Peer Review File

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Reviewer A

Comment 1: My only specific comment to be addressed by the authors is perhaps the need to reference the recently presented MARS2 data at the IASLC 2023 conference just a few weeks ago.
RESPONSE: We appreciate the reviewer's kind feedback regarding our study, and also their important reference to the data recently presented at the 2023 International Association for the Study of Lung Cancer (IASLC) meeting regarding the United Kingdom's Mesothelioma and Radical Surgery 2 (MARS2) study, which showed that results after surgery with pleurectomy/decortication were not better than non-surgical therapy for malignant pleural mesothelioma. We certainly recognize that this study's important findings may impact care going forward. The study is not yet published and so cannot be officially referenced by our manuscript, but in response to the reviewer's comment we have revised the discussion section of the manuscript to essentially say that future guidelines may change as new evidence such as the MARS2 becomes available, but that our study should still serve as a reminder that adherence to guidelines developed by mesothelioma specialists can optimize patient outcomes.
CHANGES TO THE TEXT: Lines 343-352, last paragraph of the Discussion Section, where we also reference the clinicaltrials.gov website that describes the MARS2 study.

Reviewer B

Comment 1: Surgical treatment for the epithelioid MPM is pivoted on two different techniques: extrapleural pneumonectomy (EPP) and Pleurectomy/decortication (P/D). These two techniques differs themselves for postoperative complication rate and long-term survuval, due to the different invasiveness of the two approaches. In the group of patients adherent to guidelines is not clear which surgical procedure was performed. It is well known that the survival rate associated to EPP

is lower if compared to P/D that represents the more conservative surgical treatment. This point might be a bias for the survival outcomes.

RESPONSE: We appreciate the reviewer's clinical insight, and agree outcomes after surgery likely depend on whether extrapleural pneumonectomy or pleurectomy/decortication was performed. Unfortunately, the coding for surgical procedure in our dataset does not allow us to specify which surgery was used, only that radical surgery with either procedure was used. In our original submission, we did try to thoroughly explain and address that limitation in the method section and in our discussion. In response to the reviewer comment, we have further revised the discussion section of the manuscript to more specifically address the potential survival bias raised by the reviewer. The 3rd paragraph of the discussion section, where we address the limitation of not being able to specifically identify which surgical procedure was performed, now includes this statement: "However, considering that surgical practice has trended to utilize pleurectomy/decortication rather than extrapleural pneumonectomy, the inclusion in our study of patients undergoing extrapleural pneumonectomy could be underestimating the potential benefits of adhering to guideline care that utilizes pleurectomy/decortication rather than the generally more morbid extrapleural pneumonectomy."

CHANGES TO THE TEXT: Lines 316-320, 3rd paragraph of the Discussion Section.

Comment 2: I think that the cohort of the group not adherent to guidelines should be better characterized. The patients in this group did not follow the multimodal protocol and the reason why this happened it is not clear. A possible distortion of the results can be present when the patients considered did not complete the different phases of the treatment for illness or pathologic progression. This event might affect survival data. This is a critical point, likely source of bias.

RESPONSE: We appreciate this important reviewer point, which is similar to Reviewer D Comment 1 below. We did try to identify potential reasons why guideline care was not utilized by comparing characteristics between those who did or did not get that care, and then using logistic regression analysis to identify factors associated with getting guideline care. In that analysis, we utilized clinical factors (such as age and co-morbidity scores), as well as non-clinical factors (such as socioeconomic factors) and facility factors. However, we agree that other factors that were not recorded in our dataset could also influence care given,

and particularly disease progression or patient inability to tolerate therapy as suggested by the reviewer. We have specifically acknowledged this issue in our original submission, in the 4th paragraph of our Discussion Section. In response to this comment, we have revised that aspect of the discussion to specifically acknowledge this possibility and limitation. The 4th paragraph of the Discussion Section now contains this statement: "It is therefore very important to acknowledge that providers may have planned guideline adherent care, but disease progression or patient inability to tolerate care may have prevented them from getting that care."

CHANGES TO THE TEXT: Lines 329-331, 4th paragraph of the Discussion Section.

Comment 3: The long-term survival in MPM resected patients is influenced by the recurrence rate which requires further lines of chemotherapy to prolong the life expectancy. Do you think is possible to highlight the impact of MPM recurrence comparing the two groups? And if the relapsing patients have had additional treatments?

