Journal of Nuclear Medicine, published on August 16, 2018 as doi:10.2967/jnumed.118.215376

Twelve-year Follow-up after Peptide Receptor Radionuclide Therapy (PRRT).

Michael Gabriel, MD[1,2]; Bernhard Nilica, MD[1]; Bernhard Kaiser, MSc[2]; Irene J Virgolini, MD[1]

Affiliations:

[1]Department of Nuclear Medicine, Medical University of Innsbruck, Austria

Anichstrasse 35, 6020 Innsbruck

[2]Institute of Nuclear Medicine and Endocrinology, Kepler University Hospital,

Krankenhausstrasse 9, 4020 Linz, Austria

Correspondence to:

Michael Gabriel, MD

Department of Nuclear Medicine, Medical University of Innsbruck, Austria

Anichstrasse 35, 6020 Innsbruck

Phone: +43-(0)512-504-22651

Fax: +43-(0)512-504-22906

E-mail: michael.gabriel@kepleruniklinikum.at

Conflicts of interest for all authors: none
Financing source or other support to disclose: none

Keywords: Peptide receptor radionuclide therapy, somatostatin analogs, neuroendocrine tumors, radiopharmaceutical, individualized therapy, long-term follow-up, overall survival, outcome

Short running title: Long-term follow-up after PRRT

ABSTRACT

Peptide receptor radionuclide therapy (PRRT) has been used for more than twenty years as a systemic treatment approach in inoperable or metastatic somatostatin receptor (SSTR)-positive tumors. The purpose of this study was to analyze the long-term outcome of PRRT with regard to the most commonly used radiopharmaceuticals, ^{90}Y-DOTA-Tyr^{3}-octreotide (^{90}Y-DOTA-TOC) and ^{177}Lu-DOTA-Tyr^{3}-octreotate (^{177}Lu-DOTA-TATE). **Methods:** This retrospective clinical study included a total of 44 consecutive patients (27 men) with advanced tumors and enhanced SSTR expression. Mean age at initial diagnosis was 60 years (SD 11.3, range 40 to 84 years). Median follow-up was 80 months. In the mean 5.3 ± 2.5 cycles were administered for ^{177}Lu-PRRT with mean activity of 27.2 ± 14.9 GBq per patient and 5.5 ± 2.6 cycles for ^{90}Y-PRRT with mean activity of 14.7 ± 7.3 GBq. Overall, 378 cycles were administered (mean 8.6 ± 3.4 cycles per patient) with an overall cumulative activity of 1514.1 GBq. **Results:** Median overall survival (OS) was 79 months. Twenty-one (77.8%) of the 27 men and nine (52.9%) of the 17 women had died 12 years after commencement of PRRT. Shortest duration of illness was eight months, longest 155 months. Severe side-effects (World Health Organisation (WHO) Grades III and IV) are seen in nine of the 14 patients still alive. Chronic kidney disease in combination with anemia is the most common finding in the nine patients with severe side-effects. Very poor prognosis was found for those patients who showed progressive disease (PD) in comparison with patients with cumulative disease control after initial PRRT (log-rank, $p<0.001$), while women and patients with no more than two tumor sites seem to especially benefit from PRRT not reaching significance levels. **Conclusion:** PRRT is very encouraging in terms of long-term outcome. Thirty-two percent (14/44 patients) of the patients with metastatic or inoperable disease are still alive more than 12 years after the beginning of radionuclide therapy. Possible predictors for favourable outcome are initial response to PRRT, number of affected sites and female gender.

INTRODUCTION

The expression of somatostatin receptors (SSTR) by neuroendocrine tumors (NETs) is the basis for peptide receptor-mediated radionuclide therapy (PRRT) (*1,2*). Several, mainly beta-radiation-emitting compounds labelled with different somatostatin analogues are used for this systemic treatment approach in patients with metastatic or inoperable progressive disease (PD) (*3*). Depending on the tumor / metastasis size, ^{90}yttrium (^{90}Y) beta rays with a range of approx. 12 mm in tissue are theoretically better suited for larger tumor lesions, while ^{177}lutetium (^{177}Lu) with a smaller range of approx. 2 mm is preferentially used for smaller tumors. Although there is no evidence in the clinical setting, this concept has been widely applied in clinical practice for many years. In the last decade, particularly the ^{177}Lu-labelled compound has found its way into clinical routine assuming more favourable properties in terms of kidney toxicity.

