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Clinical application of advances and innovation in radiation treatment of hepatocellular carcinoma

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Ref.: Ms. No. JCTRes-D-21-00138
Clinical application of advances and innovation in radiation ablation treatment
Journal of Clinical and Translational Research

Dear Miss Tong,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Oct 10, 2021.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: Authors conducted narrative review for the radiotherapy for HCC.
The research was very carefully designed and described about the advanced of technology for radiotherapy systemically.
There are some comments aiming to improve the excellent manuscript further:

I have a only few comments that I have listed.

Major concern
The title included "radiation ablation treatment". But you did not mentioned about ablation. It may cause the reader misunderstand something about microwave or RFA. You need to change.

Minor concern
It included too much references. You may reduce the half.

Excellent and important study which I enjoyed very much to read!

Reviewer #2: Thank you for the opportunity to review this manuscript on the role of radiotherapy in HCC. Although the work is detailed, there are several important subtopics, in my opinion, missing from it. These include:
* Discussion of ongoing trials of RT in HCC
* Mentioning of SOC systemic therapy for unresectable HCC: atezo/bev
* Mentioning of proton therapy for HCC
* Use of RT in palliative settings - 8 Gy x 1, 5Gy x 2, etc

In addition to these topic omissions, I have the following suggestions for improvement:

Title - should have HCC in it

Abstract
* Should add indication for RT also includes local control in resectable patients who are not surgical candidates
* "Quality research and datasets needed" - should also explicitly mention need for rigorous clinical studies.

Introduction
* I found the overall organization of the introduction a bit strange - the focus is on Barcelona staging and treatment options, and the majority of the introduction describes non-RT treatment. I think it is worth mentioning that Barcelona staging/treatment does not

recommend RT, and the authors wish to describe where RT could fit in - if they wish to frame it that way.
* The following sentences need references:
* 1. Surgical resection and transplantation offer the best outcomes in patients with early-stage HCC (5-year OS 60-80%)
* 2. However, the risk of local recurrence increases above 3cm
* "HCC is radiosensitive" - since classically HCC considered on more radioresistant spectrum, some context should be provided for this statement, or at least mentioning this should be discussed further.
* What is 2011 criteria?

Principles of RT
* Discussion should include definition of non-classic RILD (authors mention later, but should put upfront), since this is now more common

Photon-Based Techniques
* Would probably remove discussion of 2DCRT - used rarely, except potentially in urgent palliative settings.
* Would qualify comparisons of 3D versus IMRT - I don't think there has been RCTs for this, hard to say which reduces RILD, has better LC.

SBRT
* A bit odd that SBRT is in a different section than photon-based techniques/particle therapy? Seems like different types of categorizations - conventional versus stereotactic.
* Either way, given that SBRT is probably now the predominant form of RT for HCC, this section should be fleshed out further. For example, more discussion is needed on motion management.
* The authors mention 2 fractionations, 30 Gy in 5 or 45 Gy in 10 - the latter not technically SBRT. Would mention other dosings which are more common, and dosing based on Child-Pugh score.
* No mention of ongoing trials of SBRT including cooperative group trials.

Particle-based therapy
* No mentioning of protons.

Side effects
* Skin changes I would think are pretty rare.

Complications
* CP score >8 at baseline usually contraindication to RT
* Could include some liver metrics for RT - or need to spare 700 cc a certain dose, taken from surgical literature.

Reviewer #3: I commend the efforts made to compile such a huge information and put it in a simple format of tables and figures.
This paper indeed bridges the knowledge gaps of clinicians about HCC and radiation therapy.

Want to ask authors about their opinion on
A. Which patients should have adjuvant radiation after hcc resection?
B. Is there any data about neoadjuvant radiation ? This is not about bridge to transplant. This is may be about downstaging.
C. Is BCLC useful system to continue or, authors recommend other system?

