Early response assessment of intraarterial therapy using 3D quantitative tumour enhancement analysis on MRI in patients with liver metastases from renal cell carcinoma

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Aims and objectives

Renal Cell Carcinoma (RCC) is the most common cancer of the kidney [1]. Liver metastases from renal cell carcinoma (RCC) are not uncommon in the course of disease. In fact, approximately 20% of patients with RCC suffer from liver metastases at the date of diagnosis [2]. Thus, efforts have been undertaken to include these metastases early into the treatment progress whether surgically or as a drug target [3, 4]. In this context the hyper-vascular character of RCC metastases to the liver also makes intraarterial approaches feasible and effective. Transarterial-chemoembolization (TACE) and Yittrium-90 (Y-90) chemoembolization have been reported to be feasible and safe [5, 6]. The clinical status is highly dependent on the tumor progression within the liver. Patients that are diagnosed with liver metastasis show a significant shorter overall survival (OS). Moreover, these patients also show a significant shorter time-to-treatment failure [7]. Thus, it is crucial to evaluate tumor response early after intraarterial therapy (IAT) to guide the course of therapy. In this context it has been stated, that evaluating treatment response using volumetric and 3D measurements should be a priority [8]. Prior studies could prove the value of volumetric assessment in tumor response after IAT [9-11]. This study assessed, whether quantitative volumetric changes as seen on contrast-enhanced magnetic resonance (MR) imaging is able to evaluate early tumor response and predict survival in patients with metastatic RCC to the liver after the first session of IAT.
Methods and materials

This single-institution study retrospectively analyzed Patients with liver metastases from RCC treated at the Johns Hopkins Hospital between January 2000 and November 2014. A total of 16 patients were identified from our prospectively collected imaging database and underwent IAT procedures at our institution. 4 Patients had to be excluded due to missing pre- or post-procedure MRI and another 3 patients because they were not IAT naïve. Figure 1 illustrates the process of patient selection. All 9 finally included patients underwent a full clinical examination and laboratory diagnostics at baseline. For baseline and follow-up diagnostics patients underwent a standardized MRI protocol at our institution. Contrast-enhanced MRI was performed on a 1.5 Tesla MRI scanner (Siemens Magnetom Avanto, Erlangen, Germany with 0.1 mmol/kg intravenous gadopentetate; Magnevist; Bayer, Wayne, NJ) in the late-hepatic arterial phase (20s, portal venous phase (70 seconds) and the delayed phase (3 minutes).

3D Data Analysis

Semi-automatic image analysis was done by a radiological reader in training with 1 year of experience in the field of 3D image analysis closely supervised by a board-certified radiologist with 8 years of experience in abdominal MRI. All measurements were done using standardized electronic calipers by using Digital Imaging in Communications and Medicine (DICOM) files.

Quantitative volumetric tumor analyses of the target lesions were done using a semi-automatic 3D segmentation software (Medisys; Philips Research, Suresnes, France). A segmentation mask was semi-automatically created for every tumor lesion on the arterial phase of the contrast-enhanced baseline and follow-up MRI (Figure 2, A and B). These masks were then used for quantitative analysis of the tumor enhancement (qEASL). The arterial phase was chosen due to the hyper-vascular character of RCC metastases. Corresponding 3D models illustrate the volumetric assessment approach (Figure 2, C and D). In order to remove any background signal, the pre-contrast scan (Figure 2, E and F) was subtracted from the arterial-phase scan (Figure 2, A and B) resulting in images that only show effective contrast uptake during the arterial phase.

In the next step, a region of interest (ROI) formed by 1cm$^3$ was placed in an area of extra-tumoral liver parenchyma as a reference in order to calculate the relative contrast enhancement (Figure 2, G and H). Quantitative volumetric tumor enhancement was expressed in cubic centimeter for each lesion qEASL [cm3] and percentage of enhancing tumor volume qEASL [%]. The software automatically generated a color map in order to visualize the enhancement pattern (blue representing non-enhancing necrotic tissue and red representing viable enhancing tumor tissue; Figure 2, G and H). The accuracy, reader-independent reproducibility of semiautomatic tumor segmentation as well as the
radiological-pathological validation of 3D-quantitative tumor enhancement analysis have been reported previously [9, 12].

Furthermore, thresholds were defined for each of the values (qEASL [%] and qEASL [cm$^3$]) in order to stratify patients into two groups: responder vs. non-responder. Due to the fact that no guidelines exist for volumetric tumor response criteria, we selected cutoff values that are based on the currently used RECIST and mRECIST for vRECIST and qEASL thresholds to unify and simplify response assessment in a clinical setting. A decrease of 30% is defined as partial response (PR) using the unidimensional evaluation criteria RECIST and mRECIST. Using the formula: Volume = 4/3#r 3 this threshold corresponds to a decrease of 65% of tumor volume. Objective tumor response was defined as complete response (CR) and PR. Patients with objective response were classified as responders, and the other patients (with stable disease (SD) and progressive disease (PD)) were classified as non-responders. Table 1 shows the thresholds.

