Diffusion-weighted MRI and (68)Ga-DOTATOC PET for early monitoring of response to loco-regional (90)Y-/(177)Lu-DOTATOC therapy in patients with neuroendocrine liver metastases

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Purpose

Neuroendocrine tumors are still considered as a fairly rare disease, although available data shows that their incidence has steadily increased over the last 30 years, mainly due to raised awareness and improved diagnostic possibilities [1-4]. Our research is focused on gastroenteropancreatic neuroendocrine tumors (GEP-NET) which represent approximately 75% of all NET [5]. This entity often presents with liver metastasis at the time of diagnosis, which is a major factor for poor prognosis. Thus, in the recent years many efforts have been made to optimize the therapy of focal liver malignancies in this field. Besides the advancements in conventional therapeutic procedures as percutaneous ablative therapies, surgical resection or transarterial chemotherapy, there has been notable progress in customized therapies for metastasized GEP-NET [6-9].

A relatively new approach in this domain is the loco-regional peptide receptor radiotherapy (PRRT) with direct application of $^{90}$Y- or $^{177}$Lu-marked DOTA(0)-Phe(1)-Tyr(3)-octreotide (DOTATOC) in the hepatic artery. As most GEP-NET demonstrate an increased somatostatin receptor expression both in the primary and in secondary lesions [10-11], the radio-labelled somatostatin analog DOTATOC targets selectively on malignant tissue with only minor radiation effects on surrounding healthy structures. However, the assessment of response to this treatment remains a challenging task, as it primarily induces tumor lysis and a loss of cellular integrity which both are not necessarily associated with a reduction of tumor size. Thus, additional methods are needed to determine the therapeutic effectiveness of the loco-regional therapy. In this study, we analyzed the additive value of the functional imaging methods DW-MRI and $^{68}$Ga-DOTATOC-PET/CT to lesion size measurement with CE-MRI.
Methods and Materials

In 12 consecutive patients with 29 liver metastases of gastroenteropancreatic neuroendocrine cancer (GEP-NET) were evaluated. All patients underwent both diffusion-weighted and dynamic contrast-enhanced magnetic resonance imaging (DWI-/DCE-MRI) including breath-hold echoplanar DWI sequences (b-values 50, 300, 600s/mm$^2$) as well as $^{68}$Ga-DOTATOC PET before therapy (baseline) and after last intervention (follow-up). Largest diameter (LD), intratumoral apparent diffusion coefficient (ADC) and maximal standardised uptake value (SUVmax) were measured in all target lesions as well as in normal liver parenchyma and spleen.
Results

38 metastases were defined as target lesions and assessed with multimodal imaging. 37 of the target lesions could be identified and analyzed on baseline DW-MR images, 29 of them also on baseline PET/CT. After therapy, 35 metastases were analyzed on DW-MRI and 27 on PET/CT images. According to changes in lesion size, 27 metastases (71%) were classified as responding lesions (RL) and 11 metastases (29%) as non-responding lesions (NRL). Before therapy, LD of RL was 30.4 ± 13.4 mm (range: 16.8-77.2 mm) and the LD of NRL 33.2 ± 18.2 mm (range: 18.4-73.2). There was no significant difference between the median pre-treatment size of the two groups ($p=0.159$). On follow-up MRI 3 months after the last treatment cycle, the LD of RL decreased significantly by 11.2 ± 21.5 % ($p<0.001$), whereas NRL showed a LD increased significantly by 8.5 ± 16.4 % ($p<0.001$).

The initial ADC of RL was 1.21 ± 0.61 (range: 0.47-2.29) and of NRL 1.09 ± 0.35 (range: 0.81-1.88; $p=0.392$). On follow-up DW-MRI, ADC increased significantly both in RL (10.6 ± 38.8 %; $p=0.011$) and in NRL (18.1 ± 27.3 %; $p=0.025$). Baseline ADC of all lesions correlated weak but significantly negative both with the percental ADC change after therapy ($r=-0.361$, $p=0.033$) and the percental change of LD ($r=-0.441$, $p=0.006$). ADC values of liver and spleen did not change significantly under therapy.

On PET/CT images, 29 of the target metastases could be analyzed before and 27 after therapy. Baseline SUVmax of RL was 28.48 ± 18.54 (range: 9.44-150.31) and decreased significantly by 24.1 ± 50.2 % on follow-up PET/CT ($p=0.014$), whereas SUVmax of NRL (baseline: 22.03 ±16.67; range 11.12-40.69) increased slightly by median 3.9 ± 41.6 % ($p=0.910$). Baseline SUV showed no significant differences in the two subgroups ($p=0.253$). A significant negative correlation was observed between pretreatment SUVmax and the percental change of SUVmax after therapy ($r=-0.769$, $p<0.001$) as well as with the percental change of LD ($r=-0.482$, $p=0.009$). The SUVmax of 8 spleens could be assessed. It increased by approximately 24.3 % ($p=0.039$) under therapy whereas the SUVmax of normal appearing liver parenchyma showed no significant change.
Fig. 2: 45-year old patient with neuroendocrine hepatic metastases under i.a. DOTATOC therapy. Upper row shows baseline imaging with ce-MRI, PET and DW-MRI. Lower row shows liver of the same patient 3 months after intervention. Marked metastasis shows neither a decrease in size (and is thus classified as NRL) nor SUV. However, on CE- and DW-MRI a change of tissue structure after therapy is clearly visible. This was objectified by analysis of lesion’s mean ADC value, that in fact showed a significant increase.

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Fig. 1: Baseline and follow-up imaging of a responding lesion. Decrease in lesion size and SUVmax as well as changes on DW-MRI are clearly visible and were also objectified by our measurements.

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**Fig. 3:** left: Boxplots of ADC before (MRT1) and after (MRT2) loco-regional DOTATOC therapy for responding lesions (white) and non-responding lesions (grey). ADC increases significantly in both subgroups (RL: \( p=0.011 \); NRL: \( p=0.025 \)). right: Boxplots of SUVmax before (PET1) and after (PET2) therapy. SUVmax decreases significantly in RL (\( p=0.014 \)), whereas it only marginally changes in NRL.

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Conclusion

After loco-regional DOTATOC therapy non-responder and responder subgroups both presented a change in ADC, prior to SSR2-receptor expression changes and although morphological response according to RECIST criteria was only measurable in few lesions. Therefore, this work suggests that diffusion-weighted imaging is an earlier tumour integrity surrogate for therapeutic intervention and possible early indicator for treatment response.
References


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