

## Peer Review File

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### Reviewer A

This is a narrative review of prognostic indices for patients undergoing palliative RT and implications for appropriate choice of fractionation. The manuscript is generally well-written and proof-read, although there are several inconsistencies between text and Tables. It is a useful contribution to the literature in my opinion.

Specific points:

1. Although not a systematic review, it would be helpful and relevant to give some sense as to how many prognostic indices there are, and why these particular ones were chosen (if applicable).
  - a. Upon our initial search, there were ~500 yielded results, in which most articles discuss the clinical outcomes of palliative radiotherapy (PRT) of a single institution, retrospective experience. There were other articles that offer nomograms for various risks or side effects of offering PRT. We chose scoring systems that offer estimates of prognosis for those patients who are receiving PRT. Lung and Head and neck cancers are common primary sites requiring PRT in the United States, and gastric cancer is common in Asian countries. The multiple metastatic site models that were chosen for a few reasons. First, the initial *Chow* model discussed is one of the first to attempt prognostication for those receiving PRT and the historical context is of interest to readers. The following models are more modern, and two of them (METSSS and PAC) even have built in calculators that would be easy to use for physicians to use. The authors felt the practicality of the presented studies would offer new information that would help radiation oncologists in real time during clinic. This reflection has been included in the introduction, stating that prognostication is important for setting expectations, arranging affairs, and guiding decision making for fractionation.
2. Methods - it is usual to interrogate more than one database. This requires a comment.
  - a. A search with keywords used within PubMed, Cochrane, and Embase yielded similar results. Additionally, as this reviewer acknowledges, the methods were clear that this was not a systematic or scoping review, but a narrative review of clinically useful prognostic scoring systems. As such, we felt one database was sufficient.
3. Line 149 - why is a score of 10 missing?
  - a. In the original text of the paper by Rades et al., no patient received a score of 10 and were therefore not included.

4. Line 182 - dyspnea AT rest?
  - a. This has been corrected.
5. Tables 2 & 3 - it would be helpful to include the reference numbers.
  - a. Reference numbers are now included.
6. Table 2- for consistency with the text, Sekii should be last. Column 4 header should say median OS.
  - a. This has been corrected.
7. Table 2 - lung: are the KPS scores the wrong way around? Median survival of 12 mo. for score 12-14 conflicts with text (6 mo. in line 112). Is “hyperfractionation” accurate for score 15-17?
  - a. In the original paper by Rades et al., the KPS score <60 was given a score of 5 and KPS >70 was given a score of 3. The 12 mo survival was inadvertently represented as 6 months in the Table, we have corrected this error. For a score of 15-17, a conventional course of radiation or a longer palliative course could be recommended, not hyperfractionation (i.e., twice-daily or three-times-daily treatments sometimes utilized in definitive management of certain cancers such as head and neck cancer).
8. Line 228 - lung score is 6 rather than 7.
  - a. This has been corrected.
9. Table 3 - Chow (2002), Group C score should be greater than or equal to 20. Krishnan, last column, replace Group A-C with A-B. Several acronyms need to be defined.
  - a. This has been corrected. The ESAS (Edmonton Scoring assessment system) has been defined.
10. Line 302 - the Oswestry Risk Index has not been previously mentioned and requires some elaboration.
  - a. Further elaboration has been provided with an additional reference.
11. Line 304 - clinicAL factors?
  - a. This has been edited.
12. Lines 369-71 - this sentence needs reworking.
  - a. This has been revised into two sentences: “Additional methods to provide a personalized risk assessment of life expectancy are needed to inform clinical judgement. Further personalization may help with the selection of patients for PRT, symptomatic targets, RT techniques, and dose regimens.”

## **Reviewer B**

Overall this is a paper that will add to the existing literature. It is a good summary of some of the prognostic models out there with some context about each one.

It is important to also acknowledge that there are other prognostic models that exist, specifically for particular sites of metastatic disease (i.e. the GPA for brain mets) and other such spine specific prognostic models. It is perfectly fine to not include these, but

it is worth a mention that they were not included (perhaps because they did not arise with the including search criteria).

