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SSTR-directed radiopharmaceutical therapy in a patient with small cell lung cancer: an intrapatient comparison of SSTR-agonist and antagonist

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ABSTRACT

Purpose: Somatostatin receptor (SSTR) overexpression has been described for a subgroup of small cell lung cancer (SCLC). SSTR-directed radiopharmaceutical therapy (RPT) with well-established SSTR-agonists and newer SSTR-antagonists could offer a further therapeutic option for this devastating disease. The aim of this study is to compare therapeutic efficacy and dosimetry of SSTR-agonist and SSTR-antagonist RPT in a patient with SCLC.
Methods: We present an intrapatient dosimetric comparison between the SSTR-agonist [^{177}Lu]Lu-HA-DOTATATE and the SSTR-antagonist [^{177}Lu]Lu-SSO110 in a heavily pretreated 64-year-old male with advanced SCLC. The patient received six cycles of [^{177}Lu]Lu-HA-DOTATATE followed by one cycle of [^{177}Lu]Lu-SSO110. Multi-time-point post-therapy SPECT/CT dosimetry was performed for cycles 2 (HA-DOTATATE) and 7 (SSO-110), and single-time-point dosimetry for the remaining cycles of [^{177}Lu]Lu-HA-DOTATATE.
Results: A maintained or even increased absorbed dose coefficient (ADC) was observed from the application of [^{177}Lu]Lu-SSO110, although the patient had been treated by six cycles of [^{177}Lu]Lu-HA-DOTATATE, indicating a sustained receptor binding despite prior SSTR-directed RPT with an SSTR-agonist. ADCs for kidneys (0.58 vs. 0.4 Gy/GBq), liver (0.28 vs. 0.32 Gy/GBq), and lungs (0.58 vs. 0.36 Gy/GBq) were comparable between agonist and antagonist cycles.
Conclusion: Given the limitations of the study and that it only comprises a single patient, both [^{177}Lu]Lu-HA-DOTATATE and [^{177}Lu]Lu-SSO110 demonstrated similar biodistribution and dosimetry in this heavily pretreated patient. Even after six cycles of SSTR-directed RPT, lesion uptake of [^{177}Lu]Lu-SSO110 was preserved and should be evaluated in further studies.

1. Introduction

Small cell lung cancer (SCLC) is an extremely aggressive cancer entity associated with a very poor prognosis and early treatment resistance [1,2]. Despite multimodal therapy regimens, including chemotherapy, external beam radiation therapy, and immunotherapy [1], the 5-year overall survival rate remains remarkably low (under 10%) [3]. Lung cancer in general remains difficult to diagnose and faces challenges in treatment that require a multidisciplinary management approach. For lung cancer, the European Cancer Organisation Essential Requirements for Quality Cancer recommend a multidisciplinary team consisting of health professionals from pulmonology/respiratory medicine, pathology, radiology, nuclear medicine, thoracic surgery, radiation oncology, medical oncology, and nursing to discuss each case after diagnosis and staging in order to optimize the treatment strategy [4]. Overexpression of somatostatin receptors (SSTR) has been reported in a substantial

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subset of SCLC [5], enabling radiopharmaceutical therapy (RPT) as a novel treatment option.

Recently, SSTR-antagonists have aroused clinical interest as therapeutic option, as previous studies suggested longer tumor retention due to a larger number of binding sites and high receptor affinity of the antagonist compared to SSTR-agonists [6]. The novel SSTR-antagonist [^{177}Lu]Lu-SSO110 has already shown favorable biodistribution and pharmacokinetics in patients with NETs [7–9]. Similarly, ^{68}Ga-labeled SSTR-antagonists may potentially provide greater benefits in SSTR-directed imaging compared to agonistic tracers in SCLC [10].

Here, we present an intrapatient comparison of biodistribution and dosimetry in a patient with advanced SCLC receiving multiple cycles of [^{177}Lu]Lu-HA-DOTATATE and [^{177}Lu]Lu-SSO110.

2. Materials and methods

[^{177}Lu]Lu-HA-DOTATATE and [^{177}Lu]Lu-SSO110 are investigational radiopharmaceuticals that were administered under compassionate use under the German Medicinal Products act (AMG, § 13.2b).

