Hypertermic Intrathoracic Chemotherapy (HITHOC) for thymoma: a narrative review on indications and results

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Objective: With this narrative review, we retraced the history of hypertermic intrathoracic chemotherapy (HITHOC) since the beginning, analyzing literature on operative technique, feasibility and efficacy of this treatment. Moreover, we report the fifteen-year experience of our center in this relatively new technique, for what concerns both early postoperative results and long-term oncological outcomes.

Background: Thymomas are frequently misdiagnosed and recognized in advanced stage, often with pleural dissemination, especially when not associated to Myasthenia Gravis that allows an early diagnosis during the initial assessment. Moreover, the natural history of locally advanced thymoma is characterized by a high rate of pleural or pericardial relapses. Surgery has always been considered a milestone in thymoma's treatment, even in case of serous dissemination or relapses, although his role as exclusive therapy does not guarantee an acceptable local disease control. In case of disseminated disease, different multidisciplinary protocols have been experimented, from chemotherapy to radiation therapy, alone or associated to surgery, in order to increase overall and disease-free survival, but the breakthrough happened in the early 90s with the introduction of HITHOC following surgery. Combination of surgery and HITHOC resulted in less toxic than systemic chemotherapy and providing a good local disease control in patients with stage IVa thymomas or thymoma's pleural recurrences.

Methods: We searched PubMed for relevant literature, up to January 2020, on hypertermic intrapleural chemotherapy for thymomas (TPR or DNT), selecting only those reporting information about HITHOC protocol used, postoperative course and oncological outcomes.

Conclusions: HITHOC is a safe and feasible procedure, with a very low complication rate and negligible systemic effects of chemotherapeutic agents, effective in controlling both TPR and DNT, in particular as regards local disease-free survival.

Keywords: Hypertermic intrathoracic chemotherapy (HITHOC); thymoma; intracavitary chemotherapy; hyperthermia; redo-surgery

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Introduction

Pleural dissemination of thymoma

Thymomas are tumors arising from the thymic epithelial cells involved in directing T-cells maturation and, although rare, represent more than half of the anterior mediastinal lesions (1). They are characterized, in most cases, by an indolent behavior consisting in a tendency to local invasion and spreading along the surroundings serous membranes rather than to lymph nodes or distant organs, that are detectable in less than 5% of cases (2). Surgical resection plays a fundamental role in the management of thymomas, not only for those diagnosed in early stage, but also in advanced stage ones, often as a part of multimodal strategy (3). More in details, for resectable advanced stage thymomas, surgery with radical intent followed by postoperative radiotherapy is highly recommended whereas adjuvant chemotherapy may be administered in cases of incomplete resection. On the other hand, those initially defined as unresectable, may benefit from trimodal therapy including upfront chemotherapy, followed by surgery and/or radiotherapy, according to the level of downstaging achieved (4).

Pleural and pericardial implants may both be detected as initial presentation of stage IVa (according to Masaoka and TNM staging system), that accounts for less than 10% of all thymomas, or during the surveillance as recurrence in up to 30% of radically resected thymomas (5). In most cases, stage IVa lesions or recurrences, although spread only along the pleura, appear as multiple and diffuse droplet metastases and, consequently, surgery alone has been proven to be ineffective to achieve an efficient local control with a reported complete resection in less than two-thirds of cases, even in case of extended resection such as pleuropneumonectomy (6-8).

Due to its low incidence, the literature regarding treatment of thoracic implants or recurrences is scarce and highly heterogenous, whereas different treatment protocols, combined or not with surgery, are proposed (9). In this scenario, development of the hyperthermic chemotherapy perfusion of chest cavity emerged as new procedure to improve the local control of disease and, more generally, the oncological outcomes. Our aim is to review the current literature on this topic, analyzing pros and cons of HITHOC usage in thymomatous patients.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/atm-20-6704).

HITHOC

Hypertermic intracavitary chemotherapy: an overview

Local administration increases the efficacy of some chemotherapeutic agents by achieving high levels of drugs in the target tissues and, as consequence, reduces systemic toxicity. Since 1967 many authors reported the effects of moderate hyperthermia (41–43 ℃) both on *in vitro* and *in vivo* tumoral cells (10). These studies demonstrated that malignant cells have selected heat sensitivity mediated by various mechanisms such as nucleic acids and protein synthesis alterations, mitotic arrest, depression of aerobic tumor cells metabolism and an increased lysosomal activity that lead to cytoplasmatic damage. On these bases, in 1977 Overgaard speculated on the association between hyperthermia with irradiation and/or chemotherapy as an effective synergism against many types of cancer (11).

