Systematic Review and Meta-Analysis

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Effect of hyperthermic intrathoracic chemotherapy (HITHOC) on the malignant pleural effusion

A systematic review and meta-analysis

Hua Zhou, MD[a], Wei Wu, MM[b], Xiaoping Tang, MM[a], Jianying Zhou, MM[a], Yihong Shen, MD[a,*]

Abstract

Background: Although hyperthermic intraperitoneal chemotherapy (HIPEC) has been widely used to treat malignant ascites or as a preventive strategy for microscopic carcinomatosis following surgical resection of abdominal tumors, application of hyperthermic intrathoracic chemotherapy (HITHOC) in the treatment of malignant pleural effusion is limited. The objective of the current study was to conduct a systematic review and meta-analysis on the application of HITHOC in the palliative treatment of malignant pleural effusion.

Methods: After thorough searching of online databases, total 27 articles were included into qualitative systematic review and 5 of them were used to conduct qualitative meta-analysis.

Results: It was found that most of HITHOC was used in combination of cytoreductive surgery (CRS) including pleurectomy/decortication or after surgical resection of primary tumors, which mainly were lung cancer, thymoma or thymic carcinoma, breast cancer, and ovarian cancer. Patients who received HITHOC had significantly longer median survival length compared to the patients without HITHOC (Hedges g = 0.763, $P < 0.001$). In addition, HITHOC therapy was favored (Hedges g = 0.848, $P < 0.001$) in terms of median survival length, tumor-free survival rate, with tumor survival rate or Karnofsky performance status (KPS) scale.

Conclusion: HITHOC is a safe and effective therapy in controlling pleural effusion and increasing patient's survival rate.

Abbreviations: CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy; HITHOC = hyperthermic intrathoracic chemotherapy.

Keywords: carcinomatosis, cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, hyperthermic intrathoracic chemotherapy, malignant pleural effusion, palliative treatment, survival

1. Introduction

Malignant pleural effusion is a common disease in the clinic, with an estimated annual incidence of at least 150,000 in the USA alone.[1] It has been estimated that 15% of all kinds of cancer patients will develop pleural effusion as a result of pleural metastasis of the primary cancers.[2] Patients with malignant pleural effusion have a poor prognosis and a low median survival rate, ranging from 6 to 18 months.[3] There is no standard treatment for patients with malignant pleural effusion. Recently, hyperthermic intrathoracic chemotherapy (HITHOC) in combination with surgery and systemic chemotherapy has been used for palliative local control of the malignant pleural effusion. Combination of intrapleural injection of cytotoxic drugs with hyperthermic perfusion may offer an additional benefit in that the tumor cells are exposed directly to higher concentration of chemotherapeutic agents, such as cisplatin, mitomycin c, whereas a lower incidence of systemic side effects of toxicity may be expected.

Although hyperthermic intraperitoneal chemotherapy (HIPEC) has already been widely used for controlling ascites or microscopic peritoneal carcinomatosis following surgical resection of abdominal cancers, application of HITHOC in the malignant pleural effusion treatment has not been widely used. Therefore, the objective of this study was to evaluate the efficacy, safety, and preliminary results of HITHOC in the treatment of malignant pleural effusion resulted from various kinds of primary cancers. To accomplish this, online databases were searched and 27 articles were enrolled into the current study for systematic review and 5 articles were used for meta-analysis.

2. Materials and methods

2.1. Ethics approval

Ethical approval was waived because the present study does not review any data related to human subjects.

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[a] Department of Respiration, The First Affiliated Hospital, Zhejiang University, Hangzhou, [b] Department of Radiology, Jilin Provincial Tumor Hospital, Changchun, China.

[*] Correspondence: Yihong Shen, Department of Respiration, The First Affiliated Hospital, Zhejiang University, No. 79 Qingchun Road, Hangzhou 310003, China (e-mail: zyyy_zh@163.com).

