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Lu-PRRT Used More Intensively on Advanced Gastro-Entero-Pancreatic and Lung Neuroendocrine Neoplasms: Preliminary Results on Toxicity from a Randomized Study

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Keywords
Intensive Lu-PRRT · Neuroendocrine neoplasms · Toxicity · Personalized schedule

Abstract

Introduction: Lu-PRRT in neuroendocrine tumors is usually delivered with a total cumulative activity (TCA) of 29.6 GBq, divided into 4 cycles and with fixed interval between cycles (IBCs) of 8 weeks. Based on previous radiobiological studies, reducing IBC could improve efficacy without increasing toxicity. The purpose of this study was to evaluate safety of Lu-PRRT with two different IBC: intensive (every 5 weeks) or standard (every 8–10 weeks). ***Methods:*** From May 2016 to July 2018, patients with advanced and progressive GEP and bronchial NENs were enrolled in a prospective randomized phase II study. Patients with risk factors for toxicity (RF) were planned for a TCA of 18.5 GBq, patients without RF of 27.8 GBq, divided into 5 cycles. Patients were then randomly assigned to be treated according to the intensive or to the standard IBC. Toxicity was monitored according to CTCAE. ***Results:*** One hundred and twenty patients (61 in the intensive group and 59 in the standard one) were evaluable for overall toxicity. Five patients (4.1%) had major (G3) hematological toxicity, 2 in the intensive group and 3 in the standard one. Other G3 toxicities related to creatinine, alanine aminotransferase, nausea, and asthenia were observed in the intensive group. 112 patients (54 in the intensive group and 58 in the standard one) performed at least 2 cycles and were also evaluable for cycle-by-cycle toxicity, resulting similar between the two groups. ***Conclusion:*** According to our preliminary results, Lu-PRRT administered intensively could be considered as safe as the standard schedule, when TCA is chosen according to the RF. Further data are needed to confirm these results.

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Introduction

Neuroendocrine neoplasms (NENs) are heterogeneous tumors, relatively rare, arising from cells of the diffuse neuroendocrine system. Two-thirds of them originate in the gastro-entero-pancreatic (GEP) tract and account for approximately 1%–2% of all tumors from this site of origin [1]. Based on their cellular morphology and proliferation index (Ki67), they are classified as well-differentiated grade 1 (G1, Ki67 ≤2), grade 2 (G2, Ki67 3–20%) and grade 3 (G3, Ki67 >20%) neuroendocrine tumors (NETs), and poorly differentiated G3 and neuroendocrine carcinomas [2]. It has been widely demonstrated that the former have a less aggressive behavior than the latter [3]. NENs arising from lung represent 20–25% of all NETs and are classified as typical (TC) and atypical carcinoids (AC) NETs, large cell neuroendocrine carcinomas and small cell lung carcinomas [4].

Approximately 20% of NETs are metastatic when they are first diagnosed [5], so surgery or loco-regional therapies are not feasible. At diagnosis, 20% of the patients are affected by carcinoid syndrome (CS) [6], caused by hypersecretion of hormones and amines, above all serotonin, and mostly represented by flushing, diarrhea, and carcinoid heart disease.

Somatostatin analogs (SSAs) are considered as the first-line systemic therapy for most patients with G1-G2 metastatic well-differentiated GEP NETs. When there is progression disease despite treatment with SSAs, peptide receptor radionuclide therapy (PRRT) should be considered [7]. The phase III trial NETTER-1 demonstrated that in patients with midgut NETs, PRRT with [^{177}Lu]Lu-DOTA-TATE (Lu-PRRT) plus long-acting octreotide can provide better results in terms of objective response rate, progression-free survival (PFS) and overall survival (OS) when compared to high-dose long-acting octreotide. Regarding NETTER-1 toxicity, grade (G) 3–4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the Lu-PRRT group as compared with no patients in the control group, with no evidence of renal toxic effects [8]. After NETTER-1 study, the Food and Drug Administration (FDA), European Medicine Agency (EMA), and Agenzia Italiana del Farmaco (AIFA) approved Lu-PRRT (Lutathera®) for the treatment of advanced, progressive, unresectable or metastatic G1-G2 GEP NETs positive for somatostatin receptors (SSTRs) imaging.

For bronchial NETs, Lu-PRRT is currently being considered as a potential alternative third-line or fourth-line therapy for patients who have already been treated with SSA and everolimus [9]. Previous reports have established the promising role of this therapy in these tumors, with reported disease control rate (DCR) values of 60% [10] and 71.4%, with no significant toxicity [11]. In patients with TC, DCR was also reported as 80% by our previous study on advanced bronchial NETs [4].

According to NETTER-1 trial, Lu-PRRT is delivered at the standard activity of 7.4 GBq/cycle for 4 cycles every 8 weeks, with a total cumulative activity (TCA) of 29.6 GBq. The fixed interval between cycles (IBCs) of 8 weeks is based on the established nadir of acute toxicity, generally 3–4 weeks after Lu-PRRT, with recovery in the following 4–6 weeks. In our previous studies, the IBC of 6–8 weeks was fixed and not modified even in absence of toxicity, too [12, 13].

It has been demonstrated that a longer IBC could reduce the likelihood of tumor control probability (TCP). Conversely, shortening the IBC would have the advantage to reach the minimum effective activity (MEA) at earlier time and may decrease the percentage of surviving cancer cells in the targeted lesions, reduce tumor mass and slow tumor repopulation. This approach could consequently lower the necessary dose to counteract this effect (waste dose) [14].

Following this information, a phase II study was then designed to investigate safety and PFS in patients with somatostatin-positive tumors (basket trial) undergoing two different treatment schedules: intensive (every 5 weeks) or standard (every 8–10 weeks) for a total of 5 cycles in both groups. Herein, we report the preliminary results on the first consecutive patients affected by GEP and bronchial NENs evaluated for overall safety (120) and for cycle-by-cycle safety (112) with 4-month follow-up after the end of PRRT.

Materials and Methods

The study was promoted by Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" IRST-, Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Meldola, Italy (IRST) as IRST 100.26. It was registered on the ClinicalTrial.gov website (registration ID: NCT03454763), EudraCT registration number 2015-004727-31. The study was also reviewed and approved by the Ethical Committee on March 16, 2016 (prot. number 1745/2016).