- We appreciate the Reviewer mentioning this point. As described elsewhere, and emphasized in the updated version of the manuscript, this article is a narrative review and thus summarizes a select number of prognostic scoring systems. This is not a systematic review of all prognostic systems in PRT. In response to this point, we added a paragraph on limitations within the discussion (see last paragraph of the Discussion section). In these limitations, we also discuss that other scoring systems (e.g., GPA for brain metastases, Dutch scoring system for spine metastases) were not included. Specifically, lines 403-416 state: “This review has several strengths. First it describes PRT scoring systems that can be used for patients with metastatic or non-metastatic disease. Several of the included models are pragmatic, utilizing a limited number of readily available patient characteristics, and thus can be applied when seeing patients in the clinic or hospital wards. Despite these strengths, this review is not without limitations. For example, several of the described scoring systems are not externally validated and several are based on older, retrospective cohorts. Additionally, this is a narrative review of prognostic scoring systems relevant to clinical decision-making in patients treated with PRT, and thus does not summarize every available model. Other prognostic models – for example, the graded prognostic assessment (GPA) for brain metastases<sup>43</sup> and the Dutch scoring system for spine metastases<sup>44</sup> – do exist and were not included in this article. The goal of this review was to summarize select prognostic models to provide radiation oncologists an understanding of their application in PRT.”

I would also clarify more about the PPI. This is a previously developed model that was then used in this paper. I was confused at first because the H&N and lung had models which noted higher scores were better survival and then in the Gastric study it mentioned that PPI has higher scores are worse survival ("similar to prior studies"). These prior studies are prior PPI studies, but this is confusing after reading about the H&N and lung sites, so more clarity in the arena would be helpful.

- This reviewer highlights an important issue that can be confusing when reviewing multiple scoring systems in a single manuscript. The head and neck and lung prognostic models (Rades et al) are indeed distinct from the PPI used in the analysis of gastric cancers by Sekii. In the Rades studies, higher scores were associated with improved OS. However, in the PPI, used by Sekii and in other studies (see citation 18), higher scores are associated with worse OS. PPI and the models developed by Rades are distinct and thus their scores do not correlate. To emphasize these differences, we have added a sentence in the section on the use of PPI for palliation of gastric cancers. Specifically, line 200 clarifies “on the prognostic value of the PPI” and line 202-203 states, “This is distinct from the previously described studies by Rades et al , where higher scores were associated with improved OS.” We hope this will ameliorate the confusion about the studies in the original version.

## Reviewer C

The authors of this article address the heterogeneous nature of palliative radiotherapy and its indications with regards to patients' prognosis with a narrative review. Decision making tools for choosing appropriate palliative radiotherapy schedule are needed, the indications for palliative radiotherapy diverse and different palliative radiotherapy schedules applied. In this article, the authors summaries studies on prognostic scoring systems that can be used to aid in decision making.

The article is well written and in good English, however as for most manuscripts there is room for improvement.

### General comments

The heterogeneity of palliative radiotherapy practice patterns is the trigger for the study; however, the vastness of cancer diagnosis and treatment makes it hard to summarize in one article and conclude a recommendation. I wonder if the topic of the article is maybe too vast, at the cost of the article depth and that the article would have more depth focusing on one metastatic site or one type of cancer.

- Thank you for this comment. It is challenging to 'toe the line' of depth versus breadth for a topic such as this. This article is a narrative review and thus is intended to provide the reader with examples of prognostic models used for PRT. This article is not a systematic review and does not describe every PRT scoring system. The goal of this article is to provide radiation oncologists who treat patients with a wide variety of malignancies with PRT with examples of models that can be used to guide PRT fractionation either in patients with metastatic disease or non-metastatic disease. We have updated the text in multiple places (see Introduction and Discussion) to clarify the purpose of this article. We hope these clarifications help resolve the Reviewer's concern about article depth.

### Major comments

#### 1. Introduction

a) Line 70-74: "By consolidating and highlighting modern prognostic systems for patients treated with PRT, this pragmatic review is intended to guide radiation oncologists' practice by assisting clinical decision-making regarding patient and target selection, determination of treatment technique, total dose, and fractionation."

The article intent is very wide, and the article is missing follow-up on this in both the results and the discussions. In my understanding after reading this article the prognostic scores mainly guide in deciding which fractionation schedule and hence total dose to use.

- We have modified this sentence to reflect that patient selection and fraction are the main focuses of this article. Specifically, in lines 69-74: the revised paragraph reads: By consolidating and highlighting modern prognostic systems for patients treated with PRT, this pragmatic review is intended to guide radiation oncologists' practice by assisting clinical decision-making regarding patient selection and fractionation, as well as providing an estimate of prognosis that may help patients and their families get their affairs in order.”

b) The introduction is rather limited. The authors focus on three different cancers; lung, head and neck, and gastric cancer, as well as palliative radiotherapy for multiple metastatic sites. Why focus on only these three cancers?

