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ORIGINAL ARTICLE

^{177}Lu-PRRT in advanced gastrointestinal neuroendocrine tumors: 10-year follow-up of the IRST phase II prospective study

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Abstract

Purpose In March 2014, we reported the activity and safety of ^{177}Lu-DOTA-octreotate peptide receptor radionuclide therapy (Lu-PRRT) at two different dosages (18.5 GBq and 27.5 GBq in 5 cycles) in patients with progressive metastatic gastrointestinal neuroendocrine tumors (GI-NETs). Disease control rate (DCR) and toxicity were addressed. Herein, we report the late toxicity, progression-free survival (PFS), and overall survival (OS) in the same cohort after a 10-year follow-up.

Methods We conducted an open-label, disease-oriented prospective phase II trial. From March 2008 to June 2011, 43 patients received 3.7 GBq or 5.5 GBq of Lu-PRRT every 6 to 8 weeks, each cycle repeated 5 times. All patients showed ^{68}Gallium-DOTA-peptide PET/Octreoscan® positivity (score 3–4 Rotterdam scale) in known lesions. Tumor burden was estimated radiologically. Time-to-event data (PFS and OS) were described using Kaplan-Meier curves and compared with the log-rank test.

Results Forty-three patients (28 males and 15 females) were evaluable and were monitored for a median period of 118 months (range 12.6–139.6). Median PFS in patients receiving 18.5 GBq was 59.8 months (95% confidence interval [95% CI] 14.3–79.6), identical to that of patients treated with 27.5 GBq (59.8 months, 95% CI 23.4–82.0). Median OS was 71.0 months (95% CI 46.1–107.3) in the group who received 18.5 GBq and 97.6 months (95% CI 64.3-not reached) in the group treated with 27.5 GBq (P = 0.22). Patients with progression limited to lymph nodes showed significantly longer median PFS and OS than those with hepatic lesions (P = 0.02 for PFS and P = 0.04 for OS). Age over 65 years at the time of PRRT was also significant for OS. Of note, no late hematological or renal toxicity was observed in either group.

Conclusions The long-term follow-up of the IRST phase II study shows that Lu-PRRT is a safe and effective therapy for patients with advanced GI-NET, the most important prognostic factor being tumor burden, hepatic lesions, and age. We believe that Lu-PRRT should be offered to patients with early-stage disease.

Keywords ^{177}Lu-DOTA-octreotate · GI-NET · PRRT · Long-term follow-up · Tumor burden · Overall survival

This article is part of the Topical Collection on Oncology - Digestive tract

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Introduction

Neuroendocrine tumors (NETs) arise from diffuse neuroendocrine system cells and can occur in any part of the body. However, the most common site of disease is the gastrointestinal tract (GI) [1–3]. Although the incidence and prevalence of GI-NETs have increased over time, survival has also improved thanks to new therapeutic options, including peptide receptor radionuclide therapy (PRRT) [4–8].

In March 2014, we published the results of the IRST phase II prospective study on the use of Lu-PRRT in patients with progressive metastatic grade G1-G2 GI-NETs [9]. The study included patients with NETs arising from gastrointestinal tract excluding those with pancreatic tumors (P-NETs). The primary tumor in the majority of patients originated from the small intestine. Differently from the NETTER-1 study [6] where a very similar patient population was enrolled, our patients were treated with different activities of Lu-PRRT on the basis of kidney function and bone marrow reserve. In particular, 25 patients (aged 44–75 years) received 27.5 GBq and 18 (aged 46–82 years) received 18.5 GBq. Two important results emerged, i.e., the absence of severe toxicity even in patients at risk of side effects, and a similar disease control rate (DCR) in both groups. We also observed that fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) was an important independent prognostic factor in GI-NET patients undergoing Lu-PRRT. However, the impact of tumor burden and other prognostic factors were not evaluated at that time.