Study Protocol Objectives

The main objective of the study was to evaluate safety and PFS as co-primary objectives of the two different schedules of Lu-PRRT (intensive and standard). Secondary objectives were to evaluate the DCR, late toxicity,

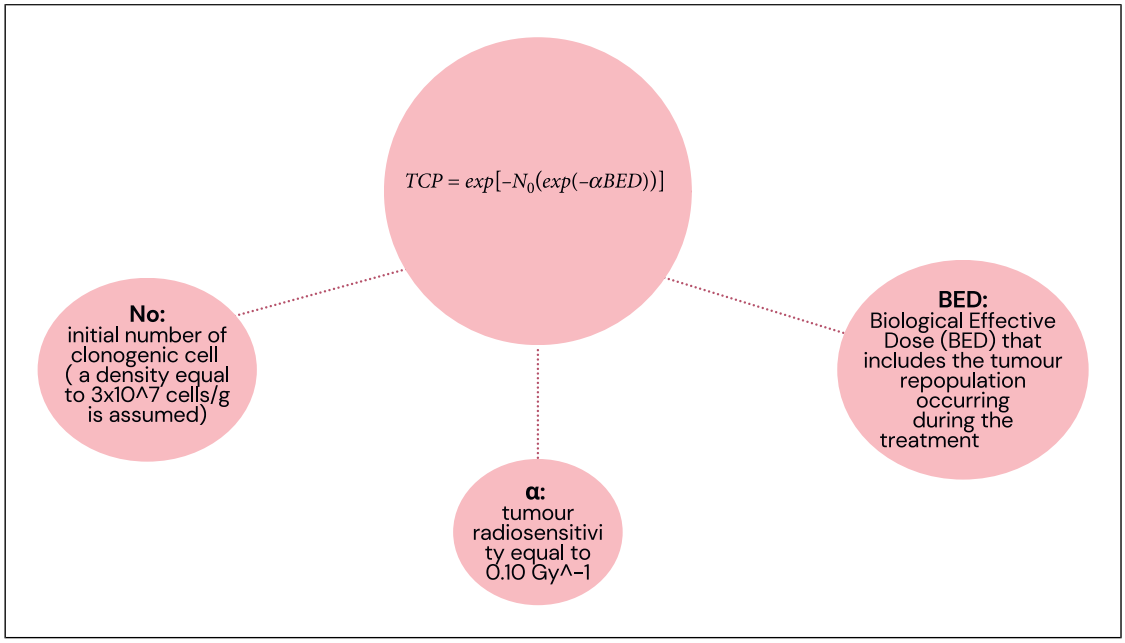

Fig. 1. Jones equation is described. According to this equation, TCP is a function of the initial number of clonogenic cells, tumor radiosensitivity and BED.

OS, and dosimetry and to confirm the prognostic and predictive role of PET FDG in a subgroup of GEP NET and bronchial NET patients. As reported above, in the present manuscript we report preliminary results on safety in a cohort of patients affected by GEP and bronchial NENs.

Study Population

Patients were referred to our attention by oncologists or multidisciplinary teams. They were considered eligible in the study if they had cytological or histological confirmation of NETs or any other type of tumors documented as SSTRs positive, with adequate uptake of SSTRs imaging (OctreoScan® and/or [68Ga]Ga DOTA PET/CT). Patients should also have measurable disease according to RECIST 1.1. Criteria. Furthermore, they should have progression disease in the pre-study period within the last 12 months, adequate hematological, liver, and renal function, life expectancy greater than 6 months and ECOG performance status <2.

Patients were excluded from the study if they performed chemotherapy and therapeutic radiotherapy within 4 weeks (2 weeks for palliative radiotherapy, hormonal, or biological therapy), if they performed previous PRRT with an adsorbed dose to the kidney of more than 23 Gy and more than 1.8 Gy for the bone marrow, and if they had previous acute toxic effects of any prior therapy not resolved to a G <1 according to CTCAE [15]. Patients with uncontrolled intercurrent illness (e.g., active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations were also excluded.

Radiobiological Model

The basis of radiobiological model used to design the clinical protocol was already described by Sarnelli et al. [16]. For sake of clarity, a summary of the main issues is reported below.

The model was based:

- on the Jones equation, reported in Figure 1 and which considers TCP as a function of the initial number of clonogenic cells, tumor radiosensitivity, and biological effective dose (BED) [17]. The tumor BED needs to account also for the tumor repopulation occurring during the treatment and its impact on wasting dose. The BED to the kidneys, considered critical organ for Lu-PRRT, is calculated based on the time, varying kidney uptake values, and different kidney masses. To evaluate the effect on the kidneys and potential toxicity, cumulative BED resulting from the IRST model was compared with threshold values reported in the literature [18]. BED after intensive treatment did not exceed threshold values of 40 Gy for patients without RF and 28 Gy for patients with RF;

