Early Prediction of Treatment Response of Neuroendocrine Hepatic Metastases after Peptide Receptor Radionuclide Therapy with $^{90}$Y-DOTATOC Using Diffusion Weighted and Dynamic Contrast-Enhanced MRI

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1. Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of mostly slowly growing malignancies originating from the cells of the diffuse neuroendocrine system and are most commonly located in the gastrointestinal tract [1]. The name is pointing at the common feature of these cells, which is the release of hormones upon neuronal input. NETs are a rare...
entity; however, their reported incidence has been steadily rising in the last decades, mainly due to improved diagnostic procedures [2, 3]. They represent a therapeutic challenge for three reasons: First, they stay clinically silent for a long time, which results in late diagnosis [4]. Second, for this reason, they often show hepatic metastases at the time of diagnosis and have therefore limited curative options [5, 6]. Third, many neuroendocrine tumors reluctantly respond to standard therapeutic approaches like chemotherapy and show substantial recurrence rates after surgical resection [4, 7]. Advanced therapeutic approaches are therefore warranted.

Particularly, the control of the hepatic metastases is crucial to mitigate symptoms, as the metastases can cause pain, compromise liver function, and release serotonin directly into the circulation, which results in carcinoid syndrome. An approach that has proven effective to control metastatic NETs is the peptide receptor radionuclide therapy (PRRT) [8–10]. It provides symptomatic relief and tumor control at the same time and is applied in more and more medical centers all over the world [11]. The mechanism of action is the selective binding of the peptide, such as DOTATOC, to somatostatin receptors that are overexpressed at the surface of neuroendocrine tumor cells. The coupled β-emitter, e.g., Yttrium-90, finally exhibits the therapeutic effect that has to be monitored.

The standard method for assessment of therapy response in oncology is RECIST 1.1 (Response evaluation Criteria In Solid Tumors) [12, 13], which rates response based on the tumor lesions’ changes in size. This approach is particularly limited in slowly growing tumors like NETs, where a robust assessment of treatment effectiveness with RECIST in accordance with the proposed frequency of tumor reevaluation in the original publication is performed after a period of several weeks after therapy [12]. This is too late for a prompt personalized adaption of therapeutic strategies and for patients with advanced and less differentiated NET grades 2 and 3. Early response assessment of those NETs within few days after PRRT can therefore be of high interest for these patients and their physicians. A currently used approach to estimate the effect of the PRRT is to measure tumor uptake and tumor-to-spleen ratio in planar posttreatment scintigraphy or SPECT/CT run a few hours to days after injection of the radiotherapeutic agent. This predominantly reflects the radiopharmaceutical’s biological distribution and the density of associated receptors.

Magnetic resonance imaging (MRI) provides additional indicators to assess tissue properties in an oncologic context, mainly using diffusion-weighted MRI (DW-MRI) and dynamic contrast-enhanced MRI (DCE-MRI) [14]. DW-MRI takes advantage of the Brownian motion of water molecules to make statements about the tissue microarchitecture that is subject to changes in the course of treatment. The apparent diffusion coefficient (ADC) provides a quantitative measurement of diffusion. The concept of intravoxel incoherent motion (IVIM) further differentiates the share of DW-MRI signal that can be attributed to diffusion (high b values) and perfusion (low b values), respectively [15]. DCE-MRI on the other hand tracks the signal variation of a tissue at multiple time points after intravenous injection of a contrast medium. The widely applied Tofts model postulates two compartments (plasma space (PS) and extravascular extracellular space (EES)) and provides the quantitative parameters $K_{\text{trans}}$ (transfer constant), $V_e$ (fractional volume of EES), and $k_{ep}$ (flux rate constant) [16]. $K_{\text{trans}}$ (in 1 per minute) is the flow from PS to EES and physiologically represents plasma blood flow, vascular permeability, and surface area. $V_e$ is the volume of EES (in %). $k_{ep}$ is the reflux rate from EES into PS and equals $K_{\text{trans}}/v_e$ (in 1 per minute). The model-independent initial area under the curve (IAUC) is the integral under the enhancement curve and more robust to noise. It reflects blood flow and vascular permeability, similar to $K_{\text{trans}}$ [17].

