Author’s response to reviews

Title: Development of a Disease-Specific Graded Prognostic Assessment index for the management of Sarcoma patients with Brain Metastases (Sarcoma-GPA).

Authors:
Anna Patrikidou (anna.patrikidou@hcahealthcare.co.uk;anna.patrikidou@sarahcannoresearch.co.uk)
Loic Chaigneau (lchaigneau@chu-besancon.fr)
Nicolas Isambert (NIsambert@cgfl.fr)
Kyriaki Kitikidou (kkitikid@fmenr.duth.gr)
Ryan Shanley (shan0219@umn.edu)
Isabelle Ray-Coquard (isabelle.ray-coquard@lyon.unicancer.fr)
Thibaud Valentin (valentin.thibaud@iuct-oncopole.fr)
Bettina Malivoir (B.MALIVOIR@chu-tours.fr)
Maryline Laigre (maryline.laigre@icm.unicancer.fr)
Jacques-Oliver Bay (jobay@chu-clermontferrand.fr)
Laurence Moureau-Zabotto (moureaul@ipc.unicancer.fr)
Emmanuelle Bompas (Emmanuelle.Bompas@ico.unicancer.fr)
Sophie Piperno-Neumann (sophie.piperno-neumann@curie.net)
Nicolas Penel (n-penel@o-lambret.fr)
Thierry Alcindor (thierry.alcindor@mcgill.ca)
Cecile Guillemet (cecile.guillemet@chb.unicancer.fr)
Florence Duffaud (florence.duffaud@ap-hm.fr)
Anne Hugli (annehugli@bluewin.ch)
Cecile Le Pechoux (cecile.lepechoux@gustaveroussy.fr)
Dear Madam,

We are delighted to submit our revised manuscript entitled “Development of a Disease-Specific Graded Prognostic Assessment index for the management of Sarcoma patients with Brain Metastases (Sarcoma-GPA)”, revised according to reviewers comments and suggestions.

We thank all reviewers for their comments and the appreciation of the collaborative project effort and the challenges involved. Please find below detailed consideration and responses to Reviewers comments:

Reviewer 1:

- Group H4, which included ASPS, had indeed the best prognosis in our cohort (20.45 months), whilst group H1 had the worst prognosis (1.22 months); these results are depicted in Figure 1A, and are in agreement with the description in the manuscript text. The sub-cohort of ASPS only (n=14) featured an OS of 17.33 months, in line with the overall good prognosis of the H4 group they belong to.
- Histological diversity of sarcoma is a challenge even for the experts of this disease, and was definitely the major challenge for this work. Exactly because of the difficulties in addressing such a heterogeneous group of tumours, our initial approach to this analysis did not include histology, in the hope of identifying other strong cross-cutting prognostic factors. However, it was impossible to obtain a powerful prognostic index without the inclusion of histology.

- There are two important reasons why we have not included treatment-related variables in the Sarcoma GPA: 1) The point of a prognostic index is to estimate survival prior to treatment in order to guide choice of treatment, rather than reflect/assess the treatment effect and 2) these data are retrospective with inherent selection bias, so these data cannot be used to determine whether one treatment is better than another. For these reasons, none of the previously described GPA indices have included treatment either.

Reviewer 2

- As discussed above, the type of treatment was not included in the analyses because the purpose of a prognostic index such as the GPA is to estimate survival prior to treatment in order to guide treatment decisions. Nonetheless, details of treatment modalities, originally reported in the Chaigneau et al 2018 Oncologist paper, are now included in our manuscript as Supplementary Table 1 (updated cohort) and cited in the manuscript. It should be also noted that the significance of treatment was indeed highlighted in the initial report by Chaigneau et al, which indicated treatment modalities (surgery, WBRT, SRS, chemotherapy) as independently significant for OS; the aim of this study was a step further, to aid decision-making on which patients we ought to treat.

- This study reports on patients managed over a very large period of time, as was necessary in order to obtain a large enough cohort, owing to the rarity of brain metastases in sarcoma patients. In this period of over 25 years since the beginning of our reporting period, management of metastatic brain disease has enormously evolved, from very conservative and restricted to more aggressive even in the presence of extracranial disease, and this evolution is reflected in the reported treatment modalities, although the latter is not the main subject of this paper.

- The aim of the histological grouping used for the index construction was to identify a meaningful way to segregate how different histologies fare according to BM patient survival, rather than using/suggesting a strict histological affinity classification. Nevertheless, a certain lineage segregation is indeed reflected in the H1-H4 grouping (for example, adipocytic tumours in H1 and musculoskeletal tumour in H2).
- There are two important reasons why we have not included treatment factors in the Sarcoma GPA: 1) The point of a prognostic index is to estimate survival prior to treatment in order to guide choice of treatment, rather than reflect/assess the treatment effect and 2) these data are retrospective with inherent selection bias, so these data cannot be used to determine whether one treatment is better than another. For these reasons, none of the previously described GPA indices have included treatment either.

- High-quality illustrations will be provided for the revised manuscript submission.

Reviewer 3

- This project’s aims was to assess the validity of the original GPA index (Sperduto JCO 2008) in sarcoma patients and to develop a sarcoma-specific GPA index; given that the study evaluates the utility of a prognostic index, OS was indeed the main endpoint variable; time to brain metastasis (TtBM) and time from first metastasis to development of brain metastasis (TMtBM) –potentially indicative of disease aggressiveness- are just some of the other analysed variables.

