Peer Review File

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Reviewer Comments

Reviewer A

This manuscript provides a fairly thorough review of external beam RT, but has 3 major flaws:

Comment 1. It does not provide significant new information for primary liver cancers compared to the recently published ASTRO clinical practice guidelines.

Reply 1. We have been asked by the chapter editors to provide an updated review of the literature for palliative therapy, which overlaps with the ASTRO clinical practice guidelines. Therefore, we will increase the focus on palliative liver radiotherapy and provide greater narration to provide readers with an evidence-based interpretation that goes beyond what can be provided by the ASTRO guidelines. The ASTRO guidelines cover the entire spectrum of primary liver cancers, including resectable tumors, as well as external beam radiation in the curative setting. They do not cover cancer metastatic to the liver. Thus, a significant portion of the ASTRO guidelines would not apply to this publication. See changes at the following locations:

Page 3, line 59-63, “Primary and secondary liver…”, and page 4, line 95-110, “Recent American Society of…”. These sections were added to provide purpose for this paper beyond what has been published previously. On page 4, lines 95-110 better frame the article, provide purpose beyond what has already been published, and set the tone for the coming discussion. This section (lines 95-110) also contains the most recent phase 3 randomized clinical-trial data for therapy in advanced HCC.

Please see page 9, lines 228-230 for recent research on a large cohort involving outcomes in a mixed pathology (primary and metastatic liver tumors) population. “Prospective data suggest…”.

Please see Table 2, 3, and 4 for listing of up-to-date sources.

Please see page 9, lines 230-238 for discussion of recent trial outcomes for SBRT, “Different strategies have been…”.

Please page 9, lines 240-247, “SBRT allows treatment for patients…”, for a discussion of outcomes by pathology and performance status, with recent recommendations.

This discussion continues into a recent landmark paper for advanced HCC patients, page 9-10, lines 249-261, “For patients with many prior…”.

Please see page 10, lines 269-271, "…recent ASTRO guidelines…" for ASTRO recommendations on which HCC patients should get SBRT.

Please see page 11, lines 298-306, "As mentioned previously, 74%...", for the most recent recommendations regarding SBRT and MVI or PVT. This addition contains new and updated information regarding management of liver tumors with PVT or MVI, which are poor prognostic parameters. Most of these patients are palliative, so additional data is discussed beyond what is possible in the guidelines.

Please see pages 12-13, lines 331-356, for integration of the most recent guidelines into our discussion of SBRT recommendations. "When treating with SBRT, doses…".

Please see page 14, lines 366-387 for up-to-date information on charged-particle therapy. "Prospective CPRT trials…".

Please see pages 15, lines 396-397 for updated evidence about partial-liver RT. "…studies that suggest…".

Please see page 15, lines 405-408, for ASTRO consensus guidelines on partial-liver 3DCRT for HCC. "Palliative 3DCRT to symptomatic…".

Please see page 15, lines 414-417, "Table 4 summarizes…", where the most recent evidence for WLRT has been included. As WLRT is an old technique, and there is not as much literature for it, the literature for WLRT is primarily older studies with a few newer prospective studies that investigate the palliative utility of WLRT, i.e. the utility of re-purposing an old technique for palliative care.

Please see page 17, lines 448-449 for the ASTRO Consensus Guidelines' stance on WLRT. "Recently, ASTRO guidelines…".

Please see page 17, lines 462-469 for updated sources on combination therapy. "These studies suggest that combining…".

The writers would also like to make the point that radiotherapy is not standard of care for primary or metastatic liver tumors. The writers were invited to collate and summarize information regarding liver radiotherapy for palliative purposes, and then to give summary recommendations based on this information. Though we were not invited to give the newest or latest information as it relates to definitive care, which is the focus of the ASTRO guidelines for HCC, there is overlap between palliative, definitive, and emergency radiotherapy in the treatment of liver tumors. The writers have sought a way to acknowledge this overlap, but also emphasize that this paper's purpose is to highlight palliation or emergency treatment data and provide

recommendations for palliative subgroups not specifically addressed by the ASTRO guidelines.

Comment 2. A review of RT for liver cancers should separate primary and metastatic liver cancers as the patient population and cancers are entirely different in terms of the overall management, patient comorbidities, RT approach, and dose constraints.

Reply 2.

We agree and have emphasized where changes were made to address the reviewer's recommendations below. This includes significant changes to the tables and paragraphs throughout the paper. However, there is significant overlap between and within publications, and a convergence of management along certain management techniques and strategies. In these cases, we sought to include both primary and secondary data to avoid duplication and have highlighted any differences in primary and secondary management, if any, for the palliative setting.

