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Protocol of a retrospective, multicenter observational study on hyperthermic intrathoracic chemotherapy in Germany

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ABSTRACT

Introduction: Objective of the "German HITOC-study" is to evaluate the hyperthermic intrathoracic chemotherapy (HITOC) as additional treatment after surgical cytoreduction for malignant pleural tumors. Even though HITOC is applied with increasing frequency, there is no standardized therapy protocol concerning the technique of HITOC, the selection as well as dosage of chemotherapeutic agents and perioperative management in order to provide a safe and comparable, standardized treatment regime.

Methods and analysis: This trial is a retrospective, multi-center observational study, which is funded by the German Research Foundation. Approximately 300 patients will be included. Four Departments of Thoracic Surgery, who are performing the most HITOC procedures in Germany, are contributing to this study: Center for Thoracic Surgery at the University Hospital Regensburg, Thoracic Clinic Heidelberg of the University of Heidelberg, Center for Thoracic Surgery of the Hospital University of Munich and the Department of Thoracic Surgery at the University Hospital Freiburg. All patients who underwent surgical cytoreduction and subsequent HITOC at one of the four centers between starting the HITOC-program in 2008 until December 2019 will be included. Information on the performed HITOC will be obtained, focusing on the technique as well as the applied perfusion solution including the chemotherapeutic agent. Furthermore, parameters of the patient's postoperative recovery will be analyzed to determine 30-day morbidity and mortality.

Ethics and dissemination: The approvals by the local ethics committee of the respective clinic and the three participating clinics have been obtained. The results will be presented in conferences and published in a peer-reviewed journal.

Registration: German Clinical Trials Register (DRKS-ID: DRKS00015012)

Keywords: HITOC, hyperthermic intrathoracic chemotherapy, chemotherapy perfusion, pleural malignancy, pleural mesothelioma

ARTICLE SUMMARY

Strengths and limitations of this study

- The results of this retrospective, multi-center study should allow a better standardization of the HITOC-procedure including perioperative safety measures and also validate the existing clinical experience.
- In the long term it could be the basis for survival analyses and further prospective studies.
- Due to the retrospective nature of our study, the implementation of hyperthermic intrathoracic chemotherapy was not uniform, which affects the analysis of 30-day morbidity and mortality
- To the best of our knowledge, this study will represent the largest cohort of patients with surgical cytoreduction and HITOC.

Abbreviations and acronyms

BSA = body surface area

eP/D = extended pleurectomy/decortication

EPP = extrapleural pneumonectomy

HITOC = hyperthermic intrathoracic chemotherapy

MPM = malignant pleural mesothelioma

P/D = pleurectomy/decortication

TC= thymic carcinoma

ZKS = Center for Clinical Studies of the University Medical Center Regensburg

INTRODUCTION

Hyperthermic intrathoracic chemotherapy (HITOC) is a local, intraoperative perfusion of the thoracic cavity with a chemotherapeutic agent after surgical cytoreduction of malignant pleural tumors. The HITOC represents an additional therapeutic option in a multimodality treatment concept especially for patients with malignant pleural mesothelioma (MPM), thymic tumors with pleural spread (stage IVa) and even in highly selected patients with pleural carcinosis (1, 2). The spreading growth pattern of these malignant tumors along the pleura impairs a microscopically complete resection and small residues of the tumor often lead to local recurrence (2). With the application of the HITOC after macroscopic complete pleural tumor resection it is expected to obtain better local tumor control and thereby improve progression-free as well as overall survival (2-4). The few existing case series or single-center retrospective studies in patients with MPM and thymic tumors have shown some encouraging results in this regard (2, 5-9). However, a prospective study showing an advantage in survival does not yet exist.

A survey of the German Society for Thoracic Surgery on the application of HITOC confirmed that approximately 350 HITOC procedures have already been performed in Germany from 2008 to 2017. Most of the procedures were conducted at University Thoracic Surgery Centers in Munich, Heidelberg, Freiburg, Regensburg and Cologne (Witten-Herdecke) (10).

Although HITOC is performed routinely in some experienced Departments of Thoracic Surgery in Germany, only feasibility studies, case series, and retrospective studies with small numbers of patients have been published so far evaluating perioperative management, technique, the selection and dosage of chemotherapeutic agents and postoperative complications (Table 1) (1, 11, 12). There is no standardized procedure of HITOC concerning the administration of chemotherapeutic agents, the dosage of the drugs, duration and temperature of the perfusion as well as the perioperative management of these patients including safety measures for the personal. As a result, clinics performing HITOC follow internationally reported experiences and developed individual protocols (10). In 2019 a clinical practice guideline on HITOC within the guideline system of the Association of the Scientific Medical Societies in Germany was

published. Due to the lack of empirical data, this guideline was based on an expert consensus (so called S1-guideline). The group of experts agreed on the key aspects of applying HITOC in thoracic surgery (Table 2) (13).

Before performing the HITOC, all patients underwent surgical cytoreduction of the pleural tumor. Therefore, pleurectomy/decortication (P/D), extended pleurectomy/decortication (eP/D) with partial and/or complete resection of the pericardium and/or diaphragm, or extrapleural pneumonectomy (EPP) is carried out to achieve a macroscopic complete resection whenever possible (14). The outcome of lung-saving procedures (P/D, eP/D) turned out to be equivalent to EPP with significantly less complications, so that these procedures should preferably be performed (8).

Usually HITOC and tumor resection are performed in the same session. Apical inflow and basal outflow drainages are placed in the thoracic cavity. The following perfusion can be carried out with an open (before wound closure) or closed (after wound closure) chest, while the procedure on the closed chest is more common. Its advantage is that no cytostatic agent can leak out of the thoracic cavity during circulation, which would be a safety risk for the practitioner (7, 10). The drainages are then connected to an external perfusion system. A stable circulation is established with a priming-volume and the perfusion solution is heated to a targeted temperature of 40-43°C (9, 15). The chemotherapeutic agents are added to the perfusate and the circulation is performed between 60 and 120 minutes. Subsequently, the perfusion solution is passively drained.

This retrospective, multi-center study will provide the first time opportunity to enroll a substantial number of study participants from experienced German centers regarding HITOC to validate the clinical experience of the individual centers and possibly form the basis for a standardized procedure with an adequate perioperative management in patients who underwent HITOC. In the long term, this database might be used for survival analyses with respect to the different tumor entities and may serve to design a prospective study.

