Peer Review File

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Answers to Reviewer A.

Comment 1:
INTRODUCTION:
This section would be enhanced if the argument for why PRRT may be helpful in NET patients is more clearly stated. Additionally, authors should state the existing gaps in knowledge re: PRRT application and how their paper seeks to fill those gaps.
Reply 1: text changed as advised, page 7, lines 148-154

Comment 2:
Line 91: "tumor entities" should be revised to "tumors"
Reply 2: changed in text, page 6, line 118

Comment 3:
Line 93: …may release hormones such as somatostatin, serotonin, and neuropeptides
Reply 3: changed in text page 6, line 120

Comment 4:
Line 96: delete "between both entities"
Reply 4: deleted

Comment 5:
Line 100-114:
This paragraph does not set up the rest of the argument well. Should be rewritten to emphasize the points that (1) there aren't a lot of systemic therapies available, no matter what tissue-of-origin, (2) tx by primary sites is different, (3) NETTER-1 was a SBNET trial, (4) surgery can be useful in metastatic disease, but has obvious limitations and drawbacks
Reply 5: Changed in text pages 6-7, lines 132-134, 148-150

Comment 6:
Line 104: the two sentences re: surgical management should be revised for clarity and to communicate the situations in which surgery may be selected for patients with metastatic tumors—i.e. to cytoreduce functional tumors and improve symptoms, possibly to improve survival, to prevent future complications, etc.
Reply 6: text changed as advised page 7, lines 152-154

Comment 7:
Line 111: revise "result in" to "have"
Reply 7: changed, page 7, line 148

Comment 8:
Line 112: should be involves
Reply 8: changed, page 7, line 149

Comment 9:
Line 144: correlations should not be reported as causal. Consider "was associated with," rather

than “resulted in”
Reply 9: changed, page 8, line 242

Comment 10:
Line 147: reference should be cited
Reply 10: reference added, page 8, line 245

MATERIALS AND METHODS
Comment 11:
Line 157: revise “und” to “and”
Reply 11: changed in text page 9, line 257

Comment 12:
Line 181: As G3 NET are included, consider clearly stating that poorly differentiated G3 tumors were excluded from the analysis to prevent any confusion
Reply 12: changed as advised, page 10, line 282

Comment 13:
Line 207: why was 8 weeks chosen as the time point at which the endpoints were calculated? Was it a biologic or pragmatic choice?
Reply 13: this was the pragmatic choice as patients were seen at this interval

RESULTS
Comment 14:
Line 222: rather than “tumor entity,” consider the phrase “primary site” or “primary tumor site”
Reply 14: changed in text, page 12, line 336

Comment 15:
Line 265: Did chromogranin A levels correlate with objective response rates? Or changes in symptom burden?
Reply 15: there was no correlation between chromA levels and objective response rates nor symptom burden
Comment 16:
Line 316: had the patients treated with SIRT previously undergone resection of their primary? In particular it would be important to know if they had a biliary anastomosis.
Reply 16: prior surgery to SIRT and in particular biliary anastomosis has not been done systematically in all patients. As many patients were referred from different external practitioners, previous treatment sequence was not standardized throughout cohort

DISCUSSION:
Comment 17:
Line 347: In patients with NET and peritoneal disease treated with PRRT, there is occasionally talk of PRRT-associated fibrosis or concern for obstruction. Was this present in any of your patients? As a high volume center, can you speak to this phenomenon and its validity?
Reply 17: the presence/absence of PRRT-associated fibrosis was not included in our study

Comment 18:
Line 368: a brief comparison of the differences between NETTER-1 and -2 would be helpful

to understand what knowledge gaps exist around treatment of patients with metastatic NET and why further study beyond NETTER-1 was necessary.
Reply 19: text changed page 19, lines 518-523

Comment 19:
Line 389: The authors should explain the purpose of this test and how it may be useful in this situation/group of patients
Reply 19: text modified, pages 19-20, lines 532-539