Please see page 4, lines 88-91, "Published guidelines, such as Barcelona…" for clarification of the BCLC staging system as being for HCC patients only, not metastatic patients.

Please see page 4, lines 101-104, "Recently, the RTOG 1112…" for discussion of recent phase III, randomized, controlled-trial data pertaining to management of HCC, not liver metastases.

Please see page 5, lines 131-132, "…mixed HCC and liver…" for discussion of different patient populations that benefit from Y-90.

Please see pages 5-6, lines 140-146, "TACE is recommended for…", for discussion of which primary liver patients benefit from TACE, and delineation of results for HCC and liver metastasis populations for non-radiation local therapies.

Please see page 7, lines 172-214 (the "Selecting Patients for Radiotherapy" section) for discussion of patient selection and nomograms that has been sub-divided by pathology.

Please see page 9, lines 228-230 for recent research on a large cohort involving outcomes in a mixed pathology (primary and metastatic liver tumors) population. "Prospective data suggest…".

Please see page 9, lines 228-238 for up-to-date sources.

Please see Table 2, 3, and 4 for division of literature by pathology. See also page 9, lines 233-234.

Please see page 9, lines 240-247 for division by pathology for outcomes, “SBRT allows treatment for patients…”, as well as page 9-10, lines 249-261, “For patients with many…”.

Please see page 11, lines 298-306 for discussion of MVI in HCC patients and SBRT, “As mentioned previously, 74%…”.

Please see pages 12-13, 318-356, for SBRT recommendations that are sub-divided by pathology. “SBRT should be considered…”

Please see Please see page 15, lines 403-408, for an updated discussion of palliative partial-liver 3DCRT for HCC pathology. “Studies support better responses…”.

Please see page 15, lines 412-419. “These considerations must be balanced…”. While most WLRT can be employed in the same way for palliation regardless of pathology, there is some discussion of differences by pathology.

Please see pages 16-17, lines 431-453 for palliative recommendations of WLRT vs. partial-liver RT by pathology. “Palliative patients of any liver pathology…”.

Please see page 17, lines 462-469 for combination palliative therapy by pathology. “These studies suggest that combining…”.

Comment 3. The majority of the manuscript does not appear to be relevant to the overall scope of this journal. A focus only on palliative RT for liver cancers would be more appropriate and relevant. The majority of the content is focused on definitive, potentially curative intent.

Reply 3. We have made changes to further focus on palliative management, remove radical management techniques as much as possible, and to explain when consideration of radical and palliative management is included or can overlap. See pages 3-4, lines 85-94, “Effective palliation remains…”, as well as pages 12-13, lines 331-356,“When treating with SBRT, doses…”.

There is substantial overlap between definitive radiotherapy and palliative radiotherapy for liver lesions. As stated in the manuscript, pages 3-4, lines 85-94, “Effective palliation remains an unmet need…”. Thus, treatment of liver tumors is on a spectrum, and there is overlap between definitive and palliative treatment. This has been further explored in the introduction, page 4, lines 95-105, “Recent American Society of…”, where the ASTRO guidelines (and other sources) advocate for dose-escalated SBRT or hypo-fractionation treatment across the spectrum of disease until prohibited by tumor location or size, underlying liver function, available technology, or healthy-liver volume.

The decision on direction and goals of care is informed by performance, goals of care, extent of disease, liver function, volume of healthy liver expected to receive radiation, risk of toxicity, vascular invasion, and other factors is discussed in page 6, lines 150-153, “Given poor prognosis of liver…”, page 6, lines 154-158, “Patients often present with advanced…”, page 10, lines 268-274, “Based on available evidence…”, page 10-11, 277-288, “Vascular tumor invasion…”, and pages 12-13, lines 331-356, “When treating with SBRT, doses…”. Hence, our discussion of the decision to embark on palliative therapy and how it can be informed by several nomograms is displayed on page 7, line 172.

Often, a patient being treated with palliative intent can be treated with definitive techniques (i.e., techniques that are shared between definitive and palliative treatment) to maximize outcomes in the palliative setting, as discussed in page 4, lines 95-105, “Recent American Society of…”, page 9, 230-233, “Different strategies have been…”, page 11, lines 290-296, “Given the severity of…”, and page 11, 298-306, “As mentioned previously, 74%...”. Also, as discussed on page 9, lines 240-247, “SBRT allows treatment for…”, and page 9-10, lines 249-261, “For patients with many…”, local control, ablative techniques, and ablation of symptom-causing disease is important for palliative benefit across a spectrum of disease, pre-treated states, liver statuses, and performance status.

