



PRRT: identikit of the perfect patient

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Abstract

Peptide receptor radionuclide therapy (PRRT) has been strengthened since the publication of NETTER-1. Nevertheless, the correct positioning in the therapeutic algorithm is debated, and no optimal sequence has yet been standardized. Possible criteria to predict the response to PRRT in neuroendocrine tumors (NET) have been proposed. The aim of this review is to define the perfect identity of the eligible patient who can mostly benefit from this therapy. Possible predictive criteria which have been analysed were: primary tumor site, grading, tumor burden, FDG PET and ⁶⁸Ga-PET uptake. Primary tumor site and ⁶⁸Ga-PET uptake do not play a pivotal role in predicting the response, while tumor burden, FDG PET uptake and grading seem to represent predictive/prognostic factors for response to PRRT. The heterogeneity in trial designs, patient populations, type of radionuclides, previous therapies and measurement of outcomes, inevitably limits the strength of our conclusions, therefore care must be taken in applying these results to clinical practice. In conclusion, the perfect patient, selected by ⁶⁸Ga-PET uptake, will likely have a relatively limited liver tumor burden, a ki67 index <20% and will respond to PRRT irrespective to primary tumor. Nevertheless, we have mostly prognostic than predictive factors to predict the efficacy of PRRT in individual patients, while a promising tool could be the NETest. However, to date, the identikit of the perfect patient for PRRT is a puzzle without some pieces and still we cannot disregard a multidisciplinary discussion of the individual case to select the patients who will mostly benefit from PRRT.

Keywords Neuroendocrine tumors · Therapeutic sequence · Peptide receptor radionuclide therapy · Predictor · Response

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1 Introduction

Over the past 2 decades, peptide receptor radionuclide therapy (PRRT), has been proved to be an effective and safe therapeutic option in patients with inoperable or metastatic well-differentiated neuroendocrine tumors (NETs) [8, 32, 34, 40, 41, 46].

Somatostatin receptor ligand (SrL) labelled with Indium-111 (¹¹¹In-DTPA-Octreotide) was the first radiopharmaceutical applied with encouraging results in terms of symptomatology. Nevertheless, objective responses were rare, while hematological side effects were also observed [40]. Subsequently, new analogues labelled with the β -emitting radionuclides Lutetium-177 and Yttrium-90 were introduced. In the following 15 years, uncontrolled trials on both radiopharmaceuticals in different types of NETs reported disease-control rates (DCR)s of 68–94% and a significant increase of overall survival (OS) and progression free survival (PFS) ([8, 13, 34], Kwekkeboom et al. 2005). Furthermore, biochemical and

symptomatic responses, and quality of life improvement have been reported [36].

Data about safety of PRRT are comforting. The most frequent acute side effects are nausea and vomiting, fatigue, abdominal pain and myelosuppression, that are generally mild, self-limiting and reversible. Carcinoid crisis is very rare. Kidney damage is a long-term side effect, but renal failure can be prevented by the coadministration of positively charged amino acids. Haematological toxicity, such as leukaemia or myelodysplastic syndromes has been reported in less than 5% of patients who received PRRT [47].

Despite this long-time experience, for many years data about efficacy and safety of PRRT derived only from few early-phase trials or retrospective studies, until the publication of the recent first randomized phase III NETTER-1 trial [74], comparing PRRT (^{177}Lu -DOTATATE) to high-dose octreotide LAR in patients with progressive inoperable or metastatic midgut NETs. The objective response rate (ORR) was 18% in the ^{177}Lu -DOTATATE group versus 3% in the control group ($p < 0.001$). The median progression-free survival (mPFS) was not reached in the ^{177}Lu -DOTATATE group and it was 8.4 months in the control group (hazard ratio for disease progression or death with ^{177}Lu -DOTATATE vs. control, 0.21; 95% CI, 0.13 to 0.33; $p < 0.001$), which represented a 79% lower risk of disease progression or death in the ^{177}Lu -DOTATATE group than in the control group. In addition, the interim analysis indicated that the estimated risk of death was 60% lower in the ^{177}Lu -DOTATE group than in the control group (hazard ratio 0.40; $P = 0.004$). These impressive results, seen in the NETTER-1 study, substantiates the use of PRRT in NET patients.

However, no sequence is as yet standardized by major international guidelines and the correct positioning of PRRT in the therapeutic algorithm is up for discussion.

The antitumor effect of PRRT is based on the radiolabeled SrL ability to bind somatostatin receptors (SSTR), highly expressed in NETs [39]. A strong expression of SSTR-2 (Krenning Scale 3–4 as fulfilled in the NETTER-1 trial) seems to have an impact on the outcome, but also site of the primary tumor, tumor load, grading and the Positron Emission Tomography (PET) with ^{68}Ga -DOTA-peptide and/or with ^{18}F -fluorodeoxyglucose (18F-FDG) uptake may influence the efficacy of PRRT. Some prospective and retrospective studies analyzed these parameters individually, while the potential role in predicting response to PRRT of these factors has never been explored globally. Moreover, according to a recent experience of [9], high predictive and prognostic power on the outcome with PRRT, are observed for the “NETest”, a specific liquid biopsy which measures neuroendocrine tumor gene expression in blood and aims at defining the biological activity of an individual NET in real time. The

achievement reported in the cited paper are promising, also regarding the prediction of response to PRRT in different types of NET.

Nevertheless, since the NETest is not widely available in clinical practice, and it has still to be tested and further validated in other studies, the identification of reliable predictors of tumor response to PRRT is still urgently needed, to improve the outcome of PRRT, providing directions in clinical decision-making, toward a more personalized therapy.

The aim of this review is to revise all potential predicting factors of response to PRRT, finally defining the perfect identity of the eligible patient who can benefit most from this therapy.

2 Methods

We performed a literature search of MEDLINE (PubMed database and PMC) and Ovid to identify potentially relevant articles on the predictive factors of efficacy of PRRT. The search was last updated September 23rd 2019. The search strategy included the following terms: “neuroendocrine tumor”, “neuroendocrine carcinoma” and “peptide receptor radionuclide therapy”. Only articles published in the English language were considered. Additional studies were identified by reviewing the references of all selected articles. The methods of potentially eligible studies were assessed independently by five reviewers (MA, AD, CDD, PM, RM). Studies considered potentially eligible were retrieved in full-text and evaluated. Disagreements were resolved by consensus or referred to another reviewer for arbitration (AF).

2.1 Eligibility criteria

Eligible studies investigated the use of either Lutetium-177 or Yttrium-90 or both in patients with histologically confirmed NET. Both retrospective and prospective studies were included; single-arm studies were also eligible. To be included, a study needed to report on participants treated with PRRT. Original articles were considered without any restriction, and Editorials and Letters were excluded. Reviews of PRRT were scrutinized for references to eligible trials, but were themselves excluded. Studies of Merkel cell carcinoma, pheochromocytoma and medullary thyroid carcinoma were also excluded, as were reports with less than five patients or where there was no report on any of the considered endpoints. Studies that examined PRRT alone were selected, while studies in combination or sequence with other therapies (eg. use of radiosensitizing chemotherapy) were excluded. Case-reports and non-English texts were excluded as well. The selected abstracts were then further assessed for a full-text evaluation.

Database searches yielded the following 2349 references: 626 from PubMed, 1003 from PMC, and 722 from the Ovid

database. Seven additional references were retrieved from the literature. Exclusion of duplicates left 2263 records, and 2180 of these did not satisfy inclusion criteria. Full texts were examined in 83 publications concerning the use of PRRT in NETs, and 26 were excluded due to the study design. Thus, 57 papers were considered for qualitative analyses of PFS, OS and ORR (Fig. 1).

3 Results

After selection of original articles from literature we recognized four parameters that more commonly were investigated as potential predictors of response to PRRT: primary, PET-uptake, tumor burden and grade (ki67 index). Some authors evaluated even performance status, that seems to have some degree of influence, however there are few data about this point, hence we decided to focus our attention on the four above stated criteria.

3.1 Primary

In 26 papers (2007–2019), 8 prospective, 17 retrospective and one prospective/retrospective – German registry, primary tumor site was evaluated according to PRRT. Table 1 shows all selected original articles. The population comprised over 4050 patients with metastatic and almost all progressive NET, mainly gastroenteropancreatic. ^{177}Lu was employed in 11 studies, ^{90}Y in 2 and both in 13. Number of cycles ranged

from 1 to 9 and cumulative dose varied usually between 14.7 and 30 GBq.

In 20 studies the role of primary in PRRT was analyzed in detail [1, 4, 5, 12, 15, 21, 24, 27, 32, 35, 42, 46, 59, 60, 68, 70, 72, 78, 79], but primary showed an impact on response to PRRT only in 8 [4, 5, 12, 21, 24, 32, 42, 60]. No association was noted between positive and negative studies and patient populations, sample size, study design or radionuclide employed (^{177}Lu or ^{90}Y).

3.1.1 “Positive studies”

GEP NET showed higher PFS, ORR and DCR than other NET in the study by [4]. PFS in GEP was 30.3 months vs 17.4 months in the total NET population, ORR was 54.2% vs 40.6% and DCR was 100% vs 93.8%. Median OS was 34.7 months in both groups. Importantly, among patients with GEP NET undergoing >1 PRRT cycles, complete responders were 25%, the highest value reported and neither CR, nor PR in other NET were reported.

[12] reported longest median OS in panNET (71 months), and lowest in bronchial (52 months) and NET of unknown origin (53 months). Median PFS was 30 m in panNET, like NET of unknown origin (29 months) and 20 m in bronchial. Best time to progression (TTP) was reported in midgut NET (42 months), and worst in bronchial NET (25 months), while panNET had 31 m and NET of unknown origin 37 months.

Again, [5] in their retrospective analysis found that the site of origin of NENs was a predictor of median overall survival.

