Diagnostic Accuracy of Diffusion-Weighted Magnetic Resonance Imaging Versus Positron Emission Tomography/Computed Tomography for Early Response Assessment of Liver Metastases to Y90-Radioembolization

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Objectives: Patients with hepatic metastases who are candidates for Y90-radioembolization (Y90-RE) usually have advanced tumor stages with involvement of both liver lobes. Per current guidelines, these patients have usually undergone several cycles of potentially hepatotoxic systemic chemotherapy before Y90-RE is at all considered, requiring split (lobar) treatment sessions to reduce hepatic toxicity. Assessing response to Y90-RE early, that is, already after the first lobar session, would be helpful to avoid an ineffective and potentially hepatotoxic second lobar treatment. We investigated the accuracy with which diffusion-weighted magnetic resonance imaging (DWI-MRI) and positron emission tomography/computed tomography (PET/CT) can provide this information.

Methods: An institutional review board–approved prospective intraindividual comparison trial on 35 patients who underwent fluorodeoxyglucose PET/CT and DWI-MRI within 6 weeks before and 6 weeks after Y90-RE to treat secondary-progressive liver metastases from solid cancers (20 colorectal, 13 breast, 2 other) was performed. An increase of minimal apparent diffusion coefficient (ADCmin) or decrease of maximum standard uptake value (SUVmax) by at least 30% was regarded as positive response. Long-term clinical and imaging follow-up was used to distinguish true- from false-response classifications.

Results: On the basis of long-term follow-up, 23 (66%) of 35 patients responded to the Y90 treatment. No significant changes of metastases size or contrast enhancement were observable on pretreatment versus posttreatment CT or magnetic resonance imaging. However, overall SUVmax decreased from 8.0 ± 3.9 to 5.5 ± 2.2 (P < 0.0001), and ADCmin increased from 0.53 ± 0.13 × 10⁻³ mm²/s to 0.77 ± 0.26 × 10⁻³ mm²/s (P < 0.0001). Pretherapeutic versus posttherapeutic changes of ADCmin and SUVmax correlated moderately (r = –0.53). In 4 of the 35 patients (11%), metastases were fluorodeoxyglucose-negative such that no response assessment was possible by PET. In 25 (71%) of the 35 patients, response classification by PET and DWI-MRI was concordant; in 6 (17%) of the 35, it was discordant. In 5 of the 6 patients with discordant classifications, follow-up confirmed diagnoses made by DWI. The positive predictive value to predict response was 22 (96%) of 23 for MRI and 15 (88%) of 17 for PET. The negative predictive value to predict absence was 11 (92%) of 12 for MRI and 10 (56%) of 18 for PET. Sensitivity for detecting response was significantly higher for MRI (96%; 22/23) than for PET (65%; 15/23) (P < 0.02).

Conclusions: Diffusion-weighted magnetic resonance imaging appears superior to PET/CT for early response assessment in patients with hepatic metastases of common solid tumors. It may be used in between lobar treatment sessions to guide further management of patients who undergo Y90-RE for hepatic metastases.

Key Words: liver metastases, liver MRI, PET/CT, SUV, DWI, ADC, response assessment, Y90, radioembolization