Both DW-MRI and DCE-MRI have proven useful for the assessment of therapy-induced changes [18, 19]. Their potential as biomarker for treatment response, before macroanatomic changes occur, has been demonstrated in other tumors (DW-MRI: [20–26] DCE-MRI: [20, 27–29]), as well as in the special case of liver metastases of neuroendocrine tumors after transcatheter arterial chemoembolization (TACE) [30], TACE and Y-90 radioembolization [31], and selective internal radiotherapy (SIRT) [32]. However, for the increasingly applied PRRT, a multiparametric MRI evaluation is still missing.

The aim of our study was therefore to evaluate if (semi-)quantitative parameters derived from DW-MRI and DCE-MRI may be used for an early prediction of response of hepatic metastases of NETs 48 hours after PRRT with $^{90}$Y-DOTATOC.

2. Materials and Methods

2.1. Patients. This prospective study was performed at the Clinic of Radiology & Nuclear Medicine at the University Hospital Basel and approved by the local ethics committee (Ethikkommission beider Basel, case number 317/11). Informed consent was obtained from all participants. Twenty patients suffering from a neuroendocrine tumor with hepatic metastases were included. All of them presented for PRRT for the first time and were at least 18 years old. Exclusion criteria were MRI-incompatible foreign bodies (e.g., pacemakers, intracranial clips, and implants), a history of epilepsy, pregnancy, and a limited kidney function (creatinine clearance <50 ml/min).

2.2. Peptide Receptor Radionuclide Therapy. PRRT followed the standard scheme at our institution with two therapy cycles at an interval of about 10 weeks. They were supplemented by four abdominal MRI examinations for the purpose of this study performed just before ($T_1$ and $T_3$) and 48 hours after administration of the radiotherapeutic agent ($T_2$ and $T_4$). In the first session, $^{90}$Y/$^{111}$In-DOTATOC was administered in all cases (100–200 mCi; mean: 168 mCi; SD: 24 mCi ± 3.7–7.4 GBq; mean: 6.2 GBq; SD: 0.9 GBq). $^{90}$Y is a β-emitter, $^{111}$In a γ-emitter used for SPECT imaging. In the second session, there was a switch to Lutetium ($^{177}$Lu) in
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2.4. Magnetic Resonance Imaging. MRI imaging was performed two times per cycle per patient on three different 1.5 Tesla scanners that were also used in the clinical routine (MAGNETOM Avanto/Symphony/Esprée, all Siemens Healthineers AG, Erlangen, Germany). The baseline MRI scan (at T1 and T2) was performed shortly before the administration of the radiotherapeutic agent. A second scan (at T2 and T4) was performed 48 hours after the injection. A Gadolinium-based contrast agent (Dotarem®, Guerbet AG, 0.1 mmol Gd/kg KG) was administered intravenously. DQ he hepatic lesions were defined, and their maximum diameter was measured before and after the administration of the radiotherapeutic agent at each of the two cycles on transversal b700 DWI series using dedicated software (Mint Lesion, Mint Medical GmbH, Heidelberg, Germany). DQ his was done by a dual board-certified radiologist and nuclear medicine physician with 11 years of professional experience (GS). The accuracy of the size measurement was determined by comparing the diameters of measurements at T1 and T2 as well as—where available—T3 and T4, assuming no change in diameter within 48 hours. The double standard deviation then served as cutoff for a significant increase or decrease in diameter between the first (average of T1 and T2) and the second treatment cycle (average of T1 and T2, if available; otherwise: only T3): lesions with an increase or decrease below the cutoff value were considered stable (SD).

2.5. Image Analysis. Image analysis was performed on a dedicated workstation separate from the scanner. A maximum of four representing lesions per patient were analyzed (51 lesions in total).

The hepatic lesions were defined, and their maximum diameter was measured before and after the administration of the radiotherapeutic agent at each of the two cycles on transversal b700 DWI series using dedicated software (Mint Lesion, Mint Medical GmbH, Heidelberg, Germany). This was done by a dual board-certified radiologist and nuclear medicine physician with 11 years of professional experience (GS). The accuracy of the size measurement was determined by comparing the diameters of measurements at T1 and T2 as well as—where available—T3 and T4, assuming no change in diameter within 48 hours. The double standard deviation then served as cutoff for a significant increase or decrease in diameter between the first (average of T1 and T2) and the second treatment cycle (average of T1 and T2, if available; otherwise: only T3): lesions with an increase or decrease above the cutoff value were considered progressive (PD) or regressive (RD), respectively. Lesions with size changes below the cutoff value were considered stable (SD).