The present study reports the impact of injected activity, FDG outcomes, hepatic lesions, and other features on progression-free survival (PFS) and overall survival (OS) in the same 43 patients after a follow-up of 10 years.

Material and methods

The study design, patient characteristics, radiopeptide preparation and administration, imaging and statistical analysis on DCR, and toxicity have previously been reported in detail [9].

Patients

Briefly, from March 2008 to June 2011, 43 patients were enrolled and evaluated in a phase II prospective protocol with primary objectives of DCR and toxicity. The main inclusion criteria were the following: patients > 18 years of age, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, histologically proven G1 or G2 GI-NETs (according to WHO classification) [10], positive Octreoscan®/^{68}Gallium-DOTA-peptide PET, and radiologic documentation of disease progression. Adequate hematological and biochemical blood parameters were required. Patients with a life expectancy < 6 months and known previous malignancies were excluded. The protocol was approved by the Area Vasta Romagna Ethics Committee (approval no. 2007-005517-20 of October 31, 2007), and by competent Italian Regulatory Authorities. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. All patients gave written informed consent. Having an FDG-PET/CT scan before PRRT was not a prerequisite for the study but was taken into account as a prognostic factor when available [11–13].

Study design

This was a disease-oriented, non-controlled, prospective phase II study. All patients were scheduled to receive 5 cycles of therapy at intervals of 6–8 weeks at one of 2 different dosages, i.e., 5.5 GBq of ^{177}Lu-DOTA-octreotate if no risks factors were present and 3.7 GBq if there were risk factors [14]. Risk factors for kidney or bone marrow toxicity were taken into consideration: creatinine levels 1.5–2 mg/dL, morphological renal abnormalities, severe drug-refractory hypertension, insulin-dependent diabetes not properly controlled by drugs, previous platinum-based chemotherapy, and age > 80 years.

Prognostic factors

Baseline tumor burden was estimated by CT or magnetic resonance imaging (MRI) according to an arbitrary 3-point scale: (1) limited, i.e., lymph nodes only; (2) intermediate, i.e., liver or liver plus lymph nodes; (3) extensive, i.e., multiple tumor lesions in parenchyma including liver, lung, peritoneum, and bone.

Hepatic involvement was defined according to a 0–1 grade scale (grade 0, no lesions; grade 1, lesions on CT/MRI). An FDG-PET/CT scan was considered positive when the maximum standardized uptake value (SUV_{max}) in at least one of previously documented lesions was > 2.5 [12]. When possible, a FDG-PET/CT scan was repeated at progression.

Statistical analysis

PFS was defined as the time from the start of Lu-PRRT to the first documented date of progression or death from any cause or last tumor evaluation, while OS was considered as the time from the start of treatment to the time of death from any cause or last follow-up. Both outcomes were estimated by the Kaplan-Meier method and compared using log-rank test. 95% confidence intervals (95% CIs) for median values were calculated with non-parametric methods. Estimated hazard ratios (HRs) and 95% CIs were calculated from univariate and

multivariate Cox regression models. No correction for multiple comparisons was made because of the exploratory nature of this study.

All *P* values were two-sided. Statistical analyses were carried out with SAS Statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics are reported in Table 1. In December 2019, 16 (37.2%) of the original 43 patients were still alive and 6 (13.9%) were still progression-free. One patient was lost during follow-up in December 2018. Table 2 reports univariate analysis of PFS and OS according to parameters including total administered activity, FDG-PET/CT outcomes, tumor burden, hepatic involvement, age, gender, and Ki-67 values. The median follow-up time was 118 months (range 12.6–139.6). Overall, median PFS was 59.8 months (95% CI 29.8–76.4) and median OS was 82.0 months (95% CI 64.0–125.6). Table 3 reports a multivariate analysis on PFS and OS taking into consideration total administered activity, FDG-PET/CT outcomes, presence or not of hepatic lesions, and age.

