Brief Report on the Use of Radiolabeled Somatostatin Analogs for the Diagnosis and Treatment of Metastatic Small-Cell Lung Cancer Patients

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Introduction: The demonstration of type 2 somatostatin receptors (SSTRs) in small-cell lung cancer (SCLC) represents the rationale for the use of positron emission tomography/computed tomography (PET/CT) to determine SSTR expression, and select patients suitable for peptide radioreceptor radionuclide therapy (PRRT) in extensive-disease stage (ED) SCLC.

Methods: We evaluated 24 ED-SCLC patients with radiolabeled SST-analog PET/CT. Lesions at PET/CT scan were semiquantitatively scored (from 0 to 3+) and compared with contrast-enhanced CT findings. Patients scored as 3+ were admitted to PRRT after dosimetric evaluation. Average injected activity/cycle was 2.6 GBq (^{90}yttrium-PRRT) or 6.0 GBq (^{177}lutetium-PRRT). PRRT efficacy was clinically and radiologically assessed.

Results: PET/CT was negative in four of 24 patients, whereas in the remaining 20 cases uptake was scored as 1+ in seven of 20, 2+ in one of 20, and 3+ in 12 of 20. Primary tumor lesions showed uptake in 16 of 24 patients. Uptake in metastatic lesions was observed in four of four adrenals, two of five brain, 12 of 16 bone, three of eight liver, and 17 of 20 lymph node lesions. Of the 12 patients eligible for PRRT, 11 were eventually treated and four of 11 patients received multiple PRRT administrations. Dosimetry resulted in a BED for kidney of 7.5 Gy (range, 4–21); bone marrow provisional dosage was 0.43 Gy (range, 0.1–1.7). Hematological PRRT toxicity occurred in three of 11 patients. No clinical or objective responses were observed with disease progression occurring approximately 48 days (range, 9–32) after PRRT.

Conclusion: Radiolabeled SST-analog PET/CT demonstrated enhanced SSTR expression in 50% of cases. Nevertheless, PRRT in ED-SCLC was ineffective, suggesting the need to anticipate or combine PRRT in a multimodality approach.

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Small-cell lung cancer (SCLC) accounts for 15% to 18% of lung cancer. The presence of metastases at diagnosis is associated with a worse prognosis (median survival of 10 months, 2-year survival rate of 10%). Diagnostic workup of SCLC included chest and abdomen computed tomography (CT), brain CT or magnetic resonance imaging, radionuclide bone scintigraphy, and bone marrow aspiration. Standard treatment for extensive-disease stage (ED) SCLC consists of platinum-based chemotherapy, followed by patient-tailored second-line therapy. The use of prophylactic cranial irradiation is questioned. For patients with symptomatic sites of disease, radiotherapy can provide palliation.[1] The research of effective treatments is crucial to improve ED-SCLC outcome. The demonstration of type 2 somatostatin receptors (SSTR) in 80% to 100% of SCLC cells[2] represents the rationale for the use of peptide radioreceptor radionuclide therapy (PRRT) in ED-SCLC, which is also successfully applied in other types of neuroendocrine tumors.[3,4] We investigated the performances of positron emission tomography/computed tomography (PET/CT) with somatostatin (SST) analogs (DOTATOC/DOTATATE) labeled with gallium-68 (^{68}Ga) in progressive ED-SCLC to select patients for subsequent PRRT. In addition, we evaluated PRRT toxicity and efficacy.

PATIENTS AND METHODS

Study Design

This was a prospective nonrandomized single-arm clinical trial performed at the Nuclear Medicine Unit of Arcispedale Santa Maria Nuova – IRCCS, Reggio Emilia (Italy), approved by local and national authorities (EudraCT numbers 2006-000897-65 and 2008-000983-17), and conducted in accordance with International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

Patients

From 2008 to 2011, we evaluated 24 ED-SCLC (M:W = 23:1) patients (mean age = 63.5 years; median age =

62.5 years; range, 41–79). All patients presented progressive disease assessed by CT scan and failed the first-line chemotherapy. Other treatments included surgery (3 of 24), radiotherapy (5 of 24), and long-acting SST analog (2 of 24). The Eastern Cooperative Oncology Group performance status was less than 2 in all patients. Asthenia was observed in all patients associated with nausea (1 of 24), muddle (2 of 24), superior mediastinal syndrome (4 of 24), and pain (13 of 24). Main comorbidities were diabetes (2 of 24) and blood hypertension (4 of 25).