- In our literature search, these specific prognostic scores for these individuals disease sites were identified and felt to be of interest, as these are common indications for palliative radiation.

c) Why is prognosis so important for a treatment which main goal is palliation? A reflection on this is needed in the introduction.

- The authors believe the inclusion of prognosis within our study is meant to be of use to the radiation oncologist during discussion with the patient and their family members. Of course, patients and their family members are often interested in knowing the potential estimated prognosis for a multitude of personal and logistical reasons relating to PRT. Similarly, depending on the overall picture of the cancer disease spread (i.e. polymetastatic versus oligometastatic, number of systemic therapies completed, and histology), having a general idea of prognosis may help guide decision making for palliative radiation. This increases the utility by limiting the number of fractions for those with poor prognosis while selecting patients who may benefit from a more durable course of PRT, as well as identifying patient at high risk of futile PRT (those who have such limited prognosis they may not survive long enough to experience the full palliative effects of PRT. In some cases, the patient's goals are more oriented toward longevity during the PRT discussion (rather than simply palliation of symptoms), and an adequate estimation of prognosis at the time of PRT can help guide the discussion. For these reasons, the authors believe it is important to include prognosis even if the intent of the radiation therapy is palliative.

## 2. Methods

a) Were other databases than PubMed queried, and if not why?

- Only PubMed was queried to develop this article. Given that this article was designed as a narrative review, its goal was to introduce the reader to scoring systems useful in the case of selecting patients for PRT and the optimal fractionation to be used (if applicable). A systematic review of all PRT scoring systems is outside the scope of this article. The Methods and Discussion (see paragraph on study limitations) sections were updated to reflect these points.

Additionally, we felt it to be an appropriate search strategy considering the use of a single database is consistent with other review articles published within this journal. Examples include: doi: 10.21037/apm-22-1338, doi: 10.21037/apm-21-363, doi: 10.21037/apm-22-693.

b) What types of studies were included? – a brief description of the studies included might be presented in a table.

- As described in Table 1 of the manuscript “Only articles discussing scoring systems that estimated survival after PRT were included. Articles must be published in English and peer-reviewed.” This point has been added to the methods section. The specific studies selected for the article are further summarized in Tables 2 and 3. Specifically, lines 83-84 read: “Only articles discussing scoring systems that estimated survival after PRT were included.”

### 3. Results

a) One study for each cancer site makes the results a summary of the study cohorts and results, without any analytical input from the authors or context. For example, limitations and strengths of each study are described in the section on multiple metastatic sites, but this is lacking in the sections covering lung, head and neck and gastric cancer.

- Thank you for this suggestion. We have added our interpretation of the strengths and limitations of the lung, head and neck, and gastric PRT scoring systems. This can be found at the end of each of the respective sections.

### 4. Discussion

a) Same comment as in 1 a) – The aim of the study is broad and coming back to this in the discussions would summarize the article contents.

- We added a sentence at the end of the first paragraph to summarize the aim of this article. Specifically, we state “This article summarizes scoring systems that radiation oncologists can use to select appropriate PRT fraction schemes for patients with metastatic and non-metastatic disease.” We believe provides additional clarity.

### Minor comments

1. Line 59-60: Nearly one third of cancer patients receive palliative radiation therapy (PRT) as a part of their cancer treatment.

The article the authors cite describes palliative radiotherapy in first line treatment. To my knowledge, it is more than third of cancer patients that at least have an indication for palliative radiotherapy, probably closer to half, however limited access to radiotherapy might limit the number that actually receives palliative radiotherapy.

- Thank you for bringing this point to our attention. After further review, we found that palliative radiotherapy is used in closer to 40-50% of patients with cancer. We have updated this sentence and the associated citations. Specifically, lines

51-52 read: “Nearly one half of cancer patients receive palliative radiation therapy (PRT) as a part of their cancer treatment<sup>1,2</sup>”

2. Line 61- 62: ...recommendations are based on multiple factors including primary histology, anatomic location, and patients’ goals of care....

Instead of primary histology primary site as written in the abstract might be more appropriate and anatomic location of metastases.

- We have adjusted this sentence to say “primary site” instead of “primary histology.” Thank you for the suggestion.

3. The cohorts behind each study described in detail that seem a little redundant, could they be shortened?

- Thank you for the suggestion, however, we feel that this level of detail is relevant to the readers understanding of the included studies. Given that each study used different populations, clinical/treatment factors, etc., we think it provides helpful context for the reader. Additionally, the reader can use this information to determine whether the scale being discussed is relevant to the patient/population they work with. As a narrative review, our hope is that this article becomes a handy reference for radiation oncologists providing PRT, that can stand alone as a reference and provide all necessary context without requiring the reader to search for the primary article (which of course they are still welcome to do with the time/interest).