Lastly, pls ensure your images are compliant to copyright.
Thanks

EDITOR:
Very detailed paper, but some important omissions on subtopics of RT for HCC. The EB did not review all stated facts/references in manuscript in detail, however these omissions do make us question whether these are also up to date. Please ensure that all elements are updated before resubmission.

Authors' response

Date: 11.09.2021

Dear Editor
Journal of Clinical and Translational Research

Re: **Manuscript ID** JCTRes-D-21-00138

Many thanks for reviewing our manuscript and for the insightful comments. We have addressed each comment and included changes within the manuscript. Please find the response to reviewers as below:

EDITOR:

Comment: Very detailed paper, but some important omissions on subtopics of RT for HCC. The EB did not review all stated facts/references in manuscript in detail, however these omissions do make us question whether these are also up to date. Please ensure that all elements are updated before resubmission.

Response:

Dear Editor, thank you for your comments. We have taken a look at the various pointers and suggestions given by the reviewers, and included further information and key topics which we have not previously included. Areas which we have decided to increase our focus on include:

- **SBRT**: 1) Role and key studies that show its safety, efficacy and utility, especially in comparison with or as an adjunct to current modalities; 2) Dose recommendations that are effective with minimal toxicity 3) Patients who are suitable for this form of radiotherapy
- **Proton beam therapy (PBT):** Highlighting the differences and advantages of PBT in comparison to photon-based techniques; Optimal tumor-specific PBT dosing; Role and utility in different patient populations and HCC stages
- **Radiotherapy in the palliative setting**
- **Complications** in terms of **RILD**, and recommended doses based on liver function and volume
- **Future development**: 1) Current trials that are underway and what readers can expect in the near future, 2) The role of radiotherapy as a neoadjuvant and as an adjuvant, and patients who may benefit from using radiotherapy as an adjunct to surgery
- The role of radiotherapy in combination with immunotherapy – e.g. results from the *IMbrave150 trial*

With this revisions, all co-authors agree that this review is exhaustive and inclusive of available evidence and ongoing advances in this field.

REVIEWER 1:

Major concern: The title included "radiation ablation treatment". But you did not mentioned about ablation. It may cause the reader misunderstand something about microwave or RFA. You need to change.

Response: Many thanks for your suggestion. We agree with your suggestion. To avoid confusion for the readers, we have changed the title to:

"Clinical application of advances and innovation in radiation treatment of Hepatocellular carcinoma"

Minor concern: It included too much references. You may reduce the half.

Response: Thank you for your suggestion. After including further information based on the suggested comments, we came up with a total of 218 references, but have since tried our best to reduce the number of citations to the current 186 (15% reduction). However, as many of the references contribute to the contents listed in the tables (which summarises the main findings from the various papers), we were unable to cut down further, and would like to seek

your understanding on this. This review paper is exhaustive, authoritative and inclusive of all evidence and ongoing initiatives in the field.

REVIEWER 2:

Comment 1.
Important subtopics missing from it:
* Discussion of ongoing trials of RT in HCC

Response: Many thanks for the suggestion. We have added ongoing trials in the section on future development

" Several trials investigating the role of radiotherapy in HCC management are underway. As PVTT involvement is commonly seen in HCC, a study done in Guangxi province, China (NCT04025437) sought to determine the safety and efficacy of neoadjuvant radiotherapy for HCC involving type I PVTT given the high 5 year recurrence rate of up to 75% post-hepatectomy. Examining the utility of combination treatment, a phase II clinical trial (NCT03535259) studied the safety and efficacy of combining IMRT with sorafenib in treatment of patients with advanced HCC. IMRT is given to the hepatic primary tumor, vein tumor thrombosis, and metastasis lymph node, in conjunction with a 400mg twice daily dose of sorafenib simultaneously. RT alone treatment gives a response of 50-60%, with high incidences of out RT field failure in the form of liver and distance metastasis while sorafenib alone treatment response rate is low (2-5%) [11,12]. We await results from this study in determining the utility of combining both modalities to achieve a synergistic effect. In the palliative setting, RT has also been investigated as a complimentary modality to best supportive care in the alleviation of pain (NCT02511522)."

