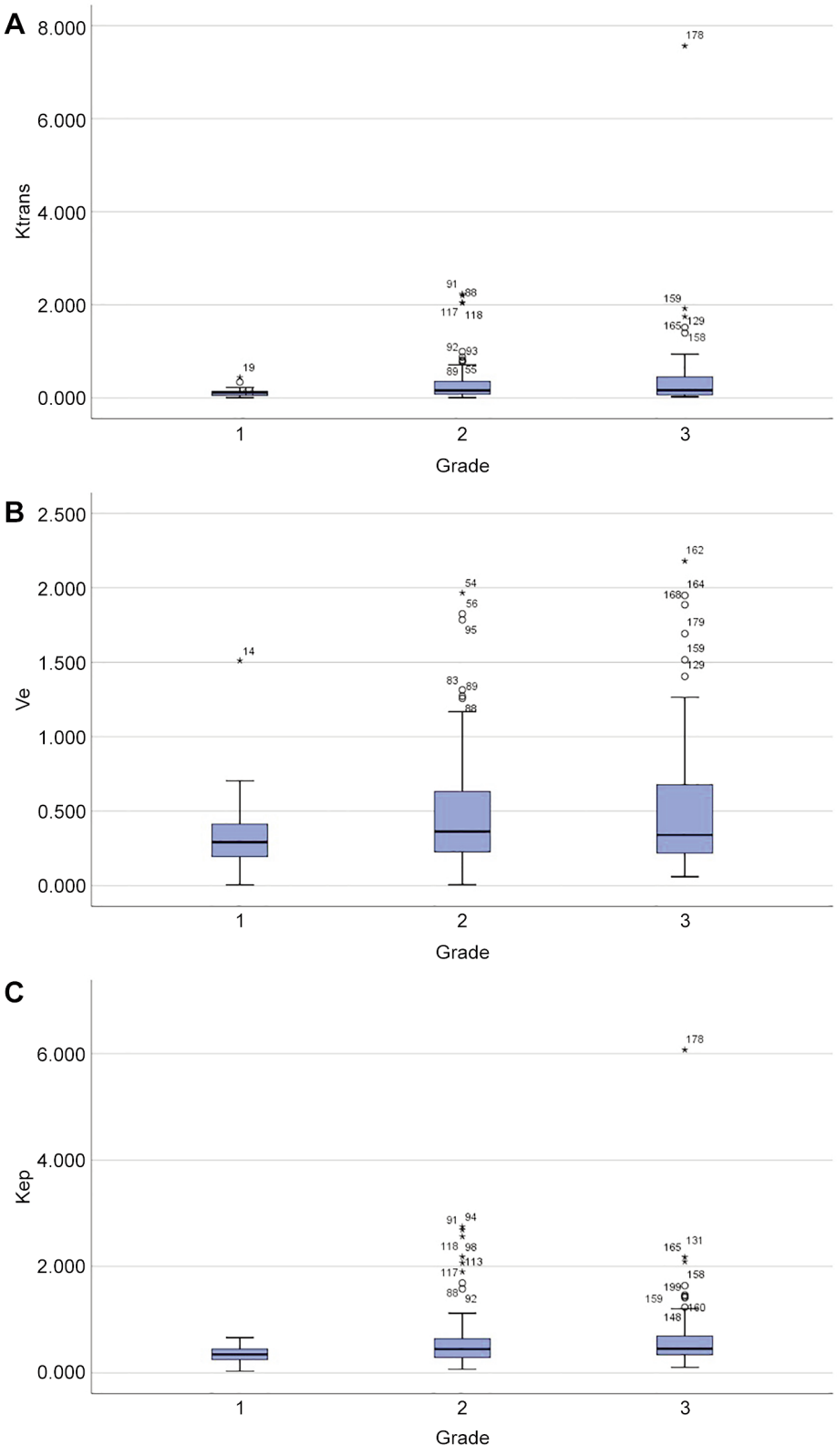

Figure 2. *Box plots of DCE MRI values in carcinomas with different tumor grades. (A) K_{trans}. There were no significant differences of K_{trans} values between several tumor grades. (B) V_e. No significant differences of V_e values between several tumor grades were observed. (C) K_{ep}. K_{ep} values did not differ significantly between several tumor grades.*