Hyperthermia increases the local effect of chemotherapeutic agents by enhancing penetration depth and cytotoxicity and by making endothelial cells of tumor vascularization more permeable. Moreover, this combination activates immune system response against tumor cells, through various mechanisms such as by activating heat shock proteins and releasing exosomes which stimulate natural killer and CD8+ T cells (12,13).

Intracavitary thermochemotherapy following surgical resection was firstly applied to peritoneal carcinomatosis and then extended to the thoracic oncologic field: in those cases, in which surgery alone may not achieve microscopically complete resection, cytoreductive surgery combined with intracavitary chemotherapy has increasingly gained attention (14). Nowadays, HITHOC is a widespread treatment for pleural and abdominal carcinomatosis originating by various types of cancer, in order to allow a better local disease control and to avoid highly demolitive resections, with a low systemic effects rate due to minimal absorption of drugs by serous membranes (15).

Indications of HITHOC

In thoracic surgery field, HITHOC is performed since the 90s, mostly in case of malignant pleural mesothelioma (MPM) and pleural spread of thymoma (stage IVa de novo thymoma, DNT, or pleural recurrences, TPR), even if its use for unilateral pleural carcinomatosis due to lung cancer or other primitive tumors as well as for rare pleural disease as the solitary fibrous tumor are also described by some authors (16-18).

Selected patients affected by MPM may benefit from surgery followed by HITHOC especially in case of epithelioid or mixed histology and early stage according to IMIG classification (namely tumor confined to a hemithorax, that involves only the parietal pleura with or without involvement of the ipsilateral visceral pleura) (19). Despite the availability of several treatments for MPM, alone or combined (surgery, intrathoracic and systemic chemotherapy, radiation therapy, immunotherapy), survival rates are still underwhelming. In fact, due to a common late diagnosis, the impaired physical condition and the coexistence of multiple comorbidities, only few patients could be addressed to a multimodal treatment approach; whereas surgery alone is ineffective to achieve a complete resection, due to the laminar tumor growth within the entire pleura (20).

However, in a systematic review and meta-analysis of 2017, Zhao *et al.* showed how, in the setting of a multimodal treatment, HITHOC seems to prolong disease-free survival (DFS) and overall survival (OS) (21).

On the experience developed in MPM, HITHOC following a macroscopic complete resection has gained an increasingly wider consensus as part of a multimodal strategy also in case of intrathoracic stage IVa thymomas or unilateral TPR after primary tumor excision, with encouraging results such as longer local DFS and a lower re-recurrence rate (22). The main aim of this procedure is always to increase the local effect of surgery by killing potential residual tumoral cells and to avoid the common side effects of chemo or radiation therapy (23). The main indication is the presence of non-bulky resectable tumoral implants confined in a hemithorax in patients judged fit for surgery; although, several authors stated that HITHOC should be avoided in case of presence of intraoperative resection of the pericardium that could not be reconstructed by suturing or patching, intraoperative opening of the contralateral pleural space or major diaphragmatic reconstruction (for the risk of chemotherapeutic agents leaking), large decortications, that could affect drugs absorption, and, lastly, in case of severe impairment of hepatic, cardiac or renal function (24).

Perfusion technique

In most cases, surgery and HITHOC are planned in a multidisciplinary setting usually including oncologists, surgeons, anesthesiologists, radiotherapists, and neurologists in presence of Myasthenia Gravis. Respiratory and cardiologic evaluation is then performed, to establish patients' suitability, while peri-operative intravenous hydration and corticosteroids are eventually administered, according to each Center protocols, to minimize HITHOC early side effects (24).

HITHOC is performed mostly intraoperatively under general anesthesia after the surgical procedure, even if Liu *et al.* in 2016 described their experience on bedside application that could be repeated in the same patient, with a very low morbidity rate (2%) (25). Perfusion is generally started after surgical treatment, ranging from the resection of the single implants to partial pleurectomy (PP), pleurectomy/decortication (P/D), even to extrapleural pneumonectomy (EPP) (23). Surgical approach is usually based on patient's status and tumor histology and extension. A perfusion dedicated system is connected to the patient through the pleural drains and, after starting circulating, perfusion saline isotonic solution is heated up to the target temperature (in literature is described a set point between 40 and 45 °C). Then, chemotherapeutic drugs are injected into the circuit by the inflow catheter, let circulate for about 60 to 120 minutes and subsequently washed out from the outflow catheter by reversing the circuit flow (24-28).

