



Cytoreductive surgery combined with hyperthermic intrathoracic chemotherapy for the treatment of thymic epithelial malignancies with pleural spread or recurrence (CHOICE): a study protocol for a prospective, open, single-arm study

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Background: Cytoreductive surgery combined with hyperthermic intrathoracic chemotherapy (S-HITHOC) may be effective in treating thymic epithelial tumors (TETs) with pleural spread or recurrence. This study will evaluate the safety and efficacy of S-HITHOC in the treatment of TETs with pleural spread or recurrence.

Methods: This study is an open, single-arm, prospective trial. Approximately 37 patients diagnosed with TETs with pleural spread or recurrence at the Zhongshan Hospital of Fudan University will be recruited and treated with S-HITHOC. The co-primary outcomes of the study are the length of postoperative hospital stay, complications, and overall quality of life (QoL). The secondary outcomes include drainage duration, volume, and cumulative pain scores.

Discussion: This trial was approved by the Zhongshan Hospital Research Ethics Committee. The study findings will be actively disseminated through manuscript publications and conference presentations. Information sheets will be provided to each participant, and informed written consent will be obtained for each evaluation. This prospective study will evaluate the effectiveness of a surgical resection combined with the HITHOC procedure in treating TETs with pleural spread or recurrence in China and will support the standardization of the procedure.

Registration: This trial was registered on Clinicaltrial.gov (No. NCT05446935).

Keywords: Cytoreductive surgery; hyperthermic intrathoracic chemotherapy (HITHOC); thymic epithelial tumors (TETs); pleural spread or recurrence; clinical trial

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Introduction

Thymic epithelial tumors (TETs), including thymoma and thymic carcinomas, are the most common anterior mediastinal tumors (1). An aggressive surgical approach is considered the mainstay of therapy for TETs, except for clinically non-resectable tumors or those with distant metastasis. TETs with pleural spread or recurrence are defined pathologically as Masaoka-Koga and tumor-node-metastasis (TNM) stage IVa. TETs are locoregional and considered potentially resectable. However, the 5-year survival rates of patients with TETs with pleural spread or recurrence have been reported to range from 33% to 46% in different studies and are significantly lower than those of patients with TETs without pleural spread or recurrence (2). Thus, it has been suggested that a multimodal treatment approach should be adopted to treat advanced-stage patients.

Currently, there is no standard approach for treating TETs with pleural spread or recurrence. However, there are several empirical therapeutic methods for treating patients with TETs with pleural spread or recurrence, including surgery combined with chemotherapy and/or radiotherapy. Multimodality treatments using neoadjuvant chemotherapy/radiotherapy followed by surgery or resection followed by adjuvant therapy have produced highly improved oncological outcomes and promising results in the treatment of patients with advanced diseases (3). However, studies focusing on a chemotherapy-based regimen for advanced TETs have indicated that the response rates were relatively heterogeneous, and ranged from 20% to 100% (4).

Cytoreductive surgery combined with hyperthermic intrathoracic chemotherapy (S-HITHOC) is an emerging technique that might improve the progression-free survival

(PFS) and overall survival (OS) of patients with TETs with pleural involvement. In recent decades, several studies have reported that S-HITHOC can achieve the local excision of recurrent cancer and improve the control of local disease with satisfactory safety and efficacy (*Table 1*) (5-12).

Theoretically, hyperthermic intrathoracic chemotherapy (HITHOC) has the advantage of directly exposing the tumor to a locally higher concentration of the antineoplastic agent with fewer systemic adverse events. Further, the combination of hyperthermia with chemotherapeutic agents may have an additive effect on pleural malignancy by increasing the effectiveness, the penetration depth, and the activation of apoptosis. To our knowledge, few studies have compared the results of surgery alone with those of S-HITHOC in the treatment of TETs with pleural spread or recurrence.