2.5.1. SPECT. SPECT analysis was performed on a dedicated workstation (Syngovia, Siemens Healthineers AG, Erlangen, Germany). ROIs containing the preselected liver metastases and the spleen were defined semi-automatically based on iso-contours by a dual board-certified radiologist and nuclear medicine physician (GS). Within each ROI, the peak signal intensity (highest number of counts per 1 ccm volume within the ROI) was recorded. The lesion-to-spleen uptake ratio was then calculated for each lesion and both therapy cycles.

2.5.2. DW-MRI. Diffusion analysis of the preselected liver metastases was conducted by a dual board-certified radiologist and nuclear medicine physician (GS) using Syngovia (Siemens Healthineers AG, Erlangen, Germany) for ADC and the Medical Imaging Interaction Toolkit (MITK, German Cancer Research Center, Heidelberg, Germany) for the IVIM parameters. Apparent diffusion coefficients (ADCs) were extracted from the ADC maps that were automatically generated by the MRI scanner (mono-exponential fitting) considering the complete tumor volume. Parameters for true diffusion (D), pseudo-diffusion (D′), and perfusion fraction (f) were calculated using a 3-parameter-fit according to the intravoxel incoherent motion model [33].

2.5.3. DCE-MRI. Perfusion analysis was performed using the commercially available Tissue4D Package in Syngovia (Siemens Healthineers AG, Erlangen, Germany) for ADC and the Medical Imaging Interaction Toolkit (MITK, German Cancer Research Center, Heidelberg, Germany) for the IVIM parameters. Apparent diffusion coefficients (ADCs) were extracted from the ADC maps that were automatically generated by the MRI scanner (mono-exponential fitting) considering the complete tumor volume. Parameters for true diffusion (D), pseudo-diffusion (D′), and perfusion fraction (f) were calculated using a 3-parameter-fit according to the intravoxel incoherent motion model [33].
2.6. Statistical Analysis. Statistical analysis was performed using SPSS 22 (IBM Corp., Armonk, NY). A \( p \)-value < 0.05 was determined to indicate statistical significance. One-way ANOVA between subjects was conducted to compare means of more than two groups. To test for homogeneity of variance, Levene’s test was performed. Histograms, normal QQ-Plots, and the Shapiro–Wilk test were used to test for normal distribution of data. Post hoc comparisons were assessed with Tukey HSD test. In cases with violated assumption of homogeneity, Welch’s \( F \)-test was used to compare means of groups and Games-Howell test was used for post hoc testing. For nonnormally distributed data, Kruskal–Wallis H test was applied to assess group differences.

3. Results

3.1. Patients. All 20 patients completed the MRI examinations at \( T_1, T_2, \) and \( T_3 \). In one patient, DCE-MRI at \( T_2 \) failed because of a technical error. Six patients (\( \approx 30\% \)) did not conduct the final MRI examination at \( T_4 \). Patients’ characteristics are listed in Table 1. The time distance between the first and the second treatment cycle was 10 weeks on average, with a standard deviation of ±2 weeks (range: 8–18 weeks).

3.2. Evaluation of Lesion Size. 51 lesions were evaluated in total (see Table 2 for characteristics). When comparing the diameters measured at \( T_1 \) vs \( T_2 \) and (where available) \( T_3 \) vs \( T_4 \), a mean test-retest variability of 2.6% with a standard deviation of 3.0% was found. Based on the double standard deviation, a cutoff value of 6% was defined as the threshold for lesion size progression or regression. Lesions with size changes less than ±6% were considered stable.

When comparing lesion sizes at the first and the second treatment cycle (average of \( T_1 \) and \( T_2 \) vs. average of \( T_3 \) and \( T_4 \); in four cases, \( T_4 \) was missing and diameter measurements at \( T_3 \) were used), 7/51 lesions showed size progression, 18/51 regression, and 26/51 remained stable. In 13 patients (33 lesions), all lesions behaved uniformly (7x SD, 5x RD, and 1x PD). Two lesions in one of the patients with PR were too small to measure at \( T_3 \). Mixed behavior of lesions was seen in 7 patients (4x stable + regressive lesions, 3x stable + progressive lesions, 1x regressive + progressive lesions). In 3 of 20 patients, \( ^{90}\text{Y}/^{111}\text{In-DOTATOC} \) was replaced by \( ^{177}\text{Lu-DOTATOC} \) in the second session because of deterioration of kidney function.

