Peer Review File

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Reviewer A

This is a well-structured and comprehensive review on the role that radiation therapy (RT) plays in malignant pleural mesothelioma (MPM). After describing many clinical trials regarding RT applied -with or without surgery- to patients with MPM the authors conclude that radiation therapy is especially well-suited for those patients with epithelioid-type pleural mesotheliomas.

COMMENTS.

1. I think that adding a few references regarding clinical questions and some technical advances in intensity modulated radiation therapy (IMRT), such as volumetric arc therapy (VMAT) would be interesting for the general reader. For example, I would suggest the following:
   - Kindler HL, Ismaila N, Armato SG 3rd, et al. Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(13):1343-1373. doi:10.1200/JCO.2017.76.6394
   - Hanna GG, John T, Ball DL. Controversies in the role of radiotherapy in pleural mesothelioma. *Transl Lung Cancer Res*. 2021;10(4):2079-2087. doi:10.21037/tlcr-20-583

Thank you for providing these references. We have updated the text to include some of the ASCO Clinical Practice Guidelines and to mention volumetric arc therapy (above articles are referenced). Changes to the text are as follows:

Pages 3-4, Lines 62-69: "Volumetric arc therapy (VMAT) is a type of IMRT that dynamically delivers radiation as the gantry rotates around the patient, allowing for better dosage delivery to the tumor while sparing healthy surrounding tissues(10)."

Page 9, Lines 187-189 (added in specifics on who made the recommendation): "A consensus expert opinion from the National Cancer Institute, International Association for the Study of Lung Cancer Research, and Mesothelioma Applied Research Foundation recommends…"

Page 9, Lines 192-195: "Clinical practice guidelines from the American Society of Clinical Oncology recommend that IMRT following lung-sparing surgery should be performed only at highly experienced centers, preferably in the context of a clinical trial, given the toxicity concerns (27)."

Page 12, Lines 259-261: "Additionally, recently published clinical guidelines recommend offering palliative radiation therapy in patients with symptomatic disease(27)."

2. Although I am aware that a deep discussion on tumor heterogeneity would be beyond the scope of the present manuscript, I believe that a specific mention to this topic in the Discussion section would be welcome, to provide the reader with a wider perspective on the problems currently related with tumor heterogeneity and mesothelioma management, including radiation therapy (see below):

   a) Malignant pleural mesothelioma is associated with high rates of morbidity and mortality, and it has been typically classified into epithelial, sarcomatoid and byphasic subtypes. According to the authors in the present manuscript, curative-intent therapy is reserved for epithelial and biphasic tumors, and the best results are obtained with epithelial ones.
   b) Hovewer, recent research has put much emphasis on the *intratumor heterogeneity* of many malignant neoplasms, including pleural mesothelioma, and this heterogeneity is linked to resistance to treatment (Marusyk A, et al. Intratumor Heterogeneity: The Rosetta Stone of Therapy Resistance. Cancer Cell. 2020 Apr 13;37(4):471-484), (Oehl K, et al. Heterogeneity in Malignant Pleural Mesothelioma. Int J Mol Sci. 2018 May 30;19(6):1603).
   c) A marked difference in genetic spatial heterogeneity was recently demonstrated in in mesothelioma samples that were taken specifically from different areas of the pleura (anterior, posterior, diaphragmatic) in each patient (Kiyotani K, et al. Integrated analysis of somatic mutations and immune microenvironment in malignant pleural mesothelioma. Oncoimmunology. 2017 Jan 6;6(2):e1278330), then finding *clearly distinct mutational patterns in different locations of the pleura within one patient*.
   d) Moreover, when a detailed molecular analysis integrating transcriptome and epigenetic data was performed on tumor samples that had been labeled as "Epithelioid Malignant Pleural Mesothelioma" by a panel based on histology appearance, *each tumor could be decomposed as a combination of epithelioid-like (E-score) and sarcomatous-like (S-score)* components, whose proportions are highly associated with prognosis (Blum Y, et al. Dissecting heterogeneity in malignant pleural mesothelioma through histo-molecular gradients for clinical applications. Nat Commun. 2019 Mar 22;10(1):1333). These authors found clearly significant differences in overall survival when a cut-off ≥ 22% in the "S-score" (sarcomatous) was applied to mesothelioma samples previously labeled as "Epithelioid".

Thank you for this suggestion and the provided references. We have included a section under the Results section titled "Tumor Heterogeneity" on pages 12-13, lines 263-283. The aforementioned references have all been included. The section reads as follows:

"As detailed in the above sections, more favorable results were achieved with radiotherapy used for the epithelioid subtype of MPM as opposed to the sarcomatoid subtype. However, recent research has emphasized the intratumor heterogeneity of certain malignant neoplasms. This intratumor heterogeneity may allow some tumor cells to survive during targeted therapy,

contributing to acquired resistance and relapse of the neoplasm(34). MPM has been shown to have both inter-tumor heterogeneity between patients and intra-tumor heterogeneity within a tumor sample of a given patient(35). A study by Kiyotani et al found heterogeneity in both the genomic landscape and immune microenvironment of MPM(36). Non-synonymous mutations and gene expression profiles differed among individual tumors as well as different tumor sites in an individual patient. Authors concluded that a single tumor-biopsy specimen may not be adequate to characterize the tumor nature; however, obtaining multiple biopsy specimens remains challenging. Blum et al described MPM heterogeneity using a bioinformatics method called WISP, allowing the proportion of epithelioid and sarcomatoid morphologies of a given tumor to be taken into account. Authors compared survival for patients with ≥ 22% of S-score (percentage of sarcomatoid components) to those with < 22% of S-score and found a hazard ratio of 6.28 (p=0.001) (37), with a difference in median overall survival of greater than 10 months between the groups. Research in the area of tumor heterogeneity in MPM is relatively new but an important consideration moving forward given the prognostic factors of different tumor subtypes and the treatment decisions made based on patient prognosis, particularly as it relates to our discussion of radiotherapy."