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2.2. Data sources

Relevant literature up to May 2016 was searched in the sites of PubMed, Embase, Cochrane library, and Web of Science with the following phrases: "hyperthermic intrapleural chemotherapy," "intrapleural hyperthermic," or "hyperthermic intrathoracic chemotherapy," or "HIPEC" and "lung," or "HITHOC". The search was limited to English and Chinese, and relevant studies were also identified by hand-searching the references of included articles.

2.3. Inclusion criteria

Studies were included in the current systematic review if: Clinical studies on the treatment of primary or secondary malignant pleural effusion using hyperthermic intrapleural or intrathoracic chemotherapy (HITHOC); ex vivo studies on the mechanism of HITHOC and human lung cancer; and studies with full text articles.

2.4. Data extraction

Information and data were carefully extracted from all included literature. Data include study name (the 1st author name), publication year, study design, total number of cases for HITHOC treatment and non-HITHOC treatment, median survival months, 1-year survival rate, 5-year survival rate, and adverse effect of HITHOC therapy.

2.5. Statistical analysis

The following forms of data were used for the data entry: median survival month, number of cases, and *P* value; event number in HITHOC treated, total number of the HITHOC treated, event number of the non-HITHOC treated, and total number of the non-HITHOC treated. The strength of HITHOC therapeutic effect on malignant pleural effusion was measured by Hedges g. A fixed effect model was adopted when no heterogeneity was observed among the studies. Otherwise, a random effect model was applied. The heterogeneity between studies was assessed by the Q-test and I^2 statistic, and $P<0.10$ and $I^2>50\%$ was considered as heterogeneous between the studies.[4] All meta-analysis was performed using the Comprehensive Meta-analysis software (Version 3, NJ).

3. Results

3.1. Study features

The process of selecting literature and final selection was outlined as in Fig. 1. After careful reading "abstract" of publications, total 45 full-text articles were retrieved. The retrieved full-text articles were then independently assessed by 2 investigators (XT and JZ). As shown in Tables 1 and 2, total 5 articles were included in the meta-analysis (quantitative synthesis)[5–9] and 22 articles were included in the systematic review (qualitative synthesis). Among the 27 articles for systematic review and meta-analysis, 4 articles were from Japan,[5,6,10,11] 4 articles from China,[7,9,12,13] 4 articles from Italy,[14–17] 4 articles from Netherlands,[18–21] 3 articles from USA,[22–24] 3 articles from Germany,[25–27] 2 articles from Israel,[28,29] 1 from Turkey,[8] 1 from Australia,[30] and 1 from Korea.[31] The earliest was reported in 1995 by Matsuzaki et al from Japan (Matsuzaki, 1995], and the latest, up to May 2016, was from China by Liu et al[13] and from Italy by Ambrogi et al.[17]

Most commonly used agent for HITHOC was cisplatin followed by doxorubicin or mitomycin C, and the temperature applied for hyperthermic therapy was between 38 and 43 °C (Tables 1 and 2). Malignant mesothelioma, thymoma or thymic carcinoma, and lung cancer were the most common primary tumor for pleural malignancies.