- In regard with progression outside the brain (extracranial metastases, ECM), the presence and type of ECM was recorded and analysed. In fact, ECM (in contrast with what was found for other tumour types in previous GPA publications) was not significant for OS in the univariate (previously Table 2, now Table 3), therefore was not analysed further.

- For the implementation of the GPA index on our sarcoma cohort, data for each of the four index components were coded according to the original GPA score, therefore cut-offs as per the original GPA score were used. For the description of the Sarcoma-GPA, cut-offs were decided based on previous GPA indices and on biological sense. Given that the study aim was to identify a meaningful, prognostic way of separating patient subgroups in terms of prognosis, in several instances different variations of cut-offs were attempted in order to identify significant, meaningful cut-offs. One such example was patient age, which is a component of the original GPA and the subsequent DS-GPAs. Despite repeated analysis with different cut-offs for this continuous variable, we were unable to identify significance, and therefore this was excluded from the final model. This is now detailed in the manuscript.

- Higher quality figures are to be submitted with the revised manuscript

- Figure 1 has now been modified to only show variables significant in MVA.
The information on the pairwise comparisons was considered important by the authors to show the strength of the constructed index, and this is why they were incorporated in the figures. At the reviewer’s suggestion, these have now been removed from all figures, except for the Sarcoma-GPA figure, within which they are presented as a separate table.

As per the reviewer’s suggestion, Table S1 is now incorporated in the manuscript as Table 1.

The reviewer suggests “there should be a table that highlights the features of the prognostic index with the score for each variable, and that this should be the main table of the manuscript together with Figure 3”. Figure 3 actually incorporates such a table (Figure 3A), created in such a way so as to avoid multiple illustrations while presenting the important features of the Sarcoma-GPA in one illustration.

The reviewer suggests “the authors should report in the discussion that the main limitation of the study is the lack of a validation of the prognostic index in an independent set. Do they have any plan for future validation?”. Both points (need for independent validation and future plans for it) are already mentioned in the manuscript Conclusion section.

The GPA index is now introduced in the Abstract (Background).

The incidence of brain metastases in sarcoma is now added in the Introduction of the manuscript; it should be noted that it was already mentioned in the Discussion section.

Some of the data published in the Chaigneau et al 2018 Oncologist paper originally reporting results of the GSF-GETO series are now included in the Introduction.

The phrase “The development of the sarcoma-specific index was done in collaboration with the team that described the original and disease-specific GPA indices” has now been moved to the Methods section.

Reviewer 4

A quantitative measure of goodness of fit has now been added by means of c-index and ROC analysis, showing improvement comparing to the original GPA.

Details on the treatment modalities patients received are now included in Supplementary Table 1.
The type of treatment was not included in the analyses because the purpose of a prognostic index such as the GPA is to estimate survival prior to treatment in order to guide treatment decisions. It should be also noted that the significance of treatment was indeed highlighted in the initial report by Chaigneau et al, which indicated treatment modalities (surgery, WBRT, SRS, chemotherapy) as independently significant for OS; the aim of this study was a step further, to aid decision-making on which patients we ought to treat.

The treating physicians individually decided the choice of treatment. The study analysis is retrospective in nature, so it did not influence treatment choices.

Higher quality figures are provided with the revised manuscript.

Figure 3A: the fact the PS refers to ECOG PS is now clarified in the figure legend.

Reviewer 5

Estimated survivals for the histology groups H1 to H3 are indeed less than 12 months. Nevertheless, as shown in the pairwise comparisons previously included in Figure 1A, all pairwise comparisons showed statistically significant difference (a relevant comment has now been added to the text, as the pairwise comparisons were removed by the figures at the suggestion of Reviewer 3. Nonetheless, with the exception of H4, we agree with the reviewer that histology on its own would probably not be enough to direct treatment decisions. The final Sarcoma-GPA index, however, further improves this and is capable to identify two subgroups with estimated OS of over 6 months (scores 2.5-3 and 3.5-4.0), compared to the other two subgroups with estimated OS of less than 6 months.

The aim of the histological grouping used for the index construction was to identify a meaningful way to segregate how different histologies fare according to BM patient survival, rather than using/suggesting a strict histological affinity classification. Nevertheless, a certain biological/lineage coherence is indeed reflected in the H1-H4 grouping (for example, adipocytic tumours in H1 and musculoskeletal tumors in H2).

The total number of the patient cohort (n=251) is included in the Results section. More details on the previously published analysis results are now included in the manuscript.

The cause of death (brain versus extracranial progression or other) was unfortunately not included in the collected variables, therefore no such analysis can be made.
Reviewer 6

- This study reports on patients managed over a very large period of time, as was necessary in order to obtain a large enough cohort, owing to the rarity of brain metastases in sarcoma patients. In this period of over 25 years since the beginning of our reporting period, management of metastatic brain disease has enormously evolved, from very conservative and restricted to more aggressive even in the presence of extracranial disease, and this evolution is reflected in the reported treatment modalities. However, the comparative analysis of treatment modalities was outside the scope of this paper.

- The date of diagnosis was indeed amongst the collected data, but it is no reported in the manuscript as not strictly related with the index development. Approximately one third of the patient cohort was treated in the decade of 1990 to 2000, and two thirds in the decade 2000 to 2010.

- The cause of death (brain versus extracranial progression or other) was unfortunately not included in the collected variables, therefore no such analysis can be made.

- A validation study is indeed planned, and will inevitably include more recently managed patients.

All authors have approved the revised manuscript.

We thank you in advance for the time and effort in considering our work for publication.

Yours sincerely,

Anna Patrikidou
for the authors