| Table 1: Patient characteristics. |
|----------------------------------|
| Characteristic                  | Patients (\( n = 20 \)) |
| Age, years                      | 59.2 (9.9)               |
| Mean (SD)                       | 61                      |
| Median                          | 10                      |
| Gender, number of patients      |                         |
| Male                            | 10                      |
| Female                          | 10                      |
| Primary tumor site, number of patients |            |
| Small bowel                     | 10                      |
| Pancreas                        | 8                       |
| Lung                            | 1                       |
| Unknown                         | 1                       |
| Histology, number of patients   |                         |
| G1/G2                           | 14                      |
| G3                              | 2                       |
| Unknown                         | 4                       |
| Treatment, number of patients   |                         |
| Only \( ^{90}\text{Y-DOTATOC} \)| 17                      |
| Switch to \( ^{177}\text{Lu-DOTATOC} \) in second therapy session | 3                      |

| Table 2: Lesion characteristics. Baseline size calculated as \( (T_1 + T_2)/2 \), size after therapy as \( (T_3 + T_4)/2 \). In four cases, the \( T_4 \) measurement was not available and therefore the diameter measured at \( T_3 \) used. |
|----------------------------------|
| Characteristic                  | Patients (\( n = 20 \)) |
| Lesions per patient             |                         |
| 1                               | 3                       |
| 2                               | 7                       |
| 3                               | 6                       |
| 4                               | 4                       |
| Size of the lesions, longest diameter |                  |
| Baseline, mean (SD)             | 41 mm (27 mm)            |
| After therapy, mean (SD)        | 36 mm (24 mm)            |
| Lesion response                 |                         |
| Regressive (number/mean diameter change) | 18/-26.0%                |
| Stable (number/mean diameter change) | 26/-0.6%                 |
| Progressive (number/mean diameter change) | 7/10.3%                  |

Figure 1: Standardized therapy and study timeline. This therapy and study cycle was repeated with a mean interval of 10 weeks (\( T_1 \) and \( T_2 \)).
as a whole rated as SD; 3x stable + progressive, as a whole rated as PD). In summary, 4 patients (20%) were rated as PD, 11 patients (55%) as SD and 5 patients (25%) as PR.

3.3. SPECT. One patient (2 lesions) had to be excluded from the analysis of SPECT data because of splenectomy. The lesion-to-spleen uptake ratio measured at time point T2 was lower in progressive lesions (1.6±1.2) than in stable (3.1±2.1) and regressive ones (3.4±2.4; Figure 2(a)). However, these differences were not statistically significant (F = 1.8, p = 0.184). There were also no statistically significant group differences at T4 (F = 1.8, p = 0.176).

When analyzing the relative differences in lesion-to-spleen uptake ratio between T1 and T3, we found a strong decrease for regressive lesions (−52% on average) and smaller decreases for stable (−21%) and progressive lesions (−11%). The difference of the means in the three groups was statistically significant (F = 5.8, p = 0.006; Figure 2(b)). Post hoc comparisons using the Tukey HSD test revealed statistically significant differences when comparing the groups of regressive vs. stable lesions (p = 0.013) and regressive vs. progressive lesions (p = 0.021). However, no statistically significant difference was found between the groups of stable vs. progressive lesions (p = 0.743).

3.4. Diffusion Weighted Imaging. For ADC values before treatment, ADC(T1) were highest in regressive lesions (1201 ± 249 × 10^{-6} mm²/s), followed by stable (1102 ± 354 × 10^{-6} mm²/s) and progressive ones (872 ± 145 × 10^{-6} mm²/s) (Figure 3(a)).

The group differences regarding ADC at T1 were not statistically significant (F = 3.1, p = 0.056). However, at T2 (F = 4.0, p = 0.026) and T3 (F = 10.4, p < 0.001), ANOVA showed statistically significant differences in mean ADC. Post hoc comparisons with Tukey HSD revealed that, at T3, only the groups with regressive vs. progressive lesions showed statistically significant differences in ADC (p = 0.027), whereas at T3, differences of the groups with regressive vs. stable (p = 0.003) and regressive vs. progressive lesions (p > 0.001) were statistically significant.

When comparing the differences in ADC before treatment and after 10 weeks ADC(T1)−ADC(T4), a higher increase in ADC was seen in regressive lesions (346 ± 322 × 10^{-6} mm²/s) than in stable (97 ± 192 × 10^{-6} mm²/s) and progressive lesions (98 ± 38 × 10^{-6} mm²/s). This difference was statistically significant (F = 6.2, p = 0.004). Post hoc testing showed that only the comparison of regressive vs. stable lesions was statistically significant (p = 0.040), while the comparison of regressive vs. progressive lesions showed a statistical trend (p = 0.058).