Fig. 1 Study selection sequence to perform the review

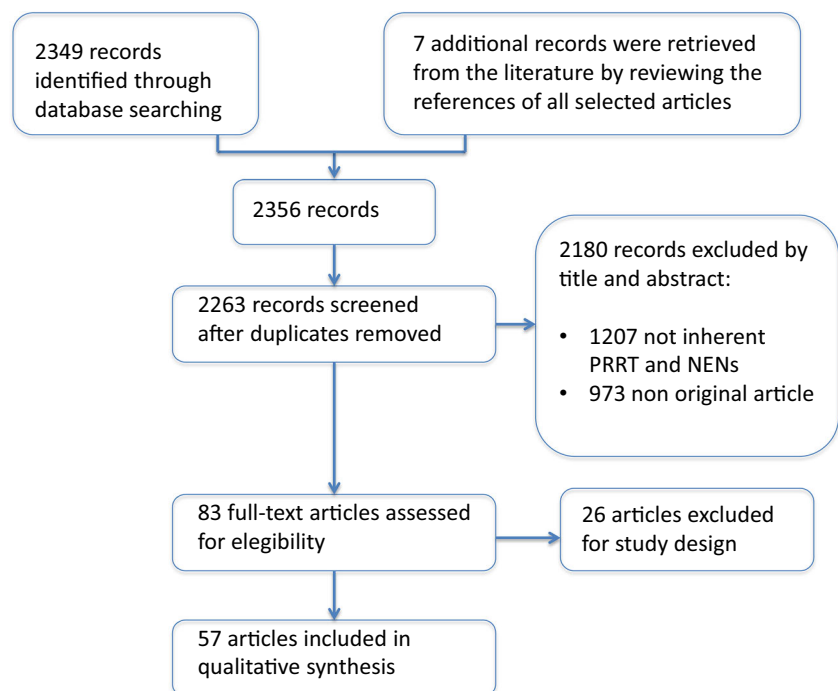


Table 1 Studies assessing role of *Primary* as predictor of different outcomes after PRRT. In light gray “Positive studies”, in gray “Negative Studies”, white for only descriptive studies

Study	Year	Type of study	N of subject (gender)	Patient population	Treatment received (¹⁷⁷ Lu/ ⁹⁰ Y)	Cycles/dose	Primary endpoint(s)	Time of evaluation of primary endpoint	Criteria	Outcome	Applied statistical analysis	Is the criterion predictive of response to therapy?
Seregni et al (Italy)	2010	prospective	26 (9 F, 17 M)	unresectable/metastatic NET	⁹⁰ Y and/or ¹⁷⁷ Lu	24 cycles	efficacy, toxicity	13m after last cycle	primary	PR, SD, PD	univariate	NA (no statistical comparison among primary)
Bodei et al (Italy)	2011	prospective	51 (25 F, 26 M)	unresectable/metastatic Octreoscan positive tumors	¹⁷⁷ Lu	6 cycles (1-7); up to 29GBq cumulative	toxicity, efficacy	6.8 weeks after second cycle, then every 6m	primary	CR, PR, SD	univariate and multivariate	NA (no statistical comparison among different primary)
Filice et al (Italy)	2012	prospective	65 (27 F, 38 M)	metastatic progressive NET	⁹⁰ Y and/or ¹⁷⁷ Lu	1.9 cycles; median cumulative 5.5 GBq	efficacy	3.6m after last cycle	primary	CR, PR, SD, PD	multivariate	NA (no statistical comparison among primary)
Delpassand et al (USA)	2014	prospective	37 (21 F, 16 M)	metastatic progressive GEP-NET	¹⁷⁷ Lu	1.4 cycles; cumulative 29.6 GBq	efficacy	3m after last cycle (at least)	primary	PFS	univariate	NA GEP only (no statistical comparison among different primary; unknown primary lowest PFS)
Hamiditabar et al (USA)	2017	prospective	144 (59 F, 85 M)	metastatic and/or inoperable progressive NET	¹⁷⁷ Lu	1.6 cycles; cumulative 29.6 GBq	efficacy	after at least 1 cycle	primary	CR, PR, SD, PD	univariate	NA (no statistical comparison among primary)
Thapa et al (India)	2016	retrospective	50 (17 F, 33 M)	metastatic/inoperable NET	¹⁷⁷ Lu	3.5 cycles; 5.55 GBq per cycle	efficacy	after at least 3 cycle	primary	tumor response	multivariate	NA (no statistical comparison among primary)
Ezzidin et al (Germany)	2011	retrospective	81 (35 F, 46 M)	metastatic advanced GEP-NET (Progressive disease in 77%)	¹⁷⁷ Lu	4 cycles (usually); mean activity of 7.9 GBq per cycle	assess influence of ki67 on tumor response	3 months after last cycles	primary	ORR	univariate	Yes (tumor response was significantly better in pNET than in GI NET); p 0.012
Pfeifer et al (Denmark)	2011	retrospective	69 (36 F, 33 M)	metastatic progressive NET	⁹⁰ Y and/or ¹⁷⁷ Lu	1.3 cycles; cumulative 15.54 GBq	efficacy, toxicity	not reported	primary	DCR, PFS	multivariate	Yes (pNET respond better than small intestinal; no difference in PFS); p=0.03
Ezzidin et al (Germany)	2014	retrospective	74 (32 F, 42 M)	metastatic progressive NET	¹⁷⁷ Lu	1.4 cycles; mean 7.9 GBq	predictors of survival	3m after last cycle	primary	PFS, OS	univariate	Yes (unknown primary worse outcome than non-pancreatic GEP NET. pFS: pNET 25m v non-pancreatic GEP NET 27m; OS 57m vs 43m); PFS (P=0.001) OS (P=0.003)
Horsch et al (Germany)	2016	retrospective /prospective (registry)	450 (211 F, 239 M)	metastatic progressive NET	¹⁷⁷ Lu and/or ⁹⁰ Y, ⁶⁷ Ga	1.8 cycles (mean 5.38GBq)	efficacy, toxicity	at last follow up (mean 24.4m)	primary	PFS, OS	univariate	Yes (primary influences OS, not PFS; small bowel less death); p 0.021 OS
Baum et al (Germany)	2016	retrospective	56 (27 F, 29 M)	metastatic progressive NET	¹⁷⁷ Lu	2.1 cycles (1.4); 7 GBq median dose	efficacy, safety	743months after last cycle	primary	PFS, OS, ORR, DCR	multivariate	Yes (higher ORR and DCR in GEP than other NET)
Brabander et al (The Netherlands)	2017	retrospective	1214 tot (443 for efficacy: 213 F, 230 M)	metastatic progressive NET	¹⁷⁷ Lu	at least 22.2 GBq; up to 750 to 800 mCi (27.8-29.6 GBq)	safety, efficacy	NA	primary	PFS, OS, TTP	univariate	Yes (pancreas longest OS, bronchial lowest; PFS lowest bronchial 20m; TTP best midgut 42m, worst 25m bronchial).
Kunikowska et al (Poland)	2017	prospective	59 (40 F, 19 M)	metastatic progressive NET	⁹⁰ Y and/or ¹⁷⁷ Lu	3.5 cycles	efficacy, toxicity	3-6-12m and every 12 m	primary	PFS, OS	univariate	Yes (PFS and OS stat significant only between small and large bowel)

Baum et al (Germany and NL)	2018	retrospective	1048 (593 M, 455 F)	advanced NET of different origins, mostly GEP-NET	⁹⁰ Y and/or ¹⁷⁷ Lu	mean 18.84 GBq (range 1.4 - 63.9)	efficacy	not specified	primary	PFS and OS	univariate and multivariate	Yes. Best OS was observed in patients with NENs of small bowel (69 months, p=0.01) if compared with the other primaries. Small bowel NENs had longer PFS compared to patients with pancreatic NENs (p<0.001); bronchial origin and unknown origin were associated with shorter PFS.
van Essen et al (The Netherlands)	2007	retrospective	16 (6 F, 10 M)	metastatic foregut NET	¹⁷⁷ Lu	intended cumulative dose 22.2-29.6 GBq	efficacy	6-8 weeks, 3 m and 6 m after the last treatment, and thereafter every 6	primary	ORR	multivariate	No (ORR comparable between foregut carcinoids of bronchial, gastric or thymic origin 50% and whole GEP NET 47%); p >0.0 (ORR)
Kwekkeboom et al (NL)	2008	retrospective	310 (146 F, 164 M)	metastatic progressive NET	¹⁷⁷ Lu	4 cycles (usually); cumulative 29.6 GBq	toxicity, efficacy	3m after last cycle	primary	TTP, OS, CR, PR, SD	multivariate	No (gastrinoma, insulinoma, VIPoma shorter duration; higher response rates in gastrinoma insulinoma, VIPoma and non-functioning NET)
Cwikla et al (Poland)	2010	prospective	60 (32 F, 28 M)	metastatic progressive GEP-NET	⁹⁰ Y	1.4 cycles; up to 15.2 GBq	efficacy, toxicity	4.6m after last cycle	primary	OS	multivariate	No (no significant differences in survival regarding primary); p 0.052
Sowa-Staszczak et al (Poland)	2011	retrospective	42 (27 F, 15 M)	disseminated and/or inoperable NET	⁹⁰ Y and/or ¹⁷⁷ Lu	1.5 cycles; up to 7.4 GBq/m2	efficacy, toxicity	not reported	primary	OS	multivariate	No (survival rates between NFPNT and NET other localizations did not show any statistically significant difference)
Seregni et al (Italy)	2014	prospective	26 (12 F, 14 M)	metastatic progressive NET	⁹⁰ Y and/or ¹⁷⁷ Lu	2008-2010	efficacy	23.4 - 33 m follow up	primary	OS, PFS	multivariate	No (No significant associations between primary and OS or PFS)
Vinjamuri et al (UK)	2013	retrospective	67 (22 F, 45 M)	metastatic progressive NET	⁹⁰ Y	2003-2012	association of radiological response and OS	3-12 m after last cycle	primary	OS	multivariate	No (no correlation between tumor site and survival; trend shorter survival in unknown primary)
Katona et al (USA and CH)	2017	retrospective	28 (14 M, 14 F)	GEP-NET and Unknown origin	⁹⁰ Y and/or ¹⁷⁷ Lu	2.5 cycles (mean) per patient (range 1-7)	efficacy and safety	within a year after the end of PRRT	primary	PFS and OS	univariate and multivariate	No, no significant difference in survival according to primary was observed (p>0.5)
Pencharz et al (UK)	2017	retrospective	79 (43 F, 36 M)	metastatic progressive NET	¹⁷⁷ Lu	1.4 cycles	efficacy, toxicity	6.8 weeks after cycle	primary	PFS	multivariate	No (trend towards better PFS in pNETs, although not statistically significant)
Sharma et al (USA)	2017	retrospective	135 (36 F, 64 M)	metastatic NET	⁹⁰ Y and/or ¹⁷⁷ Lu	1.2 cycles	efficacy, survival	within 6m after cycle	primary	OS, TTP	multivariate	No (differences in OS and TTP not statistically significant); OS 0.009; TTP 0.093
Gabriel et al (Austria)	2018	retrospective	44 (27 M, 17 F)	advanced NET	⁹⁰ Y and/or ¹⁷⁷ Lu	8.6 ± 3.4 cycles mean activity 34.4 ± 13.9 GBq	OS	not specified	primary	OS	multivariate	No. No statistical significance was observed when the site of the primary tumor was analyzed, p=0.473
Carlsen et al (multicentric)	2019	retrospective	149 (76 M, 73 F)	G3 progressive and/or metastatic GEP-NET	⁹⁰ Y and/or ¹⁷⁷ Lu or ¹¹¹ In (in 1 patient)	median 4 cycles (1-15), median activity of 18 GBq (4-85)	efficacy and toxicity	not specified	primary	PFS and OS	univariate and multivariate	No. PFS and OS were independent from primary tumor site.
Aalbersberg et al (NL and Germany)	2019	retrospective	782 (444 M, 338 F)	inoperable or metastatic NET	⁹⁰ Y and/or ¹⁷⁷ Lu	at least 3 cycles	OS and PFS	not specified	primary	PFS and OS	univariate and multivariate	No. Primary was not associated with better survival outcome.