The objectives of this study are to collect data on the standard procedure of S-HITHOC at our center and to evaluate S-HITHOC in the perioperative outcomes, including the length of postoperative hospital stay, treatment-related adverse events and complications, and European Organization for Research and Treatment of Cancer Quality of Life Questionnaires (EORTC QLQ-C30) scores. We present this article in accordance with the SPIRIT reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-759/rc>) (13).

Methods

Trial design

This study is an open, single-center phase II trial. The trial aims to evaluate the perioperative safety and efficacy of S-HITHOC in the treatment of TETs with pleural spread

Table 1 Study overview

Study	Patients (n)	Chemotherapeutic agents	Duration (min)	Temperature (°C)
Refaely <i>et al.</i> (5)	15	Cisplatin (100 mg/m ² BSA)	60	42
de Bree <i>et al.</i> (6)	3	Cisplatin (80 mg/m ² BSA); doxorubicin (15–30 mg/m ² BSA)	90	40–41
Ried <i>et al.</i> (7)	8	Cisplatin (100–150 mg/m ² BSA)	60	42
Yellin <i>et al.</i> (8)	35	Cisplatin (100 mg/m ² BSA); doxorubicin (50–60 mg)	60	43
Yu <i>et al.</i> (9)	4	Cisplatin (100 mg/m ² BSA)	120	41–43
Ambrogi <i>et al.</i> (10)	13	Cisplatin (80 mg/m ² BSA); doxorubicin (25 mg/m ² BSA)	60	42.5
Maury <i>et al.</i> (11)	19	Cisplatin (50 mg/m ² BSA); mitomycin (25 mg/m ² BSA)	90	42
Markowiak <i>et al.</i> (12)	29	Cisplatin (100–175 mg/m ² BSA); doxorubicin (0–65 mg)	60	42

BSA was calculated according to the Mosteller formula: $BSA = 0.016667 \times \text{weight}^{0.5} \times \text{height}^{0.5}$. BSA, body surface area.

