

## Peer Review File

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### Reviewer A

**Comment 1:** This paper is related to a very interesting topic, but it only announce how it is going to be done prospectively, but without any result. So, to be even considered for publication, some results are needed.

**Reply 1:** This article was a brief summary of the protocol of our prospective observational study. As of the time of this revision, the enrollment in this trial has not been completed. The comprehensive and detailed results will be reported after the enrollment is completed.

**Changes in the text:** None

### Reviewer B

I read with interest the CHOICE protocol study by Yang et colleagues on the Hyperthermic Intrathoracic Chemotherapy for the Treatment of Thymic Epithelial Malignancies with Pleural Spread or Recurrence. Herein, authors propose a prospective, open, single arm study in order to evaluate safety and effectiveness of HITHOC after cytoreductive surgery in Stage IVa TETs. The aim of the protocol is very interesting and focused on a field where we have few certainties and too many uncertainties. Since there is a protocol with several bulleted lists or tables there are just some minor issues and concerns.

**Answer:** We appreciate your positive and constructive comments and thank you for spending so valuable time reviewing our paper. Now we hope the revised paper will provide a more readable description of the methods of this study.

**Comment 1:** Regarding the use of acronymous I would like to suggest using the most common HITHOC instead of HITOC.

**Reply 1:** Thanks for your suggestion and we use “HITHOC” uniformly throughout this article.

**Changes in the text:** line 29, 35, 41, 48, 50, 54, 83, 86, 88, 93, 98, 106, 141-146, 223, 226, 231, 251, 253, 256, 259, 260, 263, 265, 267, 269, 270, 276, 285-286, 291-292, 298, 310.

**Comment 2:** Postoperative hospital stays is usually not depending from the real health

status of the patient or from the safety of the procedure, so I suggest to change the outcome in chest drains duration.

**Reply 2:** Thanks for your valuable comment. Hospital stay may be somewhat imprecise. So, we make up criteria for discharge. The criteria for hospital discharge were followed: no fever, normal chest X-ray, no drainage tube and good physical status. We consider patients “discharged” when they meet discharge criteria. At the same time, we also fully consider your opinions. Drainage time is also one of the indicators that we focus on when assessing the safety of the treatment. Therefore, we included this indicator in the secondary endpoint.

**Changes in the text:** Postoperative drainage duration: the duration from the day when drainage tubes were placed until the day when drainage tubes were moved. (line 217-218)

**Comment 3:** Many authors perform HITHOC after surgery when the patient is still under anesthesia to better manage eventual complication (more or less related to the perfusion with cytotoxic drugs). In case of severe complications related to the HITHOC, author should describe how to manage them with the patient awake and conscious.

**Reply 3:** Thanks for your comment. HITHOC can be performed safely while the patient is awake.

During bedside HITHOC, vital signs are monitored, including: heart rate, blood pressure, blood oxygen saturation, body temperature (multiple points), skin characteristics (color, rash, etc.), electrolytes, osmotic pressure, blood sugar concentration, urine output. Our treatment methods: oxygen, fluid therapy, sedation, analgesia and other symptomatic treatments. To date, no serious complication or death was found in this trial. Previous study also reported that HITHOC can be performed safely when the patient is awake [1].

**Reference:**

[1] Liu L, Zhang N, Min J, Su H, Wang H, Chen D, Sun L, Zhang H, Li W, Zhang H. Retrospective analysis on the safety of 5,759 times of bedside hyperthermic intra-peritoneal or intra-pleural chemotherapy (HIPEC). *Oncotarget*. 2016 Apr 19;7(16):21570-8. doi: 10.18632/oncotarget.7622. PMID: 26919243; PMCID: PMC5008306.

**Changes in the text:** None

**Comment 4:** Authors should better describe the surgical procedure. What do they mean for lesion resection? Partial pleurectomy, complete pleurectomy, diaphragm and pericardial resection?