The clinical efficacy of PRRT has been demonstrated in several clinical studies (*4-6*). The response rate summing up complete remission (CR), partial remission (PR), minor remission (MR) and stable disease is about 70% to 80% for ^{90}Y-DOTA-TOC and for ^{177}Lu-DOTA-TATE (*5,6*). In general, the prognosis of patients responding to PRRT is favourable, meaning that median time to progression is about three to four years. However, if PD occurs early after PRRT prognosis is very poor (*5,6*).

Despite these findings, not much is known about long-term outcome. Although this therapy approach has been available for about 20 years, experience with long-term outcome is limited. Only recent prospective study results have indicated a survival benefit as compared to established therapy procedures (*7*). Especially for metastatic midgut NETs, PRRT has been established as one major therapy strategy since only few therapeutic alternatives are available for this tumor entity with sometimes more severe side-effects (*8*). But also for pancreatic NET both available radiopharmaceuticals used for PRRT have shown advantages over other

treatment approaches with regard to progression free survival (PFS) and overall survival (OS) (*9*).

On the other hand, PRRT also entails side-effects that should also be considered in order to grasp the value of this oncological therapy. In particular, special attention has to be paid to renal function and bone marrow reserve (*10*). In 2010 the Innsbruck group published their experience with a more individualized treatment scheme (*11*). It was found that PRRT with differently labelled tracers (^{90}Y or ^{177}Lu) and different somatostatin analogues was generally well tolerated with only few serious side-effects. In particular, extended time intervals and reduced individual doses were proposed in patients with advanced tumor stages, in cases of moderate SSTR expression, and in patients of higher age. This treatment regime also included retreatment for the case of progression. However, long-term experience with this concept is still not available. Thus, the aim of the present analysis was to document the medical history of patients initially treated with PRRT at our department more than 12 years ago.

MATERIALS AND METHODS

The included patients were largely the same as published in the Journal of Nuclear Medicine (*JNM*) in 2009 (*12*) thanks to the well documented patient history after many years. Accordingly, tumors originated from neuroendocrine tissue of the gastrointestinal tract in 41 patients. In addition, three patients suffered from a carcinoid tumor of the lung and one patient each from a glomus tumor and a dendritic reticulum cell sarcoma. With a positive ^{68}Ga-DOTA-TOC PET-CT scan result patients were consecutively treated with ^{90}Y-DOTA-TOC (n=24) or ^{177}Lu-DOTA-TATE (n=19), or with both compounds (n=3) (*12*). Dosimetry was also performed using either the ^{111}In-labelled compound before the first treatment cycle of ^{90}Y-DOTATOC or during the first therapy when using ^{177}Lu-DOTA-TATE with special consideration of the kidney dose with the well-known threshold of 23 Gray which was taken from external beam radiation

(*13*). PET-CT was used for initial assessment and for restaging (*12*), which also formed the basis for analyzing quantitative parameters. The local ethics committee approved the initial study and all subjects signed written informed consent. Two men (34 and 47 years old) were lost to follow-up and thus removed from the final analysis. One of these patients had a NET of the pancreas and the other a NET of the small bowel. The present reevaluation thus included a total of 27 (61%) men and 17 (39%) women. Mean age at initial diagnosis was 60.0 years (SD 11.3), the youngest person (minimum) was 40 years and the oldest 84 years at time of initial diagnosis. Details are given in Table 1. The shortest duration of illness was eight months in a 61-year-old man who died of pneumonia; the longest is 155 months in a 60-year-old woman with a pancreatic NET and liver metastases. This female patient is still in excellent clinical condition.

In contrast to the previous publication that focused on the imaging method used, we here attempted to retrospectively evaluate the long-term outcome of this patient collective after receiving PRRT according to our individualized treatment protocol as published earlier (*11*). For the following retrospective investigation, no separate ethical approval and no formal consent have to be obtained according to Austrian law.

Median OS, meaning the time after which 50% of patients are still living and 50% have died, included the time from the initial examination by ^{68}Ga-DOTA-TOC PET-CT to the date of death, or for the survivors the last day of evaluation, namely November 4th, 2017. Median survival refers to how long patients survive with a disease in months. In particular, it is the time when half the patients are expected to be alive.

Because of the long follow-up it was found that intra- and inter-individual follow-up controls significantly differed, so that assessment of PFS was not feasible.

Median follow-up was 80 months (Q_1–Q_3: 27.5 to 136.5 months) for the whole population, while median follow-up of survivors was 139.5 months (Q_1–Q_3: 137 to 146 months) and for patients who have already died 42.5 months (Q_1–Q_3: 23 to 81 months).