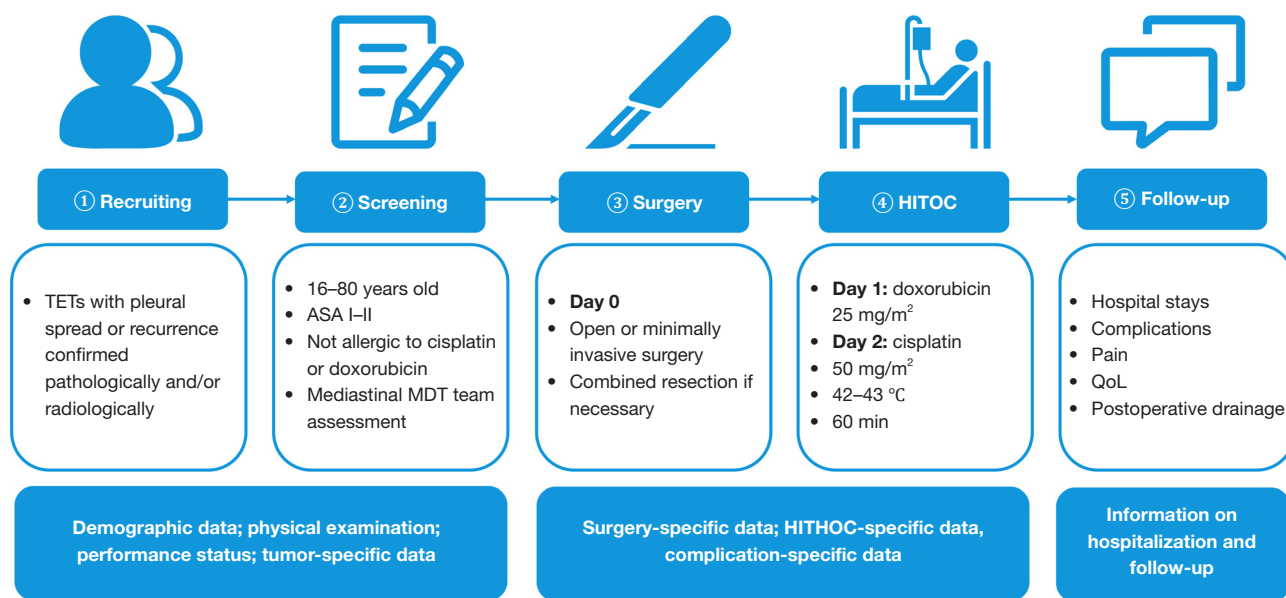


Figure 1 Study procedure. TETs, thymic epithelial tumors; ASA, American Society of Anesthesiologists; MDT, multidisciplinary treatment; HITOC, hyperthermic intrathoracic chemotherapy; QoL, quality of life.

or recurrence. The co-primary outcome measures are the length of postoperative hospital stay, complications, and EORTC QLQ-C30 scores. The principal investigator will explain the content of the research plan to each participant and ask if they agree to their treatment-related data being used in the experiment. Each participant that agrees, will then be asked to sign the written informed consent form before the study starts. The study procedure and data collected at each time point are described in *Figure 1*.

Study setting and sites

All patients diagnosed with TETs with pleural spread or recurrence at the TET multidisciplinary treatment (MDT) clinics at the Zhongshan Hospital of Fudan University will be candidates for this clinical trial. Zhongshan Hospital of Fudan University is one of the main healthcare hospitals in China, and according to the clinic census has more than 5,000,000 attendances annually. Additionally, approximately 500 patients with TETs seek medical advice at our TET MDT clinics each year. The chief surgeons participating in this study perform more than 50 surgeries for TETs and pleural tumors each year.

Surgery technique

The date for surgery is defined as day 0. Patients will be

monitored by electrocardiogram, arterial catheter, pulse oximeter, end-tidal carbon dioxide, and urine output. Minimally invasive (if possible) or open surgery will be performed on all enrolled participants to reduce the tumor burden. During the surgery, the surgeons will try to remove all the visible tumor lesions as completely as possible and will choose the most appropriate surgical method based on the location and number of the lesions. Partial pleurectomy will be used for oligometastatic pleural nodules. Complete pleurectomy will be performed selectively, taking into account the safety of the operation and will always be used for multiple nodules involving extensive dissemination on the parietal pleura. Partial diaphragm resection combined with diaphragm repair will be used for diaphragm dissemination. Partial pericardial resection combined with pericardial repair will be applied to any tumor lesions that have spread into the pericardium. Two 28-F drainage tubes will be placed in the pleural space; one will be located at the seventh intercostal space in the middle axillary line for outflow drainage, and the other will be located at the sixth intercostal space in the anterior axillary line for inflow. During the operation, the patients will receive generous fluids and blood transfusion (if necessary) to maintain adequate blood pressure and urine output. The patients will then be returned to their ward or the intensive care unit (ICU) after the operation. Patient controlled analgesia will be used for postoperative analgesia.

Complete resection (R0) and perioperative complications will be recorded in the case report forms (CRFs). R0 is defined as the microscopic removal of all gross tumors/lesions. Subtotal resection is defined as microscopic minimal residual disease. Partial resection is defined as macroscopic incomplete resection. Perioperative complications might include arrhythmia, respiratory distress, and hemorrhage.

HITHOC technique

The safety of HITHOC for each patient will be assessed by the mediastinal MDT team before HITHOC. The patients enrolled in the study will be given HITHOC regardless of their resection status. HITHOC will be performed at the ward, ICU, or surgical rooms on days 1 and 2 if the patients are without fever, hemorrhage, atelectasis, or massive pleural effusion. The HITHOC team comprises one chief surgeon, one technician, and one nurse. 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 and 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 (Figures S1,S2). The BR-TRG-I device is equipped with a dedicated heat exchanger to ensure a high temperature for the locoregional oncological treatment. The extra-corporal circuit will be primed with lactated ringer solution. Fluids will flow through the outflow drain until all the air is removed from the pleural space through a sidearm in the outflow pipe, and the initial heating perfusion will then begin. Circulation flows of 400 to 600 mL/min with an inflow temperature of 42–43 °C will be required to maintain the desired temperature. Doxorubicin will be infused at 25 mg/m² and perfused on day 1. Cisplatin will be infused at 50 mg/m² and perfused on day 2. The inflow chest tube will be removed and the excess pleural fluid will be allowed to flow freely through the outflow chest tube to a collecting system after HITHOC is performed for approximately 60 minutes.