Figure 3(d) displays the evolution of the average ADC values from time point T1, via T2 to T3. Evidently, the abovementioned increase in ADC that is measured between T1 and T3 already manifest as a trend at T2, as early as 48 hours after treatment. The differences T2 − T1 between the three subgroups, however, were not yet statistically significant (F = 1.053; p = 0.357). A sample-case illustrating the abovementioned behavior of ADC as an early indicator of treatment response in a patient with NET-HM of pancreatic origin is shown in Figure 4.

The values obtained for the diffusion coefficient D using the IVIM method corresponded well to the ADC values, yet they were associated with larger measurement errors (Figures 5(a) and 5(b)). At T1, D was highest for regressive lesions (1103 ± 217 × 10^{-6} mm²/s), followed by stable (983 ± 350 × 10^{-6} mm²/s) and progressive ones (728 ± 264 × 10^{-6} mm²/s). The group differences were statistically significant (F = 4.1, p = 0.023). A more detailed look with post hoc testing showed that only the comparison of regressive vs. progressive lesions (p = 0.017) was statistically significant. The evolution of D values over time from T1 to T4 was also comparable to that of ADC with a continuous increase seen for regressive lesions. However, when comparing the difference in D at T3 minus T1 and at T2 minus T1, no statistically significant difference between the groups was found (F = 1.7, p = 0.198 and F = 1.1, p = 0.341, respectively).

The perfusion fraction f (Figures 5(c) and 5(d)) did not show any significant differences between the three groups of lesions at T1 (F = 0.1, p = 0.912), T2 (F = 1.8, p = 0.185), and T3 (F = 0.9, p = 0.424). Measured values ranged from 0.08 in progressive lesions at T4 to 0.16 in progressive lesions at T1 and T3. Interestingly, a drop of perfusion fraction was observed for the progressive lesions at T2 and T4; however, the differences T2 − T1 (F = 0.1, p = 0.914) and T4 − T1 (F = 0.03, p = 0.968) were not statistically significant.

The pseudo-diffusion coefficient D* (Figures 5(e) and 5(f)) did not show any significant variation between the three subgroups at any time point as assessed by the Kruskal–Wallis H test due to nonnormally distributed data (T1: χ² = 1.6, p = 0.4; T2: χ² = 0.3, p = 0.847; T3: χ² = 4.9, p = 0.088). Visually, the pattern of variation of D* over time was opposite to that of f, showing an increase in D* for progressive lesions at T2 and T4. Yet these effects were not statistically significant (difference T3 − T1: p = 0.872; T2 − T1: p = 0.556). Measured values for D* ranged from 320 × 10^{-6} mm²/s for progressive lesions at T1 to 1208 × 10^{-6} mm²/s for progressive lesions at T4. In general, the measurement values for f and D* were subject to a rather large variability in between subjects and lesions (see error bars in Figure 5).

3.5. Perfusion Weighted Imaging. Because of the high sensitivity of DCE-MRI to breathing artifacts, five patients (15 lesions) had to be excluded from this part of the analysis. The values obtained for extracellular volume fraction (vₑ) are displayed in Figures 6(a) and 6(b). Statistically significant group differences in vₑ were seen at T3 (F = 3.8, p = 0.046) and for the difference T3 − T1 (F = 4.1, p = 0.025), i.e., between the first and second treatment cycles. Post hoc analyses revealed differences between vₑ at T3 for regressive vs. progressive (p = 0.011) and regressive vs. stable lesions (p = 0.010) as well as for regressive vs. progressive (p = 0.036) and regressive vs. stable lesions (p = 0.049) regarding the difference T3 − T1. This corresponds well to the increase in ADC and D seen in Figures 3(d) and 5(b), respectively. At time points T1 and T3, vₑ was also higher for regressive lesions than for stable and regressive ones, but these
Figure 2: (a) Average lesion-to-spleen uptake of the radiopharmaceutical measured after the first treatment cycle in regressive (light grey), stable (dark grey) and progressive lesions (red). (b) Average difference in lesion-to-spleen uptake of the radiopharmaceutical from T₂ to T₄ indicating significantly higher decrease for regressive lesions (light grey) than for stable (dark grey) and progressive ones (red). The asterisks indicate statistical significance (comparison regressive vs. stable \( p = 0.013 \); regressive vs. progressive \( p = 0.021 \)).