Table V. *Threshold values of Ktrans, Ve, and Kep for discrimination of tumors with high (>25%) expression of KI-67.*

	Threshold	Sensitivity	Specificity	PPV	NPV	Accuracy
K_{trans}, min^{-1}	0.3	75.5%	73.0%	64.9%	81.8%	74.0%
V_e, %	0.5	73.5%	66.2%	59.0%	79.0%	69.1%
K_{ep}, min^{-1}	0.55	63.3%	63.5%	53.4%	72.3%	63.4%

PPV, Positive predictive value; NPV, negative predictive value.

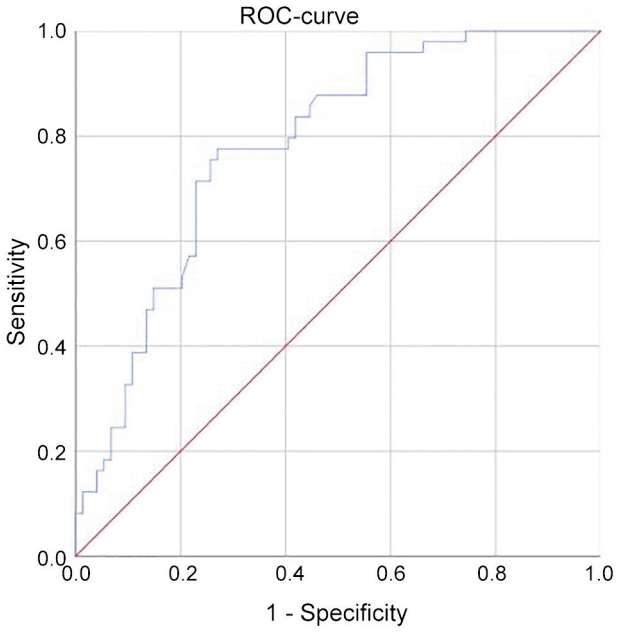

Figure 3. *Receiver operating characteristic (ROC) curve for use of K_{trans} for distinguishing of carcinomas with high proliferation potential (Ki67>25%) from tumors with low Ki 67 level (<25%). The area under the curve is 0.78. The optimal threshold value is 0.3 min^{-1} yealding a sensitivity of 75.5%, a specificity of 73.0%, an accuracy of 74.0%. The positive predictive value is 64.9%, and the negative predictive value is 81.8%.*

(Table VII). Carcinomas with T4 stage showed highest DCE MRI values in comparison to other tumor stages. However, DCE MRI values overlapped between the subgroups (Figure 4).

DCE MRI and nodal stage. Overall, in 104 BC N0 and in 96 BC N+ stages were diagnosed. All DCE MRI values were statistically significant higher in N+ tumors than in N0 lesions (Table VIII). However, the graphical distribution of DCE MRI values showed that they overlapped between the subgroups (Figure 5). Furthermore, ROC analysis also showed that DCE MRI values had very low areas under the curve in prediction of nodal stage in BC (Figure 6).

Table VI. *Areas under the curve for discrimination of tumors with different expression of KI-67 based on DCE MRI values.*

	KI-67 level				
	≥10%	≥20%	≥30%	≥40%	≥50%
K_{trans}	0.72	0.77	0.70	0.74	0.68
V_e	0.67	0.73	0.64	0.63	0.55
K_{ep}	0.63	0.67	0.67	0.72	0.70

DCE MRI, Dynamic contrast enhanced magnetic resonance imaging.

Table VII. *DCE MRI values in breast cancer with different tumor (T) stages.*

	T1	T2	T3	T4	*p*-Value
K_{trans}, min^{-1}	0.18±0.13	0.27±0.37	0.14±0.17	1.08±1.44	0.001
V_e, %	0.37±0.19	0.44±0.39	0.36±0.33	0.99±0.57	0.001
K_{ep}, min^{-1}	0.50±0.29	0.54±0.41	0.36±0.23	1.21±1.26	0.001

DCE MRI, Dynamic contrast enhanced magnetic resonance imaging.