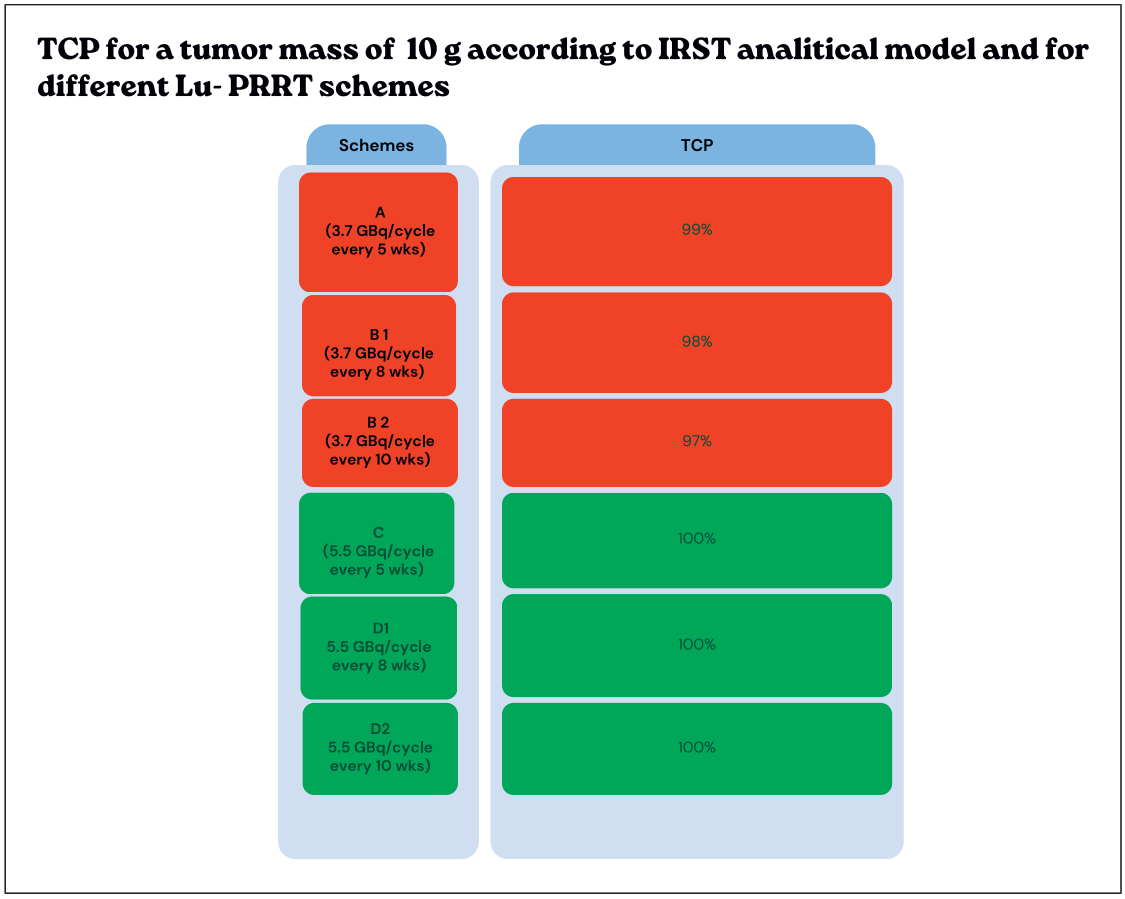

Fig. 2. We reported TCP (%) for a tumor mass of 10 g according to different dosage schemes, as derived from the IRST model. It can be noted that the theoretical TCP is always 100% for the schemes using a dosage of 5.5 Gbq/cycle, regardless of the IBC. On the contrary, for the dosage of 3.7 GBq/cycle, the theoretical TCP decreases slightly as the IBC increases, although remaining high.

- on previous dosimetric and radiobiological studies [14];
- on the activity/cycle. If less activity per cycle is planned, the same TCA can be maintained increasing the number of cycles for example from 4 to 5 [19];
- on the number of cycles;
- on previous studies highlighting the importance of RF in establishing TCA [12, 13].

In Figure 2, we reported the TCP according to IRST model and for different Lu-PRRT schemes.

Study Procedures

Patients were planned to receive a TCA of 18.5 GBq or 27.8 GBq of Lu-PRRT divided into 5 cycles (3.7 GBq/cycle or 5.5 GBq/cycle, respectively) according to the presence or absence of risk factors for toxicity (RF), which are shown in Table 1. This scheme was also used in previous IRST protocols, whose results were already published [12, 13]. Subsequently, they were randomly assigned to receive Lu-PRRT at intervals of 5 weeks in the intensive group (arm A with activity of 3.7 GBq/cycle and arm C with activity of 5.5 GBq/cycle) or of 8–10 weeks in the standard group (arm B with activity of 3.7 GBq/cycle and arm D with activity of 5.5 GBq/cycle).

A 1:1 allocation ratio was used; disease site (gastrointestinal, pulmonary, cerebral, other) and tumor grading according to ki-67 (ki-67 <20% was considered low grade, while ki-67 ≥20% was considered high grade) were considered as stratification factors. The summary of the study is reported in Figure 3.

Study Treatment

Radiopeptide Preparation and Administration

[^{177}Lu]Lu-DOTA-TATE was purchased from AAA (Advanced Accelerator Applications) as a radiopharmaceutical solution for infusion ready-to-use in monodose

Table 1. RF for toxicity

Type 1 diabetes not controlled with therapy
ECOG ≥2
Relevant renal morphological abnormalities
Previously major (G3–4) iatrogenic toxicities
Age (>80 years)
Previous PRRT
Creatinine >1.4 mg/dL

vials. Lu-PRRT administration, as well as patient's preparation, was already previously described [12]. Patients were also told to urinate frequently in the following 6-h infusion of the radiopharmaceutical. They were hospitalized for at least 24 h after the administration.

Imaging

The gamma emission of ^{177}Lu enabled the biodistribution to be monitored during treatment. Anterior and posterior whole-body images were acquired 24 h (±6) after Lu-PRRT with a 256 × 1,024 matrix using a dual-headed gamma camera (Infinia Hawkeye; GE Healthcare, Milwaukee, WI, USA) A Single Photon Emission Computed Tomography (SPECT) study was acquired if necessary.

Measurement of Effects

To assess safety, laboratory tests, medical interview, physical examination and electrocardiogram were performed at each cycle of treatment. Laboratory tests included: complete blood count with differential and platelet count, hemoglobin, total serum bilirubin, alkaline phosphatase, glucose, alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT), gamma glutamyl transferase (gamma GT), uric acid, serum creatinine, serum electrolytes (potassium, sodium, calcium, and chloride), international normalized ratio, total protein, and urinalysis. Pregnancy test was also requested in female of childbearing potential.

During follow-up, laboratory tests were performed once a month and physical examination and medical interview were performed every 4 months. Toxicity was evaluated based on any grade of adverse event (AE) from the start of treatment until 30 days after the last treatment cycle, using version 4.0 of the CTCAE [15] and considered for the maximum grade occurred. Acute toxicity refers to any AEs occurring within 30 days of the last treatment administration, while late toxicity refers to AEs occurring more than 30 days after the last treatment.

Management of Toxicities during PRRT

Dose adjustments and delays were managed according to the study protocol. In particular, the decision to modify the administration of the investigational products was based on the nature and severity of the toxicities observed, as defined by CTCAE v 4.0 [15]. Detailed information on delays, modifications, and toxicity parameters is reported in Figure 4.

Statistical Considerations

Sample size was calculated using PFS as endpoint, considering a two-tailed alpha error of 0.05, power of 80%, over 36 months and a further 24 months of follow-up, using an exponential hazard function. Considering a 10% difference in the proportion of patients without progression at 1 year between intensive and standard arm both for patients with RF and patients without RF, a total of 618 were planned to be recruited. In the present report, a preliminary analysis of the first 120 GEP and lung NEC patients is shown.

