Peritoneal Tumors and Metastases

Surgical, intraperitoneal and systemic therapy

Beate Rau
Alfred Königsrainer
Faheez Mohamed
Paul H. Sugarbaker
Editors

MOREMEDIA

Springer

Peritoneal Tumors and Metastases

Beate Rau • Alfred Königsrainer
Faheez Mohamed • Paul H. Sugarbaker
Editors

Peritoneal Tumors and Metastases

Surgical, intraperitoneal and systemic therapy

Springer

Editors
Beate Rau
Department of Surgery, Charité – Universitätsmedizin Berlin
Freie Universität Berlin and Humboldt-Universität of Berlin
Berlin, Germany

Alfred Königsrainer
Department of General, Visceral and Transplant Surgery
University Hospital of Tübingen
Comprehensive Cancer Center
Tübingen, Germany

Faheez Mohamed
Basingstoke and North Hampshire Hospital
Peritoneal Malignancy Institute
Basingstoke, UK

Paul H. Sugarbaker
Center for Gastrointestinal Malignancies
MedStar Washington Hospital Center
Washington, DC
USA

Translation from the German language edition: Peritoneale Tumoren und Metastasen edited by Rau, Beate, Piso, Pompiliu, Königsrainer, Alfred.

ISBN 978-3-030-62639-6 ISBN 978-3-030-62640-2 (eBook)
https://doi.org/10.1007/978-3-030-62640-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Why is it that a large number of world opinion leaders in gastrointestinal cancer have recently focused such great time and effort on peritoneal tumors? Carcinomatosis from gastrointestinal cancer has been a diagnosis treated by palliation for many decades. It is hard to know for sure where the stimulus for efforts such as *Therapie Peritonealer Tumoren* first started. I suggest that the origins of this new attitude toward the management of carcinomatosis had two beginnings. First, clinical research showed that dissemination of cancer on peritoneal surfaces or at a surgical resection site was a terrible ongoing problem in gastrointestinal oncology [1–3]. Something needed to be done! Second, Dedrick and colleagues borrowed pharmacologic concepts from the literature on chronic peritoneal dialysis that suggested prolonged exposure of cancer chemotherapy to peritoneal surfaces if intraperitoneal administration was used. Pharmacologic data from intraperitoneal administration of anticancer drugs showed the potential for control of small peritoneal nodules and a reduced systemic toxicity [4, 5].

The augmentation of cancer chemotherapy cytotoxicity by moderate heat had been known for several decades [6]. Also, intraperitoneal heat by itself had shown benefit for control of peritoneal carcinomatosis in animal models [7]. It was a logical next step to combine intraperitoneal chemotherapy with intraperitoneal heat in an attempt to maximize the local-regional effect. In 1980, hyperthermic intraperitoneal chemotherapy (HIPEC) was first reported [8].

Early efforts to use an adjuvant HIPEC to prevent peritoneal metastases were initiated in Japan [9–11]. Treatment of gross peritoneal cancer nodules was of little or no benefit in animal models. Also, pharmacologic studies showed surprisingly limited penetration of high concentration of heated intraperitoneal chemotherapy into the surface of peritoneal cancer nodules. Not surprisingly the clinical experiments to prevent peritoneal metastases and local recurrences with HIPEC in high-grade serosal invasive cancers, especially gastric cancer, after complete resection was positive [12]. These original experiments have been repeated many times and are uniformly successful [13]. Today these clinical experiments to use HIPEC in primary gastrointestinal cancer to reduce surgical treatment failure at the resection site and on peritoneal surfaces distant to the primary cancer persist. A large group of colorectal cancer patients are at high risk for peritoneal metastases and at least four randomized clinical trials are open for accrual [14]. Resected pancreas cancer has always had a high incidence of local regional and peritoneal

surface failure [15]. The possible benefits of adjuvant HIPEC to eliminate peritoneal metastases in selected groups of patients remain to this day. Thirty years after Koga's original efforts, a high priority for clinical investigation persists [14].

Efforts to treat established carcinomatosis were unsuccessful until the development of peritonectomy procedures and visceral resections to reduce the extent of disease [16]. The limited effects of HIPEC, especially its limited penetration into tumor tissue, demanded that disease be reduced to tiny nodules, preferably a non-visible extent of disease. The new concept of cytoreductive surgery to use surgical procedures to allow HIPEC to maintain control of peritoneal dissemination allowed the evolution of potentially curative treatment protocols for many gastrointestinal and gynecologic malignancies. *Therapie Peritonealer Tumoren* updates the current treatment options and selection factors needed for successful management of peritoneal metastases. Of course, the surgical requirements of adequate cytoreduction are presented.

So, there is good reason why these world opinion leaders have banded together to focus on the current state of the art for PREVENTION and TREATMENT of peritoneal metastases. This is a preventable condition, also treatment for cure is possible in selected patients. HIPEC is being optimized and standardized. Cytoreductive surgery is being standardized. However, peritoneal metastases are a global problem. The educational efforts to expand these efforts globally are now a reality. *Therapie Peritonealer Tumoren* is a major effort to expand a much needed educational program in peritoneal metastases.

Berlin, Germany — Beate Rau
Tübingen, Germany — Alfred Königsrainer
Basingstoke, UK — Faheez Mohamed
Washington, WA, USA — Paul H. Sugarbaker

References

1. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy: a prospective study of prognostic factors. Cancer. 1989;63:364–7.
2. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2002;89:1545–50.
3. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, et al. Peritoneal carcinomatosis from non-gynecologic malignancies. Results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;88:358–63.
4. Dedrick RL, Myers CE, Bungay PM, deVita V Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep. 1978;62:1–11.
5. Speyer JL, Collins JM, Dedrick RL, Brennan MF, Buckpitt AR, et al. Phase 1 and pharmacologic studies of 5-Fluorouracil administered intraperitoneally. Cancer Res. 1980;40:567–72.
6. Meyer JL, Kapp DS, Fessenden P, Hahn GH. Hyperthermic oncology: Current biology, physics and clinical results. Pharmac Ther. 1989;42:251–88.

7. Shiu MH, Fortner JG. Intraperitoneal hyperthermic treatment of implanted peritoneal cancer in rats. Cancer Res. 1980;40:4081–4.
8. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res. 1980;40:256–60.
9. Koga S, Hamazoe R, Maeta M, Shimizu N, Kanayama H, Osaki Y. Treatment of implanted peritoneal cancer in rats by continuous hyperthermic peritoneal perfusion in combination with an anticancer drug. Cancer Res. 1980;44:1840–2.
10. Fujimoto S, Takahashi M, Mutou T, Kobayashi K, Toyosawa T. Successful intraperitoneal hyperthermic chemoperfusion for the prevention of postoperative peritoneal recurrence in patients with advanced gastric carcinoma. Cancer. 1998;85:529–34.
11. Fujimura T, Yonemura Y, Muraoka K, Takamura H, Hirono Y, et al. Continuous hyperthermic peritoneal perfusion for the prevention of peritoneal recurrence of gastric cancer: Randomized controlled study. World J Surg. 1994;18:150–5.
12. Koga S, Hamazoe R, Maeta M, Shimizu N, Murakami A, et al. Prophylactic therapy for peritoneal recurrence of gastric cancer by continuous hyperthermic peritoneal perfusion with mitomycin C. 1988;61:232–7.
13. Yan TD, Black D, Sugarbaker PH, Zhu J, Yonemura Y, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol. 2007;14(10):2702–13.
14. Sugarbaker PH. The seven best of PSOGI 2016. Ann Surg Oncol. 2017;24(4):870–4.
15. Sugarbaker PH. Strategies to improve local control of resected pancreas adenocarcinoma. Surg Oncol. 2017;26:63–70.
16. Sugarbaker PH. Peritonectomy procedures. Ann Surg. 1995;221:29–42.

Contents

Contributors

Dieudonne Ajah Klinik Mallersdorf, Mallersdorf-Pfaffenberg, Germany

Salah E. Al-Batran Institute of Clinical Cancer Research-UCT University Cancer Center Frankfurt, Frankfurt, Germany

Thomas Bachleitner-Hofmann Department of Surgery, Medical University of Vienna, Vienna, Austria

Prisca Bartels Medical Clinic for Hematology, Oncology and Tumor-Immunology, Campus Virchow-Klinikum, Charité – University Medicine Berlin, Berlin, Germany

Ilona Baumann Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany

Stefan Beckert Department of General and Visceral Surgery, Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Germany

Department of General Surgery, Hospital Schwarzwald-Baar, Villingen-Schwenningen, Germany

Stefan Benz Klinik für Allgemein- VIszeral- und Kinderchirurgie, Boeblingen, Germany

Stephan C. Bischoff Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany

Sebastian Blaj Klinik für Allgemein- und Viszerachirurgie, Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany

Christina Bockelmann Department of Traumatology and Orthopedics, Martin Luther Krankenhaus of Berlin, Berlin, Germany

Thomas Boerner Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Hans Bösmüller Institute of Pathology, University of Tübingen, Tübingen, Germany

Andreas Brandl Digestive Unit, Champalimaud Foundation, Lisbon, Portugal

Heidi Braumüller Department of Dermatology, University Medical Center Tübingen, Tubingen, Germany

Ellen Brenner Department of Dermatology, University Medical Center Tübingen, Tübingen, Germany

Susen Burock Charité Comprehensive Cancer Center, Charité University Hospital of Berlin, Berlin, Germany

Peter Busch Funktionsoberarzt Chirurgie, Krankenhaus Agatharied, Hausham, Germany

Marcello Deraco Fondazione IRCCS Istituto Nazionale Dei Tumori di Milano, Peritoneal Surface Malignancies Unit, Milan, Italy

Falko Fend Institute of Pathology, University of Tübingen, Tübingen, Germany

Jörg Fuchs Department of Pediatric Surgery and Urology, University Children's Hospital, Tübingen, Germany

Pankaj Kumar Garg Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India

Pirus Ghadjar Charité Universitätsmedizin, Clinic for Radiation Oncology, Berlin, Germany

Olivier Glehen Department of Surgical Oncology, Centre Hospitalier Lyon-Sud, Lyon, France

Gabriel Glockzin Department of Surgery, Muenchen Klinik Bogenhausen, Munich, Germany

Ines Gockel Department of Visceral, Transplant, Thoracic and Vascular Surgery, Department of Operative Medicine (DOPM), University Hospital of Leipzig, Leipzig, Germany

Ute Goerling Charité – Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Charité Comprehensive Cancer Center, Berlin, Germany

Thomas Golombek University Cancer Center Leipzig (UCCL), University Hospital Leipzig, Leipzig, Germany

Thorsten O. Götze Department of Surgery, Institute of Clinical Cancer Research-UCT University Cancer Center Frankfurt, Frankfurt, Germany

Jens Hartmann Department of Surgery, AKH – Celle, Celle, Germany

Anja Hawliczek Zentrum für Akute und Postakute Intensivmedizin, Kreiskliniken Darmstadt-Dieburg, Kreisklinik Jugenheim, Seeheim-Jugenheim, Germany

Ruediger Hoerbelt University of Giessen, Giessen, Germany

Philipp Horvath Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany

Boris Jansen-Winkeln Department of Visceral, Transplant, Thoracic and Vascular Surgery, Department of Operative Medicine (DOPM), University Hospital of Leipzig, Leipzig, Germany

Joshua R. Kapp Department of Surgery and Transplantation, University Hospital Zurich, Zurich, Switzerland

Maik Kilian Department of Surgery, Evangelische Elisabeth Klinik, Berlin, Germany

Evangelic Elisabeth Hosipital, Berlin, Germany

Bernhard Daniel Klumpp Department for Diagnostic Radiology, Rems-Murr Hospital Winnenden, Winnenden, Germany

Alfred Königsrainer Department of Surgery, University of Tübingen, Tübingen, Germany

Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany

Department of General and Transplant Surgery, University of Tübingen, Comprehensive Cancer Center, Tübingen, Germany

Ingmar Königsrainer Department of General, Visceral and Thoracic Surgery, Academic Teaching Hospital Feldkirch, Feldkirch, Austria

Department of General and Thoracic Surgery, Academic Teaching Hospital Feldkirch, Feldkirch, Austria

Hubert Leebmann Clinic for General and Visceral Surgery, Barmherzige Brüder Hospital, Regensburg, Germany

Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany

Kuno Lehmann Department of Surgery and Transplantation, University Hospital Zurich, Zurich, Switzerland

Lieselotte Lemione Ziekenhuis Oost-Limburg, Genk, Belgium

Florian Lordick University Cancer Center Leipzig (UCCL), University Hospital Leipzig, Leipzig, Germany

Luisa Mantovani-Löffler Department of Medical Oncology and Hematology, St. George Hospital, Leipzig, Germany

Loreen März Germany Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany

Faheez Mohamed Peritoneal Malignancy Institute, Basingstoke and North Hampshire Hospital, Basingstoke, UK

Marina Münch Department of General and Visceral Surgery, Robert-Bosch Hospital, Stuttgart, Germany

Anton Oseledchyk Department of Medical Oncology, Helios Klinikum Berlin-Buch, Berlin, Germany

Eva Pachmayr Department of Surgery, Campus Virchow-Klinikum and Charité Campus Mitte, Charité – Universitätsmedizin Berlin, Berlin, Germany

Winfried Padberg University of Giessen, Giessen, Germany

Jörg Pelz Department of General-, Viszeral- and Oncologic Surgery, St. Bernward Hospital, Hildesheim, Germany

Christina Pfannenberg Department for Diagnostic and Interventional Radiology, Eberhard Karls University of Tuebingen, Tuebingen, Germany

Pompiliu Piso Clinic for General and Visceral Surgery, Barmherzige Brüder Hospital, Regensburg, Germany

Klinik für Allgemein- und Viszerachirurgie, Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany

Francois Quenet IC Val d'Aurelle, Montpellier, France

Christoph Raspé Department of Anesthesiology, Operative Intensive Care Medicine and Pain Therapy, Vivantes Auguste-Viktoria- and Wenckebach-Clinic, Berlin, Germany

Beate Rau Department of Surgery, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität of Berlin, Berlin, Germany

Horst Günter Rau Krankenhaus Martha Maria, Munich, Germany

Wieland Raue Department of Surgery, AKH-Group, Hospital of Celle, Celle, Germany

Allgemeines Krankenhaus Celle, Klinik für Allgemein-, Viszeral- und Thoraxchirurgie, Celle, Germany

Marc A. Reymond Department of General, Visceral and Transplant Surgery, University of Tübingen, Tübingen, Germany

National Center for Pleura and Peritoneum (NCPP), University of Tübingen, Tübingen, Germany

Martin Röcken Department of Dermatology, University Medical Center Tübingen, Tübingen, Germany

Amy Rohrmoser Charité – Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Charité Comprehensive Cancer Center, Berlin, Germany

Lilian Roth Department of Surgery and Transplantation, University Hospital Zurich, Zurich, Switzerland

Franz Florian Rückert Department of Anesthesiology, Ernst von Bergmann Clinic, Potsdam, Germany

Michael Sander Universitätsklinikum Gießen, UKGM GmbH, Justus-Liebig-Universität Gießen, Klinik für Anästhesiologie, Operative Intensivmedizin und Schmerztherapie, Giessen, Germany

Guido Seitz Department of Pediatric Surgery, University Hospital Giessen-Marburg, Marburg, Germany

Marianne Sinn Universitäres Cancer Center, Hamburg-Eppendorf, Hamburg, Germany

Universitätsklinikum Hamburg-Eppendorf, II. Medizinische Klinik und Poliklinik- Onkologie, Hämatologie, Knochenmarktransplantation mit der Sektion Pneumologie, Hamburg, Germany

Jesse Smith University Hospital, Charité Campus Virchow-Klinikum, Berlin, Germany

Wiebke Solass Institute of Pathology, University of Tübingen, Tübingen, Germany

Annette Staebler Institute of Pathology, University of Tübingen, Tübingen, Germany

Thomas Steffen Surgical Clinics, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Wolfgang Steurer Department of General and Visceral Surgery, Leonberg Hospital, Leonberg, Germany

Michael A. Ströhlein Department of Abdominal, Cancer, Vascular and Transplant Surgery, Cologne Merheim Medical Center, Witten/Herdecke University, Cologne, Germany

Florian Struller Department of General, Visceral and Transplant Surgery, University Hospital Erlangen, Erlangen, Germany

Department of General and Transplant Surgery, University Hospital Erlangen, Erlangen, Germany

Alexey Surov Department of Radiology, Otto-von-Guericke-University, Medical Faculty, University Hospital of Magdeburg, Magdeburg, Germany

Clemens B. Tempfer Department of Obstetrics and Gynecology, Marien Hospital Herne, Ruhr-Universität Bochum, Herne, Germany

Jürgen Tepel Surgical Department, Klinikum Osnabrueck GmbH, Osnabrück, Germany

Peter Thuss-Patience Head of Upper GI Oncology, Charité-University Medicine Berlin, Berlin, Germany

Medical Clinic for Hematology, Oncology and Tumor-Immunology, Campus Virchow-Klinikum, Charité - University Medicine Berlin, Berlin, Germany

Kurt Van der Speeten Faculty of Life Sciences, University Hasselt, Hasselt, Belgium

Arved Weimann Department of General and Visceral Surgery and Surgical Oncology, St. George Hospital, Leipzig, Germany

Thomas Wieder Department of Dermatology, University Medical Center Tübingen, Tübingen, Germany

Peter Wust Charité Universitätsmedizin, Clinic for Radiation Oncology, Berlin, Germany

Igor Yakubov Facharzt Viszeralchirurgie, Chirurgische Praxis, Fürstenfeldbruck, Germany

Can Yurttas Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany

Oliver Zivanovic Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Part I

Basics

1 Anatomy and Pathology of the Peritoneum

Wiebke Solass, Annette Staebler, Falko Fend, and Hans Bösmüller

1.1 The Normal Peritoneum

The peritoneum is approximately 2 m^2 in size—the largest serous membrane of the human body. In men, it is a closed space; in women, however, there is a connection between the peritoneal space and the external genitalia through the fallopian tube openings, the uterus, and the vagina. The peritoneum is subdivided into the parietal and the visceral peritoneum. The parietal peritoneum (approximately 30% of the total peritoneal area) covers the abdominal wall, and the visceral peritoneum (approximately 70% of the area) covers the intra-abdominal organs. The two peritoneal layers glide over one another thanks to a serous fluid film and the space between them—the peritoneal cavity. It remains a virtual space with neutral pressure, when healthy, that constantly oscillates between positive and negative pressure on respiration and diaphragm excursion.

W. Solass (✉) · A. Staebler · F. Fend · H. Bösmüller
Institute of Pathology, University of Tübingen, Tübingen, Germany
e-mail: Wiebke.solass@med.uni-tuebingen.de; Annette.staebler@med.uni-tuebingen.de; Falko.fend@med.uni-tuebingen.de; Hans.boesmueller@med.uni-tuebingen.de

1.2 Embryology

Many aspects of the functional anatomy of the gastrointestinal tract, especially of the intestines and the peritoneum, find their explanation in embryology. The human body develops from three germ layers: the endoderm, mesoderm, and ectoderm. These are basically different types of tissue that later differentiate and develop into the various specialized organs of the body. The peritoneum develops from the lateral plate mesoderm. The ovaries also develop from the mesoderm but from the intermediate plate mesoderm (Fig. 1.1).

In clinical decision-making, these different origins are relevant because the differentiation of epithelial and mesothelial markers allows the origin of peritoneal tumors to be determined (see below). Conversely, the similar embryological origin of ovarian surface epithelium and peritoneum also explains the difficulty of immunohistochemical differentiation between ovarian carcinoma and primary papillary peritoneal carcinoma.

