Peer Review File

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Reviewer A:

Comments:

Comment 1: This is a very good, comprehensive review on the role of radiotherapy in the management of pleural mesothelioma.

This is very well written, evidence-based review. I think that this has a good educational value. Division on parts of: palliative RT, prophylactic RT of surgical tracts, and adjuvant setting makes a content very clear.

Reply 1: We thank the reviewer for their positive comments and review of this manuscript.

Comment 2: SAKK trial had an update on pattern of failure after adjuvant RT published in Radiother Oncol in 2019. This further stressed no benefit of the use of radiotherapy (high percentage of n-field failure). This would be addressed.

Reply 2: We have revised the manuscript to include a discussion on the patterns of failure within the SAKK 17/04 study.

We have included the following text to read: "In an updated analysis the SAKK trialists reported the patterns of failure with relation to the radiotherapy field. Interestingly, of the 27 patients randomised to radiotherapy, only 1 patient had a local recurrence, suggesting local efficacy of radiotherapy, but overall futility as a result of failure to control out of field disease.owing to control out of field disease (23)."

Comment 3: Preoperative short course RT seems to be very attractive approach. I suggest a mention on that in the Abstract and conclusions even if still more data are needed.

Reply 3: We thank the reviewer for this comment and have include the following text in the abstract: " This overview will also consider potential emerging therapeutic strategies such as pre-operative short course hypofractionated radiotherapy."

We have also included the following text in the conclusion: "However, the convenience, low rates of toxicity and promising clinical outcomes suggest that hypofractionated pre-operative short course radiotherapy is potential therapeutic approach, but further evidence is needed."

Reviewer B:

Comments:

I would like to congratulate the authors on a superbly prepared paper. In my opinion, it is well written and broadly covers the main controversies in the role of radiotherapy in MPM.

Comment 1:
I would propose to add information concerning:
- dependence of MPM radiosensitivity on the histological subtype:
  epithelial > sarcomatoid *(Wu et al., Oncotarget, 2015)* .

Reply 1: We thank the reviewer for their kind comments above and suggestions. We have extensively searched Oncotarget for the suggested paper by Wu et al in 2015. We have been unable to find any paper which reports differential radiosensitivities by different epithelial subtype. We did find a paper by Wu L, et al entitled "Targeting the inhibitory receptor CTLA-4 on T cells increased abscopal effects in murine mesothelioma model" Oncotarget. 2015; 6:12468-12480, which references the paper "Cho BC, et al, J Thorac Oncol. 2014;9(3):397-402." Which we have already cited. Cho et al report differential recurrence rates between between epithelial histology and bi-phasic histology, suggesting that bi-phasic (non-epithelial) histology may not respond as well to high-dose hypofractionated radiation.

In response to the reviewer's suggestions we have amend the final sentence in our discussion of the SMART study to read:
"Among patients with cT1-3N0M0 disease (n=56), the median disease free survival was estimated to be 47 months and overall survival was 51 months in patients with the epithelial subtype, compared to only 8 and 10 months, respectively, in patients with the biphasic subtype, suggesting a differential response to hypofractionated radiotherapy between the epithelial and biphasic subtype."

Comment 2:
I would propose to highlight the high mortality related to fatal radiation pneumonitis (RP) of the contralateral lung noted in the early series with post-EPP IMRT (6/13 pts [46%] *[Allen et al., Int J Radiat Oncol Biol Phys, 2006]* and mention the obligatory stringent dose constraints for the single lung:
- MLD<8,5Gy
- V20<7-10%
- V10<55%
- V5<50-60%,

as well as recommended modifications of IMRT technique: restricted spacing of beams, 9 beams *(Allen et al.)*.

Reply 2:
We thank the reviewer for this suggestion and have included the following text in response to this:
"Allen et al reported outcomes for 13 patients receiving IMRT following extra-pleural pneumonectomy. Of the 6 patients who developed fatal pneumonitis in the remaining lung, the V20 was numerically higher leading the authors to recommend stringent dose constrains in this clinical setting. In patients with a single intact lung, they recommended keeping the MLD to < 8.5 Gy, the V20 to <10%, the V10 to <55% and the V5 to <60% as well as arranging the IMRT beams to avoid the remaining lung entirely.