Overall toxicity evaluation was assessed on safety population, defined as the group of patients who underwent at least one cycle of therapy. Cycle-by-cycle toxicity was assessed on patients who performed at least two cycles of therapy, to compare punctually the two groups.

Descriptive values for continuous variables were expressed as median (range), while for categorical ones, absolute numbers and percentages were reported. Comparisons among groups were done using chi-square test or Fisher's exact test as appropriate. p value <0.05 was considered statistically significant. All statistical analyses were performed using Stata/SE version 15.1 for Windows (StataCorpLP, College Station, TX, USA).

Results

Patients

From May 2016 to July 2018, 120 consecutive GEP and bronchial NENs patients were enrolled and performed at least one cycle of Lu-PRRT. 102 patients had GEP NETs and 1 patient had pancreas NEC. Seventeen patients had lung NETs including 3 TC, 8 AC, and 6 undefined carcinoids. Sixty-one patients were randomized in the intensive group (29 in arm A and 32 in arm C) and 59 patients in the standard group (28 in arm B and 31 in arm D).

Among them, 40.0% were symptomatic at baseline and 85.0% had hepatic involvement. Regarding previous treatment, 18.3% had received chemotherapy alone or in

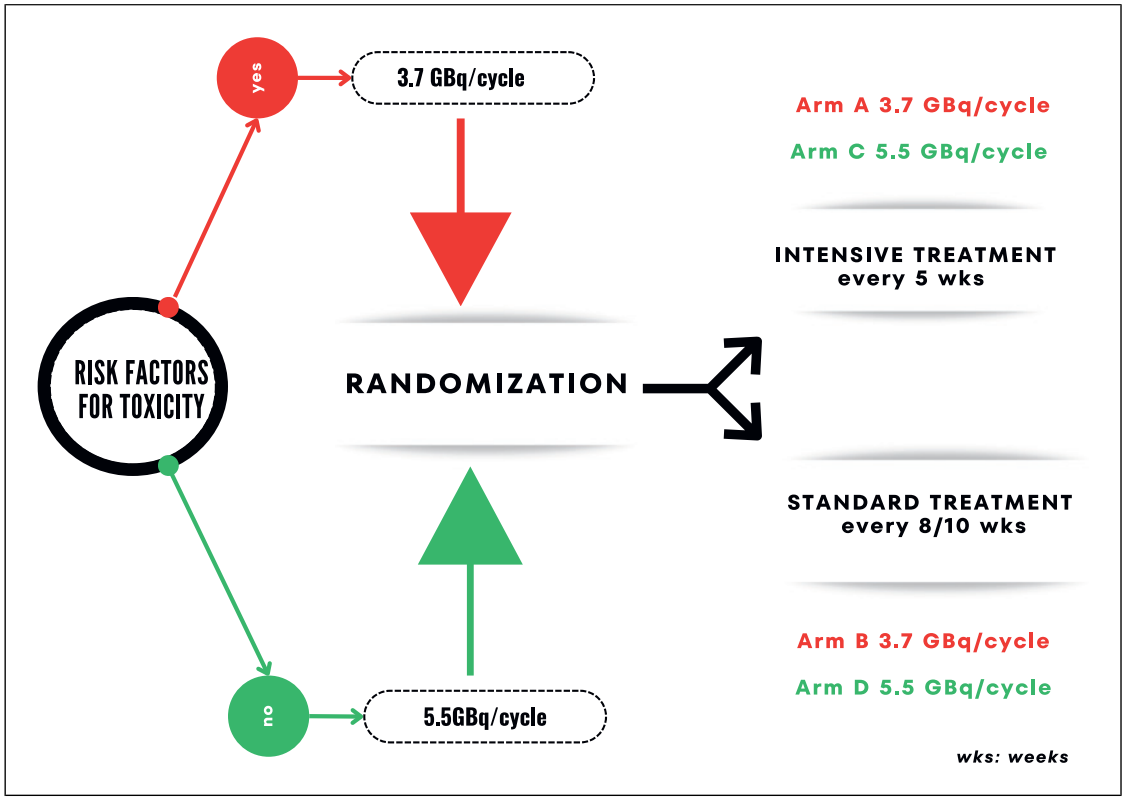

Fig. 3. We described the study design. In particular, once enrolled into the study, patients were considered for the presence of RF. If RF were present, patients were planned to receive 3.7 GBq/cycle, while in absence of RF they were planned to receive 5.5 GBq/cycle. Subsequently, patients were randomly assigned to receive PRRT with an IBC of 5 weeks (intensive) or of 8–10 weeks (standard).

combination with other therapies (except for PRRT), 9.2% had already received PRRT alone or in combination with other therapies (except for chemotherapy), 15.8% had received chemotherapy and PRRT, 0.8% had received multiple therapies. 70% of the patients had concomitant therapy with SSAs. Other baseline patients' characteristics are reported in Table 2.

Overall Toxicity

Overall toxicity was evaluated on 120 patients who performed at least one cycle of Lu-PRRT (Table 3). Regarding hematological AEs, no G4 toxicity was detected. Five patients (4.1%) had hematological G3 toxicity, 2 in the intensive group and 3 in the standard one. The most frequent AE was represented by neutropenia (4 patients, 3.3%), while anemia and thrombocytopenia occurred once. We highlighted that 1 patient with GEP NET in the intensive group with RF (arm A) presented both anemia and thrombocytopenia. Specifically, the female patient had already been treated with [^{90}Y] Y-DOTA-TOC (Y-PRRT) 4 years before (TCA 11.8 GBq). After that, she continued with SSAs until December 2016, when multiple bilobar liver metastases were detected and the patient underwent a liver transplant. Her hemoglobin at baseline was reduced, but permissive for enrollment according to the protocol inclusion criteria.

No statistical difference was found comparing the intensive group with the standard one or arm A versus B and arm C versus D. Moreover, hematological AEs were equally distributed into acute (3 events) and late toxicity (3 events).

As regards nephrotoxicity, only 1 patient in the intensive group (arm A) presented a G3 increase in creatinine 6 days after the first cycle. The male patient suffered from type II diabetes mellitus and had already been treated with Lu-PRRT approximately 2 years before (TCA 18.5 GBq).