Radioembolization (Y90-RE) is an established method for local treatment of otherwise therapy-refractory primary liver cancer and liver metastases of extrahepatic tumors.1,2 Assessing response to local therapy, such as Y90-RE, is challenging. Determining tumor size as, for example, prescribed by Response Evaluation Criteria in Solid Tumors (RECIST) can be misleading owing to therapy-induced tissue transformation into necrosis or fibrosis.2,3 Therefore, functional imaging has been proposed to improve the accuracy with which response to local treatment can be determined. The uptake of fluorodeoxyglucose (FDG) quantified via standardized uptake value (SUV) on positron emission tomography/computed tomography (PET/CT) scans has been shown to be useful for the assessment of response to local treatment, including Y90-RE. The degree of therapy-induced SUV changes is an established parameter to predict tumor response to treatment and has also been shown to provide prognostic information because it correlates with overall survival after RE.5,7 Diffusion-weighted magnetic resonance imaging (DWI-MRI) has been shown to provide diagnostic information that can be used to demonstrate treatment effects similar to PET.8,10 It has been shown that the DWI-derived apparent diffusion coefficient (ADC) of primary cancers and liver metastases increases after neoadjuvant chemotherapy,11,12 and that these ADC changes correlate with PET-derived SUV changes.13–20 However, there is only anecdotal evidence available on the use of DWI for response assessment in metastases of solid tumors to local12,22 or systemic treatment.11 Hence, although DWI has been in clinical use for a decade already10 and has been proposed for functional response assessment since then, the diagnostic accuracy with which DWI-MRI can detect early response to treatment has, so far, not been established. Moreover, it is unclear how the diagnostic accuracy of DWI with regard to early response assessment compares with the diagnostic accuracy afforded by PET.

Therefore, we set out to intraindividually compare response assessment on the basis of DWI versus PET/CT in patients with liver metastases who underwent Y90-RE and who underwent systematic clinical and imaging follow-up to validate the respective imaging diagnoses suggested by both DWI and PET/CT for response assessment.

PATIENTS AND METHODS

This institutional review board–approved prospective intraindividual diagnostic trial was conducted at an academic comprehensive cancer center. Written informed consent was obtained from all participants.
Patient Cohort

Patients meeting the following criteria were included: lobar RE performed for unresectable metastatic liver disease with at least 3 recognizable liver metastases of at least 1 cm in size, secondary progressive after appropriate systemic treatment, without prior intra-arterial therapies. To avoid repeat observations made in the same patient, every patient was included only once, although most patients underwent 2 (or more) lobar or segmental RE sessions.

Y90 Radioembolization

The decision to perform RE was made for each patient case in a dedicated gastrointestinal multidisciplinary tumor conference. The patients had progressive hepatic tumor load despite having undergone appropriate systemic chemotherapy according to guidelines established for the respective tumor entity; liver metastases were considered prognostically dominant, and the patients had a normal liver function and Eastern Cooperative Oncology Group 0/1 status. Presence of prognostically insignificant extrahepatic metastatic disease was not considered a contraindication. For RE, 90yttrium-loaded microspheres (either SIR-Spheres; SIRTEX Medical Europe, Germany or Theraspheres; BTG, Canada) were used. All patients received lobar RE, either of the right or left liver lobe. The applied activity was determined by percentage of tumor involvement of the liver and body surface area.

Pretherapeutic and Posttherapeutic Imaging Protocol

Imaging studies followed a standardized protocol (Table 1). Whole-body contrast-enhanced 18F-FDG PET/CT of the neck, thorax, abdomen, and pelvis was performed and included contrast-enhanced imaging in all baseline examinations and in 16 of the 35 patients on early follow-up PET/CT. Liver MRI was performed on a 1.5-T system and included a dynamic contrast-enhanced series as well as T2-weighted and DWI sequences in all cases.

TABLE 1. Image Acquisition Protocol for PET/CT and MRI

| Table 1A | PET/CT |
|----------|--------|
| Type of scanner | Gemini TF 16, Philips Healthcare, Best, The Netherlands |
| PET tracer | 18F-FDG |
| Dose of PET tracer | 3 MBq/kg |
| Type of contrast agent | Iopromide 300/370 (Ultravist 300/370, Bayer-Schering, Germany) |
| Dose of contrast agent | 120–148 mL |
| Collimation | Whole-body low-dose CT | 16 × 1.5 mm | Contrast-enhanced CT (portal venous phase) | 16 × 0.75 mm | n.a. |
| Pitch | 0.812 | 0.813 | n.a. |
| Rotation time | 0.4 s | 0.75 s | n.a. |
| Acquisition matrix | n.a. | n.a. | 144 × 144 |
| Field of view | n.a. | n.a. | 576 mm |
| Section thickness | 5/1 mm | 5/1 mm | 4 mm |
| Effective tube current-time product | 30 mAs | 200 mAs | n.a. |
| Tube voltage | 120 kV(p) | 120 kV(p) | n.a. |
| Acquisition time per bed position | n.a. | n.a. | 1.5 min. |
| Delay after contrast medium injection | n.a. | n.a. | 70 s |