4. Line 136: hypofractionation (e.g. 40-55 Gy in 2-2.5 Gy fractions)

I would not say 2 Gy per fraction is hypofractionation.

- We have clarified the text to say “55 Gy in 2.5 Gy fractions), which is hypofractionation.
- Lines 146-147: “moderate hypofractionation (e.g. 55 Gy in 2.5 Gy fractions)<sup>13</sup> to conventionally fractionated definitive-dose regimens”

5. The paragraph on stereotactic body radiotherapy is outside the scope of the article.

- While we appreciate the reviewer’s comment, we believe a brief (122 word) discussion of SBRT is relevant to this article. Given this article is focused on palliative radiation, and recent data supporting the use of SBRT in select patients treated with palliative intent, we would be remiss not to mention SBRT. As mentioned in the discussion, there is a growing body of literature evaluating the use of SBRT for palliation of symptoms. While an *in-depth discussion of this* is outside the scope of our article, we think it is appropriate to mention it in the discussion to provide additional context to the reader. We have added the fact that SBRT was not included in the review as one of the limitations to our article.

**Reviewer D**

The authors provide a narrative review of scoring models for the use of palliative radiotherapy (PRT) depending on the expected survival of a given patient. The review's scope is relevant as radiation oncologists often struggle when it comes to choose the right balance of palliative radiotherapy: omission, short course or long course. Overall, the review is clearly written and relevant.

Minor issues:

Introduction:

- to better prepare the reader for the results part, the dichotomization between PRT for a primary disease site or metastases could be introduced briefly as it is pursued later in the results part

- We appreciate this suggestion. The introduction has been updated to reflect the fact that palliative radiotherapy can be used for both primary disease and in the metastatic setting (sentence 2, lines 52-54). We also specify that scoring systems specific to metastatic and non-metastatic patients will be discussed in the review (sentence 8, lines 67-68).

- the last sentence would fit better into the methods section

- Thank you for this suggestion. However, per the "Instruction for Authors", this journal specifically requires this sentence be placed at the end of the introduction. Thus, this sentence will remain in place to meet the publication requirements of this journal.

Methods:

- table 1 and line 80: please check punctuations (...“palliation”, radiation”, radiotherapy”, “survival” ...)

- We have added the quotation marks as the reviewer suggests.

Results:

- please add information on external validation for each model (this is missing for example for lung cancers and head and neck cancers as presented in the review)

- The lung and head and neck cancers models developed by Rades et al have yet to be validated with an external cohort of patients. We have added this point as one of the limitations of each model.

- line 144: please check punctuation

- We have adjusted the punctuation to provide additional clarity.

- line 233-234: reference “21“ is used incorrectly for this claim. The cut-off for number metastases should be 3 and this reference would be more appropriate: 10.1001/jamaoncol.2020.7857

- Thank you for this clarification. The sentence and reference have been updated



to reflect this point.

- Table 3: Krishnan/TEACHH-model: please specify what kind of tumor site / level of ECOG etc. is assigned to how many scoring points
  - Further additions have been made to this table. The TEACHH model used both a partial score methods (PSM) and Number of risk factors (NRF) method, as described in the manuscript.
- Table 3: Please check punctuation (e.g. “prior hospitalization,“)
  - This has been corrected.

#### Discussion

- line 355: reference “21” is used incorrectly as it did not investigate SBRT
  - Thank you for bringing this to our attention. We have replaced this with a different citation that used SBRT for oligometastatic prostate cancer (Tang et al Jama Oncol 2023 - <https://pubmed.ncbi.nlm.nih.gov/37022702/>)
- the discussion section is missing a paragraph on limitations. Limitations could be discussed concerning the method of a narrative review without pre-registered systematic literature search as well as general limitations of prognostic scoring models.
  - Thank you for this point, we added a paragraph on limitations of this article (see last paragraph of Discussion section). Specifically, we note that this this article is a narrative review and thus only describes select prognostic scoring systems for PRT. It is not a systematic review of every PRT scoring system. Additionally, we identify other limitations, for example, the fact that some of the prognostic models are not externally validated or use older cohorts of patients.

#### Further remark:

- Personally, I would suggest to avoid combative language in the context of oncology: “armed” in the conclusions section of the abstract. Inspiring reading on this topic: 10.1200/JCO.20.01146
  - This has been changed to “With the”. Thank you for drawing our attention to this important use of language.