In the mean 5.3 ± 2.5 cycles were administered for ^{177}Lu-PRRT with mean activity of 27.2 ± 14.9 GBq per patient and 5.5 ± 2.6 cycles for ^{90}Y-PRRT with mean activity of 14.7 ± 7.3 GBq. Overall, 378 cycles were administered (mean 8.6 ± 3.4 cycles per patient, range 2 – 17 cycles) with an overall cumulative activity of 1514.1 GBq (mean 34.4 ± 13.9 GBq).

Imaging and Quantitative Assessment

Patient imaging and image reconstruction were performed on a dedicated PET scanner (Advance; GE Healthcare) as described elsewhere (*14*). Irregular isocontour regions of interest were drawn over the target lesion at 50% of maximum pixel value within the tumor. The lesion that was most visible and easy to define was defined as the index or target lesion. The individual patient's region of interest was placed in the same target lesion on the pre- and posttherapy PET scans for quantitative intrapatient comparison (*12*). Lesions with a diameter below 4 cm, tumor lesions with increased tracer uptake on the rim and absent uptake in the center due to necrosis were excluded from quantitative evaluation to avoid pitfalls caused by the partial volume effect.

Maximum standardized uptake value (SUVmax) was calculated using the maximum activity values in the region of interest normalized for the injected dose and patient body weight. Additionally, SUVmax before and after initial PRRT and relative changes in SUVmax were analyzed for the target lesion; further details are described elsewhere (*12*). In 16 patients individual target lesions decreased significantly in size, indicating remission to therapy. However, most patients showed no significant change in the index lesion from the visual aspect. Median SUVmax before and after were 32.2 (Q_1–Q_3: 23 – 44.5) and 25.6 (Q_1–Q_3: 16.3 – 37.6), respectively. Median relative change in SUVmax was -13.5% (Q_1–Q_3: -49.4 – 16.6).

Treatment Schedule and Evaluation of Outcome

In our concept (*11*) the ^{90}Y-labelled compound was normally used as the first choice. However, if the majority of individual lesions were smaller than 2 cm in diameter, ^{177}Lu-DOTA-

TATE was preferred for initial administration. For PRRT retreatment we normally used the ^{177}Lu-labelled compound.

Evaluation of treatment response and side-effects was described in the aforementioned publications (*11,12*). Adverse effects of therapy, for example every change in blood test results, are recorded and analysed with the World Health Organisation (WHO) side-effect scoring system for reporting results of cancer treatment. For health condition reporting the Karnofsky Performance Index (KPI) (*15*) was documented in each patient during every stay at the Nuclear Medicine Department.

Therapy after Completion of PRRT beyond Radionuclide Therapy

In addition to the application of “cold” long-acting somatostatin analogues in the majority of patients (n = 27), further two patients each were treated with chemotherapy and radiofrequency ablation. One patient with a pulmonary carcinoid received temozolamide and one with a rectal NET temozolamide and everolimus. One of the two patients treated with radiofrequency ablation of progredient liver metastases turned out to also have an exocrine tumor of the pancreatic head as a second malignant disease. After surgical removal of this tumor and radiochemtherapy with gemcitabine this patient was considered cured with regard to this non-NET. The second patient undergoing radiofrequency ablation additionally received external beam radiation of bone metastases in the lumbar spine, which were caused by a pancreatic NET.

Data Collection and Statistical Data Analysis

Patient and disease-related data were collected from hospital electronic records and imaging as well as from medical reports from outside hospitals. In addition to the descriptive part of the analysis with special consideration of the median OS, the available data were also used to

statistically analyze relationships to dependent factors, such as type of primary tumor, gender distribution, type and number of organ systems involved, kind of first radiopharmaceutical used for PRRT, initial response to therapy and SUVmax of reference lesions.

Statistical analysis was performed using R-3.3.2 (https://www.r-project .org). Graphs and tables were created using Microsoft Excel and Microsoft Word.

Lifetime analyses were used to investigate differences in predefined groups. Kaplan-Meier graphs show the probability of survival. The log-rank test was used to compare survival distribution between the groups. The semiparametric Cox proportional hazard model was used to test the influence of quantitative variables on survival, especially SUVmax before PRRT and relative changes. In all analyses $p < 0.05$ was considered statistically significant.

RESULTS

General Population

As also shown in Table 1, 21 (77.8%) of the 27 men and nine (52.9%) of the 17 women died in the meantime. Median OS was 79 months (95%CI: 41 – 125). Median survival of men was 75 months and of women 107 months. Untill now, only three women have died after the first three years of observation, thus indicating a survival benefit for women as indicated in Figure 1 and 2 without reaching statistical significance ($p = 0.195$, log-rank test). Of the overall 30 patients who died 25 died from tumor progression. Only one 84-year-old patient died from renal failure. In addition, one male patient each died from acute myeloblastic leukemia, cerebral hemorrhage, pneumonia, and a grand mal seizure without relationship to PRRT.