In addition to the above, there is also another trial included in the paragraph on the role of immunotherapy (Also under the future development section)

"Lastly, results from trials elucidating the efficacy of combining radiotherapy with immunotherapy are pending. A phase II trial combining pembrolizumab and radiotherapy (NCT03316872) is estimated to complete in 2022."

Important subtopics missing from it:

* Mentioning of SOC systemic therapy for unresectable HCC: atezo/bev

Response:
This is indeed a key emerging area of interest. Thank you for your suggestion
We have included this statement in the 3rd paragraph under Introduction.

"For patients with unresectable HCC, the recent IMbrave150 trial showed significantly better OS and 2.5 month increase in progression free survival (PFS) with atezolizumab plus bevacizumab as compared to sorafenib"

Important subtopics missing from it:

* Mentioning of proton therapy for HCC

Response:
Thank you for pointing this out. We have previously grouped proton therapy under "particle-based techniques" and have elaborated more on proton beam therapy. We have included the following information regarding proton therapy under segment 3.3 Particle therapy

"Particle therapy such as carbon ion therapy or proton beam therapy (PBT) involves the use of particles such as heavier charged carbon ions or protons. Unlike photon-based EBRT which involves the firing of X-ray beam multiple times from different angles, radiation delivery in particle-based EBRT occurs via particle accelerators which form a single beam of high energy protons to be delivered into the patient[49]. Its ability to provide more localised particle exposure compared to photon-based EBRTs allows for higher doses to be delivered while reducing the damage to surrounding tissues and unwanted side effects[50].

While an exponential decrease is seen in deeper tissues for conventional photon-based techniques, PBT's finite range allows for superior dose distribution as they deliver low doses on entering the target tissue, and only show a steep maximum (Bragg-Peak) upon reaching a specific depth (dependent on their energy). Beyond this depth, there is close to no delivery of radiation, hence, majority of their dose is delivered near the end of their target range and over a narrow range, while relatively low doses occur outside the Bragg peak region[49] 3 main delivery methods exist to allow for uniform coverage at all depths and cover the entire target volume: 1) passive scattering, uniform scanning and active scanning[51]. Moreover, as a heavier particle, carbon ions also have the added advantage of inducing irreparable damage to DNA and are less dependent on the oxygen availability of tumor tissues, allowing for increased distribution of energy during their travel through the tissue (higher linear-energy transfer) and treatment of hypoxic tumors resistant to photons[50]."
"For peripheral tumors >2cm away from the both the GIT and porta hepatis, 66GyE/10 fractions is recommended, while tumors ≤2cm of the GIT can be treated with 77.0GyE/35 fractions and tumors ≤2cm of the GIT can be treated with 72.6GyE/22 fractions"

"Patients with HCC ≤2cm of the GIT treated with PBT at a dose of 72.6 GyE/22 fractions or 77GyE/35 fractions had mOS of 33.9 months, a 3-year OS of 50%, and a grade 3 GIT hemorrhage risk of 2.1%[54]. In another phase II multicenter trial in unresectable HCC

patients, PBT (67.5 GyE/ 5 fractions) showed a 2-year LCR and OS of 94.8% and 63.2%[55]. For advanced HCC with PVTT and a median tumor size of 60mm, patients treated with PBT (median total dose 72.6 GyE in 22 fractions) had OS of 48% and 21% at 2 and 5 years respectively, with an mOS of 22 months[56].”

