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Peptide receptor radionuclide therapy with ^{90}Y -DOTATATE/ ^{90}Y -DOTATOC in patients with progressive metastatic neuroendocrine tumours: assessment of response, survival and toxicity

S Vinjamuri^{1,8}, T M Gilbert^{2,8}, M Banks³, G McKane¹, P Maltby¹, G Poston³, H Weissman⁴, D H Palmer⁵, J Vora⁶, D M Pritchard⁷ and D J Cuthbertson^{*,2}

¹Department of Nuclear Medicine, Royal Liverpool University Hospital, Liverpool, UK, L7 8XP; ²Department of Obesity and Endocrinology, University of Liverpool, Liverpool, UK, L69 3BX; ³Department of Hepatobiliary Surgery, University Hospital Aintree, Liverpool, UK, L9 7AL; ⁴Department of Nuclear Medicine, University Hospital Aintree, Liverpool, UK, L9 7AL; ⁵Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK, L69 3BX; ⁶Department of Diabetes and Endocrinology, Royal Liverpool University Hospital, Liverpool, UK, L7 8XP and ⁷Department of Gastroenterology, University of Liverpool, Liverpool, UK, L69 3BX

Background: Peptide receptor radionuclide therapy (PRRT) is an established treatment for patients with metastatic neuroendocrine tumours (NETs), although which factors are associated with an improved overall survival (OS) remains unclear. The primary aim of this study is to determine to what extent a radiological response to ^{90}Y -DOTATOC/ ^{90}Y -DOTATATE PRRT is associated with an improved OS. The association of biochemical and clinical response to OS were assessed as secondary outcome measures.

Methods: A retrospective analysis was conducted on 57 patients: radiological response was classified using RECIST criteria, biochemical response was classified using WHO criteria and clinical response was assessed subjectively. Responses were recorded as positive response (PR), stable disease (SD) or progressive disease (PD), and survival analysed.

Results: Radiological response was achieved in 71.5% (24.5% PR, 47% SD) and was associated with a greater OS (51 and 56 months, respectively), compared with PD (18 months). A biochemical or clinical response post PRRT were not associated with a statistically significant improvement in OS. However, when combined with radiological response a survival benefit was observed according to the number of outcomes (radiological, biochemical, clinical), in which a response was observed. Mild haematological toxicity was common, renal toxicity was rare.

Conclusion: In patients with progressive metastatic NETs receiving ^{90}Y -DOTATOC/ ^{90}Y -DOTATATE PRRT, a radiological response with either a PR or a SD post therapy confers a significant OS benefit.

*Correspondence: Dr DJ Cuthbertson; E-mail: daniel.cuthbertson@liverpool.ac.uk

⁸These authors contributed equally to this work.

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Neuroendocrine tumours (NETs), occurring with a prevalence of 2–4 per 100 000 people, are usually slow growing tumours although many patients present with evidence of metastatic spread to lymph nodes or liver. These tumours not only produce a variety of hormones, giving rise to the characteristic carcinoid syndrome symptoms, but also express cell-surface peptide receptors, which may be useful for diagnostic and therapeutic purposes (Kulke and Mayer, 1999; Baudin 2007).

As curative surgical resection is an option in only a minority of patients, the main goals of the treatment are to provide symptom relief, retard tumour progression and improve overall survival (OS). A number of therapeutic modalities are available, including somatostatin analogues (SSA), interferon- α , hepatic artery embolisation, cytoreductive surgery or chemotherapy (Modlin *et al*, 2008). For patients with inoperable metastatic NETs, who have progressive disease (PD) or symptoms refractory to conventional medical therapy, peptide receptor radionuclide therapy (PRRT) is available, a treatment endorsed by the European Neuroendocrine Tumour Society (ENETS; Otte *et al*, 1998; Kwekkeboom *et al*, 2009).

PRRT primarily utilises one of two radioisotopes, ⁹⁰Yttrium (⁹⁰Y) or ¹⁷⁷Lutetium (¹⁷⁷Lu), attached to a SSA via the chelating agent DOTA. ⁹⁰Yttrium may be delivered as [⁹⁰Y-DOTA⁰,Tyr³] Octreotide (⁹⁰Y-DOTATOC) or as the newer [⁹⁰Y-DOTA⁰,Tyr³] Octreotate (⁹⁰Y-DOTATATE).

Although no randomised, placebo-controlled trials using PRRT exist, PRRT with ⁹⁰Yttrium-labelled SSAs has been shown to cause tumour regression and symptomatic benefit in the vast majority of patients (Waldherr *et al*, 2001, 2002; Kwekkeboom *et al*, 2005b; Imhof *et al*, 2011). Significant haematological toxicity occurs in only 10–20% of cases, although many patients have evidence of milder bone marrow suppression that may delay further treatment cycles. With use of reno-protective amino acid infusions, renal toxicity is uncommon.

We have previously demonstrated an improved OS in patients with metastatic NETs who derived a clinical (i.e., symptomatic) or radiological benefit from ¹³¹I-MIBG therapy (Nwosu *et al*, 2008). Thus, we sought to evaluate the efficacy, safety and toxicity of ⁹⁰Yttrium-PRRT in patients with metastatic NETs and determine to what extent the radiological response to PRRT, as the primary outcome measure, was associated with OS. Furthermore, we noted the association of biochemical and clinical response to survival as secondary outcome measures, and determined the time course of bone marrow suppression/toxicity post PRRT.