PFS and OS related to activity injected and FDG-PET/CT results

The median PFS of patients who received the reduced dosage (RD) of 18.5 GBq was the same as that of patients receiving the full dosage (FD) of 27.5 GBq: 59.8 months (95% CI 14.3–79.6) and 59.8 months (95% CI 23.3–82.0), respectively ($P = 0.790$) (Fig. 1a). Median OS in RD patients was 71.0 months (95% CI 46.1–107.3) and 97.6 months (95% CI 64.3-not reached [nr]) in FD patients. Although OS in the FD group was longer, the difference was not statistically significant ($P = 0.222$) (Fig. 2a).

FDG-PET/CT scan results were available in only 33 patients, among whom 21 (64%) were FDG-PET/CT-negative. Of these, 15 (75%) were in the FD group and 6 (46%) in the RD group.

Table 1 Baseline patient characteristics

Characteristic	Total population ($n = 43$) No. of patients (%)	FD group ($n = 25$) No. of patients (%)	RD group ($n = 18$) No. of patients (%)
Median age (years (range))	65 (44–82)	62 (44–75)	70 (46–82)
Male	28 (65)	17 (68)	11 (61)
Female	15 (35)	8 (32)	7 (39)
Primary tumor site			
Small intestine (midgut)	34 (79)	19 (76)	15 (82)
Right colon	5 (12)	4 (16)	1 (6)
Stomach	2 (5)	2 (8)	0
Appendix	1 (2)	0	1 (6)
Rectum	1 (2)	0	1 (6)
Grading			
1	13 (30)	9 (36)	4 (22)
2	18 (42)	9 (36)	9 (50)
Unknown	12 (28)	7 (28)	5 (28)
FDG-PET			
Positive	12 (36)	5 (25)	7 (54)
Negative	21 (64)	15 (75)	6 (46)
Tumor burden			
1 (limited)	6 (14)	2 (8)	4 (22)
2 (intermediate)	17 (40)	11 (44)	6 (33)
3 (extensive)	20 (46)	12 (48)	8 (45)
Hepatic lesions			
Yes	37 (86)	23 (92)	14 (78)
No	6 (14)	2 (8)	4 (22)

FD full dosage group, *RD* reduced dosage group, *FDG-PET* fluorodeoxyglucose positron emission tomography

Limited disease: lymph node metastases only

Intermediate disease: liver metastases or liver plus lymph node metastases

Extensive disease: multiple sites of metastases (liver plus peritoneal carcinosis or bone or both)

Table 2 Univariate analyses according to prognostic factors

		PFS			OS		
	No. patients	No. events (%)	Median PFS (months) (95% CI)	*P*	No. events (%)	Median OS (months) (95% CI)	*P*
Overall	43	36	59.8 (29.8–76.4)	-	27	82.0 (64.0–125.6)	-
Total administered activity							
RD	18	15	59.8 (14.3–79.6)		13	71.0 (46.1–107.3)	
FD	25	21	59.8 (23.3–82.0)	0.790	14	97.6 (64.3-nr)	0.222
PET FDG results							
FDG−	21	17	66.5 (36.8–97.6)		10	nr	
FDG+	12	10	30.4 (9.0–69.0)	0.094	8	55.2 (18.6-nr)	0.135
Tumor burden							
1 (limited)	6	3	100.2 (64.0-nr)		1	nr	
2 (interme-diate)	17	17	30.9 (15.9–81.7)		13	81.7 (46.1–97.6)	
3 (exten-sive)	20	16	46.2 (14.3–76.3)	0.048	13	71.5 (31.5-nr)	0.119
Hepatic lesions							
No	6	3	100.2 (64.0-nr)		1	nr	
Yes	37	33	36.8 (23.3–69.0)	0.027	26	76.4 (51.1–107.3)	0.046
Histologic grade							
1	13	13	60.1 (23.3–76.4)		9	81.7 (50.8-nr)	
2	18	15	46.2 (16.1–83.7)	0.950	12	86.0 (51.1-nr)	0.620
Age (years)							
≤ 65	21	16	66.5 (33.2–97.9)		9	125.6 (66.5-nr)	
> 65	22	20	33.8 (14.3–79.6)	0.078	18	69.7 (46.1–89.6)	0.006
Gender							
Female	15	14	55.6 (12.6–82.0)		10	90.0 (31.5-nr)	
Male	28	22	60.0 (18.0–79.6)	0.526	17	79.0 (55.6-nr)	0.893

