

## Peer Review File

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### Reviewer Comments:

#### Reviewer A

This is a critical review of MR-guided radiation therapy for GI cancers. Overall it is well written and comprehensive. I have a few minor suggestions:

1. Cite/discuss this pancreas cancer study of 62 patients from the Miami Cancer Institute (PMID 35814383)

Reply: Thank you very much for this comment. We included this study in our review (see page 9, lines 206-210).

Changes in the text:

The same group published retrospective data of a large LAPC patient collective of 62 patients who received induction chemotherapy followed by stereotactic adaptive MRgRT with a median dose of 50 Gy (range 40-50). 2-year local control, progression-free survival and OS were 68.8%, 40.0% and 45.5%, respectively. Rates for acute and late grade 3+ toxicity were 4.8% and 4.8%, respectively (23).

2. Line 167: LAPC abbreviation is defined here although locally advanced pancreas cancer is mentioned earlier and should be abbreviated when it is first used

Reply: Thank you for this comment. We inserted the abbreviation at the place where the term is first used (see page 7, line 151).

Changes in the text:

The impact of hypofractionated radiotherapy alone or in combination with chemotherapy in locally advanced pancreatic cancer (LAPC) has been investigated in several studies.

3. Lines 184-186: Would add the NCT number for the SMART trial. The initial outcomes were presented for this trial at ASTRO 2022.

Reply: Thanks for this advice. We added the NCT number for the mentioned SMART trial (see page 8, line 197).

Changes in the text:

A prospective phase II multicenter study investigating MRgRT with 50 Gy in 5 fx for inoperable pancreatic cancer patients has been initiated by the authors (NCT03621644).

4. Consider mentioning that a phase 3 randomized trial for LAPC of chemotherapy +/- ablative 5-fraction MRgRT will soon open to accrual (NCT05585554).

Reply: Thank you for this comment. We have modified our text and added this information (see page 12, lines 287-290).

Changes in the text:

A prospective, randomized controlled trial comparing induction chemotherapy followed by stereotactic MRgRT with 50 Gy in 5 fractions and induction chemotherapy alone is estimated to start recruiting in July 2023 (NCT05585554).

5. Line 293: change “roll” to “role”.

Reply: Thank you. We corrected this mistake (see page 13, line 315).

Changes in the text:

The role of SBRT in primary liver cancers is still inconclusive (44).

6. Do the authors believe there is a need for shorter fractionation for abdominal and pelvic oligometastatic disease? Is there potential for increasing use of single-fraction ablative MRgRT especially for treating multiple metastases?

Reply: Thank you for this comment. Our review focusses on GI primary tumors, but we indeed

think that stereotactic MRgRT is a valuable option for abdominal and pelvic oligometastatic disease. We added a comment in the Conclusion section (see page 22, lines 539-541).

Changes in the text:

This review clearly focusses on GI primary tumors, but we believe that MRgRT is also a very suitable tool for treatment of abdominal and pelvic oligometastatic disease.

## **Reviewer B**

This review article is a very well written and impressively comprehensive review of the state of MRgRT using MR-Linacs for treatment of GI cancers. This will provide a useful reference for those in the field interested in understanding the applications, benefits, and relevant clinical trials to date in this space.

Specific Comments:

1. Line 44: “conceptional” should be “conceptual”

Reply: Thank you. We corrected this mistake (see page 2, line 46).

Changes in the text:

We searched for studies, reviews and conceptual articles, including the general technique of (...)

2. Line 45: “concrete” should be “specific”

Reply: Thank you. We corrected this as advised (see page 2, line 47).

Changes in the text:

(...) magnetic resonance guided radiotherapy and the specific utilization in gastrointestinal (...)

3. Line 71: Include increased noise in CBCT as well as artifacts as additional hindrances to CBCT visualization of anatomy (in addition to poor soft-tissue contrast compared to MRI). It could also be worth referencing any recent study showing that CBCT image quality is improving with faster rotation ring-gantry systems as well as the implementation of iterative

reconstruction, which can handle noise better than traditional analytic reconstruction approaches such as FDK)

Reply: Thank you. We modified the text as advised (see page 3, lines 75-76).

Changes in the text:

Furthermore, noise and artifacts can negatively influence image quality of CBCT.

4. Lines 81-90: When comparing to CBCT and mentioning the capability of MRgRT to provide real-time imaging and better soft tissue contrast, it is worth mentioning that MRI is non-ionizing, which is what enables safe real-time imaging for motion management.

Reply: Thank you for this comment. We added this aspect to the text (see page 4, lines 93-94).

Changes in the text:

MR imaging being non-ionizing enables a safe acquisition of real-time imaging for motion management.

5. Lines 82-83: This is not exactly true, as diagnostic MRI could be incorporate into offline adaptation in addition to initial target volume delineation.

Reply: Thank you for this comment. We modified the text as advised (see page 4, lines 88-89).

Changes in the text:

Before the clinical introduction of MR-linacs, the role of MR imaging in RT planning remained limited to initial target volume delineation before treatment start or diagnostic MR imaging being incorporated into offline adaptation workflows.

6. Line 94: Replace “MRI of the day” with “anatomy of the day” to be more accurate since the anatomy is based on MRI, but dose calculation is still based on physical/electron density maps that are derived in some way from CT generally.

