

Peer Review File

Article information: <https://dx.doi.org/10.21037/dmr-23-1>

Review comments

This review summarizes the need to pursue dose escalation in unresectable pancreatic cancer patients, and scans the historical transition taken since early 2000s up to now by means of variations in treatment, fractionation schemes and clinical outcomes. Dose-escalation in pancreatic cancer remains controversial, and the delivery of ablative doses is not yet adopted by most of the institutes due to the proximity of highly radiosensitive OAR to the pancreatic tumor. For this reason, the current review can be of high interest for the readers of Digestive Medicine Research. Some details, however, are missing in the current manuscript and need further clarification.

Comment 1

I have only a main concern. Although MR linacs and MR-guided RT has been a breakthrough from the last decade, other technologies are also arising to perform adaptive SBRT such as the Ethos system employing CBCT-guided RT or the CyberKnife in combination with in-room CT (PMID: 36100866, PMID: 36063981 and PMID: 35928600) which also allow to perform adaptive SBRT. I would suggest the authors to focus more (at least in section 5) on the promising use of adaptive SBRT to tackle interfraction OAR variations rather than in the specific type of technology used. For section 6, it is comprehensible to report outcomes from SMART trials, since the experience with other technologies is still very limited.

We kindly thank you for this comment and we therefore have added in some of the suggestions. The manuscript is now more organized to go from CT guided imaging/adaptations into MRI based approach in a more sequential fashion. Above references have been added.

Specific comments:

Comment 2

- According to journal guidelines, the abstract should have between 200~350 words.

We thank you for this comment. Our abstract now fits the criteria.

Comment 3

- The acronym BRPDA in L96 or acronym BR-PDAC in L110 are not defined in the text although they may refer to BRPC definition from L31. Please, choose a single acronym definition throughout the text to ease readability. Similarly, acronym NCCN in L96 is used prior to its definition in L98. Please, also change National Comprehensive Cancer Guidelines to National Comprehensive Cancer Network guidelines. Finally, although common, PS in L118, OS in 119, LC in L255, A-RT in L367, IORT in 468 should be also defined.

Reply 3: BRPDA in L96 has been changed to BRPC. BR-PDAC is defined in L108. In L96, the NCCN acronym has been defined and changed to National Comprehensive Cancer Network guidelines. PS in L118, OS in 119, LC in L255, A-RT in L367, IORT in 468 have been defined. Thank you.

Comment 4

• L147: Currently, 50 Gy in 5 fractions is being explored because adaptive RT, in which a new RT treatment plan is adjusted to the fraction anatomy, is now possible. It is true that MRLinacs performing MR-guided RT have been the predecessors in applying adaptive SBRT. Nonetheless, there are other technologies arising at the moment that also allow adaptive SBRT (see general comment). I would suggest the authors to rephrase the statement to be more focused on the application of adaptive SBRT rather in the technologies used. Same for L183.

We appreciate this comment and have rephrased it to be more inclusive and now have a more in depth review of all applications.

Comment 5

• L171: Does the “iBowel” also includes stomach and duodenum?

Yes, this has been clarified.

Comment 6

• L184-185: I believe the statement should be “Daily imaging can be used for each fraction” instead of Daily adaptive planning. While daily imaging is used for evaluation of organ motion, adaptive planning is used for adjusting the plan.

This error has been fixed. Thank you.

Comment 7

• L188: Sometimes the authors refer to the use of CBCT imaging during IMRT (L188), hence performing adaptative SBRT with conventional linacs? Sometimes the authors refer to the use of MR or CT-on rails guidance (L182-183). These swings between treatment techniques makes this paragraph difficult to comprehend. Also because it seems the authors discuss about the use of adaptive SBRT vs. the importance of target targeting, which is a completely different topic.

Thank you for this comment. We have attempted to be clearer now on whether the adaptive technique is utilizing CT guidance or MRI based techniques. The flow of the paragraph should read to touch upon the breadth of available image guidance options.

Comment 8

• L201 & Table 1: Is overall survival defined since diagnosis, since chemo or since RT is delivered?

The definition of overall survival varied between studies. Clarification of how OS was defined was added in both the text body and in the table for each study. Thank you.

Comment 9

- L279: What does the study note to improve OS? Is it due to dose escalation only?

From the study: “Higher dose (BED) was a strong independent predictor of improved OS in these patients.” This was also clarified within the paper. Thank you.

Comment 10

- L282: Do the authors mean “spare” the GI structures instead?

Yes, this error has been fixed. Thank you.

Comment 11

- L329-L332: Can the authors double-check the doses for the standard dose RT? Both cohorts presented in L330 – L331 seem to have received BED \geq 70 Gy. Do Rudra et al. compared only these two groups or also vs. standard dose RT as said in L329?

Yes, Rudra et al. compares those two groups also vs. standard dose RT. The doses for the standard dose RT have been added to the paragraph for clarification. Thank you.

Comment 12

- L356: Could you add the corresponding BED doses for SABR dose \geq 40 Gy vs $<$ 40 Gy to ease comparison with other studies? In my understanding the threshold in this study is set at BED₁₀=72Gy, right?

Yes, the corresponding BED for SABR dose \geq 40 Gy is BED₁₀ \geq 72 Gy. And the corresponding BED for SABR dose $<$ 40 Gy is BED₁₀ $<$ 72 Gy. Thank you.

Comment 13

- L351 onwards: Toesca, Jolissaint and Reyngold studies did not treat patients with MRgRT. Consider changing the title of the section or create a new section with new title.

We thank you for this comment. We have moved this accordingly to separate out the CT guidance vs the MRI guidance studies for easier reading.

Comment 14

- Table 1: Herman et al. radiation dose should be BED₁₀ = 54.8 Gy instead

This error has been fixed. Thank you.