2.1. Ethics approval and consent

The patient gave written informed consent for work up of his case, publication and consented to the Augsburg Central Biobank and the ALPS trial, which is conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (Augsburg Longitudinal Plasma Study, NCT0524513).

2.2. Patient history & treatment protocol

A 64-year-old male patient with advanced SCLC was transferred for evaluation of SSTR-directed RPT after progression on various prior therapy lines over the course of one year. Initial SSTR-directed PET imaging revealed intense SSTR-expression of all tumor manifestations (primary tumor with pleural carcinomatosis, lymph node, bone and brain metastases) and SSTR-directed RPT with [^{177}Lu]Lu-HA-DOTATATE was started. Fig. 1 provides an overview of the course of treatment. The patient showed initially an impressive response, nearly reaching complete remission after two cycles. Administration of cycle 5 was postponed upon patients request and progressive disease was visible on restaging afterwards. All tumor manifestations remained SSTR-positive, leading to administration of two further cycles of RPT. After six cycles of the SSTR-agonist [^{177}Lu]Lu-HA-DOTATATE with a median activity of 7.45 GBq (7.4–9.7 GBq; 201.35 mCi, 200–262.16 mCi), the therapy regimen was switched due to high tumor volumes and one further cycle of the SSTR-antagonist [^{177}Lu]Lu-SSO110 with 4.5 GBq (121.62 mCi) was administered intravenously. Each cycle was administered after prior treatment with antiemetic and nephroprotective medication [11]. Adverse events were assessed according to CTCAE version 5.0 [12]. Progression-free survival of 6 months and an overall survival of 8 months could be reached. Detailed patient history and extensive morpho-molecular work-up of tumor escape mechanisms is described in previous work [13].

2.3. Radiolabeling

[^{177}Lu]Lu-HA-DOTATATE was prepared using an automated synthesis module (GRP module, Scintomics, Graefelfing, Germany) equipped with single-use hardware cassettes (SC-05H) and reagent sets (SC-05), both supplied by ABX, Radeberg, Germany.

Briefly, 4.0 mg gentisic acid in 5 ml 0.04 M acetic acid was transferred into a vial containing 31 mg sodium acetate trihydrate; the resulting solution was transferred into a vial containing 13.5 mg sodium ascorbate. The final solution was used to transfer the required [^{177}Lu]LuCl3 activity in 0.04 M HCl (Lutetium (^{177}Lu) n.c.a solution for radiolabeling, Isotopia Molecular Imaging Ltd., Park Petach Tikva, Israel) to the reaction vessel, which has been preloaded with a solution of HA-DOTATATE (PiChem, Grambach, Austria) in water for injection (1 mg/ml; 18.2 µl per GBq Lu-177).

The reaction mixture was heated to 100 °C for 20 min and then passed through two sterilizing filters (Millex PVDF [GV] 0.2 µm and Cathivex-GV filter 0.22 µm, both Merck Millipore, Darmstadt, Germany) followed by 10 ml isotonic saline/DTPA solution containing 1.0 g sodium ascorbate.

[^{177}Lu]Lu-SSO110 was labeled as courtesy by Ariceum Therapeutics GmbH (Berlin, Germany) and administered on a compassionate use basis.

2.4. Image acquisition

Multiple time-point post-therapy SPECT/CT images were acquired on a GE Discovery 670 Pro SPECT/CT (GE HealthCare, Milwaukee, Wisconsin, United States) equipped with a medium energy, general purpose collimator. Multi-time-point imaging was performed for [^{177}Lu]Lu-HA-DOTATATE in cycle 2 (day 1, day 2, day 3) and the [^{177}Lu]Lu–SSO–110 administration in cycle 7 (day 0, day 1, day 2, day 7). Single-time-point SPECT/CT imaging was performed for cycle 1 and cycles 3 to 6 (day 2). Two to three bed positions covering head to thigh with each 30 angular steps per head and 10 s per step were measured. Energy windows for ^{177}Lu were set around the 113 keV (10 % width) and 208 keV (20 % width) photopeaks. A reference standard of ^{177}Lu was positioned within the FOV for calibration purposes. A low-dose CT was acquired for each imaging session using 120 kV and 55 mA. Reconstruction was performed using OSEM with 2 iterations and 10 subsets and CT-based attenuation correction.