Postoperative care and follow-up

All the adverse events and postoperative complications will be recorded, assessed, and treated. The Visual Analog 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 at 30, 90, and 180 days after surgery. For all patients who receive S-HITHOC, chest computed tomography scans will be performed every 3 months for the first postoperative 6 months, then, every 6 months for the first 2 years, and finally, annually for the rest of their lives. Further examinations will be administered as necessary, including ultrasound, puncture biopsy, and positron emission tomography-computed tomography scans.

Patient selection

Inclusion criteria

To be eligible for inclusion in this study, patients will have to meet the following inclusion criteria: (I) have undergone a pathological examination that confirms TETs; (II) have undergone an imaging examination that suggests TETs with pleural spread or recurrence; (III) be aged between 16 and 80 years old; (IV) have normal functions in the main organs; (V) have no other malignant carcinomas; and (VI) not be allergic to cisplatin or doxorubicin.

Exclusion criteria

Patients will be excluded from the study if they meet any of the following exclusion criteria: (I) have acute exacerbation of myasthenia gravis; (II) have renal dysfunction; (III) have a performance status score of more than 2; (IV) come from a vulnerable population; and/or (V) refuse to participate or withdraw from the study.

Patient and public involvement

No patient or member of the public has been involved in the design and/or will be involved in the conduct of this research.

Sample size calculation

The primary endpoint of this phase II clinical trial is the rate of treatment-related adverse events. A rate of treatment-related adverse events less than 15% is considered acceptable, and a rate of treatment-related adverse events >30% is considered unsafe. In this study, α was designed at 0.1 due to the rarity of thymic carcinomas with pleural spread or recurrence. Thus, based on Fleming's single-stage design, at the P=0.1 significance level with 80% power, a total of 37 patients will be required. Preliminary

data of mediastinal tumors from 2020 to 2021 from the MDT clinics at Zhongshan Hospital of Fudan University indicate that an average of 3 patients who fulfill the inclusion criteria are treated every month. Thus, we expect to enroll approximately 1–2 eligible patients in the study per month from August 2021 to November 2024 until at least 37 eligible patients are enrolled.

Outcomes of interest

The co-primary outcome measures in this trial are as follows:

- ❖ Treatment-related adverse events: all types and the severity of adverse events that are related to each patient's treatment will be recorded. Clavien-Dindo Classification will be used to grade the severity of the postoperative treatment-related complications. Treatment-related adverse events will be stratified according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v5.0).
- ❖ Length of postoperative hospital stay: this is defined as the duration from the date of surgery to the date that each patient meets the inclusion criteria for hospital discharge. The criteria for hospital discharge are no fever, normal chest X-ray, daily drainage less than 200 mL, and a good physical status.
- ❖ EORTC QLQ-C30 score for overall QoL: patients will be evaluated 1 day before surgery and then postoperatively in the 1st, 3rd, and 6th months using the EORTC QLQ-C30 (V3.0). QoL scores will be linearly converted to a scale ranging from 0 to 100 according to the EORTC guidelines (14). On this scale, a score of 100 represents the best QoL, while a score of 0 indicates the worst QoL.

The secondary outcome measures in this trial are as follows:

- ❖ VAS scores for postoperative pain: patients' cumulative daily pain score will be obtained at rest using the VAS from postoperative 0 to 72 hours. On the VAS, a score of 0 indicates no pain, while a score of 100 mm represents the worst possible pain. The VAS has the following ranges for pain: painless (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm) (15).
- ❖ Postoperative drainage duration: this is defined as the duration from the day when the drainage tubes are placed until the day when the drainage tubes are moved.