However, despite the mesodermal origin, the serous membranes show many similarities with epithelia—such as junctional connections (tight junctions, gap junctions, adherens junctions, desmosomes, etc.), apicobasal orientation, cytokeratins, and superficial microvilli—and thus the differential diagnosis of the various peritoneal

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_1

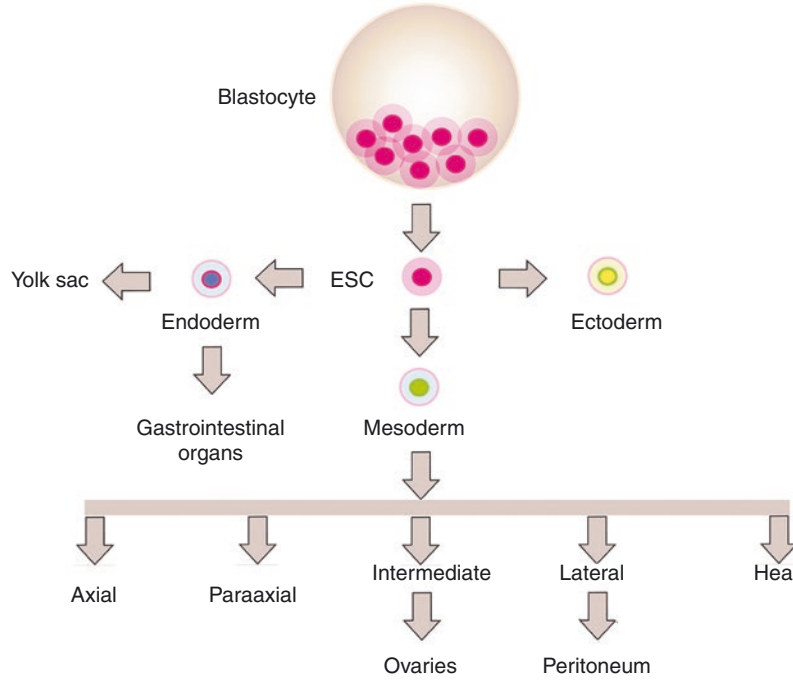


Fig. 1.1 Embryology of the mesothelium. The pleura and peritoneum stem from the lateral plate mesoderm. The ovaries develop from the intermediate plate mesoderm. By contrast, all gastrointestinal organs stem from the endoderm. ESC embryonal stem cell

tumors may remain challenging despite modern examination and characterization techniques.

The complex innervation of the peritoneum also finds its explanation in embryology. During embryogenesis, axons from the nodose ganglia and dorsal root ganglia grow into the intestine to form extrinsic innervation. Once they reach the enteric organs, they continue to grow to allow innervation. Cerebrospinal nerves of the parietal peritoneum (T6–T12) have the same segmental structure as the lower thoracic dermatomes. The enteric nervous system (ENS) is formed from the neural crest [68]. Since the intestinal tract and its appendages grow as midline organs, their splanchnic innervation is bilateral, and visceral pain is felt in the midline [82]. The visceral peritoneum itself is not innervated.

1.3 Morphology

The peritoneum consists of three layers: the mesothelium itself, a basal membrane, and a submesothelial layer (Fig. 1.2).

1.3.1 Mesothelium

The serosa itself consists of a simple layer of mesothelial cells with a central, oval nucleus and moderate cytoplasmic content. The cells are usually elongated, flat cells with a diameter of 25 µm. The mesothelial cells form an epithelial-like layer and have microvilli on their apical surface. However, this morphology varies depending on the region of the abdomen: The number and length of the microvilli vary depending on the organ and location as a sign of functional adaptation. The mesothelial cells have a cuboidal shape on the parenchymatous organs (the visceral peritoneum) and on the peritoneal side of the diaphragm but are flat at the parietal peritoneum. Flat mesothelial cells may also be stimulated by injury or other external stimuli to switch to the cuboidal shape. These cells then show an enlarged nucleus with sometimes prominent nucleoli and increased cell organelles such as mitochondria and rough endoplasmic reticulum (RER). The microvilli on the surface of the mesothelial cells secrete a protective layer, the

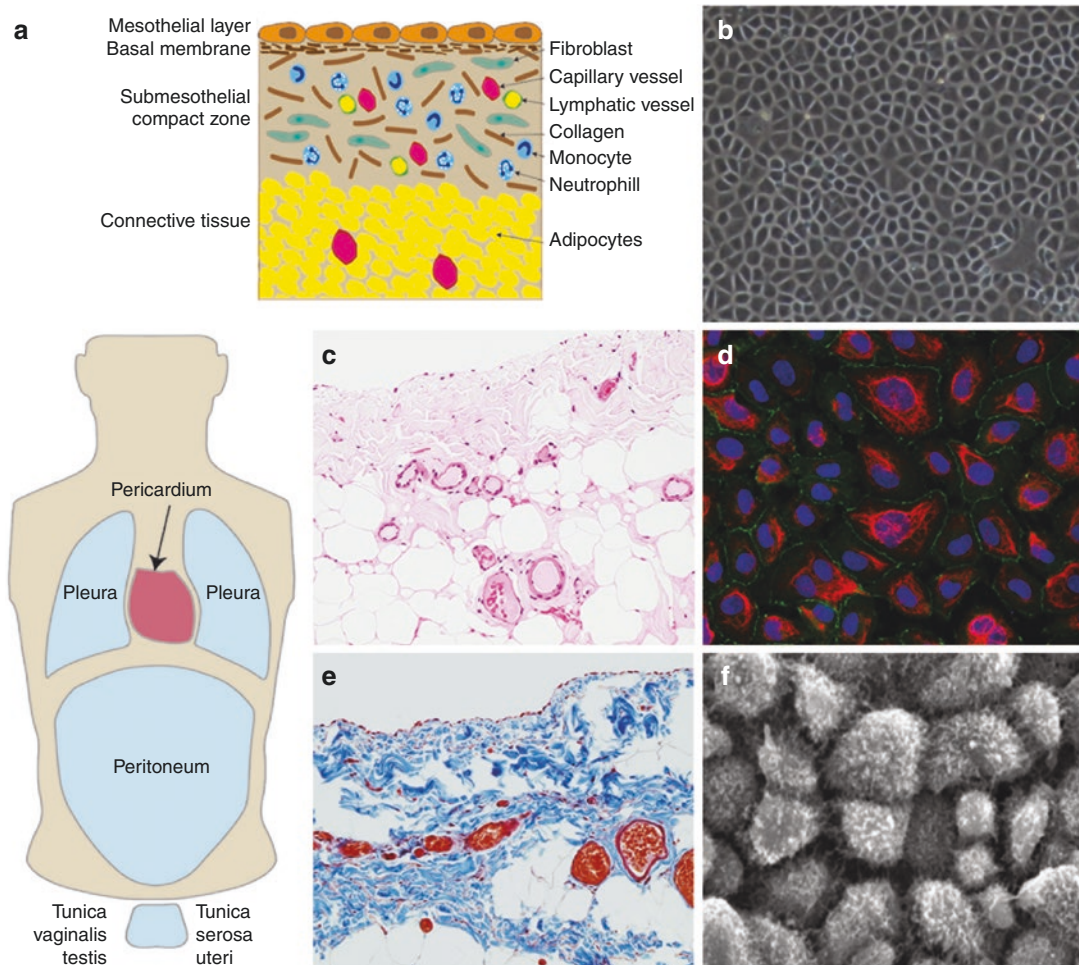


Fig. 1.2 (**a**–**f**) Morphology of the mesothelium. (**a**) The basic structure of the mesothelium consists of a simple layer of mesothelial cells, basal membrane, and submesothelial tissue with fibroblasts, blood and lymph vessels, collagen fibers, inflammatory cells, nerves, and adipocytes (*top*). The mesothelium covers the surface of the internal organs and cavities and forms the pleura, the pericardium, the tunica vaginalis testis, and the tunica serosa uteri (*bottom*). (**b**) Image from a phase-contrast microscope of parietal mesothelial cells of a rodent. (**c**) Human biopsy with a superficial layer of mesothelial cells (*yellow arrow*), below it the submesothelial connective tissue layer (HE stain). (**d**) Mesothelial cells from the parietal peritoneum of a rodent: expression of cytokeratins (*red*) and Zo-1 (*green*), a marker of the tight junction. (**e**) The Masson's trichrome stain shows the mesothelium (*red*) and collagen bundle (*blue*). (**f**) Image from a scanning electron microscope of parietal peritoneal mesothelial cells of a rodent. Many microvilli can be seen on the surface. (Courtesy of Kawanishi [39])

glycocalyx, consisting of glycosaminoglycans (GAGs) that may protect the body against infection and tumor dissemination [5]. Hyaluronic acid, which is highly hydrophilic and forms a hydrous gel polymer, is particularly important for this function [56, 98].

1.3.2 Basal Membrane

A thin basal membrane lies below the mesothelial cells. The basal membrane is connected to the underlying stroma, which contains blood vessels, nerves, and a well-developed lymphatic system.

This mechanical connection is more pronounced at the visceral peritoneum than at the parietal peritoneum. This difference explains why surgical visceral peritonectomy, as opposed to parietal peritonectomy, is usually not possible. The basal membrane is perforated by small openings at the junction of two or more mesothelial cells known as lymphatic stomata (see below).

1.3.3 Submesothelial Layer

The submesothelial layer contains the blood vessels and nerves that supply the cells above it, and it plays an essential role as a connection to the organs and other structures. In addition, this layer has a dense lymphatic system and may contain macrophages, lymphocytes, and adipocytes. The submesothelial layer of the abdomen is anatomically continuous with the submesothelial layer of the thorax, which explains the frequent passage of malignant tumors (e.g., from a malignant peritoneal mesothelioma into the pleural cavity).

1.3.4 Peritoneal Lymphatic System

The lymphatic system plays an essential role in the transport of proteins, lipids, and fluids from the peritoneal cavity into the bloodstream. The subdiaphragmatic lymphatic vessels drain 80% of the abdominal cavity, passing from there to the lymphatic duct and thus into the venous circulation. In the physiological situation (active absorption), there are only a few milliliters of fluid in the abdomen. If there is no longer homeostasis in the peritoneal cavity between fluid intake (e.g., due to immature neo-vessels with a defective, functionally incompetent basal membrane) and absorption (e.g., due to obstruction of the draining lymphatic vessels by tumor cells), ascites develops. This pathological situation is observed in about half of the patients with peritoneal metastases.

1.3.4.1 Lymphatic Stomata

The lymphatic stomata (LS) have a direct connection to the underlying submesothelial lymphatic system. They ensure the clearance of ascites, bacteria, tumor cells, and other particles from the peritoneal cavity. Their distribution in the peritoneal cavity varies and they are located mainly at the surface of the diaphragm, the greater omentum, the falciform ligament, the epiploic appendages of the colon, the interface between the mesentery and small intestine, and in the Douglas pouch. The lymphatic stomata are usually closed but may open due to various stimuli (such as increased intra-abdominal pressure).

1.3.4.2 Milky Spots

The milky spots (MS) are small lymphatic structures at the peritoneal opening of the lymphatic stomata. They consist mainly of a reservoir of macrophages and lymphocytes and play an important role in the peritoneal humoral and cellular immune defense [50]. Microscopically, milky spots contain a glomerular network of blood vessels that allows fluid exchange between the peritoneal cavity, the blood flow, and the surrounding greater omentum. The cellular components are located around the omental glomeruli and lie directly below the discontinuous mesothelial layer, which has characteristic pores and stomata, allowing direct communication with the peritoneal cavity.

The scanning electron microscope shows that macrophages from activated milky spots can significantly change their membrane activity and migrate into the peritoneal cavity through the intercellular stomata of MS [51].

1.3.5 Peritoneal Vascularization

The submesothelial layer is interspersed with blood and lymph vessels. The total effective blood flow of the human peritoneum is estimated to be about 60–100 ml/min, which is 1–2% of cardiac output. The parietal peritoneum is supplied by the circumflex, iliac, lumbar, intercostal, and epigastric arteries and forms a quadrangular network of large parallel blood vessels and their perpendicular offshoots. The parietal vessels drain into the inferior vena cava. The visceral peritoneum receives its blood supply from the

three main arteries of the splanchnic organs: the celiac trunk and the superior and inferior mesenteric arteries. These arteries are the source of multiple bifurcations into small arteries that form an extensive network through anastomoses. The visceral peritoneum drains into the portal vein. Medications absorbed by the peritoneum undergo first-pass metabolism in the liver.

Both inflammation of the peritoneum and tumor invasion induce neoangiogenesis, which develops into excessive growth of the microvascular network. The anatomy of the new vessels is abnormal; they have a defective ultrastructure and are characterized by significant size, varying diameters, tortuosity, and blood extravasation.

Diffuse neoangiogenesis can be observed even before the macroscopic appearance of peritoneal metastasis (PM). Increasing the surface area of the peritoneal capillaries also increases the proportion of cardiac output reaching the peritoneum [77–79].

1.4 Functions of the Peritoneum

In addition to being the major morphological component of serosal membranes, mesothelial cells have key functional roles [39].

One of the basic functions of mesothelial cells is to form a smooth surface that allows the internal organs to move. Furthermore, mesothelial cells have various physiological and biological functions in different processes such as tissue healing, fibrinolysis, regulation of inflammation, epithelial-mesenchymal transition (EMT), and mediation of intraperitoneal tumor cell proliferation. Research has highlighted the role of mesothelial cells in different stress conditions such as peritoneal dialysis, tissue injury and healing, and tumor progression [45].

In addition, a recent analysis of the genetic lineage tracing showed that mesothelium surrounding visceral adipose tissue may be a potential player in tissue dysfunction in obesity, including the development of fibrosis and inflammation [14].

1.4.1 Phenotypic or Biochemical Markers of Mesothelial Cells

Mesothelial cells express a wide range of phenotypic markers that are also observed in tissues similar to epithelium. These phenotypic markers include, among others, vimentin and cytokeratins [93], E-cadherin [30], N-cadherin, calretinin [16], Zo-1 [30], beta-catenin [30], Wilms tumor protein 1 (WT1) [37], mesothelin [35], and D2-40 (podoplanin) [73].

Additional biochemical markers suggest an active role of mesothelial cells in fluid transport as well as in the initiation and termination of inflammation. These biochemical markers include: aquaporin 1, Na+/K+ -ATPase, SLC [47], integrin beta-1 (CD29) [97], CD40 as a member of the tumor necrosis factor receptor family (TNF) [4], homing cell adhesion molecule (HCAM, CD44) [23, 7], intercellular cell adhesion molecule 1 (ICAM-1, CD54), vascular cell adhesion molecule 1, VCAM-1, CD106), and activated leukocyte cell adhesion molecule (ALCAM, CD166) [3].

1.4.2 Production of Cytokines and Growth Factors

Physiologically or through stimulation, mesothelial cells produce various cytokines, such as interleukin 1 (IL-1) [18], IL-6 [48], IL-8 [34], IL-15 [4], granulocyte colony-stimulating factor (G-CSF), granulocyte monocyte CSF (GM-CSF), macrophage CSF (M-CSF), monocyte chemoattractant protein-1 (MCP-1), and “regulated on activation, normal T cell expressed and secreted chemokines” (RANTES) [4].

Mesothelial cells also synthesize various growth factors such as vascular endothelial growth factor (VEGF) [24], basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), endothelin-1 [41], insulin-like growth factor (IGF), keratinocyte growth factor (KGF), hepatocyte growth factor (HGF) [1, 48], heparin-

binding epidermal growth factor-like growth factor (HB-EGF), hypoxia-inducible factor (HIF), metalloproteinases (MMP), and Snail1 (zinc-finger transcriptional repressor) [76]. Finally, mesothelial cells can form reactive oxygen species (ROS) as well as nitrate oxide (NO) and ROS scavengers, especially under stimulation by stressors such as lipopolysaccharides (LPS), asbestos, methylglyoxal (MGO), and advanced glycation end products (AGE) [76].

1.4.3 Synthesis of the Extracellular Matrix (ECM)

Mesothelial cells synthesize ECM molecules such as type I, III, and IV collagen, elastin, fibronectin, laminin, and proteoglycans. The level of ECM production is enhanced by IL-1β, TNF-α, EGF, and TGF-β [46, 62–64, 70, 94]. The renin-angiotensin system or advanced glycation end products (AGE) also stimulate ECM production [60].

Thus, mesothelial cells form a protective and nonadhesive surface for the internal organs and the surrounding tissue. Activated mesothelial cells can promote metastasis by promoting cell adhesion, invasion, and proliferation.

1.4.4 Procoagulant and Fibrinolytic Properties

Mesothelial cells control the balance between procoagulant and fibrinolytic activities through a wide range of regulators. For example, they express the tissue factor (TF), which forms fibrin by splitting fibrinogen [8]. Mesothelial cells also express TF pathway inhibitors. On the other hand, they produce fibrinolytic activators such as tissue plasminogen activator (tPA) [88], urokinase plasminogen activator (uPA), and uPA receptor (uPAR) [88].

Mesothelial cells also secrete the corresponding inhibitors: plasminogen activator inhibitor 1 (PAI-1) [75], whose secretion is regulated by TGF-β, thrombin, and other inflammatory factors such as lipopolysaccharides (LPS), TNF-α, and IL-1. Mesothelial cell defects and exposure of the basal membrane lead to an imbalance between procoagulant and fibrinolytic properties and to the formation of fibrin bands between the tissue and the organs. These bands may develop into fibrous adhesions, leading to postoperative intra-abdominal and pelvic adhesions [52], and may also be observed in pleural fibrosis in similar conditions [57].

1.4.5 Hyaluronic Acid Synthesis and Detection

Hyaluronic acid (HA) is a non-sulfated, linear glycosaminoglycan composed of repeating disaccharide units of β-(1,4)-glucuronic acid (GlcUA) and β-(1,3)-N-acetyl-glucosamine (GlcNAc). HA plays a crucial role in tissue architecture, cell motility, cell adhesion, and peritoneal proliferation processes [58]. Mesothelial cells produce primarily large hyaluronic acid molecules (HMW hyaluronic acid) with a high molecular weight between 200 and 2000 kDa. HA catabolism is controlled by hyaluronidases, mechanical forces, and oxidative stress. In degradation, hyaluronan polymers are formed that are smaller and termed low molecular weight HA (LMW-HA; <200 kDa) or HA oligomers [32]. LMW hyaluronic acid has a pro-inflammatory and carcinogenic function, whereas HMW-HA has the opposite function [58]. The HA synthesis of mesothelial cells is enhanced by inflammation and exposure to non-physiological solutions (peritoneal dialysis solution). Increased levels of hyaluronic acid may induce EMT in mesothelial cells under physiological conditions, which is critical for cell migration in wound healing and remesothelialization [98]. CD44 is the major receptor for hyaluronic acid and is responsible for binding gastric and ovarian epithelial cells to the mesothelium [59]. The interaction of hyaluronic acid with CD44 is necessary for the extravasation of activated T cells from the circulation to the site of inflammation [17]. There is also data showing that the ability of CD44 to bind hyaluronic acid correlates with the suppressive activity of $CD4^+$/CD^+ regulatory T cells [22].

1.4.6 Sialic Acid Synthesis and Detection

Sialic acid (Sia) is a ubiquitous family of glycan molecules found on the outer surface of vertebrate cells [89]. Sialic acid is involved in essential functions of the membrane, such as cell-cell, cell-virus, or cell-drug interactions. Although very little information on sialic acid in mesothelial cells has been published, N-glycolylneuraminic acid (Neu5Gc) has been detected in malignant mesotheliomas, and sialic acid-binding lectin (SBL) may induce selective apoptosis in malignant mesothelioma cells in combination with TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) [86]. Another surface mucin, mucin-16 (MUC16), is highly expressed in epithelial ovarian tumors. Interestingly, antigen 125 (Ca-125), which is a serum marker for ovarian cancer, is also a known mesothelial cell marker [44]. MUC16 binds to sialic acid-binding Ig-like lectin-9 (Siglec-9), an inhibitor of sialic acid ligands, which acts to inhibit T cells and NK cells and thus likely inhibits the anti-tumor immune response [6].

1.4.7 Immunocompetent and Regulatory Properties

The peritoneum is exposed to various aggressors and stress factors, such as tumor cells. The immune response of the peritoneum normally leads to the elimination of these aggressors and to the restoration of the integrity of the serosa. If this recovery is not successful, chronic inflammation and possibly scarring will develop [10].

Peritoneal fluid (PF) plays a crucial role in this healing process. Under physiologically healthy conditions, the peritoneal cavity contains only a few milliliters of peritoneal fluid. However, this contains growth factors, nutrients, cytokines, chemokines, and leukocytes, which are constantly exchanged between the blood and the peritoneal fluid. The majority of leukocytes in the peritoneal fluid are monocytes and macrophages; these cells degrade the pathogens and their degradation products [27]. The second most abundant cells are B1 lymphocytes. B1 lymphocytes are the source of natural antibodies, particularly IgM and IgA, with broad specificity and low antigen affinity [80]. T lymphocytes, dendritic cells, neutrophils, natural killer (NK) cells, and mastocytes are also present in the peritoneal fluid [55].

The mesothelial cells are also involved in the immune response and in the healing process. Mesothelial cells express Toll-like receptors (TLRs), which can recognize microbial components and trigger an inflammatory response by activating the NF-κB signaling pathway and activating chemokines [65]. TLR4 expression of human peritoneal cells is increased following stimulation by LPS [38]. Interestingly, TLR4 is an important receptor for hyaluronic acid [32]. In human malignant mesothelioma, the tumor cells escape the control mechanisms of the immune system through suppression of the proliferation and function of the T lymphocytes and increased recruitment of immunosuppressive regulatory T cells [28]. Furthermore, mesothelial cells can suppress the proliferation of pro-inflammatory T cells as well as $CD4^+$ and $CD8^+$ T cells through the secretion of TGF-β [43]. $CD90^+$/CD45 mesothelial cells isolated from human ascites lead to immunosuppression of $CD4^+$ T cells by expressing arginase [43]. These facts may indicate an important role for the interaction between HA-CD44 and sialic acid Siglecs in the immunomodulatory processes of the mesothelium.

1.5 Molecular Pathology of Peritoneal Metastasis

Metastasis varies with tumor origin, tumor localization, and tumor type: While gastrointestinal adenocarcinomas generally tend to metastasize to the liver, mucinous colorectal carcinomas and signet ring carcinomas are more likely to develop peritoneal metastases [29]. Colon carcinomas and gastric carcinomas metastasize within the abdominal cavity and often lead to ovarian metastases called Krukenberg tumors, which are often diagnosed simultaneously with the peritoneal metastases. Peritoneal metastasis (PM) is a multistep process consisting of the detachment of

tumor cells from the primary tumor, the proliferation of tumor cells and transport through the peritoneal cavity, and the adherence to the peritoneal surface followed by invasion, neovascularization, and tumor growth. This process is regulated by a complex system of interconnected signaling pathways and mediators. For example, neoangiogenesis is essential for metastasis and is essentially regulated by VEGF, which in turn is involved in the formation of ascites, which stimulates tumor growth (see above). Understanding the molecular steps involved in peritoneal metastasis is therefore crucial if treatment strategies for peritoneal metastases are to progress.

1.5.1 Detachment of Tumor Cells from the Primary Tumor

It is well known that vital tumor cells separate from the primary tumor by serosal infiltration or invasion into adjacent organs (UICC T4 category). In many patients, such tumor cells can be detected in peritoneal cytology without an obvious peritoneal metastasis; this is associated with a poor prognosis. Similarly, tumor perforation or transection of lymphatic vessels during surgery may result in tumor cells being flushed out into the abdominal cavity.

1.5.2 Dissemination and Transport into the Peritoneal Cavity

Once separated from tissue, the tumor cells are disseminated throughout the peritoneal cavity by the physiological fluid flow. Extensive spread of tumor cells throughout the peritoneal cavity is commonly seen in tumors with ascites, especially in advanced high-grade serous ovarian tumors. The dissemination follows the movements of the peritoneal fluid and is influenced by the abdominal anatomy [77–79]. For example, desquamated tumors of an ovarian tumor typically move along the right colon sulcus in Morrison's pouch and into the right diaphragm, where peritoneal metastases are most often located. In contrast, gastric carcinoma is more likely to spread into the left subphrenic space than into the right one. Therefore, it is not surprising that positive peritoneal cytologies in several abdominal compartments are associated with a poorer prognosis [36].

1.5.3 Adhesion to the Peritoneal Surface

The intact mesothelial layer provides excellent protection against tumor adhesion and invasion [83]. The microvilli are covered with a thin serous layer (60 μm) of peritoneal fluid and glycosaminoglycans, phospholipids, proteoglycans, surfactant, and coagulant precursors, which are secreted by the mesothelial cells. HMW-HA (see above) is another major component of the glycocalyx and is also produced locally by the mesothelial cells. It forms a protective glycocalyx slime layer against tumor cells and their adhesion. The ability of tumor cells to adhere to the mesothelium and subsequently to proliferate is determined by the communication between the tumor cell and mesothelial cells. This is regulated by ligand/receptor pairs, including α5β1 integrin/fibronectin, αVβ3 integrin/vitronectin (VN), and CD44/hyaluronic acid [91]. Tumor cells prefer to adhere to sites of the mesothelium where the ECM is freely accessible, such as the right diaphragm or the greater omentum, where the continuous mesothelial layer is interrupted by the increased occurrence of lymphatic stomata in the cribriform lamina. Peritoneal injuries after surgery are also preferred sites of tumor cell adhesion and later invasion.

1.5.4 Invasion of the Mesothelium

Two types of peritoneal invasion are distinguished: the translymphatic invasion pathway and the transperitoneal invasive pathway (Fig. 1.3).

Translymphatic Invasion Pathway
This is the most common invasion pattern. The tumor cells are first inactivated from the peritoneal

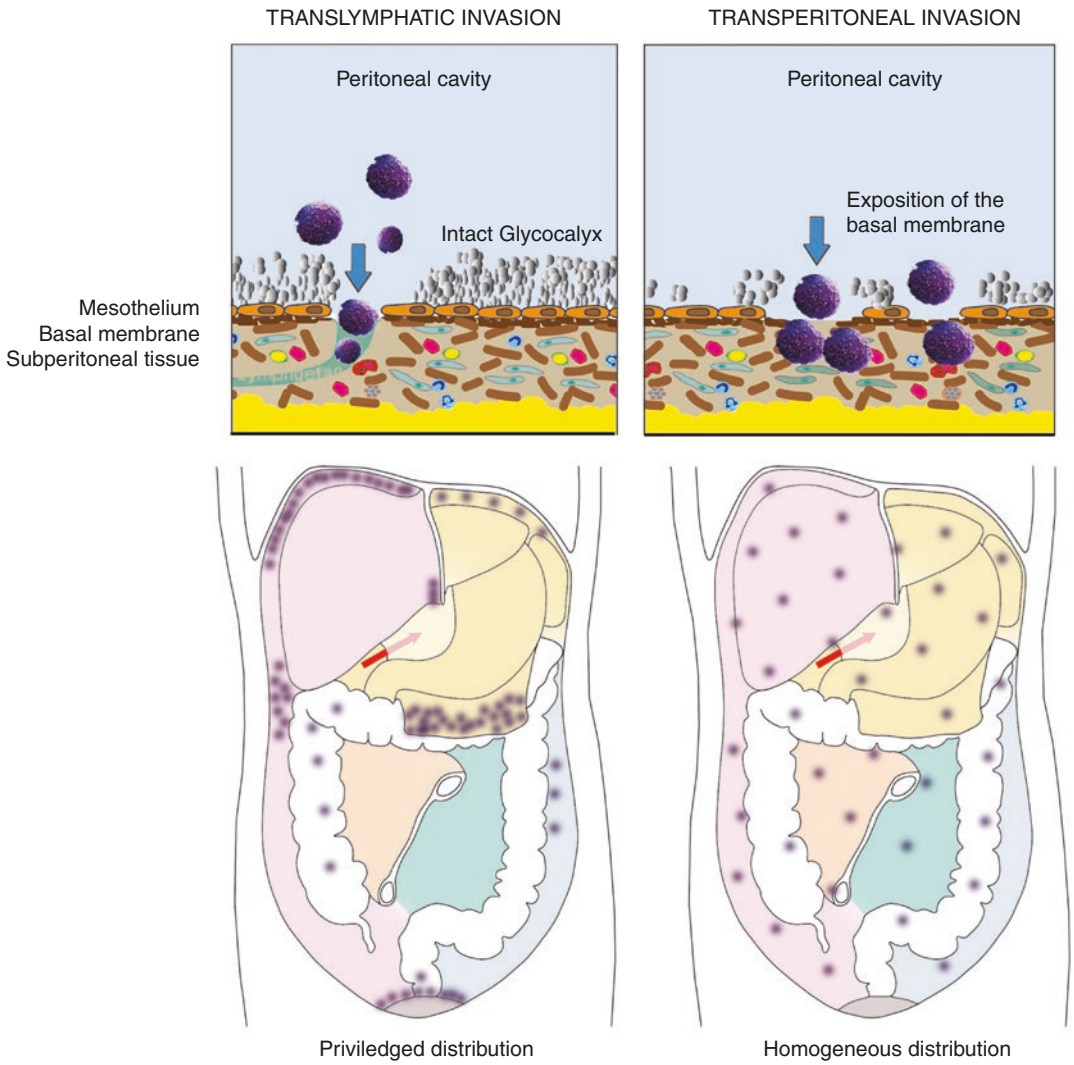


Fig. 1.3 Invasion of the mesothelium. Translymphatic invasion most often occurs at the most dense locations of the lymphatic stomata, such as in the area of the greater omentum, at the two diaphragmatic domes, at the falciform ligament, etc. In transperitoneal invasion, the invasion occurs through the mesothelium itself. There is then no preferred pattern of peritoneal metastasis

cavity by the immunocompetent defense cells in the milky spots and then evacuated through the lymphatic stomata. If this effective defense mechanism is overcome by the tumor cells, local tumor invasion occurs. This invasion occurs preferentially at the most common locations of the lymphatic stomata, such as the greater omentum, the two diaphragmatic domes, the falciform ligament, etc. (see above).

Transperitoneal Invasion Pathway

In the transperitoneal invasion pathway, the invasion occurs through the mesothelium itself. This is possible only if the glycocalyx is damaged, the mesothelial cells shrink, the basal membrane is exposed, and the wound healing processes are triggered, resulting in fibrin production and adhesion of the tumor cells. Cancerous spheroids attached to the mesothelial

monolayer use various cell adhesion molecules that promote the dissociation of mesothelial cells as well as their migration away from the invading tumor [31]. After injecting tumor cells of a gastric carcinoma into the abdomen of rodents, contraction and exfoliation of the mesothelial cells was observed. Similar observations were made after the intraperitoneal instillation of IL-6, TNF-β, and IL-8 [95]. In all these models, the tumor cells did not adhere to the mesothelial cells themselves but rather to the underlying connective tissue. In addition, electron microscope images of excised human peritoneal-associated tumors revealed that the mesothelial cells are not directly under the tumor mass, suggesting that mesothelial clearance occurred in this area [92].

However, the mesothelial cells themselves might also play a role in tumor invasion. They produce lysophosphatidic acid (LPA), which in turn facilitates adhesion and invasion [15, 81]. In addition, LPA simulates VEGF production by the mesothelial cells and might thus promote neoangiogenesis [42]. Mesothelial cells can also express matrix metalloproteinases (MMP-1 and MMP-2), which favor tumor cell invasion [67].

1.6 Neoangiogenesis

In order to grow to more than a few millimeters, peritoneal metastases require an additional nutritive blood vessel system. When tumors develop or metastasize to the peritoneum, their further growth depends on the effective invasion of the host tissue, as this is the only way to establish close contact with the superficial blood vessels. Therefore, peritoneal metastases have a tendency to initiate and grow on highly vascularized tissues such as the greater omentum, or along the mesenteric vessels, for example, at the border between the mesentery and the small intestinal serosa. Various endogenous factors influence endothelial growth. Above all, VEGF, a key mediator of angiogenesis, is involved in the peritoneal dissemination of various types of tumors (especially in ovarian carcinoma) and the resulting formation of ascites. Highly vascularized tumors are very dependent on VEGF-mediated neoangiogenesis. Peritoneal tumors express high levels of VEGF that can pass (in the high picogram to the low nanogram-per-ml range) into the plasma and ascites fluid. This explains why diffuse neoangiogenesis is already observed in the early stage of peritoneal metastasis, although only a few tumor nodules are macroscopically detectable.

VEGF initiates a cascade of events, including:

Increased Vascular Permeability

Extravasation of plasma, fibrinogen, and other plasma proteins

Activation of the coagulation cascade outside the vascular system

Deposition of extravascular fibrin gel, which acts as a temporary stroma and forms an excellent matrix for cell migration

Induction of Angiogenesis and Arteriovenogenesis

Subsequent degradation of fibrin and its replacement by granulation tissue (highly vascularized connective tissue)

Vascular resorption and collagen synthesis, resulting in the formation of a dense fibrous connective tissue layer (desmoplasia)

In peritoneal metastases, VEGF plays an essential role in peritoneal hypersecretion. VEGF secretion by the tumor cells promoted the accumulation of fluid in the peritoneal cavity in the animal model and was capable of inducing a reversible increase in microvascular permeability without degranulation of mast cells, endothelial cells, or other lesions [20]. The production of VEGF alone was enough to result in increased capillary protein permeability. In humans, VEGF levels were higher in malignant ascites than in cirrhotic ascites [99].

Other studies emphasize the pro-angiogenic role of VEGF, in particular its central role in the growth and migration of endothelial cells, the increased permeability of the endothelial barrier for plasma proteins, and the alteration of ECM. Neovascularization not only increases cap-

illary permeability; it also multiplies the surface area of the capillary filter, thus enhancing protein extravasation and the thus altering oncotic pressure. Because VEGF participates in the majority of the parameters involved in the Starling effect, it leads to increased fluid loss and increased accumulation in the peritoneal cavity [84]. The permeable neo-vessels are different from the normal vessels. During neoangiogenesis, preexisting venules and capillaries develop into abnormal, enlarged mother vessels within a few days [19]. The formation of mother vessels requires degradation of the basal membrane. These membranes are rigid, non-compressible structures consisting of type IV collagen, laminin, and proteoglycans, which limit the expansion of normal venules and capillaries by 30% [13]. The basal membrane must therefore be degraded to allow the mother vessels to grow up to 4 to 5 times the size of normal microvessels.

1.6.1 Tumor Growth

Once the tumor cells are attached to the peritoneum and have penetrated the mesothelial layer, they must acquire stable binding to the submesothelial connective tissue before they can proliferate further.

Recent data suggest that the connective tissue induces an epithelial-mesenchymal transition (EMT or MMT) of human mesothelial cells (see below). Further proliferation and survival of the tumor cells in the connective tissue layer requires interaction with the micro-environment of the tumor. In this context, cancer-associated fibroblasts (CAFs) play a crucial role. CAFs are able to produce various growth factors and components of the ECM, thus accelerating tumor growth and vascularization. The origin of the CAFs is still unclear, but there are studies that show they originate from different cell types in different tumors and from different tumor areas. One of the most likely origins are the local peritoneal fibroblasts, but precursor cells of the bone marrow, endothelial cells, epithelia, or peritoneal mesothelial cells have also been discussed [72].

1.6.2 Epithelial-Mesenchymal Transition (EMT) and Mesothelial-Mesenchymal Transition (MMT)

Epithelial-mesenchymal transition (EMT) is a fundamental biological process that occurs during normal processes of embryogenesis and tissue repair but also in many pathologies such as organ fibrosis, malignant transformation, or cancer development. When exposed to certain growth factors and/or stressors, epithelia can undergo a morphologically complex transition and become the mesenchymal phenotype. Epithelia lose their intercellular connections as well as the connection to the basal membrane and their apicobasal cell orientation. With the subsequent migration and invasion of the basal membrane and a change in the cytoskeleton, the complete transformation from an epithelial to a mesenchymal phenotype occurs.

Mesothelial cells also have the potential to undergo EMT because they have some epithelial-like properties and functions and express both mesothelial and epidermal markers [69]. This transformation process of the mesothelial cells is called mesothelial-mesenchymal transition (MMT).

Mesothelial cells can undergo MMT if they are damaged, e.g., in peritoneal dialysis or by the recruitment of CAFs. Tumor cells themselves can also be transformed into more invasive phenotypes by EMT, which in turn drives MMT of mesothelial cells [53].

MMT includes the loss of E-cadherin and expression of N-cadherin, loss of tight junctions, and expression of mesenchymal markers: fibronectin, vimentin, fibroblast-specific protein-1 (FSP-1), smooth muscular actin (α-SMA) with altered cell polarity, and cell migration [96]. MMT is induced by HIF and TGF-β and repression of E-cadherin as well as by hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), and IL-1β [96]. Most of the cytokines and chemokines released into the peritoneal cavity are secreted by peritoneal macrophages involving MCs, peripheral blood

mononuclear cells (PMNCs), fibroblasts, or tumor cells [71]. EGF is also secreted by the CAFs, which determines the progression and volume of malignant ascites in ovarian and gastric cancers [69].

1.7 Primary Peritoneal Tumors

For peritoneal tumors, a distinction is made between primary and secondary tumors. Due to the rarity of the other primary tumors, only the malignant peritoneal mesothelioma (MPM) and the primary papillary serous carcinoma of the peritoneum (PPSC) will be considered here.

Classification of primary peritoneal tumors [9]

- Adenomatoid tumor
- Polycystic mesothelioma
- Highly differentiated papillary mesothelioma
- Malignant peritoneal mesothelioma (MPM)
- Special forms of peritoneal mesotheliomas
- Primary low-grade serous tumors of the peritoneum
- Serous borderline tumor/atypical proliferative serous tumor
- Serous borderline tumor, micropapillary variant/noninvasive micropapillary serous carcinoma
- Invasive low-grade serous carcinoma (LGSC)
- Primary high-grade serous carcinoma (HGSC)
- Primary malignant mixed Müllerian tumor (MMMT)
- Primary adenosarcoma of the peritoneum
- Primary teratoma of the peritoneum
- Intra-abdominal cystic lymphangioma
- Primary effusion lymphoma of the peritoneum

1.7.1 Malignant Peritoneal Mesothelioma (MPM)

Malignant peritoneal mesothelioma is a rare entity that presents clinically with rather nonspecific symptoms and is difficult to diagnose even with further laboratory or imaging procedures, so the diagnosis is based on histology. According to the WHO, three histological subtypes are distinguished:

- Epithelioid (75% of MPM with a better prognosis)
- Sarcomatoid (very rare and poor prognosis)
- Biphasic/mixed (25% and worse prognosis than the epithelioid subtype)

This subdivision is of prognostic as well as therapeutic importance.

The *epithelioid subtype* consists of cells that resemble normal mesothelium and grow in tubulopapillary or trabecular patterns. Mitoses are rare. A possible signet ring cell component and desmoplastic response makes it difficult to distinguish this subtype from adenocarcinomas solely based on the morphology.

The *sarcomatoid subtype* consists of tightly packed spindle cells with occasional evidence of osteoid, chondroid, or muscle fibers. By definition, the biphasic subtype consists of epithelioid and sarcomatoid growth patterns of at least 10% each. As already mentioned, a diagnosis based purely on the morphological growth pattern can be difficult or even impossible; therefore, the use of immunohistochemical markers is indispensable. However, there is no single specific marker for MPM; it requires the use of a marker panel.

MPMs show the same immunohistochemical staining pattern as the pleural mesothelioma, with calretinin, WT-1 (Wilms tumor antigen 1), EMA, cytokeratin 5/6, and D2-40 (podoplanin). Typically, MPMs are negative for CEA, TTF-1, Ber-EP4, B72.3, MOC-31, BG8, and Claudin-4 [87]. The use of cytokeratin markers is helpful in distinguishing MPMs from sarcomas, lymphomas, or melanomas. In CUP (carcinoma of unknown primary), it is difficult to distinguish between MPM and peritoneal metastases and requires the use of additional immunohistochemical markers, depending on the clinical question. Table 1.1 gives an overview of the most important markers for distinguishing an MPM from peritoneal metastases of a gastrointestinal adenocarcinoma [87]. The use of two mesothelioma markers and two carcinoma markers is recommended [40].

Table 1.1 Immunohistochemical criteria for distinguishing between malignant peritoneal mesothelioma and peritoneal metastases of a primary gastrointestinal tumor

Marker	Malignant peritoneal mesothelioma	Pancreatic cancer	Colorectal cancer	Gastric cancer
Calretinin	+	(+)	–	–
WT-1	+	–		–/(+)
D2-40 (podoplanin)	+	–		–
CK5/6	+	+/–	–	–
MOC-31	–/(+)	+	+	+
BG8	–/(+)	+	+	+
Ber-EP4	–/(+)	+	+	+
B72.3	–/(+)	+	+	
CEA	–	+	+	+
CDX2	–	–/(+)	+	+/–

Courtesy of Tischoff et al. [87]
+ positive, – negative, +/– both (positive and negative), –/(+) usually negative, rarely positive

1.7.2 Primary Papillary Serous Carcinoma of the Peritoneum (PPSC)

PPSC is a very rare primary tumor of the peritoneum with an incidence of 0.7 cases/100,000 per year. Biologically, morphologically, and phenotypically, it resembles serous ovarian carcinoma, indicating a common histogenesis. The therapy regimes of both entities therefore differ little.

Due to the same embryological origin of the ovaries and the peritoneum, the two tumors have histological similarities. The clinical differentiation from the primary serous carcinoma of the ovary has been defined as follows [54]:

1. The ovaries must be normal in size or enlarged by a benign process.
2. The extraovarian involvement must be greater than the superficial involvement of both ovaries.
3. Absence of ovarian involvement; however, the ovarian surface epithelium may be affected without stromal or cortical invasion with a maximum tumor diameter of less than 5 × 5 mm.

In recent years, however, there has been a conceptual change. For most diseases, defined clinically as peritoneal or ovarian primary tumors, precursor lesions or small occult invasive carcinomas in the tubal epithelium (serous tubal intraepithelial carcinomas [STICs] or primary serous carcinomas of the tube) appear. Therefore, one suspects that the origin of most high-grade serous carcinomas of the peritoneum and the ovary is in the tubal epithelium [74]. Accordingly, the definition of primary tumors and, secondarily, the pathological staging for a subgroup of high-grade serous carcinoma (HGSC) will be changed in the next few years.

Table 1.2 Immunohistochemical criteria to distinguish between a malignant peritoneal mesothelioma (MPM) and a primary peritoneal serous carcinoma (PPSC)

Marker	Malignant peritoneal mesothelioma (MPM)	Primary peritoneal serous carcinoma (PPSC)
Calretinin	+	–
WT-1	+	+
D2-40 (podoplanin)	+	–/(+)
CK5/6	+	–/(+)
Estrogen receptor	–	+/–
Progesterone receptor	–	+/–
Thrombomodulin	+	–/(+)
MOC-31	–/(+)	+
BG8	–/(+)	+
Ber-EP4	–/(+)	+
B72.3	–/(+)	+

Courtesy of Tischoff et al. [87]
+ positive, – negative, +/– both (positive and negative), –/(+) usually negative, rarely positive

The distinction between PPSC and MPM can also be challenging (Table 1.2). Immun-

ohistochemistry, however, in most cases allows a differentiation to be made between the two tumor entities through a combination of Ber-EP4, estrogen receptors, and calretinin stains [61].

1.8 Secondary Peritoneal Tumors (Peritoneal Metastasis)

According to the current TNM classification, the term "peritoneal metastasis" includes the secondary peritoneal tumors and should therefore be preferred to the old designation "peritoneal carcinosis." Peritoneal metastasis is the most common malignant disease of the peritoneum. Although, in principle, many malignancies can show peritoneal dissemination, various gastrointestinal and gynecological malignancies in particular have the potential to grow and spread in the peritoneal cavity, especially ovarian cancer, gastric cancer, and colorectal cancers. This is associated with disease progression and poor prognosis.

For the optimal treatment of patients, it is crucial to identify the primary, which may not be easy if the first manifestation of the disease is peritoneal involvement. The morphological classification is based on the growth pattern: extracellular mucinous, tubuloglandular, papillary, dispersed small-glandular, and solid/undifferentiated. Then the immunohistochemical processing of the material is most important. In clinical routine, the initial use of CK20 and CK7 can indicate how to proceed:

- CK20 is a low molecular weight cytokeratin normally expressed in the epithelium of the gastrointestinal tract and in the urothelium.
- CK7 is normally expressed in the lungs, ovaries, endometrium, and breast but also in some tumors of the upper gastrointestinal tract.

The algorithm shown in Fig. 1.4 illustrates how the combination of CK7 and CK20 staining can lead to the differential diagnostic determination of various gastrointestinal and gynecological tumor entities. The algorithm also shows which additional stains lead to further clarification of the diagnosis.

The additional determination of the molecular tumor profile may be useful in the event of CUP as it not only allows the drug-based cancer treatment to be selected but could also prolong patient survival [33].

1.8.1 Signet Ring Carcinoma (SRC)

Signet ring carcinoma is a subtype of mucinous adenocarcinomas and may stem from almost all organs. However, 90% of signet ring cancers occur in the colon, stomach, and breast. About one third of gastric carcinomas show signet ring cell histology. Gastric signet ring cell carcinomas are defined as adenocarcinomas with >50% content of signet ring cells [2], in which the nucleus is displaced by the intracytoplasmic accumulation of mucin to the cell periphery, giving the appearance of a signet ring.

Signet ring cell carcinomas are a poorly differentiated, aggressive subtype of adenocarcinomas. They are often diagnosed at an advanced stage and are associated with an unfavorable prognosis. Signet ring cell carcinomas of the stomach are common, especially in younger patients and women [21]. They tend to metastasize to lymph nodes and the surface of the peritoneum [26]. Furthermore, this subtype is more frequently associated with a diffuse growth pattern, according to Laurén [85]. In diffuse gastric carcinoma, the loss of function of the cell adhesion protein E-cadherin is essential. This makes it easier for the cells to separate from the cell cluster and thus also leads to increased cell motility with possible diffuse metastases [11].

1.8.2 Pseudomyxoma Peritonei (PMP)

PMP is not a pathological but a clinical diagnosis defined by the appearance of mucinous ascites, an omental cake, evidence of peritoneal implants, and possible involvement of the ovaries [12]. The

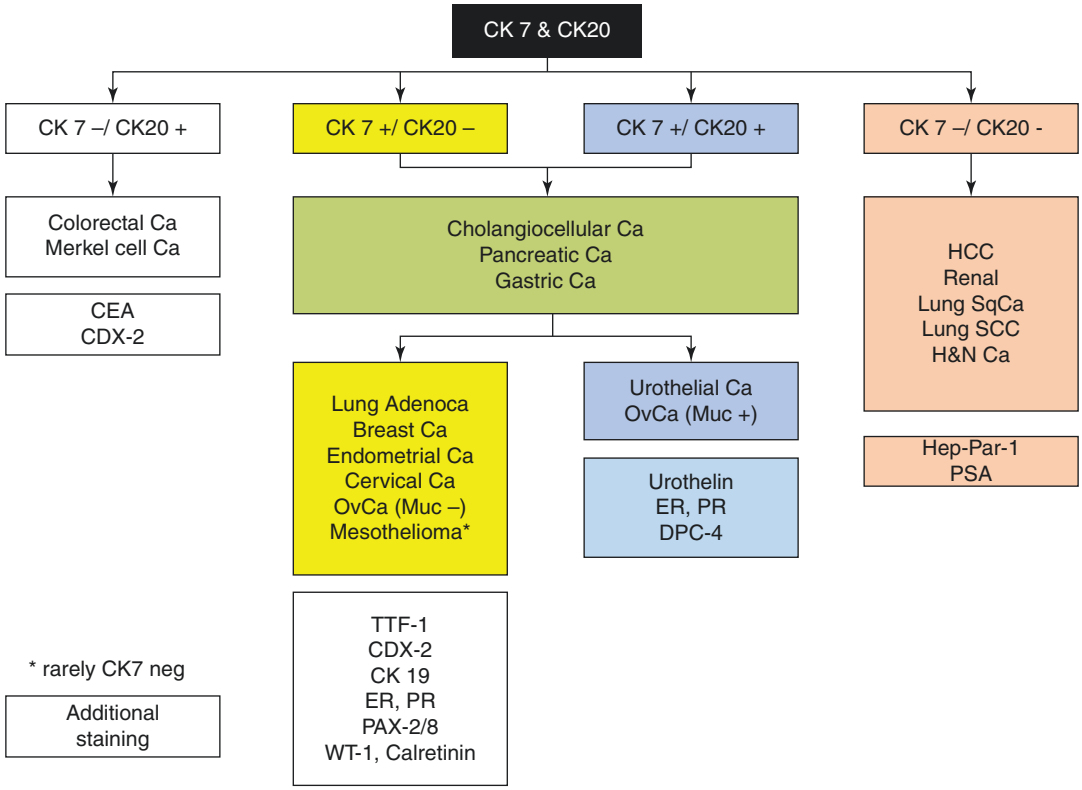


Fig. 1.4 Algorithm for the immunohistochemical determination of the primary tumor in peritoneal metastases. + positive, – negative, Ca carcinoma, HCC hepatocellular carcinoma, H&N head & neck, Muc –, non-mucinous, Muc + mucinous, OvCa ovarian carcinoma, SCC small cell carcinoma, SqCa squamous cell carcinoma [27]

most common etiology of PMP is appendiceal mucinous neoplasm, although other organ locations (ovary, colon, or pancreas) may also be the cause [90]. In most cases, PMP of the appendix is characterized by a strong expression of CK20, CDX2, and MUC2. The latter may be of differential diagnostic importance since the ovarian mucinous tumors are more likely to express MUC5A but express MUC2 only to a lesser degree [11]. The classification of PMP and primary appendiceal lesions is a confusing and much-discussed area. The Peritoneal Surface Oncology Group International (PSOGI) voted in 2015 on a uniform classification model (Table 1.3), which should eliminate the existing ambiguities, give clear definitions, and have prognostic significance in both clinical and therapeutic evaluation [11].

1.9 Pathological Assessment of the Treatment Response

Much of the progress in the treatment of solid tumors has come from the introduction of multimodal treatment approaches. The assessment of treatment response after neoadjuvant chemotherapy has prognostic relevance.

There is little information available to assess the histological response of peritoneal metastases to systemic chemotherapy and its prognostic value. Passot et al. observed complete, major, and low histologic responses in 75%, 57%, and 13%, respectively, of the peritoneal metastases after 5 years of follow-up of peritoneal metastases of colorectal cancer in patients receiving CRS and HIPEC after neoadjuvant chemotherapy [66].

Table 1.3 Classification of PMP

Lesion	Old terminology	New terminology
Mucin without epithelial cells		Acellular mucin
PMP with low-grade aspects[a]	DPAM	Low-grade mucinous carcinoma of the peritoneum
PMP with high-grade aspects[b]	PMCA	High-grade mucinous carcinoma of the peritoneum
PMP with signet ring cells	PMCA-S	High-grade mucinous carcinoma of the peritoneum with signet ring cells

Courtesy of Carr et al. [11]

[a]Low-grade: low-grade cytological atypia (enlarged nucleus, nuclear stratification, rarely mitosis figures, single cell necroses). Architecture: villiform, flat epithelial proliferations, and small papillary growths

[b]High-grade: destructive invasion into an organ wall. High-grade cytological atypia (pronounced, full-thickness nuclear stratification, vesicular nuclei, nuclear membrane irregularities, prominent nucleoli, high mitotic activity), complex architecture

Table 1.4 Peritoneal Regression Grading Score (PRGS)

Grade	Tumor cells	Regression factors
PRGS 1—complete tumor response	No vital tumor cells	Extensive fibrosis and/or acellular mucin and/or infarct-like necroses
PRGS 2—high tumor response	Few vital tumor cells (isolated, small clusters)	Fibrosis and/or acellular mucin and/or infarct-like necrosis dominate over tumor cell content
PRGS 3—mild tumor response	Dominant content of vital tumor cells	Tumor cells dominate via fibrosis and/or acellular mucin and/or infarct-like necroses
PRGS 4—no tumor response	Highly visible vital tumor cells	No regressive changes

Until now, there was no uniform regression score for peritoneal metastases that would allow a comparison of different therapeutic strategies for different tumor entities. Due to the heterogeneity in size, anatomical distribution, and different types of tissue involved, the assessment of histological therapy response is by no means easy. We proposed a four-step Peritoneal Regression Grading Score (PRGS) to increase the staging accuracy of individualized patient treatment and to allow consistent terminology in multicenter trials [77–79].

The proposed system ranges from 1 (complete tumor response) to 4 (no tumor response) and is based on the typical histological features of fibrosis, necrosis, and presence/absence of acellular mucin deposits. Furthermore, the authors recommend taking peritoneal biopsies from all four quadrants and documenting the median and the worst values if there are different results in the different samples (Table 1.4).

The availability of a consistent, shared nomenclature and staging system to assess histological tumor response in peritoneal metastasis will hopefully improve decision-making and allow the results to be summarized and compared. Although the reproducibility and prognostic significance of the PRGS still needs to be validated, the adoption of this unified standard by the broad oncological community interested in peritoneal metastasis will drive further progress in this challenging field.

References

1. Adamson IY, Bakowska J. KGF and HGF are growth factors for mesothelial cells in pleural lavage fluid after intratracheal asbestos. Exp Lung Res. 2001;27:605–16.
2. Antonioli DA, Goldman H. Changes in the location and type of gastric adenocarcinoma. Cancer. 1982;50:775–81.
3. Asahina K, Tsai SY, Li P, Ishii M, Maxson RE Jr, Sucov HM, et al. Mesenchymal origin of hepatic stellate cells, submesothelial cells, and perivascular mesenchymal cells during mouse liver development. Hepatology. 2009;49:998–1011.
4. Basok A, Shnaider A, Man L, Chaimovitz C, Douvdevani A. CD40 is expressed on human peritoneal mesothelial cells and upregulates the production of interleukin-15 and RANTES. J Am Soc Nephrol. 2001;12:695–702.
5. Baumann MH, Strange C, Sahn SA, Kinasewitz GT. Pleural macrophages differentially alter pleural mesothelial cell glycosaminoglycan production. Exp Lung Res. 1996;22:101–11.

6. Belisle JA, Horibata S, Jennifer GA, Petrie S, Kapur A. Identification of Siglec-9 as the receptor for MUC16 on human NK cells, B cells, and monocytes. Mol Cancer. 2010;9:118.
7. Borland G, Ross JA, Guy K. Forms and functions of CD44. Immunology. 1998;93:139–48.
8. Bottles KD, Laszik Z, Morrissey JH, Kinasewitz GT. Tissue factor expression in mesothelial cells: induction both in vivo and in vitro. Am J Respir Cell Mol Biol. 1997;17:164–72.
9. Brierley JD, Mary K, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th ed. Hoboken: Wiley; 2016. p. 1–272.
10. Capobianco A, Cottone L, Monno A, Manfredi AA, Rovere-Querini P. The peritoneum: healing, immunity, and diseases. J Pathol. 2017;243:137–47.
11. Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, González-Moreno S, et al. A consensus for classification and pathologic reporting of pseudomyxoma peritonei and associated appendiceal neoplasia. Am J Surg Pathol. 2016;40:14–26.
12. Carr NJ, Sobin LH. Unusual tumors of the appendix and pseudomyxoma peritonei. Semin Diagn Pathol. 1996;13:314–25.
13. Chang SH, Kanasaki K, Gocheva V, Blum G, Harper J, Moses MA, et al. VEGF-A induces angiogenesis by perturbing the cathepsin-cysteine protease inhibitor balance in venules, causing basement membrane degradation and mother vessel formation. Cancer Res. 2009;69:4537–44.
14. Chau YY, Bandiera R, Serrels A, Martínez-Estrada OM, Qing W, Lee M, et al. Visceral and subcutaneous fat have different origins and evidence supports a mesothelial source. Nat Cell Biol. 2014;16:367–75.
15. Chen YT, Chang YT, Pan SY, Chou YH, Chang FC, Yeh PY, et al. Lineage tracing reveals distinctive fates for mesothelial cells and submesothelial fibroblasts during peritoneal injury. J Am Soc Nephrol. 2014;25:2847–458.
16. Davidson B, Nielsen S, Christensen J, Asschenfeldt P, Berner A, Risberg B, et al. The role of desmin and N-cadherin in effusion cytology: a comparative study using established markers of mesothelial and epithelial cells. Am J Surg Pathol. 2001;25:1405–12.
17. DeGrendele HC, Estess P, Siegelman MH. Requirement for CD44 in activated T cell extravasation into an inflammatory site. Science. 1997;278:672–5.
18. Demetri GD, Zenzie BW, Rheinwald JG, Griffin JD. Expression of colony-stimulating factor genes by normal human mesothelial cells and human malignant mesothelioma cells lines in vitro. Blood. 1989;15:940–6.
19. Dvorak HF. Tumors: wounds that do not heal—redux. Cancer Immunol Res. 2015;3:1–11.
20. Dvorak HF, Brown LF, Detmar M, Dvorak AM. Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol. 1995;146:1029–39.
21. Esaki Y, Hirayama R, Hirokawa K. A comparison of patterns of metastasis in gastric cancer by histologic type and age. Cancer. 1990;65:2086–90.
22. Firan M, Dhillon S, Estess P, Siegelman MH. Suppressor activity and potency among regulatory T cells is discriminated by functionally active CD44. Blood. 2006;107:619–27.
23. Gardner MJ, Jones LM, Catterall JB, Turner GA. Expression of cell adhesion molecules on ovarian tumour cell lines and mesothelial cells, in relation to ovarian cancer metastasis. Cancer Lett. 1995;91:229–34.
24. Gary Lee YC, Melkerneker D, Thompson PJ, Light RW, Lane KB. Transforming growth factor beta induces vascular endothelial growth factor elaboration from pleural mesothelial cells in vivo and in vitro. Am J Respir Crit Care Med. 2002;165:88–94.
25. Hainsworth JD, Rubin MS, Spigel DR, et al. Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: a prospective trial of the Sarah Cannon research institute. J Clin Oncol. 2013;31:217–23.
26. Hass HG, Smith U, Jäger C, Schäffer M, Wellhäuber U, Hehr T, Markmann HU, Nehls O, Denzlinger C. Signet ring cell carcinoma of the stomach is significantly associated with poor prognosis and diffuse gastric cancer (Lauren's): single-center experience of 160 cases. Onkologie. 2011;34:682–6.
27. Heel KA, Hall JC. Peritoneal defences and peritoneum-associated lymphoid tissue. Br J Surg. 1996;83:1031–6.
28. Hegmans JP, Hemmes A, Hammad H, Boon L, Hoogsteden HC, Lambrecht BN. Mesothelioma environment comprises cytokines and T-regulatory cells that suppress immune responses. Eur Respir J. 2006;27:1086–95.
29. Hugen N, van de Velde CJ, de Wilt JH, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol. 2014;25:651–7.
30. Ito T, Yorioka N, Yamamoto M, Kataoka K, Yamakido M. Effect of glucose on intercellular junctions of cultured human peritoneal mesothelial cells. J Am Soc Nephrol. 2000;11:1969–79.
31. Iwanicki MP, et al. Ovarian cancer spheroids use myosin-generated force to clear the mesothelium. Cancer Discov. 2011;1:144–57.
32. Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human diseases. Physiol Rev. 2011;91:221–64.
33. Jiang H, Zhang H, Tian L, Zhang X, Xue Y. The difference in clinic-pathological features between signet ring cell carcinoma and gastric mucinous adenocarcinoma. Tumour Biol. 2013;34:2625–31.
34. Jonjić N, Peri G, Bernasconi S, Sciacca FL, Colotta F, Pelicci P, et al. Expression of adhesion molecules and chemotactic cytokines in cultured human mesothelial cells. J Exp Med. 1992;176:1165–74.

35. Kanamori-Katayama M, Kaiho A, Ishizu Y, Okamura-Oho Y, Hino O, Abe M, et al. LRRN4 and UPK3B are markers of primary mesothelial cells. PLoS One. 2011;6:e25391.
36. Kano Y, Kosugi S, Ishikawa T, Otani T, Muneoka Y, Sato Y, et al. Prognostic significance of peritoneal lavage cytology at three cavities in patients with gastric cancer. Surgery. 2015;158:1581–9.
37. Karki S, Surolia R, Hock TD, Guroji P, Zolak JS, Duggal R, et al. Wilms' tumor 1 (Wt1) regulates pleural mesothelial cell plasticity and transition into myofibroblasts in idiopathic pulmonary fibrosis. FASEB J. 2014;28:1122–31.
38. Kato S, Yuzawa Y, Tsuboi N, Maruyama S, Morita Y, Matsuguchi T, et al. Endotoxin-induced chemokine expression in murine peritoneal mesothelial cells: the role of toll-like receptor 4. J Am Soc Nephrol. 2004;15:1289–99.
39. Kawanishi K. Diverse properties of the mesothelial cells in health and disease. Pleura Peritoneum. 2016;1:79–89.
40. Kim J, Bhagwandin S, Labow DM. Malignant peritoneal mesothelioma: a review. Ann Transl Med. 2017;5:236.
41. Kimura I, Sakamoto Y, Shibasaki M, Kobayashi Y, Matsuo H. Release of endothelins and platelet-activating factor by a rat pleural mesothelial cell line. Eur Respir J. 2000;15:170–6.
42. Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiol Rev. 1994;74:761–811.
43. Kitayama J, Emoto S, Yamaguchi H, Ishigami H, Yamashita H, Seto Y, et al. CD90 (+)CD45 (−) intraperitoneal mesothelial-like cells inhibit T cell activation by production of arginase I. Cell Immunol. 2014;288:8–14.
44. Krediet RT. Dialysate cancer antigen 125 concentration as marker of peritoneal membrane status in patients treated with chronic peritoneal dialysis. Perit Dial Int. 2001;21:560–7.
45. Książek K. Mesothelial cell: a multifaceted model of aging. Ageing Res Rev. 2013;12:595–604.
46. Kuwahara M, Kuwahara M, Verma K, Ando T, Hemenway DR, Kagan E. Asbestos exposure stimulates pleural mesothelial cells to secrete the fibroblast chemoattractant, fibronectin. Am J Respir Cell Mol Biol. 1994;10:167–76.
47. Lachaud CC, Soria F, Escacena N, Quesada-Hernández E, Hmadcha A, Alió J, et al. Mesothelial cells: a cellular surrogate for tissue engineering of corneal endothelium. Invest Ophthalmol Vis Sci. 2014;55:5967–78.
48. Lanfrancone L, Boraschi D, Ghiara P, Falini B, Grignani F, Peri G, et al. Human peritoneal mesothelial cells produce many cytokines (granulocyte colony-stimulating factor [CSF], granulocyte-monocyte-CSF, macrophage-CSF, interleukin-1 [IL-1], and IL-6) and are activated and stimulated to grow by IL-1. Blood. 1992;1:2835–42.
49. Lee TC, Zhang Y, Aston C, Hintz R, Jagirdar J, Perle MA, et al. Normal human mesothelial cells and mesothelioma cell lines express insulin-like growth factor I and associated molecules. Cancer Res. 1993;53:2858–64.
50. Liu JY, Yuan JP, Geng XF, Qu AP, Li Y. Morphological study and comprehensive cellular constituents of milky spots in the human omentum. Int J Clin Exp Pathol. 2015;8:12877–84.
51. Liu JY, Geng X, Li Y. Milky spots: omental functional units and hotbeds for peritoneal cancer metastasis. Tumour Biol. 2016;37:5715–26.
52. Maciver AH, McCall M, James Shapiro AM. Intra-abdominal adhesions: cellular mechanisms and strategies for prevention. Int J Surg. 2011;9:589–94.
53. Matsuoka J, Yashiro M, Doi Y, Fuyuhiro Y, Kato Y, Shinto O, et al. Hypoxia stimulates the EMT of gastric cancer cells through autocrine TGFβ signaling. PLoS One. 2013;8:e62310.
54. McCluggage WG, Judge MJ, Clarke BA, Davidson B, Gilks CB, Hollema H, Ledermann JA, Matias-Guiu X, Mikami Y, Stewart CJ, Vang R, Hirschowitz L, International Collaboration on Cancer Reporting. Data set for reporting of ovary, fallopian tube and primary peritoneal carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR). Mod Pathol. 2015;28:1101–22. https://doi.org/10.1038/modpathol.2015.77.
55. Mier-Cabrera J, Jiménez-Zamudio L, García-Latorre E, Cruz-Orozco O, Hernández-Guerrero C. Quantitative and qualitative peritoneal immune profiles, T-cell apoptosis and oxidative stress-associated characteristics in women with minimal and mild endometriosis. BJOG. 2011;118:6–16.
56. Mutsaers SE. The mesothelial cell. Int J Biochem Cell Biol. 2004;36:9–16.
57. Mutsaers SE, Birnie K, Lansley S, Herrick SE, Lim CB, Prêle CM. Mesothelial cells in tissue repair and fibrosis. Front Pharmacol. 2015;6:113.
58. Naor D. Editorial: interaction between hyaluronic acid and its receptors (CD44, RHAMM) regulates the activity of inflammation and cancer. Front Immunol. 2016;7:39.
59. Nishimura S, Chung YS, Yashiro M, Inoue T, Sowa M. CD44 h plays an important role in peritoneal dissemination of scirrhous gastric cancer cells. Jpn J Cancer Res. 1996;87:1235–44.
60. Noh H, Ha H, Yu MR, Kim YO, Kim JH, Lee HB. Angiotensin II mediates high glucose-induced TGF-beta1 and fibronectin upregulation in HPMC through reactive oxygen species. Perit Dial Int. 2005;25:38–47.
61. Ordóñez NG. Value of immunohistochemistry in distinguishing peritoneal mesothelioma from serous carcinoma of the ovary and peritoneum: a review and update. Adv Anat Pathol. 2006;13:16–25. (Review). PubMed PMID: 16462153.
62. Owens MW, Grimes SR. Pleural mesothelial cell response to inflammation: tumor necrosis factor-

induced mitogenesis and collagen synthesis. Am J Phys. 1993;265:L382–288.
63. Owens MW, Milligan SA. Growth factor modulation of rat pleural mesothelial cell mitogenesis and collagen synthesis. Effects of epidermal growth factor and platelet-derived factor. Inflammation. 1994;18:77–87.
64. Owens MW, Milligan SA, Grisham MB. Inhibition of pleural mesothelial cell collagen synthesis by nitric oxide. Free Radic Biol Med. 1996;21:601–7.
65. Park JH, Kim YG, Shaw M, Kanneganti TD, Fujimoto Y, Fukase K, et al. Nod1/RICK and TLR signaling regulate chemokine and antimicrobial innate immune responses in mesothelial cells. J Immunol. 2007;179:514–21.
66. Passot G, You B, Boschetti G, Fontaine J, Isaac S, Decullier E, et al. Pathological response to neoadjuvant chemotherapy: a new prognosis tool for the curative management of peritoneal colorectal carcinomatosis. Ann Surg Oncol. 2014;21:2608–14.
67. Perkins RC, Broaddus VC, Shetty S, Hamilton S, Idell S. Asbestos upregulates expression of the urokinase-type plasminogen activator receptor on mesothelial cells. Am J Respir Cell Mol Biol. 1999;21:637–46.
68. Ratcliffe EM. Molecular development of the extrinsic sensory innervation of the gastrointestinal tract. Auton Neurosci. 2011;161:1–5.
69. Rynne-Vidal A, Jiménez-Heffernan JA, Fernández-Chacón C, López-Cabrera M, Sandoval P, Lin H, editors. The mesothelial origin of carcinoma associated-fibroblasts in peritoneal metastasis. Cancer. 2015;7:1994–2011.
70. Saed GM, Zhang W, Chegini N, Holmdahl L, Diamond MP. Alteration of type I and III collagen expression in human peritoneal mesothelial cells in response to hypoxia and transforming growth factor-beta1. Wound Repair Regen. 1999;7:504–10.
71. Sammour T, Mittal A, Loveday BP, Kahokehr A, Phillips AR, Windsor JA, et al. Systematic review of oxidative stress associated with pneumoperitoneum. Br J Surg. 2009;96:836–50.
72. Sandoval P, Jiménez-Heffernan JA, Rynne-Vidal Á, Pérez-Lozano ML, Gilsanz Á, Ruiz-Carpio V, Reyes R, García-Bordas J, Stamatakis K, Dotor J, Majano PL, Fresno M, Cabañas C, López-Cabrera M. Carcinoma-associated fibroblasts derive from mesothelial cells via mesothelial-to-mesenchymal transition in peritoneal metastasis. J Pathol. 2013;231:517–31.
73. Schacht V, Dadras SS, Johnson LA, Jackson DG, Hong YK, Detmar M. Up-regulation of the lymphatic marker podoplanin, a mucin-type transmembrane glycoprotein, in human squamous cell carcinomas and germ cell tumors. Am J Pathol. 2005;166:913–21.
74. Singh N, McCluggage WG, Gilks CB. High-grade serous carcinoma of tubo-ovarian origin: recent developments. Histopathology. 2017;71:339–56.
75. Sitter T, Toet K, Quax P, Kooistra T. Fibrinolytic activity of human mesothelial cells is counteracted by rapid uptake of tissue-type plasminogen activator. Kidney Int. 1999;55:120–9.
76. Sivertsen S, Hadar R, Elloul S, Vintman L, Bedrossian C, Reich R, et al. Expression of Snail, Slug and Sip1 in malignant mesothelioma effusions is associated with matrix metalloproteinase, but not with cadherin expression. Lung Cancer. 2006;54:309–17.
77. Solass W, Horvath P, Struller F, Königsrainer I, Beckert S, Königsrainer A, et al. Functional vascular anatomy of the peritoneum in health and disease. Pleura Peritoneum. 2016;1:145–58.
78. Solass W, Sempoux C, Carr NJ, Detlefsen S, Bibeau F. Peritoneal sampling and histological assessment of therapeutic response in peritoneal metastasis: proposal of the Peritoneal Regression Grading Score (PRGS). Pleura Peritoneum. 2016;1:99–107.
79. Solass W, Struller F, Horvath P, Königsrainer A, Sipos B, Weinreich FJ. Morphology of the peritoneal cavity and pathophysiological consequences. Pleura Peritoneum. 2016;1:193–201.
80. Stoermann B, Kretschmer K, Düber S, Weiss S. B-1a cells are imprinted by the microenvironment in spleen and peritoneum. Eur J Immunol. 2007;37:1613–20.
81. Strippoli R, Benedicto I, Foronda M, Perez-Lozano ML, Sánchez-Perales S, López-Cabrera M, et al. p38 maintains E-cadherin expression by modulating TAK1-NF-kappa B during epithelial-to-mesenchymal transition. J Cell Sci. 2010;123:4321–31.
82. Struller F, Weinreich FW, Horvath P, Kokkalis MK, Beckert S, Königsrainer A, Reymond MA. Peritoneal innervation: embryology and functional anatomy. Pleura Peritoneum. 2017;2(4):153–61.
83. Sugarbaker PH. Peritoneum as the first-line of defense in carcinomatosis. J Surg Oncol. 2007;95:93–6.
84. Tamsma JT, Keizer HJ, Meinders AE. Pathogenesis of malignant ascites: Starling's law of capillary hemodynamics revisited. Ann Oncol. 2001;12:1353–7. (Review).
85. Tan RY, Ngeow J. Hereditary diffuse gastric cancer: what the clinician should know. World J Gastrointest Oncol. 2015;7:153–60. https://doi.org/10.4251/wjgo.v7.i9.153.
86. Tatsuta T, Hosono M, Takahashi K, Omoto T, Kariya Y, Sugawara S, et al. Sialic acid-binding lectin (leczyme) induces apoptosis to malignant mesothelioma and exerts synergistic antitumor effects with TRAIL. Int J Oncol. 2014;44:377–84.
87. Tischoff I, Neid M, Neumann V, Tannapfel A. Pathological diagnosis and differential diagnosis. In: Tannapfel A, editor. Malignant mesothelioma. Recent results in cancer research. Berlin Heidelberg: Springer; 2011. p. 57–78.
88. van Hinsbergh VW, Kooistra T, Scheffer MA, Hajo van Bockel J, van Muijen GN. Characterization

and fibrinolytic properties of human omental tissue mesothelial cells. Comparison with endothelial cells. Blood. 1990;75:1490–7.
89. Varki A. Glycan-based interactions involving vertebrate sialic-acid-recognizing proteins. Nature. 2007;446:1023–9.
90. Wang J, El-Bahrawy MA. Expression profile of mucins in ovarian mucinous tumours: distinguishing primary ovarian from metastatic tumours. Int J Gynaecol Pathol. 2014;33:166–75.
91. Wilson RB. Changes in the coelomic microclimate during carbon dioxide laparoscopy: morphological and functional implications. Pleura Peritoneum. 2017;2:17–31.
92. Witz CA, Monotoya-Rodriguez IA, Schenken RS. Whole explants of peritoneum and endometrium: a novel model of the early endometriosis lesion. Fertil Steril. 1999;71:56–60.
93. Wu YJ, Parker LM, Binder NE, Beckett MA, Sinard JH, Griffiths CT, et al. The mesothelial keratins: a new family of cytoskeletal proteins identified in cultured mesothelial cells and nonkeratinizing epithelia. Cell. 1982;31:693–70.
94. Yang WS, Kim BS, Lee SK, Park JS, Kim SB. Interleukin-1beta stimulates the production of extracellular matrix in cultured human peritoneal mesothelial cells. Perit Dial Int. 1999;19:211–20.
95. Yonemura YE, et al. A possible role of cytokines in the formation of peritoneal dissemination. Int J Oncol. 1997;11:349–58.
96. Young VJ, Brown JK, Saunders PT, Horne AW. The role of the peritoneum in the pathogenesis of endometriosis. Hum Reprod. 2013;19:558–69.
97. Yuan ML, Tong ZH, Jin XG, Zhang JC, Wang XJ, Ma WL, et al. Regulation of CD4 (+) T cells by pleural mesothelial cells via adhesion molecule-dependent mechanisms in tuberculous pleurisy. PLoS One. 2013;8:e74624.
98. Yung S, Chan TM. Pathophysiology of the peritoneal membrane during peritoneal dialysis: the role of hyaluronan. J Biomed Biotechnol. 2011;2011:180594.
99. Zebrowski BK, Liu W, Ramirez K, Akagi Y, Mills GB, Ellis LM. Markedly elevated levels of vascular endothelial growth factor in malignant ascites. Ann Surg Oncol. 1999;6:373–8.

2 Pharmacovigilance of Local Chemotherapy in the Peritoneum

Susen Burock, Pankaj Kumar Garg, Marc A. Reymond, and Alfred Königsrainer

2.1 Introduction

Every year, thousands of substances are investigated by industrial or academic researchers, with the hope of improving cancer therapy. Only a small part of these substances will go successfully through the preclinical development steps and will reach clinical testing in human patients. Out of the substances tested in patients, only a few will enter the market.

▶ Marketing Approval Requires a Thorough Risk-Benefit Assessment

The balance between the benefits and risks of a new drug is the fundamental principle of the assessment process resulting in marketing approval. The data submitted for marketing authorization must include comprehensive information on the drug manufacturing process, its effects in preclinical studies, benefits and side effects observed in clinical trials, and the information provided to patients and physicians.

When successful, the regulatory assessment results in marketing approval for the new drug in a circumscribed indication. For example, oxaliplatin has been approved in combination with 5-fluorouracil (5-FU) and folinic acid (FA) for the treatment, among others, of metastatic colorectal cancer. Moreover, the information provided specifies the dose and the type of application of the drug, in this example, intravenous delivery of 85 mg oxaliplatin/m^2 body surface area every 2 weeks over 12 cycles. The drug information material reports precisely the frequent, less frequent, and rare side effects of the drug. Frequent side effects of oxaliplatin include, for example, allergic reactions, anemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia, peripheral sensory

S. Burock (✉)
Charité Comprehensive Cancer Center, Charité University Hospital of Berlin, Berlin, Germany
e-mail: susen.burock@charite.de

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

M. A. Reymond
National Center for Pleura and Peritoneum (NCPP), University of Tübingen, Tübingen, Germany
e-mail: marc.reymond@med.uni-tuebingen.de

A. Königsrainer
Department of Surgery, University of Tübingen, Tübingen, Germany
e-mail: alfred.koenigsrainer@med.uni-tuebingen.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_2

neuropathy, sensory disorders, dysgeusia, headache, etc.[1]

Regulatory Framework of Intraperitoneal Chemotherapy

To our knowledge, there is no drug approved for intraperitoneal delivery in Europe or the USA. Thus, drugs commonly used for intraperitoneal chemotherapy are applied "off-label," in other words, outside the approved indication, mode of delivery, and dose. For example, according to Elias' French hyperthermic intraperitoneal chemotherapy (HIPEC) protocol, oxaliplatin is delivered at a dose of 460 mg/m^2, in combination with systemic intravenous 5-FU [11, 12]. Although the dose applied to the peritoneal cavity is a multiple (about five times) of the approved dose for intravenous delivery, there was, to our knowledge, no application for regulatory approval of oxaliplatin as HIPEC.

Post-authorization Safety Studies Are Needed

The risk-benefit evaluation of a new drug continues after marketing authorization. To further evaluate the drug risks and remaining uncertainties, information is collected in the so-called post-authorization safety studies, allowing to detect rare side effects of the new drug. For example, the European Medicines Agency (EMA) evaluated in 2018 clinical trials, post-marketing cases, and literature reports on oxaliplatin. The EMA concluded that the evidence was sufficient to establish a causal relationship between oxaliplatin and acute coronary syndrome, including myocardial infarction and coronary artery syndrome.[2] The manufacturers were required to update drug information material.

Reporting the side effects of marketed drugs is critical for ensuring patient safety and is a legal obligation in many countries. In practice, however, this reporting by the end users remains sparse. One of the possible explanations may be related to the fact that these effects are attributed to the tumor progression and not to the chemotherapeutic drugs. All the clinical symptoms and changes in the quality of life are helpful to determine if side effects are related to tumor progression or chemotherapeutic agents [8].

What Is Pharmacovigilance?

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem.[3] Pharmacovigilance is regulated by law, and national drug agencies are responsible for its enforcement. For example, in Europe, marketing authorization holders and sponsors of clinical trials must report and evaluate suspected adverse drug reactions during the development and following the marketing authorization of medicinal products in the European Economic Area (EEA). Marketing authorization holders must also electronically submit information on medicinal products authorized in the European Union (EU). In Germany, side effects can be reported online by accessing a joint database of the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute, responsible for biological therapies (PEI).

The Significance of Pharmacovigilance for Intraperitoneal Drug Delivery

Intraperitoneal drug delivery has an "off-label" character. Surgeons and gynecologists cannot rely on the independent assessment of the risk-benefit ratio by a regulatory authority. There might be additional, unknown risks of local toxicity. Moreover, applying into the peritoneal cavity a dose significantly higher as the usual

[1] https://mein.sanofi.de/produkte/Eloxatin/Downloads?id=dafcc9b3-4397-4205-aeb3-581a3fa90edd, consulted on Apr 9, 2020.

[2] https://www.ema.europa.eu/en/documents/psusa/oxaliplatin-cmdh-scientific-conclusions-grounds-variation-amendments-product-information-timetable/00002229/201804_de.pdf

[3] https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview, consulted on Apr 8, 2020.