No statistical significance was observed when the site of the primary tumor was analysed, as shown in Table 2 ($p = 0.473$, log-rank test).

When considering the number of affected organ systems, it was found that 41.7% of the patients with only one system affected are still alive, while this is the case in only 27.3% of those

involving three or four systems; see Table 3. When comparing median survival between patients with one or two affected organ systems and patients with more extended disease a difference can also be assumed, namely 97 to 81 versus 23 months. Despite a clear tendency, no statistically significant difference can be observed when analysing survival probability (p = 0.192, log-rank test).

Patients Alive at Date of Censoring

Fourteen patients are still alive more than 12 years after initial PRRT, namely eight women and six men. Final evaluation showed stable disease in seven patients, PD in five and PR in two.

Of the 14 patients still alive 13 received additional cycles of PRRT during the course of disease, i.e. retreatment when disease progression was observed: eight with ^{177}Lu-DOTA-TATE, two with ^{90}Y-DOTA-TOC and three with ^{177}Lu-DOTA-TATE and ^{90}Y-DOTA-TOC. The highest activities applied to these patients were 54.93 GBq for ^{177}Lu-DOTA-TATE, 27 GBq for ^{90}Y-DOTA-TOC, and for the combined use of both treatment regimes 50 GBq (35.4 GBq ^{177}Lu-DOTA-TATE and 14.6 GBq ^{90}Y-DOTA-TOC). All of these 13 patients also received long-acting somatostatin analogues.

The majority of these patients were in good clinical condition with a KPI of 100% in eight patients, 90% in three, 80% in two and 70% in only one 61-year-old man who suffered from chronic anemia, diarrhea and renal toxicity Grade IV.

Side-Effects in Patients Alive at Date of Censoring

Overall, severe side-effects (WHO Grades III and IV) were seen in nine (64%) of 14 patients. Severe long-term nephrotoxicity (Grades III and IV) in combination with anemia was the most common finding in these patients. Furthermore, one patient suffered from Grade II nephrotoxicity and anemia. None of the remaining four cases showed nephrotoxicity. However,

one of these patients suffered from chronic diarrhea, one from moderate anemia and one from thrombopenia.

Evaluation of Therapy Response and Factors Predicting Outcome

Patients who responded well to the first PRRT in terms of stabilizing the underlying disease or showing remission had a significantly better survival probability than did those who presented with tumor progression after initial therapy ($p < 0.001$), as also shown in Table 4 and Figure 3.

A statistically significant result was also obtained for the choice of radiopharmaceutical used for therapy, meaning that patients treated with ^{177}Lu-DOTA-TATE had a significantly better survival probability than did those treated with ^{90}Y-DOTA-TOC ($p < 0.001$), as also depicted in Figure 4. Nevertheless, many of the patients were also switched to the other radiopharmaceutical during the further course of the disease.

No significant relationship was found between the duration of disease in months and the quantitative parameter SUVmax before PRRT ($p = 0.597$) or relative changes in SUVmax ($p = 0.328$).

DISCUSSION

Two decades after the introduction of PRRT, the long-term results are becoming more and more interesting. Only few reports are presently available and give an impression of the long-term efficacy, survival, and safety of PRRT. In our patient group median OS from the beginning of the first PRRT cycle was 79 months. Overall 21 (77.8%) of the 27 men and nine (52.9%) of the 17 women died, which means that nearly one-third of the treated patients are still alive more than 12 years after initial diagnosis of inoperable metastatic disease. Different studies report median OS ranging from 22 to 71 months (*4,16-20*).

This longer median OS in our patient population might be attributed to our applied concept based on the repeated use of radiopharmaceuticals in the event of recurrent progression of the underlying disease using individually adapted activities (*11*). Forrer et al. also showed that ^{177}Lu-DOTATOC therapy is feasible, safe and efficacious in patients with relapse after ^{90}Y-DOTA-TOC treatment (*2*). After all, 13 of the 14 surviving patients also received additional cycles of PRRT after the initial therapy and thus exceeded the dosimetrically calculated kidney doses by several times.

On the other hand, the surviving patients in our study population have a large proportion of serious side-effects possibly related to PRRT. Nine of the 14 patients still alive suffer from Grades III and IV side-effects; severe chronic renal toxicity in combination with anemia was the most common finding in these patients. This high rate of serious side-effects is significantly higher than in the previously published studies (*21*). Even in those seven patients who were treated throughout with ^{177}Lu-DOTA-TATE, three developed severe nephrotoxicity. Nevertheless, none of the 14 patients were dialysis-dependent and most of the patients showed a still very high KPI which underlines the positive effect of PRRT in terms of the quality of life (*22*).