Comment 20:
Line 412: again, the authors should be careful not to use language that suggests causation, rather than correlation
Reply 20: reformulated, pages 20-21, lines 561-571

Comment 21:
Line 417-419: the cited study should be described in a bit more detail to better support the author's arguments
Reply 21: explanation added, page 21, lines 579-581

Comment 22:
Line 422: which guidelines?
Repy 22: ENETS and ESMO Guidelines, precision added, page 21, line 590

Comment 23:
Line 427: Any differences in clinicopathologic factors between these two groups of patients that might explain the association? Or are we assuming this is due to accumulated hepatic toxicity? Or because previous SIRT is a surrogate for high tumor burden and thus progressive disease? A more nuanced analysis would benefit.
Reply 23: Clinicopathologic features of tumors weren't included in the analysis of patients receiving SIRT and SSA. Receiving SIRT before PRRT can be seen as a surrogate for high tumor burden and subsequently expose to a higher risk of tumor progression.
Changes in text made page 22, lines 622-624

CONCLUSION:
Comment 24
Line 457: Was the reverse tested? The absence of SIRT after PRRT is not equivalent to PRRT followed by SIRT.
Reply 24: The reverse sequence was not tested. Nonetheless, the results of our analysis could be seen as a trend, i.e. SIRT preceding PRRT showed worse and PRRT followed by SSA better outcomes.

Comment 25:
Line 459: Prospective studies are often suggested but rarely realistic
Reply 25: Randomised prospective studies are certainly needed in order to corroborate our hypothesis.

Comment 26:
FIGURE 2e: Chromogranin A: May be more useful to report the number of patients who experienced a biochemical response after therapy.
Reply 26: Chromogranin A levels did not significantly differ before and after therapy, i.e. no

significant change in blood levels before and after PRRT could be found.
p-value added, page 14, line 387, also new box and whiskers plot added (separate file)

Comment 27:
FIGURE 3: This is probably the best display of the differences in laboratory values. The line graphs could be excluded.
Reply 27: line graphs replaced with box-and-whisker plots (fig 2A-2F), please refer to separate file for new figures

Comment 28:
FIGURE 6: Consider splitting into two figures. Keep SIRT and no SIRT as FIGURE 6, put the two bar graphs describing mortality by primary tumor site as new figure.
Reply 28: New separate figures generated with separate SIRT/no SIRT and figure with mortality by primary tumor site

Comment 29:
TABLE 1: ECOG: were no patients ECOG 0?
Reply 29: 36 patients were ECOG 0 before treatment (t_0)
Mistake in table 1 where rows from ECOG 0 and ECOG 1 shifted is now corrected in table 1

Answers to Reviewer B.

Comment 1:
Line(s)71 and subsequent: When referring to changes in lab results the authors use the term "significant" which I take to mean statistically significant; is there a clinical significance to the degree of change in biomarkers?
Reply 1: Indeed in this context the term significant refers to statistically significant. No clinical significance has been found for platelet and leucocyte decrease
Precision added in text page 4, line 94

Comment 2:
76 and 79 The data is presented as increased mortality odds and increased survival odds in the abstract, but only as mortality odds in the text. Please consider whether the use of mortality odds only would aid in clarity.
Reply 2: changed to mortality odds for better clarity, page 4, line 98

Comment 3:
82 "Patients with advanced GEP-NET clearly benefit from PRRT with Lu-177-DOTATATE". I don't believe this statement is supported in the text of the paper. The data suggests some changes in biomarkers and symptoms, but there is only evidence of limited symptomatic relief and, as there is no comparison to patients without PRRT in this study, it cannot be used to infer increased survival.
Reply 3: reformulated as advised, page 5, lines 106-107

Comment 4:
122 A better data source for reference 13 would be a physics data table – Laboratoire National Henri Becquerel, the national physical laboratory for France, publishes this data at http://www.lnhb.fr/nuclear-data/nuclear-data-table/ but other equivalent sources exist.