Chemotherapy regimens used

Many authors described their experience with intracavitary hyperthermic chemotherapy (*Table 1*), but still there is no consensus about the most appropriate chemotherapeutic regimen. However, the drugs of choice are generally Cisplatin, Anthracyclines and Mitomycin, due to their direct cytotoxic activity.

Cisplatin is the most HITHOC used drug, at a mean dosage of 100 mg/m^2 in accordance with the single Center protocol and the eventual association with other agents.

Rusch *et al.* presented in 1992 a prospective phase II trial about treatment with normothermic perfusion of Cisplatin (100 mg/m^2) and Mytomicin (8 mg/m^2) in 12 MPM patients. They found out that both drugs reached higher concentration in the pleural fluid than plasma (from 3- to 5-times higher on a logarithmic scale), even if drugs' half-lives were significantly longer in plasma than pleural fluid. This last finding supports the need to adopt the same precautions of intravenous chemotherapy administration (e.g., pre-hydration) to minimize the risk of nephrotoxicity (29).

Ratto and colleagues in 1999 published a study on feasibility and pharmacokinetic in 10 MPM patients

Table 1 Various HITHOC protocols used for patients affected by TPR or DNT

Author (year)	Drugs (dosage mg/m^2)	Target temperature (℃)	Perfusion time (minutes)	Number of pleural catheters
Yellin (2001)	Cisplatin [100–200]	40.2–41.5	60	2 (1 inflow, 1 outflow)
Refaely (2001)	Cisplatin [100–200]	40.3–45	60	2 (1 inflow, 1 outflow)
de Bree (2002)	Cisplatin [50–80]; Doxorubicin [15–25]	40–41	90	4 (1 inflow, 3 outflow)
Ried (2013)	Cisplatin [100–150]*	42	60	3–5 (1–2 inflow, 2–3 outflow)
Yellin (2013)	Cisplatin [100] Doxorubicin [50–60]**	45	60	2 (1 inflow, 1 outflow)
Yu (2013)	Cisplatin [100]	42–43	120	2 (1 inflow, 1 outflow)
Ried (2014)	Cisplatin [100–150]	42	60	3–5 (1–2 inflow, 2–3 outflow)
Maury (2017)	Cisplatin [50]; Mitomycin [25]	42	90	2 (1 inflow, 1 outflow)
Aprile (2020)	Cisplatin [80]; Epirubicin [25]	42	60	2 (1 inflow, 1 outflow)

*150 mg/m^2 used only in the last two procedures; **used since 2002. HITHOC, hypertermic intrathoracic chemotherapy; TPR, pleural recurrences; DNT, de novo thymoma.

treated with surgery associated to hyper- or normothermic Cisplatin perfusion. They found out that the local tissue/perfusate ratio of platinum concentrations tended to be higher after hyperthermic perfusion rather than normothermic perfusion. Like other authors before, they also noticed a platinum concentration in the pleural space 3- to 5-times higher than the plasmatic one and no platinum-related toxicity was observed (30).

In 2013, Ried *et al.* compared two groups of patients affected by MPM or stage IVa thymoma, who received HITHOC with Cisplatin 100 mg/m^2 (1st group, 5 patients) and 150 mg/m^2 (2nd group, 5 patients), finding out that increasing the baseline dosage was not associated to elevation of serum platinum concentration, even if three patients exposed to the higher dosage reported nephrotoxicity. The mean peak of cisplatin in the serum was reached after 60 minutes of HITHOC. They encountered also lower platinum concentrations in patients underwent pneumonectomy rather than pleurectomy/decortication; this fact may indicate that lung parenchyma has a great role in drugs absorption (15).

Doxorubicin, instead, is a pharmacokinetically advantageous drug for intraperitoneal administration, due of its high molecular weight together with hydrophilic properties, that allows a slow peritoneal clearance acting at higher concentration on tumor cells implanted in the peritoneal cavity (31).

In 1998 a mice model set by Jacquet *et al.* showed that, after intraperitoneal administration of Doxorubicin at 37 and 43 ℃, there were no differences between drug plasmatic concentrations in the two groups but, in the hyperthermia group, Doxorubicin and its metabolites reached a greater tissue distribution in some abdominal organs frequently interested by metastases such as omentum, spleen, liver (32).

Van Ruth and colleagues performed in 4 years (1998–2001) 24 HITHOC for MPM using Cisplatin (80 mg/m^2) and Doxorubicin (15–35 mg/m^2) for 90 minutes of perfusion at 41 ℃. They focused their attention mostly on Doxorubicin pharmacokinetics, finding out high local concentrations with minimal systemic uptake; for what concerns Cisplatin concentrations in plasma and pleural fluid, they confirmed previous studies' results. Regarding chemotherapy side-effects, they encountered only one case of transient platinum-related nephrotoxicity probably related to inadequate perioperative hydration (33).

Mitomycin is scarcely used in these settings; Sugarbaker *et al.* analyzed pharmacokinetics of this drug (15 mg/m^2) in combination with Doxorubicin (15 mg/m^2) in three groups of patients underwent intraperitoneal, thoracoabdominal and intrathoracic hypertermic chemiotherapy perfusion (HIPEC; HITAC and HITHOC, respectively) for various types of cancer. In this regard, major finding was the lower

absorption of drugs in the HITHOC group; this led the authors to speculate that the same dosages used for HIPEC should be administered safely also in HITHOC (34).

Methods

Relevant literature up to January 2020 was searched in PubMed using as keywords: "hyperthermic intrapleural chemotherapy," "intrapleural hyperthermic," or "hyperthermic intrathoracic chemotherapy," or "HIPEC" and "thymoma," or "HITHOC". The search was limited to English language and relevant studies were identified, screened and reviewed by all the authors.

We conducted an accurate research of all studies focused on the outcomes of HITHOC in TPR or DNT published in the last two decades, and we selected only those with information about HITHOC protocol proposed and information on postoperative course as well as oncological outcomes (*Table 2*). Unpublished material, congress abstracts, and proceedings were not considered.

Results

In 2001, Yellin and colleagues published their experience on HITHOC in 27 patients affected by various tumors (of whom, 7 with DNT). They used Cisplatin beginning with a minimum dosage of 60 mg/m^2 up to 200 mg/m^2 at about 41 °C for 1 hour. There was no technical problem or hemodynamic instability during the perfusion. Regarding HITHOC toxicity, only one patient developed thrombocytopenia; there were described also nausea and non-infectious fever. After a mean follow-up of 60.2 months, 5 thymoma patients were alive without disease, one patient died for thymoma's systemic progression and another one died because of leukemia. The authors concluded that surgery associated to HITHOC may improve OS and DFS in patients affected by advanced stage thymoma (26).

In the same year, Refaely *et al.* investigated the role of HITHOC in 15 patients affected by stage IVa thymoma (10 patients) or thymic carcinoma (5 patients). Surgical resection was radical in 7 DNT patients, while 3 patients had positive resection margins (1 R1 and 2 R2). HITHOC protocol provided Cisplatin at a dosage between 100 and 200 mg/m^2 at about 43 °C for 1 hour. The procedure was devoid of complications and the authors did not report any platinum-related toxicity. Cumulative survival rates for thymoma patients were 90% at 3 years from surgery (one patient died within this period for disease progression) and 70% at 5 years. In conclusion, the author hypothesized that macroscopic complete resection of primitive thymoma and of all pleural implants followed by intraoperative HITHOC may improve OS and local disease control (35).

de Bree *et al.* in 2002 treated 14 patients (3 for TPR an 11 for early-stage MPM) with HITHOC, using a combination of Doxorubicin (15 to 25 mg/m^2) and Cisplatin (80 mg/m^2) at 40–41 °C for 90 minutes. In one case, TPR resection margins were R1 and the patient was then treated with adjuvant radiotherapy. Another patient presented a contralateral recurrence after 13 months, treated with surgery and HITHOC again. OS after a mean follow-up of 18 months was 100%. One patient presented nephrotoxicity as platinum-related side-effect. To sum up, the Dutch group postulated that HITHOC was feasible in patients with pleural metastases of thymoma and early-stage MPM, and associated with an acceptable morbidity rate, and it might provide an improved locoregional disease control (27).

In a 2013 study, Ried and colleagues reported their early experience on 16 patients (8 with stage IVa DNT, 8 with MPM). Thymoma's patients were operated on in two times (firstly by median sternotomy to resect primary tumor, then by thoracotomy to remove pleural metastasis). P/D was performed in all cases, with the intent to achieve a macroscopically complete resection of the tumor, followed by intraoperative HITHOC with Cisplatin (100 mg/m^2 for 60' at 42 °C). Four thymoma's patients already underwent neoadjuvant chemotherapy (CT) and three of them also received adjuvant chemotherapy. Adjuvant CT was administered also in other three patients that did not receive any induction treatment. All procedures were completed without any complication, even though severe postoperative morbidity occurred in two patients (pneumonia and sepsis, treated with pneumonectomy, and axillary and subclavian venous thrombosis). The authors examined oncological outcomes and, for what concerns DNT patients, found out that one patient presented mediastinal relapse of thymoma after 13 months from surgery (12.5%) and another one died of disease after 35 months (12.5%); both patients received neoadjuvant and adjuvant CT. All other patients were alive without disease after a mean follow-up of 22 months (36). A year later, always Ried *et al.* published their updated experience on stage III and IVa thymomas (respectively, 9 and 13 patients). In the latter group, 9 patients underwent postoperative HITHOC and only one patient died after 28 months for locoregional disease recurrence while in one case thymoma relapsed after 6 months from neoadjuvant

Table 2 Surgical resections, postoperative course, and oncological outcomes in various authors' experience

Author (year)	Nr. of patients	DNT/ TPR	Surgery performed + HITHOC	Perioperative morbidity (%)	Perioperative mortality	Follow-up, survival rates and oncological outcomes	HITHOC-related side-effects (%)
Yellin (2001)	7	DNT	1 EPP	-1 bleeding (14.3)	0	Mean follow-up: 60.2 months	1 thrombocytopenia (14.3)
			2 P/D	-1 prolonged air leak (14.3)		5 alive without disease (74.3)	1 nausea (14.3)
			3 PP			1 DOD after 7 months (14.3)	1 non-infectious fever (14.3)
			1 PP+wedge			1 DOC after 36 months (14.3)	
Refaely (2001)	10	DNT	9 P/D	-1 prolonged air leak (10.0)	0	3-year OS: 90%	1 leukemia*** (10.0)
			1 EPP	-1 diaphragmatic paralysis* (10.0)		5-year OS: 70%	2 non-infectious fever (20.0)
				-1 wound infection** (10.0)			
				-1 bleeding (10.0)			
De Bree (2002)	3	TPR	2 P/D	1 wound dehiscence (33.3)	0	Mean follow-up: 18 months	1 nephrotoxicity (33.3)
			1 EPP			OS: 100%	
						1 contralateral recurrence at 13 months (33.3)	
Ried (2013)	8	DNT	P/D	-1 respiratory failure+sepsis à treated with pneumonectomy (12.5)	0	Mean follow-up: 22 months	0
				-1 subclavian and axillary veins thrombosis (12.5)		DFS: 87.5% (1 relapse after 13 months)	
						OS: 87.5% (1 DOD after 35 months)	

Table 2 (*continued*)

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Author (year)	Nr. of patients	DNT/ TPR	Surgery performed + HITHOC	Perioperative morbidity (%)	Perioperative mortality	Follow-up, survival rates and oncological outcomes	HITHOC-related side-effects (%)
Yellin (2013)	14	TPR	P/D	-Prolonged air leak	0 at 30 days	Mean follow-up: 62 months	Nausea
	17	DNT	EPP	-Bleeding	2.5% at 90 days (empyema)	5-year OS: 67%	
			PP ± wedge	-Pneumonia		10-year OS: 56%	
				-Myasthenic crisis		Mean OS: 140 months	
				-Respiratory failure		5-year DFS =48%	
				-Sepsis		10-year DFS =18%	
				(Total 28.6)		5-year OS: 81%	
						10-year OS: 73%	
						Mean OS: 184 months	
						5-year DFS =61%	
						10-year DFS =43%	
Yu (2013)	4	2 DNT	CRS	1 pneumonia (25.0)	0	Follow-up: 1–4 years	2 intraoperative sinus tachycardia (50.0)
		2 TPR				DFS =100%	
						1 DOC	
Ried (2014)	9	DNT	P/D	-1 respiratory failure + sepsis (treated with pneumonectomy) (11.1)	0	Mean follow-up: 29.3 months	0
				-1 subclavian and axillary veins thrombosis (11.1)		DFI: 30.2 months	
						DFS: 89%	
						Recurrence rate: 22.7%	
						Median OS: 25 months	