Table VIII. *Comparison of DCE MRI values in BC with and without nodal metastases.*

	BC with N0 stage, M±SD	BC with N+ stage, M±SD	*p*-Value
K_{trans}, min^{-1}	0.17±0.15	0.50±0.89	0.001
V_e, %	0.37±0.21	0.60±0.52	0.001
K_{ep}, min^{-1}	0.48±0.34	0.72±0.79	0.007

DCE MRI, Dynamic contrast enhanced magnetic resonance imaging; BC, breast cancer.

Discussion

The present study is the first multicenter project regarding associations between DCE MRI and clinically relevant histopathological features in BC. Previously, the role of DCE MRI was analyzed systematically in prostate cancer, glioma,

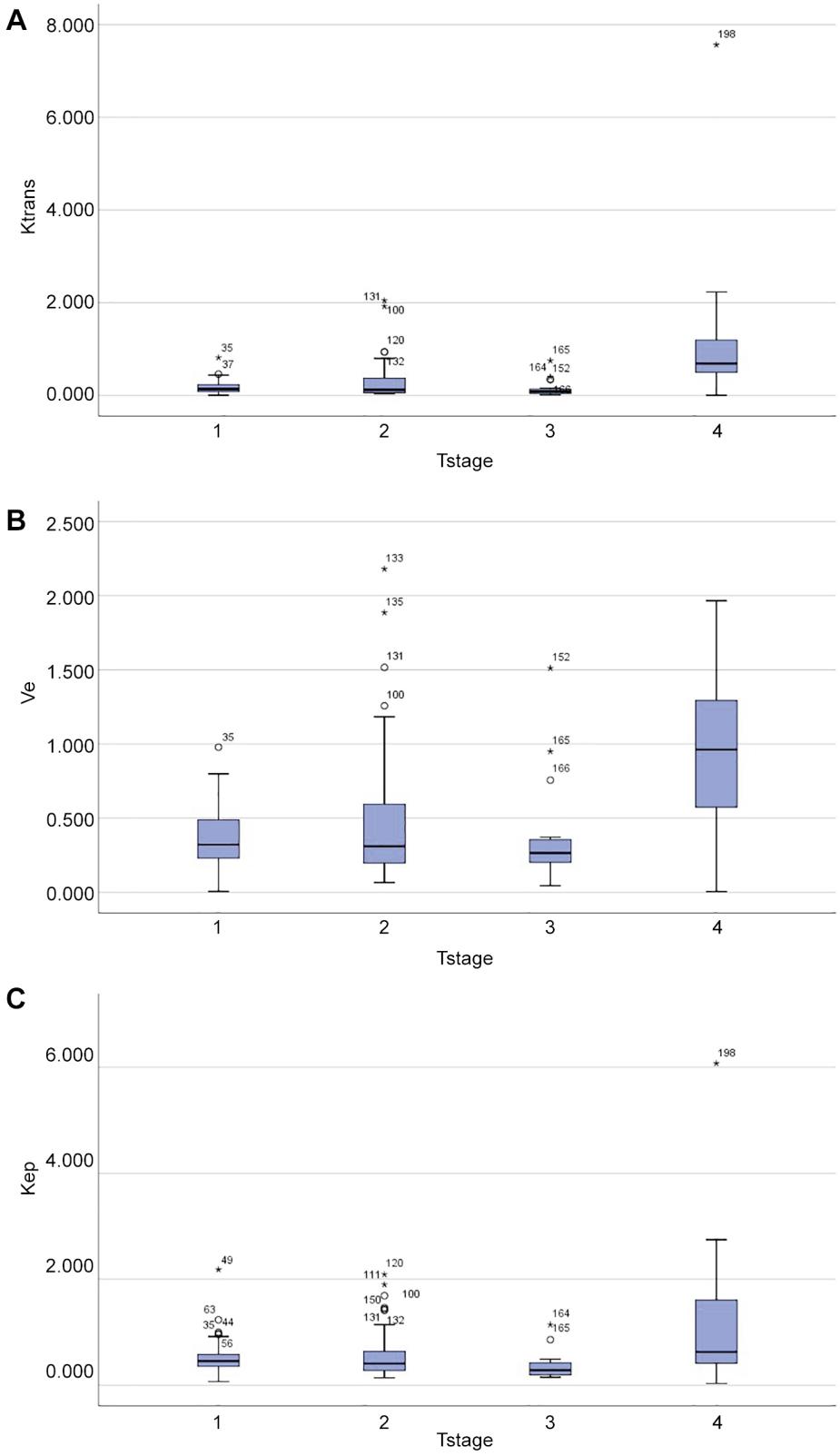

Figure 4. *Box plots of DCE MRI values in carcinomas with different tumor stages. (A) K_{trans}. K_{trans} values overlapped between the subgroups. (B) Significant overlapping of V_e values between the different tumor stages. (C) Overlapping of K_{ep} values between the different tumor stages.*

