

Peer Review File

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Reviewer A

This is a manuscript of a retrospective analysis based on nation-wide database, which examined the utility of hyperthermic intrathoracic chemotherapy (HITHOC) combined with curative intended surgery for pleural mesothelioma. Their results suggest the positive impact of HITHOC on overall survival of the subjects.

Despite the limitations of the study, which the authors described in the manuscript, the results and conclusions described in their study could potentially give important information to readers in the area.

Reply: Thank you for the kind remarks.

Changes in the text: N/A

Reviewer B

Overall, this is a great summary of a national database with just a few minor comments.

1. New wording for PM (pleural mesothelioma), not MPM anymore.

Reply: Thank you for pointing this out.

Changes in the text: The text has been changed to reflect preferred new nomenclature.

2. Methods: Line 109: Please clarify the choosing for the matching parameters histology and stage. Not really clear why surgery type for example and neoadjuvant therapy have not been included as they might cause bias for the interpretation of the results

Reply: As stated in the text, histology and stage were matched exactly, as we consider these to be the most important prognostic factors for survival. Surgery type was not matched as this was instead analyzed in a subgroup. Neoadjuvant and adjuvant chemotherapy were grouped together (due to variation in institutional preference on whether chemotherapy should be given before or after surgery) and thus was not included in matching as only preoperative and tumor characteristics were included.

Changes in the text: N/A

3. Table 1: baseline characteristics: Chemotherapy and radiotherapy are not distinguished if they have been given preoperatively as neoadjuvant or postoperatively as adjuvant therapy, this may have an impact.

Reply: These were grouped together to simplify analysis, as no impact on outcomes has been demonstrated in the literature whether these treatments are given preoperatively

versus postoperatively.

Changes in the text: N/A

4. Table 1: Histology: What do you mean by mesothelioma? not further specified? And what do you mean by fibrous? Sarcomatoid type is missing.

Reply: Thank you for identifying this error – the NCDB codes mesothelioma histologies as unknown, fibrous, epithelioid, and biphasic. In reports using the NCDB, these are generally translated as unknown (was not specified by the coding institution), and fibrous is understood to mean sarcomatoid.

Changes in the text: We have adjusted the text of Table 1 accordingly.

5. Result: Line 147 and Discussion section line 185: It would be interesting to list the reason for 30-day readmissions. Have they been purely surgical related? In which population was this seen? The ones with neoadjuvant therapy?

Reply: Thank you for the interesting question. Unfortunately, the database does not provide this level of granularity regarding reasons for readmission, so we cannot address this question in the present study.

Changes in the text: N/A

6. Result: Line 166: For the reader would it be helpful to provide in the text as well as in the figure itself the OS months in numbers. It is always hard to see the exact difference on curves/figures and sometimes even a low difference may be statistically significant.

Reply: Thank you for this remark. The median OS numbers in months have been added to the text as suggested.

Changes in the text: Line 180-181 “median survival 18.5 versus 17.9 months), with a median survival of 23.1 versus 20.9 months, line 187-188.

7. Discussion: Line 192-193: I think it would be helpful for the interpretation and analysing of the data to know which chemotherapy agent and in which manner the patients have received the intraoperative chemotherapy as well as the neoadjuvant chemotherapy. The latter should be added if possible. In my opinion, this may have a huge impact.

Reply: Thank you for this comment. This would absolutely be of interest, however, this is not provided in the database, as is stated in the discussion in the lines references above, so providing this data is not possible. Most institutions use platinum-based chemotherapy for HITHOC, but we cannot assume this is the case based on the data provided in the NCDB.

Changes in the text: N/A

8. In the reference list, I am missing a nice work of the Heidelberg group of a retrospective analysis of HITHOC by the heidelberg group. They report a maximum (for epithelioid types) OS of 38 months. I would suggest to add this paper. Transl Lung Cancer Res

. 2022 Nov;11(11):2230-2242. doi: 10.21037/tlcr-22-199. Multimodal therapy of epithelioid pleural mesothelioma: improved survival by changing the surgical treatment approach

Reply: Thank you for the suggestion; this reference has been added, and is called out in the introduction as indicated below:

Changes in the text: Added to second paragraph of introduction: “Another single institution series of patients with epithelioid histology who underwent EPD with HITHOC reported an overall survival of 38.1 months. (20)”

9. As this disease is mainly characterized by recurrence, i would appreciate to include progression free survival to OS as this gives a good understanding of the population and the tumor dynamic.