Radiopharmaceuticals Preparation

The radiolabeling of ^{68}Ga-DOTATOC/DOTATATE was performed, as previously described.[4] Indium-111 (^{111}In-), yttrium-90 (^{90}Y-), and lutetium-177 (^{177}Lu-) DOTATOC/DOTATATE were synthesized, as previously reported.[4,5]

^{68}Ga-Peptide PET/CT

^{68}Ga- DOTATOC/DOTATATE PET/CT was acquired after the informed consent signature, as previously described.[4] All studies were visually and semiquantitatively assessed. All lesions were graded using the physiological uptake of the liver as reference organ, where 0 represented lesions with no uptake, 1+ lesion with uptake fainter than liver uptake, 2+ lesions whose uptake was similar to liver uptake, and 3+ lesions showing uptake higher than liver. In case of liver metastasis, uptake in the healthy parenchyma was used as reference. PET/CT positivity was considered an a priori diagnostic step to be eligible for PRRT. Patients with radiopharmaceutical uptake scored as 3+ were considered eligible for PRRT. Results of ^{68}Ga-DOTATOC/DOTATATE PET/CT were compared with baseline CT considered as the standard procedure.

Dosimetry

Dosimetric evaluation was performed in all patients fulfilling the study criteria (Table 1) admitted to PRRT, as previously described.[4]

Therapy

PRRT consists in the intravenous administration of an average activity of 2.6 or 6.0 GBq (^{90}Y-DOTATOC/DOTATATE or ^{177}Lu-DOTATOC/DOTATATE), with an interval of approximately 2 months in case of repeated administrations. Patients were hospitalized in a shielded environment for 3 days, in accordance with local requirements. Amino-acid solution was co-administered to PRRT and extending over 2 days following radiopeptide injection, to inhibit tubular radiotracer reabsorption.[4]

PRRT Response

All patients were followed for 3 months after the last PRRT administration or until tumor progression. Clinical and radiological responses were determined comparing baseline and end-treatment data. Radiological response was determined according to the response evaluation criteria in solid tumors.[6]

For toxicity assessment blood tests were repeated before and after each PRRT administration every 2 weeks until the end of follow-up. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 of the National Cancer Institute.[7]

TABLE 1. Inclusion and Exclusion Criteria for the Therapeutic Protocol

Criteria for the Therapeutic Protocol
Inclusion criteria
Age ≥ 18 yr
Inoperable or metastatic neuroendocrine tumor histologically confirmed
Presence of at least 1 measurable lesion
Hemoglobin level (Hb) ≥ 10 g/dl
Leukocytes (WBC) ≥ 2.5×10^3/ml
Platelets ≥ 100×10^3/ml
Bilirubin levels < 2.5 mg/dl
Creatinine levels < 2 mg/dl
ECOG performance status < 2
Signed informed consent
Discontinuation of cold SST analog treatment within 4 wks
Life expectancy ≥ 6 mo
Exclusion criteria
Other treatment (such as chemotherapy or radiotherapy) or participation in any investigational drug trial within 1 mo of PRRT and for the next 2 mo
Pregnancy or lactation
Bone marrow involvement > 25%
Other concomitant tumors, except in situ basal cell carcinoma and tumors of the uterine cervix treated with radical surgery

PRRT, peptide radioreceptor radionuclide therapy; SST, somatostatin; ECOG, Eastern Cooperative Oncology Group.

Statistical Analysis

All values are expressed as median and range, as customary for nonparametric data.