In contrast to the observation made by other investigators (*23,24*), we could not find a correlation between outcome and quantitative parameters of tracer accumulation by applying SUVmax and relative changes in SUV max. This could be related to our retrospective design, but could also be a matter of insufficient assessment of SSTR distribution in tumor lesions. A recent publication, for instance, identified eight statistically independent heterogeneity parameters for time-to-progression and time-to-death, while conventional PET parameters failed in response prediction (*25*).

A very important indicator of median OS is the cumulative disease control to therapy after the first PRRT. Especially the patients who showed early progression had very poor prognosis.

The subgroups that showed a remission or stable disease showed no significant difference with regard to outcome. Therefore, this feature is not only a predictor for mid-term outcome, but also in the long-term course over many years, as already previously assumed (*5,26*). Consequently, at least stabilization of the underlying disease can be defined as a major therapeutic goal with important implications for further prognosis.

Although no significant difference can be identified, the Kaplan-Meier survival plots possibly indicate a survival benefit with regard to female gender. Since there is no apparent difference in terms of age, diagnosis, disease spread or the therapeutic methods used, it can be assumed that this is an inherent effect. It is interesting that of the women patients only three died after 2008. Whether this potential survival benefit of women is due to better response to PRRT or whether women with a metastatic NET have better survival benefits remains an unanswered question (*27*).

As shown in Table 3, when comparing the group of patients with one, two or more affected organ systems at initial diagnosis a difference can be found with regard to the percentage of patients presently alive, but this difference did not reach significance. This observation is underlined by taking into consideration the mean duration of median survival of each patient group. Patients with one or two affected organs show a median survival of 97 and 81 months, respectively, while in patients with more widespread disease, i.e. three or more affected organs, median survival was 23 months. This observation could be based on differences in tumor aggressiveness, meaning that more aggressive tumors tend to spread more widely, while not so biologically aggressive tumors show a more limited disease spread. Another analysis also confirms the favourable response and long-term outcome in patients who were treated in a phase of “early” progression rather than in a state of overt progression with higher tumor load (*28*).

According to the present analysis, the initial use of ^{177}Lu has shown significantly better results than has the use of ^{90}Y or the combination of both tracers, which obviously supports the present prevalent concept of exclusive use of ^{177}Lu-DOTA-TATE for PRRT. However, one should also bear in mind that the choice of radiopharmaceutical used for the initial treatment regime in our patient population was largely related to the size of the individual tumor lesion as depicted by PET-CT. Considering the complex situation including also the tumor dose and volume in different sized lesions (*29*), the present analysis should be cautiously interpreted, not least of all since combined use with ^{90}Y/^{177}Lu-DOTA-TATE was basically found to be highly effective, safe and showed similar results (*30,31*).

Our study has two limitations. First, this study employed a retrospective design and assessed a relatively small number of patients in a single institution. Therefore, our results may have been affected by selection bias, as also mentioned above with regard to the choice of radiopharameceutical. And second, histopathology of the included patients was rather heterogeneous in terms of the primary site, and grading a tumor-based analysis was not feasible, as indicated in Table 2.

CONCLUSION

Treatment with radiolabeled somatostatin analogues is very encouraging in terms of long-term outcome, meaning 32% of patients (14/44 patients) with metastatic or inoperable disease are still alive more than 12 years after the beginning of radionuclide therapy. Possible predictors for favourable outcome are initial response to PRRT, number of affected sites and gender. Despite chronic kidney disease in the majority of surviving patients, none of them have needed dialysis treatment and all have remained in good overall clinical condition.

DISCLOSURE

No potential conflicts of interest relevant to this article exist.

REFERENCES

1. De Jong M, Breeman WA, Kwekkeboom DJ, Valkema R, Krenning EP. Tumor imaging and therapy using radiolabeled somatostatin analogues. *Acc Chem Res.* 2009;42:873-880.

2. Forrer F, Uusijärvi H, Storch D, Maecke HR, Mueller-Brand J. Treatment with ^{177}Lu-DOTATOC of patients with relaps of neuroendocrine tumors after treatment with ^{90}Y-DOTA-TOC. *J Nucl Med.* 2005;46:1310-1316.

3. Van Essen M, Krenning EP, Kam BL, de Jong M, Valkema R, Kwekkeboom DJ. Peptide-receptor radionuclide therapy for endocrine tumors. *Nat Rev Endocrinol.* 2009;5:382-392.

4. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate: toxicity, efficacy, and survival. *J Clin Oncol.* 2008;26:2124-2130.

5. Kwekkeboom DJ, Kam BL, van Essen M, et al. Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer.* 2010;17:R53-R73.

6. Kwekkeboom DJ, de Herder WW, van Eijck CH, et al. Peptide receptor radionuclide therapy in patients with gastroenteropancreatic neuroendocrine tumors. *Semin Nucl Med.* 2010;40:78-88.

7. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376:125-135.

8. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for surveillance and medical management of midgut neuroendocrine tumors. *Pancreas.* 2017;46:707-714.

9. Baum RP, Prasad V, Hommann M, Horsch D. Survival benefits and efficacy of peptide receptor radionuclide therapy (PRRT) using Y-90/Lu-177 DOTA-TATE in pancreatic neuroendocrine tumors (pNET). *World J Nucl Med.* 2009;8:230-235.

10. Bodei L, Kwekkeboom DJ, Kidd M, Modlin IM, Krenning EP. Radiolabelled somatostatin analogue therapy of gastroenteropancreatic cancer. *Semin Nucl Med.* 2016;46:225-238.

11. Gabriel M, Andergassen U, Putzer D, et al. Individualized peptide-related-radionuclide-therapy (PRRT) concept using different radiolabelled somatostatin (SST) analogs in advanced cancer patients. *Q J Nucl Med Mol Imaging.* 2010;54:92-99.

12. Gabriel M, Oberauer A, Dobrozemsky G, et al. ^{68}Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. *J Nucl Med.* 2009;50:1427-1434.

13. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21:109-122.

14. Gabriel M, Decristoforo C, Kendler C, et al. ^{68}Gallium-DOTA-Tyr(3)-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. *J Nucl Med.* 2007;48:508-518.

15. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CC, ed. Evaluation of chemotherapeutic agents in cancer. New York: Columbia University Press,1949:191-205.

16. Valkema R, Pauwels S, Kvols LK, et al. Survival and response after peptide receptor radionuclide therapy with [^{90}Y-DOTA0,Tyr^{3}]octreotide in patients with advanced gastroenteropancreatic neuroendocrinetumors. *Semin Nucl Med.* 2006;36:147–156.

17. Bushnell DL Jr, O'Dorisio TM, O'Dorisio MS, et al. ^{90}Y-edotreotide for metastatic carcinoid refractory to octreotide. *J Clin Oncol.* 2010;28:1652–1659.

18. Cwikla JB, Sankowski A, Seklecka N, et al. Efficacy of radionuclide treatment DOTATATE Y-90 in patients with progressive metastatic gastroenteropancreatic neuroendocrine carcinomas (GEP-NETs): a phase II study. *Ann of Oncol.* 2010;21:787–794.

19. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safty of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroenedocrine tumors. *Clin Cancer Res.* 2017;23:4617-4624.

20. Vaughan E, Machta J, Walker M, Toumpanakis C, Caplin M, Navalkissoor S. Retreatment with peptide receptor radionuclide therapy in patients with progressing neuroendocrine tumours: efficacy and prognostic factors for response. *Br J Radiol*. 2018;20:20190041.

21. Van der Zwan WA, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. Radionuclide therapy in neuroendocrine tumors. *Eur J Endocrinology*. 2015;172:R1-R8.

22. Öksüz MÖ, Winter L, Pfannenberg C, et al. Peptide receptor radionuclide therapy of neuroendocrine tumors with (90)Y-DOTATOC: is treatment response predictable by pre-therapeutic uptake of (68)Ga-DOTATOC? *Diagn Interv Imaging*. 2014;95:289-300.

23. Khan S, Krenning EP, van Essen M, Kam BL, Teunissen JJ, Kwekkeboom DJ. Quality of life in 265 patients with gastroenteropancreatic or bronchial neuroendocrine tumors treated with [^{177}Lu-DOTA^{0},TYR^{3}]octreotate. *J Nucl Med.* 2011;52:1361-1368.

24. Haug AR, Auernhammer CJ, Wängler B, et al. ^{68}Ga-DOTATATE PET/CT for the early prediction of response to somatostatin receptor-mediated radionuclide therapy in patients with well-differentiated neuroendocrine tumors. *J Nucl Med.* 2010;51:1349-1356.

25. Werner RA, Lapa C, Ilhan H, et al. Survival prediction in patients undergoing radionuclide therapy based on intratumoral somatoststin-receptor heterogeneity. *Oncotarget.* 2017;8:7039-7049.

