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ORIGINAL ARTICLE

Radiolabelled somatostatin analogue treatment in gastroenteropancreatic neuroendocrine tumours: factors associated with response and suggestions for therapeutic sequence

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Abstract
Purpose Peptide receptor radionuclide therapy (PRRT) is a relatively new treatment modality for patients with unresectable or metastatic gastroenteropancreatic neuroendocrine tumours (GEP NETs). The aim of this study was to determine the time to progression of patients treated with PRRT and to identify the prognostic factors related to treatment response.
Methods Patients with sporadic GEP NETs prospectively treated with PRRT were retrospectively analysed. The primary end point was progression-free survival (PFS).
Results A total of 69 patients (37 men and 32 women; 45 with pancreatic and 24 with gastrointestinal lesion; 22 NET G1 and 41 NET G2) were treated with ^{90}Y or ^{177}Lu. The objective response rate was 27.5 % (partial response, PR), while 50.7 % had stable disease and 23.2 % had progressive disease. Significant differences in PFS were observed in relationship to the stage of the disease (44 months for stage III, 23 months for stage IV), the evidence of a PR 6 months after the end of the PRRT (39 months in patients with a PR, 22 months in patients without a PR) and previous transarterial chemoembolization (TACE, yes 13 months vs no 31 months). Stage IV, NET G2 and previous TACE were found to be significant factors for tumour progression at multivariate analysis.
Conclusion Low tumour burden and a low proliferation index represent independent prognostic factors for long PFS, while previous chemoembolization techniques represent independent prognostic factors for early tumour progression and shorter PFS. Our data suggest that chemoembolization techniques to reduce the hepatic tumour burden should be avoided.

Keywords ^{177}Lu-DOTATATE · ^{90}Y-DOTATOC · Neuroendocrine tumours · Radiotherapy · Somatostatin receptors · Therapeutic chemoembolization

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Introduction

Neuroendocrine tumours (NETs) are rare neoplasms, having an incidence of 5.25/100,000 age-adjusted for the 2004 US standard population [1]. They are considered indolent tumours, due to slow growth and a relatively good prognosis. Overexpression of somatostatin receptor subtypes (mainly sst_2) on the membrane of the NET cells [2, 3] justified the

use of somatostatin analogue treatment and peptide receptor radionuclide therapy (PRRT). When metastasized, treatment with somatostatin analogues reduced hormonal overproduction and achieved symptomatic relief in most cases, but it was rarely successful in terms of tumour size reduction [4–6]. However, it has recently been shown that long-acting somatostatin analogues significantly lengthen the time to tumour progression as compared to a placebo in patients with functionally active and inactive metastatic midgut NETs [7].

The use of radiolabelled somatostatin analogues is a relatively new treatment modality for patients with unresectable or metastatic gastroenteropancreatic (GEP) NETs. The most extensively studied radiopeptides for PRRT, derived from phase I-II trials, are ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE [8–14]. Despite the differences found in the various available studies, complete, partial and minor response was registered in up to 46 % of the patients. A clear survival benefit was also reported after the use of either ^{90}Y-DOTATOC [11, 14] or ^{177}Lu-DOTATATE [12].

The aim of this study was to determine the time to progression of patients treated with radiolabelled somatostatin analogues and to identify the prognostic factors related to treatment response.

Materials and methods

Study design and patients

The study design consisted of a multicentre, retrospective analysis of prospective institutional databases. The study included all consecutive patients with GEP NET treated with PRRT from November 1999 to September 2010 who were followed at the participating centres (i.e. Verona, Negrar, Rome and Bologna).

The inclusion criteria were: (1) a histologically confirmed diagnosis of sporadic GEP NET, (2) measurable (according to the RECIST criteria) and advanced disease not suitable for radical surgery or residual disease after debulking surgery, (3) positive ^{111}In-DTPA-octreotide (OctreoScan®) scintigraphy or positron emission tomography (PET) with ^{68}Ga-DOTANOC/TOC, (4) PRRT treatment with either ^{177}Lu-DOTATATE or ^{90}Y-DOTATOC and (5) radiological assessment every 6 months (±1 month) during the follow-up until disease progression.

