

## Peer Review File

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### Reviewer A Comments:

1. The period of search for this review as well as language of manuscripts screened should be stated.

Response: language (English only) had been already stated in the methods section. We added the time frame (1990 to 2023). However it should be mentioned again, that this work is a narrative review, not a systematic one.

2. The word “percutaneous” is not usually used to describe SBRT. Thought should be given to use other wording.

Response 2: we changed the wording to “external beam radiotherapy”.

3. In the recurrent setting, there is uncited phase 3 evidence of non inferiority of SBRT compared to RFA in small HCC. In light of this data, the sentence in lines 178-179 should be rephrased.

Response 3: We included the following sentence: “Kim et al. published the only phase III trial comparing proton beam radiotherapy (PBR) vs RFA in patients with locally recurrent HCC with a non-inferiority design. Patients with up to two lesions with a maximum size of 3 cm were eligible. Non-inferiority of PBR in terms of 2y-local-progression-free-survival was statistically confirmed, with the absolute rates even favouring for the PBR approach (93% vs 83%) [31].”

4. In table 1, reference 29 by Park is a retrospective trial.

Response 4: Thank you, was corrected.

5. In table 1, Chen et al. (PMID: 34211773) should be added to the prospective trials list.

Response 5: we added the study of Chen et al.

6. In line 205, it is stated that fiducials are usually necessary for HCC SBRT. I’d argue that the phrase is inaccurate. The Toronto experience which is the largest prospective trial published so far (Bujold et al.) did not use fiducials. RTOG 1112 also did not recommend the extensive use of fiducials, although it was permitted.

Response 6: Thank you for your comment. You correctly mentioned that in some of the existing literature SBRT has been used without fiducials. However, most of the more recent literature favors the use of implanted fiducials or radio-opaque substances delivered to the lesion for example by prior TACE. In our own experience, both is very helpful for image-guidance. Moreover, we compared intrafractional motion compensation using fiducials with an approach based on liver boundaries. In this study, the non-fiducial based approach lacked the desired accuracy for SBRT [Heinz et al., Radiat Oncol 2016;11:88]. However, we changed the wording into: “which are often used”.

7. In line 293, “Technical exection” should be corrected.

Response 7: was corrected to “technical execution”.

### **Reviewer B Comments:**

Authors handle SBRT for HCC thoroughly, so this manuscript could make readers familiar to SBRT for HCC.

### **Specific comments**

1. The contents in this subtitle are dealing with the roles of definitive SBRT. And the following categories are combination with other treatments and bridging to transplantation. Would you change the subtitle of specific situations corresponding to the followings? If the limited multifocal HCC were similar to the distinctly multifocal primary HCC, they could be merged to a single category.

Response: thank you for your comments. Categorizing the different disease situations was one of the major challenges while writing the manuscript. For the purpose of this clinical practice review, we tried to differentiate categories with clinically meaningful differences. For example, many trials with curative intent SBRT included mainly patients with 1-2 or 1-3 lesions, although the same aim might be achievable also in selected patients with 4 or 5 lesions given a limited lesion size and a favourable distribution. On the other hand, some patients will show a more limited number of lesions but with an unfavourable size and/or distribution. With our wording, we tried to distinguish between those ends of a continuum, although there is some overlap within published trials. We therefore prefer not to merge those categories.

However we added a clarification to the paragraph dealing with distinctly multifocal inoperable liver confined HCC describing the findings of Sapir et al.

2. If the locally recurrent HCC were similar to the recurrent inoperable liver confined HCC, they could be merged to a single category.

Response: See above, we changed the subtitle to locally recurrent unifocal or limited multifocal HCC.

4. The effects of SBRT for macrovascular invasion was mentioned together with other subjects. Would you describe it separately?

Response: Macrovascular invasion, especially portal vein thrombosis has been described as a negative prognostic factor in several circumstances. However this seems at least partly because its presence is a technical obstacle for some locally ablative treatments. Indeed, the presence of circumscribed (e.g. still confined to the liver) macrovascular invasion is often shifting the treatment decision towards SBRT or EBRT (in case of vascular invasion beyond the liver). The effects of SBRT itself seem not dependent on the presence of macrovascular invasion (as long as dose prescription is not influenced by adjacent organs at risk). We therefore feel that a separate paragraph is not justified.

#### **Page 8**

In lesions > 2 cm, SBRT ... in another study [33, 34].

- The reference 34 did not restrict the patient to the lesions > 2cm. Would you verify it again?