2.5. Dosimetry

Automated segmentation of lungs, kidneys, liver, and spleen was performed on the CT of each imaging time-point using MIM Contour ProtégéAI + ™ (MIM Software Inc., Cleveland, Ohio, United States) to extract image statistics per volume of interest (VOI). A spherical VOI was placed around the reference standard. Lesions were segmented using a 40 % iso-contour on the single-time-point SPECT or on day 1 SPECT image for cycles 2 and 7 and subsequently transferred to the rigidly co-registered other time-points per cycle. Manual adjustments of VOIs or VOI position were performed if deemed necessary. Self-calibration was performed per imaging time-point by assessing the counts in the reference standard and the expected decay-corrected activity in the reference standard per imaging time-point. This obtained calibration factor was used to convert the extracted count statistics of the images into values of Becquerel. MIRDfit v1.01 was used to fit the time-activity curves per VOI [14] for cycles 2 and 7 and export the time-integrated activity coefficients per VOI. Mono- and bi-exponential fit functions were used based on the available number of imaging time-points, or the trapezoidal method was used with extrapolation from the origin to the first imaging time-point and physical decay after the last imaging time-point as conservative approach. The Hänscheid method was used for single-time-point dosimetry of the other therapy cycles [15] and dosimetry was performed using mass-scaling of S-values with patient-individual organ volumes. The time-integrated activity coefficients (TIACs) were imported into MIRDcalc v1.22 [16] for dosimetry and mass-scaling used the patient-individual organ volumes multiplied by a density of 1.05 g/ccm [17].

3. Results

Dosimetry results were obtained for all cycles with complete reference standard information (cycles 2, 3, 5, 6, and 7). The TIAC per organ and lesion per cycle is provided in Table 1.

Fig. 2 displays the planar whole-body scans of day 2 after treatment to illustrate the radioactivity distribution across cycles with [^{177}Lu]Lu-