RESULTS

^{68}Ga-DOTATOC/DOTATATE PET/CT was completely negative in four of 24 cases; in the other 20 patients, uptake was scored as 1+ in seven of 20, 2+ in one of 20, and 3+ in 12 of 20, respectively. Twelve patients were eligible for PRRT. One patient was not treated because of the lack of fulfillment of the other inclusion criteria.

Table 2 summarized the results of ^{68}Ga-DOTATOC/DOTATATE PET/CT based on the site of disease localization. Figures 1 and 2 showed different patterns of radiopharmaceutical uptake at PET/CT. ^{68}Ga-DOTATOC/DOTATATE PET/CT and CT were concordant for all the sites of the disease in nine of 24 patients (37.5%). Primary tumor showed ^{68}Ga-DOTATOC/DOTATATE uptake in 16 of 24 patients (67%). Adrenals, bone, brain, liver, and lymph nodes metastasis were correctly identified by PET/CT in 100% of the cases, 12 of 16 (75%), two of five (40%), three of eight (37.5%), and 17 of 20 (85%) cases, respectively. Table 3 reports ^{68}Ga-DOTATOC/DOTATATE uptake in the 11 patients treated with PRRT.

Dosimetric estimates resulted in a biological effective dose for kidney of 7.5 Gy (range, 4–21). Bone marrow provisional dose was 0.43 Gy (range, 0.052–1.745). No toxicities were observed after radiopharmaceutical dosimetric injection.

For PRRT, ^{90}Y-DOTATOC/DOTATATE was used in seven of 11 patients, and ^{177}Lu-DOTATOC/DOTATATE was used in

TABLE 2. Score and SUVmax Values Provided by PET/CT with Radiolabeled Somatostatin Analogs Detailed for Site of Disease in All Patients Enrolled in the Study

		Site[a]					
Gallium-68-DOTATOC/DOTATATE PET/CT		**Lung (*n* = 24)**	**Adrenals (*n* = 4)**	**Brain (*n* = 5)**	**Bone (*n* = 16)**	**Liver (*n* = 8)**	**Lymph nodes (*n* = 20)**
Score	0	8/24 (33%)	—	3/5 (60%)	4/16 (25%)	5/8 (62.5%)	3/20 (15%)
	1+	8/24 (33%)	—	2/5 (40%)	2/16 (13%)	—	7/20 (35%)
	2+	1/24 (4%)	—	—	1/16 (6%)	—	1/20 (5%)
	3+	7/24 (30%)	4/4 (100%)	—	9/16 (56%)	3/8 (37.5%)	9/20 (45%)
SUVmax[b]	Mean	9.39	19.80	2.15	14.94	34.00	10.05
	Median	7.60	21.00	2.15	10.60	20.00	8.30
	Range	1.5–38	14.4–22.8	2.0–2.3	3–46	20–62	3.2–42
	Standard deviation	±8.75	±3.79	±0.21	±14.16	±24.25	±9.3

[a]Site of disease was defined according to results of baseline contrast-enhanced computed tomography scan (size of all lesions > 5 mm).
[b]SUVmax of the reference organ (healthy liver parenchyma): mean = 8.23; median = 8.4; range = 3.1–19; SD = ±3.21.
SUVmax, maximum standardized uptake value; PET, positron emission tomography; CT, computed tomography.