RESPONSE: We appreciate the reviewer's important clinical insight, but unfortunately our dataset does not report recurrence rate, or subsequent treatment if recurrence occurs. In response to the comment, we have revised the Discussion Section of the manuscript to specifically acknowledge this limitation, and also speculate on its potential impact on survival. The 4th paragraph of the Discussion Section now contains this statement:" Furthermore, the utilized dataset does not provide information regarding occurrence and treatment of disease recurrence, which can influence the primary outcome of survival."

CHANGES TO THE TEXT: Lines 334-336, 4th paragraph of the Discussion Section

Comment 4. Patients may be stratified depending on the stage.

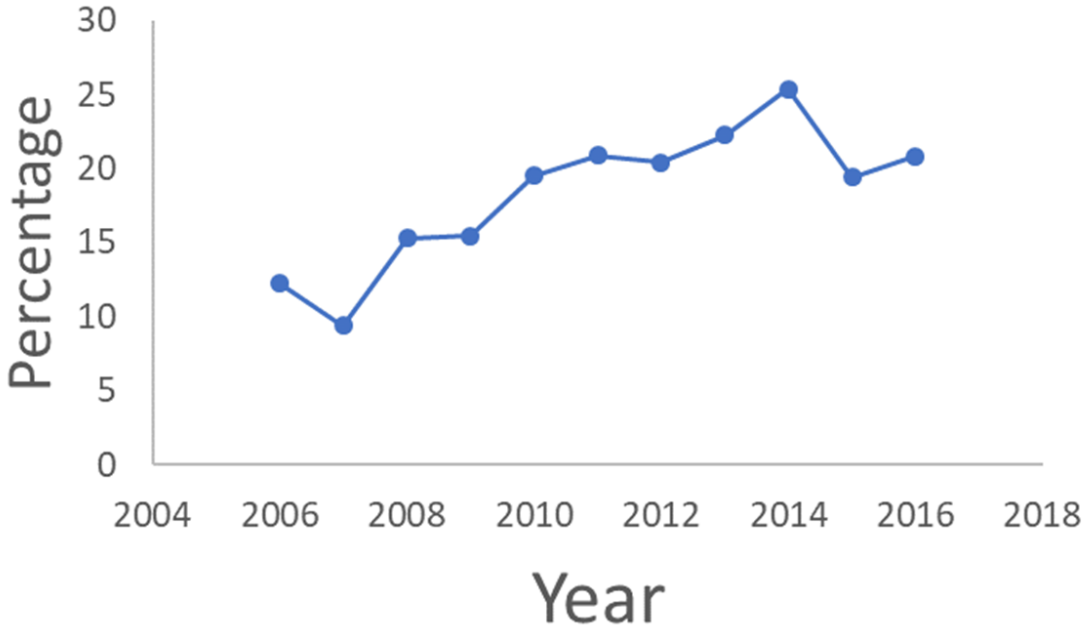
RESPONSE: We also appreciate this important point from the reviewer, which is similar to Reviewer E Comment 3. We did consider the impact of stage in our logistic regression analysis regarding the likelihood of getting guideline concordant therapy. Those results were interesting to us, as clinical stage II patients were most likely to get guideline care, followed by clinical stage III, followed by clinical stage I. Considering that the guideline recommendations do not depend on clinical stage (other than the stage not being stage IV), we felt that finding was most likely related to the fact that distinguishing between clinical

stages I-III can be difficult prior to surgery. We did also consider stage in our Cox proportional hazards model, which as expected showed worse survival with increasing stage. Unfortunately, we did not feel that performing analysis using pathologic stage would be appropriate, as some of the patients received pre-surgical therapy that could influence the pathologic stage. Given the suggestion of the reviewer, we have revised the manuscript to better highlight the potential impact of stage on getting guideline care, by adding this statement to the results section: "Patients with stage II disease (23.1% [185/802]) and stage III disease (21.8% [292/1342]) were more likely to get guideline care than stage I patients (14.4% [200/1390], (p<0.001)."

CHANGES TO THE TEXT: Lines 213-215.

Comment 5. Did you find that the adhesion to the guidelines have changed through years (the period analyzed is 2004 - 2016).?