| Table 1B | MRI |
|----------|-----|
| Type of scanner | 1.5-T Achieva, Philips Healthcare, Best, The Netherlands |
| Surface coil | Multielement 16-channel coil (Sense Torso XL) |
| Type of contrast agent | Gd-DTPA (Magnevist, Bayer-Schering, Leverkusen, Germany) |
| Dose of contrast agent | 0.1 mmol/kg of body weight |
| Dynamic series | Pulse sequence type | T2-weighted pulse sequence* | Diffusion-weighted imaging |
| TR/TE, ms | T1-weighted 3D gradient echo | 2D turbo spin echo | 2D single-shot SE EPI |
| Orientation | Axial | Axial | Axial |
| Acquisition matrix | 268 × 174 | 304 × 233 | 112 × 110 |
| Field of view | 330 mm | 310 mm | 380 mm |
| Section thickness | 8 mm | 7 mm | 7 mm |
| Breath compensation | Breath-hold | Respiratory triggering and breath-hold | Respiratory triggering |
| Sense factor | 2 | 1.4 | |
| b Values | n.a. | n.a. | 0, 50, 800 |
| No. dynamics | 1 precontrast, 3 postcontrast with bolus tracking (arterial, portal-venous, equilibrium phase) | n.a. | n.a. |

*Acquired in axial and coronal planes with and without fat saturation.

18F-FDG indicates fluorodeoxyglucose; 2D, 2-dimensional; 3D, 3-dimensional; CT, computed tomography; EPI, echo planar imaging; Gd-DTPA, gadolinium-diethylenetriamine penta-acidic acid; MRI, magnetic resonance imaging; n.a., not applicable; PET, positron emission tomography; SE, spin echo.
Analysis of Tumor Size and Contrast Enhancement

Size of target lesions was measured in accordance with RECIST guidelines on both magnetic resonance (MR) and CT images before and after treatment. Contrast enhancement of target lesions on MR and CT images was assessed by 2 radiologists in consensus according to a 5-point scale from 1 (devascularized tumor without visible arterial or late contrast enhancement) through 5 (strong perfusion with arterial enhancement well beyond that of normal liver).

Validation of Response Classification

To validate response classification, a conjoint review of all existing information on a given patient, including serological data (eg, tumor marker development) and tumor size changes on long-term follow-up (>12 months or until progression) contrast-enhanced MRI and PET/CT imaging, was used to establish presence or absence of response. Patient outcome, especially with regard to response to liver-directed treatment, was evaluated by an independent consortium that reviewed imaging findings, laboratory values including appropriate tumor marker depending on the type of primary tumor, and patient Eastern Cooperative Oncology Group performance status. A measurable and persistent decrease in size of the target lesions on follow-up imaging over time, with a follow-up of at least 6 months, was taken as evidence of response. Response was also assumed when tumor size remained stable, but a substantial drop of tumor markers occurred, and/or signs of regression such as calcifications or absence of enhancement were seen. On the basis of patient outcome, response classifications made by SUV and DWI changes were categorized as true or false. This was then used to calculate the sensitivity with which the imaging method was able to detect response to treatment, as well as positive and negative predictive values (PPV, NPV) for diagnosing presence or absence of response.

Statistical Analysis

Continuous variables are expressed as mean values ± standard deviation. The Spearman correlation coefficient assessed the degree of monotonic association between ADCmin and SUVmax. Changes in SUVmax, ADCmin, and tumor size were evaluated using the paired Wilcoxon test. Sensitivity for demonstrating response was compared using the McNemar test. All test results were analyzed in an explorative way; thus, P values of P ≤ 0.05 were regarded as statistically significant. The interpretation of correlation tests followed the guidelines according to Altman. All statistical analyses were conducted using SAS version 9.2 (SAS Institute).