- ❖ Postoperative drainage volume: this is defined as the total drainage volume during the hospital stay. Data on the daily drainage volume will be extracted from the care sheet, and the total amount of drainage will be calculated.
- ❖ PFS: this is defined as the duration from the date of S-HITHOC to the date of the first progression. Disease progression is defined as the new locoregional lesion (anterior mediastinal lesion, lung, pericardiac, or pleural invasion) or a new metastatic lesion (pericardial dissemination, pleural dissemination, or distant organ metastasis).
- ❖ OS: this is defined as the duration from the date of S-HITHOC to the date of death.

Statistical analysis

All the related data, including the demographic characteristics, tumor-specific information, surgery-specific outcomes, HITHOC-specific data, complications, hospitalization, and follow-up data, will be recorded in the CRFs and analyzed using a content analysis framework. Descriptive statistics will be presented as the mean \pm standard deviation, or the absolute number and percentage. Binary logistic regression models will be used to assess the risk factors for postoperative complications. Software package SPSS (version 26) and R software (version 4.3.1) will be used to perform the statistical analyses. The level of significance is set at $P_{\text{two-sided}} \leq 0.1$ for all the tests. No adjustments for multiple testing will be made. Standardized forms and processes will be performed for data management. Data quality checks will be carried out every 6 months.

Ethics and dissemination

The trial will be performed according to the Declaration of Helsinki (as revised in 2013). This study was approved by the Zhongshan Hospital Research Ethics Committee (No. B2021-703R). This trial was registered on clinicaltrials.gov (NCT05446935). All the study participants and/or their legally acceptable representatives will need to sign a written informed consent form in this trial. Each participant has the right to withdraw from any aspect of the trial at any time, and the reasons for cancellation will be recorded. The findings of this study will be mainly disseminated through manuscript publications in peer-reviewed journals and conference presentations.

Discussion

There is a consensus that multidisciplinary therapy is necessary to treat TETs with pleural spread or recurrence to control locoregional recurrence and improve OS. During recent decades, S-HITHOC has been increasingly used to treat TETs with pleural spread or recurrence. Yellin *et al.* reported a mean OS of 12 years after S-HITHOC in patients with TETs with pleural spread, and 5- and 10-year PFS rates of up to 47.6% and 17.9%, respectively (8). Maury *et al.* reported that after S-HITHOC, patients with pleural recurrences of thymomas had a mean OS time of 63 months and a mean local disease-free interval time of 41 months (11). Aprile *et al.* showed that an OS time of up to 64 months and a PFS time of up to 53 months could be achieved in patients with thymoma pleural relapses after S-HITHOC (16). Research has also shown that the second recurrence rate was 15.3% in the patients with thymoma pleural spread after S-HITHOC, and that S-HITHOC achieves a longer local disease-free time than surgery alone (10,16). All these studies showed that S-HITHOC is an effective protocol for the treatment of TETs with pleural spread or recurrence.

Previous studies have found no significant differences in the perioperative safety of patients who underwent S-HITHOC compared with those who underwent surgery alone (17); however, a study reported that postoperative morbidity occurred in more than 30% of the patients who underwent S-HITHOC and that this figure was obviously higher than that of the patients who underwent surgery alone (16). Most postoperative complications are associated with surgery; however, the synchronous combination of surgery and HITHOC could increase the risk of postoperative complications. In the study by Aprile *et al.*, prolonged air leakage and/or pneumothorax were observed in patients who had partial decortication associated with HITHOC (16). Cisplatin has dose-dependent renal toxicity, and the most important chemo-therapy-related complication that will need to be monitored in this study is the postoperative increase in creatinine. Moderate-to-severe nephrotoxicity was recorded in 25% to 33% of patients who received a single intravenous dose of cisplatin of 50–75 mg/m² in the previous literature (18). In several studies, HITHOC caused renal dysfunction in 8.7% to 57% of patients (1,16,17,19). However, the simultaneity of surgery and HITHOC limited the number of times that HITHOC can be performed. In these previous studies, almost all the patients received HITHOC once and thus the maximum tolerable dosages of chemotherapeutic drugs were used

to achieve the maximum oncological control. No clear consensus has been reached as to dosing in the HITHOC. Higher-dose cisplatin appears to be associated with better OS; however, it may also cause more complications, including temporary right heart failure, postoperative acute kidney failure, and bone marrow aplasia (17).

The best chemotherapy regimen for HITHOC has yet to be determined. At our center, we use doxorubicin (25 mg/m², day 1) and cisplatin (50 mg/m², day 2) for a number of reasons. First, it has been shown that a high concentration of cisplatin can be reached in the pleural cavity with manageable toxicity (20). Previous studies have reported that cisplatin dosage in the monotherapy setting and combination therapy can range from 100 to 200 and 50 to 175 mg/m², respectively, without increased toxicity (17). However, there is no obvious evidence that high-concentration regimens significantly improve disease-free survival or OS. Thus, we decided to choose a regimen with relatively low concentration to avoid short- and even long-term complications if possible. Second, no studies have compared single-agent with dual-agent HITHOC regimens in the treatment of advanced TETs or pleural carcinomas. The debate continues as to the best choice and combination of chemotherapeutic drugs for HITHOC; however, several clinical trials focusing on neoadjuvant and adjuvant chemotherapy in the treatment of most malignancies have shown that a combination of different chemotherapeutic drugs could significantly improve OS (21–23). Thus, we have chosen a two-drug regimen in our protocol. Third, it has been reported that HITHOC was mostly performed intraoperatively under general anesthesia after the surgical procedure, which limited the number of times that HITHOC could be performed. In our experience, doxorubicin and cisplatin are perfused on postoperatively days 1 and 2, respectively. It is helpful to accurately monitor the response of patients to each treatment (surgery or HITHOC) when the patient is conscious. In addition, the separation of surgery and HITHOC break the limitations related to the place at which HITHOC is administered, and most patients can receive HITHOC at their bedside. To date, this option has been applied to 11 patients with TETs with pleural spread or recurrence and has been proven to be effective and safe. Similar results were reported by Liu *et al.* in 2016, who performed bedside HITHOC that could be repeated in the same patient, and reported a morbidity rate of 2% (19). Thus, this regimen will be used in this prospective study.

Another factor determining the efficacy of HITHOC

was the target temperature of the chemotherapeutic solution. The penetration depth of cisplatin into the tissue has been reported to increase with the temperature of the intrathoracic solution (24). Target temperatures of 40–43 °C have been reported in previous studies (8,25,26). Intrapleural temperatures above 43 °C have been reported to be associated with an increased risk of pulmonary edema (7). In addition, high-temperature perfusate could increase the risk of systemic hyperthermia (27). Only a few studies have been conducted on the optimal duration of perfusion, which has been reported to vary from 60–120 minutes (9,11). However, no research appears to have compared the safety and efficacy of the different perfusion durations.

To our knowledge, this prospective study will provide the first opportunity to validate the clinical experience of our center and will enable us to gather reliable data on the standardized therapeutic management of patients who have undergone HITHOC. In the long term, the data from this trial might be used for survival analyses of advanced TETs.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-759/rc>

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-759/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-759/coif>). The authors

declare that they have no competing interests.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethics approval for this study protocol (version 1) was obtained from the Zhongshan Hospital Research Ethics Committee (No. B2021-703R) on November 16, 2020. Patients and/or the members of public will not be involved in this study's design, conduct, reporting, or dissemination plans. Written informed consent will be obtained from all the study participants. This study will conform to the provisions of the Declaration of Helsinki (as revised in 2013).

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References

- de Jong WK, Blaauwgeers JL, Schaapveld M, et al. Thymic epithelial tumours: a population-based study of the incidence, diagnostic procedures and therapy. *Eur J Cancer* 2008;44:123-30.
- Nakahara K, Ohno K, Hashimoto J, et al. Thymoma: results with complete resection and adjuvant postoperative irradiation in 141 consecutive patients. *J Thorac Cardiovasc Surg* 1988;95:1041-7.
- Turna A, Sarbay İ. Multimodality approach in treatment of thymic tumors. *J Thorac Dis* 2020;12:7626-34.
- Hejna M, Haberl I, Raderer M. Nonsurgical management of malignant thymoma. *Cancer* 1999;85:1871-84.
- Refaely Y, Simansky DA, Paley M, et al. Resection and perfusion thermochemotherapy: a new approach for the treatment of thymic malignancies with pleural spread. *Ann Thorac Surg* 2001;72:366-70.
- de Bree E, van Ruth S, Baas P, et al. Cytoreductive surgery and intraoperative hyperthermic intrathoracic chemotherapy in patients with malignant pleural mesothelioma or pleural metastases of thymoma. *Chest* 2002;121:480-7.

7. Ried M, Potzger T, Braune N, et al. Cytoreductive surgery and hyperthermic intrathoracic chemotherapy perfusion for malignant pleural tumours: perioperative management and clinical experience. *Eur J Cardiothorac Surg* 2013;43:801-7.
8. Yellin A, Simansky DA, Ben-Avi R, et al. Resection and heated pleural chemoperfusion in patients with thymic epithelial malignant disease and pleural spread: a single-institution experience. *J Thorac Cardiovasc Surg* 2013;145:83-7; discussion 87-9.
9. Yu L, Jing Y, Ma S, et al. Cytoreductive surgery combined with hyperthermic intrapleural chemotherapy to treat thymoma or thymic carcinoma with pleural dissemination. *Onco Targets Ther* 2013;6:517-21.
10. Ambrogi MC, Korasidis S, Lucchi M, et al. Pleural recurrence of thymoma: surgical resection followed by hyperthermic intrathoracic perfusion chemotherapy†. *Eur J Cardiothorac Surg* 2016;49:321-6.
11. Maury JM, Girard N, Tabutin M, et al. Intra-Thoracic Chemo-Hyperthermia for pleural recurrence of thymoma. *Lung Cancer* 2017;108:1-6.
12. Markowiak T, Neu R, Ansari MKA, et al. Surgical Cytoreduction and HITOC for Thymic Malignancies with Pleural Dissemination. *Thorac Cardiovasc Surg* 2021;69:157-64.
13. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
14. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.
15. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain* 2003;4:407-14.
16. Aprile V, Bacchin D, Korasidis S, et al. Surgical treatment of pleural recurrence of thymoma: is hyperthermic intrathoracic chemotherapy worthwhile? *Interact Cardiovasc Thorac Surg* 2020;30:765-72.
17. Vandaele T, Van Slambrouck J, Proesmans V, et al. Hyperthermic Intrathoracic Chemotherapy (HITHOC) for Pleural Disseminated Thymoma: A Systematic Literature Review. *Ann Surg Oncol* 2023;30:543-60.
18. Madias NE, Harrington JT. Platinum nephrotoxicity. *Am J Med* 1978;65:307-14.
19. Liu L, Zhang N, Min J, et al. Retrospective analysis on the safety of 5,759 times of bedside hyperthermic intra-peritoneal or intra-pleural chemotherapy (HIPEC). *Oncotarget* 2016;7:21570-8.
20. Ried M, Potzger T, Braune N, et al. Local and systemic exposure of cisplatin during hyperthermic intrathoracic chemotherapy perfusion after pleurectomy and decortication for treatment of pleural malignancies. *J Surg Oncol* 2013;107:735-40.
21. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-60.
22. Kato H, Ichinose Y, Ohta M, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med* 2004;350:1713-21.
23. Al-Batran SE, Homann N, Pauligk C, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer: The AIO-FLOT3 Trial. *JAMA Oncol* 2017;3:1237-44.
24. Markowiak T, Koller M, Zeman F, et al. Protocol of a retrospective, multicentre observational study on hyperthermic intrathoracic chemotherapy in Germany. *BMJ Open* 2020;10:e041511.
25. Ishibashi H, Kobayashi M, Takasaki C, et al. Interim results of pleurectomy/decortication and intraoperative intrapleural hyperthermic cisplatin perfusion for patients with malignant pleural mesothelioma intolerable to extrapleural pneumonectomy. *Gen Thorac Cardiovasc Surg* 2015;63:395-400.
26. de Bree E, van Ruth S, Schotborgh CE, et al. Limited cardiotoxicity after extensive thoracic surgery and intraoperative hyperthermic intrathoracic chemotherapy with doxorubicin and cisplatin. *Ann Surg Oncol* 2007;14:3019-26.
27. Kerscher C, Ried M, Hofmann HS, et al. Anaesthetic management of cytoreductive surgery followed by hyperthermic intrathoracic chemotherapy perfusion. *J Cardiothorac Surg* 2014;9:125.