Regarding hepatic toxicity, 1 patient in the intensive group (arm A) developed a G3 ALT elevation after the second cycle. The female patient was affected by pancreatic NET, had voluminous hepatic metastases and had already been widely pretreated (everolimus, temozolomide, and

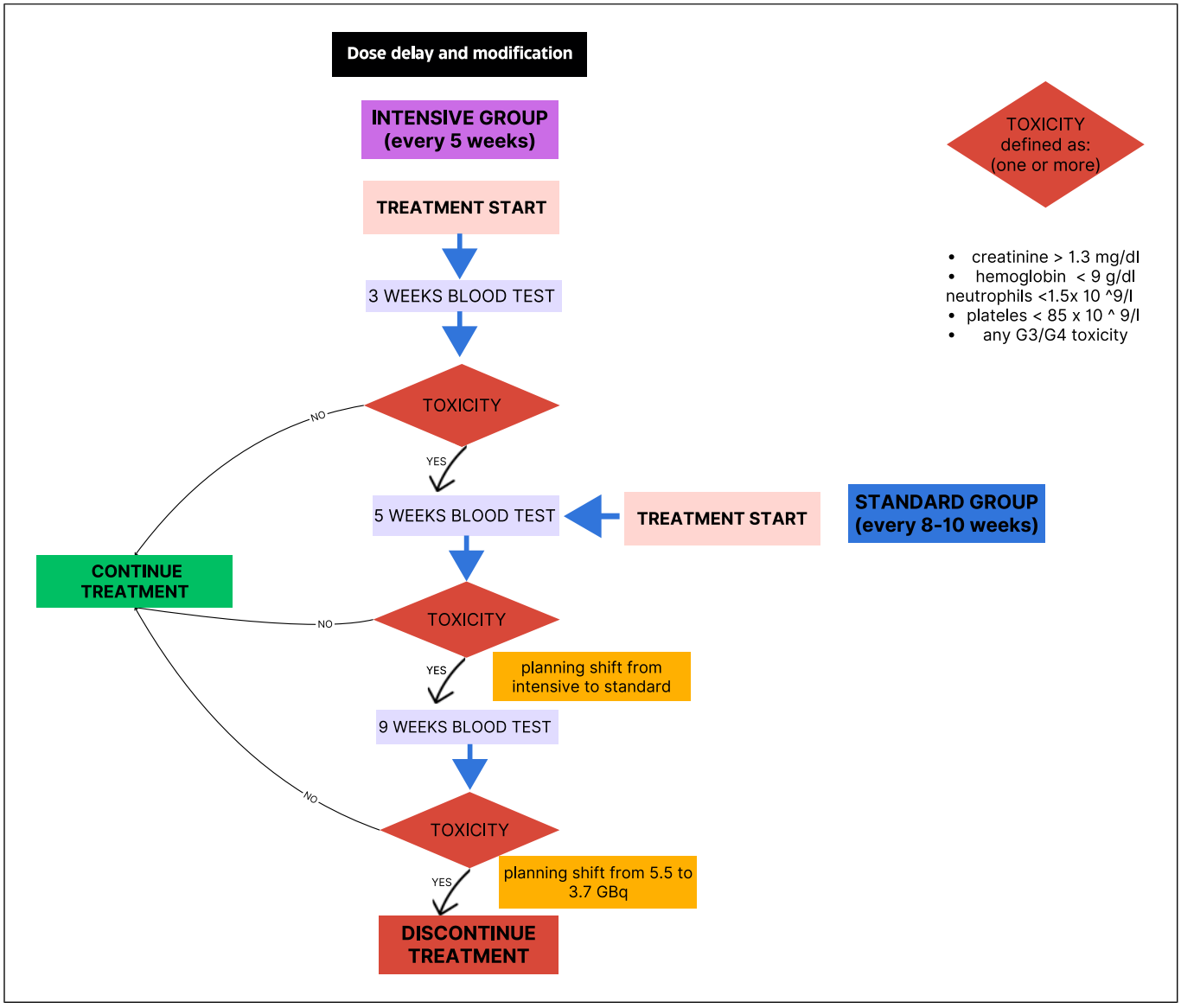

Fig. 4. We described in detail how toxicities were managed according to the protocol. It is important to underline that as well as considering G3 and G4 toxicities, we also establish more restrictive parametres for creatinine, hemoglobin and neutrophils. First blood tests after PRRT were performed according to the IBC (3 weeks in intensive group and 5 weeks in standard group). If toxicities occurred, the first possibility for the clinicians was to monitor the parameters over time and to delay the treatment. If toxicities still persisted, also the dose reduction was decided, for patients treated with 5.5 GBq/cycle. The treatment was stopped permanently if toxicities persisted despite these measures and beyond 9 weeks after PRRT.

Lu-PRRT associated with metronomic capecitabine). According to the study protocol, her treatment was delayed for 8 weeks, but she did not complete treatment because of clinical progression. No G3 or G4 elevation of AST was detected.

Considering other AEs, only 1 patient in the standard group (arm B) had G3 nausea as an acute effect after the first cycle. The male patient was affected by pancreatic NET, had been extensively pretreated (Y-PRRT, sunitinib, and everolimus) and had occasional nausea before starting re-PRRT. No G3 vomiting was found. 4 patients (3.3%) had G3 asthenia, 3 of them in the intensive group (arm A) and one in the standard group (arm B). Asthenia mainly occurred during the first cycles and affected mainly patients with small intestine NET (75% of patients).