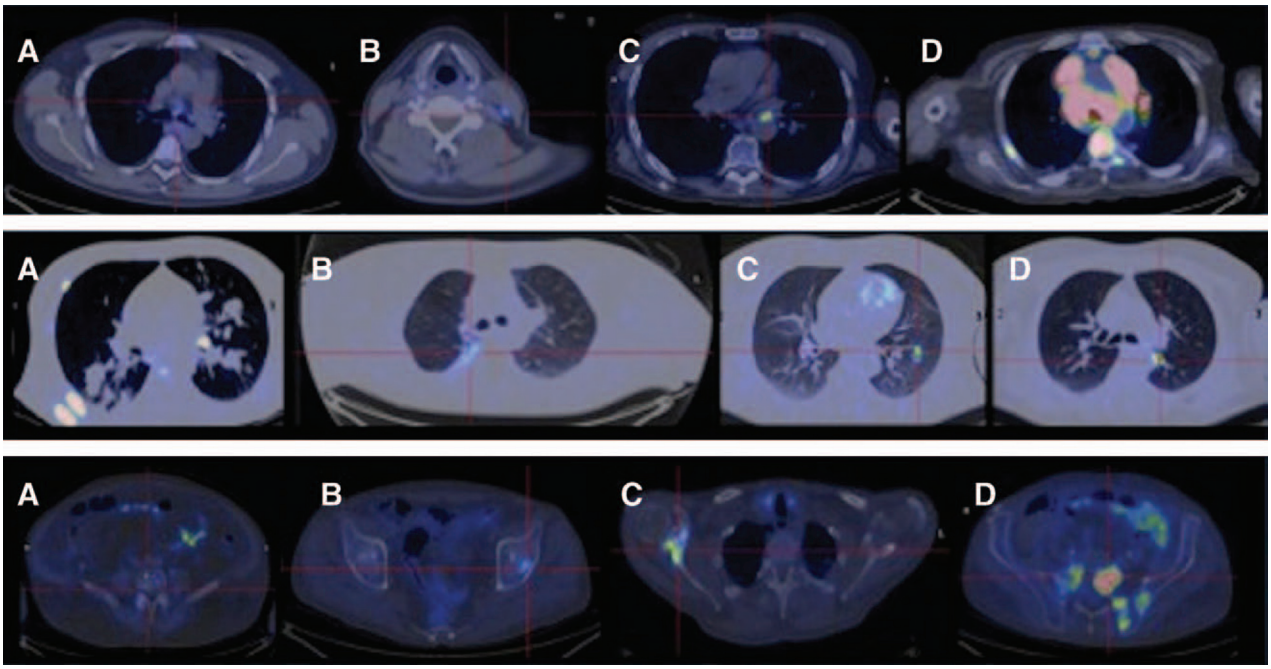

FIGURE 1. Examples of different radiopharmaceutical patterns of uptake at PET/CT, with somatostatin analogs radiolabeled with gallium-68. Lesions were graded using a semiquantitative score where 0 (*A*) represent lesions with no uptake, 1+ (*B*) lesion with uptake fainter than liver uptake, 2+ (*C*) lesions whose uptake was similar to liver uptake, and 3+ (*D*) lesions showing uptake higher than liver. Upper-fused PET/CT images showed patterns of radiotracer uptake in lymph node lesions. Middle-fused PET/CT images showed patterns of radiotracer uptake in primary tumor lesions. Lower-fused PET/CT images showed patterns of radiotracer uptake in bone lesions. PET, positron emission tomography; CT, computed tomography.

four of 11 patients. Seven patients received one PRRT administration, whereas the remaining four patients received repeated PRRT administrations (Table 4) at 76 ± 17 days apart (range, 50–89).

PRRT toxicity was mainly hematological (3 of 11), including anemia (grade 2) and thrombocytopenia (grade 2–3). In a patient (no. 3) with multiple liver metastasis, increase in bilirubin levels (grade 3) was reported after PRRT, and the subsequent CT scan documented progressive disease in liver, brain, lung, and bone lesions; therefore, this finding was considered disease related. Transient increase of creatinine (grade 1) was observed in a patient (no. 6).

We did not observe any significant clinical response. CT scan documented progressive disease for the appearance of new lesions in all treated patients (Figs. 3 and 4). Progressive disease occurred after a median of 90 (range, 7–238) or 59 days (range, 7–98), considering the first or the last PRRT administration (in case of repeated administrations), respectively.

