Peer Review File

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Reviewer Comments

I do feel this is a valuable and important topic and agree there is an underutilization of palliative treatments for pediatric patients. Perhaps some of the reasons for this is lack of awareness, which the current manuscript tries to address.

1. This is a "narrative review" so it is expected that the methodology is less strict than a more extensive systemic review. Even so I felt a little more structure and methodology would aid this manuscript to be a stronger narrative review. For example there are mentions in the conclusion about the paucity of prospective but there was no mention in the manuscript about the type of data that was found or cited for each of the item that was reviewed. The reader receives no context about the quality of the data the proposed suggestions are coming from. While there is need prospective data in this space, I don't think that you can claim (line 571) that the presented literature review highlights the paucity of prospective data...it was never discussed except in the conclusion

Reply: Thank you for the suggestion to further highlight the methodology of our "narrative review." We have expanded upon our description in the "Methods" section, including drawing more attention to Table 1, which summarizes our narrative review search strategy. In addition, we reference Supplemental Table 1 that describes the Annals of Palliative Medicine Narrative Review Reporting Checklist.

See page 4-5, line 102 – 109: "We present this article in accordance with the narrative review reporting checklist (Supplemental Table 1). Table 1 summarizes the search strategy performed to identify relevant articles on the use of RT in the palliative and emergent setting for pediatric patients (age ≤ 21). Articles were analyzed for relevance, histology specific information including dose and fractionation, and quality of data. There were no prospective studies identified on the use of RT in the palliative setting for pediatric patients. These articles were supplemented with additional current and recent clinical trials, review papers, and survey studies. In areas that lacked pediatric specific data, well-designed retrospective and prospective studies in the adult setting were evaluated. When limited data existed, expert opinions from pediatric oncologists and radiation oncologists were provided."

Please note that the Narrative Review Reporting Checklist (Supplemental Table 1) has page and line numbers that match the “clean version” of the manuscript.

Importantly, we used this as an opportunity in our “Methods” to address the absence of prospective data identified in the pediatric setting for the use of palliative RT. In the “Conclusions” section, we have modified our as below: ORIGINAL: “Our literature review highlights the paucity of prospective data for the use of RT along with histology-specific data.”

See Page 24, line 545-546: NEW: “For pediatric patients, our literature review highlights the absence of prospective data for the use of palliative RT along with histology-specific data.”

2. Several times in the review it was mentioned that "seminal literature" would be reviewed - how did you define "seminal" and were these found by the search criteria noted or by augmentation in other ways?

Reply: Thank you for this comment. We acknowledge the term “seminal literature” can be subjective. We have removed the use of this word in our “Abstract: Methods” section and the “Methods” section (see page 3, line 68-71; see page 4-5, lines 102-109)

3. for the methods section in the abstract - I think you could elaborate a bit more on your search strategy/methods

Reply: Excellent suggestion. In the “Abstract: Methods” section, we have re-written this:

ORGINAL: “A narrative review of the seminal literature and recent clinical trials was performed.”

See page 3, lines 68-71: NEW: “A narrative review was performed querying PubMed, MEDLINE, ClinicalTrials.gov databases, and supplemented with review articles, survey studies, current and recent clinical trials. When limited data existed, well-designed retrospective and prospective studies in the adult setting were evaluated and expert opinion was provided from pediatric oncologists.”

4. I realize the Principles of RT section is an overview and much is general knowledge, but it would nice to have support of more that 1 reference for the

section. For example I think the section on Pediatric specific treatment considerations was much better supported with evidence

Reply: We agree the Principles of RT section is an overview with general knowledge, but we felt it would be helpful to include this section for the non-Radiation Oncologist readership. Thank you for this suggestion to provide additional references.
We have added the following references to the "Principles of Radiotherapy" section (see page 5-6, lines 115-133):

Berman AT, Plastaras JP, Vapiwala N. Radiation oncology: a primer for medical students. J Cancer Educ. 2013;28(3):547-53.

Bernier J, Hall EJ, Giaccia A. Radiation oncology: a century of achievements. Nat Rev Cancer. 2004;4(9):737-47.

Tsang DS, Vargo JA, Goddard K, Breneman JC, Kalapurakal JA, Marcus KJ. Palliative radiation therapy for children with cancer. Pediatr Blood Cancer. 2021;68 Suppl 2:e28292.

Chandra RA, Keane FK, Voncken FEM, Thomas CR, Jr. Contemporary radiotherapy: present and future. Lancet. 2021;398(10295):171-84.

Grimm J, Marks LB, Jackson A, Kavanagh BD, Xue J, Yorke E. High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic (HyTEC): An Overview. Int J Radiat Oncol Biol Phys. 2021;110(1):1-10.

Mohan R, Grosshans D. Proton therapy - Present and future. Adv Drug Deliv Rev. 2017;109:26-

Taylor A, Powell ME. Intensity-modulated radiotherapy--what is it? Cancer Imaging. 2004;4(2):68-73.

