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IMAGE OF THE MONTH

First-in-human administration of terbium-161-labelled somatostatin receptor subtype 2 antagonist ([^{161}Tb]Tb-DOTA-LM3) in a patient with a metastatic neuroendocrine tumour of the ileum

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Here, we report on the first patient (78-year-old man) with a metastatic, hormone-active (carcinoid syndrome) ileal neuroendocrine tumour (G1, Ki-67, < 3%), who received a test infusion of 1 GBq [^{161}Tb]Tb-DOTA-LM3 in an ongoing prospective Phase 0 study. So far, the patient received long-acting octreotide, which was stopped 2 months before [^{161}Tb]Tb-DOTA-LM3 infusion.

Similar to ^{177}Lu, ^{161}Tb decays with a half-life of 6.95 days and emits medium-energy β^--radiation ($E\beta_{average}$ = 154 keV) accompanied by photons suitable for imaging and dosimetry purposes (e.g. Eγ = 49 keV [17%], 75 keV [10%]) [1]. In addition, ^{161}Tb also emits conversion electrons and high quantities of Auger electrons (1213%) with a high linear energy transfer over a short distance (< 40 keV/µm). Somatostatin receptor subtype 2 antagonists such as DOTA-LM3 bind to many more binding sites, which leads to a much higher tumour accumulation compared to somatostatin receptor subtype 2 agonists [2]. The preclinical evaluation confirmed the superior therapeutic efficacy of [^{161}Tb]Tb-DOTA-LM3 over [^{177}Lu]Lu-DOTA-LM3, [^{161}Tb]Tb-DOTATOC and [^{177}Lu]Lu-DOTATOC, where the latter is routinely used for peptide receptor radionuclide therapy [3].

Maximum intensity projection (MIP) PET image (a) 1 h after i. v. administration of [^{68}Ga]Ga-DOTATATE shows moderate tumour burden with several lymph node, liver and peritoneal metastases. MIP SPECT images 24 h (b), 168 h (c) and transaxial SPECT/CT images 168 h (d, e) after infusion of 1 GBq [^{161}Tb]Tb-DOTA-LM3 revealed good image quality for both energy windows (75 keV ± 10% and 49 keV ± 20%), despite the low photon energy. Quantitative SPECT/CT imaging was performed 3, 24, 72 and 168 h after infusion of [^{161}Tb]Tb-DOTA-LM3 using a LEHR-collimator. Tumour and organ-absorbed doses were calculated using the 75 keV-window and a Monte-Carlo-based OSEM algorithm. The long mean (range) tumour half-life of 130 (123–135) h in liver metastases (red arrows) measuring 3.1–3.3 cm in the contrast-enhanced CT scan (f, g) resulted in mean (range) tumour absorbed dose of 28 (18–39) Gy/GBq. Bone marrow (black triangles), kidney and spleen absorbed dose were determined as 0.31, 3.33 and 6.86 Gy/GBq, respectively. Additionally, a decrease of the tumour marker chromogranin A from 522 to 359 µg/L was measured within 2 months after infusion of only 1 GBq [^{161}Tb]Tb-DOTA-LM3. According to CTCAE v5.0, grade 1 thrombocytopenia and grade 3 lymphocytopenia (grade 2 lymphocytopenia was already present at the time of baseline) were observed.