Our narrative review addresses this spectrum of treatment for palliative therapy, and one of the themes underlying our main conclusions and recommendations is that palliative patients should be considered for techniques that are used for definitive or curative therapy, if they and their liver can tolerate it (page 6, lines 163-164, “Classic RILD may cause…”, and page 15, line 396-397, “…studies that suggest…”). This is true for SBRT, as it is often well tolerated with few toxicities, but only if it can be safely delivered to a certain spectrum of disease. Please see page 10, lines 263-266, “Studies of QOL also…”, and lines 268-274, “Based on available evidence…,” as well as pages 12-13, lines 331-356, “When treating with SBRT, doses…”. Thus, there will be some discussion of techniques that apply to both definitive and palliative care, as the goals and decision-making can be similar. Most unresectable liver tumors are not cured despite the use of “radical” treatment. In addition, certain patients may have a poor prognosis, and if their tumor meets planning constraints, we can give radical techniques, usually used for definitive or curative treatment, in palliative settings to maximize benefit, as discussed in SBRT Recommendations: pages 12-13, lines 331-356, “When treating with SBRT, doses…”, which details our recommendations for decision-making when deciding if and how SBRT should be used in a palliative patient to maximize clinical benefit.

When to use SBRT, partial liver RT, and WLRT, and the evidence for radical dose-escalated treatment versus low-dose treatment vs partial liver RT or WLRT is an important point of discussion for palliative patients. Please see pages 15, lines 396-397, “…studies that suggest…”, as well as page 15, lines 403-408, “Studies support better responses…”, for an updated discussion of palliative partial-liver 3DCRT for HCC pathology. Please see page 15-16, lines 404-420, “2-year OS rates…”, and our partial-liver and WLRT recommendations section, pages 16-17,

lines 431-453, “Palliative patients of any liver pathology…” for discussion of 3DCRT partial-liver vs. WLRT techniques for palliation, and in which scenarios they may be appropriate. Please see also pages 17-18, lines 456-478, “Combining RT with regional…” for discussion of how combination therapy may be used in palliative care.

Our Conclusions section on page 18, lines 480-495, “Prevalence of primary and secondary liver…” subsequently summarizes decision-making recommendations for palliative patients, and aims to provide a summary statement for helping with decisions regarding when to use the techniques discussed in the paper. Here, we attempt to encapsulate the entire conversation about spectrum of disease, spectrum of treatment, and what type of palliative radiotherapy technique may be appropriate for a given patient.

The authors were invited to write a narrative review to discuss and give recommendations for what radiotherapy techniques should be used in certain situations, and this is complicated by the fact that SBRT and some dose-escalated 3DCRT, which are definitive techniques, can be used in palliative patients. Our discussion aims to provide guidance, and we hope that our changes have satisfied the reviewer’s recommendations.

Please see page 14, lines 379-387 for discussion of how charged-particle therapy may be used in palliative patients (an ongoing area of discovery). “As with photon RT…”.

Comment 4. Title: “Emergent” should be “Emerging”. However, either word is not appropriate. External beam RT is not new or novel, as it has been applied to liver cancers for multiple decades, and therefore not “emerging.”

Reply 4. We agree. The journal originally designated that “emergent” should be in the title when the authors were invited to write the current narrative review, which is why it was originally placed in the title. Please see page 1, line 1 (and the new title and title page), “Palliative radiotherapy for hepatic…” for a title that we think better encapsulates the focus of the paper, i.e. palliative or symptom-relief radiotherapy for advanced liver tumors. This will likely better frame this review for the journal, which seeks to discuss and collate information about palliative therapy.

Reviewer B

The authors performed a narrative review of radiotherapy for patients with hepatocellular carcinoma.

Although the content of this paper is relatively well organized and interesting, some revisions are considered necessary. The points that need to be corrected are presented below.

Comment 1. On line 65, where "Unfortunately, most patients cannot undergo resection." is stated, a specific percentage of patients who cannot actually undergo resection should be stated in conjunction with the citation.

Reply 1. We agree. Starting at page 3, lines 65-72, “The liver is a common site…”, statistics have been provided for patients unable to undergo liver resection.

Comment 2. In line 155-164, it is thought that the description of trans-arterial chemo-infusion (TAI) should be added to the contents of TACE.