“For HCC>10cm, PMRC reported 1-year and 2-year OS of 64% and 36% respectively, and 2-year LCR of 87%[58]”

Important subtopics missing from it:
* Use of RT in palliative settings – 8 Gy x 1, 5Gy x 2, etc

Response:
Thank you for your suggestion. This is indeed an important area to elaborate on. We have included a paragraph under section 3.
“3.4 *RT in the Palliative Setting*
For patients with advanced stage unresectable HCC, best supportive care (BSC) is often the treatment of choice, and includes analgesics for pain management. However, symptoms such as abdominal discomfort, pain, nausea or fatigue are still often reported. Low-dose RT has proven to be useful in such settings, with a dose of 8Gy in a single fraction demonstrating a symptomatic improvement in 48% at 1 month[90]. Similarly, in a separate study evaluating the use of single dose palliative RT (8Gy in a single fraction) in symptomatic unresectable HCC patients with an index symptom of either pain or abdominal discomfort, 51.9% demonstrated clinical improvement of their index symptom at 1 month, with the treatment being well tolerated with minimal toxicities[91]. Apart from the single fraction dose, RT can also be given in 2 fractions over 2 days (10 Gy in total), with symptomatic improvement in 53-66% at 2 weeks and minimal toxicities seen[92].”

Comment 2 : Title - should have HCC in it

Response: Thank you for pointing this out. This is also suggested by another reviewer. The title would indeed be incomplete without the main subject matter of HCC included. We have changed the title to
“Clinical application of advances and innovation in radiation treatment of Hepatocellular carcinoma”

Comment 3
Abstract
* Should add indication for RT also includes local control in resectable patients who are not surgical candidates
Response: Thank you for your suggestion. We have included this in the abstract under the statement
“Radiation therapies offer local control in unresectable lesions and in patients who are not surgical candidates, palliation in metastatic disease, and a bridge to resection and transplantation in selected patients.”

* "Quality research and datasets needed" - should also explicitly mention need for rigorous clinical studies.

Response: Thank you for your suggestion. We totally agree with this opinion. There is lacuna and paucity of evidence in many issues related to HCC, which is one of the top 5 causes of cancers globally. We have included this point in the statement
"Rigorous clinical studies, quality research and comprehensive datasets will further its application in the current era of evidence-based practice in Medicine."

Comment 4
Introduction
* I found the overall organization of the introduction a bit strange - the focus is on Barcelona staging and treatment options, and the majority of the introduction describes non-RT treatment. I think it is worth mentioning that Barcelona staging/treatment does not recommend RT, and the authors wish to describe where RT could fit in - if they wish to frame it that way.

Response:
Thank you for pointing this out. Indeed it is important to mention the role of RT in BCLC. We have added the following statement in the first paragraph *"While BCLC does not recommended RT as a first line option throughout all stages, limitations in current modalities emphasize the importance of RT in bridging these gaps."*

We have also reduced the non-RT related statements to ensure that the focus is kept on the role of RT in HCC management. The following statements were removed.

"Surgical resection and transplantation offer the best outcomes in patients with early-stage HCC (5-year OS 60-80%). Resection is recommended for patients with good liver function and the absence of portal hypertension. Liver transplantation is suitable for select patients with liver dysfunction[1,3]."

"Local ablation uses temperature modification or chemicals to induce tumor cell death by coagulation necrosis."

"Patients with inaccessible tumor locations, bleeding diathesis, or poor liver function are also unsuitable for thermal ablation due to risks of injury to surrounding organs or intraperitoneal hemorrhage[8], while chemical ablation such as percutaneous ethanol injection (PEI) has high local tumor progression rates due to variable ablation zone[7]."

As we would like to highlight the limitations of current non-RT treatment modalities, we have left brief explanations of each of their limitations in the introduction to demonstrate the role of RT in bridging these gaps. We have also added in statements after each limitation to better show how RT plugs each of these gaps.