At baseline evaluation, all patients underwent a clinical evaluation, routine haematology, liver and kidney function tests, a computed tomography scan (CT) and/or magnetic resonance imaging (MRI) and somatostatin receptor scintigraphy (or PET/CT with ^{68}Ga-DOTANOC/TOC). In order to undergo the PRRT, all patients gave their informed written consent, and the therapy was approved by the local Ethics Committee. Routine haematology, liver and kidney function tests were performed before each cycle of therapy as well as at follow-up visits. For renal protection purposes, all patients were treated with amino acids before and after the injection of the tracers [8]. The intratherapeutic biodistribution of the radiopeptide was assessed using planar whole-body imaging after each cycle of therapy.

The CT scan (or MRI) was repeated 4/6 months after the end of the therapy and every 6 months (±1 month) until disease progression according to RECIST criteria (unless clinical conditions required shorter intervals). Somatostatin receptor scintigraphy or PET/CT with ^{68}Ga-DOTANOC/TOC was repeated yearly.

Clinical response and toxicity of the PRRT after each cycle of therapy was assessed. After PRRT, the clinical response was considered to be positive when there was a greater than 50 % reduction of diarrhoea and/or flushing in carcinoid syndrome, diarrhoea in Verner-Morrison syndrome, and diarrhoea and abdominal pain in Zollinger-Ellison syndrome. The toxicity was evaluated using the Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Data analysis

All data were prospectively collected at the centre where the patient had been enrolled. A unique computerized data sheet was created, and data regarding demographic, clinical and pathological features were retrospectively analysed. The histological specimens were examined by an experienced pathologist at each centre. When required, additional centralized revision of the tumour specimens was performed. The tumours were classified according to the 2010 WHO classification [15] and the novel tumour node metastasis (TNM) classification/G grading system [16, 17]. The Ki-67 proliferation index was expressed as a percentage based on the count of Ki-67-positive cells in 2,000 tumour cells in areas of the highest immunostaining using the MIB1 antibody (DBA, Milan, Italy). The tumours were measured and scored according to the RECIST criteria [18]. Progression-free survival (PFS) was defined as the interval between the beginning of the therapy and the time of progression of disease (PD). PFS was measured using the Kaplan-Meier method, and the results were compared using the log-rank test. Analysis of the predictive risk factors for PD was carried out by univariate and multivariate analysis using the Cox proportional hazards method. Risk factors were expressed as hazard ratios (HR) [95 % confidence interval (CI)]. The multivariate model was constructed using the forward stepwise method after including all variables. All analyses carried out for risk factors are listed in the tables. The distribution of the continuous variables was reported as median and interquartile range (IQR, 25th to 75th percentiles). The comparison between the subgroups was carried out using Pearson's chi-square test (Fisher's exact test was used when

necessary) or the Mann–Whitney U test for continuous variables. The p value was considered significant when less than 0.05. The statistical analysis was carried out using dedicated software (SPSS version 19.0, SPSS Inc.).

Results

Study population

One hundred and thirty-one patients with GEP NETs were enrolled at the participating centres. Of these, 62 patients (47.3 %) were excluded, 11 because the radiological assessment during follow-up was not available, 25 because the PRRT had not been concluded at the time of the data collection and 26 because they were re-treated with supplementary doses of ^{90}Y or ^{177}Lu before assessment of disease progression. Thus, a total of 69 patients were included in the final analysis. The characteristics of all 69 patients are listed in Table 1. There were 37 men and 32 women with a median age of 57.6 years (IQR 50.0–65.5 years). In 45 of the 69 patients (65.2 %), the primary lesion was located in the pancreas, whereas in 24 (34.8 %) it was in the gastrointestinal (GI) tract (21 in the ileum, 1 in the duodenum, 1 in the colon and 1 in the appendix). According to the 2010 WHO classification, 22 patients (31.9 %) had a NET G1 and 41 (59.4 %) a NET G2. In 6 of the 69 patients, histological revision was not possible due to the scarcity of the tissue samples.