Table 2. Demographics

Variable	ARM A: RF-intensive (n = 29)	ARM B: RF-standard (n = 28)	ARM C: no RF-intensive (n = 32)	ARM D: no RF-standard (n = 31)	Overall (n = 120)
Age at randomization					
Median (range)	66 (44–84)	73 (48–81)	62 (36–78)	60 (41–77)	66 (36–84)
Gender					
Female	10 (34.5)	11 (39.3)	14 (43.8)	11 (35.5)	46 (38.3)
Male	19 (65.5)	17 (60.7)	18 (56.3)	20 (64.5)	74 (61.7)
PS ECOG					
0	17 (58.6)	15 (53.6)	28 (87.5)	28 (90.3)	88 (73.3)
1	12 (41.4)	13 (46.4)	4 (12.5)	3 (9.7)	32 (26.7)
FDG PET					
Not performed	16 (57.1)	11 (40.7)	9 (29.0)	5 (16.1)	41 (34.2)
Performed	12 (42.9)	16 (59.3)	22 (71.0)	26 (83.9)	76 (63.3)
Unknown	1	1	1	0	3 (2%)
FDG PET result					
Absorber	9 (75.0)	10 (62.5)	17 (77.3)	22 (84.6)	58
Not absorber	3 (25.0)	6 (37.5)	5 (22.7)	4 (15.4)	18
Grade					
High grade (Ki-67 ≥20%)	1 (3.4)	1 (3.6)	2 (6.3)	2 (6.5)	6 (5)
Low grade (Ki 67 <20%)	28 (96.6)	27 (96.4)	30 (93.8)	29 (93.5)	114 (95)
Ethnic origin					
Caucasian/White	29 (100.0)	27 (96.4)	32 (100.0)	31 (100.0)	119
Asian	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	1
Presence of syndrome	11 (37.9)	12 (42.9)	13 (40.6)	12 (38.7)	48 (40)
Site of disease					
Lung	5 (17.2)	4 (14.3)	4 (12.5)	4 (12.9)	17 (14.2)
Gastrointestinal	24 (82.8)	24 (85.7)	28 (87.5)	27 (87.1)	103 (85.8)

RF, risk factors for toxicity.

Cycle-by-Cycle Toxicity

One hundred and twelve patients performed at least 2 cycles of Lu-PRRT, 98 with GEP NENs and 14 with lung NETs, 54 in the intensive group and 58 in the standard one.

Cycle-by-Cycle AEs among These Patients Were Analyzed

No major renal toxicity was found; indeed the only patient with a G3 increase in creatinine was stopped after the first cycle. In this analysis and differently from the overall toxicity analysis above described, G3 asthenia was present only in 1 patient in the standard group, because 2 of the 4 patients already reported recovered after the first cycle and 1 patient performed only one cycle.

Regarding G3 hematological toxicity, it was similar between the two groups (intensive and standard) and slightly higher after the third cycle, when counting 4 AEs equally distributed between the two groups. One patient in the intensive group (arm A) had G3 anemia and thrombocytopenia at the same time after the third cycle. In Table 4, cycle-by-cycle toxicities are reported.

Discussion

The approval of Lu-PRRT for well-differentiated GEP NETs has been revolutionary and is now well established in clinical practice. However, it remains valuable to propose new study protocols and publish results from previous research when possible, especially when they could give additional information on toxicity.

Table 3. Targeted G3 AEs reported among selected patients with at least 1 cycle of treatment

	ARM A: RF-intensive (n = 29)	ARM B: RF-no intensive (n = 28)	ARM C: RF-intensive (n = 32)	ARM D: RF-no intensive (n = 31)
Hematological toxicities	3	2	0	1
Anemia	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	1 (4.5)	2 (8.3)	0 (0.0)	1 (3.7)
Thrombocytopenia	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Liver toxicities	1	0	0	0
AST o GOT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT o GPT	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine increased	1	0	0	0
Gastrointestinal toxicities	0	1	0	0
Nausea	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other toxicities			0	0
Asthenia	3 (13.6)	1 (4.2)	0 (0.0)	0 (0.0)

Based on literature and differently from other trials, Lu-PRRT protocols designed by our group historically used less activity/cycle, thus preventing predictable toxicity and the consequent discontinuation of therapy [19]. We also used to increase the number of cycles to maintain the same TCA. Fortunately, the increase in the number of cycles did not lead to major scheduling challenges, and patients did not experience significant issues.

When possible, TCA was comparable to that provided in the NETTER-1 study, while for patients with RF we demonstrated that MEA should be considered 18.5 GBq [12]. Regarding gap between cycles, it was left unchanged at until 2016, the year this study was initiated, even in the absence of toxicity. So specifically, the novelty of the study was to test an intensive regimen (every 5 weeks) and a standard regimen (every 8–10 weeks), based on randomization.

Preliminary results of this study on toxicity for patients with GEP and bronchial neoplasms show that no G4 toxicities were observed, and G3 toxicities were very low. Furthermore, the intensive treatment schedule did not result in higher toxicity compared to the standard schedule, even on a cycle-by-cycle basis. The balance between the two groups remained consistent throughout the cycles with dropout rates being similar between the groups.

In particular, major hematological toxicities were low and similar between intensive and standard treatment schedules. This suggests that a 5-week IBC may be as safe as an 8–10 week IBC for bone marrow preservation, depending on the dose per cycle. The reported hematological toxicities were lower than those typically described in fixed-dose studies. For example, in the NETTER-1 phase 3 trial, grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9% of patients, respectively. Other studies have also reported similar or lower rates of severe hematological toxicity [10, 20, 21].

Regarding renal toxicity, we observed only one case of G3 increased creatinine, which occurred in a patient with a history of diabetes and recent severe hypertension. No renal impairment was detected in patients who received at least two cycles. Since the beginning of PRRT, the kidneys were considered a critical organ and nephrotoxicity was extensively investigated, above all in patients treated with Y-PRRT. Recent studies suggest that long-term nephrotoxicity after Lu-PRRT is minimal, with the increased creatinine levels primarily associated with age in patients treated with Y-PRRT [22].

The impact of Lu-PRRT on liver function is less well studied. Mild and severe hepatotoxicity rates after PRRT

Table 4. G3 AEs reported among 112 patients with at least two cycles of treatment

G3 AEs	Intensive group (IG)	Standard group (SG)
Post-cycle 2 (n = 112 patients, 54 in IG and 58 in SG)		
Anemia, thrombocytopenia, nausea, fatigue	0	0
Neutropenia	1	0
ALT o GPT	1	0
Post-cycle 3 (n = 107 patients, 50 in IG and 57 in SG)		
ALT o GPT, nausea	0	0
Anemia	1	0
Neutropenia	0	2
Thrombocytopenia	1	0
Fatigue	0	1
Post-cycle 4 (n = 99 patients, 48 in IG and 51 in SG)		
Anemia, thrombocytopenia, ALT o GPT, nausea	0	0
Neutropenia	0	1
Fatigue	0	1
Post-cycle 5 (n = 86, 44 in IG and 42 in SG)		
Anemia, neutropenia, thrombocytopenia, ALT o GPT, nausea, fatigue	0	0

are reported to be 12% and 0.4–2.5%, respectively. Liver function abnormalities are common at baseline due to hepatic metastases [23–25]. In our study, 85% of patients had liver lesions, but only 1 patient experienced G3 reversible ALT elevation.