RESPONSE: We appreciate this question, and have revised the manuscript to add the following figure that shows rate of guideline therapy for each year of the study, to allow readers to see how adhesion to the guidelines has changed over years.



CHANGES TO THE TEXT: Figure 2 has been added to the manuscript (and the previous figure 2 has been re-named figure 3.

Reviewer C

Comment 1. I suggest adding more recent references (the last one is from 2009). In addition, the latest treatment addition to pleural mesothelioma using immunotherapy should be mentioned.

RESPONSE: We appreciate the reviewer's careful reading of the manuscript, though we do want to note that half of our references are publications from the years 2010-2019. However, in response to the comment, we have revised the manuscript to multiple additional more recent references as well as some related to immunotherapy use for mesothelioma.

CHANGES TO THE TEXT: We have added multiple new references as below to the manuscript, which the numbering of references updated as necessary:

clinicaltrials.gov, trial ID NCT02040272, accessed 10/17/2023

Lapidot M, Gill RR, Mazzola E, Freyaldenhoven S, Swanson SJ, Jaklitsch MT, Sugarbaker DJ, Bueno R. Pleurectomy Decortication in the Treatment of Malignant Pleural Mesothelioma: Encouraging Results and Novel Prognostic Implications Based on Experience in 355 Consecutive Patients. Ann Surg. 2022 Jun 1;275(6):1212-1220

Voigt SL, Raman V, Jawitz OK, Bishawi M, Yang CJ, Tong BC, D'Amico TA, Harpole DH. The Role of Neoadjuvant Chemotherapy in Patients With Resectable Malignant Pleural Mesothelioma-An Institutional and National Analysis. J Natl Cancer Inst. 2020 Nov 1;112(11):1118-1127

Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol. 2011;12(8):763–772

Chevallier M, Kim F, Friedlaender A, Addeo A. Pleural Mesothelioma in the Era of Immunotherapy. Clin Med Insights Oncol. 2023 Jul 20;17:11795549231178173.

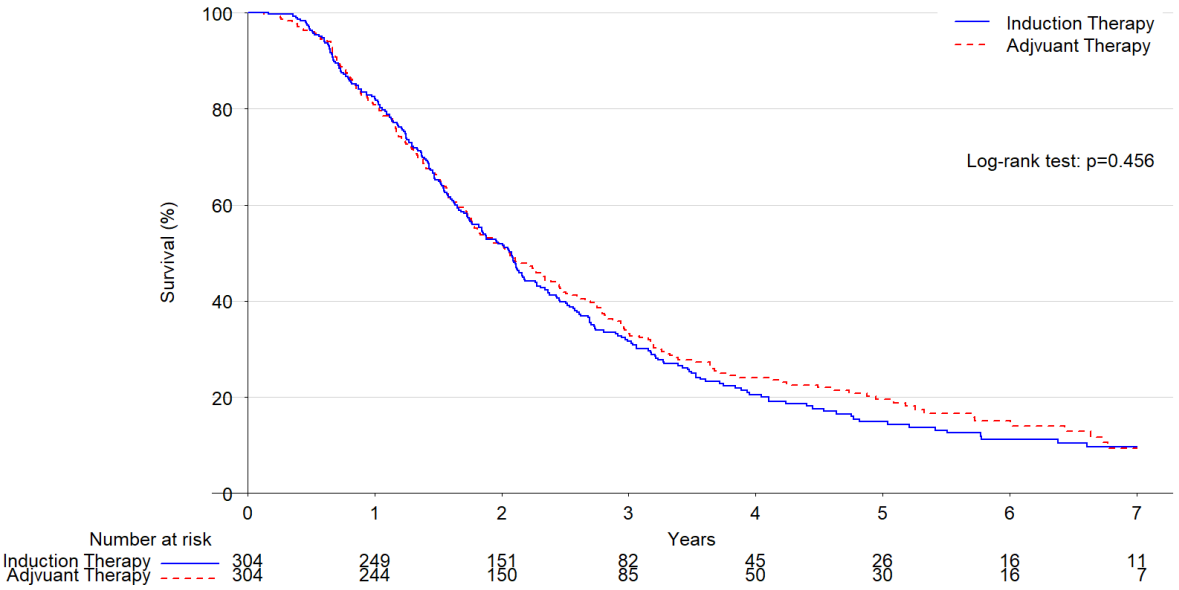
Friedberg, J.S., et al., Photodynamic Therapy (PDT) and the Evolution of a Lung Sparing Surgical Treatment for Mesothelioma. Annals Thor Surg, 2011. 91: p. 1738-45.