Response: We have rephrased the sentences for more clarity: “In the study by Wahl et al., SBRT even resulted in significantly higher local control rates than RFA in lesions > 2 cm [33]. Sapir et al. further showed in their comparative study that SBRT was clearly more effective and less toxic compared to TACE. [34].”

#### **Page 10**

1. (In the first line) ... in very large and multifocal HCC, ...

- The term of very large looks vague. Would you describe it more certainly?

Response: Sentence was rephrased, “large” was deleted: “TACE is the preferred treatment in distinctly multifocal HCC, although there seems to be a role for SBRT even in advanced situations based on suitable lesion numbers, lesion sizes and lesion distribution.”

2. (Second and third sentences) A propensity score analysis of Sapir et al ... did not differ statistically [34].

Response: “We thank the reviewer for the comment. We agree that the reference is not suitable within this paragraph. We deleted the reference including the complete sentence and included some of the information in the paragraph dealing with unifocal

or limited multifocal lesions: “Sapir et al. further showed in their comparative study that SBRT was clearly more effective (2y-LC 91% vs 23%) and less toxic compared to TACE [34].”

3. (Ref 40) The reference 40 did not analyzed SBRT data, but EBRT ones. So, it looks a little out of the theme of this analysis.

Response: You are of course correct. We cited this paper in the paragraph “Toxicity and quality of life” to demonstrate that also moderate hypofractionated EBRT is a potential treatment alternative, if SBRT is not possible. We have added the term EBRT and a statement that further discussion of EBRT Is beyond the scope of the review: “If application of ablative doses is not feasible, EBRT with moderate hypofractionation (12 – 15 fractions) is also an alternative treatment option, especially in combination with prior TACE [19,40]. However, the detailed discussion if such approaches is beyond the scope of this review.”

#### **Page 15**

1. (Third sentence) Usually patients with 1-3 lesions with maximal diameters of 5-6 cm ...

Response: The sentence was deleted.

2. (Last sentence) What is “technical exection”? Would verify it?

Response: was corrected: “technical execution”

#### **Reviewer C Comments:**

Thank you for the opportunity to review this manuscript which outlines the role of SBRT in HCC and performs a narrative review assessing efficacy compared to other therapies. This is a well evidenced narrative review. I have summarized recommendations for consideration below.

1. Correct spelling of Tyrosine (line 68).

Response: has been corrected

2. Clinical evidence: This section would benefit from a more thorough review of the current guidelines. Review the more up to date KLCA, Hong Kong, GESA, AASLD, ECGCCC, EASL and ESMO guidelines and add context to these. The Asia-Pacific guidelines which regionally have the most experience with SBRT for HCC have a

greater emphasis on SBRT inclusion.

Response: We agree with the reviewer that our description was too negative and that we did not manage to include some of the recent updates of international guidelines. We have screened now all recently published updates and included some sentences about the role of EBRT given by those guidelines: “Based on the growing evidence, SBRT was recently included at least as an option in most updates of multidisciplinary guidelines for HCC (NCCN, ESMO, KLCA, AASLD, ECGCC, GESA, Hong Kong guideline, Taiwan guideline), while some still refer to SBRT as a method under investigation without robust evidence (EASL, APASL). Due to the limited number of randomized trials showing a clear benefit compared to other local options, SBRT is mainly listed as an alternative approach in situations not suitable for other local treatments, especially in western guidelines (NCCN, ESMO). In contrast, most Asian guidelines describe a more pronounced role for SBRT [44] as a general alternative to other liver-directed therapies in unresectable patients or as a bridging to transplant (KLCA, Hong Kong, Taiwan). Moreover, the American society for therapeutic radiation oncology (ASTRO) has published recommendations for the use of EBRT including SBRT for HCC within a consensus guideline [19].

3. When referring to trials; recommend to include the NCT numbers

Response: We agree that citing the NCT numbers is of great value for ongoing trials, however we do not feel that it adds valuable information for trials already published as full papers. All NCT numbers for ongoing trials had been included.

4. Typo with references line 275 (author names present)

Response: Has been corrected.

#### **Reviewer D Comments:**

“Stereotactic body radiation therapy (SBRT) in patients with hepatocellular cancer” is a well-written, clear, brief and concise paper on a current topic in digestive oncology such as the role of SBRT in the treatment of HCC. It is an updated review that

proposes SBRT as another local treatment with radical intent, along with surgery and the rest of the treatments, with advantages that will have to be confirmed in the randomized studies currently underway. I consider that the article falls within the journal's scope and that it is of sufficient quality to be accepted for publication without requiring important changes.