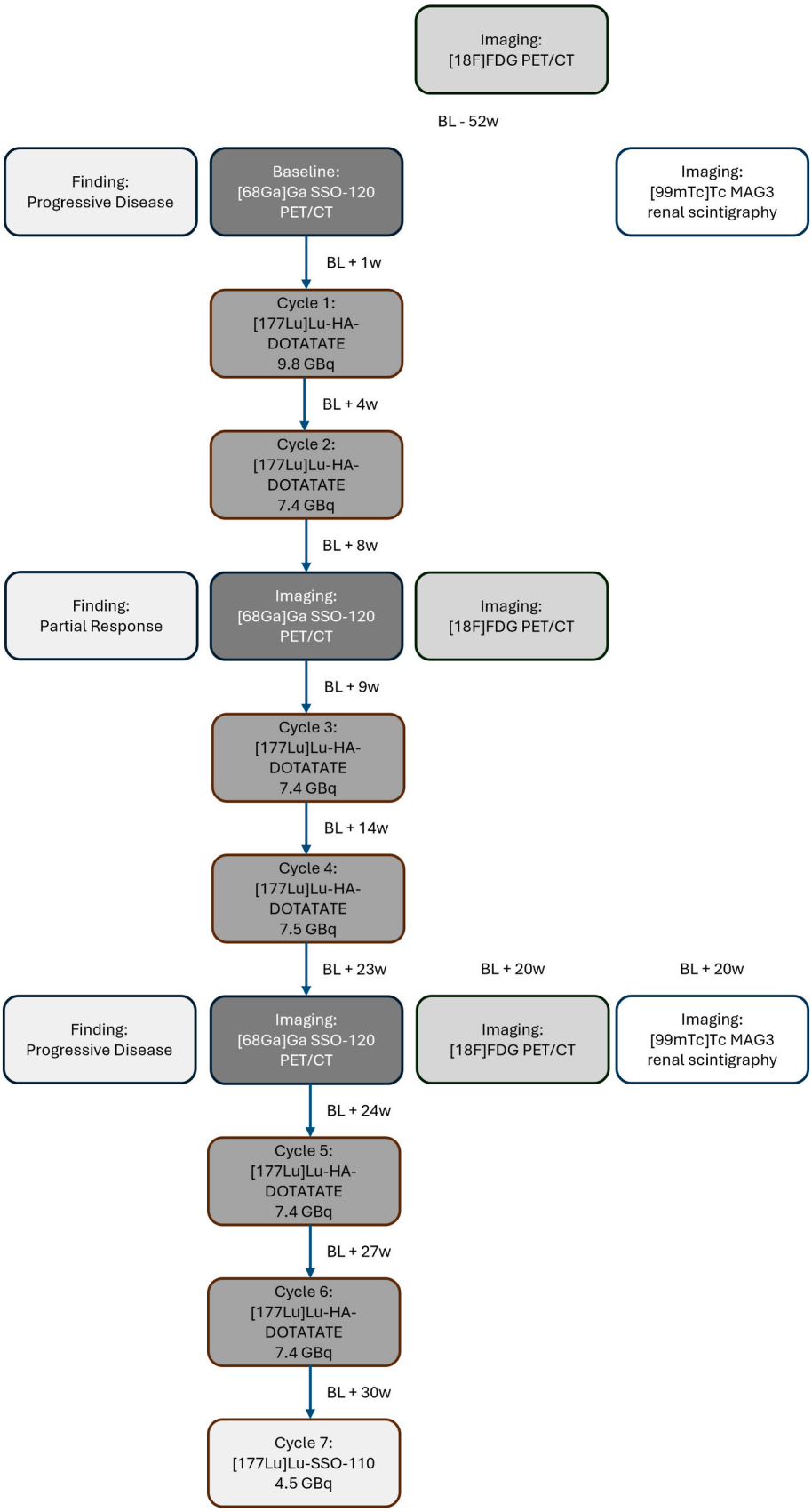

Fig. 1. Overview of the course of treatment. BL: Baseline, w: weeks.

Table 1
Time-integrated activity coefficient per cycle and volume of interest. Not available (N/A) lesion data indicates either a response or progress or that the lesion was outside the field of view (FOV) of the respective cycle.

Organ/Cycle	2	3	5	6	7
Kidneys	3.32E+00	3.10E+00	1.85E+00	2.24E+00	2.46E+00
Liver	6.90E+00	2.16E+00	6.61E+00	5.18E+00	9.97E+00
Lungs	7.62E+00	1.12E+00	3.92E+00	3.43E+00	4.75E+00
Spleen	3.96E+00	1.20E+00	8.23E-01	1.16E+00	1.00E+00
Lesion #1	3.60E-01	7.73E-02	2.07E+00	1.67E+00	1.17E+00
Lesion #2	8.18E-01	1.74E-01	2.29E+01	7.94E+00	1.71E+00
Lesion #3	N/A	N/A	7.40E-02	1.57E-01	3.34E-01
Lesion #4	N/A	1.01E-02	N/A	1.12E-01	1.70E-01
Lesion #5	N/A	N/A	N/A	1.76E-02	2.80E-02
Lesion #6	N/A	N/A	N/A	2.27E-02	5.03E-02
Lesion #7	N/A	N/A	N/A	3.73E-02	7.77E-02
Lesion #8	N/A	N/A	4.55E-02	5.20E-02	N/A

HA-DOTATATE and [^{177}Lu]Lu-SSO110. The dosimetry results are displayed in Table 2 and Fig. 3. Overall, the healthy organ absorbed dose coefficients (ADCs) are comparable, while the lesion absorbed doses vary largely across cycles.

Table 3 provides the patient's laboratory values of kidney function and hematological values for all seven therapy cycles.

4. Discussion

An intrapatient dosimetric comparison of agonists vs. antagonists SSTR-directed RPT in a heavily pretreated SCLC patient is presented in this study. Compared to a progression-free survival (PFS) of 1.6 months and overall survival (OS) of 3.3 months in a cohort of SCLC patients in third- or fourth-line therapy [18], this patient showed an encouragingly prolonged PFS of 6 months and OS of 8 months.

No indication of higher organ absorbed dose was observed when comparing the SSTR-antagonist versus SSTR-agonist, even though the SSTR-antagonist treatment took place after completion of multiple cycles with SSTR-agonist. For most organs and cycles, the ADCs in this patient were lower than in Wild et al. [9] and Schürrle et al. [18–20]; however, kidney and tumor ADCs were comparable to those found in other publications [19–21].

