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ORIGINAL ARTICLE

Cytoreductive surgery and hyperthermic intrathoracic chemotherapy (HITHOC) in the treatment of primary and metastatic pleural malignancies – is extension of indications possible?

Dejan Stojiljkovic[1,2], Nada Santrac[1,2], Dijana Mircic[3], Dusan Ristic[4], Tanja Stojiljkovic[5], Ana Cvetkovic[2,3]

[1]Department of Surgery, Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia. [2]Medical School, University of Belgrade, Belgrade, Serbia. [3]Department of Anesthesiology with Reanimatology and Intensive Care Unit, Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia. [4]Medical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Belgrade, Serbia. [5]General Hospital "Sveti Luka", Smederevo, Serbia.

Summary

Purpose: *To present the experience of our center with cytoreductive surgery (CRS) and hyperthermic intrathoracic chemotherapy (HITHOC) in the treatment of various potentially resectable chemo-sensitive pleural malignancies, primary and metastatic, limited to the unilateral thoracic inlet, as well as to address potential extension of indications for this procedure.*

Methods: *This retrospective study included patients treated with CRS+HITHOC at the Institute for Oncology and Radiology of Serbia from January 2018 to August 2021. Indications for CRS+HITHOC were: (1) potentially resectable chemo-sensitive primary or residual/recurrent thoracic malignancy, with no signs of disease outside the thoracic cavity, and (2) miscellaneous metastatic disease limited to the unilateral thoracic inlet. All HITHOC procedures were performed with 90 min cisplatin perfusion (100 mg/m^2 in 1000 ml of 5%-glucose gradually heated to 42°C).*

Results: *A total of 7 patients were included in this study, with a mean age of 41.43 ± 19.25 years (range: 16-62). R0 resections were achieved in all patients. All CRS+HITHOC procedures were uneventful, with no metabolic or hemodynamic disorders intraoperatively. Average follow-up was 25.71±9.83 months (range: 14-40). Overall survival rate was 100%. There were no local relapses in the thoracic cavity.*

Conclusions: *This study showed that CRS+HITHOC procedure might be successfully used not only for current indications, but also for a limited metastatic disease of a primary outside the thoracic cavity. Larger, multicentric studies might provide more data on oncological outcomes and cost-effectiveness of this procedure.*

Key words: *HITHOC, hyperthermic intrathoracic chemotherapy, cytoreductive surgery, pleural malignancies, metastases, indications*

Introduction

Hyperthermic intrathoracic chemotherapy (HITHOC) has been introduced for the treatment of malignant pleural effusions [1], alone or as a complementary method to cytoreductive surgery (CRS) for primary and secondary pleural malignancies [2], aiming to improve local disease control [3]. Prerequisite for performing HITHOC is absence of tumor outside the thoracic cavity.

CRS+HITHOC include surgical removal of all macroscopically visible pleural le-sions and in-

Corresponding author: Nada Santrac, MD, PhD. Department of Surgery, Surgical Oncology Clinic, Institute for Oncology and Radiology of Serbia, Pasterova 14, Belgrade, Serbia. Medical School, University of Belgrade, Dr Subotica 8, Belgrade, Serbia
Tel: +381 65 538 3070; Email: santrac.nada@gmail.com
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tracavitary application of cytotoxic agents with heated perfusion solution aiming to increase intrathoracic drug concentration, improve permeability and local cytotoxic effect of the drug, while reducing its systemic toxicity [1].

The usefulness of HITHOC, alone or with CRS, has already been shown for treatment of thymic tumors with pleural spread [4] and malignant pleural mesotheliomas [5], in well-selected patients. However, there are insufficient publications on this subject in the literature, showing great diversity of HITHOC techniques regarding choice of cytotoxic drug and its concentration, as well as volume and temperature of the perfusion system and duration of the perfusion itself.

The purpose of this study was to present the experience of our cancer center with CRS+HITHOC in the treatment of various potentially resectable chemo-sensitive pleural malignancies, primary and metastatic, limited to one hemithorax, as well as to address potential extension of indications for this procedure.

Methods

This retrospective study was conducted at the Surgical Oncology Clinic of the Institute for Oncology and Radiology of Serbia, a tertiary cancer center. It included all patients treated with CRS+HITHOC from January 2018, when this method was first introduced in our center [6], until August 2021.

CRS+HITHOC procedure

Patients' eligibility for the treatment was evaluated by a thoracic surgeon, medical oncologist, radiotherapist and anesthesiologist. Indications for CRS+HITHOC were: (1) potentially resectable chemo-sensitive primary or residual/recurrent thoracic malignancy, with no signs of disease outside the thoracic cavity, and (2) miscellaneous metastatic diseases limited to the unilateral hemithorax. Contraindications for CRS+HITHOC were renal insufficiency, impaired cardiopulmonary function, presence of contralateral thoracic tumor implants or extra-thoracic metastases.

Preoperative evaluation of disease stage included chest and abdominal computed tomography (CT) scan with contrast agents or 18-fluoro-deoxyglucose positron emission tomography (FDG PET) CT, while cardiac ul-

Table 1. Demographic characteristics, histology and previous oncological treatments

No	*Gender*	*Age*	*Tumor type*	*Initial treatments*	*Histology*
1	Female	48	Ovarian carcinoma	CRS+HIPEC (cisplatin) at the age of 42, adjuvant ChT (paclitaxel+carboplatin); peritoneal relapse 3 months later; re-do surgery	Cystadenocarcinoma serosum ovarii, G2, NG2, with peritoneal carcinomatosis
2	Male	64	Thymoma	Left posterolateral thoracotomy, thymectomy, atypical resection of the inferior left lobe (R1 resection)	Thymoma type B2, Ki67 70%, subpleural lung deposits; R0 resection
3	Male	63	Solitary fibrous tumor	Left posterolateral thoracotomy, removal of tumor mass with parietal pleura (R1 resection)	Malignant mesenchymal pleural tumor, Ki67 60%, positive margins
4	Male	55	Malignant mesothelioma	Atypical resection of the left superior lobe outside our center	Malignant pleural mesothelioma (biphasic type), positive margins
5	Female	19	Ewing sarcoma	RT and first-line ChT at the age of 13; second-line ChT with SBRT of lung metastases at the age of 17; third-line ChT with lung surgery in our center (left inferior lung wedge resection and partial left parietal pleurectomy) at the age of 18; fourth-line ChT at the age of 19	Ewing sarcoma of the sacral bone, conventional subtype
6	Female	32	Thymoma	Multiple tumor syndrome; BRCA1 and ARMC5 gene mutations confirmed; surgeries for previously diagnosed tumors: unilateral breast high-grade phyllodes tumor, rosette-forming glioneuronal tumor of the 4th ventricle, adrenocortical carcinoma and pheochromocytoma, and other specific oncological treatments	Initial thoracic surgery, no biopsy
7	Male	16	Rhabdomyosarcoma	Thoracoscopic biopsy of the chest wall tumor mass, localized posteriorly in the 7-8th left intercostal space, with suspicious pleural nodules in the left thoracic inlet; initial ChT	Alveolar rhabdomyosarcoma

CRS+HIPEC: cytoreductive surgery with hyperthermic intraperitoneal chemotherapy; ChT: chemotherapy; RT: radiotherapy; SBRT: stereotactic body radiation therapy

trasonography, anesthesiology examination, spirometry, blood analysis and complete biochemistry were done to ensure functional operability.

All patients had multidisciplinary team decision for CRS+HITHOC procedure and signed an informed consent form for the treatment.

CRS was performed under general anesthesia by a single thoracic surgeon. It included removal of primary or residual/recurrent tumor or metastases, visceral and/or parietal pleurectomy for macroscopic removal of all intrathoracic tumor implants (R1 resection), and, when indicated, resection of lung tissue, with preservation of positive intrathoracic pressure.

HITHOC procedure was performed with RanD® Performer perfusion system. Cisplatin was used as a cytotoxic agent in all patients. Drug concentration was calculated for each patient individually by a single medical oncologist, with regard to height, body weight, patient's comorbidities and previous systemic treatments (cumulative dose). Standardly, 100 mg/m^2 of cisplatin was administered, taking into account creatinine clearance. Upon completion of CRS, five chest tubes of 28 F were placed in a standard manner: two basally - for inflow, two apically - for outflow, and one superficially - for fluid level control, and connected to the device. Priming solution (1000 ml of 5 %-glucose), at initial temperature of 38°C, was administered into the pleural space and gradually heated. After achieving target temperature of 42°C, cisplatin was added in the pre-determined dose and intracavitary circulation of the drug was continued for 90 min. After drug perfusion, wash-out of dissolved cisplatin was performed through reversed inflow and outflow catheters and the temperature probe was removed. Two chest drains were positioned, anteriorly and posteriorly, with suction set to 15-25 cmH20, and the chest was closed in a standard manner.

Table 2. Overview of cytoreductive surgery indications, extent and outcomes

No	*Disease assessment*	*Indication*	*Cytoreductive surgery*	*PH after CRS+HITHOC*	*Procedure duration (min)*
1	Ovarian carcinoma pleural metastases 22 months after initial treatment	Metastatic disease limited to unilateral thoracic inlet	Right posterolateral thoracotomy, total parietal pleurectomy, partial visceral pleurectomy of the right medial lobe	R0 resection	350
2	Local relapse of thymoma 9 months after initial surgery	Recurrent disease limited to unilateral thoracic inlet	Left posterolateral re-thoracotomy, removal of tumor mass, superior mediastinal lymphadenectomy, partial visceral and parietal pleurectomy (R1 resection)	R0 resection, negative lymph nodes	400
3	Positive margins after removal of solitary fibrous tumor	Residual disease limited to unilateral thoracic inlet	Left posterolateral re-thoracotomy, atypical resection of the left inferior lung and total pleurectomy	R0 resection	410
4	Local relapse of malignant pleural mesothelioma 6 months after initial surgery outside our center	Recurrent disease limited to unilateral thoracic inlet	Left posterolateral re-thoracotomy, removal of recurrent tumor mass in the superior thoracic inlet with surrounding visceral and parietal pleura (R1 resection)	R0 resection, negative lymph nodes	360
5	Sacral bone Ewing Sa progression in the left thoracic inlet during 4th-line ChT	Metastatic disease limited to unilateral thoracic inlet	Left posterolateral re-thoracotomy, partial resection of the left inferior lung and partial left parietal and visceral pleurectomy	R0 resection	420
6	Thymic tumor mass with suspicious deposits in the lung parenchyma	Potentially resectable primary malignancy limited to mediastinum	Median sternotomy, thymectomy, anterior mediastinal lymph node dissection, extirpation of a solitary nodule from the left superior lung	Thymoma type B2, R0 resection, no lung or pleural metastases	300
7	Initial ChT for alveolar rhabdomyosarcoma of the chest wall, with radiological regression	Chemo-sensitive primary malignancy limited to unilateral thoracic inlet	Left posterolateral thoracotomy, radical left parietal pleurectomy	pCR	325

Ewing Sa: Ewing sarcoma; ChT: chemotherapy; PH: histology; CRS+HITHOC: cytoreductive surgery with hyperthermic intrathoracic chemotherapy; pCR: complete histological response

Intraoperative monitoring included: pulse oximetry, blood gases, body temperature and urinary output, and evaluation of hemodynamics using non-invasive hemodynamic device, invasive arterial blood pressure and central venous pressure. The central temperature was monitored by esophageal probe and regulated using warming/cooling blankets and cooling solutions injected through the central venous catheter.

Statistics

Data on demographics, histopathology, previous oncological treatment, preoperative evaluation, indications, CRS, HITHOC procedure, postoperative course, adverse events and oncological outcomes were collected and further evaluated using Microsoft Excel 2013.

Results

From January 1st 2018 until August 1st 2021, a total of 7 patients were treated with CRS+HITHOC at our cancer center, with a mean age of 41.43 ± 19.25 years (median: 46, range: 16-62) and female to male ratio 3:4. Tumor histology was diverse and included thymoma, malignant mesenchymal pleural tumor, malignant pleural mesothelioma, alveolar rhabdomyosarcoma, Ewing sarcoma and ovarian carcinoma. Data on the disease and history of oncological treatments prior to CRS+HITHOC are given in Table 1.

The mean duration of complete CRS+HITHOC procedure was 366.43 ± 45.34 min (median: 360, range: 330 - 420). R0 resection was confirmed on definite pathological analysis of specimens (Table 2).

All CRS+HITHOC procedures were uneventful, with no metabolic or hemodynamic disorders intraoperatively. Patients were postoperatively monitored at the Intensive Care Unit. There were no significant adverse events in the postoperative course, except in a patient treated due to ovarian carcinoma metastases, who experienced a decrease in hemoglobin level on the 2nd postoperative day, followed by complete blood count and blood pressure decline, which responded well on the applied dose of concentrated erythrocytes. Nausea, vomiting, neuropathy or renal function disorder were not observed.

After hospital discharge, all patients were evaluated by multidisciplinary teams and received additional oncological treatments (chemotherapy, irradiation) based on disease-specific protocols (Table 3).

The mean follow-up after CRS+HITHOC was 25.71 ± 9.83 months (median: 29, range: 14-40). Overall survival rate was 100 %. None of the patients had local relapse in the thoracic cavity after CRS+HITHOC. One patient with initially advanced ovarian carcinoma had disease progression in the spleen two months after CRS+HITHOC procedure, which was treated with splenectomy and systemic chemotherapy with paclitaxel and carboplatin (Table 3).

Discussion

The concept of hyperthermic cytotoxic agent perfusion is based on several facts: (1) intracavitary, local, application of the cytotoxic agent allows higher drug concentrations than in intravenous application; (2) drug concentration is maintained high, which improves cytotoxicity of the drug, while minimizing systemic adverse effects; (3) heat increases cell membrane permeability and drug penetration in tissue (3-4mm) [7]; (4) hyperthermia at 41-42°C

Table 3. Follow-up and oncological outcomes after cytoreductive surgery and HITHOC procedure

No	*Additional therapy*	*Thoracic relapse*	*Other relapse*	*Relapse-free period (months)*	*Relapse treatment*	*Lethal outcome*	*Follow-up (months)*
1	No	No	Yes, solitary metastasis in the spleen	2	Splenectomy, re-treatment with systemic ChT (paclitaxel+ carboplatin)	No	40
2	No	No	No	32	NA	No	32
3	Systemic ChT (adriamycin + ifosfamide, carboplatin + etoposide)	No	No	31	NA	No	31
4	Adjuvant irradiation	No	No	29	NA	No	29
5	Fifth-line ChT (gemcitabine + docetaxel)	No	No	19	NA	No	19
6	No	No	No	15	NA	No	15
7	No	No	No	14	NA	No	14

ChT: chemotherapy; NA: not applicable

selectively induces apoptosis [8] in malignant cells by inhibiting RNA synthesis and mitosis and increasing lysosome-induced destruction [9,10]; (5) normal cells are able to survive hyperthermia [9].

Intracavitary hyperthermic perfusion of cytotoxic agents has been introduced back in 1980s by Spratt et al [11] as HIPEC, while Matsuzaki et al published their experience with HITHOC in 1995 [12].

HIPEC has been widely used for decades for treatment of malignant ascites or abdominal and gynecological malignancies with peritoneal carcinomatosis to improve local control of potential residual microscopic disease after CRS. On the other hand, HITHOC is less commonly used for limited indications and well-selected patients, and its clinical application is not standardized in terms of cytotoxic drug's concentration, and volume, temperature and duration of the perfusion. Publications on this topic usually represent the personal experiences of individual authors or surgical teams.

A systematic review by Zhou et al [1] that included 27 publications from 1995 to 2016 showed that cisplatin was the most commonly used cytotoxic agent, followed by doxorubicin and mitomycin C, and temperature of the perfusion system varied between 38 and 43°C. Some authors combined two chemotherapeutic drugs [13].

Since the introduction of this procedure in our center, we have always used cisplatin due to national Health Insurance Fund regulations. As a priming solution we use 1000 ml of 5 %-glucose that is gradually heated from 38 to 42 °C upon administration into the pleural space. After cisplatin is added, the intracavitary circulation is continued for 90 min, although some authors report shorter perfusion time [13,14].

There is no consensus on the optimal dosage of the cytotoxic drug for HITHOC in the literature. Among possible side effects, nephrotoxicity is the major concern and limits the application of higher cisplatin doses. The majority of authors apply between 80 and 250 mg/m^2 of cisplatin [5,15], although some suggest that higher doses, compared to lower, have a better effect on survival [14]. In this study, we usually administered 100 mg/m^2 of cisplatin, taking into account creatinine clearance, comorbidities and cumulative dose of previous systemic treatments. With this protocol, all our procedures were uneventful with regard to intraoperative metabolic or hemodynamic disorders. Only one patient had a decrease in hemoglobin level, blood count and blood pressure on the 2nd postoperative day, which was normalized after concentrated erythrocytes were administered.

Literature data show rather limited indications for HITHOC, including malignant pleural mesothelioma [16,17], thymoma or thymic carcinoma (with pleural involvement or recurrent) [16,18-22] and lung adenocarcinoma with pleural dissemination [2,17].

HITHOC for pleural metastases of other cancers is rarely reported in the literature [23], although the majority of solid malignant tumors and hematologic malignancies may lead to pleural dissemination that is associated with poor prognosis and reduced survival. Disease progression of a primary cancer outside thoracic cavity requires multidisciplinary therapeutic approach and it is usually performed by systemic chemotherapy, with or without radiotherapy, given that surgery alone is of no long-term benefit, if not absolutely contraindicated. However, a problem remains for patients who have exhausted all treatment options due to progression to applied therapies or due to high cumulative dose of previous systemic chemotherapy and/or radiotherapy.

There are insufficient HITHOC publications, with limited patients' series and many variations in the procedure itself, thus assessment of the oncological outcomes cannot be adequate. Based on available literature data and results of this study, CRS+HITHOC can be referred to as a safe, feasible and efficient method in selected patients, with low morbidity and no mortality [2,13,22,24]. Given that our two patients with pleural metastases from a primary outside the thoracic cavity (ovarian cancer, Ewing sarcoma), that were previously treated for several years with various oncological treatments, had good local disease control after CRS+HITHOC, the authors believe that HITHOC could be useful not only for current indications - malignant mesotheliomas, thymomas/thymic carcinomas and locally advanced lung carcinoma [2,16-22], but also for potentially resectable chemo-sensitive miscellaneous metastatic diseases limited to unilateral hemithorax, regardless of tumor pathology and without interference with any future systemic treatments. These data might encourage reassessment and potential expansion of indications for HITHOC. However, standardization of the procedure is necessary and larger multicentric studies could provide quality data on the oncological outcomes and cost-effectiveness of the procedure.

Our cancer center is the only institution in Southeastern Europe where HITHOC procedure is performed. Given that we introduced this procedure recently, in 2018, and that it is generally rarely performed worldwide, our experience with seven patients, although small, is not negligible.

Conflict of interests

The authors declare no conflict of interests.

References

1. Zhou H, Wu W, Tang X, Zhou J, Shen Y. Effect of hyperthermic intrathoracic chemotherapy (HITHOC) on the malignant pleural effusion: A systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e5532.
2. Yi E, Kim D, Cho S, Kim K, Jheon S. Clinical outcomes of cytoreductive surgery combined with intrapleural perfusion of hyperthermic chemotherapy in advanced lung adenocarcinoma with pleural dissemination. J Thorac Dis 2016;8:1550-60.
3. Yellin A, Simansky DA, Paley M, Refaely Y. Hyperthermic pleural perfusion with cisplatin: early clinical experience. Cancer 2001;92:2197-203.
4. Refaely Y, Simansky DA, Paley M, Gottfried M, Yellin A. Resection and perfusion thermochemotherapy: a new approach for the treatment of thymic malignancies with pleural spread. Ann Thorac Surg 2001;72:366-70.
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;138:405-11.
6. Stojiljkovic D, Nikolic S, Cvetkovic A, et al. Hyperthermic intrathoracic chemotherapy (HITHOC) in ovarian carcinoma - a propos of a case. J BUON 2018;23: 153-5.
7. Jacquet P, Averbach A, Stuart OA et al. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. Cancer Chemother Pharmacol 1998;41:147-54.
8. Matsuzaki Y, Tomita M, Shimizu T, Hara M, Ayabe T, Onitsuka T. Induction of apoptosis by intrapleural perfusion hyperthermochemotherapy for malignant pleural mesothelioma. Ann Thorac Cardiovasc Surg 2008;14:161-5.
9. Dudar TE, Jain RK. Differential response of normal and tumor microcirculation to hyperthermia. Cancer Res 1984;44:605-12.
10. Overgaard J. Effect of hyperthermia on malignant cells in vivo. A review and a hypothesis. Cancer 1977;39:2637-46.
11. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 1980;40:256-60.
12. Matsuzaki Y, Shibata K, Yoshioka M et al. Intrapleural perfusion hyperthermo-chemotherapy for malignant pleural dissemination and effusion. Ann Thorac Surg 1995;59:127-31.
13. Ambrogi MC, Bertoglio P, Aprile V et al. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience. J Thorac Cardiovasc Surg 2018;155:1857-66.e2.
14. 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;24:1561-7.
15. van Ruth S, Baas P, Haas RL et al. Cytoreductive surgery combined with intraoperative hyperthermic intrathoracic chemotherapy for stage I malignant pleural mesothelioma. Ann Surg Oncol 2003;10:176-82.
16. 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.
17. Migliore M, Calvo D, Criscione A et al. Cytoreductive surgery and hyperthermic intrapleural chemotherapy for malignant pleural diseases: preliminary experience. Fut Oncol 2015;11(2 Suppl):47-52.
18. 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;145:83-9.
19. Yu L, Jing Y, Ma S, Li F, Zhang YF. Cytoreductive surgery combined with hyperthermic intrapleural chemotherapy to treat thymoma or thymic carcinoma with pleural dissemination. Onco Targets Ther 2013;6:517-21.
20. Ambrogi MC, Korasidis S, Lucchi M, Fanucchi O, Giarratana S, Melfi F et al. Pleural recurrence of thymoma: surgical resection followed by hyperthermic intrathoracic perfusion chemotherapy. Eur J Cardiothorac Surg 2016;49:321-6.
21. Maury JM, Girard N, Tabutin M et al. Intra-thoracic chemo-hyperthermia for pleural recurrence of thymoma. Lung Cancer 2017;108:1-6.
22. 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.
23. Işık AF, Sanlı M, Yılmaz M et al. Intrapleural hyperthermic perfusion chemotherapy in subjects with metastatic pleural malignancies. Respir Med 2013;107:762-7.
24. Patel MD, Damodaran D, Rangole A et al. Hyperthermic Intrathoracic Chemotherapy (HITHOC) for Pleural Malignancies-Experience from Indian Centers. Indian J Surg Oncol 2019;10(Suppl 1):91-8.