Abbreviations: M, male; F, female; GEP, gastroenteropancreatic; SI, small intestinal; GI, gastrointestinal; NFPNT, pancreatic non functioning NET; pNET, pancreatic NET; NET, neuroendocrine tumor; GBq, Gigabecquerel; mCi, millicurie; ORR, objective response rate; PFS, progression free survival; OS, overall survival; TTP, time to tumor progression; DCR, disease control rate; DFS, disease free survival; DSS, disease specific survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

Best OS was, in fact, observed in patients with NENs of small bowel (69 months, $p = 0.01$), which was statistically significant if compared with the other groups (pancreas, lung, other primaries, unknown origin). Even PFS was correlated with the site of primary tumor, having patients with small bowel NENs a longer PFS compared to patients with pancreatic NENs ($p < 0.001$); bronchial origin and unknown origin were associated with a significantly shorter PFS.

The site of primary influences OS, but not PFS in the study by [32], as patients with small bowel NET were significantly less likely to die ($p = 0.021$).

Statistically significant difference in PFS and OS between large and small bowel NET was found by [42] (OS 82.5 vs 58.1 months; PFS 40.3 vs 29.5 months). [60] reported no significant difference in PFS among panNET (27 months), NET of unknown origin (30 months) and small intestinal NET (not reached at the time of analysis).

[21] show that ORR was significantly better ($p = 0.012$) in panNET than in GI NET and in 2014 [24] reported worse outcome for NET of unknown origin than nonpancreatic GEP NET, having shorter PFS ($P = 0.001$) and OS ($P = 0.003$). PFS in panNET was 25 months vs nonpancreatic GEP NET (27 months) and OS was 57 vs 43 months.

In 2 studies, NET of unknown origin showed a trend of shorter survival [79] and the lowest PFS [18] without statistical significance.

3.1.2 “Negative studies”

Six studies [15, 17, 27, 35, 68, 79] reported no significant difference in survival according to primary. Comparable ORR between foregut carcinoids of bronchial, gastric or thymic origin (50%) and whole GEP NET (47%) was reported by [78], but time to progression (TTP) was shorter in foregut than in GEP NET.

[70] reported that TTP rates were not significantly different among pulmonary, small bowel NET and panNET ($P = 0.093$). The single result that achieved statistical significance was a longer OS in small bowel NET compared with other primary. In fact, OS after the first PRRT was 95.4, 37.3, and 20 months for small bowel, pancreatic, and NET of unknown origin, respectively ($P = 0.009$) [70].

A study by [1] showed conflicting results, founding difference in OS in the univariate analysis (small bowel NET had longer OS than pancreatic, lung and large intestine primaries) but not in the multivariate analysis. Reported median OS for non-functioning panNET was 25.7 months and for other NET was 46.7 months in the study of [72], but data were not statistically significant. A not significant trend towards a better PFS in panNETs was also reported by [59].

Regarding functionality, gastrinoma, insulinoma, VIPoma showed shorter response duration, and higher response rates were reported in gastrinoma, insulinoma, VIPoma, non-functioning NET than in carcinoid ($p < 0.01$), according to a

sub-analysis conducted on a subgroup of patients from the study of Kwekkeboom et al. [46].

In 5 studies, no correlation was reported between primary and any outcome, [8, 25, 30, 67, 75].

3.2 Pet

Ga-68 labeled somatostatin analogs and 18F-FDG PET have been evaluated as potential predictors of response to PRRT in twenty-one studies conducted from 2009 to 2019. Table 2 and 3 show all selected original articles where Gallium/FDG PET were evaluated as a predictive factor of response to PRRT. Overall, more than one thousand patients with NET were evaluated. Eight studies are prospective non-randomized clinical trials while thirteen studies are retrospective.

Concerning **⁶⁸Ga-DOTA-peptide PET**, all studies assessed tumor standardized uptake value (SUV) as a quantitative parameter, to predict response to PRRT (see Table 2). Among eleven papers that analyze ⁶⁸Ga-PET, three papers did not find any significant result that attributes a predictive role to maximum SUV (SUV_{max}) during ⁶⁸Ga-PET ([26, 27, 73]), two papers from the same group [80, 81] identified other parameters besides SUV_{max}, able to predict outcome of PRRT treatment, and six identified SUV_{max} as a predictor of response to therapy [25, 31, 38, 53, 54, 71]. All studies were performed on rather small NET series. Both negative and positive studies comprise retrospective and prospective experience and no particular features characterize a group relative to the other. No association was noted between positive and negative studies and patient populations or radionuclide employed (177Lu or 90Y).

3.2.1 “Positive studies”

In detail, pre therapeutic SUV_{max} was identified as a predictor of TTP in a population of 33 patients [31]. However, the SUV_{max} was identified as a predictor of TTP in univariate analysis only ($p = 0.04$), while, according to the Cox proportional hazards model, authors identified another parameter (the change in SUV of the tumors relative to the maximal splenic uptake – Delta SUV T/S) as the only predictor of TTP in both univariate ($p = 0.006$) and multivariate analyses ($p = 0.03$) [31]. Öksüz et al. [54] showed that ⁶⁸Ga-DOTATOC tumor uptake was strongly associated with the response to PRRT ($p < 0.001$). Furthermore, the authors identified a SUV cut-off of 17.9 to predict treatment response to PRRT. Similarly, [38], observed significant differences in the mean SUV_{max} for non-responding vs responding liver metastases in 30 NET patients, proposing a SUV_{max} cut-off of 16.4 to select patients for PRRT. Sharma et al. also investigated SUV_{max} and SUV_{mean} of ⁶⁸Ga-PET/CT as possible predictor of PRRT response. Single lesion SUV_{max} was,

Table 2 Studies assessing role of ^{68}Ga -DOTA-peptides PETas predictor of different outcomes after PRRT. In light gray “Positive studies”, in gray “Negative Studies”

Study	Year	Type of study	N of subject (gender)	Patient population	Treatment received ($^{177}\text{Lu}/^{90}\text{Y}$)	Cycles/dose	Primary endpoint(s)	Time of evaluation of primary endpoint	Criteria	Outcome	Applied statistical analysis	Is the criterion predictive of response to therapy?
Haug AR et al (Germany)	2010	prospective	33 (22 M, 11 F)	G1-G2 metastatic NET	^{90}Y or ^{177}Lu or both	1-3 cycles	TTP	3 months after the first PRRT to 33 months of follow up	^{68}Ga -DOTATATE SUVmax and tumor-to-spleen SUV ratio (SUV T/S)	TTP	univariate and multivariate	Yes. SUVmax as an accurate predictor for TTP (univariate)
Oh S et al (Korea/Germany)	2011	prospective	25 (16 M, 9 F)	progressive, metastasized NET	^{90}Y and/or ^{177}Lu	3 cycles	SUV ^{68}Ga DOTANOC PET/CT and FDG in response to PRRT	Not specified	^{68}Ga DOTATOC-PET/CT SUVs	^{68}Ga DOTATOC-PET/CT SUVs, CR, PR, SD, PD	multivariate	Yes. the response is positively correlated with the baseline SUVmax
Filice A et al (Italy)	2012	prospective	65 (30 M, 27 F)	progressive unresectable metastatic NET	^{90}Y or ^{177}Lu	maximum of 9 cycles	Efficacy	3-6 months after the last PRRT	^{68}Ga DOTATOC-PET/CT SUVs	ORR (CR, PR,SD,PD)	multivariate	Yes. The SUVmax value in the main lesion at baseline ^{68}Ga -peptide PET compared to end-treatment scan was in line with the functional response evaluation
Öksüz MÖ et al (Switzerland/Germany)	2014	retrospective	40 (23 M, 17 F)	advanced net	^{90}Y	fixed radioactivity doses	SUV ^{68}Ga DOTANOC PET/CT as predictor	3 months after PRRT	^{68}Ga DOTATOC-PET/CT SUVs	^{68}Ga DOTATOC-PET/CT SUVs tumor shrinkage, decrease of tumor markers, improving or stable clinical condition	multivariate	Yes. therapeutic ^{68}Ga -DOTATOC tumor uptake as well as assumed uptake of ^{90}Y -DOTATOC are strongly associated with the results of subsequent PRRT.
Kratochwil C et al (Germany)	2015	retrospective	30 (15 M, 15 F)	advanced NET	^{90}Y or ^{177}Lu or both	12 - 18 GBq	ORR (RECIST criteria)	Not specified	^{68}Ga SUV	ORR	univariate	Yes. a SUVmax cutoff of 16.4 to select patients for PRRT was proposed
Sharma R et al. (UK)	2019	retrospective	55 (29 M, 26 F)	metastatic NET	^{177}Lu	4 cycles	PFS - OS	after the last therapy cycle	^{68}Ga -DOTATATE single lesion SUVmax, tumour to spleen and liver SUV ratios, and SUVmax-av	Treatment response (PR,SD,PD)	univariate	Yes. Baseline SUVmax 13.0 defines a threshold below which patients have poor response to PRRT and worse PFS.
Gabriel M et al (Austria)	2009	prospective	45 (29 M, 17 F)	advanced net	^{90}Y or ^{177}Lu or both	2-7 cycles	compare ^{68}Ga -DOTATOC PET with CT or MRI using RECIST	after the last therapy cycle	^{68}Ga DOTATOC-PET/CT SUVs	ORR	multivariate	No, SUV analysis of individual lesions is of no additional value in predicting individual responses to therapy
Soydal Ç et al (Turkey)	2016	retrospective	29 (12 M, 17 F)	metastatic or inoperable NET	^{177}Lu	4 cycles	Efficacy	6 weeks after the last cycle.	^{68}Ga DOTATOC-PET/CT SUVs	Treatment response (PR,SD,PD)	univariate and multivariate	No, no significant correlation could be demonstrated between response rates and Ref SUVmax or the ratio to SUVL, SUVs, SUVp, and SUVA
Werner RA et al (Germany)	2017	retrospective	142 (71 M, 71 F)	metastatic NET	^{177}Lu	1-6 cycles	PFS - OS	Not specified	^{68}Ga DOTATOC-PET/CT Entropy, Correlation, Homogeneity, Short Zone Emphasis and Size Variation, Tissue Receptor Expression	PFS -OS	univariate and multivariate	No, but Tissue Receptor Expression (TRE) was predictor of response to PRRT
Gabriel M et al. (Austria)	2018	retrospective	44 (27 M, 17 F)	advanced NET	^{90}Y and/or ^{177}Lu	8.6 ± 3.4 cycles mean activity 34.4 ± 13.9 GBq	OS	not specified	^{68}Ga DOTATOC-PET/CT	OS	multivariate	No significant relationship was found
Werner RA et al (Germany)	2019	retrospective	31 (17 M, 14 F)	G1-G2 metastatic NET	^{177}Lu	range 1-6; mean 3.6 cycles	PFS - OS	not specified	^{68}Ga DOTATOC-PET/CT and ^{68}Ga -DOTATATE SUVs	PFS - OS	univariate and multivariate	No. All the investigated conventional PET parameters (SUVmean/max, MTV, TRE) failed in response prediction

