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# PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 71568

**Title:** Stereotactic Radiotherapy and The Potential Role of Magnetic Resonance-Guided Adaptive Techniques for Pancreatic Cancer

**Provenance and peer review**: Unsolicited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 03076942
**Position:** Peer Reviewer
**Academic degree:** MD, PhD
**Professional title:** Assistant Professor, Associate Chief Physician
**Reviewer's Country/Territory:** China
**Author's Country/Territory:** Australia

**Manuscript submission date:** 2021-09-13

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| **Scientific quality** | [ ] Grade A: Excellent [ Y] Grade B: Very good [ ] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ Y] Accept (General priority)<br>[ ] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ Y] Yes [ ] No |

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| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

Pancreatic cancer is a malignancy with one of the poorest prognoses amongst all cancers. Stereotactic body radiotherapy is a novel radiation technique that delivers high ablative radiation split into several fractions with a steep dose fall-off outside target volumes.The article describes in detail and comprehensively expounds the latest research progress. This technology has potential application in the treatment of pancreatic cancer.

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**Peer-review model:** Single blind

**Reviewer's code:** 06100005
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**Academic degree: MD**
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| | |
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| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
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**SPECIFIC COMMENTS TO AUTHORS**

Overall, this is an interesting read. However, there are a few minor changes suggested. There are a few comments about SBRT's "demonstrated" superior clinical efficacy as compared to conventional RT. I would use softeners liberally throughout the manuscript in regard to demonstrated superior LC or OS with SBRT. Best available data suggests SRT is associated with less acute toxicity (more clear) and perhaps improved efficacy (less clear). I would remove all references to SRT such as "SBRT can achieve better survival" and change to "is associated with" better survival. It has not demonstrated superior LC either. This is stated throughout the paper – e.g., in the conclusions, "SBRT has been shown to achieve a superior OS and LC." Please re-read and correct throughout the paper. Comparative effectiveness should be evaluated in a prospective fashion, whether 5 vs. 15 fractions or 5 vs. 25 fractions. Retrospective studies are hypothesis generating at best. The ongoing SOFT trial (NCT03704662), for example, is investigating if 5 fraction regimens have the same rate of nodal downstaging as conventionally fractionated radiotherapy. Similar trials will help us to be able to definitively say SBRT is at least as effective, or superior to, conventionally fractionated RT. I might suggest using a range of 1-3 weeks for hypofractionated therapy as opposed to 1-2 weeks. I would clarify the sentence about PREOPANC-1 in the introduction to say "in the cohort of patients who went to surgery" (around 2/3 of trial population). I think this was meant to be implied, but is a little unclear as it is currently written. In the fifth sentence of the discussion, it says "sharp radiation dose falloff" with SRT. However, marginal misses are of huge concern with SBRT. There is emerging data to suggest prophylactic nodal irradiation may be warranted, especially in patients who will go to surgery. Excerpt

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from PMID 33981865 "Fiducials or real time Magnetic Resonance Imaging tracking serve to localize the tumor, and accuracy of treatments is within 2–3 mm. Near-misses are of concern with such steep gradients. Modern imaging appears to underestimate the true pathologic size of the tumor by at least 4 mm, which presents additional challenges in highly conformal irradiation of pancreatic tumors, warranting further investigation of optimal tumor volumes and dosing [29], [30], [31]. Areas of clinical microscopic risk, including nodal regions, around the celiac trunk and superior mesenteric artery should be included based on patterns of failure [22], [32]. ESTRO guidelines support the consideration of elective nodal irradiation (ENI) for resectable tumors, as the importance of local control increases in the context of surgery [33]. Further, single institution data has suggested rare out of field failures with five fraction regimens mandating ENI [34]."

Although I'm a huge fan of 5 fraction regimens, it would be remiss for this review to not mention alternative fractionation schemes such as 15 fractions for tumors with gross duodenal invasion or for node positive pancreatic cancer, especially with gross abutment of luminal structures. Chris Crane is a huge proponent of 15 fractions (with the data to back it up: PMID 33704353), and has very high quality data suggesting this may be a preferred regimen for certain scenarios. I'm not sure the best place for this caveat, but the same principles of dose escalation with MRTR would apply here as well. Excerpt from PMID 33981865 "Patients or tumors which may not be candidates for surgery may be well served by more prolonged hypofractionated regimens (e.g., 67.5/15 or 75/25; BED10 98 Gy), especially for tumors less than 1 cm away from luminal structures [26]. Biologically equivalent dose ($\alpha/\beta = 10$) ranging from a minimum of 48[27] Gy to 60 [22] to 72 [24], [28] Gy have been associated with improved OS, in keeping with a minimum of 30–40/5, 35–48/10 or 38–53/15." I might also briefly mention what kind of escalation has been possible with 5 fractions: Excerpt from PMID 33981865 "Dose painting techniques are incredibly technical and vary by institution. Many centers advocate for

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dose-painting to vascular areas of concern [17], [18]. When utilizing a five-fraction regimen, a minimum of 33 [19], [20], [21] or 35[22] to 40 [23] Gy to gross disease is recommended. Further increases in total dose and dose per fraction are possible, with two studies demonstrating dose escalation up to 60 Gy in 5 fractions is dosimetrically feasible with adequate Planning Target Volume coverage and respect of Organs at Risk dose constraints [24], [25]". Further, the landmark PMID 32061993 study recommends 40 Gy covers as much of the tumor as possible when using a 5 fraction regimen, which may be worth mentioning as MRTR could maximize the 40+ Gy volume. How was the rate of conversion to resectability measured on each trial? It should probably be mentioned that post-therapeutic imaging does not correlate with resectability, so "conversion to resectability" may be a controversial topic to some readers. Excerpt from PMID 33981865 "As radiographic response does not appear to predict surgical resectability [14], [51], [52], [53], [54], the decision to proceed with exploration and possible resection would be determined by the operating surgeon after multidisciplinary review and discussion. A central review board may also be considered to assist with determination of surgical eligibility as is done in the ongoing LAPIS trial [NCT03941093]." Please, do not feel obligated to cite PMID 33981865 as this is admittedly my publication, but I figured some of these excerpts might help for you to be able to succinctly acknowledge these caveats or use as a springboard for additional references. Overall, this was a very enjoyable read. Congratulations on putting together such an interesting paper.