RESULTS

Patients and Target Lesions

Thirty-five patients (24 females, 11 males) met the inclusion criteria (Table 2). The primary tumors were colorectal cancer in 20, breast cancer in 13, as well as 1 case each of pharyngeal carcinoma and cancer of unknown primary. Because 3 target lesions were evaluated in each patient (and averaged), a total of 105 target lesions were included in the analysis.

Radioembolization

A total of 8 of the 35 patients received RE of the left liver lobe with a mean activity of 0.69 ± 0.21GBq; 27/35 patients underwent treatment of the right liver lobe with a mean activity of 1.21 ± 0.40GBq. Two patients received RE with glass microspheres; all other patients received resin microspheres.

Changes in Tumor Size and Contrast Enhancement

Size of target lesions was established on both CT and MR images. No statistically significant changes of tumor size was observed in either CT or MR imaging in the studies before vs. after treatment. As is typical for secondary liver malignancies, the vast majority of metastases was only moderately hypervascular. No significant change of contrast enhancement patterns was observed in the contrast-enhanced studies before versus that after treatment, either for dynamic contrast-enhanced MRI or for contrast-enhanced CT imaging (Table 3).
Changes in SUV

The average SUVmax change after RE was $-2.5 \pm 3.9 \text{ (} -23.6 \pm 31.4\% \text{)}$ ($P < 0.0001$) (Table 3). A total of 17 (49%) of the 35 patients showed an overall SUVmax decrease by more than 30% and were therefore classified as “responders.” Four patients (4/35; 11%) with metastatic breast cancer were classified as not assessable with PET because the respective metastases were PET-negative, that is, did not exhibit a perceivably or measurably increased SUV compared with the surrounding normal liver tissue. The remaining 14 (40%) of the 35 were classified as nonresponders.

Changes in ADC

The average ADCmin change after RE was $0.6 \pm 0.3 \times 10^{-3} \text{ mm}^2/\text{s} \ (57.7\% \pm 76.3\% \text{)}$ ($P < 0.0001$) (Table 3). A total of 23 (66%) of the 35 patients showed an increase of ADCmin by higher than 30% and were therefore categorized as responders. All metastases had a strong correlate on baseline DWI; accordingly, none of the patients was categorized as not assessable.

Correlation Between ADC and SUV Changes

For the entire group of 35 patients, pretherapeutic versus posttherapeutic changes of ADCmin and changes of SUVmax correlated moderately ($r = -0.43$). When the 4 PET-negative patients were excluded from the analysis, a moderate correlation was found between changes in ADCmin and changes in SUVmax ($r = -0.53$) (Fig. 2).

Response Classification Based on ADC and SUV Changes

Concordant response classification was observed in 25 of the 35 patients, with 15 (60%) of the 25 patients concordantly classified as responders and 10 (40%) of the 25 patients concordantly classified as nonresponders.

Discordant response classification was observed in 6 of the 35 patients. In 4 of these 6 patients, ADC-based analysis suggested...
presence, whereas the SUV-based analysis suggested absence of response. In the remaining 4 of the 35 patients with PET-negative metastases, no DWI/PET correlation of response could be established.

Results on Follow-Up

On the basis of clinical and imaging follow-up, 23 (66%) of the 35 patients responded to the Y90-treatment, whereas 12 (34%) of the 35 did not. The follow-up confirmed the ADC-based response classifications in 5 of the 6 patients with divergent response classification (Table 4).

This yields a PPV (prediction of presence of response) of 22 (96%) of 23 for DWI-MRI and 15 (88%) of 17 for PET. The NPV (prediction of absence of response) was 11 (92%) of 12 for MRI and 10 (56%) of 18 for PET. The sensitivity for demonstrating response was significantly higher for MRI (22/23; 96%) than for PET (15/23; 65%) (P < 0.02; Table 5).