in fact, predictive of both response to PRRT ($p = 0.031$) and PFS, and SUV_{mean} correlated with PRRT response ($P = 0.039$) as well. The authors also indicated a cut-off of 13.0, when considering single lesion SUV_{max} , to give high sensitivity and specificity in prognosticating a favorable treatment response. Tumor to liver SUV ratio ($\text{SUV}_{\text{T/H}}$) and tumor to spleen SUV ratio $\text{SUV}_{\text{T/S}}$ were investigated as well, but neither $\text{SUV}_{\text{T/S}}$ or $\text{SUV}_{\text{T/H}}$ were predictive of response to PRRT [71]. A significant correlation between the ORR to PRRT and the ^{68}Ga -DOTANOC PET baseline SUV_{max} was also found in the prospective trial conducted from [53], but p value was not reported. Similarly, [25] showed that the SUV_{max} in the main lesion at baseline was predictive of response as indicated by functional evaluation.

3.2.2 “Negative studies”

On the contrary, in a multicenter study [80], both SUV_{max} and SUV_{mean} of ^{68}Ga -PET/CT failed in response prediction to PRRT. However, the authors identified other textural features representing intratumoral heterogeneity, such Tissue Receptor Expression (TRE), able to predict OS ($p = 0.003$) and PFS ($p = 0.02$). Similar results were found by the same group in 2019, in their retrospective study where only panNETs were evaluated: $\text{SUV}_{\text{max/mean}}$ failed to predict PFS, whereas the intratumoral textural feature (TF) analysis, assessed by a baseline SSTR-PET, predicted response in terms of PFS [81]. The following studies also did not find any significant relationship between the response to PRRT and SUV_{max} of reference lesions [26] ($p = 0.12$), [73] ($p = 0.25$), [27] ($p = 0.59$).

Table 2 (continue)

Study	Year	Type of study	N of subject (gender)	Patient population	Treatment received ($^{177}\text{Lu}/^{90}\text{Y}$)	Cycles/dose	Primary endpoint(s)	Time of evaluation of primary endpoint	Criteria	Outcome	Applied statistical analysis	Is the criterion predictive of response to therapy?
Oh S et al (Korea/Germany)	2011	prospective	25 (16M, 9F)	Progressive, metastatic NET	^{90}Y and/or ^{177}Lu	3 Cycles	SUV changes on 18F FDG (FDG) PET/CT in response to PRRT	after PRRT	SUV changes FDG PET	ORR	-	Only descriptive data
Severi S et al (Italy)	2013	retrospective	52 (28M, 24F)	Progressive advanced NET	^{177}Lu	27.7 GBq divided into five courses	DCR, PFS	3 months after last prrt	FDG PET	ORR	multivariate	Yes, in the PET+ patients, 76 % showed DCR, while in the PET- patients the DCR was 100 %. The PFS curves in relation to the FDG PET outcomes discriminated two different prognostic courses ($p=0.033$) during the follow-up time
Delpassand ES et al (USA)	2014	prospective	37 (21 F, 16 M)	G1 G2 metastatic progressive GEP-NET	^{177}Lu	repeated cycles of 200 mCi up to the cumulative dose of 800 mCi	Efficacy	in 32 evaluable patients for an average of 14.26 months RECIST	FDG SUVmax >2.5 in 32 patients	PFS	univariate	Yes, it was found a significant correlation between a positive 18FFDG PET/CT and patient death; $p<0.03$
Paganelli G et al (Italy)	2014	prospective	43	G1,G2 advanced, progressive GEP-NET	^{177}Lu	5 cycles	Efficacy	after the end of treatment and every 6-12 months thereafter.	FDG PET	PFS/DCR	multivariate	Yes, PET FDG-negative patients had a significantly longer PFS ($p<0.025$) than positive. In terms of DCR there was a better, albeit not statistically significant outcome for FDG-negative cases ($P=0.16$).
Sansovini M et al (Italy)	2016	prospective	60 (35M, 25F)	Metastatic G1,G2 pNET	^{177}Lu	5 cycles	DCR	after PRRT for at least 12 months	FDG PET SUV>2.5	ORR	univariate and multivariate	Yes, FDG PET was found to be the only independent prognostic factors for PFS and OS; $p<0.0002$ (PFS) e $p<0.006$ (OS)
Nilica B et al (Austria)	2016	retrospective	66	Advanced NET	^{90}Y and/or ^{177}Lu	3-4 cycles	To compare Ga and FDG PET	3 month after completion of PRRT and after a further 6 – 9 months	FDG	ORR	univariate	Yes, the presence of 18F-FDG-positive tumours correlates strongly with a higher risk of progression.
Thapa P et al (India)	2016	retrospective	50 (33M 17F)	Metastatic, inoperable GEP-NET	^{177}Lu	3-5 cycles	Efficacy	after completion of PRRT and after a further 6 – 9 months	SUV FDG	ORR	multivariate	Yes. 18F-FDG SUVmax in both low-grade and high-grade NET predicted a poor outcome to treatment and was associated with disease progression.
Parghane RV et al (India)	2017	retrospective	22 (16M 6 F)	Metastatic progressive pulmonary NETS	^{177}Lu	4 cycles	ORR	after the first PRRT from range of 6 to 60 months, with an average of 24 months	FDG PET	ORR	multivariate	Yes, 7 patients in PD had moderately to intensely FDG-avid primary lung lesion.
Nicolini S et al (Italy)	2018	retrospective	33 (16M, 17F) di cui 29 sottoposti a FDG-PET	Inoperable or metastatic high grade GEP-NET	^{177}Lu	4-5 cycles	Efficacy	3, 6, 12, 18 and 24 months after the end of treatment and every 6-12 months thereafter.	FDG PET positive or negative	PFS	n.a.	Yes. FDG-negative patients with a Ki-67 index of 15–35% had a higher PFS than FDG-positive patients. No p available.
Adnan A et al (India)	2019	retrospective	27 (26 M, 1 F)	Metastatic or advanced mediastinal NET	^{177}Lu	mean 16 650 MBq 3 cycles	OS-PFS	not specified	FDG uptake	OS-PFS	bivariate	Yes. Low FDG uptake of the tumour are associated with prolonged OS and PFS in patients with metastatic or advanced mediastinal NETs
Ianniello A et al (Italy)	2015	prospective	34 (17M, 17F)	Progressive bronchial carcinoids	^{177}Lu	4-5 cycles 18.5 or 27.8 GBq	DCR, PFS, OS	median Follow-up 29 months	FDG SUVmax >2.5 29 patients	ORR	univariate	No, no statistically significant differences in mPFS of FDG PET-negative and positive patients; $p<0.2$

Abbreviations: M, male; F, female; GEP, gastroenteropancreatic; SI, small intestinal; GI, gastrointestinal; panNET, pancreatic NET; NET, neuroendocrine tumor; GBq, Gigabecquerel; mCi, millicurie; ORR, objective response rate; PFS, progression free survival; OS, overall survival; TTP, time to tumor progression; DC, disease control; DCR, disease control rate; DFS, disease free survival; DSS, disease specific survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; SUVmax, maximum standardized uptake value; n.a., not applicable

Regarding ^{18}F -FDG PET, all studies tend to divide patients in PET-positive and PET-negative, depending on a value of SUV_{max} 2.5 or more, as an arbitrary cut off to consider a lesion positive for malignancy (see Table 3). Among eleven papers that analyze ^{18}F -FDG PET, only one paper clearly defines that SUV_{max} FDG does not have a predictive role [33], while nine papers show that this criterion could have a predictive role [2, 18, 51, 52, 55, 58, 64, 69, 75]. Finally, one paper reported descriptive data only [53]. As for gallium PET, none of these studies is based on large study populations.