**Reply 4:** Thanks for your comment. During the surgery, we try to remove all visible tumor lesions as completely as possible and choose the most appropriate surgical

method based on the location and number of the lesions. Partial pleurectomy should be used for oligometastatic pleural nodules. Complete pleurectomy should be performed selectively taking into account the safety of the operation and is always used for multiple nodules involving extensive dissemination on the parietal pleura. Partial diaphragm resection combined with diaphragm repair should be used for diaphragm dissemination. Partial pericardial resection combined with pericardiac repair was applied to the tumor lesions that spread into pericardium. We added a brief description in our revised manuscript.

**Changes in the text:** During the surgery, we try to remove all visible tumor lesions as completely as possible and choose the most appropriate surgical method based on the location and number of the lesions. Partial pleurectomy should be used for oligometastatic pleural nodules. Complete pleurectomy should be performed selectively taking into account the safety of the operation and is always used for multiple nodules involving extensive dissemination on the parietal pleura. Partial diaphragm resection combined with diaphragm repair should be used for diaphragm dissemination. Partial pericardial resection combined with pericardiac repair was applied to the tumor lesions that spread into pericardium. (line 126-135)

**Comment 5:** How do authors manage the PFS in case of R2 resection?

**Reply 5:** All patients will be suggested follow-up according to the guidelines. For all patients who received S-HOTIC, chest computed tomography scans were performed every 3 months for the first postoperative 6 months, then, every 6 months for the first two years and finally yearly lifelong. Further examinations were requested when needed, including ultrasound, puncture biopsy and positron emission tomography-computed tomography scan. PFS was the duration for the patients until the date of the first progression since the date of S-HITHOC. Disease progression is defined as the new locoregional lesion (anterior mediastinal lesion, lung, pericardiac or pleural invasion) or the new metastatic lesion (pericardial dissemination, pleural dissemination or distant organs).

**Changes in the text:** Progression-free survival (PFS): the duration for the patients until the date of the first progression since the date of S-HITHOC. Disease progression is defined as the new locoregional lesion (anterior mediastinal lesion, lung, pericardiac or pleural invasion) or the new metastatic lesion (pericardial dissemination, pleural dissemination or distant organs). (line 228-231)

**Comment 6:** There are some typos (i.e. HOTIC) that should be corrected.

**Reply 6:** Thanks for your suggestion and we We use “HITHOC” uniformly throughout this article.

**Changes in the text:** line 29, 35, 41, 48, 50, 54, 83, 86, 88, 93, 98, 106, 141-146, 223,

226, 231, 251, 253, 256, 259, 260, 263, 265, 267, 269, 270, 276, 285-286, 291-292, 298, 310.

### **Reviewer C**

First of all, congratulations for your work. I think it is an accurate study and I hope that your investigation will be useful to determine one one hand the safeness and in the other hand the effectiveness (or almost an idea of it) of HITOC in pleural methastases of thymic malignancies.

I only want to suggest some formal corrections:

**Comment 1:** Lines 155, 281, 282, 155: The term HOTIC is used in stead of S-HITOC. If you plan to use this term indistinctly, please add the term to the abbreviation table.

**Reply 1:** Thanks for your suggestion. We add the “HOTIC” to the abbreviation table.

**Changes in the text:** HITHOC, hyperthermic intrathoracic chemotherapy (line 35)

**Comment 2:** Line 194: ...discharge was followed: no fever, normal chest X-ray, daily drainage drainage less than 200.

The term drainage is duplicated.

**Reply 2:** Thanks for your suggestion and we are so sorry for our mistake. We delete one word in the revised manuscript.

**Changes in the text:** delete one word “drainage”. (line 225-227)

**Comment 3:** Line 221: ...(version 26) and R software (version 4.3.1) were used to perform statistical analyses.

Consider to change the verbal tense, knowing that this is a study protocol with no results to analyse at this time.

**Reply 3:** Thanks for your suggestion and we are so sorry for our mistake. We delete one word in the revised manuscript.

**Changes in the text:** Software package SPSS (version 26) and R software (version 4.3.1) will be used to perform statistical analyses. (line 239-240)

### **Reviewer D**

**Comment 1:** I did not see any description of performance status or renal function in the inclusion criteria. Can the authors comment on these important points?

**Reply 1:** Thanks for your suggestion. The patients with renal dysfunction will be excluded due to the intolerable nephrotoxicity. Also, patients with performance status

score more than 2 will be excluded.