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Figure S1 BR-TRG-I body cavity thermal perfusion therapy system equipment.

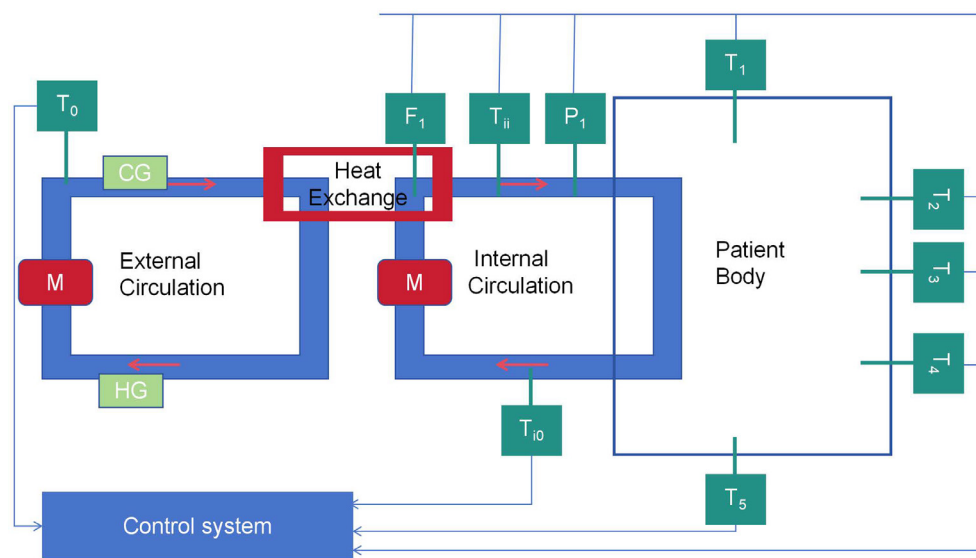


Figure S2 The overall structure of the system. BR-TRG-I body cavity thermal perfusion therapy system structure diagram description: HG, heater with a maximum power of 4 kW and an adjustable heating current; CG, semiconductor refrigerator: the maximum power is 2 kW, and its cooling power is adjustable; T_0 , the temperature of the water in the external circulation heat exchange area, with an accuracy of 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_{i0} , the temperature of the internal circulation liquid after it flows out of the human body, with an accuracy of 0.1 °C; F_1 , the flow rate of the internal circulation liquid, with an accuracy of 10 mL/min, and a resolution of 1 mL/min; P_1 , the pressure of the internal circulation liquid before entering the human body, with an accuracy of 10 mmHg, and a resolution of 1 mmHg; T_0 - T_5 , the temperature of five important parts of the human body; M_1 , the external circulation pump, running at a constant speed of 10 L/min; M_2 , the internal circulation pump; the speed can be controlled up to 600 mL/min; the accuracy is 10 mL/min; the resolution is 1 mL/min.