DISCUSSION

The introduction of generator-produced positron emitter radionuclide as gallium-68, together with the development of automated synthesizer for rapid and efficient radiolabeling of

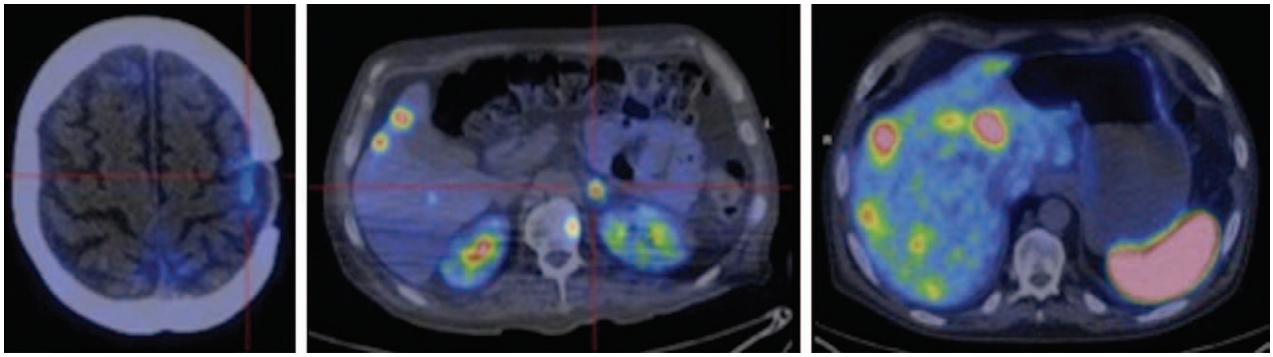

FIGURE 2. Examples of different patterns of uptake of somatostatin analogs radiolabeled with gallium-68 at fused positron emission tomography/computed tomography images. Left panel shows a brain lesion scored as 1+, middle panel shows left adrenal lesion scored as 3+, and right panel shows multiple liver lesions scored as 3+.

TABLE 3. Comparison of Baseline Contrast-Enhanced CT and PET/CT with Radiolabeled Somatostatin-Analog Findings in the 11 Patients Treated with Peptide Receptor Radionuclide Therapy

		Site of Disease					
Patient No.	**Imaging**	**Lung**	**Lymph Node**	**Bone**	**Brain**	**Adrenals**	**Liver**
1	CT scan	P	P	P	P	P	P
	^{68}Ga-DOTATATE PET/CT	3+	3+	3+	0	3+	3+
2	CT scan	P	P	P	P	N	N
	^{68}Ga-DOTATOC PET/CT	3+	1+	3+	1+	N	N
3	CT scan	P	P	P	P	N	P
	^{68}Ga-DOTATATE PET/CT	0	3+	3+	0	N	0
4	CT scan	P	P	P	N	N	N
	^{68}Ga-DOTATATE PET/CT	1+	1+	3+	N	N	N
5	CT scan	P	P	P	N	P	P
	^{68}Ga-DOTATOC PET/CT	1+	3+	2+	N	3+	0
6	CT scan	P	P	P	N	N	P
	^{68}Ga-DOTATOC PET/CT	3+	3+	3+	N	N	0
7	CT scan	P	P	N	P	N	N
	^{68}Ga-DOTATATE PET/CT	3+	1+	N	1+	N	N
8	CT scan	P	P	N	N	P	N
	^{68}Ga-DOTATOC PET/CT	3+	3+	N	N	3+	N
9	CT scan	P	P	P	N	N	P
	^{68}Ga-DOTATOC PET/CT	0	1+	3+	N	N	0
10	CT scan	P	P	P	P	N	P
	^{68}Ga-DOTATOC PET/CT	3+	3+	1+	0	N	0
11	CT scan	P	P	P	N	N	N
	^{68}Ga-DOTATOC PET/CT	3+	2+	3+	N	N	N

Radiopharmaceutical uptake in each lesion was graded from 0 to 3+, where 0 represent lesions with no uptake, 1+ lesion with uptake fainter than liver uptake, 2+ lesions with uptake similar to liver uptake, and 3+ lesions with uptake higher than liver.

CT, computed tomography; ^{68}Ga, gallium-68; N, negative; P, positive; PET, positron emission tomography.

SST analog, has opened the possibility of using PET imaging for the detection-enhanced SSTR tumor expression with higher detection rate, as compared with conventional SSTR scintigraphy.[8]

Similar results may be achieved in SCLC. In fact, when ED-SCLC patients are evaluated with ^{68}Ga-DOTATOC/DOTATATE PET/CT, we can increase tumor detection rate of conventional SSTR scintigraphy, as already observed for lung cancer patients.[9,10] The use of PET/CT results in similar performances for the primary tumor as compared with Octreoscan (67% versus 78–100%) but shows greater advantage for detection of distant metastasis (37.5–100% versus 26–75%). The identification of liver and brain metastasis were definitively more complicated with a detection rate similar to Octreoscan.[11]

In addition, based on the intensity of ^{68}Ga-DOTATOC/DOTATATE uptake at PET/CT, which was significantly high

TABLE 4. Radiopharmaceutical Administration(s) and Cumulative Administered Activity of PRRT for Each Treated Patient

	PRRT			
Patient No.	**First Administration**	**Second Administration**	**Third Administration**	**Cumulative Administered Activity**
1	^{90}Y-DOTATATE (2.5 GBq)	—	—	2.5 GBq
2	^{177}Lu-DOTATOC (5.5 GBq)	^{177}Lu-DOTATOC (5.6 GBq)	—	11.1 GBq
3	^{177}Lu-DOTATATE (3.8 GBq)	^{177}Lu-DOTATATE (3.8 GBq)	—	7.6 GBq
4	^{177}Lu-DOTATATE (5.5 GBq)	—	—	5.5 GBq
5	^{177}Lu-DOTATOC (7.8 GBq)	—	—	7.8 GBq
6	^{90}Y-DOTATOC (2.8 GBq)	^{90}Y-DOTATOC (3.1 GBq)	^{90}Y-DOTATOC (2.3 GBq)	6.1 GBq
7	^{90}Y-DOTATATE (2.5 GBq)	—	—	2.5 GBq
8	^{90}Y-DOTATOC (3.7 GBq)	—	—	3.7 GBq
9	^{90}Y-DOTATOC (3.5 GBq)	—	—	3.5 GBq
10	^{90}Y-DOTATOC (3.5 GBq)	^{90}Y-DOTATOC (3.7 GBq)	—	7.2 GBq
11	^{90}Y-DOTATOC (3.1 GBq)	—	—	3.1 GBq

PRRT, peptide receptor radionuclide therapy; ^{90}Y, yttrium-90; ^{177}Lu, lutetium-177.

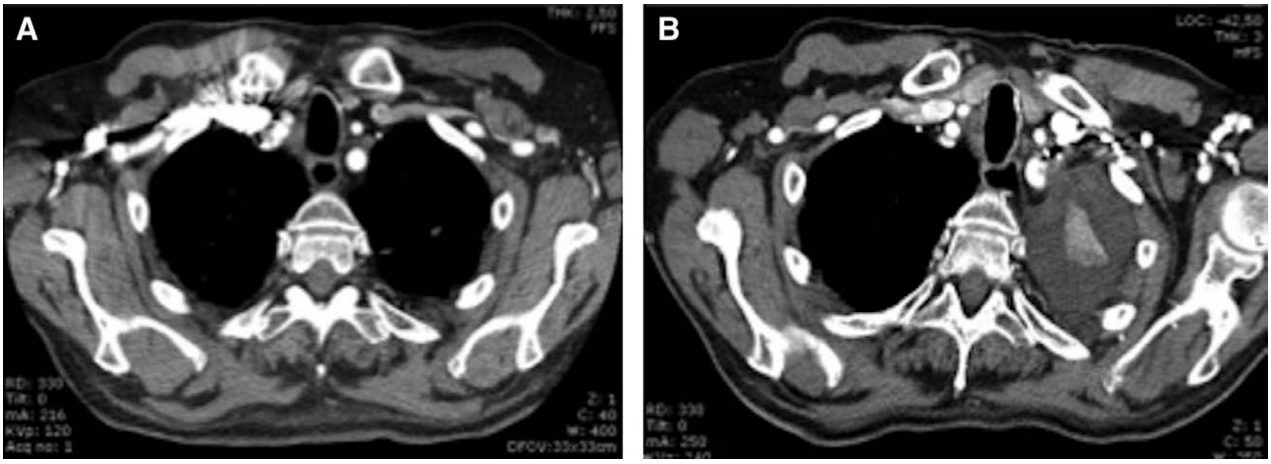

FIGURE 3. Comparison of baseline (*A*) and end-treatment (*B*) contrast-enhanced CT scans in patient no. 4. End-treatment CT scan was performed 35 days after peptide receptor radionuclide therapy. Transaxial images showed progression of disease in left lung. CT, computed tomography.

(3+) in 50% of patients, we were able to enroll a higher percentage of patients to PRRT as compared with the percentage reported for Octreoscan (28%).[11]

Unfortunately, the higher rate of patients admitted to PRRT does not translate into a significant benefit in terms of either clinical or radiological response to treatment. In fact, in the 11 patients treated with PRRT, we could not detect an antitumor effect using either ^{90}Y-, or ^{177}Lu-DOTATOC/DOTATATE, confirming data previously reported in smaller series.[11,12] The reasons for such discouraging results are still unclear. Different hypotheses may be formulated to explain the lack of antitumor effect of PRRT as acquired radioresistance in these heavily pretreated or the use of suboptimal tumor-absorbed dose. Unfortunately, in this study, we cannot address this issue because a major limitation of our work was the lack of reliable dosimetric estimate for tumor lesions. In addition, the delayed timing of PRRT could explain our negative results, because PRRT efficacy may be limited in ED-SCLC with rapidly progressive behavior.

However, the recent observations of the efficacy of combination regimens based on SST analogs and antineoplastic agents in limited-stage disease SCLC[13] and ^{177}Lu-DOTA-Tyr3-octreotate in fractionated doses,[2] suggest that the success of PRRT might be strengthened when early-stage patients are considered and high and fractionated doses are used, eventually including combination with chemotherapy. However, when designing such protocol, kidney and bone marrow toxicity should be considered. Therefore, implementation of dosimetry is warranted. In particular, limitation of renal toxicity is significant in SCLC based on previous platinum-based chemotherapy.

Therapeutic advances for SCLC strongly rely on the implementation of preclinical and translational research to better understand biology of ED-SCLC.[14,15] It is to be hoped that the use of innovative translational and multimodality approaches may help to streamline resources and rapidly develop more effective therapies for ED-SCLC.[15]