In terms of gastrointestinal side effects, 1 patient experienced acute and transient G3 nausea. Although nausea is a common side effect of Lu-PRRT, detailed studies on its incidence and severity are limited. Our findings are consistent with other studies reporting varying rates of nausea and asthenia [26, 27].

The low toxicity rate over a 4-month follow-up period is particularly notable given the unfavorable baseline characteristics of the patients, often compromised. Many patients in the study had been extensively pretreated, with 26% having ECOG PS 1, and 40% presenting symptoms of neuroendocrine syndrome. Additionally, 76.3% of patients who underwent FDG PET scans were positive, indicating a more aggressive disease profile, as previously demonstrated in our published studies and by other groups [28–31].

Furthermore, 85% of patients had liver metastases, which is a known negative prognostic factor [32]. It has also been reported that the presence of a liver metastatic burden of more than 50% liver volume could be considered as a predictor of shorter OS [33, 34].

So, the low toxicity rate could be explained with a careful patient selection according to exclusion criteria, ensuring that Lu-PRRT is not performed too soon after other therapies and that any serious toxicities from previous treatments are resolved. We also emphasize also that modulating the dosage according to patients' characteristics and increasing dose fractionation may help mitigate predictable toxicity. Based on preliminary results obtained in GEP and bronchial NET patients, it does not appear that decreasing the IBC leads to increased toxicity compared to the standard IBC of 8 weeks.

Study Limitations

This study has several limitations. The results are based on a small patient cohort, and further validation in a larger population with longer follow-up is needed. While the study was designed as a randomized trial, the small sample size and the focus on toxicity data limit our ability to fully evaluate the trial's potential. The results might be more promising when combined with efficacy data, which will be published when available. Additionally, the protocol was a "basket" trial, and data were collected from patients with GEP and lung NENs treated with Lu-PRRT, leading to some heterogeneity in the patient population.

Conclusion

In conclusion, preliminary results from the randomized phase II trial of patients with GEP and pulmonary NENs treated with Lu-PRRT indicate that the intensive treatment is safe and well tolerated. It appears

possible to develop individualized treatment regimens based on patients' clinical history and preexisting co-morbidities, potentially minimizing toxicity and therapy-related side effects. Further data are needed to confirm these results.

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Statement of Ethics

We declare that the study was performed with the approval of IRST and Area Vasta Romagna Ethics Committee (C.E.ROM.) on March 16, 2016 (prot number 1745/2016) and by the competent Italian Regulatory Authorities. It was conducted with appropriate participants' informed consent in compliance with the Helsinki Declaration and with Good Clinical Practice (GCP) guidelines, too. Written informed consent to participate in the study was obtained from participants (or their parent/legal guardian where appropriate).

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Designed the research study F.M., M.S., G.P., A.S., V.D.I., S.S., and M.M. Revised the informatics data F.F., L.Fab., and M.M. Conducted the statistical analyses, collected data, and follow-up I.G., FM, FF, M.M., L.Fab., M.S., S.N., I.M., S.S., N.R., and A.R. Wrote the paper I.G., F.M., and M.S. Reviewed the manuscript and suggested additional analyses S.N., I.M., F.F., A.S., V.D.I., A.R., N.R., M.M., and L.Fan. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the fact that they are preliminary data respect to expected total sample size of the study, but they are available from the corresponding author (I.G., ilaria.grassi@irst.emr.it) upon reasonable request.

References

1 Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia. 2017;19(12):991–1002. https://doi.org/10.1016/j.neo.2017.09.002

2 Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. Endocr Pathol. 2022;33(1):115–54. https://doi.org/10.1007/s12022-022-09708-2

3 Ambrosini V, Kunikowska J, Baudin E, Bodei L, Bouvier C, Capdevila J, et al. Consensus on molecular imaging and theranostics in neuroendocrine neoplasms. Eur J Cancer. 2021;146:56–73. https://doi.org/10.1016/j.ejca.2021.01.008

4 Ianniello A, Sansovini M, Severi S, Nicolini S, Grana CM, Massri K, et al. Peptide receptor radionuclide therapy with (177)Lu-DOTATATE in advanced bronchial carcinoids: prognostic role of thyroid transcription factor 1 and (18) F-FDG PET. Eur J Nucl Med Mol Imaging. 2016;43(6):1040–6. https://doi.org/10.1007/s00259-015-3262-8

5 Taal BG, Visser O. Epidemiology of neuroendocrine tumours. Neuroendocrinology. 2004;80(Suppl 1):3–7. https://doi.org/10.1159/000080731

6 Mulders MCF, de Herder WW, Hofland J. What is carcinoid syndrome? A critical appraisal of its proposed mediators. Endocr Rev. 2024;45(3):351–60. https://doi.org/10.1210/endrev/bnad035

7 Del Rivero J, Perez K, Kennedy EB, Mittra ES, Vijayvergia N, Arshad J, et al. Systemic therapy for tumor control in metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: ASCO guideline. J Clin Oncol. 2023;41(32):5049–67. https://doi.org/10.1200/JCO.23.01529

8 Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376(2):125–35. https://doi.org/10.1056/NEJMoa1607427

9 Baudin E, Caplin M, Garcia-Carbonero R, Fazio N, Ferolla P, Filosso PL, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(4):439–51. https://doi.org/10.1016/j.annonc.2021.01.003

10 Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. Long-term efficacy, survival, and safety of [177 Lu-DOTA 0, tyr 3] octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. Clin Cancer Res. 2017;23(16):4617–24. https://doi.org/10.1158/1078-0432.CCR-16-2743

11 Minutoli F, Cardile D, Laudicella R, Vento A, Pagano B, Baldari S. Peptide receptor radionuclide therapy of pulmonary neuroendocrine neoplasms: a single-centre experience. Nucl Med Mol Imaging. 2021;55(1):38–45. https://doi.org/10.1007/s13139-020-00679-y