Reviewer B

This review paper describes the role of radiotherapy in the multimodality treatment of malignant pleural mesothelioma. The content of the work is very comprehensive. However, the information appears to be a loose compilation of results from various studies. It is difficult to maintain an overview. Various procedures, inclusion criteria, overall survival are summarized. A comparison of the different studies is difficult.
The work is interesting as such and the authors have made great efforts to compile the information comprehensively. I recommend the following adjustments:

The paper needs to be more clearly structured. Various tables are needed, which allow a comparison of the studies. In addition to the introduction, there needs to be an overview of the approaches to multimodal therapy.
Thank you for this suggestion. We have included the following statement at the end of the introduction on Page 4, Lines 70-73 in order to clearly lay out the sections: "In this review we discuss topics including post-operative radiotherapy following EPP, post-operative radiotherapy following P/D, pre-operative radiotherapy, role of radiotherapy in procedure site metastases, palliative radiotherapy for nonresectable tumors, and the implications of tumor heterogeneity."

In order to compile the results more clearly, we have included Tables 1 and 2 on page 18. Table 1 summarizes the studies on radiation therapy following EPP, and Table 2 summarizes the studies on radiation therapy following P/D. As the subsequent sections have fewer studies and less comparable results, we have not included tables for these sections.

Authors	Year	Subjects receiving	Radiation Technique	Median Dose	Median OS	Toxicity

		RT				
Rice et al	2007	63	IMRT	45 Gy	14.2 months	Severe respiratory distress: 1 patient
Krug et al	2009	44	Not specified	45.9 Gy	29.1 months	Radiation pneumonitis: 2 patients
Gomez et al	2013	86	IMRT		14.7 months	Grade 5 pulmonary toxicity: 5 patients
Simon et qal	2018	27	IMRT	54 Gy	34.9 months (mean)	No Grade 3+ toxicities
Federico et al	2013	32	Not specified	50.4 Gy		13% experienced serious adverse events related to radiotherapy
Stahel et al	2015	27	Not specified	55.9 Gy	19.3 months	Grade 4+ pneumonitis: 2 patients

Table 1: Studies on radiation therapy following extrapleural pneumonectomy. Overall survival and serious toxicities are reported specifically for patients receiving radiotherapy when provided by the author.

RT = radiation therapy; IMRT = intensity modulated radiation therapy; OS = overall survival

Authors	Year	Subjects receiving RT	Radiation Technique	Median Dose	Median OS	Toxicity
Rosenzweig et al	2012	36	IMRT	46.8 Gy	18 months	Grade 4+ pneumonitis: 2 patients
Gupta et al	2005	123	EBRT	42.5 Gy	13.5 months	Grade 4+ pneumonitis: 2 patients
Rimner et al	2016	27	IMRT	46.8 Gy	23.7 months	No Grade 4 + toxicities

Table 2: Studies on radiation therapy following pleurectomy-decortication. Overall survival and serious toxicities are reported specifically for patients receiving radiotherapy.

RT = radiation therapy; IMRT = intensity modulated radiation therapy; EBRT = external beam radiation therapy; OS = overall survival

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Reviewer C

This is a clear, well written review article examining the role of radiotherapy in the management of malignant pleural mesothelioma. Minor revisions are suggested prior to publication.

Conclusion:

The authors are strong in their recommendations for radiotherapy to prevent recurrence of mesothelioma “Radiation therapy has been shown to be effective in preventing local recurrence and is especially well suited for epthelioid cell types” (conclusions, page 11, line 236-238). The evidence presented in the review does not support this statement for all scenarios. Post-operative radiotherapy following P/D is currently being investigated with a phase III trial (page 8), and the authors acknowledge the limited data for pre-operative radiotherapy (page 9). Radiotherapy has also not been shown to significantly reduce the incidence of procedure tract metastases (page 9).

Would the authors consider different wording to acknowledge the ongoing uncertainties regarding the role of radiotherapy.

Given the evidence presented in the review, we have revised these concluding statements on page 13, lines 287-290. The text now reads, "Radiation therapy has been shown to be effective in reducing local recurrence and appears to be especially well-suited for epithelioid cell types. Additionally, radiation therapy prior to surgery has shown benefit for certain patients, especially those with early-stage epithelioid tumors, although current evidence is limited."

Editing:

Introduction, page 3 line, 57: reference 8 is in regards to the first half of the sentence and should be moved to after the word 50%, with a different reference in place for "greatly improved safety profiles".

We have moved reference 8 to after the word 50% and included reference 9 after "improved safety profiles".

The authors use epithelial and epithelioid interchangeably when referring to pathological subtypes of mesothelioma. Whilst this may reflect the terminology used in different studies, it would be helpful to use uniform terminology in this review

Thank you for this helpful suggestion. We have changed to wording to "epithelioid" throughout the manuscript.