Fifteen (21.7 %) patients had functioning tumours (ten carcinoid syndrome, three Zollinger-Ellison syndrome, one Verner-Morrison syndrome and one symptomatic hypercalcaemia). At the beginning of the PRRT, 35 patients (50.7 %) had PD, while the remaining 34 patients had stable disease (SD, 19 naïve patients and 15 who had undergone previous treatment: 15 with somatostatin analogues, 2 with chemoembolization and 3 with chemotherapy).

Treatment with radiolabelled somatostatin analogue

Forty-nine (71.0 %) patients were treated with ^{90}Y-DOTATOC, while 20 (29.0 %) were treated with ^{177}Lu-DOTATATE. For the ^{90}Y-DOTATOC group, the median number of therapy cycles was 4 (IQR 4–5) and the median time to therapy was 7 months (IQR 6–9 months). The median cumulative dose of radiolabelled somatostatin analogue administered was 10.3 GBq (IQR 8.8–11.8 GBq) with a median dose per cycle of 2.2 GBq (IQR 2.0–2.6 GBq).

For the ^{177}Lu-DOTATATE group, the median number of therapy cycles was 4 (IQR 4–5) and the median time to therapy was 9 months (IQR 6.25–11.75 months). The median cumulative dose of radiolabelled somatostatin analogue administered was 25.2 GBq (IQR 19.0–27.2 GBq) with a median dose per cycle of 5.3 GBq (IQR 3.9–7.2 GBq).

Efficacy

At the first check-up after the last cycle of PRRT, 19 patients (27.5 %) had a partial response (PR, 31.1 % of those with pancreatic lesions and 20.8 % of those with GI tumours, p= 0.363), 50.7 % had SD (40.0 % of those with pancreatic lesions and 66.7 % of those with GI tumours, p=0.070) and 23.2 % had PD (28.9 % of those with pancreatic lesions and 12.5 % of those with GI tumours, p=0.124). In the 15 patients with functioning tumours, PRRT led to a subjective improvement of symptoms in 13 patients (86.7 %) (10 with carcinoid syndrome, 2 with Zollinger-Ellison syndrome and 1 with Verner-Morrison syndrome); 2 (13.3 %) did not have any clinical benefit.

The potential prognostic factors for predicting a PR or PD at 6 months after therapy are reported in Table 1. The significant factors correlated with PD were baseline tumour progression and previous treatment with transarterial chemoembolization (TACE). Regarding TACE, 9/12 (75 %) patients had a progressive disease after PRRT. In six patients, the progression after TACE was in and around the chemoembolized lesion(s), whilst in three patients progression was both around the chemoembolized lesion(s) and in other segments of the liver (Fig. 1a, b). The only significant factor correlated with a PR was the use of ^{177}Lu-DOTATATE as a radiolabelled somatostatin analogue.

Predictors for tumour progression

At univariate analysis, the variables considered as risk factors for tumour progression after PRRT are summarized in Table 2. The major risk factor for tumour progression was the absence of tumour response at the first check-up after the last cycle of PRRT (HR 4.021, p=0.008). Stage IV of the disease and previous TACE represent the other risk factors for tumour progression. The absence of tumour response after PRRT, histological evidence of NET G2 and previous TACE were also confirmed at multivariate analysis (Table 3, model A). If, at multivariate analysis, the factors known only after PRRT (type of radiopeptides and the absence of tumour response at the first check-up) were excluded, stage IV and previous TACE were found to be significant for tumour progression (Table 3, model B).