nr not reached

There were 7 FDG-positive (54%) patients in the RD group and 5 (25%) in the FD group. Five out of 21 (24%) patients repeated the FDG-PET scan during follow-up and two patients were found to be FDG-positive at progression. With regard to the role of glucose consumption and prognosis, Fig. 1b shows that PFS curves remained largely different for a period of around 5 years after PRRT. The prognostic value of baseline FDG-PET/CT uptake seems to be lower after 10 years. However, FDG-PET/CT-negative patients showed a median PFS of 66.5 months (95% CI 36.8–97.6) compared with 30.4 months (95% CI 9.0–69.0) for

Table 3 Multivariate analysis according to prognostic factors

	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Total administered activity (RD vs. FD)	1.18 (0.51–2.72)	0.705	1.62 (0.55–4.75)	0.376
FDG (positive vs. negative)	2.45 (0.96–6.23)	0.060	2.13 (0.73–6.19)	0.165
Hepatic lesions (yes vs. no)	3.65 (1.01–13.26)	0.049	9.04 (1.14–71.61)	0.037
Age (continuous variable)	1.05 (1.00–1.10)	0.036	1.09 (1.03–1.16)	0.005

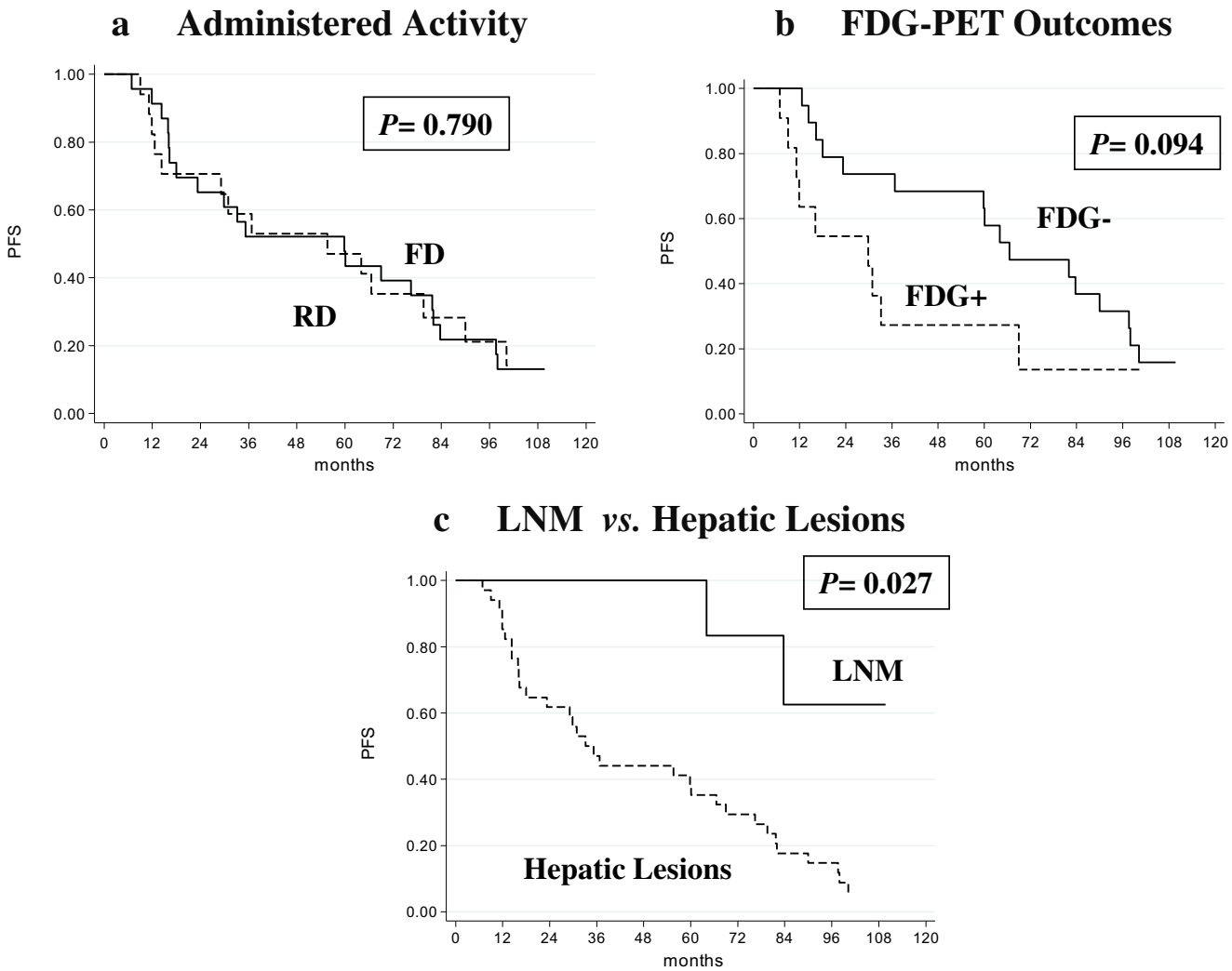

Fig. 1 Progression-free survival (PFS) according to **a** total administered activity, 18.5 GBq vs. 27.5 GBq; **b** FDG-PET/CT outcomes, negative vs. positive; **c** lymph node metastases (LNM) only vs. hepatic Lesions. *P* value was significant for LNM only vs. hepatic lesions

those with FDG-PET/CT positivity ($P = 0.094$). OS was not reached for FDG-PET/CT-negative patients and 55.2 months (95% CI 18.6-nr) for the FDG-PET/CT-positive group ($P = 0.135$) (Fig. 2b).