METHODS AND ANALYSIS

Study design

This is a retrospective, multi-center observational study to evaluate HITOC at university thoracic surgery clinics with the most performed operations including HITOC in Germany. The participating clinics include the Thoracic Surgery Center Regensburg (University Hospital Regensburg, Hospital Barmherzige Brüder Regensburg), the Department of Thoracic Surgery, Thoracic Clinic Heidelberg (University of Heidelberg), the Department of Thoracic Surgery, Medical Center, University of Freiburg and the Thoracic Surgery Center Munich, Hospital of the University of Munich (Ludwig-Maximilians-University, Campus Großhadern; Asklepios Lung Clinic Gauting). Estimating the number of patients of each participating clinic at the time of designing this study resulted in a total number of approximately 250-300 patients in the period between January 2008 and December 2019 who could be retrospectively included in this study. This will represent the largest cohort of patients who received HITOC compared to the recent international literature (Table 1) (9).

Inclusion and exclusion criteria

The study will examine patients with malignant pleural tumors who received HITOC after surgical cytoreduction between beginning of the HITOC program in 2008 and the end of December 2019 at all study centers. Patients without HITOC or without surgical cytoreduction will not be included (Table 3). Informed consent is not an eligibility criterion because data will be processed in a pseudonymized manner in accordance with EU-GDPR and BayKrG.

Study endpoints

This study aims at quality assurance and evaluation of HITOC after surgical cytoreduction at the thoracic surgical university hospitals with most experience with HITOC in Germany. For this broad assessment, a compound of endpoints was defined as shown in Table 4.

Central element of the study will be the evaluation of parameters concerning the implementation of HITOC. In particular the selection of chemotherapeutic agents by the

respective clinics will be assessed by showing which and how often certain combinations and dosages were used at leading German clinics in this field, since the approach varies internationally (Table 1). In this regard, the association of the administered cisplatin dosage with the occurrence and severity (according to the FDIGO classification) of postoperative renal insufficiency will be analyzed. Also the incidence and severity (according to the Clavien-Dindo classification) as well as the spectrum of postoperative complications after HITOC will be determined. To further evaluate the safety of the procedure, 30-day mortality will be another element of the assessment. Finally, the development of this procedure in Germany concerning the technique, perioperative management and safety over a time span of approximately eleven years will be demonstrated (Figure 1).

Documentation and data base

After identifying all patients who meet all criteria shown in Table 3, data will be documented in an electronic database. In this database information on the performed surgery and additional HITOC will be obtained, focusing on the technique as well as the applied perfusion solution. Therefore, participating clinics will enter parameters regarding the patient characteristics (age, ECOG stage, ASA stage, tumor entity, tumor stage, date of first diagnosis), performed surgery (localization, extend of surgical cytoreduction, complications), HITOC (combination and dosage of chemotherapeutics, perfusion volume, temperature, flow rate, duration of chemotherapy perfusion, complications) and perioperative management (weaning, fluid balancing, care on the intensive care unit). Data from the postoperative period (30-day morbidity) also include complications assigned to the Clavien-Dindo classification with special respect to postoperative renal insufficiency, required surgical revisions, duration of intensive medical care, hospitalization and 30-day mortality (16). In addition, first data regarding progression-free and overall survival are warranted to be analyzed (Table 5).

Data management

The Center for Clinical Studies (ZKS) of the University Medical Center Regensburg is establishing a web-based, central and uniform database, using a common Clinical Database Management System (CDMS). This system provides the capability to perform major data management activities within a consistent, auditable, integrated and EU-GDPR compliant environment. Data quality checks (regarding data ranges, validity and consistency) will be carried out regularly. In case of necessary corrections or existing data inconsistencies, a data manager will generate data queries consecutively. All data entries will be routinely recorded via audit trail, as well as data modifications and data corrections.

Statistical analyses

Subsequently, the statistical data evaluation of the study is also carried out by the ZKS of the University Hospital Regensburg.

Patient characteristics, quality assurance parameters and evaluation of HITOC after surgical cytoreduction (Table 4) will be summarized descriptively, using absolute and relative frequencies for categorical data and mean, standard deviation, median, interquartile range, minimum and maximum for metric data.

Risk factors (e.g. HITOC parameters) for 30-day mortality, in-hospital mortality and postoperative complications will be assessed by using binary logistic regression models. With regard to all outcome measurements, reference values for optimal HITOC parameters will be provided. The level of significance will be set at 5% for all statistical tests.

The results of this retrospective study are intended to contribute to a standardization of the perioperative procedure including safety measurements. To establish quality assurance in HITOC patients, benchmarks are to be defined on the basis of the study. The rate of lung-sparing resections as well as the rate of postoperative renal insufficiency, wound infections as well as the length of hospital stay after surgical cytoreduction including HITOC and the 30-day mortality will be determined and thus provide reference for clinics performing this combined procedure.

Ethics and dissemination

The study was funded by the German Research Foundation (Deutsche Forschungsgemeinschaft – DFG; GZ: RI 2905/3-1) and will be supported for 12 months after its start in January 2020. The trial is registered in the German Register of Clinical Studies (DRKS-ID: DRKS00015012, Date of registration: 03th August 2018). The approvals by the local ethics committee of the respective clinic and the three participating clinics have been obtained (reference number University Regensburg: 18-1119-104). Each patient will be assigned an identification number for pseudonymization. The study ends regularly in December 2020 when the study parameters have been evaluated and published. The results are planned to be published in a peer-reviewed journal.

Patient and public involvement

In this study, patients or the public were not involved in the design, conduct, reporting or dissemination of research.

DISCUSSION

There are different approaches in the international literature regarding the implementation and perioperative management of HITOC after surgical cytoreduction (9). A common standard for the procedure of HITOC does not yet exist, so that clinics performing this procedure orientate their protocols towards a small number of studies with often few participants (Table 1).

The available single-center studies demonstrated that the rate of complications could be acceptable with an appropriate perioperative management (1, 11, 12). To perform HITOC safely and keep HITOC-specific complications low, adequate perioperative management and an interdisciplinary approach is essential, especially between surgery, anesthesia and intensive care (17).