Reply: We completely agree with this comment. However, the NCDB does not provide data on time to recurrence or progression free survival – this is delineated as a limitation of our study in the discussion.

Changes in the text: N/A

10. Tables in general: It would be interesting how many "missing" there have been. usually this is provided as a seperate column int the table of propensity score matching

Reply: Thank you for this comment. Patients who were missing critical data, such as survival, or staging, were excluded as shown in the CONSORT diagram. Otherwise, very few patients had missing data – for example 1.2% of patients were missing data for facility type. Thus, these were omitted to streamline the already quite large tables.

Changes in the text: N/A

Reviewer C

This is a good report to understand the efficacy of intraoperative hyperthermic intrathoracic chemotherapy (HITHOC) for malignant mesothelioma.

But the authors can improve it more. I have some comments and questions.

1. In my country, HITHOC is not famous. But the authors showed its efficacy. Please add the following in Methods for surgeons who are not used to it such as me; the common indication (pathology, stage, types of surgery, etc), the regimen, and the timing of performing HITHOC in the operation, and the other details.

Reply: This point is well-taken – some of this is variable by institution. At our institution, we typically only offer surgery to patients with Stage I-III epithelioid or biphasic histology, but because this may not reflect practice at all centers (as evidenced by data shown in Table 1), we omitted this in the introduction. However, a general outline of how HITHOC can be performed has been added to the introduction, as noted below.

Changes in the text: Added to the introduction, line 91-94: “Patient selection criteria vary by institution. HITHOC is usually performed after all disease has been resected and the pericardium and diaphragm have been patched, if indicated. At our institution, for example, we then place chest tubes and temporarily close the chest, and infuse cisplatin at 42 degrees for 1 hour.”

2. What do you think about the exposure of surgeons to chemotherapy drugs? Please add it to Method and Discussion, including how to deal with it.

Reply: This has been the focus of other studies in the literature – generally, the risk is felt to be low when appropriate protective equipment is used that avoids direct or indirect skin exposure to the chemotherapy agents. We find this to be beyond the scope of this particular study and would refer readers to studies devoted specifically to this topic.

Changes in the text: N/A

3. Your study population includes stage 4 MPM patients. How many patients have received radical surgery such as P/D or EPP? How were the patients with stage4?

Reply: Thank you for this question. Unfortunately, the coding used in the NCDB does not allow us to differentiate between P/D and EPP, as indicated in our discussion. The inclusion of stage 4 patients may indicate upstaging after surgery, since most centers would not offer surgery to stage 4 patients, but since we cannot be sure why these patients were offered surgery, we have refrained from commenting on this point. The inability to understand the nuances of this is one of the limitations of using the NCDB for this type of work.

Changes in the text: N/A

4. How many patients were diagnosed with macroscopic complete resection (MCR)? In the patients with MCR, Does HITHOC also have the efficacy for their prognosis? It is important whether HITHOC can also improve the prognosis of the patients who got MCR.

Reply: Thank you for the comment. It is our belief that R status (R0, R1, etc) in mesothelioma is highly subjective. R0 resection is rarely possible even with the most thorough operation. For this reason, we did not use this variable in our analysis, as we

do not believe it is reliable.

Changes in the text: N/A

Reviewer D

This manuscript Irmina A, et al. investigated the effect of hyperthermic intrathoracic chemotherapy of malignant pleural mesothelioma.

This study is interesting and valuable for investigating HITHOC. However, there are several questions and important issues about this paper. The following questions and suggestions should help to further strengthen the study.

Major problem

It is unfortunate that there is quite a lot of limitations due to the database study, but I think it deserves recognition that it is also described in Limitation in detail. I think the major problem is that analysis of why HITHOC improves prognosis and in what treatment cohorts it benefits is insufficient. It would be better if there was an analysis of whether HITHOC itself improves prognosis or whether the combination of HITHOC and other treatments improves prognosis.

1. The conclusion is not qualified. Since confounding factors have not been eliminated, it is difficult to say that HITHOC "Independently" improves prognosis.

Reply: Thank you for this point. We state that HITHOC independently associated with improved survival, because in Cox-proportional hazards modeling, controlling to the best of our ability for confounding factors such as age, comorbidity, stage of cancer, era of treatment, receipt of chemotherapy, and radiation, HITHOC did remain statistically significantly associated with improved survival, including in several subgroup analyses. We feel this type of language is consistent with language typically used to describe this type of analysis in the literature.