Reply 2. We agree. Please see page 5, lines 137 – 139 for updated technique definitions and delineation. “Trans-arterial chemo-infusion…”.

Comment 3. Shouldn't "Prediction Outcomes" be listed before "Non-Radiation Local and Regional Therapy Options"?

Reply 3. We agree that this section was misplaced and not well-described. It describes methods and nomograms used to estimate clinical outcomes after radiotherapy only. Thus, it has been renamed “Selecting Patients for Radiotherapy,” and has been moved under “Radiation Therapy,” page 7, lines 172-214.

Comment 4. In line 222-224, “Factors to be considered when assessing patients for RT include performance status (PS), tumor histology, size, stage, local invasion (e.g. PVT), underlying liver disease, comorbidities, potential RT interactions with other therapies or anatomical structures (e.g. nearby gastrointestinal tissues), and patient’s goals of care (53).”, it is considered that liver function should also be described.

Reply 4. We agree. The sentence now reads: “Factors to consider include liver function, PS, tumor histology, size, stage, local invasion (e.g. PVT), underlying liver disease, comorbidities, potential RT interactions with other therapies or anatomical structures (e.g. nearby gastrointestinal tissues), and patient’s goals of care”. See page 6, lines 150-153.

Comment 5. In line 233-234, “Fatal hepatitis can result from whole liver RT of 35 Gy in daily fractions of 2 Gy.”, please add citations.

Reply 5. We completely agree. While the information that a whole-liver radiotherapy dose of 30-36 Gy is fatal in 2-Gy fractions is common knowledge to radiation oncologists, it may not be well known to other palliative medicine physicians. Citations have been added. See page 6, lines 160-166, “Historically, liver RT was…”.

Comment 6. In Table 2, add details of the tumor (primary or metastatic, HBV or HCV, etc.).

Reply 6. We completely agree. Please see Table 2, 3, and 4 for division by tumor pathology and other patient information. For papers with a combination of primary and secondary, we pulled additional data to clarify this distinction when available.

Comment 7. In line 298-299, “Unfortunately, there is a high risk of regional progression after these interventions despite high LC rates.”, please add citations.

Reply 7. We agree with this change. Please see page 9, line 241, “(2,15,30,35-41,43-46,96)”.

Comment 8. In the contents after line 308, It should be described in which cases SBRT is indicated for patients with liver cancer in poor condition and, conversely, in which patients SBRT should be avoided.

Reply 8. We agree. Summary recommendations have been updated on pages 12-13, lines 331-356, “When treating with SBRT, doses…”, and we have added sections as requested.

Please see page 9, lines 240-247, “SBRT allows treatment for…”, for discussion of SBRT’s role.

Please see page 9-10, lines 249-261, “For patients with many prior…”, for discussion of disease states, performance status, liver health, and more.

Please see page 10, lines 263-266, “Studies of QOL also…”, and 268-274, “Based on available evidence…”, which is a good discussion of SBRT in liver function, lesion size, and dosing.

Please see page 11, lines 285-288, “SBRT has shown good…”, and 292-306, “Studies suggest significant improvement…” for a discussion of the benefits and drawbacks of SBRT in the setting of vascular invasion, which was historically a poor-prognosis state, but now with SBRT, palliative and clinical improvement is possible.

Comment 9. In line 326-327, “Vascular invasion, such as PVT or inferior vena cava tumor thrombosis, is common in advanced HCC (10–40% at initial diagnosis).”, please add citations.

Reply 9. This has been completed. See page 10, lines 277-278, “Vascular tumor invasion…”.

Comment 10. In “SBRT and PVT”, radiation dose to large vessels is often a problem in SBRT for PVT. Patients with PVT also often have impaired liver function. Please describe the limitations and patient selection of SBRT for PVT.

Reply 10. We completely agree. Please refer to page 9-10, lines 249-261, “For patients with many prior…”, and page 10-11, lines 277-296, “Vascular tumor invasion…” for additions pertaining to patient selection and limitations. Please refer

also to page 11, line 298-306, “As mentioned previously, 74%...”, for updated information regarding management of palliative radiotherapy for liver tumors with MVI. This includes the recently presented RTOG 1112. Please, also see page 12, lines 326-329, “SBRT can also be considered…” for SBRT recommendations pertaining to MVI.

Please see also Table 2, 3, and 4 for tabulation of macrovascular invasion (MVI) and portal vein thrombus (PVT) in patient populations described by literature.

