Study protocol for the ISSPP PIPAC Database 2020

This protocol has been approved by the ExCo of the International Society for the Study of Pleura and Peritoneum (ISSPP) March 2020

Name	**International Society for the Study of Pleura and Peritoneum (ISSPP) Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) Database**
Short form	**ISSPP PIPAC Database**
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Project management and monitoring	OPEN Open Patient data Explorative Network Open Patient data Explorative Network, Region of Southern Denmark, Odense University Hospital, J.B. Winsløws Vej 9 a, 3rd floor DK-5000 Odense C, Denmark, Tel.: +45 2916 6730 e-mail: open@rsyd.dk (Contact: Janni Brødbæk, Manager for Project Coordination & Administration) Claus Fristrup (Research Project Manager, RPM) (ISSPP Database Manager), HPB Section, Odense PIPAC Center (OPC), Department of Surgery, Odense University Hospital, DK-5000 Odense C, Denmark. Claus.Wilki.Fristrup@rsyd.dk

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Register database	 Open Patient data Explorative Network, Region of Southern Denmark, Odense University Hospital, J.B. Winsløws Vej 9 a, 3rd floor DK-5000 Odense C, Denmark, Tel.: +45 2916 6730 e-mail: open@rsyd.dk
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Language	English
Background and rationale	Peritoneal carcinomatosis represents a particularly aggressive metastasis pathway of gynecological and gastrointestinal tumors. Every year, more than 167,940 new cases per year are diagnosed in Europe. Palliative systemic chemotherapy is the standard treatment in this situation. However, the efficacy of systemic chemotherapy on peritoneal carcinomatosis is hampered by limitations such as poor peritoneal vascularization and increased intra-tumoral fluid pressure. Furthermore, side effects are relatively common under systemic chemotherapy. The focus is on renal toxicity (cisplatin), neurotoxicity (oxaliplatin), cardiotoxicity (doxorubicin). Therefore, the effectiveness of chemotherapy is limited. Intraperitoneal chemotherapy is increasingly being used in the treatment of peritoneal carcinomatosis in order to optimize local drug delivery and improve clinical outcomes. However, this therapy is limited by pharmacological limitations: the poor distribution of the therapeutic principle within the abdomen and the limited diffusion into the tumor tissue (1) which is partially explained by the increased intra-tumoral interstitial fluid pressure (2). To be able to treat patients with centimetric peritoneal tumor nodules anyway, surgeons have been beginning to combine intraperitoneal chemotherapy with subtotal surgical cytoreduction for nearly 30 years (3). The rationale for this therapy is undoubtedly given and cytoreductive surgery with HIPEC is very effective in isolated cases (4). In stage IV cancer, however, this aggressive therapy remains controversial (5). It can only be offered to selected patients in good general condition and limited peritoneal carcinomatosis, because this procedure is associated with significant complications and does not promise oncological benefit in most patients. In addition, the available scientific evidence is limited (5).

	After the diagnosis of peritoneal carcinomatosis, most patients want to live and live well. There is obviously a medical need to develop a better treatment option that improves the survival and maintenance of quality of life by reducing both disease-related symptoms and side-effects. PIPAC Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is an innovative method of intraperitoneal chemotherapy for peritoneal cancer (peritoneal carcinomatosis), the basic principle of which was first published in 2000 (6) and its first application in humans at the end of 2011. Due to the better use of physical properties (pressure application, gaseous form), PIPAC is able to administer drugs in body cavities of humans (such as in the abdomen or in the chest) particularly effectively. During the PIPAC drugs (such as cisplatin, doxorubicin, oxaliplatin, paclitaxel) are used, whose effectiveness on a certain type of tumor has already been proven elsewhere. Excellent pharmacological properties of PIPAC has been demonstrated in the animal model, ex-vivo and in patients (7-9). The superiority of tissue penetration and apoptosis induction after PIPAC vs. HIPEC was independently confirmed in June 2014 with oxaliplatin using the example of colorectal carcinoma. Local administration directly at the site of the tumor and extensive control of previous pharmacological limitations of intraperitoneal chemotherapy (poor distribution within the body cavity, poor diffusion into tissue) can reduce the necessary dose of the toxic drug by a factor of 10 without sacrificing tumor efficacy. This controls the dose-dependent (10,11) local toxicity of intraperitoneal chemotherapy, significantly reduces organ toxicity (12) and the systemic side effects of the therapy. The procedure of PIPAC therapy is standardized and considered safe, and the effectiveness has been provisionally demonstrated in both pro- and retrospective studies in ovarian cancer, gastric carcinoma, colorectal carcinoma, pancreatic cancer and peritoneal mesothelioma (13).
Study aim	To include data from all PIPAC centers worldwide in a central database in order to monitor treatment quality, perform benchmarking and identify research populations
Design	Non-interventional, multicenter data registry for patients treated with PIPAC for malignant peritoneal disease. Patients are included retrospectively and prospectively by the attending physician based on their clinical and histopathological diagnosis of malignant peritoneal disease
Number of patients	Depends on the number of participating centers and procedures per center. Globally, it is estimated that up to 50-100 centers may include their patients in the database. Each center is estimated to report completion of at least 100 new cases over a five-year period.
Statistics	All data in the registry describing the patient population in terms of disease characteristics, demography and therapy are analyzed descriptively using standard statistical methods
Variables	The following variables are registered under five headings

	(Patient/Treatment/Response evaluation/Complications/Follow up) PATIENT: Registry Patient ID Date of Birth Gender Primary Tumor (incl. “other” site than specified) Primary Tumor in situ Primary Histology (incl.”other” primary histology than specified) Known date of diagnose of peritoneal metastasis Date of diagnose of peritoneal metastasis Time from primary tumor diagnosis to peritoneal metastasis Metastasis outside peritoneum Location of extraperitoneal Metastasis (incl. “other” location than specified) Previous Oncological Treatment (incl.”other” previous treatment than specified) ECOG Performance Status TREATMENT: Type of treatment Date of treatment Hospital stay Treatment within prospective Study Electrostatic Precipitation Other surgery Non access Drug(s) Oxaliplatin (mg/m2) Cisplatin (mg/m2) Doxorubicin (mg/m2) nab-Paclitaxel (mg/m2) Flow rate of infusion Exposure Time (min) PCI Score (0-39) Ascites Ascites mL Systemic Chemotherapy within 4 weeks prior to this treatment Complications RESPONSE EVALUATION: Date of biopsy Type of evaluation Mean Peritoneal Regression Grading Score (PRGS) Non PRGS evaluation COMPLICATIONS: Complication / Adverse Event (CTCAE v5.0) Other Adverse Event CTCAE Grade Dindo-Clavien Grade Date of Complication / Adverse Event FOLLOW UP: Last Contact in Institution (Date of latest follow up) Dead Date of death Reasons for stopping PIPAC
Number of participating hospitals	Open. All institutions performing PIPAC can contribute to the ISSPP PIPAC Database after having attended an official ISSPP PIPAC Training Course, obtained the ISSPP course certificate and payed the ISSPP membership fee (at least one person/institution).
Start of registration	01.05.2020

End of registration	30.04.2025
Diagnosis and inclusion criteria	Patients who have entered the treatment context of the participating center and meet the following criteria: - Patients diagnosed with malignant disease of the peritoneum - Age ≥ 18 years and in possession of the ability to understand, question and measure the requirements of the registry and education - Signed consent to participate in the register (form translated into native language)
Exclusion criteria	Patients who - Do not meet the inclusion criteria - Withdraw their consent to participate in the study
Therapy	The treatment of malignant disease is the responsibility of the treating physicians. The storage of the data has no influence on the treatment of the patient and on further therapies
Outcome	• Annual interim analysis of PIPAC activities within ISSPP PIPAC Database according to predefined variables • National and international Benchmarking of ISSPP PIPAC Database findings with reference to ISSPP PIPAC scientific evidence consensus paper • Identification of disease entities and specific procedure/patient/outcome related problems for scientific multi-center studies
Ethical and legal aspects	The ISSPP PIPAC Database is established, approved and hosted in accordance with national legislation for international databases in Denmark: - A local Research Project Manager (RPM) has been appointed - The RPM is the data responsible person (mandatory) and signer of license agreement with OPEN - The RPM is responsible for the collaboration with OPEN and the contact with external users of the database (e.g. license and passwords involving new centers) Data is transferred to OPEN, Region of Southern Denmark, based on patient consent obtained in each participating center (EU standard, General Data Protection Regulation (GDPR)) Since the database is hosted in EU this means that GDPR also applies to data transferred from institutions outside EU to the database. The database study protocol was approved by The Research Ethics Committee, University of Southern Denmark (SDU-RIO)(Reference number: 20/24599). Subsequently, each institution contributing to the database must seek local IRB approval before starting. The database will be created and used according to the protocol and the Helsinki declaration.
Publication	Once a year the Research Project Manager will provide data for the Annual ISSPP PIPAC Database Report. A report draft will be written by members of the ISSPP Registry Group (see below) and after revision and final approval by the ISSPP ExCo the results are published in *Pleura & Peritoneum*, on the ISSPP website and during the following

	international ISSPP Congress. The authorship of ISSPP PIPAC Database reports are determined by standard rules according to ICMJE (www.icmje.org)
ISSPP Registry Group	Alfred Königsrainer (Tübingen), Marc Pocard (Paris), Marc André Reymond (Tübingen), Philipp Horvath (Tübingen), Claus Fristrup (Odense), Michael Bau Mortensen (Chairman, Odense), Martin Hübner (Lausanne), Oliver Glehen (Lyon), Jimmy So (Singapore), and Hyung-Ho Kim (Seoul).
Financing	The database is supported by the ISSPP with an amount corresponding to 1/12 of an annual specialist salary for the RPM. ISSPP is a non-profit international scientific organization. The ISSPP bylaws have been submitted to and accepted by the Administrative Court in Stuttgart, Germany
Data Codebook	(enclosed)
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