Figure 3: Average ADC values measured at time points T₁ (a), T₂ (b), and T₃ (c) in lesions that were identified as regressive (light grey), stable (dark grey) and progressive (red) at long-term follow-up (T₃). Statistically significant differences are seen between regressive and progressive lesions at time point T₂ 48 hours after therapy \( (p = 0.027) \) and between regressive lesions and the two other groups at time point T₃ around 10 weeks after therapy (regressive vs. stable: \( p = 0.003 \); regressive vs. progressive: \( p < 0.001 \)). (c) Evolution of ADC values from T₁ via T₂ to T₃ for the three subgroups of lesions. Evidently, the increase in ADC that is measured between T₁ and T₃ for all subgroups already manifest as a trend at T₂, as early as 48 hours after treatment. It is most pronounced in regressive lesions. The asterisks indicate statistical significance.
differences were not statistically significant ($p = 0.209$ and $p = 0.146$, respectively). No statistically significant differences were seen when comparing T1 and T2 ($p = 0.335$).

The measured values for the transfer constants $K_{\text{trans}}$ and $k_{\text{ep}}$ are displayed in Figures 6(c) and 6(d). The parameter $K_{\text{trans}}$ showed no statistically significant group differences at any point in time (T1: $p = 0.835$; T2: $p = 0.868$; T3: $p = 0.327$) and for the differences $T_3 - T_1$ ($p = 0.611$) and $T_2 - T_1$ ($p = 0.921$). The parameter $k_{\text{ep}}$, which equals $K_{\text{trans}}/v_e$, showed no statistically significant group differences at time points T1 ($p = 0.477$) and T2 ($p = 0.495$), as well as for the differences $T_3 - T_1$ ($p = 0.271$) and $T_2 - T_1$ ($p = 0.927$). However, at T3, there was a statistically significant difference between the response groups ($F = 9.4$, $p = 0.001$) that was driven by the differences of regressive vs. progressive ($p = 0.001$) and stable vs. progressive lesions ($p = 0.04$), as revealed by post hoc analysis. For iAUC, there was no statistically significant variation at any point in time (T1: $p = 0.687$; T2: $p = 0.816$; T3: $p = 0.413$) and neither for the differences $T_3 - T_1$ ($p = 0.539$) and $T_2 - T_1$ ($p = 0.600$).

4. Discussion

The aim of this study was to investigate if diffusion-weighted and contrast-enhanced magnetic resonance imaging can help to assess early tumor response to peptide receptor radionuclide therapy (PRRT) with $^{90}\text{Y}$-DOTA-TOC in neuroendocrine hepatic metastasis (NET-HM). For this purpose, MRI was performed immediately before initiation of PRRT, as well as 48h and 10 weeks after treatment. Results were compared with posttherapy $^{90}\text{Y}/^{111}\text{In}$-DOTATOC SPECT.

The most notable result of our study is that ADC can differentiate regressive from progressive lesions as early as 48h after therapy. Lesions that were later found to be regressive in size had a significantly higher ADC at this time point than progressive lesions. The fact that apoptosis-inducing therapies like PRRT lead to an increase in ADC values due to the swelling of cells, tumor lysis, and necrosis is well known: Wulfert et al. found an increase in both responding and nonresponding lesions in their study on 38 hepatic NET after intra-arterial treatment with $^{90}\text{Y}/^{111}\text{In}$-177Lu-DOTATOC [34], which is well in line with the increase in ADC that is observed after 10 weeks in our study for all groups of lesions. However, an effect on ADC that allows for predicting treatment response of PRRT in NET-HM as early as 48h after therapy has not been reported yet. The ADC did show a continuous increase from regressive to progressive metastases (RD > SD > PD). The differences between RD/SD and SD/PD were not statistically significant.
significant, most likely due to the relatively small number of metastases analyzed.

As an extension to previously published studies on DWI in NET-HM, our study also included an analysis of perfusion effects in DW-MRI using the concept of IVIM. In this analysis, no additional effects to standard DWI were seen, except for the fact that the average $D$ observed in regressive lesions before therapy was significantly higher than in...
progressive lesions. This effect, which is also seen as a trend for ADC in standard DW-MRI, is also in accordance with the results of Wulfert et al., who described a significant correlation between baseline ADC and decrease in lesion size after therapy [34]. Interestingly, a drop of perfusion fraction accompanied by an increase in $D^*$ was observed for the progressive lesions at T2 and T4. However, this was not statistically significant and may be due to the considerable measurement variability present in our IVIM analysis.