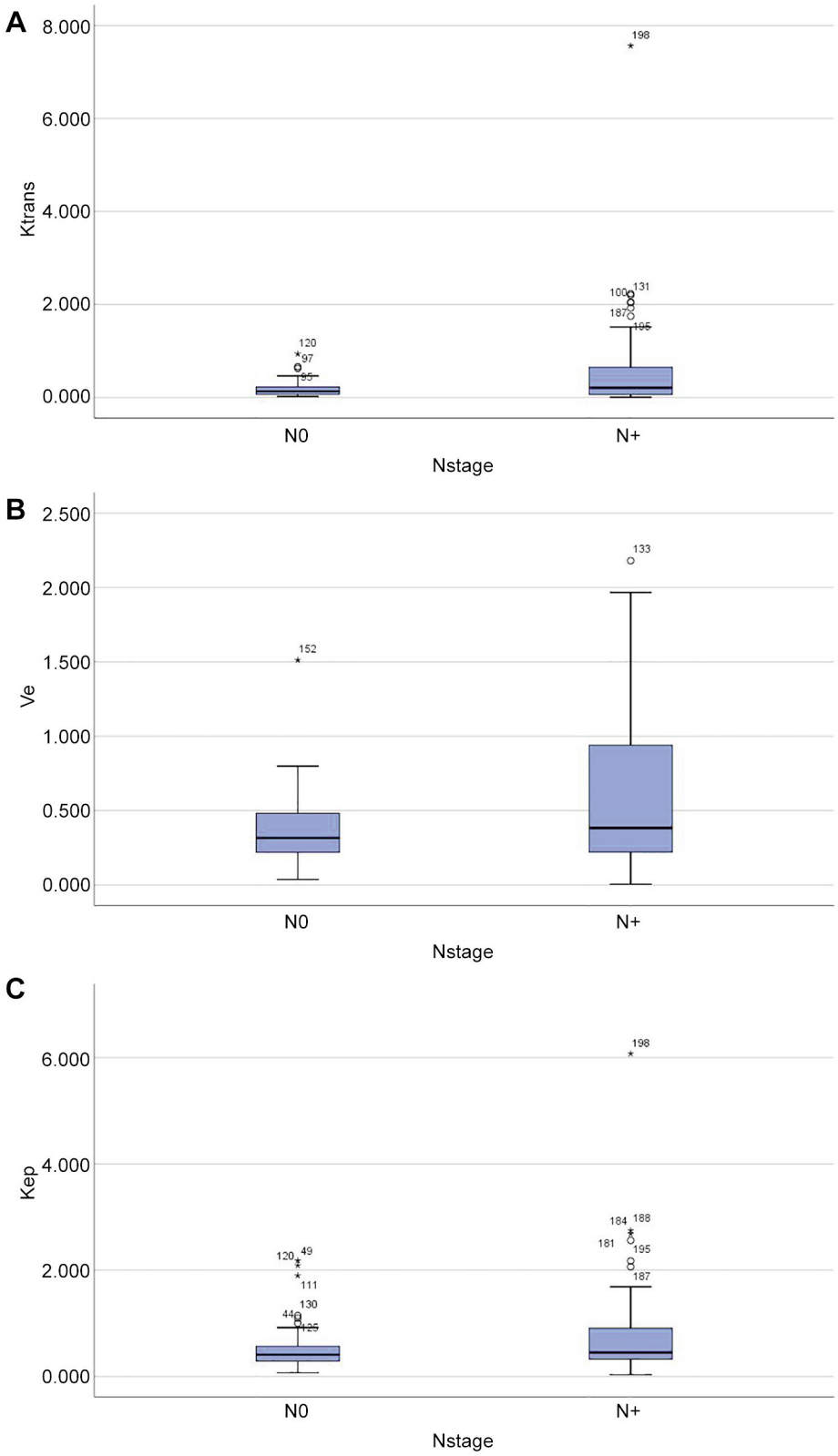

Figure 5. *Box plots of DCE MRI values in carcinomas with different nodal stages (N0, tumors without nodal metastases; N+ tumors with nodal metastases). (A) Graphical distribution of K_{trans} values showing overlapping between the subgroups. (B) Significant overlapping of V_e values between the tumors with different nodal stages. (C) Significant overlapping of K_{ep} values between the N0 and N+ tumors.*

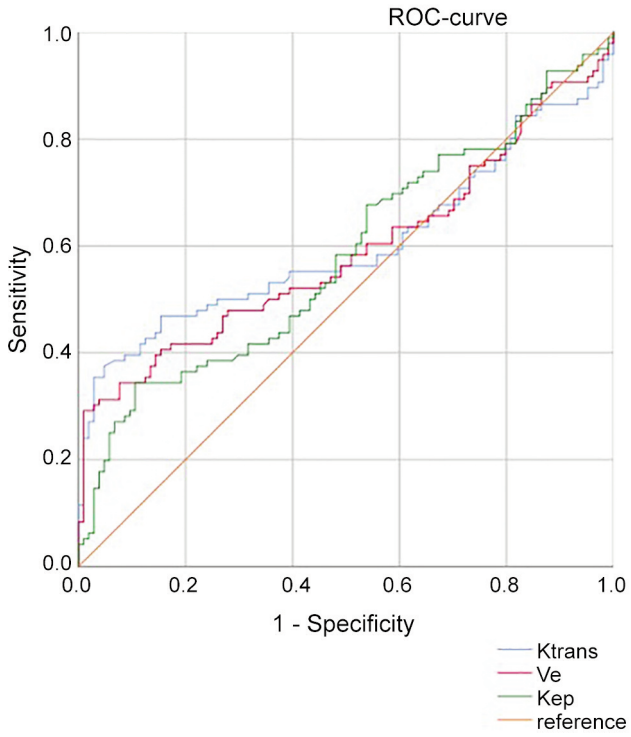

Figure 6. *Receiver operating characteristic (ROC) curve for use of DCE MRI values for distinguishing of carcinomas with and without nodal metastases. The areas under the curve for the parameters are as follows: K_{trans}, 0.60; V_e, 0.59; K_{ep}, 0.58.*

and squamous cell carcinoma of the head and neck region. In prostate cancer, it was shown that K_{trans} values were significantly higher for high-grade *versus* low-grade lesions (15). Furthermore, K_{ep} correlated positively with mean blood vessel count and mean vessel area (16). In glioma, K_{trans} and V_e values of grade 2 tumors were significantly lower than those of grade 3 (17). Moreover, K_{trans} and V_e significantly correlated with the KI-67 index (17). Finally, K_{trans} showed a significant positive correlation with microvessel density in different tumors (18). Also, in head and neck squamous cell carcinomas DCE MRI can predict relevant histopathological features. So far, K_{trans} correlated well with expression of KI-67 and V_e with the mean microvessel diameter (19).

In BC, only few studies reported data about associations between DCE MRI and histopathology. The published results are promising. For instance, it has been shown that parameters of DCE MRI were different in tumors with different hormone receptor expression and grade. So far, grade 3 cancers had higher K_{trans} and K_{ep} values in comparison to grade 1 lesions (11, 12). Mean V_e was lower in tumors with a high histologic grade than in tumors with a low histologic grade (11). Regarding expression of hormone receptors, triple negative BC showed higher K_{trans} and K_{ep}, but lower V_e values than luminal BC (12). Furthermore, V_e correlated inversely with HER 2 expression (20).

Our data showed that HER 2 rich BC had lowest K_{trans} and V_e values in comparison to other subtypes. Furthermore, triple-negative BC had highest K_{trans} values. However, as shown, values of DCE MRI overlapped significantly and, therefore, cannot be used for prediction of hormone receptor status in BC in clinical practice. Furthermore, our data indicated that DCE MRI parameters did not reflect tumor grade in BC.

Another important aspect in BC is expression of proliferation marker KI-67. It is well known that high expression of KI-67 is associated with a greater risk of death compared with lower expression rates (21). Therefore, prediction of proliferation potential of BC based on imaging is very important. According to previous reports, parameters of DCE MRI are associated with the KI-67 index. However, the reported data are controversial (12, 13, 21). For example, Kang *et al*. showed that carcinomas with high expression KI-67 showed statistically significant higher Kep values in comparison to BC with low expression of KI-67 and K_{trans} and V_e values did not differ between the tumors (12). Liu *et al*. found that only K_{trans} correlated with KI-67 (20). Koo *et al*. did not observe any statistically significant associations between DCE MRI values and KI-67 (11). Finally, Kim *et al*. identified significant relationships between K_{trans}, K_{ep} and KI-67, but not between V_e and KI-67 (22). Moreover, the previous studies used different thresholds of KI 67 expression for distinguishing tumors with low and high proliferation activity, namely 15% (12), 10% (20), and 5% (11). In one study two threshold values, 5% and 15% were analyzed (22). This fact relativizes the reported results. According to a large meta-analysis based on data of 64,196 patients, the optimal KI-67 cut-off is 25% (21). It has been shown that this cut-off is associated with a greater risk of death compared with lower expression rates (21).

In the present work, KI-67 correlated well with all DCE MRI parameters. The strongest correlation was observed with K_{trans} (r=0.44, p=0.0001). However, the optimal threshold of K_{trans} to discriminate BC with high (>25%) and low (<25%) expression of KI-67 yielded a relatively low sensitivity (75.5%) and specificity (73.0%), as well as low accuracy (74.0%). Also, this applied for several alternate thresholds of KI-67 expression ranging from 10% to 50%.

Another important clinical question is, if imaging features of primary tumors can predict occurrence of nodal and/or distant metastases. Previously, it was indicated that some MRI features of BC were associated with occurrence of nodal metastases (23). Regarding DCE MRI, presumably, perfusion parameters of primary tumor may be able to predict occurrence of lymph node metastases. In fact, BC with lymphovascular space invasion (LVSI) had higher K_{trans} and K_{ep} than tumors without LVSI (12). Our results,

however, did not confirm this hypothesis. Although DCE MRI parameters of BC differed between N0 *vs*. N+ stages, all of them overlapped significantly. Therefore, parameters of DCE MRI obtained from primary tumors cannot be used for prediction of nodal stage in BC.

The present multicenter study is the largest to date. However, there are certain limitations to address. The involved patients were investigated on different MR scanners with different technical parameters like field strength and other. Our sample consists predominantly of invasive ductal carcinomas. Therefore, this study could not compare DCE MRI values between different tumor types. Presumably, other types like lobular or mucinous carcinomas may have different DCE MRI parameters than ductal carcinomas.

Conclusion

Our multicenter study showed that DCE MRI parameters K_{trans}, K_{ep}, and V_e cannot be used as a reliable surrogate marker for hormone receptor status, tumor stage and grade in BC. K_{trans} correlated moderately with expression of KI-67 and may discriminate lesions with high and lower proliferation activity.

Availability of Data and Materials

The data that support the findings of this study are available from professor Surov but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of professor Surov.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Concept design: Surov A.; Data collection: Kim J. Y., Aiello M., Huang W., Yankeelov T.E.; Statistical analysis: Wienke A.; Manuscript writing: Surov A., Pech M.; Final approval of manuscript: Kim J. Y., Aiello M., Huang W., Yankeelov T.E., Wienke A., Pech M.

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Received August 26, 2021
Revised October 3, 2021
Accepted October 12, 2021