**Changes in the text:** We exclude the following subjects: acute exacerbation of myasthenia gravis; renal dysfunction; performance status score more than 2; vulnerable population; refusal or withdraw to participate. (line 184-185)

**Comment 2:** Please make a statement about the postoperative follow-up protocol (radiological study, frequency, etc.)? This is very important in measuring progression free survival.

**Reply 2:** All patients will be suggested follow-up according to the guidelines. For all patients who received S-HOTIC, chest computed tomography scans were performed every 3 months for the first postoperative 6 months, then, every 6 months for the first two years and finally yearly lifelong. Further examinations were requested when needed, including ultrasound, puncture biopsy and positron emission tomography-computed tomography scan. PFS was the duration for the patients until the date of the first progression since the date of S-HITHOC. Disease progression is defined as the new locoregional lesion (anterior mediastinal lesion, lung, pericardiac or pleural invasion) or the new metastatic lesion (pericardial dissemination, pleural dissemination or distant organs).

**Changes in the text:** All adverse events and postoperative complications will be recorded, assessed and treated. Visual Analog Pain Scale (VAS) score will be recorded to evaluate postoperative pain before the operation and 1, and 3 days after the operation. We will use the EORTC QLQ-C30 (V3.0) to assess the quality of life (QoL) of the patients on the 30, 90 and 180 days after surgery. For all patients who receive S-HOTIC, chest computed tomography scans will be performed every 3 months for the first postoperative 6 months, then, every 6 months for the first two years and finally yearly lifelong. Further examinations will be requested when needed, including ultrasound, puncture biopsy and positron emission tomography-computed tomography scan. PFS was the duration for the patients until the date of the first progression since the date of S-HITHOC. Disease progression is defined as the new locoregional lesion (anterior mediastinal lesion, lung, pericardiac or pleural invasion) or the new metastatic lesion (pericardial dissemination, pleural dissemination or distant organs). (line 166-173,228-231)

**Comment 3:** Regarding the surgical approach, both minimally invasive and open approaches included?

**Reply 3:** Thanks for your comment. During the surgery, we try to remove all visible tumor lesions as completely as possible and choose the most appropriate surgical method based on the location and number of the lesions. Both minimally invasive and open approaches will be considered. In the meanwhile, partial pleurectomy should be

used for oligometastatic pleural nodules. Complete pleurectomy should be performed selectively taking into account the safety of the operation and is always used for multiple nodules involving extensive dissemination on the parietal pleura. Partial diaphragm resection combined with diaphragm repair should be used for diaphragm dissemination. Partial pericardial resection combined with pericardiac repair was applied to the tumor lesions that spread into pericardium. We added a brief description in our revised manuscript.

**Changes in the text:** Minimally invasive (if possible) or open surgery will be performed for all enrolled participants to reduce tumor burden. (line 126-135)

**Comment 4:** Is there any limit in the number of pleural lesions for inclusion in this study?

**Reply 4:** We do not limit in the number of pleural lesions for inclusion in this study. Compared with those having more lesions, patients having less pleural lesions may be more benefit from the S-HITOC. When finishing the trial, we will perform a subgroup analysis to compare the efficacy between the two groups of patients.

**Changes in the text:** None

**Comment 5:** Please cite several references in discussing the increase in the risk of postoperative complications for synchronous combination of HITOC

**Reply 5:** Thanks for your comment. It is the fact that postoperative morbidity occurs in more than thirty percentages of patients who underwent S-HITHOC, which was obviously higher than that of patients underwent surgery alone [1]. It also was reported that postoperative complication rate was 31% after S-HITHOC for thymic malignancies with pleural dissemination [2]. In some studies, prolonged air leakage and/or pneumothorax was observed in patients who had partial decortication associated with HITHOC [1]. Cisplatin has dose-dependent renal toxicity, and the most important chemo-therapy-related complication to be mentioned here is the postoperative increase in creatinine. Moderate-to-severe nephrotoxicity was noted in 25% to 33% of patients receiving a single intravenous dose of cisplatin of 50 to 75mg/m<sup>2</sup>. In several studies, HITOC caused renal dysfunction in 8.7 to 57% of patients [3-5].