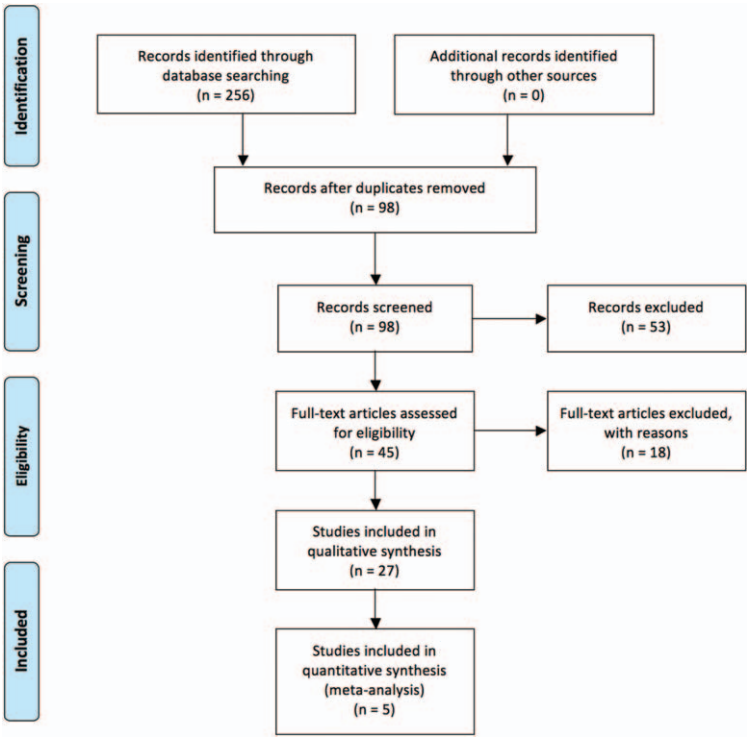

Figure 1. Flow diagram of literature search and eligible publication selection.

Table 1

Studies included in the quantitative meta-analysis.

First author	Year	Country	Study arms	N	Median survival	Other effect
Matsuzaki	1995	Japan	CRS + HITHOC	12	20	100%*
			vs CRS + precentesis	7	6	0
Matsuzaki	2004	Japan	CRS + HITHOC	11	20	25.2 ± 4.6%†
			vs CRS + precentesis	11	6	2.8 ± 2.0%
Ba	2013	China	HITHOC (48 °C)	12	13	23.13‡
			HITHOC (45 °C)	11	12.9	23.37
Isik	2013	Turkey	CRS + HITHOC	19	15	54.7%§
			vs Talc pleurodesis	13	6	0.6%
			or pleurectomy	12	8	0.8%
Zhang	2015	China	EGFR + HITHOC	9	24	4 (44%)‖
			vs non-EGFR + HITHOC	23	16	1 (4%)
			vs systemic chemo only	21	4	0

CRS = cytoreductive surgery, EGFR = epithermal growth factor receptor positive, HITHOC = hyperthermic intrathoracic chemotherapy.
* Pleural effusion control rate.
† Apoptosis rate.
‡ Karnofsky performance status scale.
§ 1-year survival rate.
‖ Tumor free-survival rate.

3.2. Efficacy of HITHOC

Of the 27 articles selected for systematic review, 5 were studied with randomized control, 15 studies reported efficacy of HITHOC without comparison to non-HITHOC treatment, 4 studies reported pharmacokinetics of chemotherapeutic drugs in the pleural cavity, 1 article was ex vivo study of penetration of chemotherapeutic drugs into lung tissue, and 1 was in vitro study on sensitivity of hyperthermic chemotherapeutic drugs on cell lines of pleural mesothelioma or other lung cancer, and 1 article reported experience of anesthesia during cytoreductive surgery (CRS) and HITHOC.

Results of the quantitative meta-analysis of the 5 RCT articles showed that average of the median survival length was significantly longer in the patients treated with HITHOC compared to the patients without HITHOC therapy (Hedges $g = 0.763$, $P < 0.001$, Fig. 2), and that HITHOC therapy was favored (Hedges $g = 0.848$, $P < 0.001$) in terms of 1-year overall survival rate, tumor-free survival rate, with tumor survival rate, or Karnofsky performance status scores, etc. (Fig. 3).

Of the 22 noncontrolled clinical studies, while 1 study reported that HITHOC did not have advantage compared to non-HITHOC therapy,[21] the rest 21 studies indicated that HITHOC seemed to be able extend patients' life. For instance, Yellin et al[28] treated 26 patients (7 mesothelioma, 11 thymoma, and 8 other cancers) with malignant pleural effusion with cisplatin-HITHOC and found that 1-year overall survival (OS) rate was 72%, 2-year OS was 65%, and 3-year OS was 44%. Investigators of the same group also reported that 3-year OS and 5-year OS in the 10 patients of thymoma were 90% and 70%, respectively, after the patients were given intraoperative HITHOC during the surgical resection.[29] Most recently, Ambrogi et al[17] from Italy reported that mean survival was 58 ± 34.4 months and 5-year survival was 92% for the 13 consecutive patients with pleural recurrence of thymoma who were treated with complete reductive surgery (CRS) + HITHOC.