Table 2 (*continued*)

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Author (year)	Nr. of patients	DNT/ TPR	Surgery performed + HITHOC	Perioperative morbidity (%)	Perioperative mortality	Follow-up, survival rates and oncological outcomes	HITHOC-related side-effects (%)
Maury (2017)	19	TPR	4 PP	-1 pyothorax (5.3)	0	Median follow-up: 39 months	1 bone marrow aplasia (5.3)
			1 EPP	-1 pneumonia (5.3)		Median OS: 63 months	2 acute reversible kidney failure (10.6)
			14 PP+wedge	-1 cardiac arrythmia (5.3%)		Median DFS: 53 months	
						Median local DFS: 41 months	
						1-year OS: 93%	
						5-year OS: 86%	
Aprile (2020)	27	TPR	PP or P/D	-5 bleedings (18.5)	0	Mean follow-up: 70.9 months	0
				-1 hydro-pneumothorax +bleeding (3.7)		10-year OS: 77%	
				-2 prolonged air leaks (7.4)		Mean OS: 153.1 months	
				-1 prolonged air leak + bleeding (3.7)		2nd recurrence rate: 44.4%	
						Mean local DFI: 88 months	
						5-year local DFI: 47%	
						10-year local DFI: 37.5%	

*3 months after surgery; ** 1 month after surgery; ***patient already undergone adjuvant chemotherapy. DNT, de novo stage IVa thymoma; TPR, thymoma pleural recurrence; EPP, extrapleural pneumonectomy; PP, partial pleurectomy; P/D, pleurectomy/decortication; CRS, cytoreductive surgery; OS, overall survival; DFS, disease-free survival; DFI, disease-free interval; DOD, dead of disease; DOC, dead of other causes; NR, not reported.

CT, surgery and HITHOC, and was successfully treated with 2nd line CT. At the end of the study, 89% of the patients were alive without disease and the median survival resulted 25 months. In conclusion the authors argued that, in advanced stage thymomas, surgery with radical intention should be considered part of a multimodal treatment comprehensive of induction CT, RT in cases of R1/R2 resections and HITHOC for pleural seeding to achieve a better local disease control (37).

In a pleural perfusion study for various thymic malignancies (stage IVa thymoma, TPR and thymic carcinoma), Yellin *et al.* used Cisplatin (100 mg/m^2) and, since 2002, also Doxorubicin (50–60 mg/m^2). They operated on 35 patients (14 TPR, 17 DNT and 4 thymic carcinomas) without any peri-procedural complication and, after a mean follow-up of 62 months, authors concluded that cytoreductive surgery and HITHOC is associated to excellent oncological results with a longer OS and DFS in DNT compared to TPR patients, as well as demolitive surgery as pleuropneumonectomy should be avoided in

favor of lung-preserving resections, due to high morbidity and mortality rate (38).

Even in 2013, Yu and colleagues published a study on 4 patients subjected to video-assisted cytoreductive surgery and HITHOC (Cisplatin 100 mg/m^2 for 2 hours) for TPR (2 patients) and stage IVa DNT (2 patients). They were followed-up for 1 to 4 years and only one patient died after 12 months for heart failure, the other three patients were alive without disease. During the procedure, the authors observed only two cases of tachycardia as hyperthermia-related side effect (39).

Maury *et al.* in their 2017 paper operated on 19 patients for TPR; their HITHOC regimen consisted in Cisplatin (50 mg/m^2) and Mitomycin (25 mg/m^2) and perfusion lasted 60 minutes at about 42 ℃. The authors reported three cases of HITHOC-related side effects (1 bone marrow aplasia and 2 acute reversible kidney failure) and three major postoperative complications (1 pyothorax, 1 cardiac arrythmia and 1 pneumonia). For what concerns oncological outcomes, after a median follow-up period of 39 months, 14 patients were alive, 12 of them with no evidence of disease. Only one patient died for thymoma-related causes. Seven patients (37%) presented tumor recurrence with a median disease-free survival of 53 months, while the median local disease-free interval was 41 months. Median OS was 63 months and 1- and 5-year survival rates were 93% and 86%, respectively. In conclusion, the authors agreed with other previous studies that HITHOC is a safe and feasible procedure, effective in prolonging disease-free survival in patients with relapsing thymoma if associated to cytoreductive lung-sparing surgery with radical intent. They also highlighted the necessity of larger studies to assess what chemotherapy regimen is more effective in this setting and the role of adjuvant chemotherapy in TPR (28).

Our group recently published twelve-year experience on TPR treatment. The study retrospectively collected data on 40 patients affected by relapsing thymoma; 27 of them received postoperative HITHOC (Cisplatin 80 mg/m^2 and Epirubicin 25 mg/m^2 at 42 ℃ for 1 hour) while 13 patients, in which HITHOC was contraindicated, underwent only cytoreductive surgery. Presently, this is the only study that compares surgery+HITHOC and surgery alone results. The two groups presented similar postoperative morbidity and no procedure-related mortality. Cumulative survival rates were also similar in the two groups (140.3 months in the surgery group, 153.1 months in the surgery + HITHOC group, P: 0.139), but they significantly differed in terms of local disease-free interval (57 months for the first group, 88 months for the second one, P: 0.046). Moreover, at multivariable analysis the only two factors affecting disease-free survival were adjuvant therapy after primitive tumor excision and HITHOC administration (P: 0.028 and 0.021, respectively). On the other hand, OS was affected only by radicality of redo-surgery. In the light of these data, we can confirm previous studies' findings on HITHOC safety and effectiveness, thanks overall to the comparative approach adopted. Moreover, surgical radicality's role is also confirmed, even if we noticed that sparing lung, pericardium and diaphragm, even at the cost of a non-radical resection, allows to avoid thymoma's cells spread leaving the patients in good conditions to be addressed to further treatments (24).

Conclusions

The cornerstone of thymoma surgical treatment is complete resection, that has proven to be the most important prognostic factor, although thymomas have high chemo- and radio-sensitive (40). In case of stage IVa tumors or recurrences occurring with pleural, pericardial or diaphragmatic implants, achieving a complete resection is unrealistic because of high probability of minimal residue, or extremely debilitating when the cost of the radicality is an extended and demolitive operation such as EPP. To reduce perioperative morbidity and mortality, lung, pericardial and diaphragmatic-sparing pleurectomy/decortication has been introduced with promising results despite the risk of potential R1 or minimal R2 resection. In this scenario, HITHOC perfusion following macroscopic radical pleural tumor resection has been developed to improve local tumor control and reduce the recurrence rate.

In our fifteen-years' experience with HITHOC in thymomatous patients, we settled as standard dosage 80 mg/m^2 for Cisplatin and 25 mg/m^2 for Epirubicin, with no evidence of HITHOC-related side-effects and good local disease control. In different reports, higher dosages seemed to be associated to similar oncological results but also with some episodes of severe chemo-related toxicity. This may suggest that increasing chemotherapy dosages is feasible but, actually, not strictly recommended, even if precise dose-dependent effects are still far to be assessed. Time of perfusion and number of pleural drainage catheters seem not to be determinants in early and long-term outcomes. Sixty minutes is the minimum described perfusion time and, in our opinion, is a good balance between oncological treatment and time under general anesthesia. We believe

that at least two pleural drainages (apical and basal) should be placed to adequately perform the complete irrigation of the whole pleural space. More than two drainages should be evaluated for each case on the base of the complexity and the extent of the intervention.

By the way, unfortunately, prospective and randomized studies to determine which is the best operative technique and the real oncological effectiveness of HITHOC are still lacking due to low incidence of cases suitable for this procedure and, to date, all the evidence is confined to retrospective studies with few patients and different protocols described. Therefore, more structured studies are needed to refine this technique as well as an international multicentric effort in involving a larger number of patients would be worthwhile. However, all the authors who experimented this technique, agreed on the safety and feasibility of the procedure with a very low complication rate and negligible systemic effects of chemotherapeutic agents, as well as they support the effectiveness of post-resection HITHOC in controlling both TPR and DNT, in particular as regards local disease-free survival.

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Footnote

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