MATERIALS AND METHODS

Patients and study design. A retrospective review was performed on 67 patients (45 male, 22 female) with metastatic NETs who had received therapeutic ⁹⁰Y-DOTATOC or ⁹⁰Y-DOTATATE at the Department of Nuclear Medicine in the Royal Liverpool University Hospital between December 2003 and November 2012. The study was registered at the hospital audit department.

Case notes were retrieved for all 67 patients. Using these, along with the patient management systems, at both the Royal Liverpool University Hospital and University Hospital Aintree, Liverpool, the following information was recorded: patient demographics; date of diagnosis; time between diagnosis and first ⁹⁰Yttrium-PRRT; number of ⁹⁰Yttrium-PRRT treatments; primary tumour site; site of metastasis; previous treatments administered; symptoms pre- and post therapy; serum chromogranin A and 24 h urinary 5HIAA pre- and post therapy; imaging (CT/MRI) scans pre- and post therapy; and full blood count (FBC) and urea and electrolyte (U&E) results pre- and post therapy. Only those patients confirmed as having gastroenteropancreatic (GEP) or pulmonary NETs were included in the subsequent analysis.

Neuroendocrine tumours were confirmed in these patients by histological diagnosis; where this information was not available, the diagnosis was based upon elevated biochemical markers (including chromogranin A and/or 24 h urinary 5HIAA) plus cross-sectional (CT/MRI) and functional imaging supportive of a NET (positive uptake on OctreoScan/DOTATATE scans) (Covidien; Petten, The Netherlands).

Selection of patients for targeted therapy. All patients were selected for ⁹⁰Yttrium-PRRT following a consensus decision made at the supra-regional Neuroendocrine Tumour Multi Disciplinary Team meeting; an ENETS-accredited service delivered by the University Hospital Aintree and Royal Liverpool University Hospital.

All those selected for ⁹⁰Yttrium-PRRT had evidence of PD in 6–12 months before receiving therapy. Of those selected for treatment, 45% were referred for clinically PD refractory to optimal medical treatment, 33% demonstrated radiological progression and 22% had mixed symptomatic and radiological progression. Each patient was scheduled to receive three individual ⁹⁰Y-DOTAOC or ⁹⁰Y-DOTATATE treatments as part of a complete therapy cycle.

Administration protocol. Before therapy, baseline haematology (FBC) and renal function (U&Es) were assessed. Therapeutic long- and short-acting octreotide was stopped at least 4 weeks and 48 h, respectively, before delivery of radionuclide therapy and was not resumed until at least 7 days after. To reduce the renal uptake of the radiolabelled octreotide, an amino acid infusion (25 g lysine and 25 g arginine; Rolleman *et al*, 2003) and Gelofusin (Vegt *et al*, 2006) were co-administered alongside the 5 GBq (100–200 μ g) of ⁹⁰Y-DOTATATE or ⁹⁰Y-DOTATOC. Patients were admitted overnight after receiving the treatment. The usual therapeutic cycle consisted of three individual dose of ⁹⁰Y-DOTATATE or ⁹⁰Y-DOTATOC being administered to each patient at 10–12 weekly intervals.

Patients were administered ⁹⁰Y-DOTATOC before April 2008; from this date onwards patients were treated with ⁹⁰Y-DOTATATE. This meant that those patients whose therapy cycle crossed this date would have received treatment with both analogues. The change in treatment analogue was not a clinical decision but an issue with supply of the drug.

Assessing response and toxicity. Radiological, biochemical and clinical responses to therapy were assessed between 3 and 12 months following completion of the final ⁹⁰Yttrium treatment. Where multiple results for these outcomes were available due to serial investigations, those closest to the last treatment date were used. Because of the progressive nature of the patients' disease before ⁹⁰Yttrium-PRRT, a response to therapy for each outcome (radiological, biochemical and clinical) was deemed to have occurred if the patient exhibited disease regression (positive response, PR) or disease stabilisation (stable disease, SD), that is, 'disease control'.

Radiological response. Radiological response was assessed using the RECIST criteria (Eisenhauer *et al*, 2009). A PR to therapy was deemed to have occurred if patients demonstrated either a complete or partial response to therapy (>30% decrease in the sum of the longest diameter for all target lesions) as determined by RECIST criteria.

Progressive disease was taken as at least a 20% increase in the sum of the longest diameter of target lesions or the appearance of one or more new lesions. Stable disease was when there was neither sufficient tumour shrinkage to qualify for PR, nor sufficient increase to qualify for PD.

Biochemical response. Biochemical response was assessed, in accordance with WHO criteria, by analysing changes in serum

chromogranin A or 24 h urinary 5HIAA concentrations pre- and post-therapy as follows: PR, complete normalisation of, or a > 50% reduction in previously elevated serum chromogranin A or 24 h urinary 5HIAA levels; PD, a 25% increase in previously elevated serum chromogranin A or 24 h urinary 5HIAs; SD, neither sufficient reduction to qualify for a PR nor a sufficient increase to qualify for PD. Fasting serum chromogranin A concentration has been shown to be an independent prognostic factor in patients with metastatic NETs (Arnold *et al*, 2008).