Comment 2. "The study was conducted…. with the declaration of Helsinki (as revised in 2013)". The sentence appears twice. Please delete one of them.

RESPONSE: We apologize for not catching this error, and the manuscript has been revised to remove the duplicate sentence.
CHANGES TO THE TEXT: Lines 187-188 in the Statistical Analysis subset of the Methods section.

Comment 3. Both median survival and 5-year survival therapy were significantly better when guideline therapy was used. Please define if survival is measured from the date of diagnosis or surgery.
RESPONSE: Follow-up in the National Cancer Database is recorded from the date of diagnosis, and the manuscript has been revised to explicitly stage that.
CHANGES TO THE TEXT: Line 157, in the Statistical Analysis subset of the Methods section.

Comment 4: The authors demonstrate no significant difference in median survival using neoadjuvant versus adjuvant therapy for resectable disease, although the 5-year survival is better with adjuvant therapy (20.1% versus 14.9 %). Please conduct a propensity score analysis comparing survival of induction versus adjuvant treatment in the cohort of guideline therapy.
RESPONSE: We appreciate this suggestion from the reviewer. In response, we have performed a propensity matched analysis of the guideline adherent patients, to address issues of potential confounding and bias in the use of induction versus adjuvant chemotherapy. Propensity scores were defined as the probability of receiving induction chemotherapy or adjuvant chemotherapy conditional on other measured covariates, which included age, sex, Charlson/Deyo comorbidity index, insurance status, education and income levels, facility type, and clinical stage. Patients were matched based on propensity scores using a 1:1 nearest neighbor algorithm, which created two groups of 304 patients each who were well matched in terms of their characteristics without significant standardized differences. Results from this propensity-matched analysis was consistent with the initial analysis, where there was no statistically significant difference in survival between patients who got induction versus adjuvant chemotherapy (5-year survival 14.9% [95% CI 10.9-20.2] versus 19.5% [95% CI 15.0-25.3], p=0.456), and also shown by a Kaplan-Meier plot:



CHANGES TO THE TEXT: We do appreciate the reviewer's important insight and suggestion, but have elected to not add this additional analysis to the manuscript. Because comparing the impact of induction versus adjuvant chemotherapy was not a primary goal of our study, and because the results of the propensity analysis are consistent with the primary analysis, we think that revising the manuscript to add this additional data could potentially clutter the study and make it less easy to follow, without providing substantial information or support of our primary study's primary findings.

Comment 5: The role and risks of neoadjuvant chemotherapy in multimodality treatment are discussed in Soroya et al. paper (November 2020 JNCI), and the prognostic factor of adjuvant therapy is demonstrated in the recent Annals of Surgery paper (June 2022)- Pleurectomy decortication in the treatment of malignant pleural mesothelioma: encouraging results and novel prognostic implications based on experience in 355 consecutive patients".

RESPONSE: We appreciate the reviewer referencing these important studies, and we have revised our manuscript to also reference them.

CHANGES TO THE TEXT: As discussed above in response to Reviewer C Comment 1, we have revised the manuscript to add multiple new references.

Comment 6: “Within the cohort of surgical patients, perioperative mortality was higher in patients who did not receive guideline-concordant therapy.” The very low rate of lymph node harvesting (median 0-table 3) might suggest inoperability(futile thoracotomy) and advanced tumor staging in most of the patients in this cohort.

RESPONSE: We appreciate the reviewer’s clinical insight. We did only include patients who were coded as having radical resection in the surgical group, so patients who only had exploratory surgery or a futile thoracotomy would not have been considered to have had surgical resection.

CHANGES TO THE TEXT: None.

Comment 7: Table 1, Pathologic Stage, Since most of the Non-guideline therapy patients were not operated on, I assume that they have just clinical staging but not pathologic. Please correct or delete the comparison.

RESPONSE: We appreciate the reviewer noting this issue, and we have deleted the reporting of pathologic stage as suggested.