Reply: Thank you. We replaced this term as advised (see page 3, line 100).

Changes in the text:

Online adaptive RT (ART) enables radiation oncologists to dynamically adjust to the patient's anatomy of the day by recontouring OAR and target volumes (...)

7. Line 104-105: The MagnetTx system is listed as in development, but to this reviewer's knowledge, this system is now FDA approved.

Reply: Thank you for this comment. We confirmed this information and modified the section (see pages 4-5, lines 105-116).

Changes in the text:

At the time of writing this review, three MRgRT devices are commercially available. (...) The third system, Aurora-RT, received FDA approval in 2022 (MagnetTx Oncology solutions, Edmonton, Alberta, Canada) (6). At least one other device is in development: the Australian MRI-linac Program (Ingham Institute, Liverpool, NSW, Australia) (7). The available systems by Elekta and Viewray currently apply IMRT using the step-and-shoot technique without the ability of performing more complex modulation approaches such as sliding window IMRT or volumetric modulated arc radiotherapy (VMAT). The Aurora-RT system is capable of VMAT, according to the manufacturer.

8. Line 210: when mentioning beam delivery, explicitly mention that realtime tracking and beam gating inevitably decreases duty cycle.

Reply: Thank you for this comment. We added this aspect to the text (see page 9, lines 225-226).

Changes in the text:

Furthermore, real-time tracking and beam gating inevitably decrease beam on duty cycle.

9. Lines 244-246: As written, it is unclear what is being increased by 2.2% vs. 4.3% (both seem to reference target V95%)

Reply: Thank you. We absolutely agree that this is unclear. We added an explanation for the "optimized PTV" (PTV – digestive OAR + 5 mm), see page 11, line 262).

Changes in the text:

(optimization structures were generated by subtracting digestive OAR + 5 mm from the PTV)

10. Line 255: It seems “adopted” should be “adapted”

Reply: Thank you. We corrected this mistake (see page 11, line 272).

Changes in the text:

(...) resulting in delivery of the non-adapted baseline plan (...)

11. Line 264: consider referencing the recent publication by Kim et al. on their first CT-STAR CBCT-guided online adaptive pancreas SBRT (The first reported case of a patient with pancreatic cancer treated with cone beam computed tomography-guided stereotactic adaptive radiotherapy (CT-STAR), Radiation Oncology, vol 17)

Reply: Thank you. We have added this case report to the section (see page 12, lines 283-285).

Changes in the text:

Kim et al. have published a case report of a successful treatment of a patient with pancreatic cancer treated with cone beam computed tomography-guided stereotactic adaptive radiotherapy (33).

12. Line 327: Consider also mentioning that IV contrast can be utilized to better visualize gross disease for liver metastasis. This is mentioned in Rosenberg et al. (Ref #60).

Reply: Thank you. We added this information (see page 14, lines 349-350).

Changes in the text:

Another option to better visualize liver metastases can be utilization of intravenous contrast (61).

13. Line 338: When listing the number of patients with HCC, cholangio, and liver mets, use

“n=26” etc. to avoid confusion with similar annotated references.

Reply: Thank you. We modified the text as advised (see page 14, lines 356-357).

Changes in the text:

(...) with stereotactic MRgRT (n=6 hepatocellular carcinomas, n=2 cholangiocarcinomas and n=18 liver metastases) (63).

14. Lines 352-353: Please briefly explain what adapt-to-position vs. adapt-to-shape means for those unfamiliar with the Elekta specific terminology.

Reply: Thanks for this advice. We added an explanation of those workflows (see page 15, lines 376-380).

Changes in the text:

An adaptive workflow based on adapt-to-position (ATP, online plan adaptation is performed based on the new patient position and optimized on the pre-treatment CT and contours) or adapt-to-shape plan adaptation (ATS, online plan adaptation is performed on the new patient anatomy and optimized on the daily MRI and adapted contours) was used.

15. Lines 456-457: consider mentioning an ongoing prospective clinical trial at Moffitt Cancer Center by Frakes et al (NCT05108428)

Reply: Thank you for this comment. We added this trial to the section (see page 19, lines 483-485).

Changes in the text:

An ongoing trial in the United States led by Frakes et al. is looking into MR guided dose-adaptation based on MR morphologic objective measurements during primary chemoradiation (NCT05108428).

16. Conclusions Section: Please add to the drawbacks (currently listed as time-consuming and staff-intensive) that the technology is itself expensive; expound on time-consuming being due

to many additional steps if re-contouring and adapting and/or decreased beam on duty cycle increasing treatment times when gating on moving anatomy; as well as patient-specific issues such as claustrophobia in generally smaller diameter machine bores and other potential contra-indications for MRI (incompatible pacemakers, ferrous implants, etc.).

Reply: Thank you for this comment. We added the mentioned aspects to the conclusions section (see pages 21-22, lines 543-548).

Changes in the text:

(...) which is mainly due to several additional steps such as re-countouring, online plan adaptation and decreased beam on duty cycle when treating moving targets. As for now, the technology of MRgRT itself is still quite expensive. Patient-specific issues include claustrophobia due to generally smaller bore diameters compared to conventional linacs and potential contra-indications for MRI such as incompatible pacemakers or implants made of ferromagnetic materials.