For DCE-MRI, the only significant observation was an increase in the extracellular volume fraction $v_e$ that occurred in regressive lesions 10 weeks after therapy, while for stable or progressive lesions, $v_e$ did not change statistically significantly. This behavior of $v_e$ probably reflects the well-known effects of the treatment in terms of tumor lysis, necrosis, and fibrosis. It is closely related to the changes in ADC described above and is completely in line with previous results of Atuegwu and colleagues [35]. Regarding $K_{\text{trans}}$ and $k_{\text{ep}}$, no significant effects of the treatment on these parameters was observed. This might be due to the low number of patients. Another reason might be the variability in quantitative DCE-MRI [36]. Our findings are in line with the quite heterogeneous results published on this topic. Zahra and colleagues reported that higher baseline $K_{\text{trans}}$ and $k_{\text{ep}}$ were positively correlated with tumor response of cervix cancer to radiation [37]. Higher baseline $K_{\text{trans}}$ and $k_{\text{ep}}$ in the responder group were also reported by Tao et al. who assessed the response 36 patients with NSCLC to chemo-
Finally, the response of the NET-HM to PRRT was also assessed with 90Y-/111In-DOTATOC SPECT, which displays the density of the somatostatin-receptor subtype 2 (SSR2) in tissue and is used as an indicator of expected treatment response of PRRT. As expected keeping in mind previous literature [40], a drop in lesion-to-spleen uptake ratio between the first and the second treatment cycles was seen that was significantly higher for regressive lesions than for stable or progressive ones. The uptake ratio after treatment cycle one, however, was not predictive of therapy response in our small group of patients, which is most likely a result of low statistical power.

Our results are affected by some limitations: First, the small sample size that is due to the exploratory nature of the study, which aimed at identifying parameters of potential prognostic value rather than carving out the exact prognostic value of each parameter. Second, the choice of the reference standard in terms of morphologic response criteria, which were calculated from the test-retest variation of size measurements over 48 h. We are well aware that the threshold of ±6% which resulted from our calculations is far below the thresholds for response assessment proposed in RECIST (12), mRECIST [41], or the EASL response criteria [42]. It was chosen to be more sensitive for changes in diameter, as it is well known that the usually applied response criteria for solid tumors are limited in slowly growing tumors like NET [40]. As the rates of treatment response in our study cohort (20% PD, 55% SD, 25% RD) are consistent with previous reports on PRRT [43], we are convinced that the ±6% threshold eventually represents a reasonable value in this setting. Third, no long-term follow-up imaging and patient survival data were available as reference standard due to the fact that patients underwent follow-up imaging mostly at other centers. Fourth, some series had to be excluded from DW-MRI and DCE-MRI analyses because of imaging artifacts. These may be avoided by the use of modern sequences that apply respiratory triggering or self-gating technologies. Fifth, one of the assumptions of Tukey HSD test is independence of observations. However, one can argue that the observations are not fully independent due to the fact that in some cases, up to four lesions were measured in one liver. Due to the fact that NET is a rare entity, we did not want to exclude data by including only one metastasis per liver. Therefore, we chose to accept this statistical limitation. Finally, no double reading was performed, so interrater variability is not accounted for in our analysis.

5. Conclusion

In conclusion, diffusion restriction quantified as ADC was the most sensitive MRI parameter to predict treatment response of NET after PRRT among those investigated in our study. ADC was able to differentiate regressive from progressive NET-HMs as early as 48 hours after PRRT. DW-MRI therefore may complement scintigraphy/SPECT for early prediction of treatment response in the framework of PRRT. Assessment of perfusion parameters using IVIM and DCE-MRI did not show an additional benefit in our study but may nevertheless be useful to investigate pathophysiological aspects of PRRT in a preclinical setting.

Data Availability

A large part of the data are patient data and thus confidential. Upon request, a minimal anonymized dataset will be available to interested researchers.

Conflicts of Interest

Markus Klarhöfer is an employee of Siemens Healthcare AG (Switzerland) and declares no conflicts of interest regarding this study. All other authors declare that they have no conflicts of interest.

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