CHANGES TO THE TEXT: Line 501 in table 1.

Reviewer D

Comment 1: The manuscript is well-written, however, as the authors stated in the manuscript, their results are just based on patient selection of mesothelioma. At least, it should be clarified the reasons why other patients did not receive guideline-concordant therapy.

RESPONSE: We appreciate the very important insight by the reviewer. Unfortunately, a limitation of the dataset is that specific details regarding clinical decision making are not available. This comment, though, is somewhat similar to Reviewer B Comment 2 above. As discussed above in the response to that comment, the Discussion section has been revised to address this important topic.

CHANGES TO THE TEXT: Lines 329-331, 4th paragraph of the Discussion Section.

Reviewer E

Comment 1: How was mesothelioma diagnosed? Although tissue diagnosis is considered as the principle in MPM, were there any cases of pleural fluid cytology only? If you included the cases diagnosed by cytology alone, you may need to be excluded them (as some might be mixed with non-MPM).

RESPONSE: We appreciate this important clinical insight from the reviewer. In response, we have revised the manuscript to add the method of diagnostic confirmation to Table 1, and have added this statement to the results section: "The overwhelming majority of patients in both groups had the diagnosis confirmed by histology, though the non-guideline adherent group had slightly more patients diagnosed by cytology.

CHANGES TO TEXT: Line 501 (table 1) and lines 209-211.

Comment 2: In the present study, the prognosis was the same whether chemotherapy was induction or adjuvant. How many patients were scheduled to receive adjuvant but were not able to receive adjuvant due to surgical invasion? Also, when EPP and PD were examined separately, was there any difference between induction and adjuvant? In the case of EPP, it seems that adjuvant chemotherapy is difficult to be administered.

RESPONSE: We appreciate this important comment, which is similar to Reviewer B Comment 1, Reviewer C Comment 4, and Reviewer C Comment 5. As discussed in response to those comment as well as in general, a limitation of the study is that we do not know if patients were planned to get adjuvant therapy but could not proceed due to progression or inability to tolerate therapy. In addition, we cannot distinguish between EPP and PD, and the Methods section as well as the Discussion section address these topics.

CHANGE TO THE TEXT: Lines 316-320 and lines 329-331 of the Discussion Section.

Comment 3: What was the outcome by stage, I think adding some figures about that would increase the value of this research.

RESPONSE: We appreciate the reviewer addressing this important topic, and this comment is similar to Reviewer B Comment 4 and Reviewer C Comment 7. As discussed above, we did consider the impact of stage in our logistic regression analysis regarding the likelihood of getting guideline concordant therapy. Those results were interesting to us, as clinical stage

II patients were most likely to get guideline care, followed by clinical stage III, followed by clinical stage I. Considering that the guideline recommendations do not depend on clinical stage (other than the stage not being stage IV), we felt that finding was most likely related to the fact that distinguishing between clinical stages I-III can be difficult prior to surgery. We did also consider stage in our Cox proportional hazards model, which as expected showed worse survival with increasing stage. Unfortunately, we did not feel that performing analysis using pathologic stage would be appropriate, as some of the patients received pre-surgical therapy that could influence the pathologic stage. Given the suggestions of the reviewers, we have revised the manuscript to better highlight the potential impact of stage on getting guideline care, by adding this statement to the results section: "Patients with stage II disease (23.1% [185/802]) and stage III disease (21.8% [292/1342]) were more likely to get guideline care than stage I patients (14.4% [200/1390], ($p<0.001$)."
CHANGES TO THE TEXT: Lines 213-215.

Comment 4: Some MPM patients cannot receive standard therapy because of their comorbidities. What do the authors think about that? What should we do for these patients according to the results of this study? If you can, please describe that in the discussion.

RESPONSE: We appreciate the reviewer's clinical insight, and this very important issue. Although the utilized National Cancer Database does not contain specific details, a co-morbidity score is available for patients. This co-morbidity score was included in both the logistic regression model examining the use of guideline therapy, as well as the Cox proportional hazards model, so that our findings regarding the use and impact of guideline concordant therapy was adjusted for patient co-morbidities. In addition, the 3rd paragraph of the Discussion section also explores the limitations of not knowing specific details regarding factors that could influence the ability to tolerate therapy. The question of what to do for patients who cannot tolerate therapy is certainly an important issue, but one that we don't feel we can answer within our study design. We still state, though, that our general clinical practice is that patients who cannot tolerate aggressive therapy may be best managed with best supportive care practice.
CHANGES TO THE TEXT: None.