PFS and OS related to tumor burden, hepatic lesions, Ki-67, and age

Six (14%) patients had grade 1 tumor burden with lymph node metastases only, 17 (39.5%) grade 2 with liver metastases (+/− lymph nodes), and 20 (46.5%) grade 3 with liver localization plus one or other sites including bone, peritoneal carcinosis, and lung. Six (14%) patients did not have hepatic lesions while 37 (86%) had liver involvement.

PFS rates were significantly different for tumor burden and the presence of hepatic lesions. In particular, 20 patients with grade 3 tumor burden showed a median PFS of 46.2 (95% CI 14.3–76.3) months vs. 30.9 months (95% CI 15.9–81.7) for those with grade 2 and 100.2 months (95% CI 64.0-nr) for grade 1 patients ($P = 0.048$). Median PFS was 100.2 months (95% CI 64.0-nr) for the 6 patients with lymph node metastases only and 36.8 months (95% CI 23.3–69.0) for the other 37 with hepatic lesions ($P = 0.027$) (Fig. 1c).

Median OS was 71.5 months (95% CI 31.5-nr) for patients with grade 3 tumor burden, 81.7 months (95% CI 46.1–97.6) for those with grade 2, and has not yet been reached for the grade 1 tumor burden group ($P = 0.119$).

Median OS was 76.4 months (95% CI 51.1–107.3) for patients with liver lesions (Fig. 2c) and was not reached for those with lymph node metastases only ($P = 0.046$). Of the 6 patients without liver localizations, 3 progressed and one died. This last patient was treated at the age of 75 and died, not from disease progression, but from a stroke at the age of 79.

Ki-67 results were available in 31 patients, 13 classified as grade G1 and 18 as G2. No significant differences were observed for either PFS or OS on the basis of the Ki-67 G score (Table 2). Patients aged < 65 years had a median PFS of 66.5 months (95% CI 3.2–97.9) and those > 65 years showed

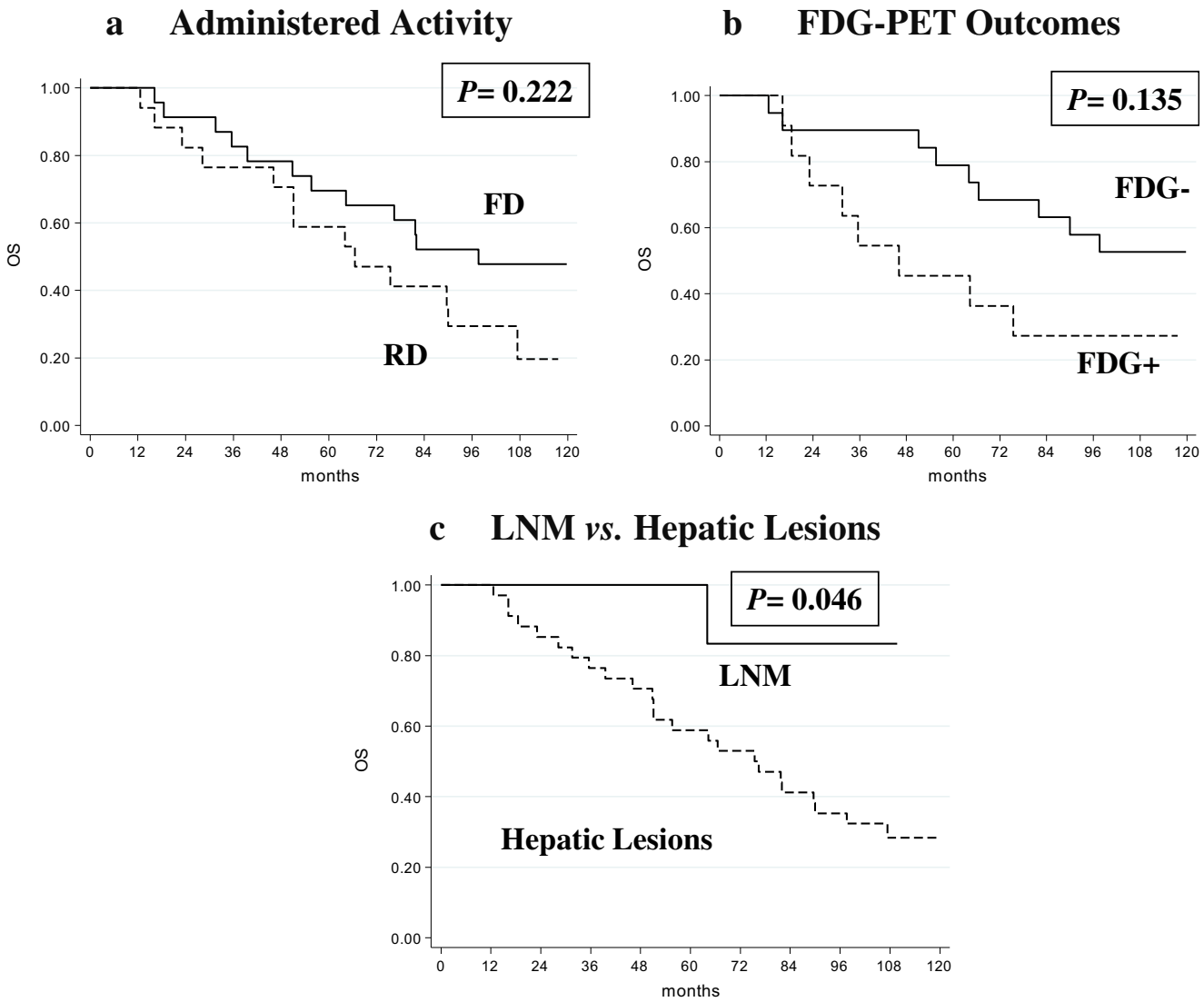

Fig. 2 Overall survival (OS) according to **a** total administered activity; **b** FDG-PET/CT outcomes; **c** LNM only vs. hepatic lesions. *P* value was significant for LNM only vs. hepatic lesions

a PFS of 33.8 months (95% CI 14.3–79.6) with a *P* value of 0.078. Median OS was 69.7 months (95% CI 46.1–89.6) and 125.6 months (95% CI 6.5-nr) for the under 65 and over 65 groups, respectively ($P = 0.006$).

Multivariate Cox regression models, including treatment total administered activity, FDG-PET/CT, hepatic lesions, and age, indicated that hepatic lesions remained an independent predictor of both PFS (HR = 3.65, 95% CI 1.01–13.26, $P = 0.049$) and OS (HR = 9.04, 95% CI 1.03–71.61, $P = 0.037$ (Table 3)).

Toxicity

There were no unresolved toxicities and no new long-term side effects during the 10-year follow-up. Furthermore, no cases of renal impairment and no cases of grade 3 or 4 hematological toxicity were reported, even in patients at high risk of side effects.

Discussion

This prospective phase II trial provides the results of a long-term follow-up in 43 patients with advanced G1-G2 GI-NETs treated with Lu-PRRT. Two different cumulative activities were administered: 18.5 GBq and 27.5 GBq based on the presence or not of risk factors for kidney and bone marrow toxicity according to our previous experience in phase I-II studies [14, 15]. A median follow-up of 118 months showed a remarkable overall median PFS of 59.8 months (95% CI 29.8–79.6) and a median OS of 82.0 months (95% CI 64.0–125.6). These results strongly suggest that Lu-PRRT is a valid therapeutic option and compares well with other active

treatments in this disease setting [16]. Notably, none of the treated patients, including those at risk of developing delayed toxicity, had any side effects. In particular, there were no cases of significant creatinine clearance loss, grade 3–4 anemia, or myelodysplastic syndrome. This was likely due to the personalized treatment plan based on the presence of risk factors for toxicity. With regard to the planned activity injected, we were surprised to observe that there were no substantial differences in PFS and OS between patients who received the FD of 27.5 GBq and those who received the RD of 18.5 GBq. Unlike pancreatic neuroendocrine neoplasia where the cumulative activity of 27.5 GBq showed, in a similar protocol, better results than 18.5 GBq [17], the cumulative activity of 18.5 GBq in 5 cycles could be considered the minimum effective dosage in low-grade GI-NETs. This outcome, along with the absence of long-term toxicity, paves the way for randomized trials conducted in earlier stages for patients at risk of disease progression. In this regard, prognostic factors such as FDG-PET/CT, Ki-67, and tumor burden were investigated in the present report.

It has been seen that many tumors, including NETs, have an increased, predominantly anaerobic, glycolytic activity, especially when the tumor is aggressive (so-called "Warburg effect") [18]. Several studies have analyzed the prognostic value of FDG-PET/CT in NETs [11–13]. Our findings confirmed that FDG-PET/CT had a prognostic value in a small number of G1-G2 GI-NET patients treated with Lu-PRRT, especially evident in the first 5 years of follow-up. However, over time, the OS curves overlapped, losing their statistical significance. This aspect may be related to the progression of tumors towards more aggressive forms during the 10-year follow-up. It is likely that, as the disease progresses, tumor metabolism changes to anaerobic glycolysis, typical of the most aggressive forms of the disease. FDG-PET/CT should be repeated at disease progression and could be an alternative to a more invasive second biopsy when a dedifferentiation is suspected. A limitation of the present analysis is the small number of patients who underwent a baseline FDG-PET scan. However, 10–12 years ago, FDG-PET was not generally used in NET patients. A randomized study on NETs is currently ongoing at our institute in which patients are treated on the basis of tumor FDG avidity. FDG-PET/CT-positive patients are randomized to receive Lu-PPRT at a cumulative activity of 27.5 GBq or Lu-PRRT 27.5 GBq plus chemotherapy (metronomic capecitabine 1500 mg/die) (LUCAS study EudraCT no. 2014-003067-38). The hypothesis is that capecitabine, the oral prodrug of 5-fluorouracil (5-FU), is active in gastroenteropancreatic (GEP) tumors and may also act as a radiosensitizer of PRRT [19].

Regardless of the injected activity or FDG-PET outcomes, this study indicates that tumor burden and hepatic involvement were the important prognostic factors for Lu-PRRT [20]. Age over 65 years at the time of PRRT was also significant for OS. Ezziddin et al. previously reported that Lu-PRRT in GEP-NET patients with hepatic involvement ≥ 25% of liver volume at baseline imaging (CT or MRI) had a significantly shorter median OS than those with lower liver involvement [21]. In agreement with other authors [22, 23], we observed a negative impact of tumor burden in GI-NET patients undergoing Lu-PRRT at late stages of disease.

The NETTER-1 study reported that Lu-PRRT not only improves PFS but also delays decline in quality of life in these advanced patients [6]. At present, European Neuroendocrine Tumor Society (ENETS) guidelines indicate Lu-PRRT as an option after other treatments have failed [1]. A more recent ENETS consensus paper on the standard of care for neuroendocrine tumors reported that "in certain situations Lu-PRRT may well be considered earlier in the treatment pathway" [24]. We believe that the present work, despite some limitations, offers further data to support a more timely use of PRRT in GI-NETs, especially in patients with FDG-positive lesions. Thanks to the NETTER trial, the commercial availability of ^{177}Lu-DOTA-octreotate would probably facilitate its use, but other randomized trials are needed to better identify the role/usefulness of Lu-PRRT in the therapeutic algorithm of GI-NETs. In our opinion, in order to further reduce potential side effects, the cumulative injected activity of 27–29 GBq of ^{177}Lu-DOTA-octreotate routinely used in the current clinical setting should be divided into 5 cycles at a lower activity per cycle on the basis of patient characteristics [15].

In conclusion, the results from the IRST phase II study with a median follow-up of 118 months strongly suggest that Lu-PRRT is a safe and effective therapeutic option for patients with advanced GI-NETs. Patients with progression limited to lymph nodes showed significantly longer median PFS and OS than those with hepatic lesions. We thus believe that Lu-PRRT could be offered to GI-NET patients at earlier stages of disease.

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Author contributions Giovanni Paganelli: study concept and design, manuscript drafting; Stefano Severi: coordinated the different tasks of the project and worked on preparation, treatment, and follow-up of patients; Maddalena Sansovini, Silvia Nicolini, Grassi Ilaria, and Luca Urso: worked on enrolment, preparation, treatment, and follow-up of patients; Elena Amadori: reviewed morphological imaging during enrolment, treatment, and follow-up; Federica Matteucci: worked on the diagnostic and therapeutic scintigraphy examinations of the patients; Corrado Cittanti: reviewed the manuscript; Mattia Altini: reviewed the manuscript; Valentina Di Iorio: prepared the radiopharmaceutical drug; Toni Ibrahim and Alberto Bongiovanni: worked on enrolment and follow-up of patients; Emanuela Scarpi: data analysis; Manuela Monti: data collection; Giovanni Paganelli: coordinated and supervised the different tasks of the project. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The protocol was approved by the Area Vasta Romagna Ethics Committee (approval no. 2007-005517-20 of October 31, 2007), and by the competent Italian Regulatory Authorities. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and with Good Clinical Practice (GCP) guidelines.

Informed consent All patients gave informed consent. Having an ^{18}FDG-PET scan before PRRT was not a prerequisite for the study but was taken into account as a prognostic factor when available.

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