**DISCUSSION**

In this cohort of 35 patients with liver metastases caused by common solid cancers, we found a moderate inverse correlation between ADCmin and SUVmax changes after the Y90-RE (r = −0.53). Both functional imaging methods helped detect response to treatment early, that is, before any statistically significant changes of tumor size or those of contrast enhancement were observable on contrast-enhanced MRI or CT imaging. However, we found that changes of DWI-derived parameters (ADCmin) were more accurate in predicting response than that of PET-derived parameters (SUVmax), both in terms of demonstrating response as well as in terms of suggesting absence of response. This, together with the fact that, in 11% of patients (4/35), response assessment based on PET was a priori impossible because metastases were PET-negative on baseline PET, led to the fact that DWI proved to be significantly more sensitive than PET: DWI helped predict response with a sensitivity and PPV of 96%, compared with 65% and 88%, respectively, for PET.

Positron emission tomography/computed tomography is currently considered to represent the standard of reference for assessing early response to nonsurgical, systemic, or regional treatment of liver metastases. There is a growing body of evidence to suggest that DWI can provide similar, although physiologically more or less unrelated, diagnostic information. Probably owing to the high cellularity, the high interstitial pressure, and/or the irregular internal architecture, diffusion of free water is restricted in cancerous tissue, yielding low ADC values. This has been exploited for oncologic applications in several ways: (1) to improve detection of cancer, for example, of liver metastases in hepatic MRI or of lymph node metastases in whole-body MRI; (2) to provide an imaging biomarker for tumor cellularity and, hence, biologic importance of, for example, prostate cancer; (3) to help predict response of, for example, rectal cancer to regional or systemic treatment; and (4) to monitor response to neoadjuvant chemotherapy or radiochemotherapy of primary breast, gastrointestinal, and rectal cancers and also, more recently, to assess response to local treatment of hepatocellular cancer.

However, there is little evidence on the use of DWI to monitor treatment response of liver metastases. Moreover, beyond mere correlation studies, the actual diagnostic accuracy (ie, sensitivity and predictive values) with which DWI or PET detects early response to treatment has not yet been established. This, however, is important if functional imaging is to be used to guide treatment decisions in clinical interventional oncology.

Transarterial radioembolization by 90yttrium (Y90-RE) is recognized as a salvage treatment option mainly for patients with hepatocellular cancer but is increasingly used also in patients with secondary liver cancer due to colorectal, neuroendocrine, and breast cancer who exhibit a hepatic tumor load that appears prognostically relevant and does not respond to appropriate systemic treatment. Y90-radioembolization is a palliative regional treatment option that is well suited to document the utility of early response assessment. Patients with hepatic metastases who are candidates for Y90-RE usually have advanced tumor stages with involvement of both liver lobes. Per current guidelines, these patients have usually undergone several cycles of systemic chemotherapy before Y90-RE is at all considered as a potential treatment option.

**TABLE 4. Comparison of Response Assessment With Patient Outcome**

|                     | Validation: Responder | Validation: Nonresponder | Sum |
|---------------------|-----------------------|--------------------------|-----|
| **Response assessment based on PET** |                       |                          |     |
| PET positive        | 15                    | 2                        | 17  |
| PET negative        | 4                     | 10                       | 14  |
| PET inconclusive    | 4                     | 0                        | 4   |
| **Sum**             | 23                    | 12                       | 35  |
| **Response assessment based on DWI** |                       |                          |     |
| DWI positive        | 22                    | 1                        | 23  |
| DWI negative        | 1                     | 11                       | 12  |
| DWI inconclusive    | 0                     | 0                        | 0   |
| **Sum**             | 23                    | 12                       | 35  |