The kidney ADC decreased from 0.58 Gy/GBq (cycle 2, [^{177}Lu]Lu-HA-DOTATATE) to 0.40 Gy/GBq (cycle 7, [^{177}Lu]Lu–SSO–110). When using the average absorbed doses of cycles 3 and 5 for cycle 4 and the same absorbed doses for cycles 1 and 2, the cumulative kidney absorbed dose of 25.01 Gy across cycles would exceed the conservative threshold of 23 Gy for kidney toxicity from external beam radiation therapy [22]. Notably, the patient tolerated the antagonist cycle well, with no decrease in renal function or aggravation of hematologic toxicity (Table 3), despite the previously received six therapeutic SSTR-agonist

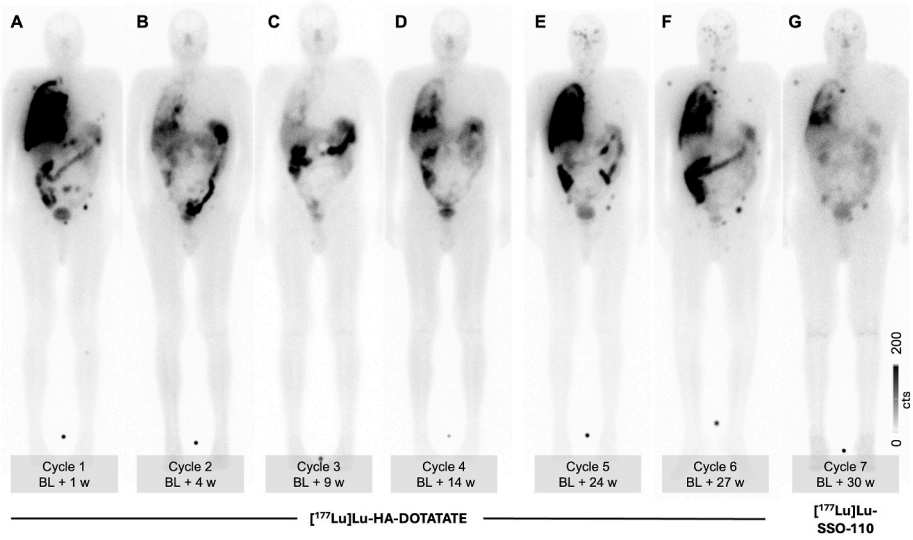

Fig. 2. Overview of post-therapeutic planar whole-body scans (anterior view) of cycles 1-7 at 48h after application of [^{177}Lu]Lu-HA-DOTATATE and [^{177}Lu]Lu–SSO–110. BL: Baseline, w: weeks.

Table 2
Dosimetry results across therapy cycles – normalized per administered activity and absolute values. N/A: not available because lesion was not present/was not present within imaging field of view (FOV).

Organ/Cycle	2 [^{177}Lu]Lu-HA DOTATATE		3 [^{177}Lu]Lu-HA DOTATATE		5 [^{177}Lu]Lu-HA DOTATATE		6 [^{177}Lu]Lu-HA DOTATATE		7 [^{177}Lu]Lu–SSO–110	
	[Gy/GBq]	[Gy]	[Gy/GBq]	[Gy]	[Gy/GBq]	[Gy]	[Gy/GBq]	[Gy]	[Gy/GBq]	[Gy]
Kidneys	0.58	4.30	0.44	4.08	0.42	3.16	0.38	2.84	0.40	1.66
Liver	0.28	2.04	0.10	0.77	0.37	2.79	0.20	1.53	0.32	1.30
Lungs	0.58	4.28	0.09	0.63	0.30	2.23	0.26	1.95	0.36	1.49
Spleen	1.74	12.82	0.09	0.63	0.30	2.25	0.70	5.26	0.60	2.44
Lesion #1 (primary tumor)	1.15	8.48	0.15	1.08	1.66	12.51	0.97	7.28	0.88	3.59
Lesion #2 (lung tissue/pleura)	2.42	17.84	0.14	1.04	1.98	14.92	1.21	9.06	1.13	4.64
Lesion #3 (bone)	N/A	N/A	N/A	N/A	0.73	5.51	1.16	8.68	3.01	12.35
Lesion #4 (bone)	N/A	N/A	0.06	0.41	N/A	N/A	1.41	10.56	2.55	10.46
Lesion #5 (brain)	N/A	N/A	N/A	N/A	N/A	N/A	0.23	1.73	0.41	1.68
Lesion #6 (bone)	N/A	N/A	N/A	N/A	N/A	N/A	0.49	3.69	0.88	3.60
Lesion #7 (bone)	N/A	N/A	N/A	N/A	N/A	N/A	0.40	3.01	0.91	3.73
Lesion #8 (bone)	N/A	N/A	N/A	N/A	0.33	2.52	0.79	5.91	N/A	N/A

