Visualization of tumor heterogeneity in neuroendocrine tumors by positron emission tomography

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A 50-year-old woman was diagnosed 15 months ago with a well-differentiated neuroendocrine tumor (NET) of the pancreatic tail (Ki-67: 10 %) and synchronous liver metastases. Consecutively, systemic treatment with octreotide was initiated. Due to progression, 2nd line treatment with peptide receptor radionuclide therapy (PRRT) using the ^{177}Lu-labeled somatostatin analog DOTA-D-Phe1-Tyr3-octreotide (DOTATOC) was initiated. After three cycles of PRRT, somatostatin receptor (SSTR)-based positron emission tomography (PET) with ^{68}Ga-labeled DOTATOC in combination with contrast-enhanced computed tomography (CE-CT) was performed for restaging. In comparison to pre-therapeutic imaging, DOTATOC-PET demonstrated no significant change of both primary and known liver metastases highly expressing SSTR subtype II (Fig. 1, left). However, CE-CT revealed numerous significantly progressive, SSTR-negative intrahepatic lesions, highly suspicious for undifferentiated metastases. Accordingly, a PET/CT with the glucose analog [^{18}F]fluordeoxyglucose (FDG) was performed. FDG-PET depicted increased focal uptake in all SSTR-negative lesions corroborating the CT findings (Fig. 1, right). Interestingly, almost all SSTR-positive lesions showed no or only weak FDG-accumulation (Fig. 1).

The patient underwent CT-guided liver biopsy of an SSTR-negative, FDG-positive liver lesion confirming poorly differentiated metastasis of the known NET with a proliferative activity (Ki-67) of 15 %. Consequently, PRRT was stopped and patient management was changed to chemotherapy with streptozotocin and 5-fluorouracil. The patient underwent four treatment cycles. Recently, 12-months' follow-up revealed stable disease.

SSTR-PET/CT has been established as the standard imaging tool for well-differentiated NET due to a superior tumor detection rate compared to conventional receptor scintigraphy and multi-slice CT [1]. FDG-PET/CT as a marker of increased glucose use of tumor cells has low sensitivity in well-differentiated NET. However, in advanced disease and intermediate- and high-grade tumors, a mixture of well- and poorly differentiated tumor lesions may be present. In aggressive NET with high proliferation rates, FDG-PET/CT remains the radiopharmaceutical of choice [2, 3]. Therefore, in conjunction with (multi-phase) CE-CT, functional imaging with both SSTR- and FDG-PET may be performed for comprehensive tumor assessment, help to address different biological properties of NET, and to guide re-biopsies to de-differentiated tumor lesions in order to overcome histologic selection bias. In our case, the combination of SSTR- and FDG-PET directly impacted on diagnostic work-up as well as patient management by revealing a multitude of vital, SSTR-negative liver metastases. Its value for therapeutic decision-making has been recently shown to be >50 % [4].

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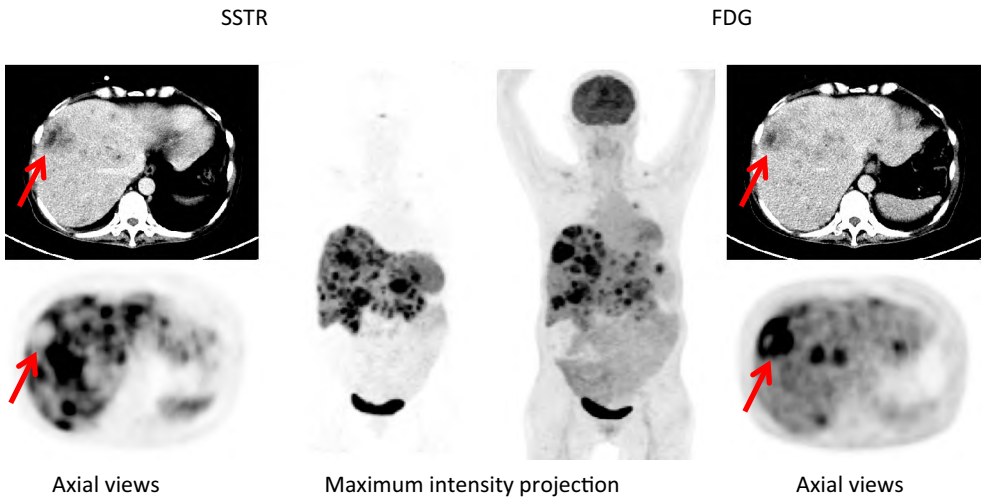

Fig. 1 Tumor heterogeneity in NET depicted by FDG- and somatostatin receptor (SSTR)-based PET/CT. Given are both axial views as well as maximum intensity projections of SSTR-based [^{68}Ga]-DOTATOC-PET (left) and FDG-PET (right). SSTR-PET demonstrates numerous liver metastases highly expressing SSTR subtype II. However, CE-CT reveals further suspicious intrahepatic lesions without tracer accumulation (arrows). FDG-PET depicts increased focal uptake in all SSTR-negative lesions corroborating the CT findings (arrows). Interestingly, the SSTR-positive lesions show no or only weak FDG uptake (maximum intensity projections). Liver biopsy of an SSTR-negative, FDG-positive liver lesion confirms metastasis with a proliferative activity (Ki67) of 15 %. Consequently, patient management is changed to chemotherapy with streptozotocin and 5-fluorouracil

Conflict of interest The authors declare that there is no conflict of interest.

Human and Animal Rights and Informed Consent For this type of study, formal consent is not required. This article does not contain any study with animals performed by any of the authors. There is informed consent by the patient included in the study.

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