Comment 3:

I would also consider to mention:
- the PET/CT role in MPM radiotherapy planning: it improves target delineation and that potentially translates into better local control;

Reply 3:
We have included the following text in the section on "Remaining Answers for Radiotherapy in Mesothelioma": "So how best to plan and deliver radiotherapy in mesothelioma? In terms of planning and simulation there is some suggestive evidence that PET/CT may better guide target volume delineation Radiotherapy planning may be better informed by the use of PET/CT as compared to CT alone to guide target volume delineation. In a planning study of 13 patients, PET/CT was shown to reduce the risk of geographic miss."

Comment 4:
- the location of most common contouring errors – costophrenic, costodiaphragmatic, cardiophrenic angles; role of 4DCT (to assess diaphragmatic respiratory motion) and radio-opaque clips placement in the regions of interest (inferior extent of diaphragm and crura, anterior medial pleural reflection, grossly involved LN, region of chest wall invasion and close resection margins) during surgery;

Reply 4:
We have included the following text to address this recommendation: "Addressing this issue of the complex target volume delineation in this setting, Gomez et al, set out clear contouring guidelines in their expert opinion paper [13]. In this they recommend covering the costophrenic, costodiaphragmatic and cardiophrenic angles to ensure coverage of the entirety of the pleural recesses as well as a number of other planning recommendations."

Given the lack of evidence for 4DCT and marker clips, we have not included these in the current manuscript.

Comment 5:
- the controversy of fissure irradiation (usually not performed due to risk of unacceptable lung toxicity and relatively low risk of recurrence in this area ≈15%);

Reply 5:
This is addressed in the following sentence already included: "The clinical target volume at risk is also more complex because of the possibility of recurrence in the unstripped visceral pleura of the fissures deep within the lung."

Comment 6:

- possible activation of immune system modulated by high dose hypofractionated RT in the SMART approach (in addition to "pure" cytotoxic effect - sterilizing the edges of tumor that is expected to limit the risk of spillage at the time of surgery);

Reply 6:
This is included in the following sentence:

"In addition to the in addition to directly cytotoxic effect of radiation sterilizing the surgical field and thus limiting the risk of spillage at the time of surgery, one postulated underlying mechanism for the excellent results seen with the SMART protocol, is that radiotherapy is immunostimulatory and thus enhances an abscopal effect.

Comment 7:
- additional interesting clinical trials in the field:
· MesoRT - accelerated hypofractionated RT in MPM after P/D or biopsy (ClinicalTrials.gov Identifier: NCT03269227), recriuting
· MESO-PRIME: pembrolizumab+SBRT in MPM (ClinicalTrials.gov Identifier: NCT04166734), not yet recruiting
· Atezolizumab, Pemetrexed Disodium, Cisplatin, and Surgery With or Without Radiation Therapy in Treating Patients With Stage I-III Pleural Malignant Mesothelioma (ClinicalTrials.gov Identifier: NCT03228537), active, nor recruiting

Reply 7:
We are grateful for this suggestion has have include the above studies in the following text:

"This potential combination of immunotherapy and radiotherapy is being investigated by a number of clinical trials in set-up. The MESO-PRIME study plans to investigate if stereotactic ablative radiotherapy (SABR) when used a priming dose can enhance the efficacy of pembrolizumab in mesothelioma. The MESO-PRIME investigators plan to deliver an immunostimulatory dose of SABR to a suitable part of the tumor, but not to all areas of disease. Similarly, a Phase 1 study seeks to examine the safety of the combination of atezolizumab, pemetrexed, cisplatin, and surgery with or without radiotherapy patients with stage I-III mesothelioma."

We have not included Meso-RT as it largely addresses the safety of hypofractionation in patients with MPM patients after pleurectomy / decortication or biopsy. The post biopsy setting is already covered by PIT study and the role of hypofractionation has been already addressed and discussed by the SMART study. Thus we think study is unlikely to have impact and we have not included this.

Comment 8:
- Is there any data on cardiac RT-dependent toxicity in left-sided MPMs?

Reply 8: Although there is a highly likely relationship, we could not find any supporting data, presumably owing to the poor survival outcomes for mesothelioma.

Comment 9:
- Is there a role for SBRT in oligoprogressive or oligometastatic MPM?"

Reply 9: Finally, the role of SABR in the treatment of recurrent or metastatic mesothelioma has not been well reported. Schröder et al report a series of 21 patients treated with SABR for oligorecurrence of malignant pleural mesothelioma. Only 1 patient experienced a grade 3 toxicity and the 12-month local

control rate was 73.5%, suggesting both feasibility and efficacy for this approach. It is likely that SABR will be become more widely used in the treatment of oligometastatic and progressive disease.