12 Paganelli G, Sansovini M, Ambrosetti A, Severi S, Monti M, Scarpi E, et al. 177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study. Eur J Nucl Med Mol Imaging. 2014;41(10):1845–51. https://doi.org/10.1007/s00259-014-2735-5

13 Sansovini M, Severi S, Ianniello A, Nicolini S, Fantini L, Mezzenga E, et al. Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with 177Lu-DOTATATE. Eur J Nucl Med Mol Imaging. 2017;44(3):490–9. https://doi.org/10.1007/s00259-016-3533-z

14 Strigari L, Benassi M, Chiesa C, Cremonesi M, Bodei L, D'Andrea M. Dosimetry in nuclear medicine therapy: radiobiology application and results. Q J Nucl Med Mol Imaging. 2011;55(2):205–21.
15 US Department of Health and Human Services NIH; National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (Accessed February 27 2016).
16 Sarnelli A, Guerriero F, Botta F, Ferrari M, Strigari L, Bodei L, et al. Therapeutic schemes in ^{177}Lu and 90Y-PRRT: radiobiological considerations. Q J Nucl Med Mol Imaging. 2017;61(2):216–31. https://doi.org/10.23736/S1824-4785.16.02744-8
17 Jones B, Dale RG. Mathematical models of tumour and normal tissue response. Acta Oncol. 1999;38(7):883–93. https://doi.org/10.1080/028418699432572
18 Bodei L, Cremonesi M, Ferrari M, Pacifici M, Grana CM, Bartolomei M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and ^{177}Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging. 2008;35(10):1847–56. https://doi.org/10.1007/s00259-008-0778-1
19 Bodei L, Cremonesi M, Grana CM, Fazio N, Iodice S, Baio SM, et al. Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. 2011;38(12):2125–35. https://doi.org/10.1007/s00259-011-1902-1
20 van der Zwan WA, Brabander T, Kam BLR, Teunissen JJM, Feelders RA, Hofland J, et al. Salvage peptide receptor radionuclide therapy with [^{177}Lu-DOTA, Tyr3] octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2019;46(3):704–17. https://doi.org/10.1007/s00259-018-4158-1
21 Sabet A, Ezziddin K, Pape UF, Ahmadzadehfar H, Mayer K, Pöppel T, et al. Long-term hematotoxicity after peptide receptor radionuclide therapy with 177Lu-octreotate. J Nucl Med. 2013;54(11):1857–61. https://doi.org/10.2967/jnumed.112.119347
22 Baum RP, Fan X, Jakobsson V, Yu F, Schuchardt C, Chen X, et al. Long-term nephrotoxicity after PRRT: myth or reality. Theranostics. 2024;14(2):451–9. https://doi.org/10.7150/thno.92487
23 Becx MN, Minczeles NS, Brabander T, de Herder WW, Nonnekens J, Hofland J. A clinical guide to peptide receptor radionuclide therapy with 177Lu-dotatate in neuroendocrine tumor patients. Cancers. 2022;14(23):5792. https://doi.org/10.3390/cancers14235792
24 Zhang J, Kulkarni HR, Singh A, Niepsch K, Müller D, Baum RP. Peptide receptor radionuclide therapy in grade 3 neuroendocrine neoplasms: safety and survival analysis in 69 patients. J Nucl Med. 2019;60(3):377–85. https://doi.org/10.2967/jnumed.118.215848
25 European Medicines Agency. Lutathera. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/lutathera#authorisation-details-section (Accessed February 8 2023).
26 Del Prete M, Buteau FA, Arsenault F, Saighi N, Bouchard LO, Beaulieu A, et al. Personalized 177Lu-octreotate peptide receptor radionuclide therapy of neuroendocrine tumours: initial results from the P-PRRT trial. Eur J Nucl Med Mol Imaging. 2019;46(3):728–42. https://doi.org/10.1007/s00259-018-4209-7
27 Sundlöv A, Gleisner KS, Tennvall J, Ljungberg M, Warfvinge CF, Holgersson K, et al. Phase II trial demonstrates the efficacy and safety of individualized, dosimetry-based 177Lu-DOTATATE treatment of NET patients. Eur J Nucl Med Mol Imaging. 2022;49(11):3830–40. https://doi.org/10.1007/s00259-022-05786-w
28 Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res. 2010;16(3):978–85. https://doi.org/10.1158/1078-0432.CCR-09-1759
29 Severi S, Nanni O, Bodei L, Sansovini M, Ianniello A, Nicoletti S, et al. Role of 18FDG PET/CT in patients treated with 177Lu-DOTATATE for advanced differentiated neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013;40(6):881–8. https://doi.org/10.1007/s00259-013-2369-z
30 Hinterleitner M, Pfeiffer R, Trautwein NF, Sipos B, Singer S, Nadalin S, et al. Treatment modalities favoring outcome in well-differentiated neuroendocrine tumors G3. Front Endocrinol. 2023;14:1285529. https://doi.org/10.3389/fendo.2023.1285529
31 Nicolini S, Bodei L, Bongiovanni A, Sansovini M, Grassi I, Ibrahim T, et al. Combined use of 177Lu-DOTATATE and metronomic capecitabine (Lu-X) in FDG-positive gastro-entero-pancreatic neuroendocrine tumors. Eur J Nucl Med Mol Imaging. 2021;48(10):3260–7. https://doi.org/10.1007/s00259-021-05236-z
32 Frilling A, Sotiropoulos GC, Li J, Kornasiewicz O, Plöckinger U. Multimodal management of neuroendocrine liver metastases. HPB Oxf. 2010;12(6):361–79. https://doi.org/10.1111/j.1477-2574.2010.00175.x
33 Laskaratos FM, Walker M, Wilkins D, Tuck A, Ramakrishnan S, Phillips E, et al. Evaluation of clinical prognostic factors and further delineation of the effect of mesenteric fibrosis on survival in advanced midgut neuroendocrine tumours. Neuroendocrinology. 2018;107(3):292–304. https://doi.org/10.1159/000493317
34 Swiha MM, Sutherland DEK, Sistani G, Khatami A, Abazid RM, Mujoomdar A, et al. Survival predictors of 177Lu-Dotatate peptide receptor radionuclide therapy (PRRT) in patients with progressive well-differentiated neuroendocrine tumors (NETS). J Cancer Res Clin Oncol. 2022;148(1):225–36. https://doi.org/10.1007/s00432-021-03672-w