Clinical (symptomatic) response. A positive clinical response was defined as patients reporting either complete resolution or a decrease in the intensity of symptoms. These symptoms included: abdominal pain, flushing, bloating, diarrhoea, weight loss, fatigue, sweats, breathlessness, vomiting, haemoptysis and anorexia. Progressive Disease was reported if an increase in symptom intensity/frequency occurred. Stable Disease was recorded following no change in symptoms.

Toxicity. Toxicity was assessed using the National Cancer Institute Common Terminology of Adverse Events v 4.0 (CTCAE). These criteria were applied to results from FBCs and renal function tests (U&Es) taken every 2 weeks over a 10-week period following each individual ⁹⁰Yttrium treatment.

Statistical analysis. Survival outcomes were plotted using the Kaplan–Meier method. In addition, we recorded the survival probabilities at 6, 12, 24 and 48 months. Log-rank tests were applied to test for evidence of a difference in survival curves between response groups. OS is quoted as median (months) with accompanying 95% confidence interval. Multivariable Cox regression modelling was used to compare response groups adjusting for baseline differences in age and serum chromogranin A concentration. We limited the number of variables examined in a multivariable model to 3 in order to satisfy the 10 events per variable rule of thumb for stable parameter estimates (Van Belle, 2002). As a result, we did not adjust for other variables that may have prognostic relevance such as proliferative (Ki67) index. Fisher's exact tests were used to assess the association between the observed clinical, biochemical and radiological responses. All results were considered statistically significant at the 5% level; no corrections were made for multiple comparisons. Statistical analysis was undertaken using Stata version 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. StataCorp LP, College Station, TX, USA).

RESULTS

Patient characteristics. Of the 67 patients, 61 patients were confirmed as having GEP or pulmonary NETs and were included in the subsequent analysis. Those excluded had diagnoses including pheochromocytomas, paragangliomas and medullary thyroid cancers. Of those identified as having a GEP or pulmonary NET, a further four patients were excluded due to a lack of sufficiently completed records giving a total 57 patients.

The mean age at the time of diagnosis was 53.7 years and therapy 57.4 years. The median time between diagnosis and treatment was 27 months (range 4–237).

The most common presenting symptoms were flushing, diarrhoea and abdominal pain (54%, 47% and 30%, respectively).

Primary disease sites included the small bowel (35%), pancreas (26%) appendix (7%) and lung (3.5%). The primary site could not be identified in 23% (Table 1). A histological diagnosis was available in 40 out of 57 patients: 35 patients had confirmed carcinoid disease and five had pancreatic NETs (three insulinomas, one glucagonoma and one somatostatinoma). The proliferative

Table 1. Baseline patient characteristics

Patient characteristic	Number of patients (%)
Total number of patients	57
Female	21 (37)
Male	36 (63)
Mean age at diagnosis (years)	53.7
Mean age at treatment (years)	57.4
Site of primary tumour	
Small bowel	20 (35)
Pancreas	15 (26)
Lung	2 (3.5)
Colon	1 (1.7)
Appendix	4 (7)
Stomach	1 (1.7)
Liver	1 (1.7)
Unknown	13 (23)
Site of metastasis	
Liver	53 (93)
Lymph nodes	16 (28)
Lung	4 (7)
Bone	11 (19)
Ovarian	2 (3.5)
Peritoneal	1 (1.7)
Presenting symptom	
Diarrhoea	27 (47)
Flushing	31 (54)
Abdominal pain	17 (30)
Weight loss	10 (17.5)
Fatigue/tiredness	9 (16)
Breathlessness	5 (9)
Sweats	5 (9)
Vomiting	3 (5)
Hypoglycaemia	1 (1.7)
Jaundice	1 (1.7)
Dizziness	1 (1.7)
Anxiety	1 (1.7)
Previous treatment	
Small bowel resection	11 (19)
Hemicolectomy	6 (10.5)
Pancreatic resection	4 (7)
Stenting/bypass	4 (7)
Somatostatin analogues	33 (58)
Chemotherapy	10 (17.5)
Interferon- α	6 (10.5)
Hepatic chemoembolisation	3 (5)
Radiotherapy	1 (1.7)

index, Ki67s, was available in 24 out of 40 patients (13 Grade 1, 11 Grade 2, 0 Grade 3).

All patients had metastatic disease, with the most common location being the liver (93%), followed by regional lymph nodes (28%) and bone (19%). The vast majority of patients had already received other treatments for their condition including surgical intervention (44%), chemotherapy (17.5%) and interferon- α (10.5%; Table 1).

Of these 57 patients, 15 were treated solely with ⁹⁰Y-DOTATOC and 33 were treated solely with ⁹⁰Y-DOTATATE. Nine patients' therapy cycle crossed the date at which the treatment analogue was changed and as a result had 1 or 2 treatments with

⁹⁰Y-DOTATOC; ⁹⁰Y-DOTATATE was used to complete the therapy cycle.

All patients were due to have three individual treatments with ⁹⁰Y-DOTATOC or ⁹⁰Y-DOTATATE as part of a therapy cycle: 36 patients received all three treatments, 12 received two treatments and 9 received only one treatment. The reasons for not completing the therapy cycle included: patient choice; treatment side effects; patient fitness and death.