Changes in the text: N/A

2. It has been reported that HITHOC was effective when added as one of the multidisciplinary treatments. Could you compare HITHOC plus chemotherapy or radiotherapy vs. HITHOC alone? Since it is inferred that the presence or absence of chemotherapy contributes to prognosis, is it possible to compare between the groups; surgery plus chemotherapy and HITHOC vs. surgery plus HITHOC vs. surgery only? It would be more useful if we could also separate chemotherapy into adjuvant and neoadjuvant if possible.

Reply: Thank you for this comment. As shown in the multivariable analysis in Table 2,

chemotherapy and HITHOC were each independently associated with improved survival, while radiation was not. This is consistent with prior mesothelioma literature. For example, the hazard ratios in the propensity matched cohort indicate a 39% improvement in survival attributable to chemotherapy, and a 27% improvement attributable to HITHOC, and these are independent.

Regarding adjuvant versus neoadjuvant chemotherapy - these were grouped together to simplify analysis, as no impact on outcomes has been demonstrated in the literature whether these treatments are given preoperatively versus postoperatively, and practice varies between institutions.

Changes in the text: N/A

3. You states that the rate of chemotherapy and radiation therapy is lower in the group that underwent HITHOC. In addition, there is a description that the HITHOC group may have more healthy patients. But as mentioned in Line224, why there were more chemotherapy received e in the non-HITHOC group? It seems to me that the HITHOC group is more amenable to multimodality treatment.

Reply: One of the limitations of a database review is the inability to understand individual treatment decisions. At our institution, medically-fit patients who are candidates for the most aggressive approach undergo induction chemotherapy, followed by radical surgery with HITHOC. Other centers have different practice patterns, and may prefer surgery upfront, and may even employ adjuvant radiation, which will contribute to variations in the data that cannot be teased out from this database.

Changes in the text: N/A

4. There were many stage IV cases. Does local control by HITHOC or radical surgery contribute to the prognosis even at stage IV?

Reply: We were surprised by the fraction of stage IV patients - the inclusion of stage 4 patients may indicate upstaging after surgery, since most centers would not offer surgery to stage 4 patients, but since we cannot be sure why these patients were offered surgery, we have refrained from commenting on this point. The inability to understand the nuances of this is one of the limitations of using the NCDB for this type of work.

Changes in the text: N/A

5. How about adding non-epithelioid survival in Figure 2 as well, or in groups where there were significant differences, such as the radical surgery group?

Reply: Given the low numbers of non-epithelioid patients, especially in the HITHOC group, we did not feel it was statistically appropriate to perform sub-analysis on this group, or to include these in Figure 2

Changes in the text: N/A

Minor problem

1. There was no “sarcomatoid” in histology in Table 1.

Reply: Thank you for this observation – this error has been fixed.

Changes in the text: See Figure 1.

2. Please add the radical surgery group and the non-radical surgery group to Table 1.

Reply: Table 1 shows the entire cohort as well as propensity matched groups within the entire cohort. Table 4 shows the radical surgery subgroup, including the propensity matched sub-analysis.

Changes in the text: N/A

3. There was no description about HITHOC in general. You mention in limitation that it varies from each facility, but please add an explanation of how typical HITHOC are performed and what side effect occurred.

Reply: Thank you for this comment - a general outline of how HITHOC can be performed has been added to the introduction, as noted below.

Changes in the text: Added to the introduction line 91-94: “Patient selection criteria likely vary by institution. HITHOC is usually performed after all disease has been resected and the pericardium and diaphragm have been patched, if indicated. At our institution, for example, we then place chest tubes and temporarily close the chest, and infuse cisplatin at 42 degrees for 1 hour.”

4 . Are there any reports of differences between EPP and PD regarding the effectiveness of HITHOC?

Reply: Most single institution studies performing HITHOC do so in conjunction with P/D. Those that include both types of operations are small, and comparison between surgical approaches is not feasible.

Changes in the text: N/A

Reviewer E

HITHOC therapy is a growing concern among MPM multimodal treatment worldwide, and it is mandatory to understand its specific role in OS and outcomes.

Although the relevant conclusions of your paper mainly confirm data already published by other smaller studies, I suggest some revisions to ameliorate the paper.

1) Line 76-79: Authors should avoid or reduce the comment about HIPEC if it is needed to introduce the HITOC topic. You better go straight to the point.