Progression-free survival

Overall, median PFS was 28 months (Fig. 2). Significant differences in PFS were observed in relationship to the stage of the disease (44 months for stage III, 23 months for stage IV, p=0.009), the evidence of a PR 6 months after the end of the PRRT (39 months in patients with a PR, 22 months in patients without a PR, p=0.004) and previous TACE (yes

Table 1 General features of the 69 patients treated with PRRT overall and according to the response to therapy

			Progressive disease 6 months after therapy					Partial response 6 months after therapy				
	Total (n=69)		Yes (n=16)		No (n=53)		p	Yes (n=19)		No (n=50)		p
Characteristic	n	%	n	%	n	%		n	%	n	%	
Sex												
Male	37	53.6	8	21.6	29	78.4	0.740	12	32.4	25	67.6	0.328
Female	32	46.4	8	25.0	24	75.0		7	21.9	25	78.1	
Primary site												
Pancreas	45	65.2	13	28.9	32	71.1	0.124	14	31.1	31	68.9	0.363
Gastrointestinal	24	34.8	3	12.5	21	87.5		5	20.8	19	79.2	
WHO												
NET G1	22	31.9	2	9.1	20	90.9	0.060	4	18.2	18	81.8	0.249
NET G2	41	59.4	12	29.3	29	70.7		13	31.7	28	68.3	
Not evaluable	6	8.7										
Median Ki-67	3.7		5.0		3.0		0.181	4.0		3.0		0.178
IQR	1.4–7.0		2.3–8.0		1.0–7.0			2.2–11.8		1.0–6.9		
Stage												
III	15	21.7	2	13.3	13	86.7	0.494	3	20.0	12	80.0	0.534
IV	54	78.3	14	25.9	40	74.1		16	29.6	38	70.4	
Functional status												
Nonfunctioning	54	78.3	13	24.1	41	75.9	1.000	15	27.8	39	71.2	1.000
Functioning	15	21.7	3	20.0	13	80.0		4	26.7	11	73.3	
Previous treatments												
Surgery	38	55.1	10	26.3	28	73.7	0.496	10	26.3	28	73.7	0.802
TACE	12	17.4	6	50.0	6	50.0	***0.025***	2	16.7	10	83.3	0.489
Chemotherapy	9	13.0	1	11.1	8	88.9	0.674	3	33.3	6	66.7	0.699
Somatostatin analogues	67	97.2	15	22.4	52	77.6	0.413	19	28.4	48	71.6	1.000
Baseline tumour progression	35	50.7	12	34.3	23	65.7	***0.027***	9	25.7	26	74.3	0.731
Type of PRRT												
^{90}Y	49	71.0	13	26.5	36	73.5	0.364	10	20.4	39	79.6	***0.038***
^{177}Lu	20	29.0	3	15.0	17	85.0		9	45.0	11	55.0	
Median dose (GBq)	11.2		10.7		11.8		0.467	12.5		10.9		0.398
IQR	9.7–18.5		8.7–17.8		9.8–18.6			9.1–21.7		9.8–16.6		

NET neuroendocrine tumour, *IQR* interquartile range, *TACE* transarterial chemoembolization, *PRRT* peptide receptor radionuclide therapy. Values in boldface/italic: $p < 0.05$

13 months vs no 31 months, p=0.002, Fig. 3). No statistical difference was found according to tumour differentiation (median 35 months for NET G1 and 23 months for NET G2, p=0.077), primary site (pancreas vs GI: 23 vs 31 months,

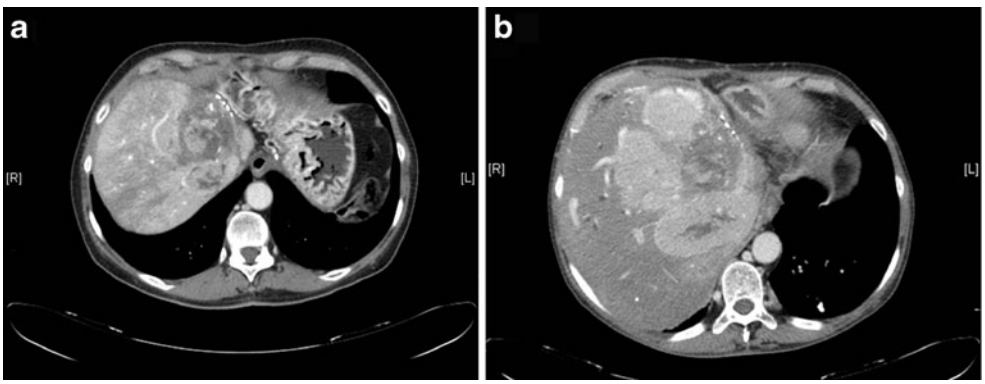


Fig. 1 A 57-year-old woman with liver metastases from a pancreatic NET (NET G2, WHO 2010). **a** Liver lesion after TACE. **b** Progression of the disease around the embolized lesion 6 months after PRRT with ^{177}Lu