26. Hamiditabar M, Ali M, Roys J, et al. Peptide receptor radionuclide therapy with ^{177}Lu-octreotate in patients with somatostatin receptor expressing neuroendocrine tumors: six years´assessment. *Clin Nucl Med.* 2017;42:436-443.

27. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer.* 2015;121:589-597.

28. Ezzeddin S, Attassi M, Yong-Hing CJ, et al. Predictors of long-term outcome in patients with well-differentiated gastrenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with ^{177}Lu-octreotate. *J Nucl Med.* 2014;55:183-190.

29. Ilan E, Sandström M, Wassberg C, et al. Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using ^{177}Lu-DOTATATE. *J Nucl Med.* 2015;56:177-182.

30. Kunikowska J, Pawlak D, Bak MI, Kos-Kudla B, Mikolajczak R, Krolicki L. Long-term results and tolerability of tandem peptide receptor radionuclide therapy with ^{90}Y/^{177}Lu-DOTATATE in neuroendocrine tumors with respect to the primary location: a 10-year study. *Ann Nucl Med.* 2017;31:347-356.

31. Lorenzoni A, Capozza A, Artale S, Mascauro M, Sergni EC. Impressive response to tandem treatment with [^{90}Y]DOTATOC and [^{177}Lu]DOTATOC in grade 3 pancreatic neuroendocrine carcinoma. *Clin Nucl Med*. 2018;43:506-508.

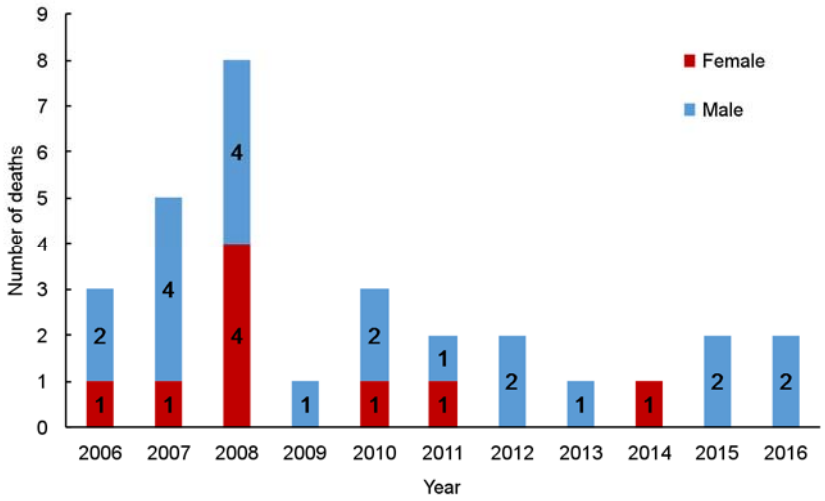

Figure 1.

This figure shows the number of deaths in the various years. Of the female patients three died after 2008.

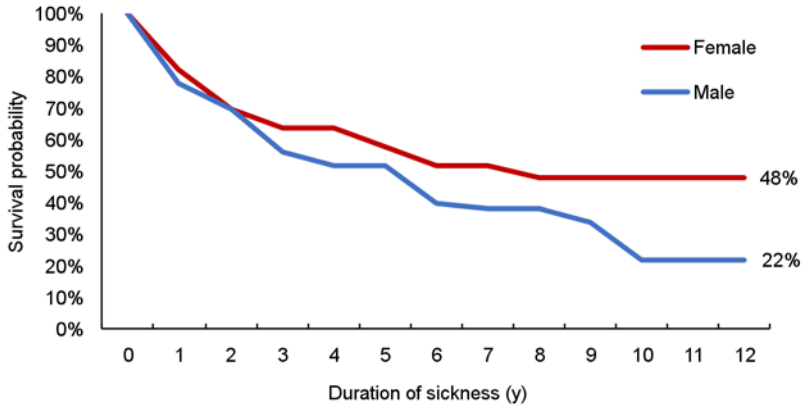

Figure 2.

The following lifespan curves show a clear gender difference. However, the log-rank test gives a *p* value of 0.195.