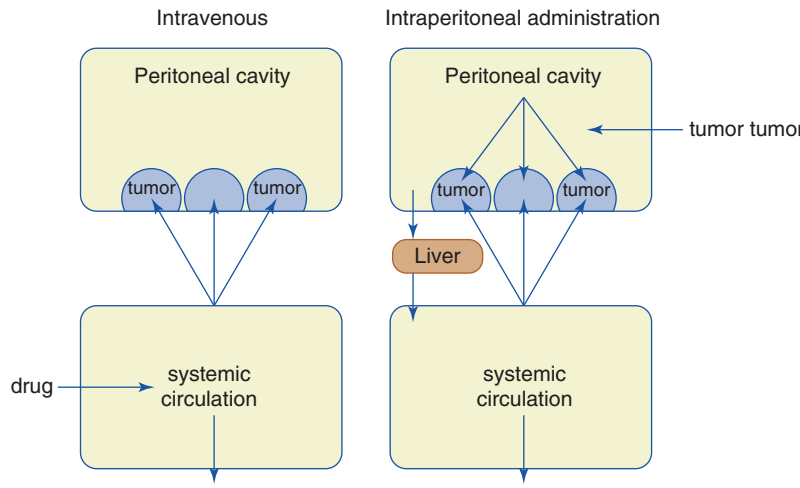


Fig. 2.1 Schematic representation of the principles of intraperitoneal chemotherapy [20]. The pharmacokinetic rationale of perioperative intraperitoneal cancer chemotherapy is based on the dose intensification provided by the peritoneal-plasma barrier

intravenous dose might result in significant systemic toxicities. Thus, when they perform intraperitoneal chemotherapy, surgeons and gynecologists endorse a particular responsibility. Therefore, they must report on the side effects observed in their patients.

For example, in 2014 (12 years after first publication on the intraperitoneal application of oxaliplatin), a pharmacodynamics study showed an incidence of intra-abdominal bleeding of 22.7%, neuropathy 18.7%, and grade 3/4 thrombocytopenia 13.3% [2]. There was significant variability in peritoneal and systemic oxaliplatin exposures, leading to differences in hematological toxicity between patients. The drug information was updated and now includes that "Peritoneal bleeding can occur when oxaliplatin is administered intraperitoneally (off-label administration)."[4]

2.2 Basics of Pharmacokinetics and Pharmacodynamics (PK/PD) of Intraperitoneal Chemotherapy

Pharmacokinetics (PK) examines what the body does to the drug; pharmacodynamics (PD) investigates what the drug does to the body. Surgeons and gynecologists need a basic knowledge of pharmacodynamics and pharmacokinetics to apply chemotherapy into the abdomen of their patients. This knowledge is also required for pharmacovigilance duties, for example, to ascertain the causality between intraperitoneal drug application and the side effect observed.

Intraperitoneal chemotherapy has demonstrated significant pharmacologic and clinical advantages over traditional intravenous administration for cancers restricted to the peritoneal cavity [16]. The basic principle of intraperitoneal chemotherapy is to attain a higher concentration of the chemotherapeutic agents locally over the tumors without having the side effects of the drugs if the same dose were given systemically (Fig. 2.1).

Intraperitoneal chemotherapy is associated with a significant pharmacokinetic and pharmacodynamic benefit. It can, alone or in combination with systemic chemotherapy (bidirectional chemotherapy), be used for treating primary and secondary peritoneal surface malignancies [4].

▶ Local Administration Enhances Dose Exposition of the Target Tissue

High intraperitoneal drug concentration and direct tumor exposure constitute the two key aspects enabling the eradication of tumor cells within the abdomen. However, these favorable pharmacokinetic parameters may not correlate with the drug amount entering peritoneal tumor

[4] https://mein.sanofi.de/produkte/Eloxatin/Downloads?id=dafcc9b3-4397-4205-aeb3-581a3fa90edd, consulted on Apr 9, 2020.

nodules. It is more critical to achieving adequate tumor tissue penetration and concentration of the drug rather than high drug concentrations in the peritoneal fluid only [3].

Limited tissue penetration remains a significant limitation of intraperitoneal chemotherapy. Drug penetration into solid tumors is a complex mass transport process that involves multiple parameters not only related to the used cytotoxic agent but also the tumor tissue properties and even the therapeutic setup [37]. Most cytotoxic agents are macromolecules and are transported into the tissue by convection rather than diffusion; in other words, they are transported together with liquids along a gradient.

Different anticancer drugs have a varied depth of penetration, which depends upon molecular weight, chemical structure, and fat solubility and, to a lesser extent, on clearance. In an animal model, cisplatin was shown to have a particularly high intratumor concentration (1–2 mm from the surface of the tumor) after intraperitoneal administration. In contrast, when cisplatin was given systemically, there was a significantly lower concentration of the drug at the periphery of the tumor, thus underlining the advantage of intraperitoneal administration [26]. In comparison, the penetration depth of carboplatin was found to be less than 0.5 mm when administered intraperitoneally. The reasons for this difference in the pharmacokinetics of carboplatin and cisplatin are the lower fat/water distribution (coefficient for carboplatin <0.00004 and cisplatin <0.008), the higher molecular weight of carboplatin (371.3 kDa vs. 300.6 kDa), and the difference in activation speed of both the drugs [27].

Doxorubicin, an anthracycline drug commonly used for intraperitoneal delivery, has a tissue penetration limited to a few cell layers. Advanced formulations and mild hyperthermia (see below) might contribute to an improved tissue uptake and concentration of doxorubicin [9].

▶ Rationale for the Combination of HIPEC with Cytoreductive Surgery

An essential criterion for the effectiveness of local chemotherapy is the direct contact with the tumor surface and the ability of anticancer drugs to get into the tumor. Therefore, optimal debulking surgery resulting in minimal residual tumor tissue is a critical factor for the effectiveness of intraperitoneal chemotherapy [41]. Moreover, entero-enteral and entero-parietal adhesions are removed during surgery, enabling access of chemotherapy to all abdominal compartments, including the lesser sac [35].

▶ Local Delivery Can Minimize Systemic Toxicity

The portal vein first transports drugs administered into the peritoneal cavity to the liver, where they are metabolized. This physiological process has consequences both on the toxicity and the choice of the drug. Large amounts of the drug enter the liver and can cause severe damage to the parenchyma. Particular caution is needed when hepatotoxic drugs are used (such as taxanes). Therefore, physicians should monitor liver function after intraperitoneal chemotherapy.

The hepatic enzymes effectively degrade drugs such as cytarabine and 5-fluorouracil during their first pass through the liver. After the first hepatic passage, these drugs reach the systemic circulation only in small amounts. Therefore, the toxicity profile of these drugs is distinctly better when administered intraperitoneally than intravenously. Intraperitoneal delivery of drugs with a low hepatic metabolism (e.g., cisplatin and carboplatin) does not have this advantage since they reach systemic circulation in large amounts.

▶ Hyperthermia Can Enhance Drug Uptake into the Peritoneal Tissue

Hyperthermia can improve the depth of tissue penetration of drugs administered into the peritoneal cavity [16]. The thermal enhancement of the drugs' activity and penetration depth is already observed at temperatures above 39–40 °C [32, 38]. However, in preclinical studies, the additional pharmacological effect of hyperthermia has been found to be moderate [15]. There is no comparative clinical study documenting that

HIPEC is superior to normothermic intraperitoneal chemotherapy [4].

Hyperthermia Can Enhance the Cytotoxic Effect of Chemotherapeutic Drugs

Hyperthermic drug sensitization can be seen for a number of anticancer drugs, especially of alkylating agents [21]. Cytotoxic agents acting synergistically with hyperthermia include mitomycin C, cisplatin, melphalan, mitoxantrone, bleomycin, and doxorubicin. Hyperthermia delays the repair of DNA damage caused by cisplatin or doxorubicin, acting upstream of different repair pathways to block histone polyADP-ribosylation (PARylation). Furthermore, hyperthermia produces induction of double-strand breaks (DSB) and cell cytotoxicity after chemotherapy [33].

However, all cytotoxic agents do not benefit of hyperthermia. For example, targeted agents consist of antibodies in which stability and function can be damaged by prolonged or pronounced hyperthermia, so that their manufacturers do not expect them to be heated during application. Within the regulatory assessment, the stability of bevacizumab has only been tested up to a temperature of 30 °C, and a loss of 20–30% potency was observed after 3 months of storage at this temperature.[5]

Influence of Hyperthermia on the Immune Response

Hyperthermia improves cytotoxicity via a variety of mechanisms, targeting both the tumor and its microenvironment. Raising the temperature of the tumor and surrounding tissues to 42–43 °C makes the tumor more immune responsive [28]. Hyperthermia also modifies the tumor microenvironment by inducing and synthesizing heat shock proteins (HSP). HSP play a cytoprotective role in cells exposed to stressful conditions. Some HSP are secreted to the cell exterior and prompt the immune system to react [43]. Hyperthermia can potentiate the anticancer effects of some chemotherapy agents such as mitomycin C, which also causes immune-mediated cytotoxicity [39, 44]. However, the complex interplay of hyperthermia with the innate and adaptive immune response in the peritoneal cavity has not yet been sufficiently explored. In particular, a combination of HIPEC with immune checkpoint inhibitors might be further investigated.

Bioactivity of the Peritoneal Perfusate

The bioactivity of the peritoneal perfusate might differ considerably from the applied dose. For example, compared with amounts of oxaliplatin expected in peritoneal perfusates by calculation, only 10–15% of the parent drug could be detected by liquid chromatography/mass spectrometry (LC-MS) during HIPEC in human patients. Additionally, platinum compounds were detected consistent with oxaliplatin transformation. Thus, the actual cytotoxic potential of oxaliplatin and its derivatives over time might differ from the clinical expectations [24].

Duration of Exposition

The optimal length of chemoperfusion is determined by an optimal balance between local efficacy and systemic toxicity. A longer duration may lead to the absorption of an increased amount of drug to the systemic compartment and results in more toxicity. On the other hand, a shorter exposition time might compromise the drug's anticancer effect. For example, the results of the randomized PRODIGE 7 trial failed to show a difference in overall survival between patients undergoing cytoreductive surgery (CRS) alone versus CRS combined with HIPEC using high-dose oxaliplatin [1]. For almost 20 years, we know that oxaliplatin is a drug with verified efficacy in colorectal cancer [5]. Thus, the negative results of the PRODIGE 7 trial cannot be explained by the drug chosen but rather by pharmacological variables, in this case, a high intraperitoneal dose (five times the usual intravenous dose) associated with chemoperfusion for only 30 minutes [23].

[5] https://www.ema.europa.eu/en/documents/scientific-discussion/avastin-epar-scientific-discussion_en.pdf

Infused Volume

A larger volume of peritoneal fluid can enlarge the contact surface of the chemotherapeutic drugs with the peritoneum [10, 22]. Also, the instillation of a large volume of fluid results in an increase in pressure, which can further improve the tumor penetration of the drugs. On the other hand, intra-abdominal pressure may compromise respiratory and hemodynamic functions [40].

Drug Clearance from the Abdominal Cavity

Chemotherapeutic agents are cleared from the peritoneal cavity through active absorption into the retroperitoneal capillary vessels [36]. Venous drainage of the parietal peritoneum runs directly into the systemic circulation, while venous blood from the visceral peritoneum goes to the liver through the portal vein. Only a small part of the drug is cleared through the lymphatic system [19].

In general, the intraperitoneal dosage of the drugs depends upon the rate at which they are absorbed from the peritoneal cavity and the rate of plasma clearance. A higher amount of a drug can be applied to the peritoneal cavity if it is absorbed slowly and has a fast plasma clearance; this drug will have lower systemic concentration and fewer gastrointestinal and hematological side effects. Examples are heavily ionized or poorly fat-soluble substances.

The carrier solution also affects the clearance of the intraperitoneally administered drugs. An isotonic solution or dextrose-based dialysis solution are used as carriers for intraperitoneal chemotherapy. In theory, using a hypotonic solution might increase drug tissue uptake. For example, in Elias' HIPEC protocol, oxaliplatin was diluted in 5% glucose/dextrose solution. However, this hypotonic carrier solution was of little use in increasing drug tumor penetration and may cause significant thrombocytopenia and intraperitoneal hemorrhage [11–13].

Variability Between HIPEC Protocols

Although the HIPEC procedure is adopted throughout the world, major differences exist between treatment protocols, and at least 60 different HIPEC protocols have been published [42]. There is no consensus on the applied dose, duration, carrier solution, perfusate volume, perfusate concentration, use of an open vs. closed technique, or the usefulness of additional flushing with crystalloids at the end of the HIPEC procedure. These differences can play an important role in the pharmacokinetics (PK) of oxaliplatin and thereby might influence the efficacy and/or safety of the HIPEC procedure [6].

Novel Drug Delivery Systems

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel minimally invasive drug delivery system addressing the current limitations of intraperitoneal chemotherapy. The rationale of PIPAC is:

- Optimizing homogeneity of drug distribution by applying an aerosol rather than a liquid solution
- Applying increased intraperitoneal hydrostatic pressure to counteract elevated intratumoral interstitial fluid pressure
- Limiting blood outflow during drug application
- Steering environmental parameters (temperature, pH, electrostatic charge, etc.) in the peritoneal cavity for best tissue target effect

Experimentally, PIPAC achieved better tissue penetration of oxaliplatin than HIPEC in organoids [14]. In the swine, PIPAC made tissue concentration comparable with HIPEC by applying a fraction of the dose (20%). Oxaliplatin concentration in the visceral peritoneum was significantly higher after PIPAC than after HIPEC [17]. The superior pharmacological properties of PIPAC have been confirmed in the clinical set-

ting. PIPAC was able to induce objective radiological and histological regression of peritoneal metastases of colorectal origin [7, 18]. Thus, it is not possible to extrapolate the results of oxaliplatin applied as HIPEC to other drug delivery techniques.

Favorable tumor characteristics and beneficial properties of the cytotoxic chemotherapeutic agents used for intraperitoneal chemotherapy

Properties of the cytotoxic drugs used:

- Proven cytotoxic effect in the respective tumor entity
- Concentration-dependent activity
- Low peritoneal clearance (low fat solubility, high molecular weight)
- Rapid plasma clearance
- High first-pass liver metabolism
- Low peritoneal toxicity
- Synergy with hyperthermia
- Administration in an active form and low metabolism in the peritoneal cavity

Favorable tumor characteristics

- Disease limited to the peritoneal cavity
- Small residual tumor volume
- Sensitive cytotoxic drugs
- Well-perfused tumors

2.3 Side Effects of Intraperitoneal Chemotherapy

Systemic side effects of intraperitoneal chemotherapy arise from active absorption of cytotoxic substances from the peritoneal cavity into the systemic circulation. Thus, these side effects are similar to those of intravenous administration. These systemic side effects depend upon the drug administered and include:

- Renal failure (i.e., after cisplatin administration)
- Neurotoxicity (i.e., after oxaliplatin)
- Higher-grade hematological toxicities
- Bone marrow suppression with subsequent leukopenia and thrombocytopenia (i.e., after mitomycin C)

In an overview of ovarian cancer, toxicities following the intraperitoneal administration of cytotoxic drugs were fewer compared to intravenous administration; but this does not apply to infections and gastrointestinal side effects such as nausea, vomiting, and abdominal pain (Table 2.1, [30]). Intraperitoneal chemotherapy can also cause hemodynamic and cardiovascular side effects. These side effects are caused by elevated intra-abdominal pressure following the infusion of a large volume of the carrier fluid.

▶ Local Side Effects of Intraperitoneal Chemotherapy

Despite the high concentration of cytotoxic chemotherapy in the peritoneal cavity, acute gastrointestinal toxicity is rare, which is probably due to the high capillary density and the consequent rapid removal of the cytotoxic agents. Chronic local side effects are adhesions and bowel thickening—both of which may result in bowel obstruction. Cisplatin, when used for intraperitoneal chemotherapy, has been shown to have a better local toxicity profile than other agents [29]. Other local side effects include infections and chemical peritonitis.

▶ Bidirectional Chemotherapy May Cause Both Local and Systemic Side Effects

It is difficult to ascertain a causal relationship of side effects when systemic chemotherapy, intraperitoneal chemotherapy, and hyperthermia are given simultaneously. However, the time lag between the administration of the cytotoxic drugs and the onset of side effects varies between intraperitoneal chemotherapy and systemic therapy. For example, the peak of bone marrow suppression following intraperitoneal chemotherapy with mitomycin C is usually observed at 2 weeks following surgery, whereas it occurs after 4–6 weeks of systemic administration [25].

Table 2.1 Toxicity of intraperitoneal chemotherapy compared with intravenous administration (according to the [30])

Symptom	Study	Toxicity after intravenous administration (%)	Toxicity after intraperitoneal administration (%)	*p*-Value
Hearing impairment (>Grade 2)	Alberts et al.	15	5	$p < 0.001$
Tinnitus (>Grade 2)	Alberts et al.	14	7	$p = 0.01$
Anemia (>Grade 3)	Alberts et al.	25	26	ns
	Gadducci et al.	8	6	N/A
	Kirmani et al.	3	7	N/A
	Yen et al.	12	7	ns
Granulocytopenia	Alberts et al.	69	56	$p = 0.002$
Leucopenia (>Grade 3)	Alberts et al.	50	40	$p = 0.04$
	Armstrong et al.	64	76	$p < 0.001$
	Gadducci et al.	19	24	N/A
	Kirmani et al.	21	19	N/A
	Markman et al.	62	77	N/A
	Polyzos et al.	18	5	$p < 0.01$
	Yen et al.	21	10	$p = 0.033$
Thrombocytopenia (>Grade 3)	Alberts et al.	9	8	ns
	Armstrong et al.	4	12	$p < 0.001$
	Gadducci et al.	2	0	N/A
	Kirmani et al.	0	5	N/A
	Markman et al.	3	49	N/A
	Polyzos et al.	10	3	$p < 0.09$
	Yen et al.	10	7	ns
Fatigue (>Grade 3)	Armstrong et al.	4	18	$p < 0.001$
	Markman et al.	1	3	N/A
Fever (>Grade 3)	Armstrong et al.	4	9	$p = 0.02$
	Markman et al.	1	3	N/A
Gastrointestinal toxicity (>Grade 3)	Armstrong et al.	24	46	$p < 0.001$
	Markman et al.	17	37	N/A
	Gadducci et al.	26	37	N/A
Nausea/vomiting (Grade 2)	Piccart et al.	N / A	82	N/A
Infection (>Grade 3)	Armstrong et al.	6	16	$p = 0.001$
	Markman et al.	1	4	N/A
Metabolic toxicities (>Grade 3)	Markman et al.	1	10	N/A
Hepatic toxicity	Armstrong et al.	<1	3	$p = 0.05$
Renal toxicity	Armstrong et al.	2	7	$p = 0.03$
Creatinine clearance (>Grade 3)	Markman et al.	1	5	N/A
Neuromuscular disorders at the end of therapy (>Grade 2)	Alberts et al.	25	15	$p = 0.02$
Neurotoxicity				
(Grade 2 or 3)	Piccart et al.	N/A	15	N/A
	Armstrong et al.	9	19	$p < 0.001$
(>Grade 3)	Markman et al.	9	12	N/A
Abdominal pain				
(Grade 1 or 2)	Piccart et al.	N/A	38	N/A
(<Grade 2)	Piccart et al.	N/A	38	N/A
(>Grade 3)	Armstrong et al.	1	11	$p < 0.001$

▶ Anaphylactic Reaction

Anaphylactic reactions have been reported during intraperitoneal chemotherapy [31, 34].

2.4 Conclusion

Intraperitoneal administration of chemotherapy has documented pharmacologic advantages over intravenous delivery for treating metastatic disease limited to the peritoneal cavity. However, the effectiveness of intraperitoneal chemotherapy depends upon several factors, including the cytotoxic agents and the tumor characteristics. Controlled clinical trials are needed to increase the evidence available. Systematic, uniform reporting of the side effects of cytotoxic agents after intraperitoneal chemotherapy is needed to improve patient safety.