Response to therapy. In all, 57 patients received a total of 141 treatments of ⁹⁰Y-DOTATOC/DOTATATE (median 3, range 1–3). Information on radiological response was available for 49 out of 57 patients, on biochemical response for 35 out of 57 patients and on clinical response for all patients. A radiological response was observed in 71.5% of patients post therapy

(PR 24.5%, SD 47%) with the remaining 28.5% having evidence of PD. A biochemical response was observed in 69% of patients (PR 23%, SD 46%) with 31% having PD and a clinical response was observed in 86% (PR 49%, SD 37%) with PD in 14%. The Fisher’s exact tests were unable to demonstrate an association between any response types ($P > 0.1$), for example, a positive radiological response was not necessarily associated with a positive clinical response.

Overall Survival. During a median follow up of 32 months (range 4–104), 31 (54.3%) patients died with a median survival time of 46 months (95% CI: 34, 56) from the date of first ⁹⁰Yttrium PRRT and 95 months (95% CI: 70,120) from date of diagnosis.

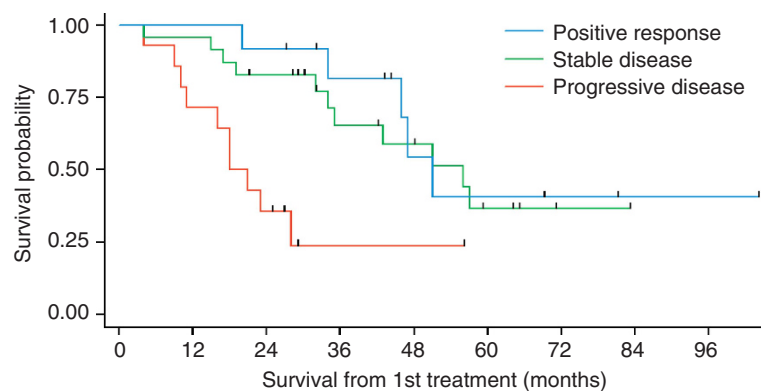
The Kaplan–Meier curves demonstrate that those who had a radiological response to therapy (PR or SD), thereby achieving ‘disease control’, had a significantly improved survival compared to those with disease progression (51 (34, –) and 56 (34, –) months vs 18 (10, –) months; $P = 0.0020$; Table 2 and Figure 1). We also examined the probability of survival according to the radiological response at fixed time points (6, 12, 24 and 48 months) post therapy (Table 3). Interestingly, no additional survival benefit was demonstrated in those patients who had a PR vs SD radiologically post therapy (Figure 1).

Similarly, there was no statistically significant survival benefit between patients who reported a PR or SD clinically post therapy

Table 2. Median survival according to clinical, radiological or biochemical response		
Responses	Number (%)	Median survival in months (95% CI)
Radiological response		
Progressive disease	14/49 (28.5)	18 (10, –)
Stable disease	23/49 (47)	56 (34, –)
Positive response	12/49 (24.5)	51 (34, –)
Biochemical response		
Progressive disease	11/35 (31)	35 (18, –)
Stable disease	16/35 (46)	56 (46, –)
Positive response	8/35 (23)	34 (19, –)
Clinical response		
Progressive disease	8/57 (14)	11 (4, –)
Stable disease	21/57 (37)	56 (23, –)
Positive response	28/57 (49)	47 (35, –)
No. outcomes in which a response was achieved		
One	16/57 (28)	32 (18, 46)
Two	21/57 (37)	57 (23, –)
Three	17/57 (30)	56 (43, –)

Abbreviation: CI = confidence interval.

Table 3. Probability of survival according to radiological response at 6, 12, 24 and 48 months			
Radiological response	Time (months)	Deaths	Survivor function
Progressive disease	6	1	0.9286
	12	3	0.7143
	24	5	0.3571
	48	1	0.2381
Stable disease	6	1	0.9565
	12	0	0.9565
	24	3	0.8261
	48	4	0.5872
Positive response	6	0	1
	12	0	1
	24	1	0.9167
	48	3	0.5432



No. at risk (failures)	
Positive response	12 (0) 12 (1) 12 (1) 8 (2) 4 (1) 3 (0) 2 (0) 1 (0) 1
Stable disease	23 (1) 22 (3) 18 (3) 11 (1) 9 (3) 4 (0) 1 (0) 0 (0) 0
Progressive disease	14 (4) 10 (5) 5 (1) 1 (0) 1 (0) 0 (0) 0 (0) 0 (0) 0

Figure 1. Kaplan–Meier survival analysis showing radiological response according to PR, SD or PD. Log-rank test, $P = 0.0020$.

(Figure 2). Although it would appear that individuals with a clinical response post therapy (PR or SD) have a clear survival advantage over those demonstrating PD clinically, the actual difference in OS times were not statistically significant (Table 2 and Figure 2), $P=0.2208$, possibly owing to the few patients ($n=8$) in the PD category.

Biochemical response to therapy also appeared not to have a significant impact upon OS. However, when biochemical and clinical responses were combined with radiological response, an improved OS was observed according to the number of outcomes (radiological, biochemical, clinical) in which ‘disease control’ (PR or SD) was achieved (Table 2 and Figure 3).