Surgical resection is limited to patients with good liver function, missing a large proportion, as 90% of HCC arises from cirrhosis[6]. *"On the other hand, RT is applicable to a wider pool of patients, demonstrating efficacy and safety even in the treatment of cirrhotics[88]."*

As transplantation is limited by donor shortage, and a long waiting period leads to tumor progression and dropout[1], "*RT's role in bridging and downstaging enables more patients to qualify for curative treatment."*

TACE allows selective delivery of chemotherapy, but patients with impaired liver or renal function or poor portal vein blood flow are less suitable[9], "*making RT a useful alternative for such patients.*"

Recently immune checkpoint inhibitors and gene-targeted oncolytic viral therapy have an emerging role in advanced HCC[1]…. *"The role of RT as an immunomodulator makes it especially relevant, with the potential of enhancing such new modalities in HCC treatment."*

*** The following sentences need references:**

* 1. Surgical resection and transplantation offer the best outcomes in patients with early-stage HCC (5-year OS 60-80%)

Response:

Thank you for pointing this out. As we have decided to remove this statement (for reasons as mentioned above, and also to avoid overlap as we have elaborated on the 5 year OS of curative treatment in a previous statement), we have removed the references.

* 2. However, the risk of local recurrence increases above 3cm

Response:

Thank you for identifying this. We have included the citation to support this statement.

* "HCC is radiosensitive" - since classically HCC considered on more radioresistant spectrum, some context should be provided for this statement, or at least mentioning this should be discussed further.

Response:

Thank you for pointing this out. We have added a statement before this to ensure clarity. *"While classically deemed to be radioresistant, present-day radiobiologic studies show that HCC has similar radiosensitivity to other common epithelial tumors treated with radiotherapy [15]."*

* What is 2011 criteria?

Response:

Thank you for pointing this out. We have removed the confusion. We meant to convey that the EASL criteria published in 2011 was still reported. We have edited the statement as - *"As the update is fairly recent, most guidelines still use the old guidelines, which assesses liver function based on the Child's score alone[3]."*

Comment 5

Principles of RT

* Discussion should include definition of non-classic RILD (authors mention later, but should put upfront), since this is now more common

Response:

Thank you for your suggestion. We have shifted the relevant information on classic and non-classic RILD from the section on complications to the section on Principles of RT, and added a few points to illustrate both modalities better.

"Two types of RILD exist. Historically, classic RILD occurred as a complication in up to 5-10% of patients 2 weeks to 4 months after mean liver dose of 30-35Gy is given using conventionally fractionated regimens, and is thought to be due to veno-occlusive disease as a result of fibrosis[17]. As a more subacute form, this manifests as anicteric hepatomegaly, ascites and elevated alkaline phosphatase (ALP) up to 2x, while transaminases and bilirubin remain

unchanged[18]. Symptoms of fatigue, abdominal pain, hepatomegaly may be noted on clinical history and examination.
However, with advancements in radiation dose planning and newer modalities of radiation delivery, non-classic RILD has become the more common manifestation, and is defined as an elevation of serum transaminase (>5x upper limit of normal) and worsening of CP score ≥2[17]. The ALP is usually normal. The non-classic variation typically develops in patients with a background of cirrhosis or viral hepatitis, and is thought to be a consequence of reactivating hepatitis and a loss of regenerating hepatocytes[17]."

Comment 6

Photon-Based Techniques

* Would probably remove discussion of 2DCRT - used rarely, except potentially in urgent palliative settings.

Response:

Thank you for your suggestion. We have excluded the discussion on 2DCRT and only left a brief description of it there to show why it has fallen out of favor, the progress of RT techniques and the advantages of 3DCRT in comparison to these older modalities.

"2DCRT demonstrated a median OS (mOS) of 9.4 months for HCC patients with regional lymph node metastasis[21]. However, compared to 3DCRT or IMRT, 2DCRT has a lower mOS and 3-year OS[22]."

* Would qualify comparisons of 3D versus IMRT - I don't think there has been RCTs for this, hard to say which reduces RILD, has better LC.

Response:

Thank you for pointing this out. We have added a qualifying statement at the bottom of the paragraph.

"Large scale randomised controlled trials (RCT) comparing these modalities are required to confirm these findings"

Comment 7

SBRT

* A bit odd that SBRT is in a different section than photon-based techniques/particle therapy? Seems like different types of categorizations - conventional versus stereotactic.

Response:

Thanks for this observation. Yes, we have categorised it into subsections based on conventional versus stereotactic, but have ensured that photon-based techniques, particle therapy and SBRT are all under the same section under External beam radiation therapy.

