

Please find the revisions for the manuscript entitled: “Carbon Ion Radiotherapy: An Evidence-Based Review and Summary Recommendations of Clinical Outcomes for Skull-Base Chordomas and Chondrosarcomas.” I thank you for your constructive feedback and considering the revised manuscript for publication.

Review 2

any published studies not included.. This sounds as if there might be a systematic bias by including studies more or less on an undefined way. Please specify the method. Figure 1: 183 of 224 screened studies were excluded. It is not described why these were excluded	Thank for this comment, we have updated the manuscript to clarify these issues in the following: “The search terms included “Heavy Ion Radiotherapy,” as this was defined as “The use of a heavy ion particle beam for radiotherapy, such as the HEAVY IONS of CARBON,” by the National Library of Medicine, ensuring that a broad initial search criteria would capture all potentially eligible published studies. Additionally, references for selected studies were reviewed and any publications not included in the search were manually added and reviewed in the screening. In total, 227 peer-reviewed articles written in English were extracted and included for evaluation. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, and the protocol has not been registered. The principle and senior authors initially screened the abstracts of these studies using an only abstract review application, Covidence (Melbourne, Australia), which led to exclusion of 183 articles. As this review focused on grading the evidence of available clinical outcomes, reasons for exclusion included prohibitively small series, studies of experimental systemic agents, non-included pathologies or disease sites, incomplete radiation description, studies with significant heterogeneity or imbalance, and those reporting primarily technical or basic research. Twenty-four publications that report outcomes, toxicity, or relevant clinical information after carbon therapy for skull-base chordoma or
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	chondrosarcoma were identified as depicted in the PRISMA flow diagram in Figure 1. Supplemental tables 1 and 2 summarize the key findings as ordered by level of evidence in reverse chronological order separated by histologic diagnosis. The level of evidence was graded per the Oxford Centre for Evidence-Based Medicine, "The Oxford 2011 Levels of Evidence," using an online iterative approach[15]. All studies included were then peer reviewed across all authors who reviewed the manuscript for those inclusions and level of evidence grading. The paper was circulated among co-authors for peer review as published in other consensus recommendations and international statements[16]."
Table 1: One might suspect that the reported outcomes from institutions with repeated publications include data from the same patients, possibly influencing the conclusions. This should be addressed in the methods and in the discussion. Which efforts were done to avoid weighting double publications. The role of reviews in contrast to the reported patient studies with small patient numbers should be clarified and discussed later on.	These are wonderful points and very much an issue with the present literature. We did address this by grouping cohorts published multiple times in the supplemental tables and in the results section. However, you are correct that it is not possible to completely remove this bias so a limitations section addressing this issue has been added to the manuscript to better describe these issues: "This study has several limitations as it is a systematic and evidence-based review that relies predominantly on retrospective studies, cohorts with overlapping patient populations, limited prospective interventions, and no randomized clinical trials. Additionally, because of the narrow geographic scope of the operating carbon centers worldwide, it may not accurately represent the global diversity of the disease, potentially leading to skewed treatment outcomes and selection biases in the patients that have the physical capacity and socioeconomic resources to travel for therapy. Patients from underrepresented regions may have unique characteristics or access to different healthcare resources that are not adequately captured in the review,

	rendering the findings less generalizable. Moreover, the concentration of research within a few centers can introduce institutional and regional biases and variations in clinical practices, all of which can impact the overall quality and reliability of the evidence. Lastly, the reporting and heterogeneity of treatment technique, plan optimization methods, and number of beam and treatment specifics have been inconsistent across the literature. Therefore, when interpreting the results, it is essential to acknowledge these constraints as yet another layer of potential bias that must be considered when comparing treatment options and the strength of the consensus-based recommendations.”
Results: A repetition of the information already presented in the tables is unnecessary and makes the results hard to read. I would prefer to summarize and interpret the tables contents with regard to the parameters presented (local control/ OS / Tox).	A summary paragraph has been added to the discussion and more in depth comparisons to other forms of radiotherapy. The tables have been moved to the supplemental materials to improve the readability and reduce the repetition.