Reply: Thank you for this suggestion. The authors feel that some readers may be more familiar with HIPEC, and less familiar with HITHOC, so we thought it was useful to draw the parallel. Also, as we reference, there is more data on the efficacy of HIPEC in reducing recurrence, and we feel this is relevant to point out as it lends support to the use of HITHOC.

Changes in the text: N/A

2) Line 146: Authors report the data about the increased readmission rate in HITHOC pts. A more in-deep commentary or hypothesis should follow this result in the discussion section.

Reply: Unfortunately, the database does not provide further granularity regarding reasons for readmission, so we cannot address this question in the present study.

Changes in the text: N/A

3) Line 191: according to the limitation you described, a Table reporting a resume of the most diffused HITHOC types or manners of med administration should be helpful for readers, including comments and references about pro and contra for each HITHOC style.

Reply: This point is well-taken – indications for and method of delivering HITHOC vary by institution, and the NCDB does not allow us to know any detail about methods used in our cohort. However, a general outline of how HITHOC can be performed has been added to the introduction, as noted below, which we hope will be helpful for readers.

Changes in the text: Added to the introduction, line 91-94: “Patient selection criteria vary by institution. HITHOC is usually performed after all disease has been resected and the pericardium and diaphragm have been patched, if indicated. At our institution, for example, we then place chest tubes and temporarily close the chest, and infuse cisplatin at 42 degrees for 1 hour.”

4) Line 199: I partially agree with the Authors' comment. Reversing your paradigm, we could suppose HITOC is one of the leading causes of Length of Stay extension (e.g., toxicity, local effects, adverse effects, etcetera...). In this state of mind, we should not refuse the hypothesis that HITHOC could have been primarily administered in pts underwent less invasive radical surgery (e.g., ePD instead of EPP) due to its helpful adjuvant meaning.

Reply: Thank you for this comment. It is unfortunately not possible to discern in the NCDB which patients underwent eP/D versus EPP, and this is of course a significant limitation of our study, as discussed in detail in our discussion section.

Changes in the text: N/A

5) Table 2: following Authors' opinion, is the statistically significant data of "Year of diagnosis" regarding 201-2016 ($p=0.024$) important? Should it be considered a confounding factor or, on the contrary, a detector that justifies modifications and improvements on MPM diagnosis and treatments?

Reply: Thank you for this question. As the reviewer suggests, we do believe this effect of "era" on survival likely reflects improvements in diagnosis, perioperative care, oncologic care, etc. This is why we felt it was important to include this as a variable – since use of HITHOC has increased over time, if era was not included as a variable, it could confound outcomes in favor of HITHOC.

Changes in the text: N/A

6) Minor spell checks and language revision is suggested.

The spelling and language have been checked for correctness.

Reviewer F

In this article, authors have performed a case-control study and a propensity-score matching to analyze the impact of hyperthermic intrathoracic chemotherapy (HITHOC) during the surgical resection of a malignant pleural mesothelioma (MPM) concerning short-term and long-term outcomes.

Concerning the introduction:

The introduction is well written and is a short overview of the question of the surgery for MPM which is a burden subject. Nevertheless, it seems that we are moving towards eP/D rather than EPP, which is reserved for certain indications in the recent literature, and this is not clear in your introduction. Concerning per operative adjuvant treatment as HITHOC, the authors could have mentioned other alternatives such as hyperthermic povidone iodine (Lang-Lazdunski et al.) or dynamic phototherapy (Friedberg et al.) ... for example.

Reply: Thank you for this comment – it is our institutional practice to perform eP/D. However, since some centers remain committed to EPP, and guidelines do not indicate one approach should be favored over the other, we have chosen to keep the introduction neutral on this topic. Similarly, since the NCDB does not provide any data on the use of heated iodine or phototherapy, we felt this was beyond the scope of our work to discuss.

Changes in the text: N/A

Concerning the methodology:

Population and data:

Data were extracted from the national cancer database (NCDB) which is a clinical oncology database sourced from hospital registry data collected in more than 1,500 Cancer-accredited centers. Nevertheless, like the French EPITHOR database, data-quality is the key, and we still regret missing data. The choice of this database is still one of the best.

How many missing data do you have for each criterion reported in the tables?

Related death data are available in this database? Are you sure that the death is the consequence of the MPM or another non-oncologic reason?