* Either way, given that SBRT is probably now the predominant form of RT for HCC, this section should be fleshed out further. For example, more discussion is needed on motion management.

* The authors mention 2 fractionations, 30 Gy in 5 or 45 Gy in 10 - the latter not technically SBRT. Would mention other dosings which are more common, and dosing based on Child-Pugh score.

* No mention of ongoing trials of SBRT including cooperative group trials.

Response to above three comments on SBRT:
Thank you for your detailed suggestions. Indeed this is an important area that we should elaborate on. We have provided further explanations and included more studies under the SBRT segment to ensure that adequate emphasis is placed on this. We have added the following elaborations and paragraphs, highlighting the doses used, further studies on the efficacy of SBRT, and ongoing trials

The following was removed to avoid confusion as per recommended.
"In HCC patients with palliative intent treatment, SBRT at 45Gy/10 fractions has 1- and 3-year OS rates of 62% and 28%, respectively[39]."

The following were included in subsection 3.2 SBRT:
Fractional doses delivered are much higher, *"ranging between 5-10Gy compared to conventional radiotherapy (typical daily dose 1.8-3 Gy)[9],"* allowing abbreviated treatment duration (1-2 weeks vs. 5-7 weeks)[31].
"SBRT thus results in better dose distributions and high LCR (87-100%)[32]."

"A consecutive phase I to II study of 102 CP A patients treated with 6-fraction SBRT to a median total dose of 36 Gy (range: 24-54 Gy) demonstrated 1-year LCR of 87% for tumors with a median diameter of 7.2 cm[33]. A separate study including CP A and CP B7 patients displayed similar results when treated to a median total dose of 48 Gy in 3 fractions (range: 36-48) and 40 Gy in 5 fractions respectively. LCR of 91% was seen in CP A patients, but is slightly lower (82%) in CP-B7 patients. Higher rates of liver toxicity were also seen in CP B7 patients, with 38% experiencing grade ≥3 toxicity (vs 11% in CP A), pointing to the need for a dose reduction in such patients[34]. Other factors that may portend a poorer prognosis include the presence of PVTT, multinodular disease and high serum AFP[32]."

"To identify the optimal dose and fractionation regimens for SBRT, a multicenter retrospective study classified 602 patients based on the SBRT dose received. Higher doses were associated with better OS, PFS and LCR, and the following doses were recommended: Biologically effective dose (BED_{10}) ≥ 100 Gy as a first-line ablative dose, or equivalent dose in 2 Gy fractions (EQD2) ≥ 74 Gy as a second-line radical dose, and EQD2 < 74 Gy as palliative irradiation[33]. In keeping the risk of RILD ≤ 5%, D50 (dose that would result in a 50% LC) at 6 and 9 months was 53 Gy EQD2 and 84 Gy EQD2 respectively[34]. This was slightly higher in a separate study in Korea (D50 = 62.9 Gy EQD2)[35]. In general, common dose regimens such as 40-48 Gy in 3 fractions and 35-40 Gy in 5 fractions can achieve a 2-year LCR of 90%[32].

While a dose-response relationship is widely-established, clinical value in terms of translation into survival advantage have been mixed[36], with some suggesting that a critical threshold has to be attained before OS can be improved. A multicenter trial demonstrated this threshold to be BED ≥ 53 Gy10[37]. A separate study showed that doses >54 Gy in 3 fractions (BED = 152 Gy10, EQD2 = 126 Gy) achieved LCR of 100% with a 2-year OS of 71%, while patients receiving <45 Gy in 3 fractions (BED = 113 Gy10, EQD2 = 94 Gy) experienced a lower 2-year LCR and OS rate (64% and 30% respectively)[35]"

"SBRT demonstrates improved response and survival in small HCC, with a complete response (CR) and partial response (PR) rate of 15.5% and 45.7% respectively, and 1-year and 3-year OS rate of 86.0% and 53.8% respectively. For HCC between 2.1-3cm and ≤2cm,

SBRT showed a high LCR of 93.3% and 100% respectively. However in patients with HCC>3cm, LCR is lower (76.3%) [51]."