Table 2 Risk factors for disease progression after PRRT during follow-up at univariate analysis

Variable	HR	95 % CI	*p*
Female gender	1.255	0.664–2.371	0.484
Primary tumour (pancreas vs GI)	1.420	0.739–2.730	0.293
WHO 2010 (NET G2 vs NET G1)	1.861	0.921–3.762	0.083
Stage IV vs III	***3.509***	***1.298–9.485***	***0.013***
Previous surgery	0.948	0.505–1.782	0.869
Previous TACE	***3.312***	***1.507–7.279***	***0.003***
Previous chemotherapy	0.939	0.364–2.418	0.896
Baseline tumour progression	1.616	0.857–3.049	0.138
PR 6 months after PRRT (no vs yes)	***4.021***	***1.428–11.326***	***0.008***
Type of PRRT (^{90}Y vs ^{177}Lu)	2.099	0.958–4.596	0.064

NET neuroendocrine tumour, *TACE* transarterial chemoembolization, *PR* partial response, *PRRT* peptide receptor radionuclide therapy. Values in boldface/italic: $p < 0.05$

p=0.285), baseline tumour progression (PD vs SD: 21 vs 34 months, p=0.130) and type of radiolabelled somatostatin analogue used for therapy (^{90}Y 23 months, ^{177}Lu 35 months, p=0.055).

Toxicity

In the 69 patients, nausea and vomiting within 24 h after treatment, due to the amino acid infusion, occurred in 11.6 % of the patients. In one case, acute diarrhoea grade 2 was observed. Haematological toxicity, grades 1 and 2, occurred in 29 patients (42.0 %), while grade 3 occurred in 1 case (1.4 %). Regarding renal toxicity, grade 1 occurred in seven cases (10.1 %).

Discussion

In clinical practice, treatment with radiolabelled somatostatin analogues has already been recognized as a promising tool in the management of patients with unresectable or metastasized NETs. Kwekkeboom et al. in 2008 and Imhof et al. in 2011 [12, 14] reported high tumour response rates and a long PFS for ^{177}Lu and ^{90}Y, respectively. However, these studies investigated the significant factors predicting disease-specific survival, but predictors for tumour response were not evaluated. The present study was aimed at detecting possible predictors of tumour response to treatment in a large and relatively homogeneous series of advanced GEP NETs treated with PRRT. Moreover, efficacy in terms of objective response rate and PFS were also evaluated.

The principal results of this study confirmed the important role of PRRT in the management of patients with locally advanced or metastatic NETs. In particular, the treatment with radiolabelled somatostatin analogues showed more efficacy in the presence of low tumour burden (stage III) and a low proliferation index (G1). Our study demonstrated the negative role of previous treatment with TACE in terms of objective response and PFS.

The central role of PRRT in GEP NETs is highlighted by the high objective response rate as well as a long PFS; a PR was observed in 28.8 % of the patients, while none had a complete response. Acknowledging the inherent problems of inter-study comparisons, our

Table 3 Risk factors for disease progression after PRRT during follow-up at multivariate analysis

Variable	HR	95 % CI	*p*
Model A			
WHO 2010 (NET G2 vs NET G1)	3.481	1.509–7.828	0.003
Previous TACE	3.526	1.518–8.189	0.003
PR 6 months after PRRT (no vs yes)	6.631	2.180–20.165	0.001
Model B			
Stage IV vs III	3.854	1.233–12.047	0.020
Previous TACE	2.707	1.215–6.034	0.015

Model A: multivariate analysis was performed with all of the factors reported in Table 2. Model B: multivariate analysis was performed without the factors which were evident only after PRRT (i.e. PR 6 months after PRRT and type of radiopeptides)

NET neuroendocrine tumour, *TACE* transarterial chemoembolization, *PR* partial response, *PRRT* peptide receptor radionuclide therapy

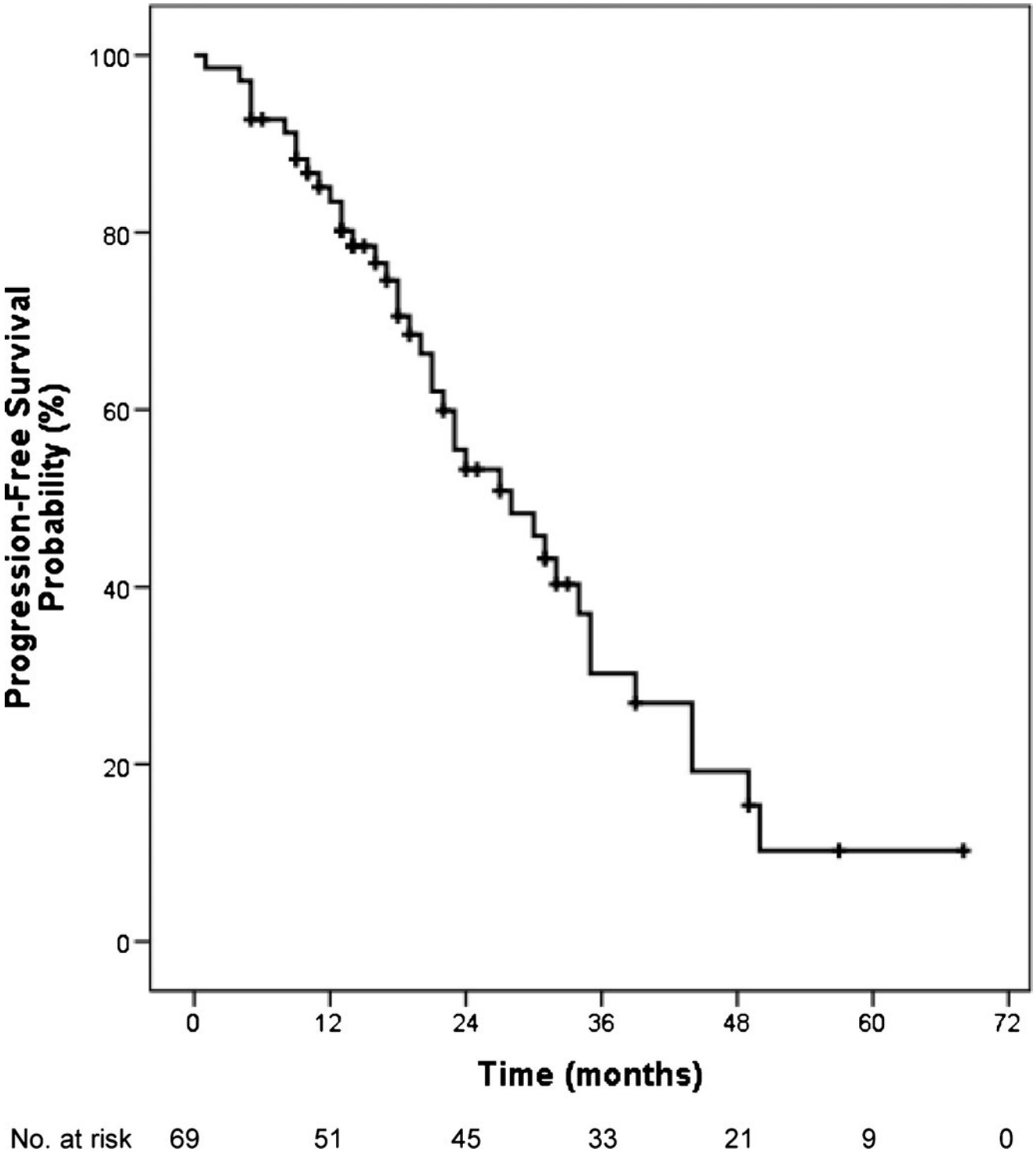
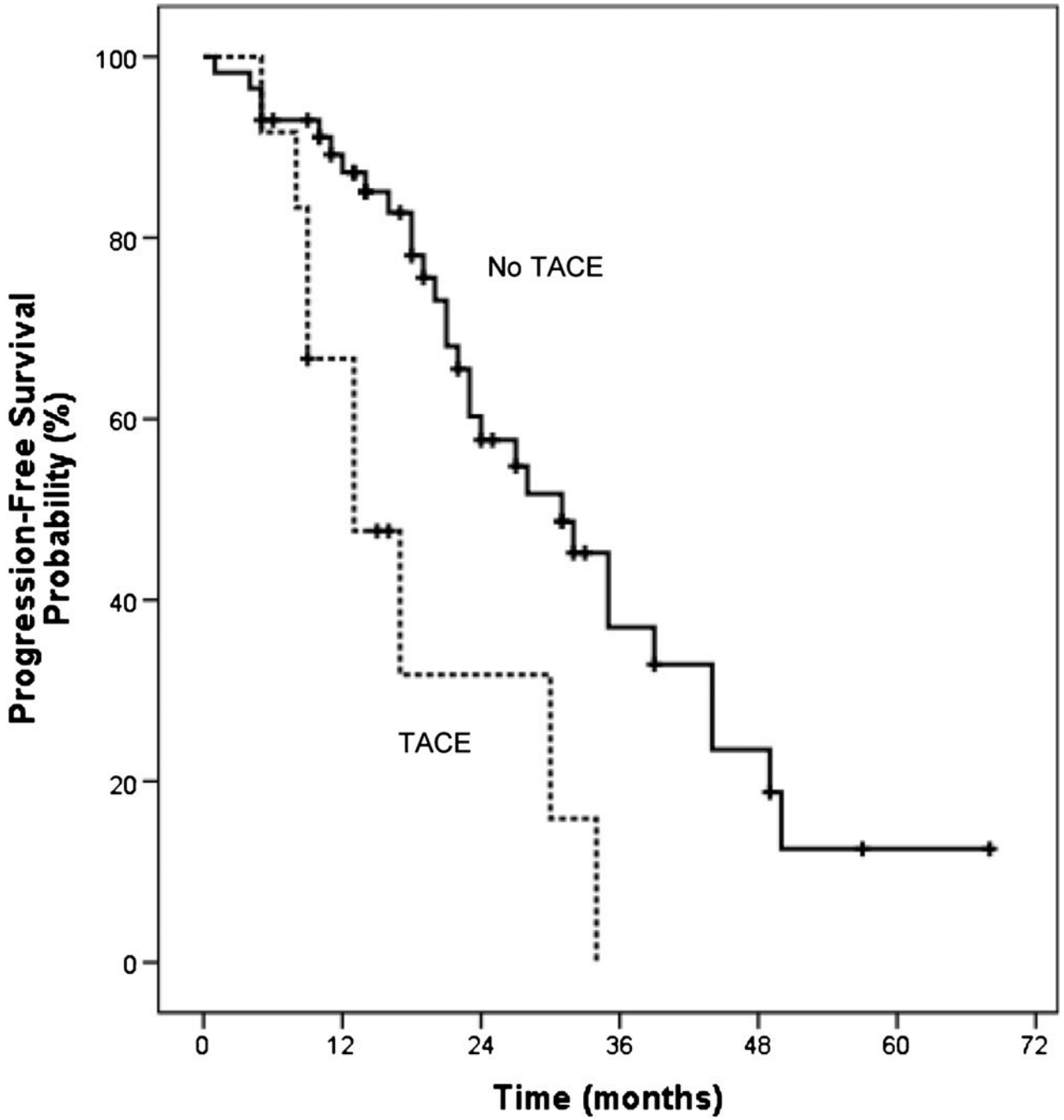