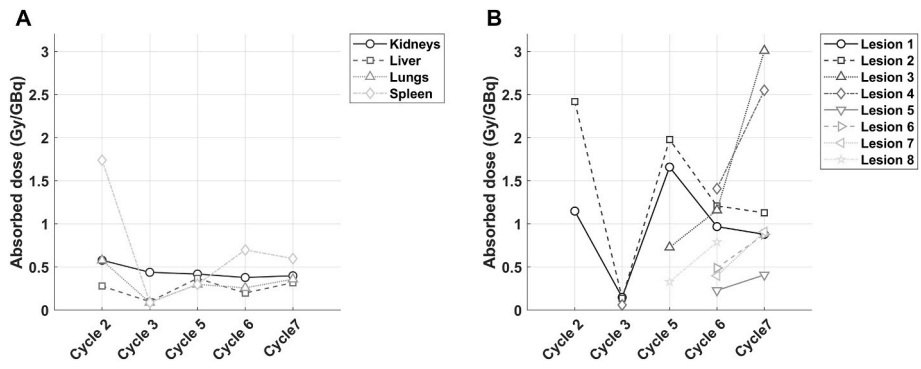

Fig. 3. Absorbed dose per administered activity across cycles and for organs **(A)** and lesions **(B)** resulting from administration of [^{177}Lu]Lu-HA-DOTATATE (cycle 2, 3, 5, 6) and from [^{177}Lu]Lu–SSO–110 for cycle 7. Lesion 1: primary tumor; Lesion 2: lung tissue/pleura; Lesions 3, 4, 6, 7, 8: bone metastases; Lesion 5: brain metastasis.

Table 3
Laboratory values of kidney function and hematological values for all seven cycles.

Cycle	1	2	3	4	5	6	7
Creatinine [mg/dl]	0.52	0.55	0.61	0.57	0.65	0.58	0.67
GFR (CKD-EPI) [ml/min/1,73m^2]	>90	>90	>90	>90	>90	>90	>90
Hemoglobin [g/l]	125	109	114	119	134	119	114
Leukocytes [/nl]	16.85	9.81	4.54	4.91	6.88	8.38	4.86
Thrombocytes [/nl]	338	370	280	178	173	98	87

radiopharmaceutical administrations and related kidney absorbed doses.

The variations in liver and lung ADCs across cycles can be attributed to the response and/or progress of the lesions in close proximity (Fig. 2). The liver ADC dropped from 0.28 Gy/GBq (cycle 2) to 0.10 Gy/GBq (cycle 3), followed by a large increase to 0.37 Gy/GBq (cycle 5). The ADC variation is likely attributable to variation in tumor burden rather than antagonist vs. agonist. The assumed cumulative liver absorbed dose of 13.00 Gy is far below the liver toxicity threshold of 30 Gy from Yttrium-90 liver radioembolization [23].

The lung ADC decreased from 0.58 Gy/GBq to 0.36 Gy/GBq (cycle 2 to 7). The estimated cumulative absorbed dose to the lungs of 17.00 Gy is close to the threshold of 17.5 Gy from EBRT [22], but far from the 30 to 50 Gy from Yttrium-90 liver radioembolization [23]. No signs of decreasing lung function were observed over the course of disease.

The primary tumor (Lesion 1), and the pleural metastasis (Lesion 2), showed decrease and increase of absorbed dose that compares with the visual assessment of uptake in the planar whole-body scans (Fig. 2) and corresponds to the initial response followed by progression. The new lesions with onset in cycles 5 and 6 had increasing ADCs towards cycle 7 despite extensive pretreatment, which may indicate a higher efficacy and ongoing therapeutic effect of the SSTR-antagonist [^{177}Lu]Lu-SSO110 compared to the SSTR-agonist [^{177}Lu]Lu-HA-DOTATATE, even after extensive pretreatment and emerging radioresistance.