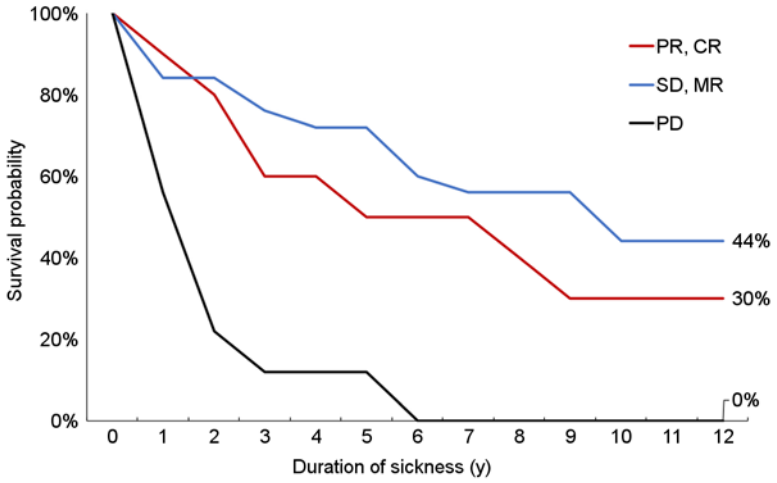

Figure 3.

Kaplan-Meier curves clearly indicate that patients who showed cumulative disease control (CR+PR+MR+SD) after the initial PRRT regime had a significantly better result in terms of OS than did patients with PD, (p <0.001, log-rank).

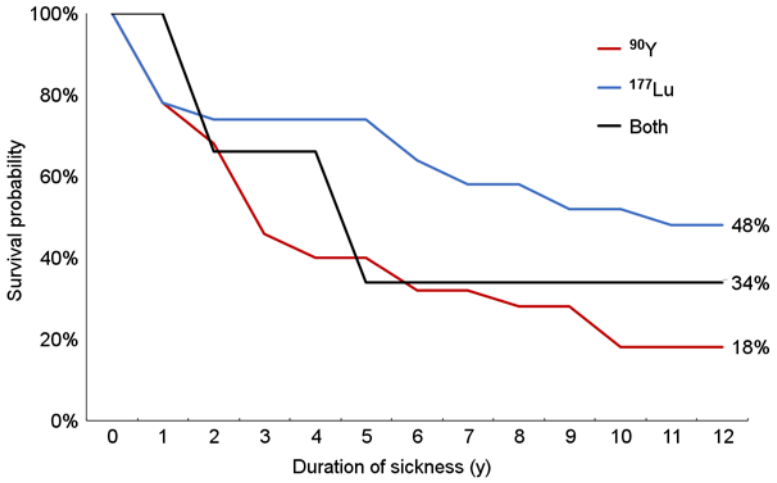

Figure 4.

The following graph shows that only 18% of the patients initially treated with ^{90}Y-therapy are alive after 12 years, while nearly 48% of patients in the ^{177}Lu group are alive.

TABLES

Table 1.

Sex	life_status	no.	mean	SD	min	max
Female	alive	8	55.4	6.2	47	64
	dead	9	62.1	13.2	41	78
Male	alive	6	56.2	6.4	47	62
	dead	21	62.0	12.7	40	84
All	alive	14	55.7	6.0	47	64
	dead	30	62.0	12.6	40	84
	both	44	60.0	11.3	40	84

Age of the deceased patients at the date of death or of the survivors on the final date of evaluation.

Table 2.

Primary tumor	alive	dead	%alive	mean age diagnosis	median survival in months (95% CI)
NET of pancreas	4	12	25.0%	59.3 (11.9)	42 (23;107)
NET of small bowel	6	9	40.0%	58.1 (10.6)	125 (30;NA)
NET unknown primary	2	2	50.0%	59.8 (10.4)	NA (75;NA)
NET of lung	1	3	25.0%	65.8 (5.9)	49 (8;NA)
NET of rectum	1	2	33.3%	67.0 (17.0)	115 (20;NA)
Reticulumsarcoma, Glomustumor	0	2	0.0%	58.5 (20.5)	51.0 (23;79)

Analysis with regard to type of primary tumor.

Table 3.

Number of systems	alive	dead	%alive	mean age diagnosis	median survival in months (95% CI)
1	5	7	41.7%	60.8 (9.4)	97 (23;NA)
2	6	15	28.6%	60.0 (10.6)	81 (41;127)
3,4	3	8	27.3%	59.3 (14.8)	23 (18;NA)

Analysis according to number of affected organ systems.

Table 4.

Respond to therapy	alive	dead	%alive	mean age diagnosis	median survival in months (95% CI)
PR,CR	3	7	30.0%	65.6 (10.7)	86 (23;NA)
SD,MR	11	14	44.0%	57.2 (10.2)	125 (79;NA)
PD	0	9	0.0%	61.6 (13.2)	25 (16;46)

Analysis in terms of initial response to therapy and median OS. PR, partial response; CR, complete response; SD, stable disease; MR, minor response; PD, progressive disease.