Statistical Analysis

Descriptive statistics were used to summarize the data. Overall survival time (OS) was defined as date of baseline MRI to date of death or noted last known alive. Patients lost in follow-up, alive at the end-of-observation date (Nov. 5$^{th}$, 2014) were censored.

Kaplan-Meier survival curves were created and plotted for each value using the described thresholds. Median OS and the 95% CI were calculated. P-Values #0.05 were defined as a statistically significant difference. The predictive value of each parameter was assessed by Cox proportional hazard ratio (HR). Quantitative enhancement analysis of baseline and follow-up MRI were compared using the Wilcoxon-signed-rank test. Statistical analysis was performed using a statistic software (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Version 3.1.2, Vienna, Austria, 2014).
Fig. 1: Figure 1: Flowchart of the patient selection process. A total of 4 patients were excluded due to missing MRI. In addition, 3 patients were excluded due to prior IAT treatment. 9 patients were included to the response to treatment and overall survival analysis.

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Fig. 2: Baseline (left column) and follow-up MRI (right column) of a representative patient. A and B. Tumor segmentation on a contrast-enhanced T1-weighted MR sequence at the arterial phase (20s) of a contrast enhanced MRI. C and D. 3D tumor mass 3D-rendering model. E and F. Pre-contrast sequence to demonstrate background signal intensity of the tumors in the pre-contrast phase. G and H. qEASL color maps of the tumor on the subtracted MR imaging scan [the pre-contrast scan (E and F) was subtracted from the arterial phase scan (A and B) to remove any background signal intensity]. Color maps: red represents maximum enhancement and blue represents no enhancement, normalized by the ROI. Green box: 3D ROI used as the reference background of image intensity.

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Table 1. Response criteria.

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<th>qEASL [cm³]</th>
<th>qEASL [%]</th>
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<tr>
<td><strong>CR</strong></td>
<td>Disappearance of all enhancing tissue in all target lesions</td>
<td>Disappearance of all enhancing tissue in all target lesions</td>
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<tr>
<td><strong>PR</strong></td>
<td>≥65% decrease in the sum of enhancing tissue volume of the lesions</td>
<td>≥65% decrease in the sum of percentage of enhancing tissue of the lesions</td>
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<tr>
<td><strong>PD</strong></td>
<td>≥73% increase in the sum of enhancing tissue volume of the lesions</td>
<td>≥73% increase in the sum of percentage of enhancing tissue of the lesions</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>Any case that does not qualify for either CR, PR, or PD</td>
<td>Any case that does not qualify for either CR, PR, or PD</td>
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Fig. 3: Table 1. qEASL response to treatment criteria.

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Results

Mean patients age of the cohort was 66 ± 8 years and 4 patients (44.4%) were female. At the end-of-observation date 7 patients were deceased. Median OS of the entire study cohort was 10.7 months (range, 6.2 - 114.0 months). Mean time between baseline MRI and IAT was 12 ± 10 days and mean time between IAT and follow-up MRI was 22 ± 20 days. 8 Patients underwent TACE and one patient Y-90 radioembolization. A mean of 2.6 ± 1.2 IAT procedures (range, 1-4) were performed per patient, for a total of 23 procedures. 2 patients (22.2%) underwent only one IAT session. After the first IAT, the number of patients who underwent a total of two, three and four sessions of IAT was 3 (33.3%), 1 (11.1%) and 3 (33.3%), respectively.

Comparing pre- and post-treatment values mean qEASL [cm3] decreased from 102.75 to 80.79cm3 (p=0.0547) classifying 3 patients as PR and 6 SD. Stratified by the above mentioned thresholds median OS was 31.2 vs. 10.5 months, (log-rank p=0.20); HR: 0.40 (95% CI: 0.08-1.46) within these groups. qEASL [%] decreased from 63.4 to 36.8% (p<0.05), classifying 4 patients PR and 5 SD. A clear trend for differentiation of responders and non-responders by median OS was shown (29.2 vs. 10.4 months, (log-rank p=0.10) HR: 0.36 (95% CI: 0.03-1.09)).
Conclusion

The main finding of this study is that quantitative tumor enhancement analysis of response to treatment has the potential of being a prognostic discriminator with regard of OS in patients with metastatic RCC to the liver. Despite the small cohort, our results indicate a clear trend towards an association between treatment-response measured with qEASL [% and cm\(^3\)] and improved survival after IAT. These findings could contribute to a general trend of shifting tumor assessment from one- and two-dimensional analysis towards a volumetric and enhancement based tumor evaluation [13]. 3D quantitative response assessment of RCC liver metastases will be further explored. A larger study is in progress.
References