Brown LC, Lester RA, Grams MP, Haddock MG, Olivier KR, Arndt CA, et al. Stereotactic body radiotherapy for metastatic and recurrent ewing sarcoma and osteosarcoma. Sarcoma. 2014;2014:418270.

Abel S, Lee S, Ludmir EB, Verma V. Principles and Applications of Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy. Hematol Oncol Clin North Am. 2019;33(6):977-87.

5. In section on palliation for Leukemias and lymphomas, I think you could add for

leukemias and lymphomas to line 179 - to clarify that all the following scenarios are for L&L cases.

Reply: See page 8, line 180: We have modified this sub header per your recommendation to state: “Indications for Palliative Radiotherapy for Leukemias and Lymphomas.” We agree this will clarify the following scenarios are for L&L cases.

6. In the parenchymal brain mets section - line 288 please give a reference for the safety of treating 15 mets and the correlation to treatment volume.

Reply: Thank you for the opportunity to clarify this omission. We have added the following supportive references to this statement, which provide the data supporting safety of treating up to 15 brain metastases and the correlation to treatment volume (Yamamoto et al.) (see page 12, line 283).

Yamamoto M, Sato Y, Higuchi Y, Kasuya H, Barfod BE. A Cohort Study of Stereotactic Radiosurgery Results for Patients With 5 to 15 Versus 2 to 4 Brain Metastatic Tumors. Adv Radiat Oncol. 2020;5(3):358-68.

In addition, we have provided the recent American Associati8on of Physicists in Medicine (AAPM) HyTec (High Dose per Fraction, Hypofractionated Treatment Effects in the Clinic) working group manuscript on dose-volume considerations for single and multi-fraction radiosurgery for the brain (Milao et al.).

Milano MT, Grimm J, Niemierko A, Soltys SG, Moiseenko V, Redmond KJ, et al. Single- and Multifraction Stereotactic Radiosurgery Dose/Volume Tolerances of the Brain. Int J Radiat Oncol Biol Phys. 2021;110(1):68-86.

7. There are many statements or claims in the manuscript that don't have a citation next to the statement which makes it hard for readers to know where the evidence came from (For example, in line 261-262 it states that the boom boom technique is less durable compared to more protracted course and it is not followed by a reference. The FORT trial that supports this in referenced in the same paragraph, but prior to the statement. As it is an evidence-based review, it is imperative that all statements of fact are validated with evidence.

Reply: Thank you for this opportunity to clarify. While the FORT trial (Hoskin et al) is referenced adjacent to the section of the sentence describing the “Boom

Boom" (2 Gy x 2 fractions) technique, we agree that placing this reference again at the end of the sentence will help to improve validity to the statement of less durability compared to a more protracted course of radiation. This edit has been applied to the text (see page 11, line 257).

8. line 391, please include the number of fractions that went with the 36 Gy.

Reply: Excellent suggestion. In the Osteosarcoma sub section (see page 17, lines 377-378), we have added this statement "(3 weekly fractions of 6 Gy over 2 weeks)" to the sentence below to better provide the reader increased information about the potential biologic effectiveness of this dose-fractionation regimen:

"In 1992, Lombardi et al. showed a complete or partial radiologic response in 81% of symptomatic lesions treated with a total dose of 36 Gy (3 weekly fractions of 6 Gy over 2 weeks)."

9. It would be helpful to have a table like table 2 showing the commonly used doses for treating the solid tumors that you discussed if one could be constructed

Reply: Thank you for this recommendation. We have added Table 4 to provide suggested palliative doses for pediatric solid tumors. Please note, we also added a comment at the bottom of both Tables 2 (see page 37, Table 2) and 4 (see page 39, Table 4) to allow for provider discretion regarding the selection of dose and fractionation based on a comprehensive evaluation and goals of care.

Table 4. Suggested palliative radiotherapy doses for pediatric solid tumors.

HISTOLOGY	INDICATION	DOSE AND FRACTIONATION	EXPECTED RESPONSE
NEUROBLASTOMA	All sites	20 Gy in 5	>80% symptomatic relief
	Vision loss	4.5 Gy in 3	N/A†
	Hepatomegaly	4.5 Gy in 3	N/A†

OSTEOSARCOMA	All sites	36 – 45 Gy in 12 - 15	>75% response rate
	SBRT‡	40 Gy in 5	60% response rate
EWING SARCOMA	All sites	30 Gy in 10	84% symptomatic relief
	SBRT‡	30-40 Gy in 5	100% symptomatic relief
RHABDOMYOSARCOMA	All sites	30 Gy in 10	64% pain relief
	SBRT‡	30-35 Gy in 5	83% 1-year local control

KEY:

†N/A – OFTEN USED AS A BRIDGE TO SYSTEMIC THERAPY IN THE NEWLY DIAGNOSED SETTING. LIMITED CASE NUMBERS TO PROVIDE EXECTED RESPONSE RATE.

‡FOR THE PROPERLY SELECTED PATIENT (KPS > 50-60%, SIZE ≤ 5 CM, NON-EMERGENT)

NOTE: Provider discretion is permitted for dose-fractionation variations based on comprehensive patient evaluation and goals of care.