References

1. Ceelen W. HIPEC with oxaliplatin for colorectal peritoneal metastasis: the end of the road? Eur J Surg Oncol. 2019;45:400–2.
2. Chalret du Rieu Q, White-Koning M, Picaud L, Lochon I, Marsili S, Gladieff L, et al. Population pharmacokinetics of peritoneal, plasma ultrafiltrated and protein-bound oxaliplatin concentrations in patients with disseminated peritoneal cancer after intraperitoneal hyperthermic chemoperfusion of oxaliplatin following cytoreductive surgery: correlation between oxaliplatin exposure and thrombocytopenia. Cancer Chemother Pharmacol. 2014;74:571–82.
3. De Bree E, Witkamp AJ, Zoetmulder FAN. Intraperitoneal chemotherapy for colorectal cancer. J Surg Oncol. 2002;79:46–61.
4. De Bree E, Michelakis D, Stamatiou D, Romanos J, Zoras O. Pharmacological principles of intraperitoneal and bidirectional chemotherapy. Pleura Peritoneum. 2017;2:47–62.
5. De Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol. 2000;18:2938–47.
6. De Jong LAW, Elekonawo FMK, de Reuver PR, Bremers AJA, de Wilt JHW, Jansman FGA, et al. Hyperthermic intraperitoneal chemotherapy with oxaliplatin for peritoneal carcinomatosis: a clinical pharmacological perspective on a surgical procedure. Br J Clin Pharmacol. 2019;85:47–58.
7. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Color Dis. 2016;18:364–71.
8. Di MM, Gallo C, Leighl NB, et al. Symptomatic Toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol. 2015;33:910–5.
9. Eetezadi S, De Souza R, Vythilingam M, Lessa Cataldi R, Allen C. Effects of doxorubicin delivery systems and mild hyperthermia on tissue penetration in 3D cell culture models of ovarian cancer residual disease. Mol Pharm. 2015;12:3973–85.
10. Elias D, Sideris ML. Pharmacokinetics of heated intraoperative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis. Surg Oncol Clin N Am. 2003;12:755–69.
11. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, et al. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol. 2002;13:267–72.
12. Elias D, El OA, Bonnay M, Paci A, Ducreux M, Antoun S, Lasser P, Laurent S, Bourget P. Human pharmacokinetic study of heated intraperitoneal oxaliplatin in increasingly hypotonic solutions after complete resection of peritoneal carcinomatosis. Oncology. 2002;63:346–52.
13. Elias D, Raynard B, Bonnay M, Pocard M. Heated intraoperative intraperitoneal oxaliplatin alone and in combination with irinotecan intraperitoneally: pharmacologic studies. Eur J Surg Oncol. 2006;32:607–13.
14. Eveno C, Haidara A, Ali I, Pimpie C, Mirshahi M, Pocard M. Experimental pharmacokinetics evaluation of chemotherapy delivery by PIPAC for colon cancer: first evidence for efficacy. Pleura Peritoneum. 2017;2:103–9.
15. Facy O, Al Samman S, Magnin G, Ghiringhelli F, Ladoire S, Chauffert B, et al. High pressure enhances the effect of hyperthermia in intraperitoneal chemotherapy with oxaliplatin: an experimental study. Ann Surg. 2012;256:1084–8.
16. Flessner MF. Pharmacokinetic problems in peritoneal drug administration: an update after 20 years. Pleura Peritoneum. 2016;1:183–91.
17. Giger-Pabst U, Bucur P, Roger S, Falkenstein TA, Tabchouri N, Le Pape A, et al. Comparison of tissue and blood concentrations of oxaliplatin administrated by different modalities of intraperitoneal chemotherapy. Ann Surg Oncol. 2019;26:4445–51.
18. Gockel I, Jansen-Winkeln B, Haase L, Niebisch S, Moulla Y, Lyros O, et al. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in patients with peritoneal metastasized colorectal, appendiceal and small bowel cancer. Tumori. 2020;106:70–8.

19. Hasovits C, Clarke S. Pharmacokinetics and pharmacodynamics of intraperitoneal cancer chemotherapeutics. Clin Pharmacokinet. 2012;51:203–24.
20. Howell SB. Pharmacologic principles of intraperitoneal chemotherapy for the treatment of ovarian cancer. Int J Gynecol Cancer. 2008;18(Suppl 1):20–5.
21. Kampinga HH. Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. Int J Hyperth. 2006;22:191–6.
22. Keshaviah P, Emerson PF, Vonesh EF, Brandes JC. Relationship between body size, fill volume, and mass transfer area coefficient in peritoneal dialysis. J Am Soc Nephrol. 1994;4:1820–6.
23. Königsrainer A, Rau B. Cytoreductive Surgery (CRS) and Hyperthermic IntraPeritoneal Chemotherapy (HIPEC): don't throw the baby out with the bathwater. Pleura Peritoneum. 2018;3:20180131.
24. Löffler MW, Schuster H, Zeck A, Quilitz N, Weinreich J, Tolios A, et al. Pharmacodynamics of oxaliplatin-derived platinum compounds during hyperthermic intraperitoneal chemotherapy (HIPEC): an emerging aspect supporting the rational design of treatment protocols. Ann Surg Oncol. 2017;24:1650–7.
25. Loggie BW, Fleming RA. Complications of heated chemotherapy intraperitoneally and strategies for prevention. Cancer Treat Res. 1996;82:221–33.
26. Los G, Mutsaers PH, Lenglet WJ, Baldew GS, McVie JG. Platinum distribution in intraperitoneal tumors after intraperitoneal cisplatin treatment. Cancer Chemother Pharmacol. 1990;25:389–94.
27. Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. Cancer Chemother Pharmacol. 1991;28:159–65.
28. Mahmood J, Shukla HD, Soman S, Samanta S, Singh P, Kamlapurkar S, et al. Immunotherapy, radiotherapy, and hyperthermia: a combined therapeutic approach in pancreatic cancer treatment. Cancers (Basel). 2018;28:10. pii: E469. https://doi.org/10.3390/cancers10120469.
29. Markman M, Cleary S, Howell SB, Lucas WE. Complications of extensive adhesion formation after intraperitoneally chemotherapy. Surg Gynecol Obstet. 1986;162:445–8.
30. National Cancer Institute (ed). NCI Clinical arrival announcement: intraperitoneal chemotherapy for ovarian cancer; 2006. https://ctep.cancer.gov/highlights/docs/clin_annc_010506.pdf.
31. Ozgüroglu M, Demir G, Demirelli F, Mandel NM. Anaphylaxis from intraperitoneal infusion of cisplatin: a case report. Am J Clin Oncol. 1999;22:172–3.
32. Panteix G, Guillaumont M, Cherpin L, Cuichard J, Gilly FN, Carry PY, et al. Study of the pharmacokinetics of mitomycin C in humans during intraperitoneal chemohyperthermia with special mention of the concentration in local tissues. Oncology. 1993;50:366–70.
33. Schaaf L, Schwab M, Ulmer C, Heine S, Mürdter TE, Schmid JO, et al. Hyperthermia synergizes with chemotherapy by inhibiting PARP1-dependent DNA replication arrest. Cancer Res. 2016;76:2868–75.
34. Shukunami K, Kurokawa T, Kawakami Y, Kubo M, Kotsuji F. Hypersensitivity reactions to intraperitoneal administration of carboplatin in ovarian cancer: the first report of a case. Gynecol Oncol. 1999;72:431–2.
35. Solass W, Struller F, Horvath P, Königsrainer A, Sipos B, Weinreich FJ. Morphology of the peritoneal cavity and pathophysiological consequences. Pleura Peritoneum. 2016;1:193–201.
36. Solass W, Horvath P, Struller F, Königsrainer I, Beckert S, Königsrainer A, et al. Functional vascular anatomy of the peritoneum in health and disease. Pleura Peritoneum. 2016;1:145–58.
37. Steuperaert M, Debbaut C, Segers P, Ceelen W. Modelling drug transport during intraperitoneal chemotherapy. Pleura Peritoneum. 2017;2:73–83.
38. Storm FK. Clinical hyperthermia and chemotherapy. Radiol Clin N Am. 1989;27:621–7.
39. Toraya-Brown S, Fiering S. Local tumor hyperthermia as immunotherapy for metastatic cancer. Int J Hyperth. 2014;30:531–9.
40. Van der Speeten K, Stuart OA, Sugarbaker PH. Pharmacokinetics and pharmacodynamics of perioperative cancer chemotherapy in peritoneal surface malignancy. Cancer J. 2009;15:216–24.
41. Winner KR, Steinkamp MP, Lee RJ, Swat M, Muller CY, Moses ME, et al. Spatial modeling of drug delivery routes for treatment of disseminated ovarian cancer. Cancer Res. 2016;76:1320–34.
42. Yurttas C, Hoffmann G, Tolios A, Haen SP, Schwab M, Königsrainer I, et al. Systematic review of variations in hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal metastasis from colorectal cancer. J Clin Med. 2018;7(12):567.
43. Zininga T, Ramatsui L, Shonhai A. Heat shock proteins as Immunomodulants. Molecules. 2018;23(11):pii: E2846. https://doi.org/10.3390/molecules23112846.
44. Zunino B, Rubio-Patino C, Villa E, Meynet O, Proics E, Cornille A, et al. Hyperthermic intraperitoneal chemotherapy leads to immune to anticancer response via exposure of cell surface heat shock protein 90. Oncogene. 2016;35:261–8.

Part II

Diagnostic and Natural Course

Diagnostic Imaging of Peritoneal Tumors

3

Bernhard Daniel Klumpp
and Christina Pfannenberg

3.1 Introduction

Peritoneal metastases from a variety of primary tumors are the most common presentation of peritoneal disease often with a poor prognosis. In contrast, primary peritoneal tumors such as mesothelioma and primary serous carcinoma are much less common. Peritoneal metastases are challenging to identify even for the most advanced cross-sectional imaging techniques due to the variety of morphologic appearances. When considering surgical approaches with curative intent, it is crucial to identify the location and extent of peritoneal metastases accurately and to rule out extraperitoneal tumor spread.

3.2 Requirements for Diagnostic Imaging

Peritoneal malignancy has been regarded for a long time as a state of disease beyond cure, associated with a short survival of only months. In recent years, however, patient survival and prognosis has improved significantly by the introduction of new therapeutic procedures including the combined multivisceral resection of all involved organs, peritonectomy, and hyperthermic intraperitoneal chemotherapy (HIPEC). Following complete cytoreduction, prolonged survival is possible in patients with peritoneal disease. The extent and location of peritoneal malignancy determines whether complete cytoreduction can be achieved. Consequently, the task of diagnostic imaging is not merely to detect the presence of peritoneal disease but also to describe its morphology accurately [11]. Extensive tumor spread beyond feasible surgical resection, extraperitoneal metastases, and peritoneal sites not accessible to surgical resection have to be identified preoperatively [21]. Underestimation of peritoneal disease extent on preoperative imaging can result in morbidity and mortality from surgery with no benefit in terms of survival or quality of life.

B. D. Klumpp (✉)
Department for Diagnostic Radiology, Rems-Murr Hospital Winnenden, Winnenden, Germany
e-mail: bernhard.klumpp@rems-murr-kliniken.de

C. Pfannenberg
Department for Diagnostic and Interventional Radiology, Eberhard Karls University of Tuebingen, Tuebingen, Germany
e-mail: Christina.pfannenberg@med.uni-tuebingen.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_3

In summary, diagnostic imaging has to meet the following requirements in patients with peritoneal malignancy:

- Diagnosis of peritoneal disease
- Assessment of tumor spread
- Identification of unfavorable sites of disease
- Evaluation of response to systemic therapy
- Diagnosis of recurrent disease

3.3 Routes of Dissemination and Imaging: Findings of Peritoneal Tumors

Primary peritoneal tumors such as peritoneal mesothelioma are rare and appear as an irregularly shaped nodular mass of the peritoneum with increased contrast enhancement after intravenous contrast administration on cross-sectional imaging [12]. Progressive disease causes infiltration of adjacent structures, ascites, and peritoneal dissemination.

By contrast, peritoneal metastases can present in a variety of ways depending on the primary tumor. The principle pathways of peritoneal tumor dissemination are:

- Direct invasion of the peritoneum (gastric, pancreatic, appendiceal, colorectal, and ovarian carcinoma)
- Intraperitoneal seeding due to ascites or surgical procedures (gastric, ovarian, and colorectal carcinoma)
- Lymphatic via lymphatic vessels of the mesentery and omentum (ovarian and colorectal carcinoma)
- Hematogenous, arising from extraperitoneal primary sites (breast, melanoma)

Peritoneal metastases often occur in preferred anatomical regions characterized as either sites of fluid reabsorption or gravity dependent areas.

▶ Common sites are the rectovesical pouch, ileocecal region, paracolic recesses, sigmoid mesentery, porta hepatis, diaphragmatic dome, and falciform ligament

These areas require special attention during the preoperative diagnostic workup [19].

The presence of ascites is regarded as a major indicator of peritoneal metastases. It is important to try and differentiate between serous and mucinous ascites as the latter may represent pseudomyxoma peritonei from mucinous tumors of the appendix or signet ring cell gastric tumors, and in the case of an increased density of liquid or septations, the presence of pseudomyxoma should be assumed. Indicative, on cross-sectional images, is the expansive effect of mucinous tumor with displacement of anatomical structures, especially the omentum, the mesentery, and the bowel, as well as the indentation of visceral surfaces, especially the liver (scalloping). Solid formations of peritoneal carcinomatosis usually appear as single or multiple nodular structures of different size with contrast enhancement after administration of intravenous contrast materials—in some cases, with calcifications (especially serous adenocarcinomas). 18F-FDG PET/CT images commonly depict increased glucose consumption and, in diffusion-weighted MRI images, a restricted molecular diffusion in peritoneal carcinomatosis. Whereas macronodular peritoneal metastases can be detected reliably by most cross-sectional imaging techniques, micronodular dissemination covering the visceral surfaces can evade any diagnostic imaging [7].

Extensive involvement of the greater omentum represents a special type of peritoneal dissemination (omental cake) characterized by plaque-shaped tissue of sometimes considerable size extending in the ventral abdomen. Unfavorable sites when considering cytoreductive surgery are involvement of the porta hepatis, which is represented by linear tissue formations along central parts of the portal vein and the small bowel serosa and mesentery trunk. Whereas focal macronodular tumors affecting the small bowel can be identified reliably as circumscribed masses, which can subsequently be resected, extensive laminar dissemination will frequently prevent complete cytoreduction. On cross-sectional imaging, bowel and mesenteric vascu-

lar sheaths appear extensively thickened and puckered (stellate mesentery).

Systematic reporting of imaging findings ensures focus is brought on tumor location and extent which helps guide decision-making on operability.. The PAUSE score includes the features of the primary tumor and peritoneal cancer index (P), ascites and abdominal wall involvement (A), unfavorable sites of peritoneal disease (U), small bowel and mesenteric involvement (S), and extraperitoneal dissemination (E) providing a useful reporting system for selecting patients with peritoneal disease for surgery [2].

- Tumor dissemination into peritoneum occurs contiguously, via ascites, lymphatically, or hematogenously
- Ascites is an important indicator of peritoneal metastases
- The peritoneal tumor distribution pattern is variable: macronodular, micronodular, diffuse laminar
- Micronodular and diffuse tumor dissemination can completely evade any diagnostic imaging

3.4 Diagnostic Imaging Techniques

3.4.1 Ultrasound

Abdominal ultrasound can provide initial clues to the presence of peritoneal disease, particularly in the presence of ascites. While superficial macronodular peritoneal disease can be identified reliably as low-signal, irregularly shaped masses, the detection of lesions in the central section of the peritoneal cavity is difficult due to overlying bowel gas and fat [23]. The value of ultrasound in detecting peritoneal metastases is limited by its sensitivity, field of view, and dependence on operator experience (Table 3.1) [15].

Abdominal ultrasound is not suitable for the assessment of peritoneal disease before cytoreductive surgery.

For surveillance, ultrasound can provide some indication of recurrent disease if ascites is present. The benefits of abdominal ultrasound are its broad availability and ease of use. Consequently, it may provide some initial information when peritoneal disease is suspected.

Table 3.1 Advantages and disadvantages of different diagnostic imaging modalities for the diagnosis of peritoneal tumors

Modality	Advantage	Disadvantage	Conclusion
Ultrasound	Broad availability Limited effort Good sensitivity for superficial tumors	Limited sensitivity for tumors in the central abdomen Dependence of image quality on examiner and patient	Diagnosis of peritoneal disease possible Not suitable for staging of peritoneal disease
CT	Broad availability Short examination duration Reliable high sensitivity Excellent spatial resolution	Radiation exposure Limited sensitivity for small bowel involvement and micronodular spread	Standard imaging modality for peritoneal tumors Reliable high diagnostic accuracy
MRI	Excellent soft tissue contrast Contrast-enhanced dynamic and diffusion-weighted imaging provide good sensitivity and specificity	Long examination duration Dependence of image quality on patient cooperation Image quality less robust	Excellent diagnostic accuracy under optimal conditions Image quality less robust than CT
PET/CT	Superior diagnostic accuracy for small bowel involvement, micronodular spread, and recurrent disease	Radiation exposure Long examination duration Higher financial cost Limited sensitivity for mucinous tumors	Excellent diagnostic accuracy Higher financial cost Limited availability

3.4.2 Computed Tomography (CT)

Computed tomography is the most widely applied diagnostic imaging modality for the diagnosis of peritoneal disease [6]. *Its advantages are the excellent spatial resolution, short examination time, low susceptibility to motion artifacts, and ready availability* (Table 3.1).

The diagnostic accuracy of computed tomography is continually improving with advances in technology, resulting in a sensitivity ranging between 80% and 90% and a specificity between 78% and 90% [17]. Modern multidetector CT provides high-resolution three-dimensional datasets suitable for multiplanar image reconstructions, allowing the assessment of anatomically challenging regions such as the subphrenic spaces [8]. One prerequisite for an accurate examination technique is the application of an intravenous contrast agent, an oral contrast application, optimal intestinal distension (1.5 l negative contrast agent, e.g., mannitol 2.5% or water), and the application of spasmolytic substances to suppress intestinal peristalsis. If using positive intestinal contrast, this should be carefully diluted to prevent obscuring of peritoneal disease by artifact due to excessive density of orally administered positive contrast media. In addition to the examination technique and the experience of the reporting radiologist, the tumor size, morphology (nodular, plaque), and location of disease influence the diagnostic accuracy of CT, as is reflected in the range of specificity and sensitivity in the literature. The sensitivity for small lesions of less than 1 cm decreases below 50% [3]. Regarding location the porta hepatis, small bowel, mesentery, pelvis, and subdiaphragmatic sites are regarded as challenging and thus associated with reduced sensitivity for the detection of peritoneal disease [22]. These limitations restrict the diagnostic performance of CT, as the involvement of the mesentery and small bowel is crucial for the selection of patients suitable for cytoreductive surgery.

3.4.3 Magnetic Resonance Imaging (MRI)

MRI provides superior soft tissue contrast compared with CT, which is beneficial for the detection of peritoneal disease.

Recent developments in coil and sequence technology, including diffusion-weighted imaging (DWI), have improved the diagnostic value of MRI in the diagnosis of peritoneal disease [10] (Table 3.1). While global diagnostic accuracy is comparable for CT and MRI (sensitivity about 90%), diffusion-weighted imaging provides improved sensitivity for micronodular and laminar peritoneal lesions compared with CT (DWI 85–90%, CT 22–33%) [4, 16] (Fig. 3.1). As for CT, optimized examination protocols are also required for high diagnostic accuracy in MRI. In addition to adequate intestinal preparation with oral application of a mannitol solution and the addition of diffusion-weighted imaging, the examination protocol should include axial and coronal fat-suppressed contrast-enhanced T1w sequences in the early and late phase after contrast injection (5–10 min. p.i.), as peritoneal lesions typically exhibit delayed contrast enhancement [20]. The extent of peritoneal disease depicted by DWI is regarded as an independent predictor of overall and disease-free survival [5]. Despite these benefits, MRI is subject to several limitations, including increased financial cost and limited availability, longer examination time, and consequent vulnerability of image quality to motion artifact. As a result, the prevalence of MRI as a diagnostic imaging modality is lower than that of CT, in spite of its inherent advantages, such as increased sensitivity for micronodular lesions and the lack of radiation exposure.