Hazard ratios of survival. For the purposes of regression analysis, patients classified as PR or SD were pooled in order to limit the number of parameters estimated. In the univariate Cox regression analysis, higher baseline serum chromogranin A concentration was found to be associated with an increased hazard of death (for a 100 pmol l^{-1} change: HR 1.18, 95% CI 1.06, 1.30; $P=0.0020$;

Table 4). Being a radiological responder was demonstrated to considerably reduce the hazard of death (HR 0.24, 95% CI 0.10, 0.57; $P=0.0010$). Age, biochemical or clinical response group were not found to affect survival in univariate analysis ($P>0.05$).

When we included both baseline serum chromogranin A concentration and age in a multivariable Cox regression model alongside radiological response group, the hazard ratios were virtually unchanged compared with those in the univariate analyses (Table 4). Neither clinical nor biochemical response group added sufficient information for inclusion in this multivariable model, as measured by Akaike’s Information Criteria. In other attempted multivariable models, after adjusting for baseline serum chromogranin A concentration and age, neither clinical or biochemical response group were found to affect survival (not shown).

Effect of primary tumour site on survival. The effect of primary disease site on OS was also assessed. Tumours were sub-grouped into those arising from the small and large bowel, pancreas and unknown primary site. There was no correlation between tumour

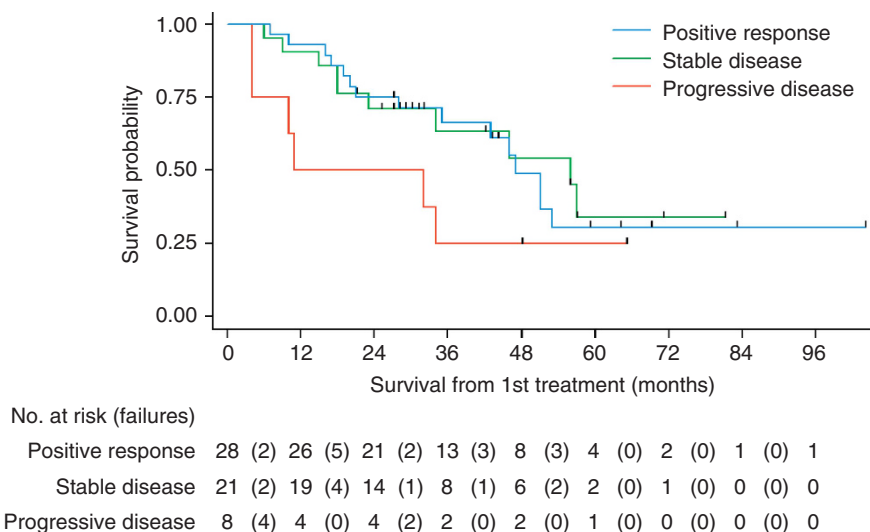


Figure 2. Kaplan–Meier survival analysis showing clinical response according to PR, SD or PD. Log-rank test, $P=0.2208$.

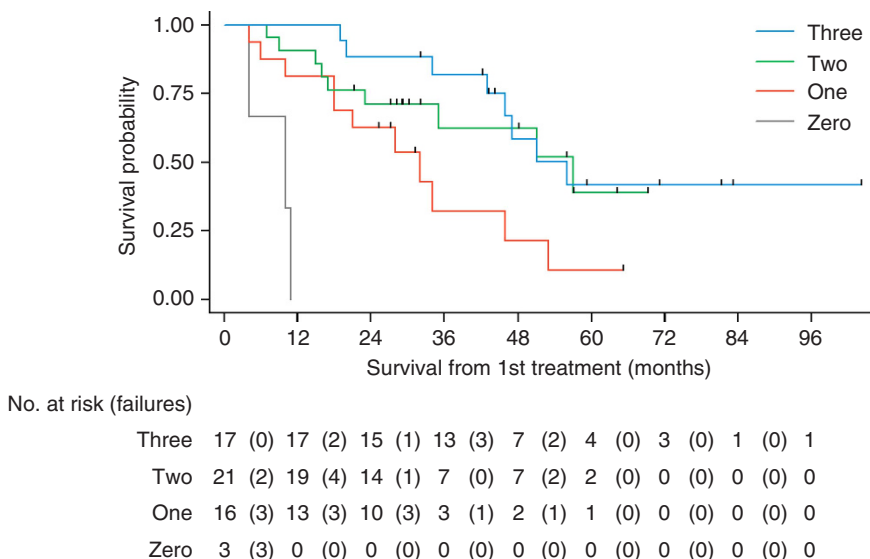


Figure 3. Kaplan–Meier survival analysis showing differences in survival between those who achieved disease control across none, 1, 2 or 3 of the outcomes (clinical, biochemical, radiological) used to assess response to therapy. Log-rank test, $P\text{-value}<0.00005$.

site and patient survival post ⁹⁰Yttrium PRRT. However, trends are visible with individuals whose primary disease site could not be identified typically having a shorter survival.

Effect of number of treatments of PRRT on survival. An additional analysis into the effect of the number of ⁹⁰Yttrium PRRT treatments administered showed a trend of increasing OS with each additional ⁹⁰Yttrium treatment (16 vs 20 vs 51 months for treatment 1, 2 and 3, respectively), however, this was not statistically significant (*P* = 0.081). Similarly, the number of ⁹⁰Yttrium treatments administered did not have a statistically significant effect on whether patients recorded PD, SD or PR post therapy.

Toxicity

Haematological/renal toxicity. Overall, a total of 51 individuals had at least one episode of anaemia during the 10-week period following one of their treatments. In all, 43 individuals experienced at least one episode of leucopenaia and 38 developed thrombocytopenaia. Only six patients developed renal impairment after treatment (5 Grade 1, 1 Grade 2). Table 5 shows the number of patients experiencing haematological toxicity after each individual treatment and the grade of that toxicity reflecting its severity (graded using the NCI CTCAE criteria). This table shows that the

proportion of people experiencing anaemia, leucopenia or thrombocytopenaia increased with each subsequent treatment. The proportion of those with severe G3/4 toxicities increased between treatments 1 and 2 but decreased after treatment 3. Furthermore, the proportion of patients with multiple (≥2) haematological toxicities increased over the course of the therapy cycle (55.3%, 58.2% and 86%, following treatments 1, 2 and 3, respectively). Following the final treatment, >50% of all patients had developed anaemia, leucopenia and thrombocytopenaia (pancytopenaia). Figure 4 shows the temporal relationship of the haematological toxicities to the point at which treatment was administered. No patient died as a result of haematological or renal toxicity.

General. Patients experienced a number of other side effects including: lethargy (18.6%) nausea and vomiting (14%), weight loss (7%) and pain (7%). No patient had a carcinoid crisis following treatment or any acute reactions during infusion of the radio-nuclide therapy.

DISCUSSION

We observed positive radiological, biochemical and clinical responses in 24.5%, 23% and 49% of patients, respectively, although if SD was included, an overall response to therapy resulting in ‘disease control’ was achieved in 71.5%, 69% and 86% of patients, respectively. The results of this study clearly demonstrate that patients who have a radiological response to PRRT with ⁹⁰Y-DOTATOC or ⁹⁰Y-DOTATATE have a significant improvement in OS. This OS benefit is still observed after adjustment for baseline differences between individuals for age and serum chromogranin A concentrations. We also demonstrate a predictable time course for myelosuppression following administration of therapy and with the use of reno-protective amino acid administration renal toxicity was observed only rarely.

Differences in various factors including study design, therapy dosage, criteria used to determine response and follow-up intervals make direct comparisons between studies difficult. In an early phase II study of 41 patients treated with ⁹⁰Y-DOTATOC, Waldherr *et al* (2001) found that 85% had ‘disease control’ with only 15% of patients with PD and that 83% of patients had significant clinical benefit. Similarly, Forrer *et al* (2006) previously reported the response in 116 patients treated with ⁹⁰Y-DOTATOC and noted disease control in 89% of patients (27% PR; 62% SD), whereas 83% had a reduction in clinical symptoms. In an early phase I study of 58 patients with advanced GEP-NETs, Valkema *et al* (2006) reported that 57% of patients demonstrated some

Table 4. Hazard ratios of survival

Variable	HR	95% CI		P-value
		Lower	Upper	
Univariate Cox regression				
Radiological group	0.24	0.10	0.57	0.0010
Clinical group	0.47	0.19	1.14	0.0940
Biochemistry group	0.55	0.20	1.52	0.2520
CgA (100 unit change)	1.18	1.06	1.30	0.0020
Age	1.03	0.98	1.08	0.3020
Multivariable Cox regression				
Variable	HR	Lower	Upper	P-value
Radiological group	0.19	0.07	0.50	0.001
CgA (per 100 units)	1.17	1.04	1.32	0.011
Age	0.99	0.93	1.05	0.657

Abbreviation: CI = confidence interval; HR = hazard ratio.

Table 5. Number of patients with deranged haematological results pre- and post treatment cycles

Toxicity	Haematology	Pre-treatment		Post treatment				Total post treatment (%)
		G1	G2	G1	G2	G3	G4	
Cycle 1 (n = 57)	Anaemia	24	0	37	4	0	0	41/57 (72)
	Leucopenaia	1	0	14	8	6	0	28/57 (49)
	Thrombocytopenaia	6	0	19	3	3	3	28/57 (49)
Cycle 2 (n = 48)	Anaemia	23	1	27	3	4	0	34/48 (71)
	Leucopenaia	7	0	11	7	7	0	25/48 (52)
	Thrombocytopenaia	3	0	12	5	4	3	24/48 (50)
Cycle 3 (n = 36)	Anaemia	16	4	25	5	1	0	31/36 (86)
	Leucopenaia	6	2	17	6	4	0	27/36 (75)
	Thrombocytopenaia	4	0	16	2	5	1	24/36 (66)

Patients are categorised into grades 1–4 according to the severity of the toxicity as determined by the NCI CTCAE criteria.