Reviewer F

Comment 1: The authors present in analysis of the NCDB, specifically querying the outcomes of patients receiving guideline concordant care for epithelioid malignant pleural mesothelioma. The analysis is well done, however, the limitations of the NCDB strain the interpretation of the data. The NCDB is a rather good quality database. Yet, given the heterogeneity of coding that goes into surgical variables for mesothelioma, I'm not certain that this analysis truly answers the question put forth by the authors. Specifically, it seems to me that younger, likely healthier patients, receive guideline concordant care, and the roughly 80% of people who did not receive guideline concordant care may have not for a variety of reasons (as was thoroughly stated in the limitations section of the manuscript). This suggests to me that providers are largely selecting the correct treatment option for patients that often are rather sick with a devastating disease. I do not have any suggestions for improvement of the manuscript. I suppose my one question for the authors is what does this add to the literature that other NCDB analyses (from the same group) do not already add and are published elsewhere in the literature?

RESPONSE: We appreciate the reviewer's insightful comments, and their recognition of the limitations of our dataset and study, which we did also attempt to fully acknowledge in our original submission. We do feel that our study does provide clinically useful information beyond other previously published studies, and specifically feel that our focusing our analysis on guideline concordance can add recognition to (A) the importance of guideline adherence in treatment of this deadly disease and (B) call attention to the fact that currently guideline adherence is low. Although patient characteristics or disease progression may have prevented guideline therapy in some cases, we feel that at least some patients may not have been given guideline therapy due to either a lack of awareness by their providers or a bias that treatment was futile due to the inherent poor prognosis associated with mesothelioma. We hope that our study can improve the awareness of the importance of guidelines, such that at least some patients' treatment, and subsequently outcomes, can be improved.

CHANGES TO THE TEXT: None

Reviewer G

Comment 1: Line 44: Clarify the definition of guideline-concordant therapy. It has mentioned (in line 63, multi-modality therapy) and seem to indicate that the guideline-concordant therapy includes triple therapy of surgery, chemotherapy, and radiation therapy (lines 81-83). But then later it is mentioned (in line 86-89) that the guideline therapy is chemotherapy plus surgery, adjuvant radiation.

RESPONSE: We appreciate the careful review of the manuscript, and also appreciate that the term "multimodality therapy" may imply chemotherapy, radiation therapy and surgery. To avoid causing any confusion, we have removed the term multimodality therapy from the "what is known and what is new" section. We have also revised the "NCCN Guideline Therapy" subsection of the Methods section, in an attempt to more clearly define "guideline-concordant therapy".

CHANGES TO THE TEXT: Lines 60-62 and lines 138-139.

Comment 2: Line 199: There are other additional adjuvant therapies, e.g., photodynamic therapy + surgery, that will significantly improve the mesothelioma outcome to a median survival of 41.2 months for a population of mesothelioma patients with epithelial histology (stages III-IV) and is not included as part of the discussion, see reference: Friedberg, J.S., et al., Photodynamic Therapy (PDT) and the Evolution of a Lung Sparing Surgical Treatment for Mesothelioma. Annals Thor Surg, 2011. 91: p. 1738-45. and Photodynamic therapy for lung cancer and malignant pleural mesothelioma. Simone CB 2nd, Cengel KA. Semin Oncol. 2014 Dec;41(6):820-30. doi: 10.1053/j.seminoncol.2014.09.017. Epub 2014 Oct 7. PMID: 25499640

RESPONSE: We appreciate the reviewer bringing up these other important therapies. We did not initially include reference or mention to them in our study, because they are not currently part of the NCCN guidelines regarding mesothelioma care and therefore outside the scope of our study goals. However, we do feel it's important to acknowledge that there are other adjunct treatments that can benefit mesothelioma patients, as suggested by the reviewer. Therefore, we have revised our discussion section to acknowledge that additional therapies beyond guideline therapy such as photodynamic therapy can further improve patient prognosis, and also added an additional reference.

CHANGES TO THE TEXT: Lines 281-284.