Fig. 2 PFS in 69 patients with GEP NETs treated with radiolabelled somatostatin analogues

results are better than those reported in studies regarding chemotherapy in GEP NETs, which are usually less than 20 % [19–21], or targeted therapies, such as sunitinib (9.3 %) [22] and everolimus (5 %) [23]. These data suggest a potentially strong role of PRRT in the reduction of the disease burden also in the setting of neoadjuvant therapy.

Regarding time to progression, PRRT has a very long PFS (28 months) [11, 12] when compared to that reported for chemotherapy (median PFS less than 18 months) [20,



No. at risk

No TACE	57	44	21	9	5	1	0
TACE	12	7	2	0	0	0	0

Figure 3.

Fig. 3 PFS in 69 patients with GEP NETs treated with radiolabelled somatostatin analogues, according to previous TACE

21] or other targeted therapies, such as sunitinib and everolimus (11.4 and 11.0 months, respectively) [22, 23].

The differences in terms of PFS were less evident if we considered only patients with progressive disease at the start of the PRRT (21 months). Interestingly, we did not find significant differences in median PFS according to the primary site of the tumours (GI vs pancreatic origins: 31 vs 23 months). Regarding pancreatic NETs, in our series, PRRT showed longer PFS when compared to that reported in a recent paper by Panzuto et al. in which the median PFS for metastatic pancreatic NETs, treated or not treated with antitumoural therapy (such as PRRT, somatostatin analogues and/or chemotherapy), was 15 and 7 months, respectively [24]. On the other hand, PRRT in GI NETs has a median PFS similar to that reported by Panzuto et al. (31 vs 36 months) in a large retrospective analysis of metastatic jejunoileal NETs [25].

Assessments of the factors which can identify patients who may benefit from PRRT demonstrate the role of tumour burden and the proliferation index. Tumour burden was a well-known significant predictor of disease-specific survival [12, 14]. In these studies, a significant correlation between survival and the extent of liver involvement was reported. In the present study the independent role of the stage of the disease in PFS after PRRT was documented. These data confirmed that PRRT is more efficacious in patients with limited disease and suggest it be initiated as early as possible.

An expected risk factor for tumour progression was the degree of the tumour proliferation index according to the WHO classification (NET G2 vs NET G1, HR 3.481, $p=0.003$ at multivariate analysis). In general, it is well known that Ki-67 is a major prognostic factor for NETs [26–28]. However, our data confirmed the role of tumour differentiation and Ki-67 as crucial therapeutic prognostic factors for response to PRRT in NETs as well.

However, the more relevant clinical result of the present study was that previous TACE was an independent risk factor for disease progression. This evidence has never previously been reported and may be due to the fact that embolization impairs the possibility of the radiopeptide reaching the ischaemic area. This finding might have an important implication in the algorithm and the sequence of therapeutic options. In fact, it is well known, as was also confirmed in the present study, that PRRT is more efficacious in the presence of minor tumour burden [12, 14]. In order to reach this end, it has been suggested that cytoreductive surgery and/or ablative therapies [i.e. TACE and radiofrequency thermal ablation (RFTA)] should precede PRRT courses. Our data suggested that chemoembolization techniques to reduce the hepatic tumour burden should be avoided.

This study might have some potential biases due to the retrospective evaluation and a certain degree of heterogeneity of the population enrolled. However, this population includes: (1) only GEP NETs (no lung or other sites) and (2) patients with advanced disease without re-treatment with supplementary doses. However, the heterogeneity of the population (i.e. pancreas vs gastroenteric, ^{90}Y vs ^{177}Lu, stage III vs stage IV, previous therapy) might represent, at the same time, a strength of the study, since it allows a better understanding of potential factors which might affect PRRT results. Univariable and multivariable analyses have been applied in order to reduce these potential biases due to the heterogeneity.

In conclusion, treatment with radiolabelled somatostatin analogues is an important therapeutic option in the management of patients with unresectable or metastasized NETs, allowing a high objective response rate and long PFS. Low tumour burden and a low proliferation index represent independent prognostic factors for long PFS, while previous TACE represents an independent prognostic factor for both early tumour progression and shorter PFS. These data confirmed the fact that PRRT should be performed discerningly in the sequence of therapeutic options and suggests that the pre-procedural use of TACE for reducing the hepatic tumour burden should be avoided. Prospective and comparative studies are necessary to confirm these data.

Conflicts of interest None.

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