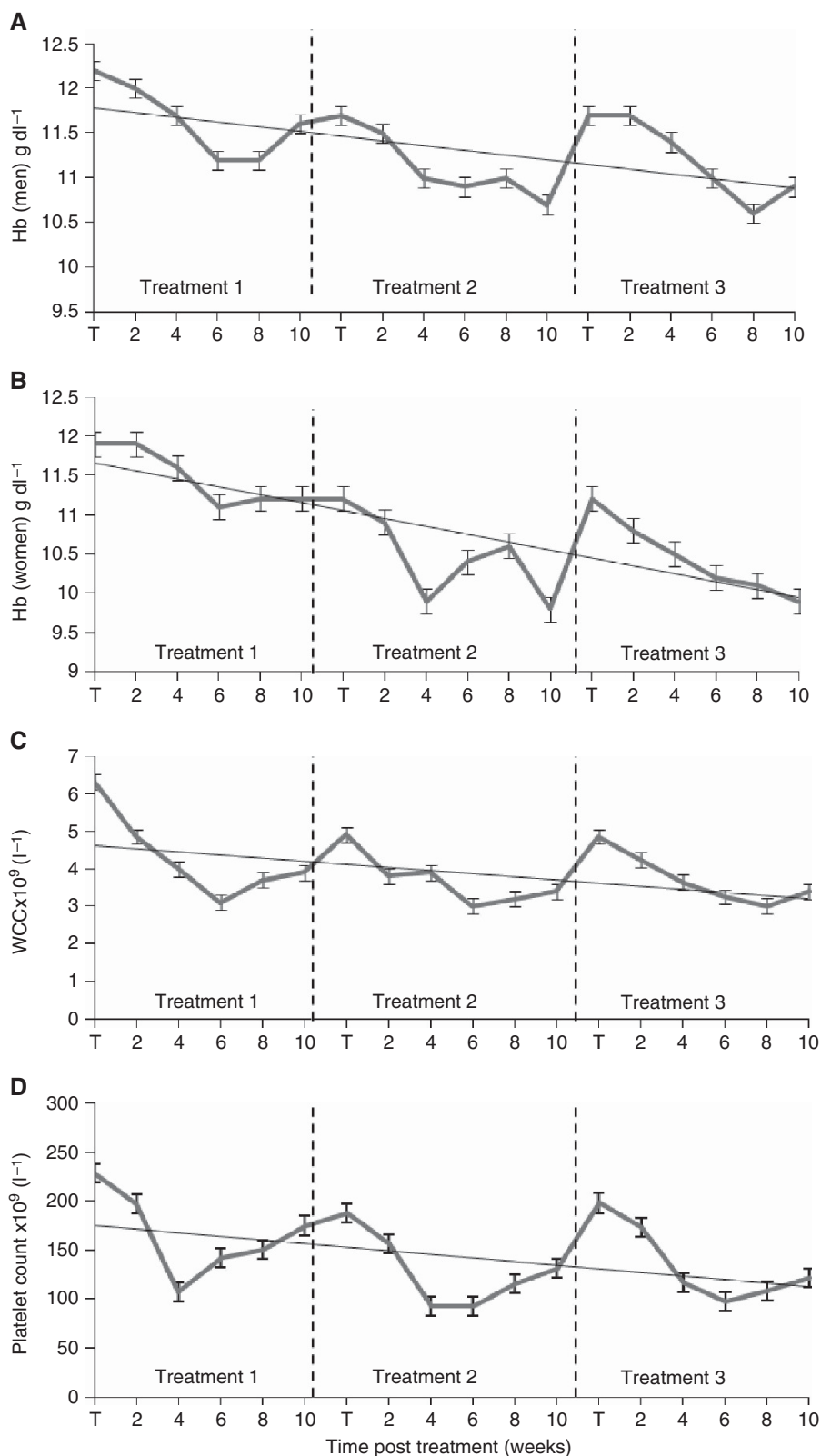


Figure 4. Time course of haematological parameters: haemoglobin in (A) men and (B) women, (C) white-cell count (WCC), and (D) platelets, following therapy.

improvement in their disease status. Imhof *et al* (2011) reported outcome in 1109 patients after a phase II study involving Y90-DOTATOC and showed clinical, biochemical and radiological responses in 30%, 15% and 35%, respectively. More recently, it has been suggested that DOTATATE therapy may be more effective, as DOTATATE has a nine-fold higher affinity for somatostatin

subtype 2 receptors than DOTATOC. Cwikla *et al* (2010) examined response of Y⁹⁰-DOTATATE therapy in 60 patients and demonstrated clear efficacy with high rates of clinical or radiological response. Our small sample size precluded a comparison between those patients treated with ⁹⁰Y-DOTATATE or ⁹⁰Y-DOTATOC.

We did not necessarily observe that responses were consistent across each outcome, for example, a radiological response did not correlate with a clinical response. This may be due to the inadequacies of the current criteria used to classify response of NETs to targeted therapy. Neuroendocrine tumours, particularly when cystic, may enlarge post therapy due to tumour necrosis and inflammatory change. Thus, current criteria may classify a PR as PD. Alternative criteria may be more appropriate in the specific context of NETs (Benjamin *et al*, 2007). It has also been proposed that cross-sectional imaging using CT/MRI scans may not be the best imaging modality to assess treatment response and that functional PET/OctreoScans may be more informative (Haug *et al*, 2010).