Reply 4: table placement added in text, (see separate file for table)

Comment 5:
142-147 I feel a reference is warranted here?
Reply 5: Reference added, page 8, line 245

Comment 6:
159-160 I struggled to understand this sentence – is KISIM a patient database? Perhaps rephrasing would aid the reader?
Reply 6: sentence reformulated, KISIM is an electronic patient register of the hospital, added page 9, line 260

Comment 7:
164-170 How long was the follow-up for these patients? This is a question I have considered throughout the text, and there appears to be no statement of the duration of follow-up time.
Reply 7: maximal follow-up time was 248 months
(please refer to page 17, line 471 of reviewed version with line numbers).

Comment 8:
186-188 Technically, in radionuclide therapies you administer an activity not a dose. I am also interested in the how the activity was adapted to individual patients. With the move to personalised radiation dosimetry in radionuclide therapies, details of dose adaptation is becoming more important in understanding the dose profile to the patient and subsequent side-effects and survival data.
Reply 8:

- The term 'dose' has been changed to 'activity' throughout the manuscript
- Activity dosages have been administered according to the radionuclide manufacturer's protocol which stipulates a standard activity that has to be given. As there is not sufficient randomized research that activity adjustments should be made with Lutetium, minor adjustments of administered activities have been made according to patient's renal function
- Precisions made in text, page 10, lines 289-292

Comment 9:
191-192 "…the reference dosage activity was…" I think this should read "…the reference dose rate was…"
Reply 9: changed to reference activity, page 10, line 295

Comment 10:
207-209 I'm unclear whether the measures examined included symptom burden at 8 weeks and survival at 8 weeks, or symptom burden at 8 weeks and overall survival at the end of the follow up period. If it is the latter (and I suspect it is), is there some standardisation of the follow up period? As you are recruiting patients who had PRRT over a five year period you may be comparing mortality at 5 years and mortality at 10 years which will skew your comparisons.
Reply 10:

- Symptom burden at 8 weeks and overall survival at end of follow-up.
- Standardization of follow-up period was extremely difficult as many patients were referred from external institutions. Heterogeneity of treatment time and intervals is a limitation of our study and the fact that many patients were sent from whole Switzerland and abroad made standardized follow-up more difficult.

- Precision added in text, page 11, lines 318-320

Comment 11:
217 The text refers to table 1, but this appears to be labelled as table 3 at line 660
Reply 11: mislabeling of table 3 changed to table 1 (please refer to separate file)

Comment 12:
219 The text refers to supplemental figures 1 and 2, but unfortunately these figures are missing and there is no further reference to the changes in body weight in the text.
Reply 12: prescision on weight changes added in text, page 12, lines 332-334

Comment 13:
224 Table 2 has been mislabelled as table 4 at line 662
Reply: mislabeling of table 4 changed to table 2 (please refer to separate file)

Comment 14:
255-266 I'm unclear at which time points the biochemical and blood count results refer to, and this is common throughout the rest of the paper. For individual patients, are these prior to all cycles of PRRT and after completion of all cycles of PRRT? Or are these the mean of each patients pre- and post-PRRT cycle values averaged over all cycles? If it is the latter, I'm not sure that this is an appropriate way to present this data – by averaging it may mask incomplete recovery between fractions and/or worsening results after each subsequent fraction. Please also see comments on figures 2A-F
Reply 14: values were taken prior to all cycles of PRRT and after completion of all PRRT cycles, not averaged. The idea was to evaluate the 'overall' tolerability of the treatment and biochemical changes pre and post PRRT. As not all patients received the same number of cycles, values were collected prior to any PRRT and after completion of all PRRT cycles for an individual patient
Precision added page 14, lines 392-393

Comment 15:
266 The figures in the brackets appear to be GFR measurements, however they are labelled as percentages. I am unclear as to what these are percentages of – should these be filtration rates with units of ml/min?
Reply 15: yes, ml/min not %, p-values added page 14, lines 387-388

