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Imaging of CD8⁺ cytotoxic T-cells by [^{89}Zr]Zr-Df-IAB22M2C PET/MRI: First clinical experience in patients with metastatic cancer

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INTRODUCTION

CD8⁺ cytotoxic T cells are key players in anti-cancer immune responses as they destroy MHC class I-dependent tumor cells. Therefore, the spatial distribution of CD8⁺ cytotoxic T cells might represent an important surrogate for the response to cancer immunotherapy including immune checkpoint inhibitor therapy ICT. The radiolabeled minibody [^{89}Zr]Zr-Df-IAB22M2C is characterized by a high affinity to human CD8 and was already investigated in a phase I study. Here, we present our first experience with the non invasive *in vivo* assessment of the whole body CD8 T cell distribution in cancer patients using clinical [^{89}Zr]Zr-Df-IAB22M2C PET/MRI.

METHODS

In total 8 patients with metastasized cancers (5 x malignant melanoma; 1 x choroidal melanoma, 1 x NSCLC and 1 x sarcoma) were studied before (n = 3) or during (n = 5) ICT. Multiparametric PET/MRI was performed 24 h after injection of 74.2±17.9 MBq [^{89}Zr]Zr-Df-IAB22M2C (1.1 - 1.8 mg Df-IAB22M2C) on a Siemens Biograph mMR System (SiemensHealthineers, Erlangen, Germany). The whole body distribution of the [^{89}Zr]Zr-Df-IAB22M2C tracer was analysed with a special focus on tumors/metastases as well as primary and secondary lymphatic organs.

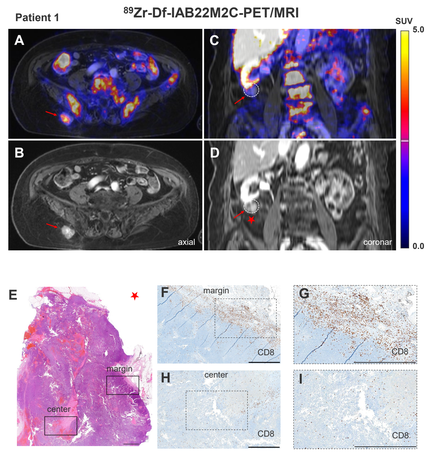
RESULTS

The PET tracer [^{89}Zr]Zr-Df-IAB22M2C was well tolerated without any reported side effects. The PET/MRI acquisitions 24h p.i. of [^{89}Zr]Zr-Df-IAB22M2C revealed a comparably low background signal with only a minor blood pool and unspecific tissue retention. Regarding the primary and secondary lymphoid organs we observed a high interpatient variability of the tracer uptake. Four out of five patients with previous ICT exhibited a relatively high [^{89}Zr]Zr-Df-IAB22M2C uptake in the bone marrow. Also a large number of non metastatic lymph nodes yielded a pronounced [^{89}Zr]Zr-Df-IAB22M2C uptake in four patients. Strikingly, a low [^{89}Zr]Zr-Df-IAB22M2C uptake in the spleen compared to the liver was observed in 4 out of the 5 patients with cancer progression during ICT. Interestingly, only one metastasis with an intense tracer was detected in this patient cohort.

CONCLUSION & OUTLOOK

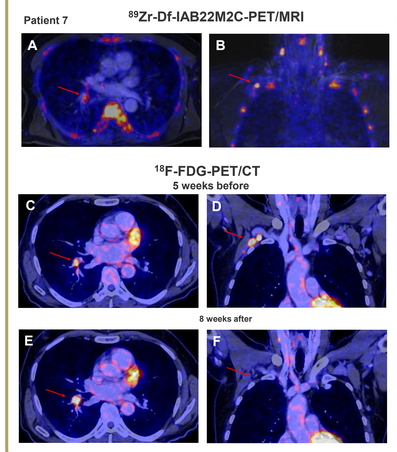
These first clinical experiences revealed the feasibility to assess potential immune-related changes by [^{89}Zr]Zr-Df-IAB22M2C PET/MRI. Considering these results we hypothesize that the whole body distribution of CD8⁺ cytotoxic T-cells assessed by non-invasive *in vivo* [^{89}Zr]Zr-Df-IAB22M2C PET/MRI might be associated with the response to cancer immunotherapy which needs to be investigated in subsequent prospective trials.