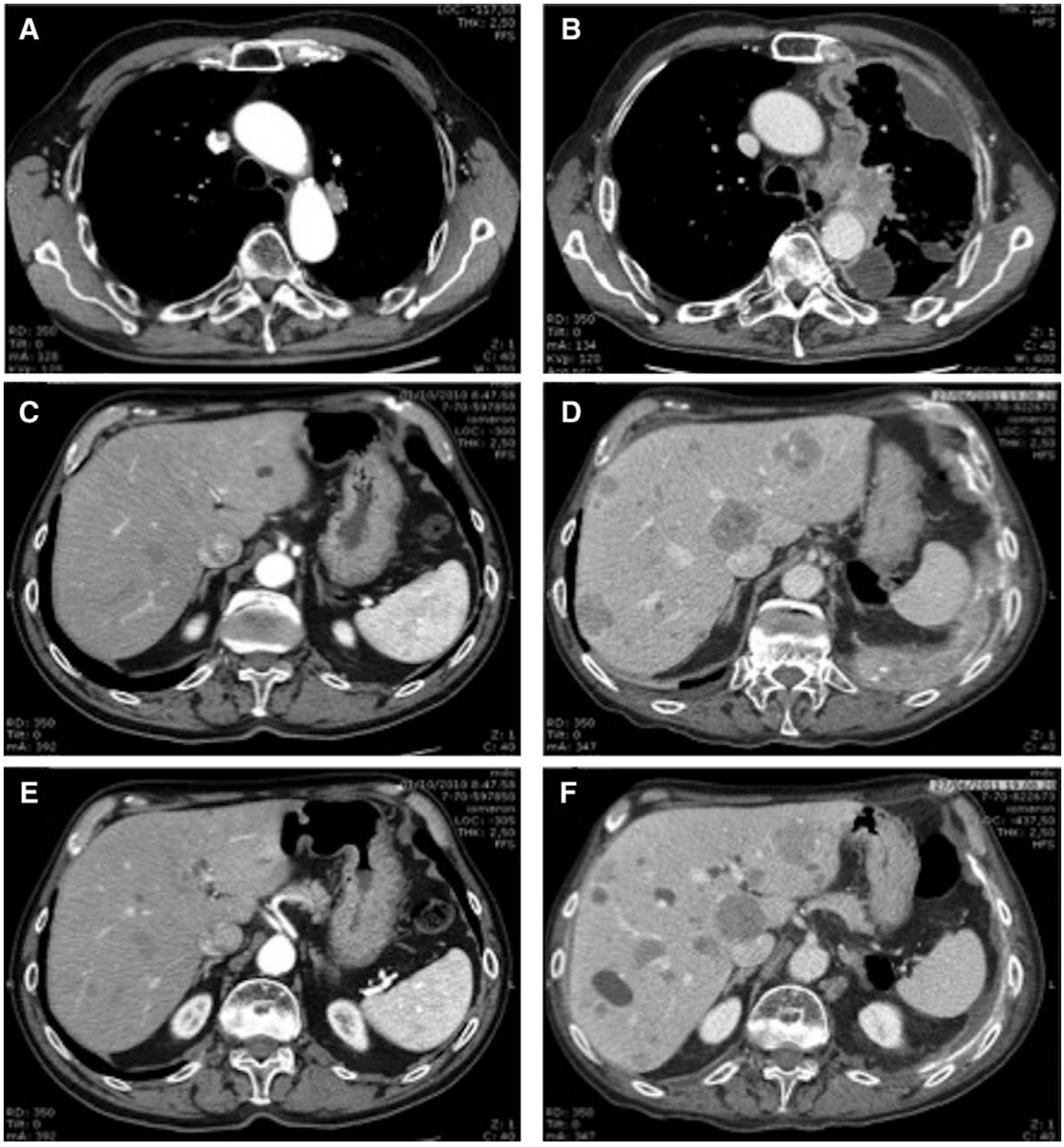

FIGURE 4. Comparison of baseline (*A*, *C*, and *E*) and end-treatment (*B*, *D*, and *F*) contrast-enhanced CT scans in patient no. 2. End-treatment CT scan was performed 48 days after peptide receptor radionuclide therapy. Transaxial images clearly showed progression of disease in left lung, vertebral body (*A*, *B*), and liver (*C*–*F*). CT, computed tomography.

CONCLUSIONS

^{68}Ga-DOTATOC/DOTATATE PET/CT increases tumor detection rate in ED-SCLC, mainly because of a major number of metastasis visualization as compared with Octreoscan, increasing significantly the number of patients suitable for PRRT. However, PRRT, using a fractionated administration of either ^{90}Y- or ^{77}Lu-DOTATOC/DOTATATE is ineffective in ED-SCLC patients, resulting in disease progression in all cases. Hematological toxicity was observed in 27% of cases. No significant renal toxicity was recorded. Indeed, such disappointing results support the hypothesis of application of PRRT in early-stage disease, using an appropriate timing schedule and eventually, a multimodality approach.

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