Comment 16:
268-275 There is a wealth of really interesting data in this paragraph, but the formatting is confusing and makes it difficult to interpret. Might a table of the data help in understanding? A different plot of the data may also help in reader understanding (more later)
Reply 16: new table added for better understanding of values (please see table in separate file)

Comment 17:
268-275 There are a lot of abbreviations in this section which are not defined anywhere – this might be easily addressed if a table of data is included.
Reply 17: Abbreviations explained in new table 4 (please refer to separate file)

Comment 18:
268-275 Again, it is unclear at which point the measurements were taken – following all cycles, averaged over each cycle etc.

Reply 18: measurements were taken prior to all PRRT cycles and after completion of all cycles, precision added to text page 14, lines 392-393

Comment 19:
294 Where is the data demonstrating the time between diagnosis and PRRT and outcome?
Reply 19: Please refer to page 15, lines 424-426
"There was no significant correlation between the time between diagnosis and PRRT onset and survival (Chi-square-test, p = 0,384)"
In figure 4 the first arrow indicates in a graphic way the time elapsed (in years) between initial diagnosis and initiation of the first PRRT cycle. Outcome is not demonstrated in this graph. The figure indicates the timepoint of PRRT on a timeline in relation to other therapy modalities (key added to figure)

Comment 20:
302 When summing the percentage of patients with P-NET and GE-NET as presented in the text, the total is 99.5 %.
Reply 20: This is a typing mistake, thank you. Corrected, page 16, line 433

Comment 21:
314-317 I am concerned there may not be enough data to have any validity in comparisons of post-SIRT mortality between P-NET and GE-NET patients, particularly given the heterogeneous treatment regimens and follow-up periods.
Reply 21: Indeed. We are aware that the numbers of patients analyzed in the subgroups are very limited. We might suggest that the results could cautiously be interpreted as a trend but obviously this would have to be proven with larger patient samples.
Precision added page 16, lines 448-449

Comment 22:
319-322 The text refers to comparisons of ECOG and HRQoL scores compared between patients who had and had not had previous SIRT, but the data does not appear anywhere.
Reply 22: As no significant differences in ECOG score nor HRQoL was found when comparing groups with or without SIRT, the data was not presented graphically, data added page 16, lines 453-454

Comment 23:
408 There is comment on the number of treatments prior to PRRT, however this data is not presented in the results section.
Reply 23: please refer to page 17, lines 461-463
"An analysis of the potential impact of the number of previous treatments on survival showed no significant correlation between the number of therapies and the outcome (Chi-square-test, p = 0,281)"
As patients received between 0-5 other treatment modalities before receiving PRRT (chemotherapy, surgery, radiotherapy etc.) we couldn't find a correlation between the number of treatments prior to PRRT and survival

Comment 24:
425-429 The data for the sub-group analysis of blood results or HRQoL scores was not presented in the results.
Reply 24: data added page 16, lines 451-454

Comment 25:

424-426 I feel the paper would benefit from a stronger discussion about the reason behind the increased mortality rate in the group which previously received SIRT. As you have stated, there is very little published data in the literature about the benefits or detriment of prior SIRT treatment and so this is one of the most important findings of your paper – did this patient group have more advanced disease before PRRT? What was the timing between diagnosis-SIRT-PRRT-Death? Had this group of patients simply had longer follow-up between PRRT and the end of the study?
Reply: precision added in text, page 22, lines 605-623

Comment 26:
457 "…and reduces survival compared to using this sequence vice versa". This data is not presented in the text and no comparison appears to have been made? If this can be demonstrated by the data analysis it would be an important finding and would deserve more prominence.
Reply 26: The sequence PRRT followed by SIRT has not been analyzed as only 2 patients had documented SIRT once PRRT cycles were terminated.
Passage modified, page 24, line 667