3.2.3 “Positive studies”

A retrospective study [69] showed the capacity of FDG PET to characterize the aggressiveness of NETs, both in terms of PFS ($p=0.033$) and DCR ($p=0.02$). [64] confirmed these data in a prospective study on pancreatic NETs. Median PFS in the PET-positive group was 21.2 months, while in the PET-negative group, it was 68.7 months ($P<0.0002$). Median OS was not reached in the PET-negative group and was 63.8 months in the PET-positive group ($p=0.006$). Similarly, PFS was significantly

Table 3 Studies assessing role of *Tumor Burden* as predictor of different outcomes after PRRT. In light gray “Positive studies”, in gray “Negative Studies”, white for only descriptive studies

Study	Year	Type of study	N of subject (gender)	Patient population	Treatment received ($^{177}\text{Lu}/^{90}\text{Y}$)	Cycles/dose	Primary endpoint(s)	Time of evaluation of primary endpoint	Criteria	Outcome	Imaging evaluation of tumor response	Applied statistical analysis	Is the criterion predictive of response to therapy?
Brabander T et al (NL)	2017	retrospective	443 (230 M, 213 F)	GEP and bronchial NET	^{177}Lu	at least 22.2 GBq; up to 750 to 800 mCi (27.8-29.6 GBq)	Efficacy, safety	3 months after the end of PRRT	liver metastases, bone metastases	ORR-OS	CT or MRI (RECIST 1.1)	univariate	Not evaluated
Kwekkeboom DJ et al (NL)	2003	retrospective	35 (14 M, 21 F)	GEP-NET	^{177}Lu	100-150-200 mCi	Efficacy, toxicity	3-6 months after the end of PRRT	diffuse liver metastases	DCR (CR+PR+SD)	CT or MRI (WHO criteria)	univariate	Yes; $p < 0.05$
Valkema R et al (multicentric)	2006	phase I dose escalation study	58 (33 M, 25 F)	GEP-NET	^{90}Y	dose-escalating study with cumulative doses of 47 mCi to 886 mCi	Finding the tolerable dose	6 weeks after the end of PRRT	liver metastases	OS	TC or MRI or US (SWOG criteria)	multivariate	Yes, was predictor of shorter OS; $p < 0.001$
Kwekkeboom DJ et al (NL)	2008	retrospective	310 (164 M, 146 F)	GEP-NET	^{177}Lu	4 cycles (usually); cumulative 29.6 GBq	Efficacy, toxicity	3 months after the end of PRRT	bone metastases, extent of liver involvement	PFS, OS	CT or MRI (SWOG criteria)	multivariate	Yes, was predictor of DFS e DSS; $p < 0.01$
Marincek N et al (USA)	2013	clinical phase I dose escalation study	359 (204 M, 155 F)	NET	^{90}Y	low dose (median: 2.4 GBq/cycle), intermediate dose (median: 3.3 GBq/cycle), high dose (median: 6.7 GBq/cycle)	Efficacy	3 months after the end of PRRT	previous surgery, bone metastases	OS	not reported	multivariate	Yes, was predictor of shorter OS; $p < 0.05$
Campagna D et al (Italy)	2013	retrospective	69 (37 M, 32 F)	GEP-NET	^{90}Y and/or ^{177}Lu	^{90}Y 4 cycles, 10.3 GBq median cumulative dose; ^{177}Lu 4 cycles, 25.2 GBq cumulative dose	Efficacy	4-6 months after the end of PRRT	Stage IV	ORR-PFS	CT or MRI (RECIST)	multivariate	Yes, was predictor of progression; $p < 0.02$
Delpassand ES et al (USA)	2014	non-randomized phase II trial	37 (16 M, 21 F)	G1-G2 GEP-NET	^{177}Lu	1-4 cycles; cumulative 29.6 GBq	Efficacy	3 months after the end of PRRT	<50% liver involvement	PFS	CT or MRI or Octreoscan or 18F-FDG PET (RECIST)	univariate	Yes
Ezzidin S et al a (Germany)	2014	retrospective	68 (35 M, 33 F)	G1-G2 pNET	^{177}Lu	4 cycles (usually); mean activity of 8 GBq per cycle	Efficacy	3 months after the end of PRRT	<25% liver involvement	DCR (PR+MR+SD)	CT or MRI (SWOG criteria and RECIST 1.1)	multivariate	Yes, was predictor of shorter OS; $p < 0.017$
Ezzidin S et al b (Germany)	2014	retrospective	74 (42 M, 32 F)	G1-G2 GEP-NET	^{177}Lu	4 cycles (usually); mean activity of 7.9 GBq per cycle	Predictors of survival	3 months after the end of PRRT	<25% liver involvement	PFS and OS	CT or MRI (SWOG criteria)	multivariate	Yes, was predictor of shorter OS; $p < 0.044$
Bertani E et al (Italy)	2016	retrospective	94 (47 M, 47 F)	G1-G2 pNET	^{90}Y and/or ^{177}Lu	^{177}Lu : 750 mCi in 5 cycles or 800 mCi in 8 cycles. ^{90}Y : 300 mCi fractionated in 4 cycles	Impact of primary tumor resection on response to PRRT	3-6 months after the end of PRRT	resection of the primary	ORR-PFS-OS	CT or MRI (RECIST)	univariate	Yes; $p < 0.002$
Mariniello A et al (Italy)	2015	retrospective	114 (81 M, 33 F)	Bronchopulmonary carcinoid	^{90}Y and/or ^{177}Lu	cumulative activity 750-800 mCi ^{177}Lu , 200-300 mCi ^{90}Y , 357-179mCi ^{177}Lu + 185-117 mCi ^{90}Y	Efficacy, toxicity	6-12 months after the end of PRRT	liver metastases	PFS, OS	CT or MRI (RECIST)	univariate	Yes, was predictor of shorter OS; $p < 0.03$
Yalchin S et al (UK)	2017	retrospective	133 (59 M, 74 F)	Midgut NET	^{90}Y and/or ^{177}Lu	4 cycles (usually); mean activity of 7.4 GBq per cycle	Efficacy, predictors of survival	3 months after the end of PRRT	≤ 50 liver tumor burden	progression or death a 1 year, OS	CT or MRI (RECIST 1.1)	multivariate	Yes, is a strong predictor of response, PFS and OS; $p < 0.004$ (response), $p < 0.0005$ (PFS), $p < 0.0005$ (OS)
Sabet A et al (Germany)	2015	retrospective	61 (34 M, 27 F)	G1-G2 SI-NET	^{177}Lu	4 cycles (usually); mean activity of 8.1 GBq per cycle	Efficacy, predictors of survival	3 months after the end of PRRT	<25% liver involvement	PFS	CT or MRI (RECIST and SWOG criteria)	multivariate	No
Pencharz D et al (UK)	2017	retrospective	79 (36 M, 43 F)	G1-G2 GEP and thoracic NET	^{177}Lu	1-4 cycles; mean activity of 7.4 GBq per cycle	Efficacy, toxicity	6-8 weeks after the end of PRRT	liver tumor load, bone metastases	PFS	CT or MRI (RECIST 1.1)	multivariate	No
Sabet A et al (Germany)	2017	retrospective	22 (16 M, 6 F)	Pulmonary NET	^{177}Lu	4 cycles (usually); mean activity of 7.9 GBq per cycle	Efficacy, toxicity	3 months after the end of PRRT	≤ 50 liver tumor burden	DCR, PFS, OS	CT or MRI (RECIST 1.1)	multivariate	No
Katona BW et al (USA-CH)	2017	retrospective	28 (14 M, 14 F)	GEP-NET and Unknown origin	^{90}Y and/or ^{177}Lu	2.5 cycles (mean) per patient (range 1-7)	Efficacy, safety	within a year after the end of PRRT	<25% liver involvement	PFS and OS	CT or MRI (RECIST 1.1)	univariate and multivariate	No. Hepatic tumor burden involving $\geq 25\%$ of the liver parenchyma was not associated with statistically significant differences in PFS or OS.

Abbreviations: M, male; F, female; GEP, gastroenteropancreatic; SI, small intestinal; NET, neuroendocrine tumor; GBq, Gigabecquerel; mCi, millicurie; ORR, objective response rate; PFS, progression free survival; OS, overall survival; TTP, time to tumor progression; DCR, disease control rate; DFS, disease free survival; DSS, disease specific survival; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasonography; RECIST, Response Evaluation Criteria in Solid Tumors; SWOG, Southwest Oncology Group

longer in PET-negative patients in the prospective study from [55] ($p = 0.02$). Accordingly, DCR was better, but no significantly different, in PET-negative cases ($P = 0.16$). Data from Adnan et al., in their retrospective study which considered only mediastinal NETs, are consistent with what reported thus far, where lower lesional FDG uptake was associated with longer PFS ($p = 0.002$) and OS ($p = 0.043$) [2]. FDG PET predicted survival also in patients with high Ki 67 proliferation index (15–35%) in the retrospective study by [52]: the PFS in FDG negative patients was 65.5 months versus 23.0 months in the FDG-positive patients (no p value is reported though).

Finally, [18] did not confirm data about PFS. Median PFS in PET-positive patients was lower but not statistically different from PET-negative patients ($P = 0.058$). However, a significant correlation between a positive 18F-FDG PET and patient death ($P = 0.03$) was found. Moreover, other studies reported the possible role of FDG PET in predicting response to PRRT, with only descriptive data. In particular, a high ^{18}F -FDG SUV_{max} is associated with a poor outcome to PRRT and with disease progression [51, 53, 75]. This finding also emerged from a retrospective study [58] conducted on 22 patients with pulmonary NET.

3.2.4 “Negative studies”

In a prospective trial on progressive bronchial carcinoids [33] median PFS was lower in FDG PET-positive patients (15.3 months) than in PET-negative patients (26.4 months), but no significant differences were found ($p = 0.201$).

3.3 Tumor burden

Tumor burden (TB) has been evaluated as potential predictor of response to PRRT in sixteen studies conducted from 2003 to 2019. Table 4 shows all selected original articles where TB was evaluated as a predictive factor of response to PRRT. Overall, 1496 patients (807 males and 689 females) with NET were evaluated. One study is a prospective non-randomized phase II clinical trial, two papers are phase I dose escalation studies, while thirteen studies are retrospective. ^{177}Lu was employed in nine studies, ^{90}Y in two and both in five. The main parameter assessed as predictor of response to PRRT or associated with survival was the liver TB, however, authors considered even the presence of other metastatic sites, such as bone metastases, or resection of primary tumor. When liver TB was evaluated, different cut-off were applied, more frequently <25 or $<50\%$ of liver involvement. Several studies did not identify a precise cut-off of liver involvement to stratify patients. The patient populations were affected by neuroendocrine neoplasia (NENs) of the GEP tract in the majority of cases. Only four studies were performed on bronchial NENs or on mixed case series of GEP and thoracic NENs. Almost all patients treated with PRRT were affected by a metastatic and mainly progressive NET. Tumor burden was assessed by CT or MRI in all studies except one and response to treatment was evaluated according to the RECIST criteria in most studies. Five out of sixteen studies consider also the SWOG criteria and only one study evaluated tumor response to treatment by the WHO criteria.

Among sixteen papers that analyze liver TB, four papers [35, 59, 62, 63] did not find any significant result that attributes a predictive role to liver TB, one paper [12] describes the presence of liver metastases as a predictor of overall survival, and eleven identified liver TB as a predictor of response to therapy [6, 14, 18, 23, 24, 43, 46, 49, 50, 77, 82]. Both negative and positive studies comprise retrospective and prospective experiences and no particular features characterize a group relative to the other, nor regarding patient populations or radionuclide employed (^{177}Lu or ^{90}Y).

For instance, some article evaluated the impact of liver TB on ORR after PRRT. [43] observed that after PRRT DCR was achieved in 6 (54.5%) out of 11 patients with diffuse liver metastases and in 21 (91.3%) out of 23 patients without diffuse liver metastases ($p =$

0.01). Similarly, [82] observed that PR and SD at 1 year after PRRT were more frequent in patients with liver TB $\leq 50\%$ (70.8%) with respect to patients with liver tumor load $>50\%$ (38.6%; $p < 0.001$). Authors concluded that hepatic TB is a strong predictor of response to PRRT, of PFS and OS. However, two other studies [23, 63] failed to demonstrate a higher DCR in patients with a low liver TB. Additional reports evaluated the impact of liver TB on disease free survival (DFS) after PRRT. Most of these studies [18, 24, 43, 46, 62, 63, 82] reported in patients with low liver TB ($<25\%$ or $<50\%$, according to the different criteria considered to define the liver tumor load in each study) a statistically significant longer DFS, which ranged from 21 to 49 months after PRRT, relative to patients with a high liver TB where DFS was shorter (ranging from 8 to 28 months). A similar difference was also noted when comparing patients without and with bone metastases: OS was N.R. vs. 25.0 months ($p = 0.03$) and PFS was N.R. vs. 12.0 months ($p = 0.003$). Conversely, these findings were not confirmed by other studies [35, 49, 59] that reported a not significant different DFS when patients were stratified according to the liver TB.

3.4 Grade

Grade (G) has been evaluated as potential predictor of response to PRRT in seventeen papers (2 prospective, 14 retrospective, and 1 retrospective/prospective study -German registry) conducted from 2010 to 2019. Another three retrospective studies stratified the population on the percentage of Ki67 antigen expression [1, 15, 52] and one of them distinguished well-differentiate from poorly differentiated [15]. The population comprised 3561 patients with metastatic and almost all progressive NET, mainly gastroenteropancreatic. ^{177}Lu was employed in 11 studies, and both ^{90}Y and/or ^{177}Lu in 9. Number of cycles ranged from 1 to 8 and cumulative dose was usually between 18.5 and 31.6 GBq. Table 4 shows all selected original articles.

In 20 studies the role of grade in PRRT was analyzed in detail ([14, 17, 21–23, 32, 49, 59, 60] [24], [1, 5, 9, 15, 19, 35, 52, 61, 62, 82]), and this criterion showed an impact on response to PRRT in 14 ([14, 21, 23, 24], Horsch et al 2016, [1, 5, 9, 15, 19, 35, 52, 59, 61]). No association was noted between positive and negative studies and patient populations, sample size, study design or radionuclide employed (^{177}Lu or ^{90}Y).

3.5 “Positive studies”

In particular six papers defined grade as a predictor of PD [5, 14, 21, 35, 52, 59]. Campana et al. showed that higher grade in NETs is a risk factor for tumor progression after PRRT both at

Table 4 Studies assessing role of *ki67* index as predictor of different outcomes after PRRT. In light gray “Positive studies”, in gray “Negative Studies”

Study	Year	Type of study	N of subject (gender)	Patient population	Treatment received (¹⁷⁷ Lu/ ⁹⁰ Y)	Cycles/dose	Primary endpoint(s)	Time of evaluation of primary endpoint	Criteria	Outcome	Pathology assessment	Applied statistical analysis	Is the criterion predictive of response to therapy?
Ezziddin S. et al a (Germany)	2011	retrospective	81 (46 M, 35 F)	metastatic advanced GEP NET (radiological progressive disease in 77%)	¹⁷⁷ Lu	4 cycles (usually); mean activity of 7.9 GBq per cycle	Ki67- influence on tumor response	3 months after last cycle, then every 6 months	ki67	ORR	a) 38 surgical resection; 43 biopsy b) NS	univariate	Yes (G3 was predictor of tumor progression); p 0.001
Campana D. et al (Italy)	2013	retrospective	69 (37 M, 32 F)	sporadic advanced GEP NET (radiological progressive disease in 50.7%)	⁹⁰ Y (71%) or ¹⁷⁷ Lu (29%)	90Y 4 cycles, 10.3 GBq median cumulative dose; 177Lu 4 cycles, 25.2 GBq cumulative dose	Efficacy	6 months after last cycle and until PD	ki67 (G2 vs G1)	ORR-PFS	a) NS b) NS	univariate-multivariate	Yes (G2 was a risk factor of tumor progression.); p 0.003
Sabet A. et al (Germany)	2013	retrospective	68 (39 M, 29 F)	metastatic advanced GEP NET with Bone Metastases (radiological progressive disease not reported)	¹⁷⁷ Lu	4 cycles (usually); mean activity of 8.1 GBq per cycle	Efficacy and predictors of survival	3 months after last cycle, then every 6 months	ki67 >10%	ORR, TTP, OS	a) NS b) NS	multivariate	Yes (ki67 index is an independent predictor of shorter TTP and OS); 0.004 (TTP) 0.008 (OS)
Ezziddin S. et al a (Germany)	2014	retrospective	68 (35 M, 33 F)	metastatic advanced pan-NET (radiological progressive disease in 67.6%)	¹⁷⁷ Lu	4 cycles (usually); mean activity of 8 GBq per cycle	Efficacy	3 months after last cycle, then every 6 months	ki67 (G2 vs G1)	ORR - PFS and OS	a) NS b) NS	univariate-multivariate	Yes (G2 is associated with a shorter PFS even with a cut-off of 5%) tumor grading was an independent predictor of OS and PFS; p 0.04
Ezziddin S. et al b (Germany)	2014	retrospective	74 (42 M, 32 F)	metastatic advanced GEP NET (radiological progressive disease in 76%)	¹⁷⁷ Lu	4 cycles (usually); mean activity of 7.9 GBq per cycle	Predictors of survival	3 months after last cycle, then every 6 months	ki67 >10%	PFS and OS	a) 35 surgical resection; 39 biopsy b) NS	univariate-multivariate	Yes (ki67 index is an independent predictor of survival); p 0.004
Horsch D. et al (Germany)	2016	retrospective /prospective (registry)	450 (211 F, 239 M)	metastatic progressive NET	⁹⁰ Y (17%) or ¹⁷⁷ Lu (54%) or combined (29%)	1-8 cycles; mean activity of 5.38 GBq per cycle	Efficacy, toxicity	at last follow up (mean 24.4m)	G1 vs G2 vs G3	PFS, OS	a) NS b) N	univariate	Yes (grading influences OS, not PFS; significantly OS between G1 and G3, not between G1 and G2); p 0.0098 (OS)
Bodel L. et al (USA)	2016	prospective	54 (37 M, 17 F)	metastatic advanced NET (radiological progressive disease in 72%)	¹⁷⁷ Lu	1-4 cycles; median cumulative dose 18.5	Efficacy	3-6 months after last cycle	G1 vs G2 vs G3	ORR	a) NS b) NS	multivariate	Yes (grading was associated with PRRT outcome); p 0.004
Pencharz D. et al (UK)	2017	retrospective	79 (36 M, 43 F)	metastatic progressive NET (GEP, Lung, Other)	¹⁷⁷ Lu	1-4 cycles; mean activity of 7.4 GBq per cycle	Efficacy, toxicity	6-8 weeks after cycle	G1 vs G2 vs G3	PFS	a) NS b) NS	multivariate	Yes (G3 is associated with shorter PFS); p 0.04
Katona BW et al (US and CH)	2017	retrospective	28 (14 M, 14 F)	GEP NET and Unknown origin	⁹⁰ Y and/or ¹⁷⁷ Lu	2.5 cycles (mean) per patient (range 1-7)	Efficacy and safety	within a year after the end of PRRT	G1 vs G2 vs G3	PFS and OS	a) NS b) NS	univariate and multivariate	Yes. G3 group showed both shorter OS (p=0.04) and PFS (p=0.03) compared to G1 and G2 groups.
Baum RP et al. (Germany and NL)	2018	retrospective	1048 (593 M, 455 F)	advanced NET of different origins, mostly GEP-NET	⁹⁰ Y and/or ¹⁷⁷ Lu	mean 18.84 GBq (range 1.4 - 63.9)	Efficacy	not specified	G1 vs G2 vs G3	OS and PFS	a) NS b) NS	univariate and multivariate	Yes. G1 had better OS than G2, and G2 better than G3. PFS was shorter only in patients with G3 tumors (p<0.001), without any significant difference between G1 and G2 tumors
Nicolini S et al (Italy)	2018	retrospective	33 (16M, 17F) di cui 29 sottoposti a FDG-PET	inoperable or metastatic high grade GEP-NET	¹⁷⁷ Lu	4-5 cycles	Efficacy	3, 6, 12, 18 and 24 months after the end of treatment and every 6-12 months thereafter.	ki67 > 35%	PFS	a) NS b) Primary	na	Yes. DCR and PFS were significantly better in patients with a Ki-67 index of ≤35% than in those with a Ki-67 index of >35%.
Demirci et al (Turkey)	2018	retrospective	186	progressive and/or metastatic NET	¹⁷⁷ Lu	doses ranging from 3.7 to 8.1 GBq (mean 5.04 GBq) median of 6 cycles (range: 3-12)	Efficacy	not specified	G1 vs G2 vs G3	OS and PFS	a) NS b) NS	univariate	Yes. OS rates were 61.9, 52.2 and 38.4 months, respectively (p<0.05)
Carlsen EA et al (multicentric)	2019	retrospective	149 (76 M, 73 F)	G3 progressive and/or metastatic GEP-NET	⁹⁰ Y or ¹⁷⁷ Lu or ²¹¹ In (1 patient)	median 4 cycles (1-15), median activity of 18 GBq (4-85)	Efficacy and toxicity	not specified	ki67 ≥55%	OS and PFS	a) NS b) NS	univariate and multivariate	Yes. PFS and OS were significantly longer for patients with a Ki-67 21–54% (P<0.001).
Aalbersberg EA et al (NL and Germany)	2019	retrospective	782 (444 M, 338 F)	inoperable or metastatic NET	⁹⁰ Y and/or ¹⁷⁷ Lu	3-6 cycles	OS and PFS	not specified	ki67<5% and ki67<10%	OS and PFS	a) NS b) NS	Univariate and multivariate	Yes. lower PFS in patients with Ki-67< 5% and lower OS in patients with Ki67>10%
Cwikla J.B. et al (Poland)	2010	prospective	60 (28 M, 32 F)	metastatic progressive GEP NET	¹⁷⁷ Lu	1-4 cycles; up to 15.2 GBq (mean activity of 11.2 GBq per cycle)	Efficacy, toxicity	6 months after last cycle	ki67 (G2 vs G1)	ORR - PFS and OS	a) NS b) NS	multivariate	No (grade was not predictive of OS e PFS, but was predictor of ORR in G1 vs G2 only at 12 months); p <0.05
Ezziddin S. et al b (Germany)	2011	retrospective	42 (26 M, 16 F)	metastatic advanced GEP NET with Bone Metastases (radiological progressive disease not reported)	¹⁷⁷ Lu	4 cycles (usually); mean activity of 8.1 GBq per cycle	Efficacy	3 months after last cycle, then every 6 months	ki67 >10%	ORR - PFS and OS	a) 19 surgical resection; 23 biopsy b) NS	univariate-multivariate	No (propensity toward earlier progression with increased ki67>10%, but not statistically significant); p 0.083
Pfeifer A. K. et al (Denmark)	2011	retrospective	69 (33 M, 36 F)	metastatic progressive NET (GEP, Lung)	⁹⁰ Y (76%), ¹⁷⁷ Lu (23%)	1-3 cycles; mean cumulative 15.54 GBq	Efficacy, toxicity	not specified	G1 vs G2	ORR, PFS	a) NS b) NS	univariate	No, no difference on ORR (p 0.64 and PFS p (0.7) between low-grade NETs (G1) vs intermediate-high NETs (G2+3 case of G3); 0.03
Sabet A. et al (Germany)	2015	retrospective	61 (34 M, 27 F)	metastatic advanced small intestinal NET (radiological progressive disease in 75%)	¹⁷⁷ Lu	4 cycles (usually); mean activity of 7.9 GBq per cycle	Efficacy, toxicity	3 months after last cycle, then every 6 months	ki67 (</> 2%)	ORR, PFS	a) 40 surgical resection; 21 biopsy b) NS	univariate	No; p=0.238
Mariniello A. et al (Italy)	2016	retrospective	114 (81 M, 33 F)	metastatic advanced bronchopulmonary carcinoma	⁹⁰ Y (39%) or ¹⁷⁷ Lu (42%) or combined (18%)	cumulative activity 750-800 mCi 177Lu, 200-300 mCi 90Y, 357-179mCi 177Lu+ 185-117 mCi 90Y	Efficacy, toxicity	6-12 months after the end of PRRT	ki67	ORR - PFS and OS	a) NS b) NS	univariate	No at multivariate analysis (higher ki67% is a negative prognostic factor for OS and a risk factor for disease recurrence, but only at univariate analysis) ; p 0.003 (OS); p 0.006 (PFS)
Yalchin M. et al (UK)	2017	retrospective	133 (59 M, 74 F)	metastatic progressive midgut NET (radiological progressive disease not reported)	⁹⁰ Y (83.5%) or ¹⁷⁷ Lu (16.5%)	4 cycles (usually); mean activity of 7.4 GBq per cycle	Efficacy, predictors of survival	progression or death at 1 year	ki67 >10%	ORR, PFS and OS	a) NS b) NS	univariate - multivariate	No at multivariate analysis (Ki67% predictor of outcome (0.009), PFS (0.006) and OS (<0.0005) only at univariate analysis); 0.1(outcome), 0.052 (PFS), 0.09 (PFS)

Abbreviations: M, male; F, female; GEP, gastroenteropancreatic; NET, neuroendocrine tumor; GBq, Gigabecquerel; mCi, millicurie; ORR, objective response rate; PFS, progression free survival; OS, overall survival; TTP, time to tumor progression; na, not applicable; ns, not specified

univariate and multivariate analysis (G2 vs G1, p 0.003). [21] reported that ki67 index was higher in PD group than in the other response groups (p 0.001). A rate of 71% of G3 NETs was in PD after PRRT vs 11% in G1 + G2 NETs; p 0.001). No statistically difference was demonstrated between G1 and G2 tumors [21]. G3 tumors were also found to be associated with shorter PFS, together with gender, in a paper by [59]. [52] considered for their retrospective analysis only patients with high Ki67 proliferation index ($>15\%$) and found that DCR was 87% in patients with a Ki-67 index of $\leq 35\%$ (9% PR + 78% SD) and 30% in patients with a Ki-67 index of $>35\%$, although no p is reported. Ten studies reported grade as a predictor of OS [1, 5, 15, 19, 23, 24, 32, 35, 52, 61]. A paper by [24] focused on the predictors of long-term outcome after PRRT. Among different factors assessed at univariate and multivariate analysis, ki67 index proved to be the strongest predictor of OS. Tumors with ki67 $> 10\%$ showed earlier progression after PRRT compared to tumors with Ki67 $< 10\%$ (median PFS 19 vs 31 months) and this translated in a shorter survival time (median OS 34 vs 55 months, p 0.004). The same group [23] in a cohort of G1 and G2 panNET found that G2 is associated with a shorter PFS, when analyzed with WHO 2010 cut-off of ki67 2%, and even when the analysis was performed applying a cut-off of 5% (median PFS 24 vs 40 months, p 0.03). Moreover, the study demonstrated that tumor grading was an independent predictor of OS ($\leq 2\%$ vs $>2\%$, median OS not reached vs 49 months respectively). In fact, ki67 index ($\leq 2\%$ or $> 2\%$) remained significant (p 0.044) in the multivariate analysis among factors contributing to OS.

Best OS was achieved, in the large cohort of patients studied by [5], in the G1 group (88 months, p = 0.0025), followed by G2. G3 NENs were observed to have the shortest overall survival with 23 months. Compared to G2, OS of G1 patients was significantly longer and significantly shorter in the G3 group (p = 0.0023). PFS was found to be significantly shorter only in patients with G3 tumors (p $<$ 0.001), without any significant difference between G1 and G2 tumors [5].

Similar results were described by [35], in which study the only significant difference was between the G3 group and the other groups, with the first one showing both shorter OS (p = 0.04) and PFS (p = 0.03) [35]. [19] also found positive correlation between histological grade and OS rates (P $<$ 0.05).

A multi-institutional registry study with prospective follow-up [32], in a large cohort of 450 NET patients, reported that grading had no significant impact on PFS, but determined significant differences in OS between G1 and G3 groups (median OS 33 months for G3 tumors, p 0.0098). However, the statistically significance was not maintained between G1 and G2 groups. In a cohort of only G3 neoplasms (Ki67 $>$ 20%), Carlsen and collaborators defined two different populations on the base of Ki67 index (21–55% and $>$ 55%), finding that median PFS and OS were significantly longer for patients with

a Ki-67 21–54% (P $<$ 0.001); another parameter evaluated in the study was the grade of differentiation of the primary tumor: well-differentiated tumor had longer OS and PFS than poorly differentiated (P $<$ 0.001) even in an all-G3 neoplasms cohort [15]. Consistent with these results are the findings by [52], also considering only patients with a high Ki67 proliferation index; in this study, a significant difference in PFS (26.3 vs 6.8 months, p = 0.005) and OS (52.9 vs 12.6 months, p = 0.012) was found using a cut off of a Ki67 of 35%. A different stratification was operated by [1], dividing its large cohort of patients in four quartiles considering the Ki67 valor (Q1 $<$ 2%, Q2 2–5%, Q3 5–10%, Q4 $>$ 10%); in their study they found significantly lower OS for Q4 subgroup only when compared with Q1 subgroup (p = 0.01).

Sabet et al. in 2013 performed a retrospective analysis of a cohort of GEP NET with bone metastases (BM). The results of this paper demonstrated that ki67 $>$ 10% was associated with a shorter TTP (p 0.004). Furthermore, ki67 index was an important prognostic factor that had an impact on OS in this cohort of patients, remaining significant on multivariate analysis (ki67 $>$ 10% vs ki67 $<$ 10% median OS 30 vs 55 months, p 0.008) [61].

A study by Cwikla et al. in 2009 reported that the differences in OS and PFS in patients with G1 and G2 tumors were not statistically significant. On the contrary, G1 and G2 tumors were different in terms of ORR evaluated at 12 months by RECIST criteria (p $<$ 0.05) (Cwikla et al 2009).

3.6 “Negative studies”

Six studies [17, 22, 49, 60, 62, 82] reported no significant difference neither in ORR nor in survival (PFS or OS) according to G after PRRT. In some of these studies [49, 82] the influence of G on ORR, PFS and OS was significant only at univariate analysis but not maintained at subsequently multivariate analysis.

4 The NETest

The parameters so far described to predict tumor response and patient survival are all based on radiological, istological or nuclear evidences; different from that, the “NETest” consists of a liquid biopsy, evaluating in real time the transcriptional tumor profile (or its “gene signature”) by blood sample. The NETest aims at defining the neoplasm precise biological activity, including diagnostic accuracy, prognostic value, and predictive therapeutic assessment.

The push for the development of such test are to be found in some of the limitations of most prognostic and predictive factors for NENs evaluation, such as low reproducibility and high inter-variability. The diagnostic accuracy of this mRNA-

based evaluation seems to be able to identify all NEN types, including small non metastatic tumors.

Regarding the predictive efficacy of the NETest prior to PRRT, an algorithm that integrates specific gene transcripts with tissue Ki67 values (either from primary or metastasis) was developed by the authors to generate a PRRT Predictive Quotient (PPQ) characterized by two prediction outputs: “PRRT-responder” or “PRRT-non-responder”. The authors developed and validated the PPQ in three prospective studies, enrolling a total of 158 ¹⁷⁷Lu-PRRT treated patients: in these different cohorts, fifty-one marker genes were measured to best predict PRRT efficacy and it was observed that PPQ correlated accurately with PRRT both in responders (97%) and in non-responders (91%); even changes in gene expression reflected in treatment response assessment scored with RECIST. Conversely, no gene signature is available at the moment for the assessment of the risk for myelo- or nephrotoxicity in PRRT [10]. They conclude that the NETest showed results thus far unmatched by other commonly used markers.

The impressive results showed in the paper by [10] are undoubtedly promising, still, yet to be confirmed in other studies, which are certainly eagerly needed, in order to further assess the value and accuracy of NETest in diagnosing and predicting outcome in patients with NETs.

5 Discussion

PRRT is now a well defined therapeutic option to treat GEP NET patients after failure of SSA, while predictors of tumor response to PRRT and patient survival after treatment has not yet been found.

The present study tried to define the identikit of the “perfect patient” to candidate to PRRT. However, to distinguish between predictors of response factors and prognostic factors is challenging. The inhomogeneous distribution of primaries, small sample size of the studies and different outcomes taken into consideration, together with the different follow up and timing of evaluation, may have hampered the chance to identify which patients may benefit from PRRT more than others in terms of survival or tumor response.

Regarding **primary origin**, GEP NET seem to be more responsive than non-GEP NET, both in terms of ORR [4] than PFS [4, 5], while among the GEP tumors, panNET show a better ORR than small intestinal NET[60].

If the studies reporting primary site to be a predictor factor of response to PRRT are few, little more are the ones showing absence of any correlation between primary tumor and ORR [17, 59, 68, 70, 78, 79]. The reported evidence that panNET respond better than small intestinal NET, but without any significant difference in PFS, is likely to correlate to the known phenomenon of shorter PFS of patients with panNET despite a more pronounced initial response to PRRT in terms

of ORR [44, 46]. In the setting of NEN with unknown primary, PRRT is a potentially effective therapeutic option, although there are not univocal data in literature [3].

Although also concerning **tumor burden** (TB) no concordant conclusions can be drawn, most of these studies ([18, 23, 24, 46] e [43, 77, 82], [49], Kolasinska-Cwilla et al.) reported, in patients with low liver TB (<25% or <50%, according to the different criteria considered to define the liver tumor load in each study), a statistically significant longer DFS after PRRT than in patients with a high liver TB (DFS range 21–49 months vs 8–28 months). Not only the presence of liver metastases, but also the overall tumor load, including other metastatic sites and even the primary tumor (if not resectable), should be taken into account when considering PRRT as appropriate choice for patients with advanced NETs. For instance, some evidences reported that patients with bone metastases had a higher risk of progression after PRRT than those without bone metastases [46]. Similarly, the stage of disease seems to significantly affect the hazard ratio for disease progression after PRRT [14]. In summary, some evidences from retrospective studies suggest that patients with a low TB, especially in the liver, may benefit most from PRRT. Therefore, waiting for tumor progression before PRRT administration or choosing PRRT for patients with a large tumor load might be not appropriate. The TB must be included and carefully weighed in the multidisciplinary discussion of the individual patient for the indication to PRRT.

Somatostatin receptor imaging is a mandatory prerequisite for the use of PRRT. First studies were based on Somatostatin Receptor Scintigraphy (SRS) with ¹¹¹In-pentetreotide (Octreoscan) but, in recent years, ⁶⁸Ga-DOTA-peptides PET/CT showed a better diagnostic performance than SRS. At now, ⁶⁸Ga-PET represents the method of choice for the “in vivo” evaluation of SSTR expression, allowing also the calculation of semiquantitative parameters such as SUVmax and improving imaging resolution. At this purpose, the collection of further data with the larger number of PET scans performed today, will allow us to draw conclusion in a comparative, retrospective analysis including the Octreoscan era. Among the papers analyzed, a half identified SUVmax as a predictor of response to therapy, whereas the remaining half either did not find significance or identified other parameters able to predict outcome of PRRT treatment. Three studies identified a SUVmax cut-off to select patients for PRRT, but to establish the potential ability to predict response to PRRT further studies are needed. In conclusion, Gallium uptake is an inclusion criterion for PRRT, but poorly correlates with response to therapy and it is not a predictive factor in an individual patient. This confirms that the expression of sstr is not the unique determinant of efficacy of PRRT [24].

On the contrary, **¹⁸F-FDG PET** seems to have a role in predicting disease progression, tumor response and survival in patients with advanced NETs, treated with PRRT. Most studies suggest that the patients with negative baseline scan may benefit from PRRT more than positive patients, also showing that a high ¹⁸F-FDG SUV_{max} is associated with a poor outcome to PRRT and with disease progression [51–53, 75]. Similar results also emerged in 22 patients with pulmonary NET, evaluated retrospectively [58]. Therefore, **¹⁸F-FDG PET** must be taken into account during therapeutic decision-making and multidisciplinary assessment of different patients.

The most interesting and promising criterion to predict response to PRRT seems to be **ki67 index**. Although in general the ki67 index is being recognized as a powerful determinant of survival in patients with GEP NETs and it is known as a major prognostic factor for NETs [56, 57, 65], its relevance in metastatic disease and potential cutoff values for the different treatment modalities are still undefined because of a lack of data. Keeping this concept in mind, nevertheless we have found many evidences in the literature that attribute to the degree a predictive value of response (ORR) or survival (PFS) after PRRT [1, 5, 9, 14, 15, 19, 21, 23, 24, 32, 35, 52, 59, 61].

ki67 index proved to be the strongest predictor of outcome in that patient cohort [24]. Authors reported that, even though G2 tumors with a ki67 index >10% respond in a similar manner to lesions with ki67 < 10% (accordingly to their previous results above stated), G2 NENs with ki67 > 10% show earlier progression after PRRT (median PFS of 19 vs 31 months). Although it is well known that grade affect prognoses of NENs in general, this evidence shows that grade provides prognostic stratification in a uniformly treated cohort of PRRT pretreated patients.

Moreover, [14] confirmed the role of grade as crucial therapeutic prognostic factors for response to PRRT in NETs. In fact, grade was a risk factor for PD at multivariate analysis (NET G2 vs NET G1, HR 3.481, $p = 0.003$). Similar findings were reported in another five recent studies [1, 5, 15, 35], where different populations were analyzed and different Ki67 proliferation index thresholds used, but all found significance about longer survival associated with lower grade.

Again, the recent study by [9] demonstrated that multiple regression analysis identified only grading as factors associated with PRRT outcome ($p = 0.004$), a part from the new promising NET test.

Proliferation index calculated by ki67 labeling has some limitation that could influence part of these reported results. One of these limits is the intratumoral heterogeneity of ki67 index [28]. Although it is well known that Ki67 may differ between primary lesion to synchronous or metachronous metastases and even between two different sites of metastases, [28] in none, but one, of cited papers it is specified whether the pathology sample was harvested from the primary or

metastatic lesions. The origin from surgical specimen or simple biopsy was reported only in the 25% of the considered report, as well. Anyway, despite such limitation and potentially confounding factors, evidence about the predictive role of grade on PRRT was found by most of the authors. In this respect, to overcome issues of temporal and spatial inaccuracy of ki67 index, an alternative tool such as a FDG PET could provide a whole imaging of the aggressiveness of tumor, with a picture of all metastatic sites together and at same time ([7], Garin et al 2009).

However, we must to consider that other studies ([22, 49, 60, 62, 82]) in literature do not define grade as predictor of response after PRRT and one study reported some conflicting, but finally negative, results [17]. Another limit of these conclusions about grade is that some authors in their papers consider grade category (WHO 2010, G1, G2, G3 groups), while others consider different cut-off of ki67 such as 2%, 5%, 10% and 20%. A cut-off of ki67 has not been univocally identified.

Finally, we must consider that PRRT efficacy is affected by previous therapies and little evidence is available about the appropriate position of PRRT in the NET treatment sequence. In this respect it would have been of great interest to assess the response to PRRT based on the positioning of this therapy: in first, second line or further lines. However, of course, this data is not reported in all studies in a homogeneous way. Two of the wider and most recent case series have only partially analyzed the problem [1, 5].

Baum et al., out of a study population of more than 1000 patients, showed a significant disadvantage in terms of OS in a subgroup of patients who had received PRRT after more than three previous lines, and who represented around 19% of the enrolled population. In contrast, statistically longer OS was recorded in the group of second-line PRRT-treated patients (28% of patients enrolled).

This data, however, can also be interpreted as a consequence of the fact that OS is a factor that reflects patient's prognosis and it is evident that a patient, who has already performed more than 3 treatment lines, is later in his history natural disease. The outcome of these patients will be probably more influenced by their advanced stage than sequence of therapies received. In the series published in 2019 from Aalbersberg et al., while reporting the percentages of treatment naive patients, of those in the first, second or subsequent lines, then does not analyze the response based on treatment line. On the other hand, a lower effectiveness of PRRT when performed after chemotherapy or interferon is reported. The NETTER-1 trial [74] demonstrated a lower risk of disease progression or death of 79%, in a setting of second line treatment, after failure of "cold" somatostatin analogues. For the future, further insight on sequence will be derived from the NETTER-2 trial, although it will be conduct on a different population (clinicaltrials.gov).

Amongst future prospective, the recent study by [10] demonstrated that an algorithm including circulating NET transcripts and Ki67 proliferation index from primary or metastatic lesions correlated accurately with PRRT responders vs non responders and predicted PRRT efficacy. The gene signature that characterizes the NETest showed promising and impressive results on discerning such patients, but not enough studies have confirmed these results so far and NETest, to date, is not routinely performed.

In conclusion, to date we have mostly prognostic (tumor burden, FDG uptake, grade) than predictive factors to predict efficacy for PRRT. The perfect patient, selected by Gallium DOTA-peptide PET uptake (or other somatostatin receptor imaging), will be likely characterized by a FDG PET negative scans, a relatively limited liver TB, a ki67 index <20% and will respond to PRRT irrespective to primary tumor origin. Nevertheless, at this moment the identikit of the perfect patient for PRRT therapy is a puzzle without some pieces. Still we cannot disregard a multidisciplinary discussion of the individual case to select the patients who will mostly benefit from the PRRT treatment.

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Compliance with ethical standards

Declaration of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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