DWI indicates diffusion-weighted imaging; PET, positron emission tomography.
treatment option. Many systemic chemotherapy regimens are potentially hepatotoxic and may impair the functional reserve of the liver, a fact that may not be readily obvious from regular liver function tests. The concept of all types of transarterial treatment strategies implies that the active agent (eg, Y90 particles) should lodge preferentially in the vascular network that is built around malignant liver tissue and that is supplied mainly by the hepatic artery.25 Whereas a high degree of arterIALIZATION is reliably present in primary liver (hepatocellular) cancer, this supply is more variable in patients with secondary liver tumors.26-30 In addition, angiogenic agents (eg, bevacizumab), an integral part of many contemporary systemic treatment regimens for liver metastases, may modify the type and degree of effective arterial supply and, accordingly, the gradient between metastatic and normal liver arterIALIZATION.39,40 Accordingly, although Y90-RE has been shown to be a safe and effective treatment for patients with secondary liver cancer, patient selection is challenging because the final dose distribution is difficult to anticipate.41,42

To reduce the risk for Y90-RE-induced liver function impairment, Y90-RE for diffuse liver metastases is provided in a lobar fashion.43 This means that patients usually undergo treatment of one half of the liver at a time, whereas the second treatment session for the other half is provided 4 to 8 weeks apart, depending on the clinical tolerability and liver function after the first treatment session. So far, guidelines do not require or support the use of imaging to assess response in between lobar treatment sessions.44 This is because it has been shown that early response to Y90-RE is difficult to detect; tumor size changes may take a couple of months to be observable on state-of-the-art cross-sectional imaging methods. However, to avoid additional and possibly futile strain to the patient, it would be highly desirable to know about the therapeutic efficacy of Y90-RE in the individual patient before treatment of the second half of the liver is initiated. In patients with secondary liver cancer, this would also be important for further patient management, for example, initiation of further systemic chemotherapy.

In our study, PET/CT and DWI-MRI were obtained early after the first treatment session, that is, within 35 days after lobar Y90-RE, to investigate the accuracy with which DWI-MRI can predict response to treatment compared with FDG-PET. Our results suggest that this accuracy is not only comparable but indeed also significantly higher than that achieved by PET imaging. The 2 methods yielded concordant results with regard to response classification in 25 (81%) of 31 patients who were PET-positive. In 5 of 6 patients with diverging classification of response, clinical and imaging follow-up confirmed the response assessment provided by DWI-MRI. In another 4 patients, each with metastatic breast cancer, PET was not useful for response assessment because the metastases were PET-negative. This translated into a significantly higher sensitivity of DWI-MRI versus PET (P < 0.02) for demonstrating early response in patients undergoing Y90-RE procedures. Our results suggest that, in patients undergoing lobar Y90 therapy for secondary liver tumors, it may be useful to perform DWI after the first treatment session. Failure to respond to lobar RE, as diagnosed by the absence of an increase of ADCmin, may then be used to spare the patient from an unnecessary (ie, ineffective) additional treatment session of the contralateral lobe. This will be important especially in patients with borderline liver function. Although such close monitoring of treatment response will not be needed in the majority of patients undergoing systemic chemotherapy for liver metastases, further research on the use of DWI-MRI for assessing response not only to local but also to systemic treatment seems justified.

Besides, our results underscore once more the utility of Y90-RE for palliative treatment of patients with therapy-refractory liver metastases. Of the 35 patients with prognostically relevant hepatic metastases who had been progressive under state-of-the-art systemic chemotherapy and targeted therapy, 23 (66%) did respond to the treatment.

The main limitation of our study is the small number of patients; further prospective studies are needed to validate our results in a larger group of patients. Moreover, all patients had advanced stages of liver metastases and had undergone a number of different systemic therapy cycles; this may confound the results of response assessment. However, our patients underwent systemic treatment in accordance with current international guidelines on the basis of decisions made in multidisciplinary tumor conferences in each individual patient case; accordingly, it is likely that the confounding effects of prior systemic chemotherapy will be representative for all patients with liver metastases treated with Y90-RE.

We conclude that DWI-MRI appears superior to PET/CT for early assessment of treatment response in patients with hepatic metastases of common solid tumors (colorectal, breast). Diffusion-weighted magnetic resonance imaging accurately predicts response before changes of tumor size or contrast enhancement are observable on contemporary cross-sectional imaging such as contrast-enhanced MRI or CT. It may therefore be useful to guide treatment decisions in patients undergoing lobar Y90-RE.

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