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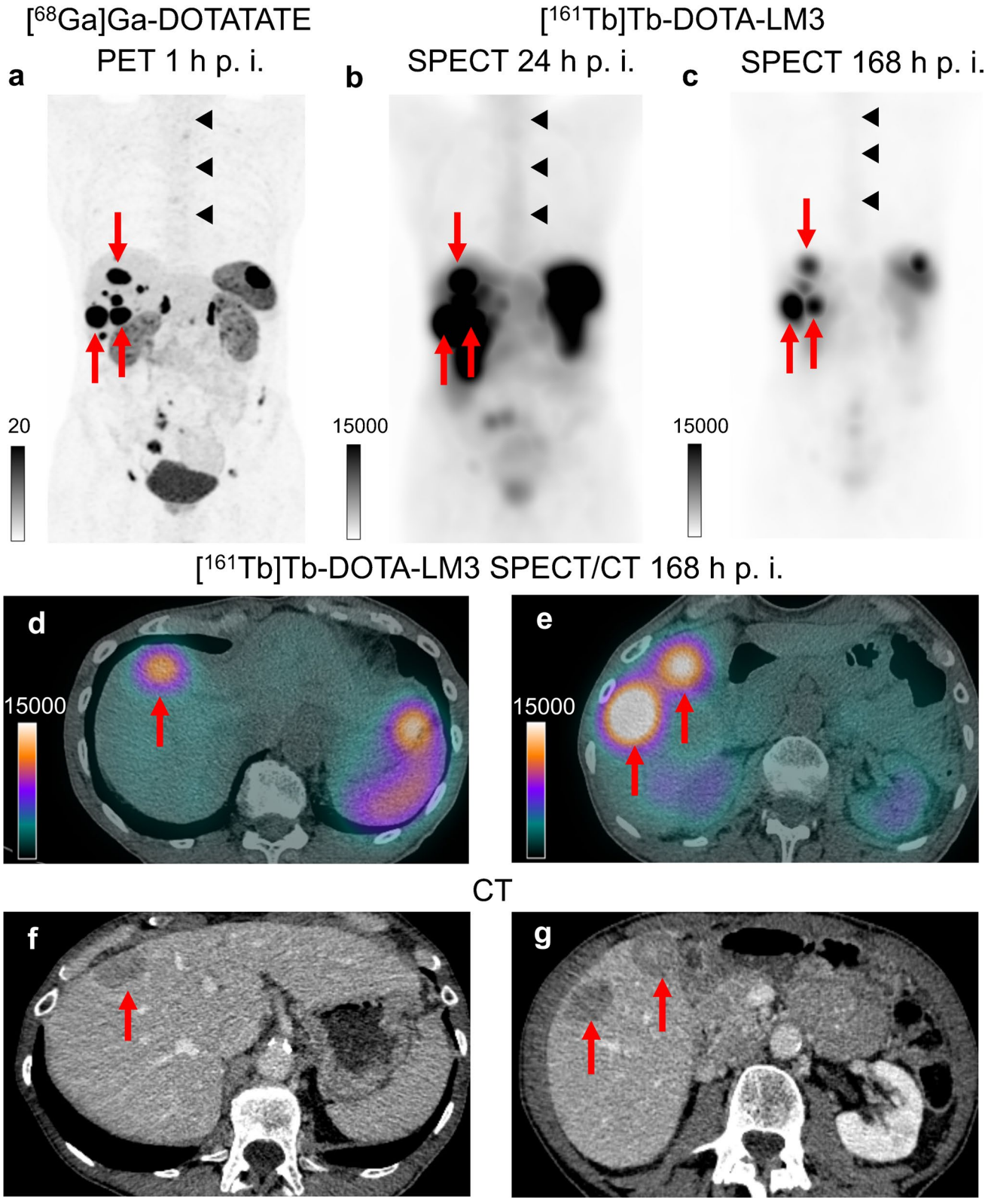
The case presented shows the potential of [^{161}Tb]Tb-DOTA-LM3 as a promising alternative to the current standard peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTATOC/[^{177}Lu]Lu-DOTATATE (Lutathera®) for patients with metastatic gastroenteropancreatic neuroendocrine tumours.



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Data availability Data will be made available upon reasonable request.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Northwest and Central Switzerland (01.03.2022, No: 2022-00162).

Consent to participate Informed consent was obtained from the patient before the inclusion into the study. The patient gave written informed consent to anonymously use their clinical and imaging data for publication.

Competing interests CM, RS, NM, MF and DW are listed as inventors on patent application US 2023/0165981, which contains [^{161}Tb]Tb-DOTA-LM3. PB is a co-founder of Theravision AB.

Clinical trial registration This study is registered with ClinicalTrials.gov (NCT05359146).

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