This intrapatient dosimetric comparison, especially with respect to the new lesions with onset in cycles 5 and 6, showed an increase in lesion absorbed dose for the SSTR-antagonist compared to the SSTR-agonist, whereas healthy organ absorbed doses overall decreased. While a generalization of these findings is limited due to a single patient case, the results are promising and demonstrate that the SSTR-antagonist may lead to higher therapeutic efficacy than the SSTR-agonist. In this work, higher lesion ADC was observed despite the extensive previous treatment (4 + 2 cycles) with the SSTR-agonist in this patient; hence, a first-line treatment using an SSTR-antagonist may lead to different biodistribution, uptake, and dosimetric findings than observed herein. Future perspectives require a prospective clinical trial design that compares the efficacy of SSTR-antagonist and SSTR-agonist, including the application as first-line or second-line RPT as well as dosimetry analyses.

5. Limitations

This retrospective analysis has a few limitations. It is a single patient case with intrapatient comparison of [^{177}Lu]Lu-HA-DOTATATE and [^{177}Lu]Lu-SSO110 over the total course of RPTs. The comparison of [^{177}Lu]Lu-HA-DOTATATE and [^{177}Lu]Lu-SSO110 in the same patient implies that the two different radiopharmaceuticals were administered one after the other and hence at different phases of the disease. This limits the comparability of the dosimetry and outcome analysis for the lesions, while the comparison of the biodistribution and dosimetry of healthy organs remains valid despite potential pre-damage that was not observed in this individual patient. Future clinical trials are warranted to further investigate the results presented herein.

Due to software limitations in this retrospective analysis, no scatter correction was applied during reconstruction of the ^{177}Lu SPECT images. However, we deem this to be of minor impact on the dosimetry comparison since it applies to all images of all cycles. No dosimetry was available for cycles 1 and 4 due to missing activity information of the reference source. Cycles 2 and 7 were based on multiple time-point SPECT/CT dosimetry, while cycles 3, 5, and 6 were based on the Hänscheid method using a single-time-point SPECT/CT. Lesion dosimetry was performed under the assumption of soft tissue density for all lesions using spherical S-values in MIRDcalc v1.22. No partial volume correction was applied. No bone marrow dosimetry was performed due to lack of blood samples, multiple time-point imaging for all therapy cycles, and SPECT image FOV acquisition and sub-optimal reconstruction.

6. Conclusion

Given the limitations of the study, the biodistribution of [^{177}Lu]Lu-HA-DOTATATE and [^{177}Lu]Lu-SSO110 appeared to be similar. Compared to [^{177}Lu]Lu-HA-DOTATATE, [^{177}Lu]Lu-SSO110 demonstrated maintained or enhanced lesion uptake, despite prior progression to [^{177}Lu]Lu-HA-DOTATATE RPT, indicating an ongoing treatment effect that might overcome escape mechanisms. These results support the

potential clinical utility of SSTR antagonists in SCLC.

CRediT authorship contribution statement

Julia F. Brosch-Lenz: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Niklas Dreher:** Writing – review & editing, Writing – original draft, Conceptualization. **Jan Bäßler:** Writing – review & editing, Software, Formal analysis, Data curation. **Marianne Patt:** Writing – review & editing, Writing – original draft, Conceptualization. **Nic G. Reitsam:** Writing – review & editing, Writing – original draft, Conceptualization. **Helen Scholtissek:** Writing – review & editing, Writing – original draft, Conceptualization. **Jörg Patt:** Writing – review & editing, Writing – original draft, Conceptualization. **Martin Trepel:** Writing – review & editing, Writing – original draft, Conceptualization. **Ralph A. Bundschuh:** Writing – review & editing, Writing – original draft, Conceptualization. **Alexander Dierks:** Writing – review & editing, Writing – original draft, Conceptualization. **Constantin Lapa:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Johanna S. Enke:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ralph A Bundschuh reports a relationship with Bayer Healthcare (Leverkusen, Germany), Novartis (Nürnberg, Germany), Terumo GmbH (Eschborn, Germany), and Eisai GmbH (Frankfurt, Germany), Blue Earth Therapeutics (Oxford, UK) that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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