Concerning the comorbidity assessment, ASA score was available? Charlson's index is not frequently used.

Reply: This point is well-taken – Patients who were missing critical data, such as survival, or staging, were excluded as shown in the CONSORT diagram. Otherwise, very few patients had missing data – for example 1.2% of patients were missing data for facility type. Thus, these were omitted to streamline the already quite large tables. Regarding cause of death, this is not given in the NCDB, so we can only report overall survival data. However, given the natural history of mesothelioma, it seems likely that the vast majority of patients' deaths will be related to their mesothelioma. Regarding ASA – this is not reported in the NCDB – Charlson score is the only available indicator of comorbidity.

Changes in the text: N/A

Surgery, eP/D or EPP, and patient volume:

In the introduction, you have mentioned that the type of resection, eP/D or EPP has an “important” impact on short-term and long-term survivals. I regret that you can't analyse the role of eP/D compared to EPP associated to HITHOC. As you have mentioned, how can we say that only HITHOC will impact survivals? Can it be completed in each center?

Surgery of MPM is a difficult surgery. Patient-volume, or the number of cases operated on per year per surgeon impacts survival. Do you have the number of cases per year per center and per surgeon? Can it be taken in account for the statistical analyses, with a threshold?

Reply: These are certainly major limitations of our paper. By using the NCDB, we are able to achieve a higher n than previously reported studies, but unfortunately are not able to know the exact operation that was performed, nor does NCDB report information on center or surgeon volumes – the only information about centers is the “type” – community, cancer center, academic, etc, which we have included, and may indirectly address the issue of experience that the reviewer is inquiring about. More

HITHOC was performed at academic centers, but we were able to control for this in the matched analysis.

Changes in the text: N/A

HITHOC:

Concerning HITHOC, different protocols can be used, it's sometimes an "homemade recipe" in each center, do you have more details about the protocol used? If it's a footnote for example, in how many cases is it reported and what was the protocol?

Reply: Unfortunately, no details about HITHOC protocols are available from the NCDB data at all. This is listed as a limitation in the discussion section.

Changes in the text: N/A

Concerning the results

Results are well reported and clearly presented.

Reply: Thank you for this nice comment.

- Patient characteristics:

Do you have an explanation why HITHOC patients are less likely to receive adjuvant therapy? Is it due to post operative adverse events?

Reply: This is definitely an interesting question that we cannot answer with our data. We feel most likely this reflects different practice patterns at different institutions, especially given the lack of strong guidelines from groups like the NCCN on how multimodal treatment should be sequenced. Our practice is neoadjuvant chemo, followed by eP/D with HITHOC in appropriately selected patients, but others prefer upfront surgery and some favor adjuvant radiation. Possibly, some centers pursue a period of surveillance after HITHOC, as opposed to giving adjuvant chemotherapy.

Changes in the text: N/A

- Survival Analysis:

Do you have any information about the role of the kind of resection? Death is only related to MPM?

Reply: The NCDB only provides overall survival.

Changes in the text: N/A

- Radical Surgery sub-analysis:

Can you precise the type of resection if it's a non-radial resection? Is it a debulking, or an unforeseen too much invasive MPM and a R1 resection cannot be performed? It's always a surprise to read some surgeons are performing "palliative" surgery for MPM. But sometimes, we faced to a non-resectable MPM, and in a precise area we can be R2, so impact of HITHOC is still debated.

Reply: We acknowledge this is a major limitation, but the codes used in the NCDB regarding surgery type are quite unrevealing. It is possible in some cases the surgeon may have backed out due to extent of disease, or some sort of “palliative” surgery was performed, but the details of this are really not discernible from this database. Our hope is that the strength of the large size of the cohort can overcome these limitations in availability of some details.

Changes in the text: N/A

- Concerning the tables:

Table 1: If histology is mesothelioma, that means you don't have more precisions?

Reply: This was an error that has been corrected.

Changes in the text: Please see Table 1 for corrected histology groups.

Concerning the discussion:

It's a well written discussion, with a good description of your limitations and strenghts. You can only describe “what you have” on this database.

It's a great picture of HITHOC with available data, but many questions are unsolved! Good references also.

Maybe some missing information about the kind of surgery may be underlined earlier in your manuscript.

Nevertheless, your work is still impressive, and have several strengths as you mention. Thank you again for these nice comments.

So ok, for the unanswered question about the kind of resection, eP/D or EPP an of the receipt of HITHOC.... We will “never” have theses answers! From the NCDB! But maybe you need to report the geography of the cases and the number per center, because the patient volume can impact short-term and long-term survivals and associated to HITHOC you can bring interesting conclusions! Can you do this?

Maybe in another report, you can report other adjuvant per operative treatment?

Reply: We agree that the NCDB cannot provide this precise answer unfortunately, but hope readers still find the data valuable. As outlined above, NCDB also does not include center volume.

Changes in the text: N/A

Concerning the conclusion:

Short, need to mention again that it's according available data.

Reply: This point is well received – we have added to the conclusion as below

Changes in the text: Line 276: “this retrospective large database review finds that

HITHOC is independently associated with improved patient survival”

Reviewer G

This article is interesting. It is well received and it give a lot of informations on HITHOC. It also gives new hope to patients with MPM. Regarding the use of HITHOC during reoperation it is something that should be further discussed as it has been already presented (1). Furthermore, the results obtained justifies further studies on HITHOC.

Reply: Thank you for the kind comments. Use of HITHOC during surgery for recurrence was not in the scope of our manuscript, so we have opted not to include this.

Changes in the text: N/A

Tabel 1 Histology Fibrous which does not exist in table 2 and 4. Perhaps it is sarcomatoid. Please revise.

Reply: Thank you for this observation – this error has been corrected in Table 1.

Changes in the text: See change in Table 1.

1) Poon SS, et al. Salvage debulking surgery and hyperthermic intrathoracic chemotherapy for massive recurrent mesothelioma in the mediastinum. *Interact Cardiovasc Thorac Surg.* 2022 Jun 15;35(1):ivac034. doi: 10.1093/icvts/ivac034. PMID: 35218349; PMCID: PMC9252109.

Reviewer H

The authors have reported the impact of HITHOC on survival in patients with malignant pleural mesothelioma using a large national database.

The study is overall well written and designed on a large cohort of patients and these are definitely the strengths of this paper.

My issues are as follows:

- Why did you choose 2006-2017 as time frame?

Reply: Thank you for this question – at the time we began the study, this was the most current NCDB cohort with appropriate available follow up survival data.

Changes in the text: N/A.

- In "methods" a detailed explanation of how HITHOC technique is performed should be added

- Are there some criteria, adopted among the different US centers enrolled in this study, to perform HITHOC for not? This is an important aspect to point out

Reply: Both of these points are well-taken, however, the technique for HITHOC as well

as the patient selection criteria are variable by institution. At our institution, we typically only offer surgery to patients with Stage I-III epithelioid or biphasic histology, but because this may not reflect practice at all centers (as evidenced by data shown in Table 1), we have refrained from commenting on this, as there is not standardization. The same goes for HITHOC technique details. However, as suggested by this reviewer and other reviewers, a general outline of how HITHOC can be performed has been added to the introduction, as noted below.

Changes in the text: Added to the introduction, line 91-94: “Patient selection criteria vary by institution. HITHOC is usually performed after all disease has been resected and the pericardium and diaphragm have been patched, if indicated. At our institution, for example, we then place chest tubes and temporarily close the chest, and infuse cisplatin at 42 degrees for 1 hour.”

- Data regarding post-operative complications should be reported. Are there any significant differences between the two groups?

Reply: Thank you for this question – the NCDB does not provide significant detail regarding complications. However, we did include length of stay, 30day readmission, and 30day mortality as surrogates of postoperative complications, and these are included in Table 1.

Changes in the text: N/A.

- Information regarding any neoadjuvant treatments should be added. Did some patients receive induction therapy?

Reply: Thank you for this question - our variable “chemotherapy” groups together neoadjuvant and adjuvant chemotherapy - these were grouped together to simplify analysis, as no impact on outcomes has been demonstrated in the literature whether these treatments are given preoperatively versus postoperatively, and guidelines support either approach.

Changes in the text: N/A

- Do you have data regarding the relapse rate (local and distant) in the two groups? A comparison of this aspect between the two groups should be added

Reply: As discussed in the limitations section of the discussion, the NCDB does not provide recurrence data, so we are limited to only reporting overall survival, which is certainly a limitation, since we would expect HITHOC to have a positive impact on local recurrence, which is a major problem in pleural mesothelioma.

Changes in the text: N/A

In my opinion, the main issue which can add an important bias in the main conclusion

of the study ("HITHOC is associated with overall survival advantage"), is the missing information regarding the surgical technique performed (pleurectomy/decortication, extended pleurectomy decortication, extra pleural pneumonectomy)!

Reply: Thank you for this comment – we tried to address in detail in our discussion the significant limitation that we cannot know which surgical technique was used in these patients based on the information available in the database.

Changes in the text: N/A

Reviewer I

I found that the manuscript is well-written and the topic is extremely interesting.

Briefly, you state that HITHOC is associated with improved 30, 90 day-mortality at PSM analysis, with increased 30-day readmission rate and longer length of stay. 5-year OR at Kaplan-Meier did not differ between the groups after PSM.

You performed 2 sub-analysis (epithelioid histology and radical surgery) and noticed that HITHOC improved overall survival. Therefore, I suggest that both abstract results and conclusion of the manuscript should be revised are reconciled to the subpopulation analyzed and not generalized to the overall patient's population.

Reply: Thank you for this thoughtful point – after PSM, the Kaplan Meier did not differ, however, the Cox analysis, which controls for covariates, did demonstrate a survival benefit associated with HITHOC in the overall cohort. We therefore kept the conclusion generalized to the overall population, and this is addressed in the discussion lines 242-245.

Changes in the text: N/A

I think that a reasonable conclusion from this study could be that the use of HITHOC should be carefully evaluated and further studies are required to identify the subgroup of patients that can benefit from this treatment.

Reply: We agree with the reviewer on this sentiment, and for this reason our conclusion is phrased as “this study provides support for further investigation of the use of HITHOC”.

Changes in the text: N/A

I have some questions:

- How many patients were included in the 2 subgroup analysis? Please report this information also in the main text and tables

Reply:

There were 1912 patients in the epithelioid subgroup, and 1632 patients in the “radical

surgery” subgroup – this information has been added to the main text and tables as suggested.

Changes in the text: Please see additions in line 186, line 192, and titles of Tables 3 and 4.

- Do you have causes for readmission in NCDB?

Reply: Unfortunately, the NCDB does not provide causes of readmission.

Changes in the text: N/A

Reviewer J

The study is based on a wide national database and the large number of patients included is a valuable strength. On the other hand, some inaccuracies are intrinsic to the nature of the data and many of them cannot be overcome. Anyway, in my opinion there are some issues that should be addressed to increase the scientific value of the paper:

- According to guidelines, and as reported in the Introduction (lines 63-65), patients affected by pleural mesothelioma in clinical stage IIIB or IV and/or with sarcomatoid or biphasic histology, should not undergo surgery with curative intent, but only systemic therapy (NCCN Guidelines, Version 1.2023). Moreover, in those cases, obtaining a macroscopic complete resection is nearly impossible unless performing a really demolitive surgery, which may contraindicate HITHOC. In this study, the overall cohort comprehends patients with stage III and IV pleural mesothelioma, and this can be understood by considering that not every patient underwent surgery with radical intent. However, I cannot imagine how patients with stage III and IV pleural mesothelioma may have been subjected to radical surgery (Table 3).

Reply: This point regarding patient selection is well-taken, and is somewhat difficult to parse with the available data from NCDB. We suspect a potential explanation is that some of the patients with stage 3-4 disease may have been upstaged on final pathology.

Changes in the text: N/A

- In my opinion the term “radical surgery” should be substituted with “macroscopic complete resection (MCR)” to better reflect the surgeon’s aims.

Reply: Thank you for this comment. As the reviewer points out, a major limitation of this dataset is the inability to be sure what operative approach was taken – this is acknowledged in the discussion. Regarding MCR – with the codes provided, we cannot really be sure whether the surgeon felt that MCR was achieved in the what we have called the radical subgroup, which is why we have chosen a more generic term.

Changes in the text: N/A

- The Authors should specify which pleural mesothelioma staging system have they adopted.

Reply: The NCDB uses the AJCC staging system.

Changes in the text: N/A

- Lines 121: histology is not mentioned in the list of variables included in the Cox-regression model.

Reply: Histology is listed in the methods and shown in the tables.

Changes in the text: N/A

- Lines 164-169 and Table 3: is the multivariable analysis on the epithelioid histology subgroup performed on the Propensity-Matched Cohort, or is it related to the Overall cohort?

Reply: Table 3 reflects the epithelioid subgroup; it is not matched.

Changes in the text: N/A

- It would be really interesting knowing HITHOC-related morbidity rates (in the discussion, line 184, the Authors state that HITHOC may increase short-term morbidity) and the causes of readmission.

Reply: We appreciate the comment. Unfortunately, NCDB does not provide any data on postoperative complications, other than those listed (length of stay, readmission).

Changes in the text: N/A

- Can the Authors discern the role of chemotherapy from the HITHOC-related benefit? Results, especially multivariable analysis, show a significant role of both therapies. Hence, probably (as already hypothesized in other papers), their role is synergic and surgery+HITHOC without systemic therapy would not give to patients the same results of chemotherapy alone, or of all the three treatments (moreover, data on local recurrence is not available, so it is not possible to evaluate the local effect of HITHOC). This issue should be better addressed in the discussion.

Reply: This point is certainly well-taken. We do not feel our study is equipped to comment on the potential synergy of chemotherapy and HITHOC, which is why we have refrained from additional discussion on this point. It is notable that both emerge as independently significantly associated with an impact on survival – it is our institutional practice for patients to be treated with neoadjuvant chemotherapy followed by eP/D with HITHOC in appropriate surgical candidates.

Changes in the text: N/A

- Table 1: probably there is a mistake in the “histology” section, divided into “mesothelioma”, “fibrous”, “epithelioid” and “biphasic”. Actually, it should be divided into “epithelioid”, “sarcomatoid” and “biphasic” mesothelioma.

Reply: Thank you for this observation – this error has been fixed.

Changes in the text: See Figure 1.

- Tables: Charlson-Deyo comorbidity index score for oncologic patients cannot be <2 (solid malignant neoplasm= 2 points). How can some mesothelioma patients have a CCI of 0 or 1 point?

Reply: The NCDB uses a mapped CCI. From the NCDB Data Dictionary: “Because of the small proportion of cases with a Charlson Comorbidity score exceeding 3, the data have been truncated to 0, 1, 2, 3 (greater than or equal to 3). A score of 0 indicates “no comorbid conditions recorded”, or none of the values shown below. Patients with a score of 0 could still have comorbidities if they are conditions that are not included in the mapping table below. Note that the patient's cancer is not directly reflected in the recorded score.

Changes in the text: N/A

- Bibliography on HITHOC effects on pleural mesothelioma is incomplete (DOI: 10.1016/j.jtcvs.2017.10.070, DOI: 10.3390/jcm10173801)

Reply: Thank you for these suggestions. The first has been added as a reference, the second is a narrative review so has not been added.

Changes in the text: Added reference line 95.

Reviewer K

The authors report a very interesting study on the prognostic impact of HITHOC in MPM by investigating National Cancer Database data. It’s a fine work, honest analysis and a properly written paper that carries an important sound message with some novelty in the present literature. Indeed, as correctly reported by the Authors, MPM cannot be easily studied through randomized clinical trials and large retrospective series enforced by propensity-score match analysis are welcome. In my opinion the manuscript, after a few additional works, could be of great interest for publication on Journal of Thoracic Disease.

1) It could be interesting to clearly report the prognostic impact of HITHOC in the different subset of patients. For example, Is it efficacy in sarcomatoid MPM? In Age>75? In Stage >II? Despite these data may be extracted by the table, I suggest to highlight these because of great interest for the physicians. Please also discuss on the “best

candidate for HITHOC procedure"

Reply: Thank you for this suggestion. However, these subgroups are really quite small – for example there are only 13 sarcomatoid patients who underwent HITHOC, so we did not feel it was appropriate to perform additional subgroup analyses. At our institution, we offer HITHOC to epithelioid or biphasic histology stage 1-3 medically fit patients, but because this is a database study as opposed to a review of our experience, we have refrained from commenting on this.

Changes in the text: N/A

2) Type of surgery is not clearly reported (EPP or P/D) and this is probably the best limitation of this study in my opinion (as declared by the Authors). You should emphasize more this point in the discussion, because this bias may be potentially influencing the overall result of the study.

Reply: Thank you for this comment. As the reviewer points out, a major limitation of this dataset is the inability to be sure what operative approach was taken – we feel this is acknowledged and emphasized in the discussion.

Changes in the text: N/A

3) Type and dosage of CHT used during HITHOC is not reported. If available, these data may be included and evaluated in the analysis because they be potentially associated to short as well as long-term results

Reply: Unfortunately, this is not reported in the NCDB, so cannot be analyzed.

Changes in the text: N/A