Figure 1



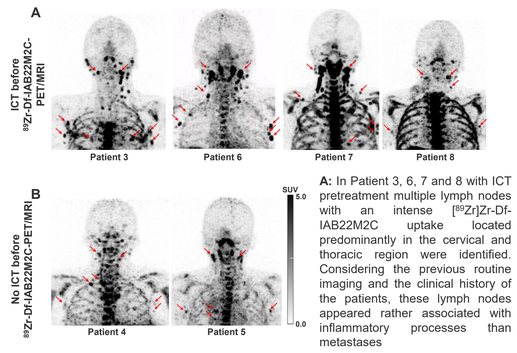
A/B: Axial fused [^{89}Zr]Zr-Df-IAB22M2C PET/MRI and MRI of a metastasis with intense tracer uptake in the right gluteal subcutaneous tissue of Patient 1 after three cycles of ipilimumab until 6 weeks before the scan. **C/D:** Coronal fused ^{89}Zr]Zr-Df-IAB22M2C PET/MRI and MRI of a pararenal metastasis of Patient 1 without relevant [tracer uptake after ipilimumab treatment. **E-I:** The pararenal metastasis of Patient 1 (red star) was resected. **E:** Histopathological analysis revealed a monotonous cell proliferation in the metastasis. The immunohistochemistry revealed some areas with dense infiltrates of CD8⁺ T cells in the margin of the lesion **(H)**; magnification **(I)**, while only mild infiltration of CD8⁺ T cells in the center of the metastasis (focally moderate around the necrotic areas) was observed **(F)**; magnification **(G)**. Scale: 1mm for both H&E and CD8 immunohistochemistry images.

Figure 2



A/B: Fused [^{89}Zr]Zr-Df-IAB22M2C PET/MRI of Patient 7 after 4 cycles of combined ICT using ipilimumab and nivolumab until 6 weeks before the scan indicated only a faint tracer uptake in a hilar lymph node metastasis **(A)**, whereas an intense tracer uptake was found in an axillary lymph node metastasis (B). **C/D:** Fused [^{18}F]FDG PET/CT images of Patient 7 five weeks before [^{89}Zr]Zr-Df-IAB22M2C PET/MRI, indicated an intense glucose uptake of both the axillary and the hilar lymph node metastasis, which thus were considered to be viable tumor tissue. **E/F:** Eight weeks after the [^{89}Zr]Zr-Df-IAB22M2C PET/MRI the follow up [^{18}F]FDG PET/CT of Patient 7 revealed a decrease of the axillary lymph node metastasis under ICT, while the hilar lymph node metastasis increased in size and [^{18}F]FDG uptake under ICT-monotherapy with Nivolumab.

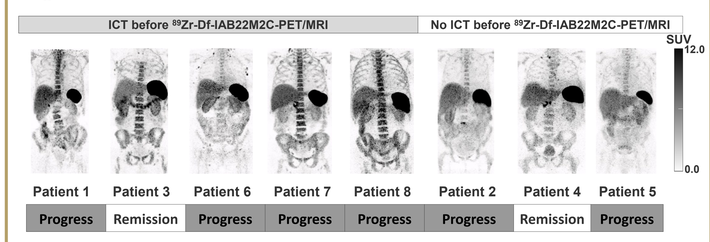
Figure 3



A: In Patient 3, 6, 7 and 8 with ICT pretreatment multiple lymph nodes with an intense [^{89}Zr]Zr-Df-IAB22M2C uptake located predominantly in the cervical and thoracic region were identified. Considering the previous routine imaging and the clinical history of the patients, these lymph nodes appeared rather associated with inflammatory processes than metastases

B: In Patient 4 and 5 without ICT pretreatment an intense [^{89}Zr]Zr-Df-IAB22M2C uptake in the lymph nodes was evident. These lymph nodes have been considered as non-malignant according to the previous routine imaging and the clinical history.

Figure 4



A high [^{89}Zr]Zr-Df-IAB22M2C uptake in the bone marrow was observed in the majority of the patients with ICT pretreatment, whereas patients without ICT pretreatment exhibited a relatively low [^{89}Zr]Zr-Df-IAB22M2C uptake in the bone marrow.

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