3.3. Side effects of HITHOC

Although most of the 27 articles enrolled into the current systematic review and meta-analysis reported that there was no perioperative or HITHOC-associated mortality, 1 study by Yellin et al[28] reported that 1 patient died of complications related to technical error. In addition, morbidity associated with CRS + HITHOC was reported in several noncontrolled studies. For instance, Yellin et al[28] reported 8 out of 26 cases suffered from complications including empyema, thrombocytopenia, bleeding, and air leak; other morbidities such as atrial fibrillation, pulmonary emboli, chest pain, fever, dyspnea, bronchopleural fistula, and pneumothorax have also been reported.[13,14,19,20,28]

Most recently, Liu et al[13] from China retrospectively analyzed the safety of bedside hyperthermic intraperitoneal chemotherapy (HIPEC) and HITHOC. From September 2007 to July 2015, Liu et al has performed 5759 times of bedside HIPEC or HITHOC in 985 cases of malignant peritoneal carcinomatosis or pleural malignancies. Of them, 1510 times was HITHOC for 315 cases of malignant pleural effusion, with an average of 5 times HITHOC for each patient. They reported that overall HIPEC- or HITHOC-associated mortality was zero. However, overall HITHOC-associated incidence of adverse effect was 2.0% specifically, 0.6% pneumothorax, 0.3% cytotoxic agent-induced pleural inflammation, 0.5% pain at puncture location, and 0.3% failure of HITHOC procedure.[13]

3.4. Pharmacokinetics of cytotoxic agents during the HITHOC

Of the 27 articles enrolled into the current study, 4 articles reported on the pharmacokinetics of cytotoxic agent applied in the HITHOC,[14,22,23,26] and 2 articles were ex vivo or in vitro studies on the potential mechanisms of hyperthermic chemotherapy.[16,24]

Lombardi et al[14] reported that intrapleural paclitaxel concentrations were very high (478 ± 187 mg/L, N = 18) after injection of 120 mg/m^2 paclitaxel, which declined slowly (mean 24 hours reduction ~30%), and detectable but low taxol plasma levels were found in most of the patients (0.045 ± 0.073 mg/L). Sugarbaker et al[22,23] reported that approximately 41% of mitomycin C or 72% of doxorubicin were absorbed by thoracic cavity, while 75% mitomycin C or 90% doxorubicin were absorbed by abdominal cavity. However, there was a considerably more rapid clearance from the abdomen as compared to the thorax.[23] They also observed a persistently high concentration

Table 2

Studies enrolled for qualitative and systematic review.