Comment 11. As for whole-liver RT (WLRT), it is a relatively old treatment method, and the authors' citations also refer to those from the 1970s and 1980s. In palliative irradiation, it is generally considered that 3DCRT should be used if possible, and that WLRT should be indicated only in some cases. Please explain how the authors think about this.

Reply 11. Please see Please see page 15, lines 403-408, “Studies support better responses…”, and pages 15-16, lines 404-420, “2-year OS rates…”, for an updated discussion of palliative partial-liver 3DCRT vs, WLRT. Please also see our partial-liver and WLRT summary section, pages 16-17, lines 431-453, “Palliative patients of any…”. WLRT is an older, simple technique that can be used effectively for palliation. HERE Please see pages 17-18, lines 457-478, “Combining RT with regional…”, for discussion concerning the possible efficacy but increased toxicity of combining WLRT or 3DCRT with other therapies.

Comment 12. In line 379-380, although the authors describe it as “These options provide rapid planning with simple techniques and potentially lower toxicity.” SBRT is actually thought to have fewer side effects because the dose to the surrounding liver and other risk organs can be reduced compared to WLRT.

Reply 12. Please see page 4, lines 99-108, “Dose-escalation for all liver-confined…”, page 9, lines 230-233, “Different strategies have been…”, page 10, lines 268-274, “Based on available evidence…”, page 12, lines 310-314 “Large lesions may also…”, page 13, lines 338-352, “For patients with multiple…”, and pages 16-17, lines 431-453, “Palliative patients of any…” for discussions of techniques in different settings of liver health, tumor size, performance status, and sparing normal liver in radiotherapy. SBRT provides lower radiation dose to the surrounding normal liver than older techniques through planning techniques, but as tumor size or multifocality grows, SBRT dosing can become dangerous to the remaining liver tissue (also depending on liver function, etc.), as discussed in page 13, lines 338-352, “For patients with multiple…”.

Once it becomes unsafe to do SBRT, and patients display large tumors, multiple tumors, or poor-prognostic features, partial techniques (3DCRT) with longer fractionation can be used to lessen toxicity to surrounding liver tissue, while still

escalating dose to the tumor. Whole-liver RT, or WLRT, is for patients who are very symptomatic, have diffuse disease, cannot hold their breath, need rapid symptom relief, and have poor performance status. The goal of whole-liver RT is pure palliation, whereas SBRT and partial 3DCRT techniques are for patients who may need palliation but can tolerate a treatment that also offers some local control and survival advantage. Please see page 15-16, lines 404-420, “2-year OS rates…”, and pages 16-17, lines 431-453, “Palliative patients of any…”, for this discussion.

Whole-liver techniques are low dose, so they do not pose toxicity risk. You can cover the whole liver for pure symptom relief. This reply (12.)) is a good extension of one of the main discussion threads written in the paper, namely that liver malignancy and its radiotherapy treatments are on a spectrum, and there is utility of definitive techniques for palliative or definitive care until it becomes unsafe to do so, or the patient’s performance status or goals necessitate purely palliative, simple techniques.

Comment 13. Shouldn't "Charge Particle Therapy" be listed before "Partial and Whole-Liver RT"?

Reply 13. This section has been modified to transition better from SBRT and SBRT recommendations into emerging techniques to improve SBRT, before going to partial and whole-liver RT. Please see page 13, line 358 for the start of the section “Charged Particle Therapy”.

Comment 14. It seems that the description of charged particle therapy is not sufficient. Please add information such as re-irradiation for recurrence after radiotherapy and treatment for large tumors.

Reply 14. Please see the section titled “Charged Particle Therapy” on pages 13-14, lines 359-387, “Radiation therapy with charged particles…”, for an expanded discussion on charged-particle therapy in liver palliation. Due to the word limit and short number of publications in this area, this paragraph represents a more comprehensive discussion of charged particle therapy as a developing area of palliative liver radiotherapy that we have streamlined for the purposes of fitting the narrative review parameters.

Reviewer C

This is a comprehensive review regarding the selection, classification, effectiveness, and recommendations of radiotherapy for liver cancer. However, there are some issues that need to be addressed. Please see the comments below.

Comment 1: Manuscript Type

I suggest this manuscript as a Scoping Review, not a Narrative Review. This is because the authors have provided a very detailed and specific search method,

considered multiple databases with a comprehensive timeframe, and a summary of the included literature.

Reply 1. Thank you for acknowledging the extent of the literature review completed for this narrative review. The authors have provided a methods section on pages 4-5, lines 112-119, "Methods… Search methods are summarized…" that matches the requirements set forth by the journal for including in a narrative review methods section. Please see the narrative review checklist, inserted below.

2.2.3 Narrative Review (Also Called Literature Review)

We strongly welcome the submission of narrative reviews, although our editors may still consider traditional reviews for publication. A narrative review aims to provide readers with a cutting-edge, scholarly, evolving developments and evidence-based overview on a clinical or mechanistic subject by searching, selecting, compiling, and summarizing the available literature. Through a narrative review, readers could gain a more comprehensive and enlightening knowledge on a particular field. A narrative review is less methodologically demanding than a systematic review, as it does not require a search of all literature in a field, nor does it necessarily require a rigorous appraisal on the included literature.

Abstract: Structured with

- Background and Objective: describe relevant background, reasons for conducting this review and primary objectives of this review.
- Methods: briefly describe the search strategy, including databases, time frame, and language considerations.
- Key Content and Findings: describe what the literature review will mainly contain and any key findings.
- Conclusions: describe the main conclusions and how the review may potentially impact future researches, clinical practice and policy making.

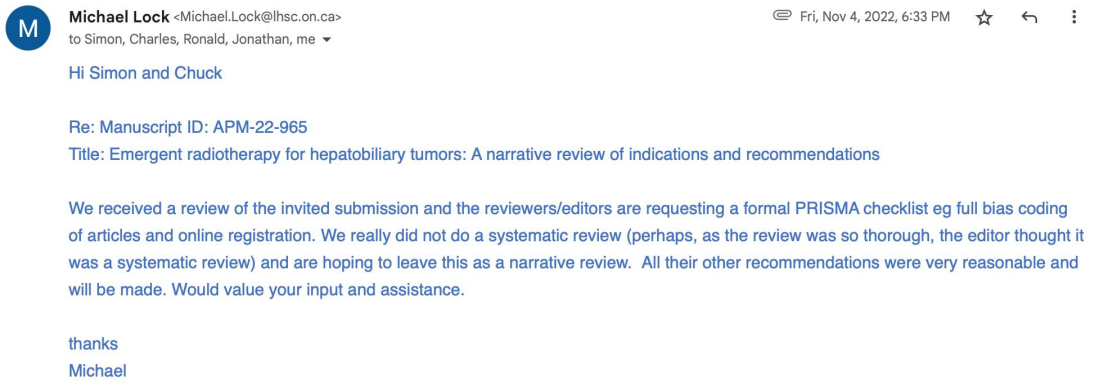
Main text: Arranged as Introduction, Methods, Main Body and Conclusions. The Methods section should include a completed table as follows:

Narrative Review Checklist

Section/Topic	Item No	Item
TITLE		
Title	1	Identify the report as a Narrative Review or Literature Review.
ABSTRACT		
Structured summary	2	Provide a structured summary with the subsections as: Background and Objective, Methods, Key Content and Findings, Conclusions.
INTRODUCTION		
Rationale/background	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Specify the key question(s) identified for the review topic.
METHODS		
Research selection	5	Specify the process for identifying the literature search (eg, years considered, language, publication status, study design, and databases of coverage).
DISCUSSION/SUMMARY		
Narrative	6	Discuss: 1) research reviewed including fundamental or key findings, 2) limitations and/or quality of research reviewed, and 3) need for future research.
Summary	7	Provide an overall interpretation of the narrative review in the context of clinical practice for health professionals, policy development and implementation, or future research.

In discussion with the Special Edition editors who invited this submission, we feel that the conversion to a "scoping review" may be beyond that requested. Please see the below email thread. The a priori completion of the PRISMA checklist, bias review, and online registration in a retrospective manner may be inappropriate and unethical

and may also further delay the publication of the associated articles as well. We also understand that the other submissions did not receive the request to convert their submissions to a ”scoping review.” Therefore, we hope the APM would be agreeable to our wish to leave the submission as a “narrative review.”