[1] Aprile V, Bacchin D, Korasidis S, et al. Surgical treatment of pleural recurrence of thymoma: is hyperthermic intrathoracic chemotherapy worthwhile? *Interact Cardiovasc Thorac Surg*. May 1 2020;30(5):765-772. doi:10.1093/icvts/ivaa019.

[2] Markowiak T, Neu R, Ansari MKA, Großer C, Klinkhammer-Schalke M, Hofmann HS, Ried M. Surgical Cytoreduction and HITOC for Thymic Malignancies with Pleural Dissemination. *Thorac Cardiovasc Surg*. 2021 Mar;69(2):157-164. doi: 10.1055/s-0039-1700883. Epub 2019 Nov 15. PMID: 31731316.

[3] Markowiak T, Kerner N, Neu R, Potzger T, Großer C, Zeman F, Hofmann HS, Ried

M. Adequate nephroprotection reduces renal complications after hyperthermic intrathoracic chemotherapy. *J Surg Oncol*. 2019 Dec;120(7):1220-1226. doi: 10.1002/jso.25726. Epub 2019 Oct 10. PMID: 31602673.

[4] Richards WG, Zellos L, Bueno R, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. *J Clin Oncol* 2006; 24(10):1561–1567.

[5] Tilleman TR, Richards WG, Zellos L, et al. Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. *J Thorac Cardiovasc Surg* 2009;138(02):405–411

**Changes in the text:** It is the fact that postoperative morbidity occurs in more than thirty percentages of patients who underwent S-HITHOC, which was obviously higher than that of patients underwent surgery alone. It also was reported that postoperative complication rate was 31% after S-HITHOC for thymic malignancies with pleural dissemination. In some studies, prolonged air leakage and/or pneumothorax was observed in patients who had partial decortication associated with HITHOC. Cisplatin has dose-dependent renal toxicity, and the most important chemo-therapy-related complication to be mentioned here is the postoperative increase in creatinine. Moderate-to-severe nephrotoxicity was noted in 25% to 33% of patients receiving a single intravenous dose of cisplatin of 50 to 75mg/m<sup>2</sup>. In several studies, HITOC caused renal dysfunction in 8.7 to 57% of patients. (line 268-279)

## Reviewer E

**Comment:** The authors have designed a feasibility study for patients with pleural spread TET, and have adequately described it in the text. However, readers may want to know more about the details of the perfusion system. Please provide more information about how the system works, and include detailed photos of the device as Figures. This minor revision should be made before publication in JTD.

## Reply 1:

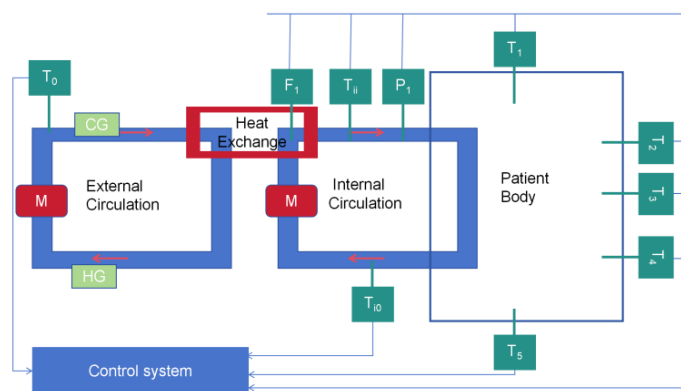
Thanks for your suggestion. The BR-TRG-I body cavity thermal perfusion therapy system consists of four parts: a control system, an external circulation system, a heat exchanger, and an internal circulation system. The external circulation system includes heaters, refrigerators, external circulation pumps, etc. (the overall structure of the system is shown in eFigure 1 and eFigure 2). The internal circulation system includes the internal circulation pump, the human body, etc. Heat is exchanged between the external circulation system and the internal circulation system through a heat exchanger to keep the temperature of the chemical liquid in the internal circulation constant. The

external circulation system is filled with closed water, and control the temperature of the internal circulation liquid through the water bath method, thereby achieving the purpose of controlling the body cavity temperature. The heating source and cooling source are all in the external circulation system, and the volume of water is 5L. The internal circulatory system is connected with the human body cavity and forms a closed circulation body with the body cavity. The liquid is medicinal liquid with a volume of 4L. The intraperitoneal liquid volume can be increased by increasing the volume of the perfused liquid during the body cavity thermal perfusion process.