First author	Year	Country	Study design	Primary tumors	Median survival	1 year OS	3 year OS
Yellin	2001	Israel	CRS+ HITHOC (38 °C)	7 MPM 11 thymoma 8 others	26 m	72%	44%
Refaely	2001	Israel	CRS+ HITHOC (40.3–43 °C)	10 thymoma 4 TC 1 CT	?	70%* 90%†	55%* 70%†
de Bree	2002	Netherlands	CRS+ HITHOC	11 MPM 3 thymoma	1 m		
van Ruth	2003	Netherlands	CRS+ HITHOC	22 MPM	11 m	42%	
Shigemura	2003	Japan	Thoraciscopic HITHOC	5 Lung ca	19 m	Longest 32 months	
de Bree	2007	Netherlands	CRS+ HITHOC	13 MPM	?	Limited side effects	
van Sandick	2008	Netherlands	CRS+ HITHOC+ Radiotherapy	20 MPM	11 m	70% complications	
Chua	2009	Australia	CRS+ HITHOC	5 PMP	One died at 38 m, 4 alive 4.6–47.4 m 2 peritoneal recurrence		
Lombardi	2012	Italy	Pharmacokinetics	11 Ovarian 7 breast ca	8.9 m chest pain, fever, dyspnea were frequent side effects		
Sugarbaker	2012	USA	Pharmacokinetics	25 MPM	Mitomycin C and doxorubicin		
Sugarbaker	2012	USA	Pharmacokinetics	5 PMP	HITAC		
Ried	2013	Germany	Pharmacokinetics	5 MPM 5 thymoma	Cisplatin to 150 mg/m^2 was safe		
Ried	2013	Germany	CRS+ HITHOC (42° × 60 minutes)	8 MPM 8 thymoma	22 m		
Yu	2013	China	CRS + HITHOC (42 °C × 2 hours)	4 Thymoma	Followed up for 1–4 years, 1 diedof heart failure 1 year after No local recurrence or metastases		
Cameron	2013	USA	In vitro study	6 Different cell lines tested	Using 2 drugs combination seems most effective		
Kerscher	2014	Germany	Anesthesia for	Summarized experiences of anesthesia and intensive care			
Ishibashi	2014	Japan	CRS+ HITHOC	4 MPM	One recurrent 11 m after; Other 3 survived 23–41 m without recurrent disease		
Migliore	2015	Italy	CRS+ HITHOC	6 MPM	Mean survival 13.6 m 2 AC		
Moon	2015	Korea	CRS+ HITHOC	11 Breast 10 Lung ca 6 ovarian 7 others	3- and 7-month recurrence-free rates were 86.9% and 73.9%		
Ried	2015	Italy	In vitro penetration study		The median penetration depth of Cisplatin was about 3–4 mm		
Liu	2016	China	Bedside HITHOC	1510 times malignant pleural effusion	HITHOC for 315 cases of Safety study 0% mortality, 0.6% pneumothorax		
Ambrogi	2016	Italy	CRS+ HITHOC	13 Thymoma 47.2 ± 25.5 m	Disease-free interval: Mean survival: 58 ± 34.4 m 5-year actuarial survival: 92%		

AC = adenocarcinoma, CRS = cytoreductive surgery (including pleurectomy and decortication), CT = carcinoma in thymic cyst, HITHOC = hyperthermic intrathoracic chemotherapy, MPM = malignant pleural mesothelioma, OS = overall survival, TC = thymic carcinoma.

* For entire 15 cases.

† For thymoma only.

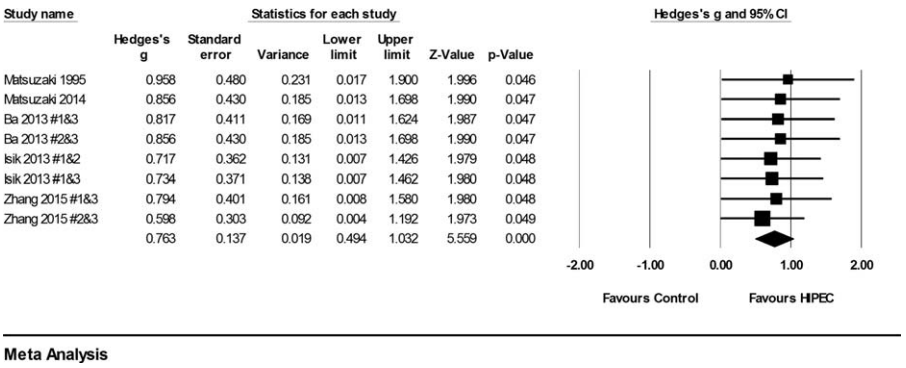

Figure 2. Forest plot for median survival length. A fixed effect model was used due to nonsignificant heterogeneity of publications ($I^2 = 0.01\%$, $P = 0.99$). Effect size was assessed by Hedges g and 95% CI, and the median survival length was in favors HITHOC (Hedges g = 0.763, $P < 0.001$). Ba #1: patients treated with B-ultrasound-guided intrapleural hyperthermic perfusion with 48 °C distilled water; Ba #2: patients treated with B-ultrasound-guided intrapleural hyperthermic perfusion with 45 °C physiologic saline solution plus cisplatin; Ba #3: patients without HIPTHOC. Isilk #1: patients treated with HITHOC following surgical intervention; Isilk #2: patients treated with talc pleurodesis followed by systemic treatment; Isilk #3: patients treated with pleurectomy/decortication followed by systemic treatment. Zhang #1: patients were EGFR positive and treated with HITHOC; Zhang #2: patients were EGFR negative but treated with HITHOC; Zhang #3: patients were not treated with HITHOC. EGFR = epithermal growth factor receptor positive, HITHOC = hyperthermic intrathoracic chemotherapy.

of intrapleural drugs as compared to plasma concentrations when the patients were given HITHOC.[22] Similarly, Ried and coworkers[27] from Italy reported that the mean area under curves (AUCs) of cisplatin in the perfusate were approximately 55 to 58 times greater than detected in the serum, and found that elevation of the cisplatin dosage to 150 mg/m^2 did not lead to a significant increase of the systemic cisplatin concentration.

Using different cell lines and in vitro culture experiments, Cameron and Hou[24] reported that hyperthermia (42 °C) plus cisplatin alone modestly reduced the clonogenic potential of the lung cancer cells, and found that hyperthermic intrapleural chemotherapy seemed to be most effective when using 2-drug combinations. Although intrapleural administration of cytotoxic drugs could significantly increase local concentration of the drugs, the limited tissue penetration of the drugs is a disadvantage of intrapleural chemotherapy. In this regard, using the lung tissues obtained from 12 patients underwent pulmonary wedge resections, Ried et al[16] investigated the penetration of cisplatin depth and per tissue concentration of cisplatin. They found that cisplatin penetrated into the human lung tissue at ex vivo hyperthermic exposure (cisplatin: 0.05 mg/mL; 60 minutes, 42 °C), and the depth was approximately 3 to 4 mm.[16]

4. Discussion

The optimal treatment of primary and recurrent malignant pleural effusion still remains an open and critical question. Malignant pleural effusion has a high rate of recurrence, thus, identification of the best treatment to prolong the time to progression and extend overall survival while maintain the patient's quality of life is one of the main objectives for pulmonary oncologists. Recently, HITHOC has been applied during or after a complete or partial CRS. In the current study, we presented systematic review and meta-analysis on 27 articles to determine the effect of HITHOC on controlling disease progress of pleural effusion and potential adverse effects. After searching online databases, extracting relevant statistical data and performing meta-analysis, and systematic review, we found that HITHOC has dramatic effect on extending patient's median survival length and 1 to 5 year survival rate, especially in the

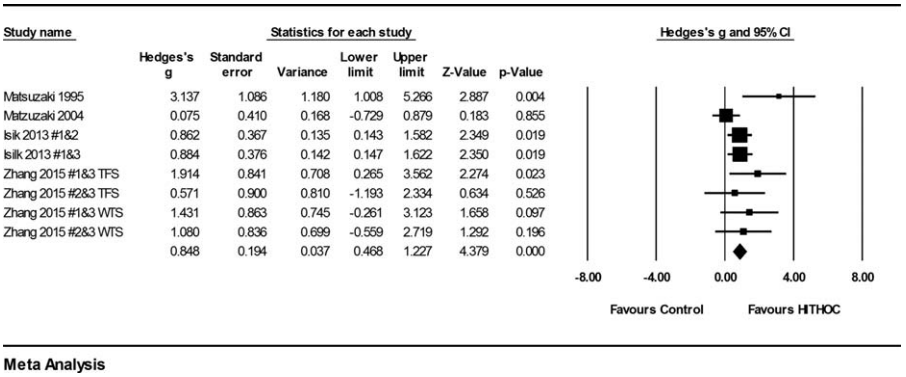

Figure 3. Forest plot for efficacy of HITHOC. A fixed effect model was used due to significant heterogeneity of publications ($I^2 = 31.23\%$, $P = 0.179$). Effect size was assessed by Hedges g and 95% CI, and the efficacy of the treatment was in favor of HITHOC therapy (Hedges g = 0.848, $P < 0.001$). Matsuzaki studies: response rate and apoptosis rate comparison. Isilk study: comparison of 1-year overall survival rate. Zhang study: comparison of TFS rate and WTS rate. HITHOC = hyperthermic intrathoracic chemotherapy, TFS = tumor free survival, WTS = with tumor survival.

patients with thymoma. HITHOC during or following CRS is a safe and effective therapy to control malignant pleural effusion.

Through the systematic review of the 27 articles included in the current study, we found that, in addition to mesothelioma, the most common primary sites which metastasis to the pleura are lung cancer, thymoma, breast cancer, and ovarian cancer. Although 1 study indicated that HITHOC had no advantage in the treatment of malignant mesothelioma, the rest of studies reported that patients with MPE benefited from the HITHOC treatment. Meta-analysis results of 5 studies also indicated that combination of thoracic CRS, which allows maximal removal of macroscopic tumor and HITHOC, which allows direct delivery of the cytotoxic agent to the tumor cells, provides patients with a long-term survival.

Most popular cytotoxic drugs used for HITHOC are cisplatin followed by doxorubicin and mitomycin C, and 41 to 43 °C was most commonly used in HITHOC. Intrapleural chemotherapy allows for a much higher concentration in the thoracic cavity compared to intravenous chemotherapy, thereby improving cytotoxicity while minimizing systemic adverse effect. Pharmacokinetic studies of the cytotoxic drugs used for HITHOC indicated that a persistently high concentration of intrapleural drug can be achieved when the patients were given HITHOC, and that cytotoxic drugs can penetrate into lung tissue 3 to 4 mm. Thus, the ability of penetration of cytotoxic drugs (such as cisplatin) into the lung tissues may improve the local therapy of residual microscopic tumor cells on the lung surface with the use of HITHOC in patients with malignant pleural tumors after lung-sparing radical tumor resections

Kerscher et al[27] reported their experiences of the anesthesia and intensive care management in patients undergoing HITHOC, and they indicated that anesthesia during the procedure of CRS + HITHOC may lead to unexpected side effects including high pressure of intrathoracic and central venous system, and potential risk of systemic hyperthermia. They further reported an impairment of coagulation in postoperative laboratory analysis in 2 out of 20 patients (10%).[27] Although most cases of HITHOC were performed during CRS and patients were under systemic anesthesia, Liu et al[13] reported a procedure of bedside HITHOC. They used local anesthesia and puncture technology, and thus the patients remained awake during the whole HITHOC procedure. In addition, repeated HITHOC was performed in the same patient in that neither systemic anesthesia nor complicated surgical procedure was required. Unique advantage of their HITHOC was that the procedure was performed in a treatment room (not in an operation room) with local anesthesia and puncture technique.

The combination of heat and cytotoxic drugs dramatically increase capacity of destroying cancer cells through several mechanisms.

(1) The combination of heat and cytotoxic drug treatment results in increased membrane permeability and improved membrane transport.
(2) Heat may alter cellular metabolism and change drug pharmacokinetics and excretion, both of which can increase the cytotoxicity of certain chemotherapeutic agents.[20]
(3) Heat increases drug penetration in tissue in a temperature-dependent manner.[32,33]

In this regard, evidence from experimental and clinical studies indicated that malignant cells are selectively killed by hyperthermia in the range of 41 to 42 °C.[34–36] Heat not only inhibits RNA synthesis and mitosis arrest, but also increases the number of unstable lysosomes with increased destructive capacity. In addition, malignant cells are more sensitive to heat compared to the normal cells and thus, malignant cells undergo apoptosis at 41 to 43 °C while normal cells are able to survive.[37]

The major limitation of the current review is that only 5 studies were eligible for the meta-analysis and case numbers included in each study was small. In addition, techniques of HITHOC used in the 27 articles are heterogeneous including difference of cytotoxic drug and their concentration, equipment used for HITHOC, volume and temperature of the perfusion solution, and circulation duration, etc. Thus, it is in urgent situation to standardize the method of HITHOC in the clinical application. Although a large number of randomized and controlled clinical trials are necessary to further confirm the therapeutic advantage of HITHOC in the treatment of malignant pleural effusion, findings of the current systematic review and meta-analysis indicate that HITHOC is an effective and safe therapeutic procedure for extending patient's life and controlling disease progress.

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