Comment 27:
Figures 2A-F These are not the correct plots for presentation of this type of data; there is no relationship between patients and using lines to join the results of different patients infers they are linked.
A more powerful way to demonstrate the outcomes would be to use something paired data in a box and whisker plot which will show the distribution of results and how the results vary after PRRT. Examples of this can be found online (and I would recommend reading this paper Beyond Bar and Line Graphs: Time for a New Data Presentation Paradigm | PLOS Biology https://doi.org/10.1371/journal.pbio.1002128 for more information)
Reply 27: figures 2A-2F replaced by box and whisker plots, please refer to separate file for new figures

Comment 28:
Figure 3 There needs to be more explanation of the abbreviations in the key
Reply 28: key added to figure (please refer to separate file for figures)

Comment 29:
Figure 4 Unfortunately image compression has resulted in loss of resolution – is there a better version of this? In addition, I'm not sure what the image demonstrates – does the interval between treatments post-PRRT indicate treatment duration? And what are the interventions?
Reply 29: Numbers in intervals post-PRRT indicate elapsed time (in months) and T1 T2 T3 (=interventions) stand for treatment modalities other than PRRT (e.g. chemotherapy, radiotherapy etc.)
Key to figure added to figure (please refer to separate file)

Comment 30:
Figure 5 I don't believe this figure adds value to the paper; consider removing this in the interests of brevity.
Reply 30: figure 5 removed

Comment 31:
Figure 6 This figure is one of the more important in the paper; perhaps consider splitting this into two separate plots, one for SIRT/No SIRT and another for P-NET/GE-NET to make it

easier to interpret the data. If this is not possible, a better description of the plots would aid in reader understanding. I would also consider using stacked bar-chart to demonstrate the difference in group sizes as well as the proportion in each outcome.
Reply 31: figure 6 splitted as suggested in separate plots (please refer to separate file)

Comment 32:
Table 3 As mentioned earlier, the table has been mislabeled as table 3 rather than table 1.
Reply 32: Revised

Comment 33:
Table 3 Is the data presented in the table that at diagnosis, at time of first cycle of PRRT, at end of the first cycle of PRRT, or at the end of all cycles of PRRT? Explanation of this would be beneficial in better understanding the patient cohort.
Reply 33: table represents data before start with PRRT
Precision added to table (please refer to separate file)

Comment 34:
Table 3 The ECOG data only runs from 1-4, whereas in table 4 the data is stratified into 0-4. Should the first category in this table be "0-1"?
Reply 34: yes, this is a mistake, thank you. Corrected in table.

Comment 35:
Table 1 Given the heterogeneity of the patient population you have examined, perhaps a table giving data at an individual patient level might be beneficial? For example:
Patient 1 – Female, 23 years, ECOG prior PRRT =1, post PRRT =1, P-NET, G1,…
Patient 2 – Male, 83 years, ECOG prior PRRT =1, post PRRT =0, GE-NET, G1,…
Reply 35: thank you for this valuable comment. Although such a table might be beneficial, we fear that it would add too much data to the paper which is why we decided to summarize patient characteristic data in table 1.

Comment 36:
General comments
The manuscript would benefit with a thorough proof-reading by one author as the terminology used varies during the paper (for example, the terms "pancreatic tumor", "pancreatic NET", "PNET" and "P-NET" are used interchangeably). In addition, the use of sub-script and super-script notation varies through the paper (e.g. "Tyr3" and "Tyr3") and would aid in interpretation. There are also some typographic errors which should be corrected
Reply 36: done

Comment 37:
Some restructuring of the paper would strengthen the arguments, particularly in the discussion where the argument moved back and forth from the effect of SIRT and the effect of SSAs. Addressing each separately would help to clarify the message of the paper and better outline the strengths and limitations of the data
Reply 37: Discussion restructured and precisions added
Page 21, lines 580-589
Page 22, lines 620-625

Comment 38:
Abbreviations are not consistently defined in the text which slows reading and comprehension – If the journal allows, a table of abbreviations may be beneficial

Reply 38: abbreviations defined when first used, table of abbreviations at the beginning