"A study of 37 nonmetastatic HCC patients receiving a dose of 50Gy/5 fractions showed that HCC provided good LCR (95%) and 1-year OS of 87% with only 1/9 patients with Child-Pugh ≥B8 experiencing grade ≥3 hepatic toxicity[56]"

"A study of 37 nonmetastatic HCC patients receiving a dose of 50Gy/5 fractions showed that HCC provided good LCR (95%) and 1-year OS of 87% with only 1/9 patients with Child-Pugh ≥B8 experiencing grade ≥3 hepatic toxicity[56]. SBRT is also safe as a bridge-to-transplant and acts as a complimentary alternative to TACE and RFA, demonstrating comparable OS and dropout rates[57,58]. For advanced HCC, SBRT at a dose of 45Gy/10 fractions demonstrated LCR of 91%, with 1- and 3-year OS rates of 62% and 28% respectively[59]."

The following was included in section 9. Combination therapy
"However, a propensity score analysis in HCC patients with PVTT demonstrated significant improvement in survival when TACE was combined with SBRT (10.9 months vs 4.1 months for patients treated with TACE alone)[179]."

Comment 8
Particle-based therapy
* No mentioning of protons.
Response:
Thank you for pointing this out. We have included the following information regarding proton therapy under segment 3.3 Particle therapy

"Particle therapy such as carbon ion therapy or proton beam therapy (PBT) involves the use of particles such as heavier charged carbon ions or protons. Unlike photon-based EBRT which involves the firing of X-ray beam multiple times from different angles, radiation delivery in particle-based EBRT occurs via particle accelerators which form a single beam of high energy protons to be delivered into the patient[49]. Its ability to provide more localised particle exposure compared to photon-based EBRTs allows for higher doses to be delivered while reducing the damage to surrounding tissues and unwanted side effects[50].

While an exponential decrease is seen in deeper tissues for conventional photon-based techniques, PBT's finite range allows for superior dose distribution as they deliver low doses on entering the target tissue, and only show a steep maximum (Bragg-Peak) upon reaching a specific depth (dependent on their energy). Beyond this depth, there is close to no delivery of radiation, hence, majority of their dose is delivered near the end of their target range and over a narrow range, while relatively low doses occur outside the Bragg peak region[49] 3 main delivery methods exist to allow for uniform coverage at all depths and cover the entire target volume: 1) passive scattering, uniform scanning and active scanning[51]. Moreover, as a heavier particle, carbon ions also have the added advantage of inducing irreparable damage to DNA and are less dependent on the oxygen availability of tumor tissues, allowing for increased distribution of energy during their travel through the tissue (higher linear-energy transfer) and treatment of hypoxic tumors resistant to photons[50]."
"For peripheral tumors >2cm away from the both the GIT and porta hepatis, 66GyE/10 fractions is recommended, while tumors ≤2cm of the GIT can be treated with 77.0GyE/35 fractions and tumors ≤2cm of the GIT can be treated with 72.6GyE/22 fractions"

"Patients with HCC ≤2cm of the GIT treated with PBT at a dose of 72.6 GyE/22 fractions or 77GyE/35 fractions had mOS of 33.9 months, a 3-year OS of 50%, and a grade 3 GIT hemorrhage risk of 2.1%[54]. In another phase II multicenter trial in unresectable HCC patients, PBT (67.5 GyE/ 5 fractions) showed a 2-year LCR and OS of 94.8% and 63.2%[55]. For advanced HCC with PVTT and a median tumor size of 60mm, patients treated with PBT (median total dose 72.6 GyE in 22 fractions) had OS of 48% and 21% at 2 and 5 years respectively, with an mOS of 22 months[56]."

"For HCC>10cm, PMRC reported 1-year and 2-year OS of 64% and 36% respectively, and 2-year LCR of 87%[58]"

Comment 9

Side effects

* Skin changes I would think are pretty rare.