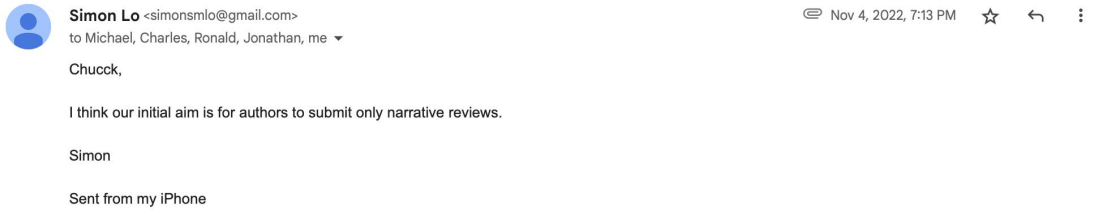
Michael Lock <Michael.Lock@lhsc.on.ca> Fri, Nov 4, 2022, 6:33 PM
to Simon, Charles, Ronald, Jonathan, me

Hi Simon and Chuck

Re: Manuscript ID: APM-22-965
Title: Emergent radiotherapy for hepatobiliary tumors: A narrative review of indications and recommendations

We received a review of the invited submission and the reviewers/editors are requesting a formal PRISMA checklist eg full bias coding of articles and online registration. We really did not do a systematic review (perhaps, as the review was so thorough, the editor thought it was a systematic review) and are hoping to leave this as a narrative review. All their other recommendations were very reasonable and will be made. Would value your input and assistance.

thanks
Michael



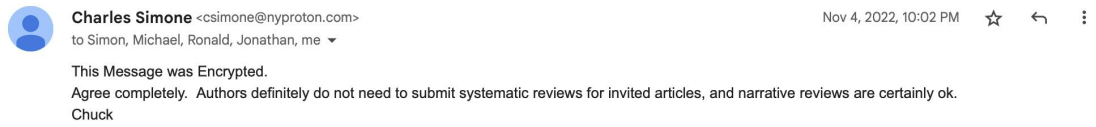
Simon Lo <simonsmlo@gmail.com> Nov 4, 2022, 7:13 PM
to Michael, Charles, Ronald, Jonathan, me

Chucck,

I think our initial aim is for authors to submit only narrative reviews.

Simon

Sent from my iPhone



Charles Simone <csimone@nyproton.com> Nov 4, 2022, 10:02 PM
to Simon, Michael, Ronald, Jonathan, me

This Message was Encrypted.
Agree completely. Authors definitely do not need to submit systematic reviews for invited articles, and narrative reviews are certainly ok.
Chuck

Comment 2: Title
"hepatobiliary tumors": There does not seem to be any mention of cholangiocarcinoma.

Reply 2. We have changed the title to “hepatic tumors.” See page 1, line 1, “Palliative radiotherapy for hepatic…”. Due to length, word-count limitations, and attempt to provide a thorough discussion, any discussion of cholangiocarcinoma, bile duct cancer, or gallbladder carcinoma will have to be addressed in a separate paper in order to thoroughly explore, discuss, and shed light on the spectrum of treatment approaches for these relatively rare and poorly understood cancers.

Comment 3: Discussion
Could the authors explain the rationale for the structure of the Discussion? Despite the informative discussion section, it is somewhat confusing: why suddenly jump to this section and what does this section tell us? I think the author needs to optimize the

overall structure of this review in order to guide the reader step by step to a deeper understanding.

For example, as the abstract states "This narrative review aims to synthesize the evidence and offer recommendations for radiotherapy use in curative and palliative clinical scenarios", the authors could consider summarizing for different patients, including the recommended treatment (radiotherapy or multidisciplinary combination), the advantages (efficacy, safety), and limitations (side effects, precautions) of radiotherapy in different conditions (e.g., stage, tumor volume). This may also better reflect the purpose and focus of therapeutic and palliative radiotherapy.

Could the authors objectively discuss why only 10% of the references in this review are from the past three years (16/159)? In particular, the literatures summarized in Table 4 were published before 1981, are these results still applicable now? Are there any updates?

Reply 3. Please refer to the “Main Body” heading on page 5, line 121, “Main Body…” which has replaced “Discussion,” and the “Conclusions” heading on page 18, line 480. The manuscript was structured per the instructions set forth by APM in the narrative review checklist, as well as the online submission requirements for a narrative review (see below). As the checklist and the online requirements do not match (for example, the checklist asks for “Discussion,” whereas the online requirements ask for “Main Body” to describe the same section), the names “Main Body” and “Discussion” were considered interchangeable to describe the same section, as was “Summary” and “Conclusion.” “Discussion” has been changed to “Main Body” to address this reply. Each section within the “Main Body” reviews fundamental and key findings, limitations, quality of research, need for future research, and recommendations for that section. The “Conclusions” section provides overall interpretation in the context of clinical practice.