3.4.4 Positron Emission Tomography/Computed Tomography (PET/CT)

The hybrid imaging technique PET/CT combines metabolic tissue characterization (glucose metabolism) with high-resolution morphologic imaging.

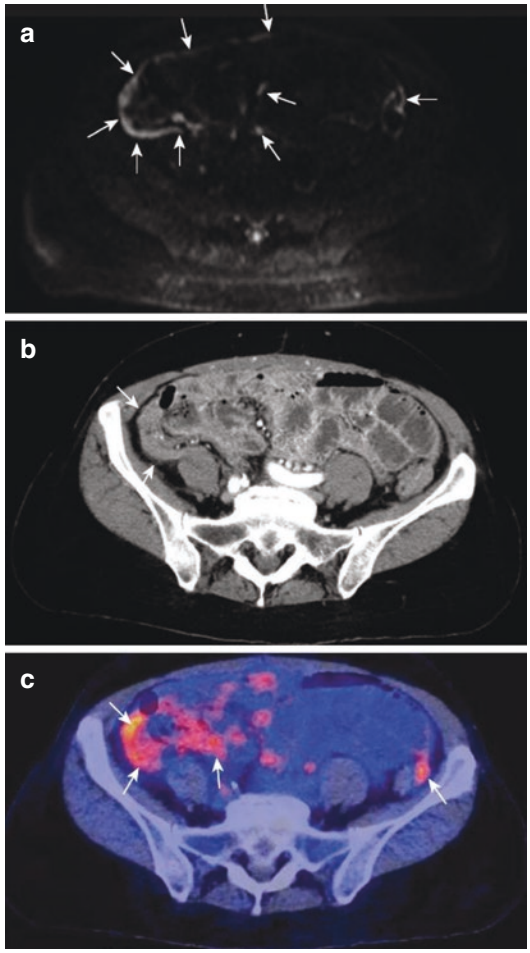


Fig. 3.1 (**a**–**c**) Diffusion-weighted imaging (**a**), CT (**b**), and 18F-FDG-PET/CT (**c**) of a 63-year-old female patient with peritoneal metastases originating from ovarian carcinoma: the diffusion-weighted image depicts a laminar involvement of the peritoneal surface extending into the paracolic gutters bilaterally and on the visceral peritoneum of the ileum. The CT depicts a discrete thickening of the peritoneum with increased contrast enhancement. A reliable identification of peritoneal disease is not possible. PET/CT exhibits increased glucose utilization in the paracolic gutters, corresponding with the more pronounced tumor manifestations on the DWI image. The laminar involvement especially of the parietal peritoneum along the abdominal wall and the visceral peritoneum along the small bowel is missed by CT as well as PET/CT and could only be identified by diffusion-weighted imaging in this patient

CT and 18F-FDG-PET complement each other perfectly in the evaluation of peritoneal lesions, providing improved diagnostic accuracy by using merged PET and CT images [18].

Peritoneal disease presents either as a focal mass with increased FDG uptake or as a diffuse laminar FDG uptake along the peritoneum [9] (Fig. 3.2). Consequently, sensitivity increases especially for micronodular peritoneal disease, which might be missed by morphologic imaging using CT or MRI. Hybrid imaging plays an important role for the exclusion of extraperitoneal metastases, especially in uncertain findings on conventional imaging, as extraperitoneal metastases are, in general, regarded as a contraindication for cytoreductive surgery. Clinical studies of the role of PET/CT for the preoperative assessment of peritoneal disease are not numerous, and the comparability of results is limited due to different examination protocols and standards of reference. Nevertheless, most studies indicate concordantly improved diagnostic accuracy compared with CT alone. Published sensitivities and specificities range between 80% and 100% [13] (Table 3.1). Adequate imaging protocols, including intravenous contrast application, intestinal distension using negative oral contrast, thin slice collimation, and multiplanar image reconstructions, are mandatory. The limitations of PET/CT are restricted sensitivity for small lesions of less than 1 cm and for mucinous tumors that exhibit low or no FDG uptake at all [1]. Compared with CT, the long examination duration, increased use of resources, and limited availability are unfavorable.

- Ultrasound enables the detection of peritoneal disease; quantification, however, is poor.
- Contrast-enhanced MDCT is the standard imaging modality, providing good sensitivity; an adapted examination protocol is required.
- MRI with diffusion-weighted imaging is, under ideal conditions, superior to CT; however, imaging quality is less robust.
- Hybrid PET/CT provides excellent diagnostic accuracy for peritoneal tumors; however, accuracy is limited in mucinous tumors and cost is high.
- A requirement for all imaging modalities is adequate patient preparation, an imaging protocol adapted to the clinical indication, and an experienced radiologist.

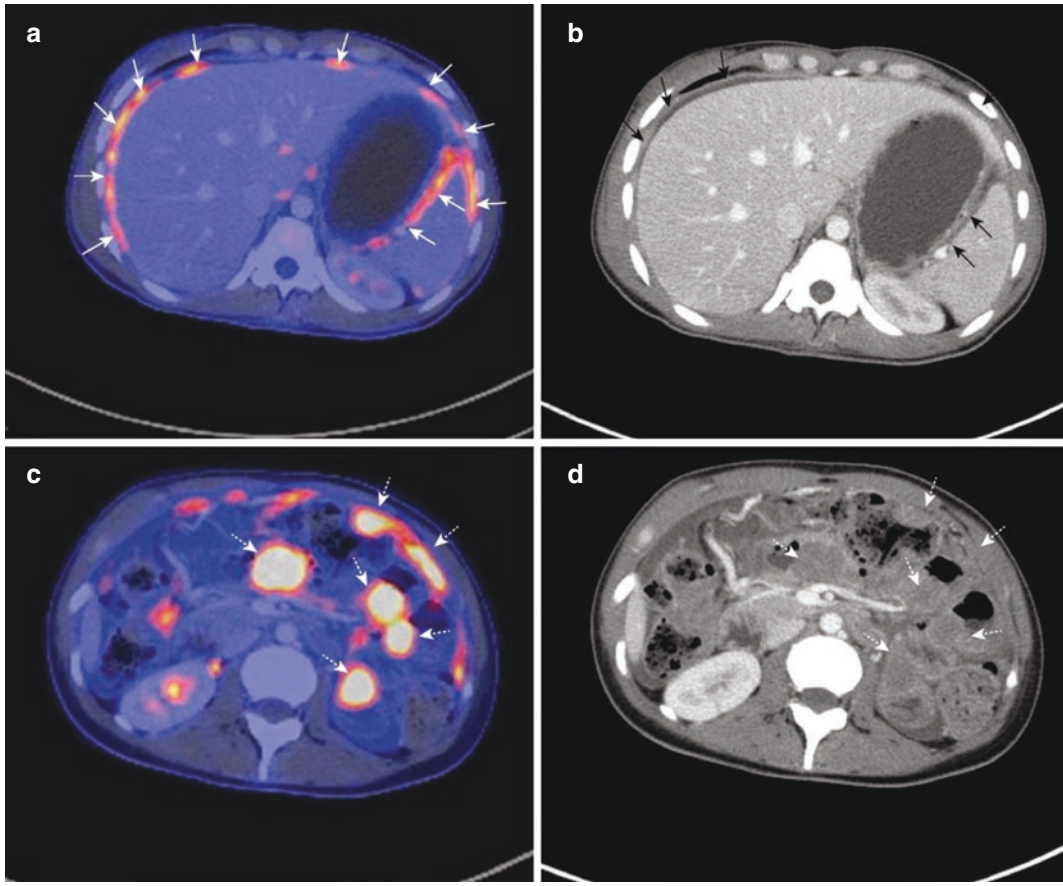


Fig. 3.2 (**a**–**d**) The 18F-FDG-PET/CT images of a 34-year-old patient with peritoneal malignant mesothelioma depict two different patterns of peritoneal tumor dissemination: (**a**, **b**) hypermetabolic laminar diffuse thickening of the complete peritoneum, (**c**, **d**) hypermetabolic focal macronodular interenteric masses. On corresponding CT images, macronodular masses are partially visible; diffuse peritoneal infiltration below the diaphragm and on the hepatic and splenic capsule is displayed at best as discrete thickening. Merged CT and 18F-FDG-PET images display distinctly extensive tumor dissemination by markedly increased glucose utilization

3.5 Diagnostic Imaging in Follow-Up Care and Diagnosis of Relapse

During the follow-up period, frequent cross-sectional imaging is used in patients after cytoreductive surgery. The frequency and length of the follow-up period depend on the underlying malignant disease and status of cytoreduction. After cytoreductive surgery, the differentiation between therapy-associated postsurgical findings and residual or recurrent tumor is a major challenge. Postsurgical thickening of the mesentery and intestinal wall due to granulation tissue and scarring are challenging even for functional imaging, as focal inflammation is associated with increased contrast enhancement and glucose utilization. Intestinal stenoses caused by postsurgical adhesions have to be discriminated from stenosing tumor relapse. The morphologic appearance of recurrent peritoneal disease after surgical cytoreduction and HIPEC may also differ from its initial appearance. Recurrent peritoneal disease is frequently characterized by diffuse laminar infiltration of visceral surfaces, especially the intestinal wall, which hampers its differentiation from benign post-therapeutic findings for all imaging modalities. Compared to

CT alone, PET/CT provides improved diagnostic accuracy for recurrent peritoneal disease; the accurate quantification is, however, frequently impossible [14]. Compared with the initial staging examination, image interpretation in recurrent disease is significantly more demanding and dependent on the experience of the examining physician and available information on preceding therapeutic procedures.

- Diagnosis of recurrence after HIPEC is much more challenging than the primary diagnosis.
- Sensitivity and specificity are restricted for all imaging modalities by post-therapeutic tissue alterations.
- Sensitivity of diagnostic imaging is usually sufficient for detection of recurrent disease. Quantification of recurrence is in general restricted.
- PET/CT provides the best results in the diagnosis of recurrent peritoneal disease.

3.6 Conclusion

High-resolution cross-sectional imaging techniques such as CT and MRI as well as functional imaging including FDG-PET/CT and diffusion-weighted MRI provide excellent diagnostic accuracy in the detection of peritoneal disease. Contrast-enhanced CT is the method-of-choice diagnostic imaging modality due to its availability, y, cost efficiency, and reliably good diagnostic results. Compared with other imaging modalities, diffusion-weighted MRI and PET/CT provide superior diagnostic accuracy. Requirements for a successful diagnostic workup are an optimized examination protocol and experienced radiologists. Despite great technological advances, the diagnosis of peritoneal disease remains challenging. In early stages, small lesions of varying morphologic appearance frequently remain undetected, resulting in an underestimation of peritoneal tumor dissemination. Compared with the primary diagnosis, the diagnostic accuracy for recurrent disease is markedly reduced for all imaging modalities, especially in quantifying tumor recurrence.

References

1. Brendle C, Schwenzer NF, Rempp H, et al. Assessment of metastatic colorectal cancer with hybrid imaging: comparison of reading performance using different combinations of anatomical and functional imaging techniques in PET/MRI and PET/CT in a short case series. Eur J Nucl Med Mol Imaging. 2016;43:123–32.
2. Chandramohan A, Thrower A, Smith SA, et al. "PAUSE": a method for communicating radiological extent of peritoneal malignancy. Clin Radiol. 2017;72:972–80.
3. Coakley FV, Choi PH, Gougoutas CA, et al. Peritoneal metastases: detection with spiral CT in patients with ovarian cancer. Radiology. 2002;223:495–9.
4. Dresen RC, De Vuysere S, De Keyzer F, et al. Whole-body diffusion weighted MRI for operaibility assessment in patients with colorectal cancer and peritoneal metastases. Cancer Imaging. 2019;19:1.
5. Engbersen MP, Aalbers AGJ, Van't Sant-Jansen I, et al. Extent of peritoneal metastases on preoperative DWI-MRI is predictive of disease-free and overall survival for CRS/HIPEC candidates with colorectal cancer. Ann Surg Oncol. 2020;27(9):3516–24.
6. Forstner R. Radiological staging of ovarian cancer: imaging findings and contribution of CT and MRI. Eur Radiol. 2007;17:3223–46.
7. Forstner R, Hricak H, Powell CB, et al. Ovarian cancer recurrence: value of MR imaging. Radiology. 1995;196:715–20.
8. Franiel T, Diederichs G, Engelken F, et al. Multidetector CT in peritoneal carcinomatosis: diagnostic role of thin slices and multiplanar reconstructions. Abdom Imaging. 2009;34:49–54.
9. Funicelli L, Travaini LL, Landoni F, et al. Peritoneal carcinomatosis from ovarian cancer: the role of CT and [18F]FDG- PET/CT. Abdom Imaging. 2010;35:701–7.
10. Iafrate F, Ciolina M, Sammartino P, et al. Peritoneal carcinomatosis: imaging with 64-MDCT and 3T MRI with diffusion-weighted imaging. Abdom Imaging. 2012;37:616–27.
11. Jacquet P, Jelinek JS, Steves MA, et al. Evaluation of computed tomography in patients with peritoneal carcinomatosis. Cancer. 1993;72:1631–163.
12. Jörgensen M, Prokop M. Peritonealhöhle und Retroperitoneum. In: Prokop M, Galanski M, Schaefer-Prokop C, van der Molen AJ, editors. Ganzkörper-Computertomographie, vol. 2. Stuttgart, New York: Auflage, Georg Thieme Verlag KG; 2007. p. 629–59.
13. Klumpp BD, Schwenzer N, Aschoff P, et al. Preoperative assessment of peritoneal carcinomatosis: intraindividual comparison of 18F-FDG PET/CT and MRI. Abdom Imaging. 2013;38:64–71.
14. Klumpp B, Schwenzer NF, Gatidis S, et al. Assessment of relapse in patients with peritoneal carcinomatosis after cytoreductive surgery and hyperthermic intra-

peritoneal chemotherapy using F-18-FDG-PET/CT. Fortschr Roentgenstr. 2014;186:359–66.
15. Kyriazi S, Kaye SB, de Souza NM. Imaging ovarian cancer and peritoneal metastases – current and emerging techniques. Nat Rev Clin Oncol. 2010;7:381–93.
16. Low RN, Semelka RC, Worawattanakul S, et al. Extrahepatic abdominal imaging in patients with malignancy: comparison of MR imaging and helical CT in 164 patients. J Magn Reson Imaging. 2000;12:269–77.
17. Marin D, Catalano C, Baski M, et al. 64-section multidetector row CT in the preoperative diagnosis of peritoneal carcinomatosis: correlation with histopathological findings. Abdom Imaging. 2010;35:694–700.
18. Pfannenberg C, Koenigsrainer I, Aschoff P, et al. F-FDG-PET/CT to select patients with peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2009;16:1295–303.
19. Pfannenberg C, Schwenzer NF, Bruecher BL. State-of the art imaging of peritoneal carcinomatosis. Fortschr Roentgenstr. 2012;184:205–13.
20. Ricke J, Sehouli J, Hach C, et al. Prospective evaluation of contrast-enhanced MRI in the depiction of peritoneal spread in primary or recurrent ovarian cancer. Eur Radiol. 2003;13:943–9.
21. Sala E, Kataoka MY, Priest AN, et al. Advanced ovarian cancer: multiparametric MR imaging demonstrates response- and metastasis-specific effects. Radiology. 2012;263:149–59.
22. Tempany CM, Zou KH, Silverman SG, et al. Staging of advanced ovarian cancer: comparison of imaging modalities-report from the Radiology Oncology Group. Radiology. 2000;215:761–7.
23. Testa A, Ludovisi M, Mascilini F, et al. Ultrasound evaluation of intra-abdominal sites of disease to predict the likelihood of suboptimal cytoreduction in advanced ovarian cancer: a prospective study. Ultrasound Obstet Gynecol. 2011;39:99–105.

4 The Diagnostic Role of Laparoscopy in Patients with Peritoneal Malignancy

Andreas Brandl and Beate Rau

4.1 Introduction and Indication

Diagnostic laparoscopy is an operative procedure to examine the abdominal cavity for tumor affecting organs or the peritoneum. The procedure is performed under general anesthesia. After insufflation of carbon dioxide into the abdominal cavity, a camera is inserted for inspection. In cases where peritoneal metastases are discovered during this procedure, the Peritoneal Cancer Index (PCI) is assessed. The PCI is a score from 0 to 39, which quantitatively reflects the extent of the intraperitoneal tumor burden. It is a useful predictor for the prognosis of the patient as its value correlates with overall survival in many different diseases [15].

In order to calculate the PCI, the abdominal cavity is divided into nine regions, starting with the right-sided diaphragm and moving clockwise. The periumbilical area is numbered 0, additionally the regions 9–12 divide the small intestine. In addition to the location of affected areas, the size of each peritoneal lesion is required in order to calculate the PCI. The extent of the peritoneal metastases is defined by the lesion-size score. For evaluation, the largest lesion per area counts, whereas a primary tumor that can be resected is not considered in the PCI. The absence of a peritoneal lesion in a region is given the value 0, for lesions ≤0.5 cm the value is 1, for lesions ≤5 cm the value is 2, and for all larger or confluent lesions the value 3 is given. Finally, the summation of all different regions delivers a total value of between 0 and 39—the PCI score.

▶ The PCI score can usually be assessed with minimal risk in a staging laparoscopy. It provides an estimation of the potential for resectable cytoreductive surgery to achieve a tumor-free abdominal cavity.

Laparoscopy is a key element in patient selection. In order to deliver an estimation of the potential for a postoperative tumor-free abdominal cavity, the distribution pattern of peritoneal metastases, especially the involvement of the small bowel, and the nature of the peritoneal lesions (solid, infiltrative, mucinous) are of central importance. This important information is often not established by routine radiologic examinations.

Laparoscopy allows for the detection of peritoneal metastases in patients with gastrointestinal or gynecological tumors. Since synchronous peritoneal metastases from gastric cancer are

A. Brandl (✉)
Digestive Unit, Champalimaud Foundation, Lisbon, Portugal
e-mail: andreas.brandl@fundacaochampalimaud.pt

B. Rau
Department of Surgery, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität of Berlin, Berlin, Germany
e-mail: beate.rau@charite.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_4

relatively common (15–18%), diagnostic laparoscopy is recommended for staging of all patients with gastric cancer and a T category of T3 or T4 according to the guidelines. For all other types of cancer, diagnostic laparoscopy is indicated in cases of radiographic signs of peritoneal metastases in patients in order to evaluate the indication for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Common radiologic signs for peritoneal metastases are ascites in the absence of liver cirrhosis, thickening of the greater omentum, or thickening of the parietal peritoneum.

4.2 Basics of Diagnostic Laparoscopy

Diagnostic laparoscopy is the gold standard in the assessment of peritoneal metastases (Fig. 4.1).

- The sensitivity and specificity of diagnostic laparoscopy for the detection of peritoneal metastases is significantly higher than computed tomography (CT) or magnetic resonance imaging (MRI) (Table 4.1).

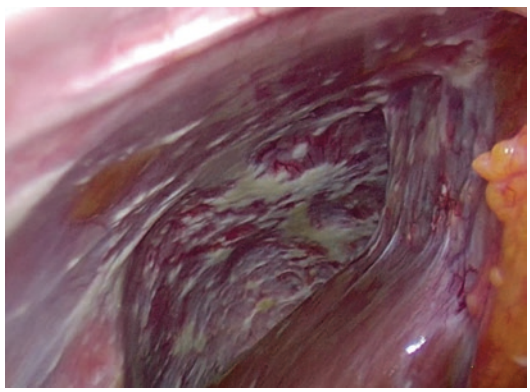


Fig. 4.1 Peritoneal metastasis of gastric cancer in region 1

Laparoscopy has a sensitivity in the detection of peritoneal metastases of 74–100% and a specificity of 83–100% in patients with gastric cancer. Despite the benefits of this minimally invasive procedure, laparoscopy naturally has its limitations. Adhesions after previous abdominal surgery may limit access to the peritoneal cavity. In rare cases, an extensive adhesiolysis is necessary for peritoneal evaluation. Due to the risk of organ injuries, especially of the small intestine, the extent of adhesiolysis should be carefully considered in each case. