Aus der Klinik für Radiologie
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DISSERTATION

Gadoxetsäure-verstärkte Magnetresonanztomographie als bildgestützter Leberfunktionstest

Gadoxetic acid-enhanced magnetic resonance imaging as an imaging-based liver function test

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Table of contents

Abbreviations:

AUC	Area under the curve
DHCE-MRI	Dynamic hepatobiliary contrast enhanced magnetic resonance imaging
FLR	Future liver remnant
FLV	Functional liver volume
Gd-EOB-DTPA	Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid
Gd-BOPTA	Gadolinium diethylenetriaminepentaacetic acid
HBP	Hepatobiliary phase
HEF	Hepatic extraction fraction
HUI	Hepatocellular uptake index
ICG	Indocyanine green
ICG-PDR	ICG plasma disappearance rate
irBF	input relative blood flow
LiMAx-Test	Liver Maximum function capacity test
LMR	Liver-to-muscle ratio
LSR	Liver-to-spleen ratio
MELD	Model for End-Stage Liver Disease
MRI	Magnetic resonance imaging
MRP2	Multidrug resistance-associated protein 2
MTT	Mean transit time
NETs	Neuroendocrine tumors
OATP	Anion-transporting polypeptides
PHLF	Post-hepatectomy liver failure
PVE	Portal vein embolization
RE	Relative enhancement
ROC	Receiver operating characteristic
SPECT	Single photon emission computed tomography
SI	Signal intensity
^{99m}Tc-GSA	Technetium–99m diethylenetriaminepentaacetic acid galactosyl human serum albumin
T1 RR (△%)	T1 reduction rate
TLV	Total liver volume
T1 pre	T1 relaxation time pre-contrast
T1 post	T1 relaxation time post-contrast

I. Abstract:

I.I. English version:

The aim of the study is to further corroborate the validity of gadoxetic acid-enhanced magnetic resonance imaging (MRI) as an imaging-based liver function test. In this context, we compared gadoxetic acid-enhanced MRI T1 relaxometry-derived indices with the ^{13}C-methacetin breath test (LiMAx test) in 53 patients who underwent MRI examinations less than 30 days apart from the LiMAx test. [**Original work1**]

For further validation, we assessed the consistency of gadoxetic acid-enhanced MRI as an imaging-based liver function test across serial examinations, different MRI scanners and field strengths (1.5 T and 3.0 T) and investigated variable factors that may affect the uptake of gadoxetic acid, i.e., predictors of relative enhancement (RE) of the liver in the hepatobiliary phase (HBP). We retrospectively investigated 554 patients who underwent two or more gadoxetic acid-enhanced MRI examinations. RE of the liver in the HBP, liver-to-muscle ratio (LMR), liver-to-spleen ratio (LSR) and T1 reduction rate (T1 RR) were calculated. [**Original work 2**]

In a subgroup analysis of patients undergoing chemotherapy (n = 238), we observed a significant decrease in RE, i.e., liver function, between two consecutive MRI examinations. Based on this observation, we conducted a study to evaluate the hepatotoxicity of different chemotherapeutic agents using gadoxetic acid-enhanced MRI in 129 patients with neuroendocrine tumors (NETs) who underwent at least two serial MRI examinations (a total of 539 MRI). [**Original work 3**]

In conclusion, the significant correlation of T1 relaxometry derived-indices with LiMAx test, the consistency and reproducibility of RE of the liver over time and across different MRI scanners and field strengths, as well as the possibility of estimating chemotherapy-induced liver impairment, i.e., the hepatotoxic effect of different chemotherapeutic agents using gadoxetic acid-enhanced MRI, represent the major findings in our studies. These observations further emphasize gadoxetic acid-enhanced MRI as an imaging-based liver function test, which could have a paramount influence on patient care as it may be easily integrated into clinical routine.

I.II. deutsche Version

Ziel der Studien war es, die Validität der Gadoxetsäure-verstärkten (Gd-EOB) MRT als bildgestützten Leberfunktionstest zu validieren. In diesem Zusammenhang haben wir bei 53 Patienten retrospektiv die Gd-EOB-verstärkte T1-Relaxometrie mit dem ^{13}C-Methacetin-Atemtest (LiMAx-Test) verglichen, bei denen sowohl eine MRT als auch der LiMAx-Test durchgeführt wurde. [**Originalarbeit1**]

Weitere Arbeiten hatten die Bewertung der longitudinalen Konsistenz und Reproduzierbarkeit der Gd-EOB-verstärkten MRT als Leberfunktionstest zum Ziel. Desweiteren sollte der Einfluß verschiedener Geräte und Magnetfeldstärken (1,5 T und 3,0 T) sowie die Bestimmung von Faktoren, die die Aufnahme von Gd-EOB beeinflussen können, d.h. Prädiktoren der relativen Enhancement der Leber untersucht werden [**Originalarbeit 2**]. In einer Subgruppen-Analyse von Patienten, bei denen eine Chemotherapie durchgeführt wurde (n = 238), beobachteten wir eine signifikante Abnahme des relativen Enhancements, d.h. der Leberfunktion, zwischen zwei konsekutiven MRT-Untersuchungen. Aufgrund dieser Feststellung führten wir eine weitere Studie durch, um mittels Gd-EOB-verstärkter MRT bei 129 Patienten die Hepatotoxizität verschiedener Chemotherapeutika mit neuroendokrinen Tumoren (NETs) zu bewerten, die sich zwei oder mehr seriellen MRT-Untersuchungen unterzogen (insgesamt 539 MRT). [**Originalarbeit 3**]

Zusammenfassend stellen die signifikante Korrelation der T1-Relaxometrie mit dem LiMAx-Test, die Konsistenz und Reproduzierbarkeit des relativen Enhancements über die Zeit und über verschiedene Geräte und Magnetfeldstärken sowie die Möglichkeit der Abschätzung der Chemotherapie-induzierten Leberschädigung, d.h. der hepatotoxischen Wirkung verschiedener Chemotherapeutika, unter Verwendung der Gd-EOB-verstärkten MRT, die Hauptergebnisse unserer Studien dar. Diese Beobachtungen validieren die Gd-EOB-verstärkte MRT als bildgestützten Leberfunktionstest, der einen großen Einfluss auf die Patientenversorgung haben könnte, da er sich einfach in die klinische Routine integrieren lässt.

II. Synopsis

II.I Introduction and objectives

II.I.I. Imaging-based liver function measurement

Liver function comprise a diversity of subfunctions such as biotransformation, synthesis of variable proteins and clotting factors, excretion of substances like bilirubin, storage of vitamins and glycogen, and immunological functions. In routine clinical practice, evaluation of functional liver capacity is essential in monitoring of patients with chronic liver disease, oncology patients, and patients with hepatic malignancy to select the most suitable therapeutic intervention. Specifically, evaluation of functional liver capacity is a cornerstone for predicting risk of post-hepatectomy liver failure (PHLF) in patients undergoing major liver resection, as well as evaluating and follow up of liver transplantation patients.[1, 2]

The currently available liver function tests such as the ^{13}C-methacetin breath test (LiMAx test; LIver MAximum function capacity, Humedics GmbH, Berlin, Germany), indocyanine green (ICG) test and clinical score-based models as Child-Pugh classification and Model for End-Stage Liver Disease (MELD) score are global liver function tests with limited role in evaluating regional liver function which is of great importance in patients with regional disparities of liver function as in primary sclerosing cholangitis, prolonged unilateral cholestasis or after portal vein embolization (PVE).[3, 4] In addition, segmental liver function evaluation is critical in patients undergoing liver resection for hepatic malignancies since resections are becoming more radical, increasing the risk of PHLF (reported incidence of 0.7 - 9.1%).[5, 6]

As an alternative, imaging-based liver function tests add spatial and temporal information about regional liver function. They are based on intravenous application of imaging-measurable substances which are taken up by the hepatocytes and then either excreted in bile or degraded. Measurement of uptake and excretion of these substances – in parts of or the whole liver – can be performed either at a fixed time point or dynamically to determine kinetics using nuclear imaging and MRI as imaging-based liver function tests. [1, 7]

II.I.II. Nuclear imaging techniques as imaging-based liver function test

Nuclear imaging techniques are either planar using single or dual head gamma camera or three-dimensionally via single-photon emission computed tomography (SPECT). However, hepatobiliary scintigraphy (HBS) has a low diagnostic accuracy considering the low temporal and spatial resolution as well as the planar acquisition which results in an overlap of the left and right liver sectors. As a result, patients undergo additional imaging for diagnostic purposes. By Combining SPECT-CT with HBS, additional information on regional functional capacity can be assessed.[1, 2, 8]

Hepatobiliary tracers used in nuclear imaging are currently based on ^{99m}technetium (^{99m}Tc). In clinical practice, ^{99m}Tc-labeled diethylenetriaminepentaacetic acid galactosyl human serum albumin (GSA) scintigraphy and ^{99m}Tc-mebrofenin HBS are the two nuclear imaging techniques used as imaging-based liver function tests.[1, 9]

Different studies have suggested preoperative ^{99m}Tc-GSA scintigraphy to estimate volume of the future liver remnant (FLR) and predict PHLF.[10, 11] However, ^{99m}Tc-GSA scintigraphy is only available in Japan.[12]

As for ^{99m}Tc-Mebrofenin HBS, various studies have indicated its value in preoperative workup before major hepatectomy for evaluation of FRL and prediction of PHLF, as well as stratification of PVE and evaluation of segmental liver function.[2, 7–9] Erdogan et al. reported a correlation between ^{99m}Tc-Mebrofenin and ICG for evaluation of total liver function in addition to the added information about segmental functional capacity.[13] Cieslak et al. concluded that preoperative ^{99m}Tc-Mebrofenin improved the outcome after major liver resection with lower PHLF by assigning PVE according to liver function.[14]

II.I.III. Gadoxetic acid-enhanced MRI as an imaging-based liver function test: a review

Gadoxetic acid (Gd-EOB-DTPA, gadoxetate disodium; Primovist®/Eovist®, Bayer HealthCare, Berlin, Germany) and gadobenate-dimeglumine (Gd-BOPTA; MultiHance®, Bracco-Byk Gulden, Constance) are the two MRI hepatocyte-specific contrast agents approved in Germany.[1] However, the percentage of hepatocellular uptake and biliary excretion differs between Gd-BOPTA (3–5%) and gadoxetic acid (50%). Due to the low hepatocellular uptake and biliary excretion, Gd-BOPTA has not been able to match up to gadoxetic acid as an imaging-based liver function test.[15, 16]

Gadoxetic acid is absorbed via organic anion-transporting polypeptides (OATP 1B1/1B3), which are transporters exclusively expressed on the membrane of the hepatocytes, and subsequently excreted into the biliary system via multidrug resistance-associated protein 2 (MRP2) without any biotransformation.[17] By sharing similar pharmacokinetics with mebrofenin, (both are absorbed by hepatocytes and excreted in bile without any metabolic changes), the application of gadoxetic acid-enhanced MRI as a surrogate imaging-based liver function test analogous to ^{99m}Tc-mebrofenin HBS is justified, specifically considering the higher temporal and spatial resolution and lack of ionizing radiation.[1, 8]

Different approaches of varying complexity have been described to estimate global and regional liver function using gadoxetic acid-enhanced MRI. By far, evaluation of gadoxetic acid kinetics by signal intensity (SI) curves in dynamic hepatobiliary contrast enhanced MRI (DHCE-MRI) is the most complex approach.[1, 16] The complexity of this approach is mainly because signal intensity curves must be determined for each individual voxel. Different indices are extracted including hepatic extraction fraction (HEF), input relative blood flow (irBF), and mean transit time (MTT).[18, 19]

Another approach is evaluation of SI-based indices. However, these indices are not absolute values and could be influenced by variable non-disease related technical parameters, such as strength of the radiofrequency amplifier, potency of receiver coils, as well as the differences between MRI scanners and field strengths. Consequently, quantitative evaluation of liver enhancement, i.e., liver function should not be based on

SI changes before and after gadoxetic acid administration. Alternatively, several methods have been reported based on SI measurements including RE of the liver as well as SI adjustment with tissues without transporter-mediated cellular gadoxetic acid uptake such as spleen (liver-to-spleen ratio [LSR]) and paravertebral muscle (liver-to-muscle ratio [LMR]).[17, 20, 21] By taking the liver volume into consideration, hepatocellular uptake index (HUI) had a significant correlation with the ICG plasma disappearance rate (ICG-PDR) as reported by Yamada et al.[22]

T1 relaxometry represents an alternative to SI-based indices where T1 relaxation time is reduced after gadoxetic acid administration because of its paramagnetic characteristic. Unlike SI-based indices, T1 relaxometry measurements are less variable (i.e., absolute) and not influenced by the fore-mentioned technical parameters. The calculated measurements include the T1 reduction rate (T1 RR, △%) which represents the rate of reduction of T1 relaxation time between unenhanced and contrast-enhanced phases and T1 relaxation velocity index (ΔR1). [20, 21, 23] Katsube et al. were the first to evaluate gadoxetic acid-enhanced T1 relaxometry for assessment of liver function. They demonstrated a significantly longer post-contrast T1 relaxation time (T1 post) in patients with impaired liver function.[24] Recent studies demonstrated superiority of T1 relaxometry measurements over SI-based indices for evaluation of global and segmental liver function.[25, 26]

Noda et al. correlated enhancement of the biliary tract, in the form of SI ratio of the biliary tract to paravertebral muscles in gadoxetic acid-enhanced MRI, with different scoring models. The study revealed a significant correlation of SI ratio in the common bile duct and cystic duct with the Child-Pugh classification, MELD score and aspartate aminotransferase-to-platelet ratio index (APRI).[27]

Different studies have validated gadoxetic acid-enhanced MRI-based indices for prediction of PHLF such as RE[28, 29], remnant hepatocyte uptake index (rHUI)[29], as well as DHCE-MRI-based indices including HEF, irBF, HEFmL (HEF multiplied by the whole liver volume) and remnant HEFmL (HEF multiplied by residual liver volume)[30].

Noda et al. investigated a new gadoxetic acid-enhanced MRI-based index, the hepatocyte fraction (HeF). Their results demonstrated a moderately negative correlation between this new biomarker and the Child–Pugh classification ($r = -0.58$, $P < 0.0001$) as well as a fair to moderately negative correlation with the MELD score ($r = -0.57$, $P < 0.0001$).[31]
Yoon et al. demonstrated a significant negative correlation between the hepatocyte uptake ratio, a another recent gadoxetic acid-enhanced MRI quantitative index for the amount of gadoxetic acid uptake into hepatocytes in T1 mapping and a dual-compartment model, and ICG retention test (ICG-R_{15}).[32]

The aim of the present studies was to further validate gadoxetic acid-enhanced MRI as an imaging-based liver function test.

II.II. Patients and methods:

In **original work 1**, out of 597 patients who underwent gadoxetic acid-enhanced MRI examinations including T1 relaxometry between January 2015 and October 2016, we retrospectively identified 168 patients who were also evaluated with the LiMAx test. Of these 168 patients, 53 patients underwent MRI examinations < 30 days apart from the LiMAx test. Variable MRI-derived indices including T1 relaxation time before (T1 pre) and 20 min after gadoxetic acid administration (T1 post), T1 RR [((T1 pre – T1 post)／T1 pre) × 100 (%)], total liver volume (TLV), and functional liver volume (FLV) were determined. In addition, patients were classified into three subgroups depending on liver function evaluation by LiMAx test: patients considered to have normal liver function (LiMAx result of >315 mg/kg/h), patients with impaired liver function (LiMAx result of <315 mg/kg/h) and patients with heavily impaired liver function (LiMAx result of <140 mg/kg/h).
Pearson correlations, multiple linear regression analysis, and receiver operating characteristic (ROC) curve analysis were performed for T1 relaxometry-derived indices (T1 RR, T1 RR x TLV, T1 RR x FLV, and T1 post), liver volumetry indices (TLV, FLV), and bilirubin to identify the best predictor of liver function as determined by the LiMAx test. A LiMAx of 315 mg/kg/h and 140 mg/kg/h were used as cutoffs for ROC analysis.

In **original work 2**, we retrospectively identified a total of 1,116 patients who underwent at least 2 serial gadoxetic acid-enhanced MRI examinations between August 2014 and April 2018. The exclusion criteria were: 1. previous locoregional interventional treatments for liver tumors (n = 534), 2. previous PVE (n = 13), 3. liver transplantation after the first MRI examination (n = 2), and 4. technical problems during the examination resulting in incomplete MRI (n = 13). After exclusion, 554 patients were included in the analysis.
RE of the liver in the HBP, LSR, and LMR were calculated. T1 RR was calculated in a small group of patients (n=26) with available T1 mapping. The indices were calculated as follows:

- RE = (SI in HBP − SI unenhanced)／SI unenhanced
- LMR = liver SI in HBP/muscle SI in HBP
- LSR = liver SI in HBP／spleen SI in HBP
- T1 RR = ((T1 unenhanced − T1 in HBP)／T1 unenhanced) × 100 (%)

Multiple linear regression analysis was used to investigate the possible predictors of RE of the liver, i.e., liver function. Repeated measures analysis was performed using Linear mixed model and Greenhouse–Geisser test with the timepoint of MRI serving as a fixed variable.

In **original work 3**, we retrospectively identified a total of 129 patients with NETs who underwent two or more serial gadoxetic acid-enhanced MRI examinations (a total of 539 MRI scans) between January 2014 and December 2018 and started chemotherapy in the beginning of that time period. The chemotherapeutic agents were classified into 4 groups depending on the degree of hepatotoxicity, with either no (group 1), minimal (group 2), moderate (group 3), or severe (group 4) hepatotoxic effect. The aim of the grouping was to calculate a “hepatotoxicity score” which was calculated for the period before and the period after starting the chemotherapy. RE of the liver in the HBP ((SI in HBP − SI unenhanced)／SI unenhanced) was evaluated using linear mixed model analysis with respect to different factors as fixed variables including the time between MRI examinations, primary chemotherapy, hepatotoxicity score as well as age and gender. In addition, binary logistic regression was used to verify whether the hepatotoxicity score predicts a significant impact of chemotherapeutic agents on RE and subsequently liver function.

II.III. Results:

In **original work 1**, all T1 relaxometry-derived indices (T1 RR, T1 RR x TLV, T1 RR x FLV, and T1 post) showed a statistically significant Pearson correlation ($P < 0.001$) with LiMAx test results and a statistically significant capacity to discriminate between patients with LiMAx > 315 mg/kg/h and patients with LiMAx < 315 mg/kg/h ($P < 0.001$) with T1 RR demonstrating the greatest area under the curve (AUC; 0.859). T1 RR critical value of 47% predicted LiMAx > 315 mg/kg/h with 94% sensitivity and 73% specificity. Similarly, all the previously mentioned relaxometry-derived indices (T1 RR, T1 RR x TLV, T1 RR x FLV, and T1 post) demonstrated a statistically significant capacity to differentiate patients with LiMAx > 140 mg/kg/h from patients with LiMAx < 140 mg/kg/h ($P < 0.001$) with T1 post yielding the greatest AUC (0.966), while T1 RR yielded the second greatest AUC (0.956). A T1 post critical value of 573 msec predicted LiMAx < 140 mg/kg/h with 100% sensitivity and 91% specificity. In multiple linear regression analysis with LiMAx test as the dependent variable, only T1 RR proved to be a statistically significant predictor of the outcome ($P < 0.001$). In addition, there was no significant difference between the 1.5 T and 3 T field strengths regarding the ratio of LiMAx test to TI RR measurements ($p=0.178$) in Mann–Whitney U-test.

In **original work 2**, paired t-test and Greenhous–Geisser test revealed no statistically significant difference in RE, LSR, LMR, or T1 RR between any two consecutive MRI examinations, while a statistically significant difference between the first and fourth MRI scans was noted with the Greenhous–Geisser test. However, this significance was not confirmed in the linear mixed model analysis. There was a significant negative correlation of patient age with RE of the liver in the HBP ($r = -0.130$, $p = 0.002$), LSR ($r= -0.220$, $p < 0.001$), and LMR ($r = -0.117$, $p = 0.006$), while no significant correlation was noted with T1 RR ($p = 0.870$). In a subgroup analysis of patients without liver cirrhosis, this correlation was more marked ($r = - 0.215$, $- 0.299$ and $- 0.188$ for RE, LSR and LMR respectively). In multiple linear regression analysis of different factors that may affect the uptake of gadoxetic acid, only age, liver cirrhosis and serum bilirubin were statistically significant predictors, i.e., significant predictors of RE of the liver.

In **original work 3**, other than age, linear mixed model analysis identified chemotherapeutic agents with moderate or severe hepatotoxic effects, i.e., hepatotoxicity score 3 or 4 respectively (Etoposide/Cisplatin, Etoposide/Carboplatin, FOLFOX, Octreotide + Interferon, Lanreotide + Interferon, Sunitinib, and Temozolamide/ Capecitabine) as factors with a statistically significant negative impact on RE of the liver. On the contrary, chemotherapeutic agents with hepatotoxicity score 1 or 2, i.e. agent with no or only minimal hepatotoxic effect (Capecitabine, Everolimus, Octreotide, Lanreotide, Streptozotocin/5-Fluorouracil and Temozolomide) had no significant impact on RE. That is to say, the higher the hepatoxicity score of the chemotherapeutic agent, the higher the tendency of a greater decline of RE over time. Binary logistic regression analysis confirmed the results and yielded a perfect prediction ($p < 0.001$, R-squared of 0.7872) of the hepatotoxicity score ascribed to the chemotherapeutic agents.

II.IV. Discussion:

As an imaging-based liver function test, gadoxetic acid-enhanced MRI has been recently investigated and correlated with different model-based clinical scores (Child-Pugh classification [33, 34] and MELD score [35, 36]), dynamic liver function tests (ICG [22, 23, 30, 37], and LiMAx test [17, 20]), and nuclear imaging techniques (^{99m}Tc-mebrofenin HBS [2, 8] and ^{99m}Tc- GSA scintigraphy [12, 37]).

Other than the easy integration into routine clinical practice, assessment of spatial and temporal distribution of liver function is a paramount advantage of gadoxetic acid-enhanced MRI over laboratory investigations and clinical scoring models. The absence of ionizing radiation is an added advantage over scintigraphy.[1]

The aim of the following studies was to further validate gadoxetic acid-enhanced MRI as an imaging-based liver function test.

In **original work 1**, gadoxetic acid-enhanced MRI was compared with LiMAx test. We selected LiMAx test, a novel dynamic bedside test which is considered a gold standard for evaluation of functional liver capacity[38], because of its superiority over other liver function tests such as ICG-PDR based on a better correlation between residual LiMAx and post hepatectomy liver volume, compared to the residual ICG-PDR.[38]

In addition, the shared metabolic pathway between ICG and gadoxetic acid may cause them to correlate better with each other rather than with the actual liver function.[34, 38] On the contrary, the metabolic pathway of ^{13}C-methacetin in LiMAx test is completely different as it is exclusively metabolized in hepatocytes by cytochrome P450 1A2 (CYP1A2)[20] making the LiMAx test more preferable for the corroboration of gadoxetic acid-enhanced MRI as an imaging-based liver function test.

In our results, TI RR demonstrated the highest ability to predict liver function in correlation with the LiMAx test. On the contrary, liver volumetry-derived indices (TLV and FLV) had no significant correlation with the LiMAx test. This observation was in disagreement with previous studies supporting liver volumtery-derived indices for evaluation of liver function.[22, 23] However, these studies correlated the volumetry-derived indices with the ICG-PDR and not with LiMAx test which might explain the discrepancy.

Further prospective studies directly comparing SI-based indices (RE) with T1 relaxometry in correlation with LiMAx test are recommended to further validate T1 relaxometry as an imaging-based liver function test and to further emphasize its superiority over SI-based indices which was already suggested by several previous studies.[25, 26] Specifically, since T1 relaxometry is not routinely implemented in the standard liver MRI examination. Our study concluded that, as assessed by LiMAx test, gadoxetic acid-enhanced T1 relaxometry can quantitatively estimate liver function. Our study was in agreement with two studies by Haimerl et al. comparing signal intensity-based indices[17] and T1 relaxometry[20] in gadoxetic acid-enhanced MRI with LiMAx test.

In **original work 2**, the consistency and reproducibility of RE of the liver over short periods of time and across different MRI scanner types and field strengths further underscore gadoxetic acid-enhanced MRI as an imaging-based liver function test. Another finding in our study was the negative correlation between patient age and RE as well as with LSR and LMR and this correlation was more evident in non-cirrhotic patients. This observation was consistent with a previous study by Verloh et al.[39] Other than age, only liver cirrhosis and serum bilirubin were statistically significant predictors of RE and consequently, liver function. Our results were consistent with variable previous studies. Zhao et al. concluded that RE was significantly higher in patients without liver cirrhosis and in Child-Pugh class A patients than in patients with Child-Pugh class B and C ($P<0.001$). In addition, they demonstrated a statistically negative correlation ($P<0.01$) of RE with serum total bilirubin ($r=-0.263$), albumin ($r=0.328$) and prothrombin time ($r=-0.24$).[40] Kim et al. revealed similar results regarding the negative correlation between RE and the stage of liver cirrhosis. Furthermore, serum total bilirubin, albumin, sodium, aspartate aminotransferase, platelet count, prothrombin activity, as well as the presence of ascites demonstrated a significant correlation with RE.[33]

In our study, the RE the liver in the HBP gradually decreased over longer period of time. The reduction in RE was also observed in a subgroup of patients who underwent liver resection (n = 42 patients) between two successive MRI scans.

In a subgroup of patients who underwent chemotherapy (238 patients), a statistically significant decrease in RE between two consecutive MRI examinations was primarily attributed to the hepatotoxicity induced by chemotherapeutic agents.

Original work 3 was based on this finding. We investigated the possibility of concomitant assessment of the hepatotoxicity of different chemotherapeutic agents in patients with NETs using gadoxetic acid-enhanced MRI, which is already included in the routine follow-up schemes of these patients either to monitor or exclude liver metastases. Far as we know, we were the first to analyze the hepatotoxic effect of chemotherapy using gadoxetic acid-enhanced MRI.

In this retrospective study, we observed that monitoring of liver function in oncology patients using liver function tests such as the ICG-PDR or the LiMAx test, was not routinely performed, possibly for cost reasons. Alternatively, surrogate parameters as serum bilirubin, albumin, and international normalized ratio (INR) were used. However, these laboratory investigations are susceptible to different factors that may alter their values, which can be completely unrelated to the chemotherapy-induced hepatotoxic effects such as hyperbilirubinemia due to biliary obstruction, hypoalbuminemia secondary to diminished protein intake or malabsorption and anticoagulation therapy effect on INR.

Our results further corroborate the current hepatotoxicity classification system of different chemotherapeutic agents and validates gadoxetic acid-enhanced MRI for assessment of the hepatotoxic effect of different chemotherapeutic agents and consequently, as an imaging-based liver function test. Further prospective studies are needed to validate our results and to address other malignancies such as colorectal cancer.

Our studies had several limitations. The retrospective design was a common limitation between the three studies. In **original work 1**, the study was limited by the small total number of patients (n = 53), and in particular, the small number of patients with severely impaired liver function (n = 8). In **original work 2**, the rather small number of patients examined with T1 mapping sequences (n = 26), may have rendered the results of this subgroup analysis less valid. In **original work 3**, gadoxetic-acid-enhanced MRI was not correlated with other liver function tests to further corroborate its validity. In addition, the

underrepresentation of category 4 chemotherapeutic agents may have limited the validity of the results with respect to this group.

II.V. Summary and Conclusion:

Since the introduction of the hepatocyte-specific contrast agent - gadoxetic acid - in clinical practice, gadoxetic acid-enhanced MRI has been thoroughly investigated as an imaging-based liver function test. Advantages of this modality include the easy integration into routine diagnostic work up in a cost neutral manner, non-invasiveness, absence of ionizing radiations, plus the concomitant evaluation of liver vasculature, and biliary tree (both anatomical and functional), as well as characterization of hepatic focal lesions. Specifically, the high temporal and spatial resolution, and the ability to estimate regional functional liver capacity are the most important advantages over other liver function tests.

The significant correlation of T1 relaxometry derived-indices with LiMAx test, the consistency and reproducibility of RE of the liver over time and across different MRI scanners and field strengths, as well as the possibility of estimating chemotherapy-induced liver impairment, i.e., the hepatotoxic effect of different chemotherapeutic agents using gadoxetic acid-enhanced MRI, represent the major findings in our studies. These observations further emphasize gadoxetic acid-enhanced MRI as an imaging-based liver function test, which could have a paramount influence on patient care as it may be easily integrated into clinical routine.

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III. Statutory declaration:

“I, Aboelyazid Elkilany by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic "Gadoxetic acid-enhanced magnetic resonance imaging as an imaging-based liver function test" "Gadoxetsäure-verstärkte Magnetresonanztomographie als bildgestützter Leberfunktionstest" independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice. I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of own contribution to the publications:

Aboelyazid Elkilany contributed the following to the below listed publications:

Publication 1:

Theilig D, Tsereteli A, **Elkilany A**, Raabe P, Lüdemann L, Malinowski M, Stockmann M, Pratschke J, Hamm B, Denecke T, Geisel D. Gd-EOB-DTPA-enhanced MRI T1 relaxometry as an imaging-based liver function test compared with ^{13}C-methacetin breath test. Acta Radiol. (2019). https://doi.org/10.1177/0284185119861314

Contribution:

After extensive literature research and familiarization with the topic of gadoxetic acid-enhanced MRI as an imaging-based liver function test, Dr. med. Dorothea Theilig developed the project idea independently under the expert guidance of PD. Dr. med. Dominik Geisel and Univ.-Prof. Dr. med. Timm Denecke. Dr. med. Dorothea Theilig and Mrs. Ana Tsereteli developed the study design together with PD. Dr. med. Dominik Geisel. Dr. med. Dorothea Theilig and Mrs. Ana Tsereteli carried out the detailed planning as well as the selection of the inclusion and exclusion criteria under the expert guidance of PD. Dr. med. Dominik Geisel and Univ.-Prof. Dr. med. Timm Denecke, and in consultation with and following the scientific discourse of the co-authors. Mrs. Ana Tsereteli and **Mr. Elkilany** collected the clinical, laboratory and radiologic primary data and performed the analysis of MRI examinations. PD. Dr. med. Dominik Geisel personally carried out the statistical analysis in consultation with the statisticians. Subsequently, PD. Dr. med. Dominik Geisel, Dr. med. Dorothea Theilig, Mrs. Ani Tsereteli and **Mr. Elkilany** interpreted the results in consultation with the co-authors and prepared all tables and figures. Finally, PD. Dr. med. Dominik Geisel, Dr. med. Dorothea Theilig, Mrs. Ani Tsereteli and **Mr. Elkilany** wrote the manuscript. The manuscript was subsequently proof-read by the co-authors. The manuscript was subjected to multiple peer-reviewed revision proposals. The manuscript was accepted and published at Acta Radiologica in the first round with minor revisions.

Publication 2:

Theilig D, **Elkilany A**, Schmelzle M, Müller T, Hamm B, Denecke T, Geisel D. Consistency of hepatocellular gadoxetic acid uptake in serial MRI examinations for evaluation of liver function. Abdom Radiol (2019). https://doi.org/10.1007/s00261-019-02036-w

Contribution:

After extensive literature research and familiarization with the topic of gadoxetic acid-enhanced MRI as an imaging-based liver function test, Dr. med. Dorothea Theilig developed the project idea independently under the expert guidance of PD. Dr. med. Dominik Geisel and Univ.-Prof. Dr. med. Timm Denecke. **Mr. Elkilany** developed the study design together with PD. Dr. med. Dominik Geisel. **Mr. Elkilany** carried out the detailed planning as well as the selection of the inclusion and exclusion criteria under the expert guidance of PD. Dr. med. Dominik Geisel and Univ.-Prof. Dr. med. Timm Denecke, and in consultation with and following the scientific discourse of the co-authors. **Mr. Elkilany** independently collected the clinical, laboratory and radiologic primary data and performed the analysis of MRI examinations. PD. Dr. med. Dominik Geisel and **Mr. Elkilany** carried out the statistical analysis in consultation with the statisticians. Subsequently. PD Dr. med. Dominik Geisel, Dr. med. Dorothea Theilig and **Mr. Elkilany** interpreted the results in consultation with the co-authors and prepared all tables and figures. PD Dr. med. Dominik Geisel, Dr. med. Dorothea Theilig and **Mr. Eliklany** wrote the manuscript. The manuscript was subsequently proof-read by the co-authors. The manuscript was subjected to peer-reviewed revision proposals by two journals. The manuscript was accepted and published at Abdominal Radiology in the first round with minor revisions.

Publication 3:

Theilig D, **Elkilany A**, Jann H, Roderburg C, Hamm B, Fehrenbach U, Geisel D. Evaluating hepatotoxic effects of chemotherapeutic agents with gadoxetic-acid-enhanced magnetic resonance imaging. Eur J Radiol 2019. DOI: https://doi.org/10.1016/j.ejrad.2019.108807

Contribution:

After extensive literature research and familiarization with the topic of gadoxetic acid-enhanced MRI as an imaging-based liver function test, specifically the finding of decreased RE over serial examinations in patients receiving chemotherapy in **original work 2 (see**

publication list, section VI), **Mr. Elkilany** developed the project idea independently under the expert guidance of PD. Dr. med. Dominik Geisel. **Mr. Elkilany** developed the study design together with PD. Dr. med. Dominik Geisel. **Mr. Elkilany** carried out the detailed planning as well as the selection of the inclusion and exclusion criteria independently, under the expert guidance of PD. Dr. med. Dominik Geisel, and in consultation with and following the scientific discourse of the co-authors. **Mr. Elkilany** independently collected the clinical, laboratory and radiologic primary data and performed the analysis of MRI examinations. Subsequently, all the data were checked by the co-authors. PD. Dr. med. Dominik Geisel, Dr. med. Dorothea Theilig, and **Mr. Elkilany** personally carried out the statistical analysis in consultation with the statisticians. Subsequently, PD. Dr. med. Dominik Geisel, Dr. med. Dorothea Theilig and **Mr. Elkilany** interpreted the results in consultation with the co-authors and prepared all tables and figures. Finally, PD. Dr. med. Dominik Geisel, Dr. med. Dorothea Theilig and **Mr. Elkilany** wrote the manuscript. The manuscript was subsequently proofread by the co-authors. The manuscript was accepted and published at European Journal of Radiology in the first round with minor revisions.

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Signature, date and stamp of first supervising university professor / lecturer

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Signature of doctoral candidate

IV. Extract from the Journal Summary List: (ISI Web of Knowledge℠) / Publications

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI
Selected Categories: **"RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"** Selected Category Scheme: WoS
Gesamtanzahl: 128 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	8,104	10.247	0.026360
2	European Heart Journal-Cardiovascular Imaging	4,630	8.336	0.020640
3	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	14,983	7.704	0.024870
4	RADIOLOGY	54,109	7.469	0.063710
5	JOURNAL OF NUCLEAR MEDICINE	27,101	7.439	0.037560
6	CLINICAL NUCLEAR MEDICINE	4,756	6.281	0.006950
7	INVESTIGATIVE RADIOLOGY	6,486	6.224	0.012410
8	Circulation-Cardiovascular Imaging	5,438	6.221	0.020160
9	IEEE TRANSACTIONS ON MEDICAL IMAGING	17,837	6.131	0.024200
10	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	12,420	5.654	0.018820
11	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	46,595	5.554	0.055060
12	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	4,918	5.457	0.013530
13	NEUROIMAGE	92,719	5.426	0.152610
14	MEDICAL IMAGE ANALYSIS	6,383	5.356	0.011900
15	RADIOTHERAPY AND ONCOLOGY	17,184	4.942	0.027840
16	HUMAN BRAIN MAPPING	20,334	4.927	0.042810
17	SEMINARS IN NUCLEAR MEDICINE	2,285	4.558	0.002990
18	ULTRASCHALL IN DER MEDIZIN	2,201	4.389	0.004310
19	MAGNETIC RESONANCE IN MEDICINE	31,440	4.082	0.034130
20	EUROPEAN RADIOLOGY	18,615	4.027	0.034120
20	SEMINARS IN RADIATION ONCOLOGY	2,480	4.027	0.003620
22	JOURNAL OF NUCLEAR CARDIOLOGY	3,508	3.847	0.004120
23	AMERICAN JOURNAL OF NEURORADIOLOGY	22,667	3.653	0.029840
24	JOURNAL OF MAGNETIC RESONANCE IMAGING	16,398	3.612	0.027440
25	MOLECULAR IMAGING AND BIOLOGY	2,415	3.608	0.005480

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
26	Biomedical Optics Express	8,120	3.482	0.022750
27	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,350	3.440	0.004040
28	Journal of the American College of Radiology	3,228	3.383	0.007340
29	RADIOGRAPHICS	11,207	3.249	0.008990
30	AMERICAN JOURNAL OF ROENTGENOLOGY	33,453	3.125	0.031050
31	Journal of Cardiovascular Computed Tomography	1,608	3.095	0.004280
32	KOREAN JOURNAL OF RADIOLOGY	2,331	3.072	0.004670
33	NMR IN BIOMEDICINE	7,537	3.031	0.014150
34	CANCER IMAGING	1,150	3.016	0.002250
35	Contrast Media & Molecular Imaging	1,215	2.934	0.002490
36	MEDICAL PHYSICS	25,701	2.884	0.035220
37	Radiation Oncology	5,157	2.862	0.013540
38	EUROPEAN JOURNAL OF RADIOLOGY	12,571	2.843	0.025400
39	Clinical Neuroradiology	630	2.790	0.002090
40	JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY	9,021	2.758	0.012460
41	JOURNAL OF NEURORADIOLOGY	949	2.706	0.001620
42	PHYSICS IN MEDICINE AND BIOLOGY	24,912	2.665	0.032160
43	ULTRASOUND IN MEDICINE AND BIOLOGY	10,316	2.645	0.013450
44	EJNMMI Research	1,110	2.630	0.004030
45	MAGNETIC RESONANCE IMAGING	7,194	2.564	0.011680
46	RADIATION RESEARCH	8,468	2.530	0.006760
47	STRAHLENTHERAPIE UND ONKOLOGIE	2,820	2.459	0.004600
48	ABDOMINAL IMAGING	3,203	2.443	0.005940
49	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	2,190	2.435	0.002730
49	Dose-Response	824	2.435	0.001320
51	ULTRASONICS	6,518	2.377	0.009140
52	QUARTERLY JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	1,032	2.368	0.001450
53	JOURNAL OF BIOMEDICAL OPTICS	13,503	2.367	0.019540
54	NEURORADIOLOGY	5,420	2.346	0.007640
55	ULTRASONIC IMAGING	1,076	2.300	0.000690
56	CLINICAL RADIOLOGY	6,234	2.282	0.008470

Selected JCR Year: 2017; Selected Categories: "RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
57	Physica Medica-European Journal of Medical Physics	1,915	2.240	0.005110
58	QUANTITATIVE IMAGING IN MEDICINE AND SURGERY	861	2.231	0.002490
59	Brachytherapy	1,991	2.227	0.004240
60	CARDIOVASCULAR AND INTERVENTIONAL RADIOLOGY	5,429	2.210	0.009530
61	NUCLEAR MEDICINE AND BIOLOGY	3,880	2.203	0.004770
62	Journal of Contemporary Brachytherapy	556	2.146	0.001210
63	Diagnostic and Interventional Imaging	1,127	2.115	0.003010
64	ACADEMIC RADIOLOGY	5,399	2.110	0.009190
65	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	2,951	2.036	0.008210
66	JOURNAL OF RADIATION RESEARCH	2,439	2.031	0.004140
67	INTERNATIONAL JOURNAL OF RADIATION BIOLOGY	4,307	1.970	0.003240
68	International Journal of Computer Assisted Radiology and Surgery	2,099	1.961	0.004320
69	JOURNAL OF NEUROIMAGING	1,952	1.953	0.004640
70	Zeitschrift fur Medizinische Physik	519	1.891	0.001450
71	DENTOMAXILLOFACIAL RADIOLOGY	2,617	1.848	0.003500
72	MAGNETIC RESONANCE MATERIALS IN PHYSICS BIOLOGY AND MEDICINE	1,473	1.832	0.003150
73	PEDIATRIC RADIOLOGY	6,350	1.826	0.008180
74	ACTA RADIOLOGICA	4,304	1.823	0.006360
75	Radiologia Medica	2,001	1.819	0.003590
76	BRITISH JOURNAL OF RADIOLOGY	8,804	1.814	0.013010
77	Magnetic Resonance Imaging Clinics of North America	931	1.740	0.001780
78	Radiology and Oncology	706	1.722	0.001390
79	RADIOLOGIC CLINICS OF NORTH AMERICA	2,441	1.695	0.002180
80	CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS	1,619	1.682	0.001850
81	ANNALS OF NUCLEAR MEDICINE	2,133	1.656	0.003120

Selected JCR Year: 2017; Selected Categories: "RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"

Publication 1:

Theilig D, Tsereteli A, **Elkilany A**, Raabe P, Lüdemann L, Malinowski M, Stockmann M, Pratschke J, Hamm B, Denecke T, Geisel D

Gd-EOB-DTPA-enhanced MRI T1 relaxometry as an imaging-based liver function test compared with ^{13}C-methacetin breath test.

Acta Radiol. 2019 Jul 19. [Epub ahead of print]

DOI: https://doi.org/10.1177/0284185119861314

Impact factor 2017: 1.823

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI Selected Categories: **"RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"** Selected Category Scheme: WoS

Gesamtanzahl: 128 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	8,104	10.247	0.026360
2	European Heart Journal-Cardiovascular Imaging	4,630	8.336	0.020640
3	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	14,983	7.704	0.024870
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5	JOURNAL OF NUCLEAR MEDICINE	27,101	7.439	0.037560
6	CLINICAL NUCLEAR MEDICINE	4,756	6.281	0.006950
7	INVESTIGATIVE RADIOLOGY	6,486	6.224	0.012410
8	Circulation-Cardiovascular Imaging	5,438	6.221	0.020160
9	IEEE TRANSACTIONS ON MEDICAL IMAGING	17,837	6.131	0.024200
10	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	12,420	5.654	0.018820
11	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	46,595	5.554	0.055060
12	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	4,918	5.457	0.013530
13	NEUROIMAGE	92,719	5.426	0.152610
14	MEDICAL IMAGE ANALYSIS	6,383	5.356	0.011900
15	RADIOTHERAPY AND ONCOLOGY	17,184	4.942	0.027840
16	HUMAN BRAIN MAPPING	20,334	4.927	0.042810
17	SEMINARS IN NUCLEAR MEDICINE	2,285	4.558	0.002990
18	ULTRASCHALL IN DER MEDIZIN	2,201	4.389	0.004310
19	MAGNETIC RESONANCE IN MEDICINE	31,440	4.082	0.034130
20	EUROPEAN RADIOLOGY	18,615	4.027	0.034120
20	SEMINARS IN RADIATION ONCOLOGY	2,480	4.027	0.003620
22	JOURNAL OF NUCLEAR CARDIOLOGY	3,508	3.847	0.004120
23	AMERICAN JOURNAL OF NEURORADIOLOGY	22,667	3.653	0.029840
24	JOURNAL OF MAGNETIC RESONANCE IMAGING	16,398	3.612	0.027440
25	MOLECULAR IMAGING AND BIOLOGY	2,415	3.608	0.005480

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
26	Biomedical Optics Express	8,120	3.482	0.022750
27	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,350	3.440	0.004040
28	Journal of the American College of Radiology	3,228	3.383	0.007340
29	RADIOGRAPHICS	11,207	3.249	0.008990
30	AMERICAN JOURNAL OF ROENTGENOLOGY	33,453	3.125	0.031050
31	Journal of Cardiovascular Computed Tomography	1,608	3.095	0.004280
32	KOREAN JOURNAL OF RADIOLOGY	2,331	3.072	0.004670
33	NMR IN BIOMEDICINE	7,537	3.031	0.014150
34	CANCER IMAGING	1,150	3.016	0.002250
35	Contrast Media & Molecular Imaging	1,215	2.934	0.002490
36	MEDICAL PHYSICS	25,701	2.884	0.035220
37	Radiation Oncology	5,157	2.862	0.013540
38	EUROPEAN JOURNAL OF RADIOLOGY	12,571	2.843	0.025400
39	Clinical Neuroradiology	630	2.790	0.002090
40	JOURNAL OF VASCULAR AND INTERVENTIONAL RADIOLOGY	9,021	2.758	0.012460
41	JOURNAL OF NEURORADIOLOGY	949	2.706	0.001620
42	PHYSICS IN MEDICINE AND BIOLOGY	24,912	2.665	0.032160
43	ULTRASOUND IN MEDICINE AND BIOLOGY	10,316	2.645	0.013450
44	EJNMMI Research	1,110	2.630	0.004030
45	MAGNETIC RESONANCE IMAGING	7,194	2.564	0.011680
46	RADIATION RESEARCH	8,468	2.530	0.006760
47	STRAHLENTHERAPIE UND ONKOLOGIE	2,820	2.459	0.004600
48	ABDOMINAL IMAGING	3,203	2.443	0.005940
49	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	2,190	2.435	0.002730
49	Dose-Response	824	2.435	0.001320
51	ULTRASONICS	6,518	2.377	0.009140
52	QUARTERLY JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	1,032	2.368	0.001450
53	JOURNAL OF BIOMEDICAL OPTICS	13,503	2.367	0.019540
54	NEURORADIOLOGY	5,420	2.346	0.007640
55	ULTRASONIC IMAGING	1,076	2.300	0.000690
56	CLINICAL RADIOLOGY	6,234	2.282	0.008470

Selected JCR Year: 2017; Selected Categories: "RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
57	Physica Medica-European Journal of Medical Physics	1,915	2.240	0.005110
58	QUANTITATIVE IMAGING IN MEDICINE AND SURGERY	861	2.231	0.002490
59	Brachytherapy	1,991	2.227	0.004240
60	CARDIOVASCULAR AND INTERVENTIONAL RADIOLOGY	5,429	2.210	0.009530
61	NUCLEAR MEDICINE AND BIOLOGY	3,880	2.203	0.004770
62	Journal of Contemporary Brachytherapy	556	2.146	0.001210
63	Diagnostic and Interventional Imaging	1,127	2.115	0.003010
64	ACADEMIC RADIOLOGY	5,399	2.110	0.009190
65	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	2,951	2.036	0.008210
66	JOURNAL OF RADIATION RESEARCH	2,439	2.031	0.004140
67	INTERNATIONAL JOURNAL OF RADIATION BIOLOGY	4,307	1.970	0.003240
68	International Journal of Computer Assisted Radiology and Surgery	2,099	1.961	0.004320
69	JOURNAL OF NEUROIMAGING	1,952	1.953	0.004640
70	Zeitschrift fur Medizinische Physik	519	1.891	0.001450
71	DENTOMAXILLOFACIAL RADIOLOGY	2,617	1.848	0.003500
72	MAGNETIC RESONANCE MATERIALS IN PHYSICS BIOLOGY AND MEDICINE	1,473	1.832	0.003150
73	PEDIATRIC RADIOLOGY	6,350	1.826	0.008180
74	ACTA RADIOLOGICA	4,304	1.823	0.006360
75	Radiologia Medica	2,001	1.819	0.003590
76	BRITISH JOURNAL OF RADIOLOGY	8,804	1.814	0.013010
77	Magnetic Resonance Imaging Clinics of North America	931	1.740	0.001780
78	Radiology and Oncology	706	1.722	0.001390
79	RADIOLOGIC CLINICS OF NORTH AMERICA	2,441	1.695	0.002180
80	CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS	1,619	1.682	0.001850
81	ANNALS OF NUCLEAR MEDICINE	2,133	1.656	0.003120

Selected JCR Year: 2017; Selected Categories: "RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
82	ROFO-FORTSCHRITTE AUF DEM GEBIET DER RONTGENSTRAHLEN UND DER BILDGEBENDEN VERFAHREN	1,462	1.636	0.002200
83	BMC MEDICAL IMAGING	815	1.635	0.001690
84	JOURNAL OF THORACIC IMAGING	1,311	1.624	0.002200
85	Diagnostic and Interventional Radiology	1,164	1.618	0.002300
86	SKELETAL RADIOLOGY	5,482	1.567	0.007550
87	JOURNAL OF DIGITAL IMAGING	1,680	1.536	0.002750
88	JOURNAL OF ULTRASOUND IN MEDICINE	6,500	1.530	0.008700
89	RADIATION AND ENVIRONMENTAL BIOPHYSICS	1,362	1.527	0.001740
90	SEMINARS IN MUSCULOSKELETAL RADIOLOGY	802	1.521	0.001310
91	Medical Ultrasonography	739	1.512	0.001750
92	Abdominal Radiology	533	1.506	0.001220
93	NUCLEAR MEDICINE COMMUNICATIONS	2,848	1.495	0.004230
94	Journal of Medical Imaging and Radiation Oncology	1,113	1.478	0.002660
95	Magnetic Resonance in Medical Sciences	649	1.455	0.001320
96	Molecular Imaging	1,134	1.414	0.001610
97	NUKLEARMEDIZIN-NUCLEAR MEDICINE	600	1.352	0.000760
98	Journal of Applied Clinical Medical Physics	2,182	1.301	0.005370
99	JOURNAL OF COMPUTER ASSISTED TOMOGRAPHY	5,296	1.292	0.004040
100	NEUROIMAGING CLINICS OF NORTH AMERICA	1,102	1.275	0.001260
101	JOURNAL OF RADIOLOGICAL PROTECTION	984	1.274	0.002030
102	Revista Espanola de Medicina Nuclear e Imagen Molecular	435	1.202	0.000880
103	Journal of Innovative Optical Health Sciences	418	1.136	0.000640
104	Cancer Radiotherapie	812	1.128	0.001010
105	APPLIED RADIATION AND ISOTOPES	7,237	1.123	0.009390
106	SEMINARS IN ULTRASOUND CT AND MRI	871	1.062	0.001110

Selected JCR Year: 2017; Selected Categories: "RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"

Publication 2:

Theilig D, **Elkilany A**, Schmelzle M, Müller T, Hamm B, Denecke T, Geisel D
Consistency of hepatocellular gadoxetic acid uptake in serial MRI examinations for evaluation of liver function.
Abdom Radiol 2019;44:2759–2768
DOI: https://doi.org/10.1007/s00261-019-02036-w
Impact Factor 2017: 1.506

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI Selected Categories: **"RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"** Selected Category Scheme: WoS

Gesamtanzahl: 129 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	JACC-Cardiovascular Imaging	8,801	10.975	0.026160
2	MEDICAL IMAGE ANALYSIS	7,694	8.880	0.013370
3	IEEE TRANSACTIONS ON MEDICAL IMAGING	19,545	7.816	0.024990
4	RADIOLOGY	54,641	7.608	0.061300
5	JOURNAL OF NUCLEAR MEDICINE	27,551	7.354	0.037990
6	EUROPEAN JOURNAL OF NUCLEAR MEDICINE AND MOLECULAR IMAGING	15,406	7.182	0.024760
7	CLINICAL NUCLEAR MEDICINE	4,922	6.498	0.007680
8	INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS	45,833	6.203	0.046810
9	INVESTIGATIVE RADIOLOGY	6,563	6.091	0.011150
10	Circulation-Cardiovascular Imaging	5,456	5.813	0.018480
11	NEUROIMAGE	99,720	5.812	0.132720
12	ULTRASOUND IN OBSTETRICS & GYNECOLOGY	12,336	5.595	0.020140
13	European Heart Journal-Cardiovascular Imaging	5,498	5.260	0.021650
14	RADIOTHERAPY AND ONCOLOGY	17,873	5.252	0.027470
15	Photoacoustics	512	5.250	0.001330
16	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,113	5.070	0.014020
17	ULTRASCHALL IN DER MEDIZIN	2,238	4.613	0.003700
18	HUMAN BRAIN MAPPING	22,040	4.554	0.043230
19	JOURNAL OF NUCLEAR CARDIOLOGY	3,711	4.112	0.004480
20	EUROPEAN RADIOLOGY	19,597	3.962	0.033870

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	RADIOGRAPHICS	11,768	3.923	0.009170
22	Biomedical Optics Express	9,547	3.910	0.021750
23	MAGNETIC RESONANCE IN MEDICINE	32,648	3.858	0.034990
24	SEMINARS IN NUCLEAR MEDICINE	2,245	3.798	0.002710
25	Journal of the American College of Radiology	4,191	3.785	0.009760
26	JOURNAL OF MAGNETIC RESONANCE IMAGING	17,147	3.732	0.027800
27	KOREAN JOURNAL OF RADIOLOGY	2,687	3.730	0.004800
28	INTERNATIONAL JOURNAL OF HYPERTHERMIA	3,552	3.589	0.004020
29	EJNMMI Physics	394	3.475	0.001350
30	NMR IN BIOMEDICINE	7,511	3.414	0.014790
31	MOLECULAR IMAGING AND BIOLOGY	2,543	3.341	0.005360
32	Journal of Cardiovascular Computed Tomography	1,711	3.316	0.004430
33	COMPUTERIZED MEDICAL IMAGING AND GRAPHICS	2,464	3.298	0.002990
34	AMERICAN JOURNAL OF NEURORADIOLOGY	23,231	3.256	0.028010
35	MEDICAL PHYSICS	26,715	3.177	0.030870
36	AMERICAN JOURNAL OF ROENTGENOLOGY	33,633	3.161	0.028540
37	CANCER IMAGING	1,406	3.153	0.002220
38	Quantitative Imaging in Medicine and Surgery	1,072	3.074	0.002420
39	PHYSICS IN MEDICINE AND BIOLOGY	27,458	3.030	0.031970
40	EJNMMI Research	1,408	3.000	0.004320
41	EUROPEAN JOURNAL OF RADIOLOGY	12,871	2.948	0.019480
42	Radiation Oncology	5,669	2.895	0.012980

Selected JCR Year: 2018; Selected Categories: "RADIOLOGY, NUCLEAR MEDICINE and MEDICAL IMAGING"

Publication 3:

Theilig D*, **Elkilany A***, Jann H, Roderburg C, Hamm B, Fehrenbach U, Geisel D

Evaluating hepatotoxic effects of chemotherapeutic agents with gadoxetic-acid-enhanced magnetic resonance imaging

Eur J Radiol 2019;124:108807

DOI: https://doi.org/10.1016/j.ejrad.2019.108807

* Equally contributed

Impact Factor 2018: 2.948

V. Curriculum Vitae:

For reasons of data protection, the curriculum vitae is not published in the online version.

VI. Complete list of publications:

Selected Publications:

Publication 1:

Theilig D, Tsereteli A, **Elkilany A**, Raabe P, Lüdemann L, Malinowski M, Stockmann M, Pratschke J, Hamm B, Denecke T, Geisel D
Gd-EOB-DTPA-enhanced MRI T1 relaxometry as an imaging-based liver function test compared with ^{13}C-methacetin breath test.
Acta Radiol. 2019 Jul 19. [Epub ahead of print]
DOI: https://doi.org/10.1177/0284185119861314
Impact factor 2017: 1.823

Publication 2:

Theilig D, **Elkilany A**, Schmelzle M, Müller T, Hamm B, Denecke T, Geisel D
Consistency of hepatocellular gadoxetic acid uptake in serial MRI examinations for evaluation of liver function.
Abdom Radiol 2019;44:2759–2768
DOI: https://doi.org/10.1007/s00261-019-02036-w
Impact Factor 2017: 1.506

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Theilig D*, **Elkilany A***, Jann H, Roderburg C, Hamm B, Fehrenbach U, Geisel D
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DOI: https://doi.org/10.1016/j.ejrad.2019.108807
* Equally contributed
Impact Factor 2018: 2.948

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Aboelyazid Elkilany, 2020