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METHODS		
Research selection	5	Specify the process for identifying the literature search (eg, years considered, language, publication status, study design, and databases of coverage).
DISCUSSION/SUMMARY		
Narrative	6	Discuss: 1) research reviewed including fundamental or key findings, 2) limitations and/or quality of research reviewed, and 3) need for future research.
Summary	7	Provide an overall interpretation of the narrative review in the context of clinical practice for health professionals, policy development and implementation, or future research.

2.2.3 Narrative Review (Also Called Literature Review)

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- Methods: briefly describe the search strategy, including databases, time frame, and language considerations.
- Key Content and Findings: describe what the literature review will mainly contain and any key findings.
- Conclusions: describe the main conclusions and how the review may potentially impact future researches, clinical practice and policy making.

Main text: Arranged as Introduction, Methods, Main Body and Conclusions. The Methods section should include a completed table as follows:

Please see below for updated literature.

We have been asked by the chapter editors to provide an updated review of the literature for palliative therapy, which overlaps with the ASTRO clinical practice guidelines. Therefore, we will increase the focus on palliative liver radiotherapy and provide greater narration to provide readers with an evidence-based interpretation that goes beyond what can be provided by the ASTRO guidelines. The ASTRO guidelines cover the entire spectrum of primary liver cancers, including resectable tumors, as well as external beam radiation in the curative setting. They do not cover cancer metastatic to the liver. See changes at the following locations:

Page 3, line 59-63, “Primary and secondary liver…”, and page 4, line 95-110, “Recent American Society of…”. These sections were added to provide purpose of this paper beyond what has been published previously. On page 4, lines 95-110 better frame the

article, provide purpose beyond what has already been published, and set the tone for the coming discussion. This section (lines 95-110) also contains the most recent phase 3 randomized clinical-trial data for therapy in advanced HCC.

Please see page 9, lines 228-230 for recent research on a large cohort involving outcomes in a mixed pathology (primary and metastatic liver tumors) population. “Prospective data suggest…”.

Please see Table 2, 3, and 4 for listing of up-to-date sources.

Please see page 9, lines 230-238 for discussion of recent trial outcomes for SBRT, “Different strategies have been…”.

Please page 9, lines 240-247, “SBRT allows treatment for patients…”, for discussion outcomes by pathology and performance status, with recent recommendations. This discussion continues into a recent landmark paper for advanced HCC patients, page 9-10, lines 249-261, “For patients with many prior…”..

Please see page 10, lines 269-271, “…recent ASTRO guidelines…” for ASTRO recommendations on which HCC patients should get SBRT.

Please see page 11, lines 298-306, “As mentioned previously, 74%...”, for the most recent recommendations regarding SBRT and MVI or PVT. This addition contains new and updated information regarding management of liver tumors with PVT or MVI, which are poor prognostic parameters. Most of these patients are palliative, so additional data is discussed beyond what is possible in the guidelines.

Please see pages 12-13, lines 331-356, for integration of the most recent guidelines into our discussion of SBRT recommendations. “When treating with SBRT, doses…”.

Please see page 14, lines 366-387 for up-to-date information on charged-particle therapy. “Prospective CPRT trials…”.

Please see pages 15, lines 396-397 for updated evidence about partial-liver RT. “…studies that suggest…”.

Please see page 15, lines 405-408, for ASTRO consensus guidelines on partial-liver 3DCRT for HCC. “Palliative 3DCRT to symptomatic…”.

Please see page 15, lines 414-417, “Table 4 summarizes…”, where the most recent evidence for WLRT has been included. As WLRT is an old technique, and there is not as much literature for it, the literature for WLRT is primarily older studies with a few newer prospective studies that investigate the palliative utility of WLRT, i.e. the utility of re-purposing an old technique for palliative care.

Please see page 17, lines 448-449 for the ASTRO Consensus Guidelines' stance on WLRT. "Recently, ASTRO guidelines…".

Please see page 17, lines 462-469 for updated sources on combination therapy. "These studies suggest that combining…".

The writers would also like to make the point that radiotherapy is not standard of care for primary or metastatic liver tumors. The writers were invited to collate and summarize information regarding liver radiotherapy for palliative purposes, and then to give summary recommendations based on this information. Though we were not invited to give the newest or latest information as it relates to definitive care, which is the focus of the ASTRO guidelines for HCC, there is overlap between palliative, definitive, and emergency radiotherapy in the treatment of liver tumors. The writers have sought a way to acknowledge this overlap, but also emphasize that this paper's purpose is to highlight palliation or emergency treatment data and provide recommendations for palliative subgroups not specifically addressed by the ASTRO guidelines.