According to your suggestion, we added two supplemental figure into the revised manuscript.



**eFigure 1. BR-TRG-I body cavity thermal perfusion therapy system equipment**



**eFigure 2. The overall structure of the system.**



BR-TRG-I body cavity thermal perfusion therapy system structure diagram description:  
HG, Heater with a maximum power of 4kW and adjustable heating current.

CG, Semiconductor Refrigerator: The maximum power is 2kW, and its cooling power is adjustable.

$T_o$ : Temperature of water in external circulation heat exchange area, accuracy 0.1°C.

$T_{ii}$ : The temperature of the internal circulation liquid before it enters the human body, with an accuracy of 0.1°C.

$T_{io}$ : The temperature of the internal circulation liquid after it flows out of the human body, with an accuracy of 0.1°C.

$F_i$ : Flow rate of internal circulation liquid, accuracy 10mL/min, resolution 1mL/min.

$P$ : The pressure of the internal circulation liquid before entering the human body, accuracy 10mmHg, resolution 1mmHg.

$T_0 \sim T_5$ : The temperature of five important parts of the human body.

$M_1$ : External circulation pump, running at a constant speed of 10L/min.

$M_2$ : Internal circulation pump, the speed can be controlled up to 600mL/min, the accuracy is 10mL/min, with resolution 1mL/min.

**Changes in the text:** When performing HITHOC, we will use the BR-TRG-I type device [Guangzhou Bright Medical Technology, Guangzhou, China], a dedicated perfusion system approved by the Chinese Food & Drug Agency. The BR-TRG-I body cavity thermal perfusion therapy system consists of four parts: a control system, an external circulation system, a heat exchanger and an internal circulation system (eFigure 1-2). (line 152-156)

## Reviewer F

I agree to this prospective study for cytoreductive surgery combined with hyperthermic intrathoracic chemotherapy for thymic epithelial tumors with pleural implantation.

There are several typographical errors as follows.

**Comment 1:** Page 2, List of abbrevi. The description of S-HITOC is not fully shown.

**Reply 1:** Thanks for your suggestion and according to suggestion from the reviewers, we use “S-HITHOC” uniformly throughout this article and the description of S-HITOC is fully shown in the list of abbreviation.

**Changes in the text:** line 29, 35, 41, 48, 50, 54, 83, 86, 88, 93, 98, 106, 141-146, 223, 226, 231, 251, 253, 256, 259, 260, 263, 265, 267, 269, 270, 276, 285-286, 291-292, 298, 310.

**Comment 2:** Page 10. Line 243. “A study by Aprile et al. Showed that” should be corrected to “A study by Aprile et al. showed that”.

**Reply 2:** Thanks for your suggestion and we corrected the sentence according to your suggestion.

**Changes in the text:** A study by Aprile et al. Showed that OS could be achieved for up to 64 months and PFS be achieved up to 53 months. (line 263)

**Comment 3:** Page 10. Line 252. “that of patients underwent surgery alone” should be corrected to “that of patients who underwent surgery alone” ,

**Reply 3:** Thanks for your suggestion and we corrected the description according to your suggestion.

**Changes in the text:** Previous literature showed no significant difference in perioperative safety for patients underwent S-HITHOC compared with those who underwent surgery alone. (line 269)

**Comment 4:** Page 11. Line 274. What is HITHOC?

**Reply 4:** We are sorry that our description makes you misleading. HITHOC is hyperthermic intrathoracic chemotherapy. We use “HITHOC” uniformly throughout this article.

**Changes in the text:** line 29, 35, 41, 48, 50, 54, 83, 86, 88, 93, 98, 106, 141-146, 223, 226, 231, 251, 253, 256, 259, 260, 263, 265, 267, 269, 270, 276, 285-286, 291-292, 298, 310.