In the published research, cisplatin is always part of the perfusion solution. However, the dose administered varies, but usually it is applied in doses lower than 175 mg/m^2 body surface area BSA; Table 1) (1, 10, 18-20). The application of higher doses of cisplatin seems to be

associated with better overall survival, but also might cause more complications. Our study group described that the cisplatin concentration in patient serum increases to only about 2% of the intrathoracic concentration, although if the cisplatin dosage is increased up to 150 mg/m^2 BSA (6, 21). As a result, much higher concentrations can be achieved locally in the tissue than with systemic administration (15). However, high intrathoracic concentrations lead to an increased incidence of postoperative complications (e.g. renal insufficiency), for which reason the maximum tolerable dose of cisplatin was identified at 225 mg/m^2 BSA (6). Concerning postoperative renal insufficiency, the use of protective measures such as nephroprotective agents and fluid balancing may have a preventive effect (22). First introduced by Sugarbaker et al. in HITOC, it is currently also being practiced in a few more studies (6, 22).

The application of a second chemotherapeutic agent is also heterogeneous. The considerations of applied agents were guided by the experience in systemic therapy. Superiority over systemic cisplatin monotherapy has been demonstrated in both MPM and thymoma patients (23, 24). In some clinics, cisplatin is combined with doxorubicin, epirubicin, gemcitabine or mitomycin, whereas other clinics use cisplatin alone (5, 18, 25).

Another factor where the protocols differ in international compare is the target temperature of the chemotherapeutic solution. During perfusion, it is constantly measured using two probes at the inflow and outflow drainage (6). It has been shown that the penetration depth of cisplatin into the tissue increases with the temperature of the intrathoracic solution. Applied temperatures of 40-43°C are described in the literature (1, 26-28). Intrapleural temperatures above 43°C are supposed with an increased risk of pulmonary edema and should therefore be avoided (29). Also, high temperatures of the perfusate lead to an increased risk of systemic hyperthermia (17). Regarding the optimal duration of perfusion only little research exists and thus varies between 60 and 120 minutes (19, 25).

Conclusion

In summary, the German HITOC-Study will include the biggest study population with surgical cytoreduction and HITOC since now. It will retrospectively evaluate the additional HITOC-

procedure with main respect to quality assurance and it will support a standardization of the procedure. Results are expected in 2021.

Trial status:

At the time of manuscript submission, data base is finished and data collection started in April 2020. The following analyses are planned to be completed by the end of 2020.

Declarations

Author contributions: TM and MR wrote the manuscript. FZ, GH and MK proved the manuscript regarding the study design and the described statistical analysis. HSH and all collaborators revised the manuscript critically. All authors approved the final version of the manuscript.

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Competing interests: Nothing to declare.

FIGURE LEGENDS

Figure 1: Flow-chart of the study design

TABLES

Table 1: Study overview

Author, year (reference number)	Patients (primary tumors)	Chemotherapeutic agents, duration, temperature
Refaely et al., 2001 (18)	n=15 (thymoma/TC)	cisplatin (100mg/m^2 BSA); 60 min; 42°C
De Bree et al., 2002 (5)	n=3 (thymoma/TC) n=11 (MPM)	cisplatin (80mg/m^2 BSA) + doxorubicin (15-30mg/m^2 BSA); 90 min; 40-41°C
Richards et al., 2006 (6)	n=44 (MPM)	cisplatin (low-dose: 50-150mg/m^2 BSA; high-dose: 175-250mg/m^2 BSA); 60 min; 42°C
Zellos et al., 2009 (11)	n=29 (MPM)	cisplatin (75-200mg/m^2 BSA); 60 min; 42°C
Tillemann et al., 2009 (12)	n=92 (MPM)	cisplatin (225mg/m^2 BSA); 60 min; 42°C
Ried et al., 2013 (2)	n=8 (MPM) n=8 (thymoma/TC)	cisplatin (100-150mg/m^2 BSA); 60 min; 42°C
Sugarbaker et al., 2013 (1)	n=72 (MPM)	cisplatin (175-225mg/m^2 BSA); 60 min; 42°C
Yellin et al., 2013 (26)	n=35 (thymoma/TC)	cisplatin (100mg/m^2 BSA) + doxorubicin (50-60mg, 60 min; 43°C
Yu et al.; 2013 (19)	n=4 (thymoma/TC)	cisplatin (100mg/m^2 BSA); 120 min; 41-43°C
Migliore et al., 2015 (4)	n=6 (MPM) n=2 (lung cancer)	cisplatin (120mg/m^2 BSA); 60 min; 42.5°C
Ishibashi et al., 2015 (28)	n=14 (MPM)	cisplatin (80mg/m^2 BSA); 60 min; 42°C
Ambrogi et al., 2016 (20)	n=13 (thymoma/TC)	cisplatin (80mg/m^2 BSA) + doxorubicin (25mg/m^2 BSA); 60 min; 42.5°C
Bertoglio et al., 2017 (30)	n=26 (MPM)	cisplatin (80mg/m^2 BSA) + doxorubicin (25mg/m^2 BSA); 60 min; 42.5°C
Maury et al., 2017 (25)	n=19 (thymoma/TC)	cisplatin (50mg/m^2 BSA) + mitomycin (25mg/m^2 BSA); 90 min; 42°C
Ambrogi et al., 2018 (8)	n=49 (MPM)	cisplatin (80mg/m^2 BSA) + epirubicin (25mg/m^2 BSA); 60 min; 42.5°C
Burt et al., 2018 (7)	n=104 (MPM)	cisplatin (175-225mg/m^2 BSA) + gemcitabine (100-1200mg/m^2 BSA); 60 min; 40-42°C

Markowiak et al., 2019 (3)	n=29 (thymoma/TC)	cisplatin (100-175mg/m^2 BSA) + doxorubicin (0-65mg); 60 min; 42°C

BSA = Body surface area, MPM = malignant pleural mesothelioma, TC= thymic carcinoma

Table 2: Consensus-based expert recommendation (excerpt) (13)

	Content; consensus strength
Nomenclature	– Hyperthermic intrathoracic chemotherapy (HITOC); 100%
Technique	– One session; 100% – Closed thorax; 100% – Temperature of 42°C on the outflow drainage; 100% – Duration of 60min; 100%
Chemotherapeutic agents	– Application of cisplatin; 100% – Maximum dosage of 225mg/m² BSA; 100% – Dosage between 150 and 175mg/m² BSA; 100%
Perioperative management	– Perioperative fluid balancing and forced diuresis; 100% – Drug-based nephroprotection may be considered; 100% – Safety-management including protective clothing of the personnel and disposal of drain fluids; 100%
Indications	– Malignant pleural mesothelioma; 100% – Stage IVa thymoma; 100% – Secondary pleural carcinosis; 100%

BSA=Body surface area

Table 3: Inclusion- and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years	• Treatment without HITOC
• Malignant pleural tumor	• HITOC without surgical cytoreduction
• Surgical cytoreduction and HITOC	
• Treatment period: 2008-2019	

HITOC=hyperthermic intrathoracic chemotherapy

Table 4: Study Endpoints (Quality assurance and implementation of intraoperative HITOC after surgical cytoreduction)

Study endpoints
• dosing of the intrathoracic chemotherapeutic agent
• postoperative renal failure (dependence on cisplatin dosage)
• 30-day morbidity and mortality
• development of the technique, perioperative management and complication spectrum over time of HITOC

HITOC=hyperthermic intrathoracic chemotherapy

Table 5: Overview of data collection with respect to subgroups

Subgroups of data collection
– Demographic data
– Physical examination
– Performance status
– Tumor specific data
– Surgery specific data (intra-, postoperative)
– HITOC specific data
– Renal function
– Information on hospitalization
– Follow-up

HITOC=hyperthermic intrathoracic chemotherapy

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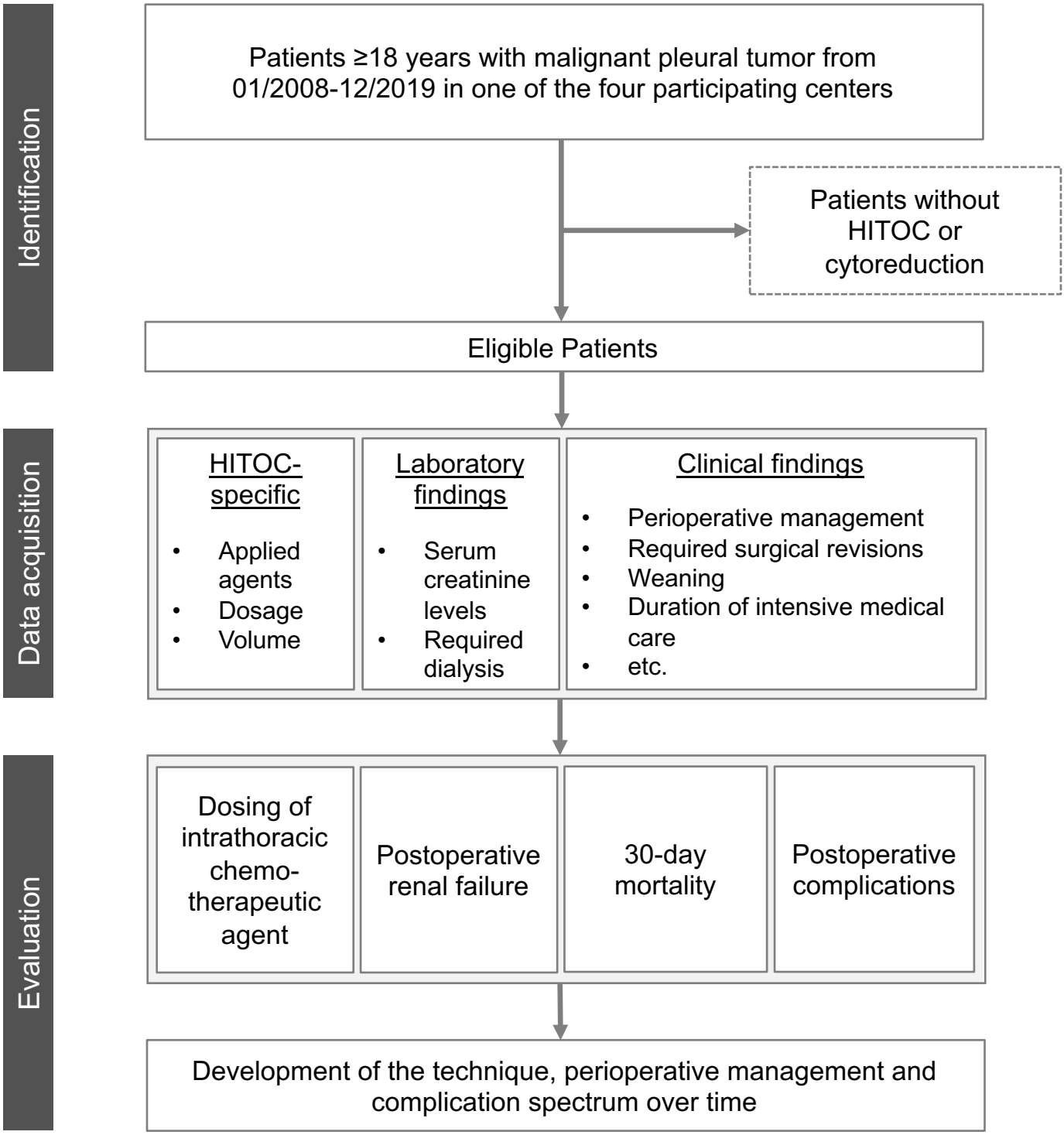
Identification
Patients ≥18 years with malignant pleural tumor from 01/2008-12/2019 in one of the four participating centers
Patients without HITOC or cytoreduction
Eligible Patients
Data acquisition
HITOC-specific
Applied agents
Dosage
Volume
Laboratory findings
Serum creatinine levels
Required dialysis
Clinical findings
Perioperative management
Required surgical revisions
Weaning
Duration of intensive medical care
etc.
Evaluation
Dosing of intrathoracic chemo-therapeutic agent
Postoperative renal failure
30-day mortality
Postoperative complications
Development of the technique, perioperative management and complication spectrum over time

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	(7)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not applicable
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Protocol of a retrospective, multicenter observational study on hyperthermic intrathoracic chemotherapy in Germany

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Protocol of a retrospective, multicenter observational study on hyperthermic intrathoracic chemotherapy in Germany

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ABSTRACT

Introduction: Objective of the "German HITOC-study" is to evaluate the hyperthermic intrathoracic chemotherapy (HITOC) as additional treatment after surgical cytoreduction for malignant pleural tumors. Even though HITOC is applied with increasing frequency, there is no standardized therapy protocol concerning the technique of HITOC, the selection as well as dosage of chemotherapeutic agents and perioperative management in order to provide a safe and comparable, standardized treatment regime.

Methods and analysis: This trial is a retrospective, multi-center observational study, which is funded by the German Research Foundation. Approximately 300 patients will be included. Four Departments of Thoracic Surgery, who are performing the most HITOC procedures in Germany, are contributing to this study: Center for Thoracic Surgery at the University Hospital Regensburg, Thoracic Clinic Heidelberg of the University of Heidelberg, Center for Thoracic Surgery of the Hospital University of Munich and the Department of Thoracic Surgery at the University Hospital Freiburg. All patients who underwent surgical cytoreduction and subsequent HITOC at one of the four centers between starting the HITOC-program in 2008 until December 2019 will be included. Information on the performed HITOC will be obtained, focusing on the technique as well as the applied perfusion solution including the chemotherapeutic agent. Furthermore, parameters of the patient's postoperative recovery will be analyzed to determine 30-day morbidity and mortality.

Ethics and dissemination: The approvals by the local ethics committee of the respective clinic and the three participating clinics have been obtained. The results will be presented in conferences and published in a peer-reviewed journal.

Registration: German Clinical Trials Register (DRKS-ID: DRKS00015012)

Keywords: HITOC, hyperthermic intrathoracic chemotherapy, chemotherapy perfusion, pleural malignancy, pleural mesothelioma

ARTICLE SUMMARY

Strengths and limitations of this study

- The results of this retrospective, multi-center study should allow a better standardization of the HITOC-procedure including perioperative safety measures and also validate the existing clinical experience.
- In the long term it could be the basis for survival analyses and further prospective studies.
- Due to the retrospective nature of our study, the implementation of hyperthermic intrathoracic chemotherapy was not uniform, which affects the analysis of 30-day morbidity and mortality
- To the best of our knowledge, this study will represent the largest cohort of patients with surgical cytoreduction and HITOC.

Abbreviations and acronyms

BSA = body surface area

eP/D = extended pleurectomy/decortication

EPP = extrapleural pneumonectomy

HITOC = hyperthermic intrathoracic chemotherapy

MPM = malignant pleural mesothelioma

P/D = pleurectomy/decortication

TC= thymic carcinoma

ZKS = Center for Clinical Studies of the University Medical Center Regensburg

INTRODUCTION

Hyperthermic intrathoracic chemotherapy (HITOC) is a local, intraoperative perfusion of the thoracic cavity with a chemotherapeutic agent after surgical cytoreduction of malignant pleural tumors. The HITOC represents an additional therapeutic option in a multimodality treatment concept especially for patients with malignant pleural mesothelioma (MPM), thymic tumors with pleural spread (stage IVa) and even in highly selected patients with pleural carcinosis (1, 2). The spreading growth pattern of these malignant tumors along the pleura impairs a microscopically complete resection and small residues of the tumor often lead to local recurrence (2). With the application of the HITOC after macroscopic complete pleural tumor resection it is expected to obtain better local tumor control and thereby improve progression-free as well as overall survival (2-4). The few existing case series or single-center retrospective studies in patients with MPM and thymic tumors have shown some encouraging results in this regard (2, 5-9). However, a prospective study showing an advantage in survival does not yet exist.

A survey of the German Society for Thoracic Surgery on the application of HITOC confirmed that approximately 350 HITOC procedures have already been performed in Germany from 2008 to 2017. Most of the procedures were conducted at University Thoracic Surgery Centers in Munich, Heidelberg, Freiburg, Regensburg and Cologne (Witten-Herdecke) (10).

Although HITOC is performed routinely in some experienced Departments of Thoracic Surgery in Germany, only feasibility studies, case series, and retrospective studies with small numbers of patients have been published so far evaluating perioperative management, technique, the selection and dosage of chemotherapeutic agents and postoperative complications (1, 11, 12) (Table 1). There is no standardized procedure of HITOC concerning the administration of chemotherapeutic agents, the dosage of the drugs, duration and temperature of the perfusion as well as the perioperative management of these patients including safety measures for the personal. As a result, clinics performing HITOC follow internationally reported experiences and developed individual protocols (10). In 2019 a clinical practice guideline on HITOC within the guideline system of the Association of the Scientific Medical Societies in Germany was

published. Due to the lack of empirical data, this guideline was based on an expert consensus (so called S1-guideline). The group of experts agreed on the key aspects of applying HITOC in thoracic surgery (Table 2) (20).

Before performing the HITOC, all patients underwent surgical cytoreduction of the pleural tumor. Therefore, pleurectomy/decortication (P/D), extended pleurectomy/decortication (eP/D) with partial and/or complete resection of the pericardium and/or diaphragm, or extrapleural pneumonectomy (EPP) is carried out to achieve a macroscopic complete resection whenever possible (21). The outcome of lung-saving procedures (P/D, eP/D) turned out to be equivalent to EPP with significantly less complications, so that these procedures should preferably be performed (8).

Usually HITOC and tumor resection are performed in the same session. Apical inflow and basal outflow drainages are placed in the thoracic cavity. The following perfusion can be carried out with an open (before wound closure) or closed (after wound closure) chest, while the procedure on the closed chest is more common. Its advantage is that no cytostatic agent can leak out of the thoracic cavity during circulation, which would be a safety risk for the practitioner (7, 10). The drainages are then connected to an external perfusion system. A stable circulation is established with a priming-volume and the perfusion solution is heated to a targeted temperature of 40-43°C (9, 22). The chemotherapeutic agents are added to the perfusate and the circulation is performed between 60 and 120 minutes. Subsequently, the perfusion solution is passively drained.

This retrospective, multi-center study will provide the first time opportunity to enroll a substantial number of study participants from experienced German centers regarding HITOC to validate the clinical experience of the individual centers and possibly form the basis for a standardized procedure with an adequate perioperative management in patients who underwent HITOC. In the long term, this database might be used for survival analyses with respect to the different tumor entities and may serve to design a prospective study.

METHODS AND ANALYSIS

Study design

This is a retrospective, multi-center observational study to evaluate HITOC at university thoracic surgery clinics with the most performed operations including HITOC in Germany. The participating clinics include the Thoracic Surgery Center Regensburg (University Hospital Regensburg, Hospital Barmherzige Brüder Regensburg), the Department of Thoracic Surgery, Thoracic Clinic Heidelberg (University of Heidelberg), the Department of Thoracic Surgery, Medical Center, University of Freiburg and the Thoracic Surgery Center Munich, Hospital of the University of Munich (Ludwig-Maximilians-University, Campus Großhadern; Asklepios Lung Clinic Gauting). Estimating the number of patients of each participating clinic at the time of designing this study resulted in a total number of approximately 250-300 patients in the period between January 2008 and December 2019 who could be retrospectively included in this study. This will represent the largest cohort of patients who received HITOC compared to the recent international literature (Table 1) (9).

Inclusion and exclusion criteria

The study will examine patients with malignant pleural tumors who received HITOC after surgical cytoreduction between beginning of the HITOC program in 2008 and the end of December 2019 at all study centers. Patients without HITOC or without surgical cytoreduction will not be included (Table 3). Informed consent is not an eligibility criterion because data will be processed in a pseudonymized manner in accordance with EU-GDPR and BayKrG.

Study endpoints

This study aims at quality assurance and evaluation of HITOC after surgical cytoreduction at the thoracic surgical university hospitals with most experience with HITOC in Germany. For this broad assessment, a compound of endpoints was defined as shown in Table 4.

Central element of the study will be the evaluation of parameters concerning the implementation of HITOC. In particular the selection of chemotherapeutic agents by the

respective clinics will be assessed by showing which and how often certain combinations and dosages were used at leading German clinics in this field, since the approach varies internationally (Table 1). In this regard, the association of the administered cisplatin dosage with the occurrence and severity (according to the FDIGO classification) of postoperative renal insufficiency will be analyzed. Also the incidence and severity (according to the Clavien-Dindo classification) as well as the spectrum of postoperative complications after HITOC will be determined. To further evaluate the safety of the procedure, 30-day mortality will be another element of the assessment. Finally, the development of this procedure in Germany concerning the technique, perioperative management and safety over a time span of approximately eleven years will be demonstrated (Figure 1).

Documentation and data base

After identifying all patients who meet all criteria shown in Table 3, data will be documented in an electronic database. In this database information on the performed surgery and additional HITOC will be obtained, focusing on the technique as well as the applied perfusion solution. Therefore, participating clinics will enter parameters regarding the patient characteristics (age, ECOG stage, ASA stage, tumor entity, tumor stage, date of first diagnosis), performed surgery (localization, extend of surgical cytoreduction, complications), HITOC (combination and dosage of chemotherapeutics, perfusion volume, temperature, flow rate, duration of chemotherapy perfusion, complications) and perioperative management (weaning, fluid balancing, care on the intensive care unit). Data from the postoperative period (30-day morbidity) also include complications assigned to the Clavien-Dindo classification with special respect to postoperative renal insufficiency, required surgical revisions, duration of intensive medical care, hospitalization and 30-day mortality (23). In addition, first data regarding progression-free and overall survival are warranted to be analyzed (Table 5).

Data management

The Center for Clinical Studies (ZKS) of the University Medical Center Regensburg is establishing a web-based, central and uniform database, using a common Clinical Database Management System (CDMS). This system provides the capability to perform major data management activities within a consistent, auditable, integrated and EU-GDPR compliant environment. Data quality checks (regarding data ranges, validity and consistency) will be carried out regularly. In case of necessary corrections or existing data inconsistencies, a data manager will generate data queries consecutively. All data entries will be routinely recorded via audit trail, as well as data modifications and data corrections.

Statistical analyses

Subsequently, the statistical data evaluation of the study is also carried out by the ZKS of the University Hospital Regensburg.

Patient characteristics, quality assurance parameters and evaluation of HITOC after surgical cytoreduction (Table 4) will be summarized descriptively, using absolute and relative frequencies for categorical data and mean, standard deviation, median, interquartile range, minimum and maximum for metric data.

Risk factors (e.g. HITOC parameters) for 30-day mortality, in-hospital mortality and postoperative complications will be assessed by using binary logistic regression models. With regard to all outcome measurements, reference values for optimal HITOC parameters will be provided. The level of significance will be set at 5% for all statistical tests.

The results of this retrospective study are intended to contribute to a standardization of the perioperative procedure including safety measurements. To establish quality assurance in HITOC patients, benchmarks are to be defined on the basis of the study. The rate of lung-sparing resections as well as the rate of postoperative renal insufficiency, wound infections as well as the length of hospital stay after surgical cytoreduction including HITOC and the 30-day mortality will be determined and thus provide reference for clinics performing this combined procedure.

Ethics and dissemination

The study was funded by the German Research Foundation (Deutsche Forschungsgemeinschaft – DFG; GZ: RI 2905/3-1) and will be supported for 12 months after its start in January 2020. The trial is registered in the German Register of Clinical Studies (DRKS-ID: DRKS00015012, Date of registration: 03th August 2018). The approvals by the local ethics committee of the respective clinic and the three participating clinics have been obtained (reference number University Regensburg: 18-1119-104). Each patient will be assigned an identification number for pseudonymization. The study ends regularly in December 2020 when the study parameters have been evaluated and published. The results are planned to be published in a peer-reviewed journal.

Patient and public involvement

In this study, patients or the public were not involved in the design, conduct, reporting or dissemination of research.

DISCUSSION

There are different approaches in the international literature regarding the implementation and perioperative management of HITOC after surgical cytoreduction (9). A common standard for the procedure of HITOC does not yet exist, so that clinics performing this procedure orientate their protocols towards a small number of studies with often few participants (Table 1).

The available single-center studies demonstrated that the rate of complications could be acceptable with an appropriate perioperative management (1, 11, 12). To perform HITOC safely and keep HITOC-specific complications low, adequate perioperative management and an interdisciplinary approach is essential, especially between surgery, anesthesia and intensive care (24).

In the published research, cisplatin is always part of the perfusion solution. However, the dose administered varies, but usually it is applied in doses lower than 175 mg/m^2 body surface area BSA; Table 1) (1, 10, 13, 15, 17). The application of higher doses of cisplatin seems to be

associated with better overall survival, but also might cause more complications. Our study group described that the cisplatin concentration in patient serum increases to only about 2% of the intrathoracic concentration, although if the cisplatin dosage is increased up to 150 mg/m^2 BSA (6, 25). As a result, much higher concentrations can be achieved locally in the tissue than with systemic administration (22). However, high intrathoracic concentrations lead to an increased incidence of postoperative complications (e.g. renal insufficiency), for which reason the maximum tolerable dose of cisplatin was identified at 225 mg/m^2 BSA (6). Concerning postoperative renal insufficiency, the use of protective measures such as nephroprotective agents and fluid balancing may have a preventive effect (26). First introduced by Sugarbaker et al. in HITOC, it is currently also being practiced in a few more studies (6, 26).

The application of a second chemotherapeutic agent is also heterogeneous. The considerations of applied agents were guided by the experience in systemic therapy. Superiority over systemic cisplatin monotherapy has been demonstrated in both MPM and thymoma patients (27, 28). In some clinics, cisplatin is combined with doxorubicin, epirubicin, gemcitabine or mitomycin, whereas other clinics use cisplatin alone (5, 13, 19).

Another factor where the protocols differ in international compare is the target temperature of the chemotherapeutic solution. During perfusion, it is constantly measured using two probes at the inflow and outflow drainage (6). It has been shown that the penetration depth of cisplatin into the tissue increases with the temperature of the intrathoracic solution. Applied temperatures of 40-43°C are described in the literature (1, 14, 16, 29). Intrapleural temperatures above 43°C are supposed with an increased risk of pulmonary edema and should therefore be avoided (30). Also, high temperatures of the perfusate lead to an increased risk of systemic hyperthermia (24). Regarding the optimal duration of perfusion only little research exists and thus varies between 60 and 120 minutes (15, 19).

Conclusion

In summary, the German HITOC-Study will include the biggest study population with surgical cytoreduction and HITOC since now. It will retrospectively evaluate the additional HITOC-

procedure with main respect to quality assurance and it will support a standardization of the procedure. Results are expected in 2021.

Trial status:

At the time of manuscript submission, data base is finished and data collection started in April 2020. The following analyses are planned to be completed by the end of 2020.

Declarations

Author contributions: TM and MR wrote the manuscript. FZ, GH and MK proved the manuscript regarding the study design and the described statistical analysis. HSH and all collaborators of the HITOC Study Group revised the manuscript critically. All authors approved the final version of the manuscript.

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Competing interests: Nothing to declare.

FIGURE LEGENDS

Figure 1: Flow-chart of the study design

TABLES

Table 1: Study overview

Author, year (reference number)	Patients (primary tumors)	Chemotherapeutic agents, duration, temperature
Refaely et al., 2001 (13)	n=15 (thymoma/TC)	cisplatin (100mg/m^2 BSA); 60 min; 42°C
De Bree et al., 2002 (5)	n=3 (thymoma/TC) n=11 (MPM)	cisplatin (80mg/m^2 BSA) + doxorubicin (15-30mg/m^2 BSA); 90 min; 40-41°C
Richards et al., 2006 (6)	n=44 (MPM)	cisplatin (low-dose: 50-150mg/m^2 BSA; high-dose: 175-250mg/m^2 BSA); 60 min; 42°C
Zellos et al., 2009 (11)	n=29 (MPM)	cisplatin (75-200mg/m^2 BSA); 60 min; 42°C
Tillemann et al., 2009 (12)	n=92 (MPM)	cisplatin (225mg/m^2 BSA); 60 min; 42°C
Ried et al., 2013 (2)	n=8 (MPM) n=8 (thymoma/TC)	cisplatin (100-150mg/m^2 BSA); 60 min; 42°C
Sugarbaker et al., 2013 (1)	n=72 (MPM)	cisplatin (175-225mg/m^2 BSA); 60 min; 42°C
Yellin et al., 2013 (14)	n=35 (thymoma/TC)	cisplatin (100mg/m^2 BSA) + doxorubicin (50-60mg, 60 min; 43°C
Yu et al.; 2013 (15)	n=4 (thymoma/TC)	cisplatin (100mg/m^2 BSA); 120 min; 41-43°C
Migliore et al., 2015 (4)	n=6 (MPM) n=2 (lung cancer)	cisplatin (120mg/m^2 BSA); 60 min; 42.5°C
Ishibashi et al., 2015 (16)	n=14 (MPM)	cisplatin (80mg/m^2 BSA); 60 min; 42°C
Ambrogi et al., 2016 (17)	n=13 (thymoma/TC)	cisplatin (80mg/m^2 BSA) + doxorubicin (25mg/m^2 BSA); 60 min; 42.5°C
Bertoglio et al., 2017 (18)	n=26 (MPM)	cisplatin (80mg/m^2 BSA) + doxorubicin (25mg/m^2 BSA); 60 min; 42.5°C
Maury et al., 2017 (19)	n=19 (thymoma/TC)	cisplatin (50mg/m^2 BSA) + mitomycin (25mg/m^2 BSA); 90 min; 42°C
Ambrogi et al., 2018 (8)	n=49 (MPM)	cisplatin (80mg/m^2 BSA) + epirubicin (25mg/m^2 BSA); 60 min; 42.5°C
Burt et al., 2018 (7)	n=104 (MPM)	cisplatin (175-225mg/m^2 BSA) + gemcitabine (100-1200mg/m^2 BSA); 60 min; 40-42°C

Markowiak et al., 2019 (3)	n=29 (thymoma/TC)	cisplatin (100-175mg/m^2 BSA) + doxorubicin (0-65mg); 60 min; 42°C

BSA = Body surface area, MPM = malignant pleural mesothelioma, TC= thymic carcinoma

Table 2: Consensus-based expert recommendation (excerpt) (20)

	Content; consensus strength
Nomenclature	– Hyperthermic intrathoracic chemotherapy (HITOC); 100%
Technique	– One session; 100% – Closed thorax; 100% – Temperature of 42°C on the outflow drainage; 100% – Duration of 60min; 100%
Chemotherapeutic agents	– Application of cisplatin; 100% – Maximum dosage of 225mg/m² BSA; 100% – Dosage between 150 and 175mg/m² BSA; 100%
Perioperative management	– Perioperative fluid balancing and forced diuresis; 100% – Drug-based nephroprotection may be considered; 100% – Safety-management including protective clothing of the personnel and disposal of drain fluids; 100%
Indications	– Malignant pleural mesothelioma; 100% – Stage IVa thymoma; 100% – Secondary pleural carcinosis; 100%

BSA=Body surface area

Table 3: Inclusion- and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years	• Treatment without HITOC
• Malignant pleural tumor	• HITOC without surgical cytoreduction
• Surgical cytoreduction and HITOC	
• Treatment period: 2008-2019	

HITOC=hyperthermic intrathoracic chemotherapy

Table 4: Study Endpoints (Quality assurance and implementation of intraoperative HITOC after surgical cytoreduction)

Study endpoints
• dosing of the intrathoracic chemotherapeutic agent
• postoperative renal failure (dependence on cisplatin dosage)
• 30-day morbidity and mortality
• development of the technique, perioperative management and complication spectrum over time of HITOC

HITOC=hyperthermic intrathoracic chemotherapy

Table 5: Overview of data collection with respect to subgroups

Subgroups of data collection
– Demographic data
– Physical examination
– Performance status
– Tumor specific data
– Surgery specific data (intra-, postoperative)
– HITOC specific data
– Renal function
– Information on hospitalization
– Follow-up

HITOC=hyperthermic intrathoracic chemotherapy

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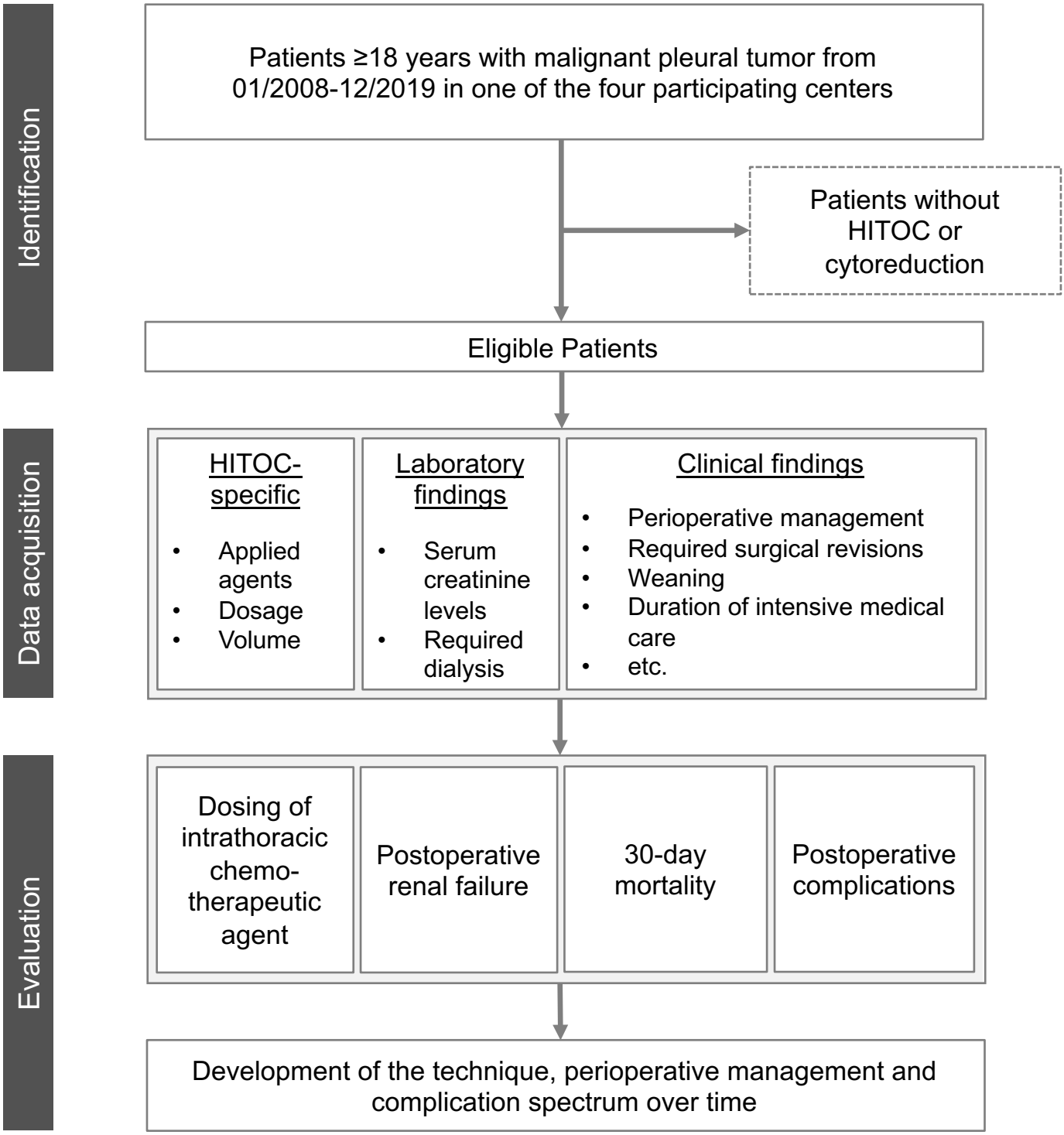
Identification
Patients ≥18 years with malignant pleural tumor from 01/2008-12/2019 in one of the four participating centers
Patients without HITOC or cytoreduction
Eligible Patients
Data acquisition
HITOC-specific
Applied agents
Dosage
Volume
Laboratory findings
Serum creatinine levels
Required dialysis
Clinical findings
Perioperative management
Required surgical revisions
Weaning
Duration of intensive medical care
etc.
Evaluation
Dosing of intrathoracic chemo-therapeutic agent
Postoperative renal failure
30-day mortality
Postoperative complications
Development of the technique, perioperative management and complication spectrum over time

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8,9
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	(7)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Not applicable
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Not applicable
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	Not applicable
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10,11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.