Response:

Thank you for pointing this out. We have removed "local skin changes" from the list of common side effects.

Comment 10

Complications

* CP score >8 at baseline usually contraindication to RT

Response:

Thank you for pointing this out. In practise, the CP score is dynamic. Some patients may be optimized and CP score could be restored to lower score, and thus could be suitable for RT. Locally, we also place emphasis on the variable that determines the CP score. As for example, if CP score is high due to low albumin, it is discounted sometimes as against to elevated CP score due to hyperbilirubinemia. However, we have removed the statement "those with CP score>8" to avoid confusion

* Could include some liver metrics for RT - or need to spare 700 cc a certain dose, taken from surgical literature.

Response: Thank you for pointing this out. We have included the following statement to elaborate on the liver metrics that should be considered for RT.

"Similar to the need to preserve an adequate future liver remnant post-hepatectomy, a critical minimum volume of 700cc of liver should be spared by SBRT (by receiving <15Gy) given the importance of ensuring sufficient liver function[176]."

REVIEWER 3:

Comment 1

Which patients should have adjuvant radiation after hcc resection?

Response:

Thank you for your suggestion. We have included the following paragraph to elaborate further on patients that may benefit from adjuvant radiation

"While curative hepatectomy is the standard treatment of choice for HCC patients with adequate liver function, high rates of intrahepatic recurrences post-resection (70-100% after 5 years) make adjuvant radiotherapy increasingly relevant[95]. Risk factors for post-operative recurrence include: tumor size (especially >5cm), number, and histopathological grade; microvascular invasion and macrovascular invasion; presence of stellate nodules, underlying liver disease, and surgical factors (extent of resection and resection margins)[187]. Microvascular invasion (MVI) is the most commonly reported, and is an independent prognostic factor associated with early postoperative recurrence and poor OS. While a resection margin of 2cm has been deemed to be sage in reducing post-operative recurrence, cirrhotic patients often have limited liver reserves. Adjuvant radiotherapy is a promising adjunct, resulting in significantly longer recurrence-free survival and OS in patients with MVI, as compared to TACE[95]."

Comment 2

Is there any data about neoadjuvant radiation ? This is not about bridge to transplant. This is may be about downstaging.

Response:

Yes, thank you for your suggestion. We have included a paragraph on neoadjuvant therapy in section 10. Future developments

"Radiotherapy also offers a possibility of downstaging when used as a neoadjuvant treatment. Compared to surgery alone, patients treated with neoadjuvant 3DCRT had significantly improved survival outcomes (1-year OS 75.2% vs 43.1% for hepatectomy-alone patients) and lower recurrence rates, attributed to the decrease in tumor volume and downstaging of the PVTT type following neoadjuvant radiotherapy[191,192]. As IL-6 levels were significantly higher in pre-radiotherapy serum and tumor tissues of non-responders, overexpression of IL-6 may be signal ae poorer prognosis[191]. A retrospective analysis of 244 patients also showed neoadjuvant radiotherapy to be superior to post-operative radiotherapy, with a significant improvement in OS seen[193]."

Comment 3

Is BCLC useful system to continue or, authors recommend other system?

Response:

Thank you for the thought-provoking question. We believe BCLC will continue to be mentioned in HCC literature, similar to Milan criteria for liver transplantation. We have commented on this under section 10. future directions

"As BCLC has acted as a cornerstone for several guidelines mentioned above, evidence-based updates regarding the role of radiotherapy based on substantiation by robust evidence is necessary to guide physicians for the optimal treatment of HCC patients."

Comment 4

Pls ensure your images are compliant to copyright.

Response: Thank you for the reminder. The images and tables were generated by our team and are compliant to copyright. Thank you.

2nd Editorial decision
29-Sep-2021

Ref.: Ms. No. JCTRes-D-21-00138R1
Clinical application of advances and innovation in radiation treatment of hepatocellular carcinoma
Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: