

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-454>

Reviewer A

Comment 1: the article is interesting and there are a lot of useful information. I have an important point to pose: there is a lot of confusion about the term hyperthermic intrathoracic chemotherapy, I found HITHOC, HIOC, HITOC and you are using HIEC, which is clearly another different acronymous. I made a research on Medline and the acronymous HITHOC is the most used in thoracic surgery. On the other side none use HIEC in thoracic surgery but in abdominal surgery. I suggest to change HIEC in HITHOC in such a way the article could have more chances to be read by thoracic surgeons.

Reply 1: Thank you for offering this suggestion. We note the ambiguity of abbreviation for hyperthermic intrathoracic chemotherapy and will proceed with using “HITHOC” to promote continuity in the literature.

Changes in the text: The abbreviation “HITEC” was changed to “HITHOC” throughout the manuscript.

Comment 2: Line 153 Rush and colleagues paper is not on hyperthermic intrathoracic chemotherapy but intrapleural chemotherapy with cis platinum. Please revise.

Reply 2: We appreciate the identification of this oversight. This reference and associated statement have been removed from the manuscript as it does not directly pertain to the topic of focus.

Changes in the text: The following statement previously found on Line 153 was deleted from the manuscript, as was the associated reference: “Rusch and colleagues were among the first to describe HITEC in the management of MPM in their phase II trial in the mid-1990s”. Additionally, the sentence “Several clinical trials subsequently followed, each of which demonstrated increased median overall survival as well as five-year survival rates when HITEC was used in combination with CRS”, originally found on lines 154-156 was edited. This now reads “In recent decades, several clinical trials have been completed evaluating the efficacy of HITHOC when used in combination with CRS. These demonstrated increased median overall survival as well as five-year survival rates” and can be found at lines 170-172.

Comment 3: Technique: having performed many operations using HITHOC there are two questions. Do you collapse the lung? why don't use the two chest drains as cannulas and so you do not need to reopen the chest?

Reply 3: We appreciate these questions and note their significance. In answer to the

first question, we utilize a dual lumen endotracheal tube to facilitate single-lung ventilation for the duration of the case. As such, during the HITHOC portion of the operation, the ipsilateral lung remains collapsed. We have updated the manuscript to more clearly reflect our ventilatory strategy. Regarding the second question, we note that there may be ambiguity in practice across institutions. Our standard approach involves a temporary closure of the chest to enable HITHOC circulation. Following conclusion of HITHOC, we proceed with completing pericardial and diaphragmatic reconstruction with establishment of hemostasis immediately prior to final closure of the chest. We have further delineated this approach in the manuscript for clarity.

Changes in the text: We have inserted the following at Lines 252-254: “The utilization of a double lumen endotracheal tube enables single-lung ventilation, ensuring that the ipsilateral lung remains collapsed for the duration of the case.”. Additionally, at Lines 278-281 we have included “Temporary closure of the chest enables HITHOC circulation with subsequent completion of diaphragmatic, pulmonary, or pericardial reconstructions. Additionally, this approach allows for confirmation of hemostasis following HITHOC and immediately prior to the conclusion of the case” to further clarify our approach utilizing a temporary closure of the thoracotomy during HITHOC circulation.

Comment 4: Moreover, a recent systematic review considers the possibility to use HITHOC in case of malignant pleural effusion and pleural nodules secondary to lung cancer stage IVa (1). this can add power to the article.

(1) Eur Respir Rev. 2019 Jul 31;28(153):190018. doi: 10.1183/16000617.0018-2019. PMID: 31366459; PMCID: PMC9489167.

Reply 4: Thank you for providing this systematic review for inclusion. We have included the suggested citation in the “Other Indications (for HITHOC)” section of this manuscript.

Changes in the text: The sentence, “Similarly, Migliore et al. demonstrate favorable outcomes with the utilization of HITHOC for malignant pleural effusion secondary to non-small cell lung cancer, however encourage further investigation in the form of a randomized controlled trial” with associated citation was added at Lines 225-228.

Reviewer B

This manuscript reviews the rationale and indications for HITEC use from the literature on different pleural malignancies. In addition, the authors describe the application of this treatment method in their institution for MPM. This manuscript demonstrates the efficacy of HITEC, mainly in MPM and thymic tumors. Despite the favorable outcomes demonstrated in multiple studies, especially for MPM, the guidelines have no clear recommendation regarding its use. The authors suggest standardization of HITEC

therapy (in means of indication and technique) and call for a pleural cancer index that may assist in achieving this goal. This review is important and interesting.

I have some questions and suggestions for the authors:

Comment 1: Malignant Pleural Mesothelioma paragraph:

Line 137- “Neoadjuvant therapy remains a mainstay of MPM treatment.” Neoadjuvant therapy for MPM is an optional treatment used, for example, in the SMART trial, but it is not necessarily the mainstay. The use of neoadjuvant versus adjuvant therapy for MPM is controversial in the literature. Several papers claim worse postoperative outcomes after inductive chemotherapy than upfront surgery (The Role of Neoadjuvant Chemotherapy in Patients with Resectable Malignant Pleural Mesothelioma—An Institutional and National Analysis JNCI 2020).

Reply 1: We note the ambiguity in the initial phrasing and appreciate the need for clarification. We have changed the language in this section to better reflect the varying utilization of chemotherapy as a neoadjuvant or adjuvant therapy in the management of pleural malignancies. We have also included the suggested reference provided.

Changes in the text: The text now reads: “Chemotherapy remains a mainstay of MPM treatment with a variety of protocols existing for the varying histologic subtypes and stages.(15-17) Standard practice for patients with surgically treatable disease consists of four cycles of neoadjuvant or adjuvant cisplatin-pemetrexed therapy. With the CheckMate 743 trial demonstrating overall survival benefit in non-surgical candidates with MPM, current perioperative research efforts are investigating immunotherapy or chemoimmunotherapy in the neoadjuvant and maintenance settings. Results of these studies are incomplete but carry the potential to change the systemic therapy landscape for MPM.(18) Despite multimodality treatment for MPM, studies have revealed an overall recurrence rate between 60-80% in patients treated with chemotherapy and P/D.(19-21)” at Lines 144-152.

Comment 2: Line 165- Please elaborate on known complications due to HITEC use.

Reply 2: We have further reviewed the referenced articles in this section and have included the complications of HITHOC described by the cited literature. We further expand on the complications of HITHOC in the discussion (Lines 367-383) based on literature review and our personal institutional experience and have provided further specification in this section. Additionally, we have included a table for reference (Table 3).

Changes in the text: The previously included text at Line 165 was deleted and now reads “Each of these studies note minimal associated complications, the majority of which are attributed to surgical resection rather than HITHOC use” at Line 179-181. Additionally, Table 3 was included describing the complications associated with P/D.

Comment 3: Line 202-205- The referred paper concerns HIPEC, not HITEC.

Reply 3: We appreciate identification of this oversight. We have removed this reference and instead have included several studies demonstrating the potential utility of HITHOC in primary ovarian malignancies with pleural involvement.

Changes in the text: The sentence, “Additionally, recent discussion from the Cleveland Clinic offers a succinct review of the application of HITHOC in ovarian cancer with pleural metastasis, citing a nearly 12-month extension in overall survival”, originally at lines 202-205 has been deleted. This was replaced with: “Additionally, several retrospective studies have evaluated the utility of HITHOC in ovarian cancer with pleural involvement with promising results” at Lines 228-229.

Comment 4: Technique paragraph:

The authors use HITEC in their institution for epithelioid mesothelioma:

*Please elaborate on the indications in your institution. Do all the patients receive HITEC with P/D? Are there any reasons for not adding HITEC after P/D in your institution? Any known indications from the literature

Reply 4: We have clarified the text to better describe the indications for HITHOC at our institution. All patients evaluated for P/D are also considered for HITHOC. Patients that are not candidates for HITHOC are those with pre-existing renal disease that decline postoperative dialysis, as well as those with persistent marrow suppression preoperatively.

Changes in the text: The text previously read “Despite the vast majority of literature detailing HITHOC in these two settings, a wide variety of potential applications persists outside of these two indications”. We have edited this to read “In reviewing current literature, the most common indications for the application of HITHOC in CRS include malignant pleural mesothelioma and thymic pleural malignancies. There are patients with select subtypes of pleural carcinomatosis who may benefit, however these cases remain infrequent and should be considered on a case-by-case basis” at Lines 103-104. Additionally, at Lines 104-106 we have included “There are patients with select subtypes of pleural carcinomatosis who may benefit, however these cases remain infrequent and should be considered on a case-by-case basis.

Comment 5: Discussion paragraph

High-risk patient group- Who is included in this group and is not a candidate for HITEC during CRS?

Reply 5: We appreciate the need for further clarification regarding those that are considered candidates for HITEC at our institution and have included the below text.

Changes in the text: We have removed the text “The risks of adding HITHOC to CRS

must be considered, particularly in high-risk patient groups”. This text now reads “At our institution, all patients undergo extensive preoperative evaluation and those that are considered candidates for P/D are also considered for HITHOC. We consider excluding HITHOC in patients with chronic renal insufficiency or those with severe marrow suppression.

Our evaluation process for P/D and HITHOC therapy includes internal pathology review, clinical staging, multi-disciplinary tumor board discussion, and diagnostic testing to evaluate cardiac, pulmonary, and renal function. Clinical staging involves contrasted chest CT and PET scan. An MRI of the brain is only performed in select cases. Diagnostic tests include baseline labs, pulmonary function tests, and nuclear cardiac stress or stress echocardiogram. If concerns for pulmonary hypertension exist, a right heart catheterization is ordered in select patients. We perform endobronchial ultrasound (EBUS) or mediastinoscopy in conjunction with diagnostic laparoscopy in possible surgical candidates” at Lines 232-250

Comment 6: Rationale and Knowledge Gap:

Line 84- Reference 4 is about melanoma. Please check its relevance.

Reply 6: We appreciate this comment and recognize the error. The citation has been corrected to reflect recent studies demonstrating the use of HITHOC in malignant pleural mesothelioma (Dawson et al) and thymic tumors with pleural dissemination (Aprile et al).

Changes in the text: The citations in Line 85 were updated to better reflect the claim that “The safety and efficacy of HITHOC in pleural malignancies has been well demonstrated, particularly for malignant pleural mesothelioma (MPM) and thymic tumors with pleural dissemination”.

Reviewer C

Comment 1: You use the abbreviation HITEC. In the literature, HITOC is mostly used, so I recommend adapting this.

Reply 1: Thank you for offering this suggestion. We note the ambiguity of abbreviation for hyperthermic intrathoracic chemotherapy and will proceed with using “HITHOC” to promote continuity in the literature.

Changes in the text: The abbreviation “HITEC” was changed to “HITHOC” throughout the manuscript.

Comment 2: page 5, line 102: HITEC after CRS.

Reply 2: Thank you for this suggestion. We have adopted the change.

Changes in the text: Line 102 previously read “The most common indications for the

application of HITHOC in CRS include malignant pleural mesothelioma and thymic pleural malignancies”. This now reads “The most common indications for the application of HITHOC after CRS include malignant pleural mesothelioma and thymic pleural malignancies” at Lines 103-104.

Comment 3: page 11, lines 256-257: why do you fractionate the cisplatin dose during HITHOC? I am not aware of this procedure in the literature or at our thoracic surgery centres in Germany. The chemotherapy circulates in a closed circuit. Please explain this procedure. In addition, you should also describe the procedure described in the literature.

Reply 3: We are happy to provide further explanation of our standard HITHOC circuit setup and have done so below. This procedure mirrors the standardized approach detailed by Aprile and colleagues in their recent review. This citation has been included for reference.

Changes in the text: Lines 256-257 previously read “We utilize cisplatin 225mg/m² of BSA at 42 degrees Celsius instilled through a roller pump, Hyperthermia Treatment Pump (Belmont Medical Technologies, Billerica MA, USA). It is introduced and circulated in the chest for approximately 60 minutes following CRS”. This now reads, “The HITHOC circuit consists of two drainage cannulas (outflow) and two return cannulas (inflow). We initially fill the circuit with approximately 2-3L of normal saline fluid; following proper placement of the cannulas the heated fluid is infused to the patient to fill the thoracic cavity through the return cannulas. Once the thoracic cavity is adequately filled, the drainage line is opened to allow circulation and lavage. The drainage line sends the heated saline to an open, hard-shelled reservoir, then through the Belmont Procedure kit and device which heats the fluid and pumps it back to the patient through the return cannulas. Once target temperature (42 degrees Celsius) is achieved, the chemotherapeutic agent is added directly to the hard-shell reservoir to ensure full mixing with the heated, circulating saline. Circulation of the chemotherapy is then continued for 60 minutes. Administration immediately following CRS enables exposure of the entire pleural space to cytotoxic agent prior to formation of post-operative adhesions that would induce compartmentalization. The dose is fractionated, giving one third at initiation of HITHOC, an additional third at 20 min, and the final third at 40 min. Arterial blood gas monitoring is performed every 20 minutes during HITHOC infusion. At the end of the treatment period, the chemotherapeutic fluid is “chased” through the circuit with normal saline and re-routed into a waste bag, displacing the chemotherapeutic agent with approximately 2L of normal saline. Once adequately “chased” into the waste bag, the remaining fluid in the chest is drained from the patient into the reservoir using vacuum assist prior to reopening the thoracotomy incision”. This text was included at Lines 301-323. Additionally, the citation for Aprile

et al (*HITHOC for thymoma*) was included for reference to other similar techniques.

Comment 4: If I have understood correctly, you perform a re-thoracotomy after the HITOC to stop the blood flow. Why? In my experience, this procedure is not usual and above all not necessary. In addition, it poses risks for the staff, as direct exposure to cisplatin is possible. The 60-minute hyperthermic perfusion also promotes haemostasis. Please describe not only your guidelines but also the procedure described in the literature.

Reply 4: We appreciate the confusion that may be associated with the technique and have included clarification regarding our operative approach in the text as demonstrated below.

Changes in the text: “Temporary closure of the chest enables HITHOC circulation with subsequent completion of diaphragmatic, pulmonary, or pericardial reconstructions. Additionally, this approach allows for confirmation of hemostasis following HITHOC and immediately prior to the conclusion of the case” was included at Lines 278-281 for clarification.

Comment 5: Why are patients re-intubated and not extubated if clinically justifiable? Especially prolonged pulmonary fistulas benefit from rapid extubation.

Reply 5: Thank you for this question as it highlights a lack of clarity in our previous manuscript. As we use a dual-lumen endotracheal tube for intubation to facilitate single-lung ventilation, we exchange the dual-lumen tube for a single-lumen to enable bronchoscopy at the conclusion of the case. We do so in order to eliminate secretions and optimize respiratory status for extubation in the operating room. Patients only remain intubated post-operatively if parameters for safe extubation are not met. In this circumstance the patient is transferred to the ICU with a goal of early extubation as soon as is safe.

Changes in the text: The text previously read, “The patient is then reintubated with a single lumen endotracheal tube and completion bronchoscopy is performed”. This was updated to “The patient is then reintubated with a single lumen endotracheal tube and completion bronchoscopy is performed. Patients who meet criteria are extubated in the operating room. If a patient does not meet appropriate respiratory or hemodynamic parameters, they are relocated to the ICU and remain intubated. Early extubation is favored to reduced positive ventilatory pressure effects on air leak and bronchopleural fistula” on Lines 329-333.

Comment 6: The tables on tumour classifications are not helpful in my view. Rather, a table on the surgical procedure/technique of HITOC with the most important steps would be useful in the context of this review article. Perhaps including a comparison of

their technique versus the technique described in the literature. Here you could also show and discuss differences.

Reply 6: We appreciate the need for increased clarity regarding the surgical procedure of HITHOC. We have included a table depicting the procedural steps with a comparison to the technique described in the literature (Table 1) Additionally, we have deleted the tables with tumor classifications (Tables 1, 2, 3) and their associated reference text.

Changes in the text: Tables previously denoted as “Table 1, Table 2, and Table 3” were removed from the text. “Table 1” is reflective of HITHOC operative technique and was included and referenced on Line 262.

Comment 7: An illustration of HITOC would be helpful for the reader.

Reply 7: Thank you for this suggestion. In lieu of an illustration, we have provided intraoperative images for inclusion.

Changes in the text: The included images depicting (1) inflow and outflow cannulas (2) intrathoracic temperature probes (3) temporary closure of the thorax (4) preoperative and postoperative intrathoracic views have been included and are referenced on Lines 274, 275, 277 and 326 respectively. .

Comment 8: Please also check the literature. for a review article you should update and add to the references.

Reply 8: We appreciate this suggestion. We have included an additional systematic review by Migliore et al (Reference 29) as well as a recent publication by Voigt et al (Reference 17). Additional changes to references as requested by other reviewers were also included.

Changes in the text: These references are included at appropriate locations in the text on Lines 145 and 228.

Comment 9: In addition, you should describe more in detail the technique of HITOC described by experienced high-volume centers in the literature, possible chemotherapeutic agents (which? dosage? complications? dose-escalation?) and the perioperative management for HITOC. There ist a lot of literature available and this is important for future standardization of HITOC.

Reply 9: Thank you for requesting this clarification. We have included the operative technique in Table 1 and possible chemotherapeutic agents in Table 2.

Changes in the text: Tables 1 and 2 are referenced in the text at Lines 262 and 297.

Comment 10: A table including recommendations for HITOC (indications, technique, chemotherapeutic agents, dosages) would be helpful for the readers.

Reply 10: Thank you for this feedback. We have included a table (Table 1 detailing the

operative technique, as well as Table 2 detailing common chemotherapeutic regimens with associated dosages) to clarify this information.

Changes in the text: Tables 1 and 2 are referenced on Lines 262 and 297 respectively.

Reviewer D

Comment 1: The paper written by Campany et al. entitled "Hyperthermic Intrapleural Chemotherapy: An Update" is an overview on the hyperthermic intrathoracic chemotherapy in pleural malignancies. The paper is well written and easy flowing, but in its current form, I am not convinced it could add something innovative to what is already known.

I would restructure it as a systematic review to summarize all the current evidences on this topic; this will add scientific validity, making the conclusions more consistent.

Reply 1: We appreciate the request to transition the manuscript to a systematic review format and have attempted to include further references and clarification of operative technique throughout the manuscript. We are hopeful that such changes provide adequate information to suffice as a narrative review of current literature with inclusion of institutional practices.

Changes in the text: See previous comments for referenced changes.