As with the findings of Imhof *et al* (2011), we demonstrate that a radiological response to therapy was associated with a longer survival. Importantly, when comparing the survival using the three individual responses of PR, SD and PD there were no significant differences in survival between those with a PR or SD radiologically (Figure 1 and Table 2). This phenomenon was also reported by Cwikla *et al* (2010).

Significantly, however, we observed that the benefit in OS was clearly related to the number of outcomes in which a response to therapy was observed, such that the greatest benefit was seen in those patients who had multiple responses achieving 'disease control' in two or three of clinical, biochemical and radiological outcomes (Figure 3).

The number of treatments administered appeared to positively influence OS with those receiving three treatments demonstrating a longer OS compared with those receiving two or one, although this was not statistically significant. Caution should also be taken when interpreting these results as confounding factors, such as baseline health, disease progression and death, which lead to patient withdrawal from the treatment cycle, are not accounted for. To fully ascertain the effect of the number of radionuclide therapies administered on survival, further randomised studies are required.

An important variation that affects response rates and survival is the point during the course of disease at which therapy is administered. An objective tumour response after PRRT is more likely to be observed in patients with PD, hence, our inclusion in this study of patients with PD or refractory disease at the time of therapy. However, Kwekkeboom *et al* (2008) demonstrated a shorter median OS in those patients with a poor performance score and those with extensive liver involvement, suggesting that targeted therapy should be administered at an earlier point in the evolution of disease. The relatively late introduction of PRRT during the clinical course of disease in our patients may also explain why primary disease site had no effect on response to therapy and OS post PRRT. However, it should also be noted that the relatively low number of subjects within this study may have precluded any meaningful comparison.

Overall, renal toxicity was rare, reflecting the benefits of using a reno-protective infusion of amino acids, whereas the development of mild G1 and G2 haematological toxicity was almost universal. The mean number of patients experiencing severe G3/4 haematological toxicity over the course of the therapy cycle (16%) was comparable to results obtained in other studies (Cwikla *et al*, 2010).

An important point to note in this study is that a relatively large proportion of individuals demonstrated a normocytic anaemia before commencing treatment (42% pre-treatment 1, 50% pre-treatment 2, 55% pre-treatment 3); presumably secondary to chronic disease. All of these patients developed a worsening of their anaemia following treatment, although the grade of the anaemia did not alter in severity according to the NCI CTCAE criteria. The peak of the acute toxic effects of treatment tended to occur 6–10 weeks post therapy. In addition, a cumulative toxic effect occurred such that the number of patients developing multiple (≥ 2) haematological toxicities increased over the course of the therapy cycle (55.8%, 58.2% and 86%, following treatment 1, 2 and 3, respectively). Most cases of myelosuppression resolved

spontaneously and no patients died as a result of renal or haematological toxicity.

There remain many questions regarding the application of targeted therapy to patients with metastatic NETs. First, we are unable to draw firm conclusions on the effect of our therapy on OS from this, or indeed from any other published study, because randomised, controlled trials with radiolabelled SSAs have not been performed (Kwekkeboom *et al*, 2005a,b). The optimal timing of the intervention with targeted therapy is uncertain with some advocating its use earlier in the course of disease (Kwekkeboom *et al*, 2005b; Kwekkeboom *et al*, 2008). Combination PRRT using ⁹⁰Yttrium- and ¹⁷⁷Lutetium- labelled SSAs is also a potential therapeutic consideration with the few studies conducted thus far showing increased response rates and survival times (Villard *et al*, 2012).

The retrospective nature of our analysis led to incomplete data availability and heterogeneity in the data set. We chose radiological response as the primary outcome measure, as it can be measured most objectively using well-validated criteria. For biochemical response, one of the two secondary outcome measures, incomplete biochemical data (available on 35 out of 57 patients), and the interference of various drugs (e.g., proton pump inhibitors; Mosli *et al*, 2012) and renal function (Bech *et al*, 2012) on serum chromogranin A concentrations, makes serial changes less reliable as an objective measure of response.

Structured clinical questionnaires such as the European Organisation for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30) are not used as a component of clinical data collection during our follow-up clinics, because of their lack of specificity for NETs. As a result, clinical response was assessed subjectively with its inherent limitations. It should also be noted that the only validated disease-specific quality-of-life score questionnaire for patients with NETs, EORTC QLQ-NET21, was not available at the time clinical data were recorded for the majority patients (Davies *et al*, 2006). In the absence of such clinical questionnaires, this information regarding symptoms intensity/frequency reported at follow-up clinic represents the most reliable from data available to us to assess clinical response to therapy. Despite these limitations, data on clinical and biochemical response, when analysed in conjunction with radiological response to determine the total number of positive outcomes (one, two or three) to PRRT, were able to provide useful prognostic information regarding differences in survival (Figure 3).

The need for improved standardisation and validated end points of clinical trials for NETs has been recognised (Kulke *et al*, 2011) and the results of further studies should include a prospective detailed quality-of-life assessment, which can inform patients' treatment selection, determine resource allocation and influence healthcare policy (Ramage *et al*, 2011).

Nonetheless, on the basis of this analysis, we demonstrate that ⁹⁰Y-DOTATOC and ⁹⁰Y-DOTATATE are effective treatments that can improve survival in patients with progressive or symptomatic metastatic NETs and this benefit appears to be similar in those whose disease is stabilised to those whose disease regresses.

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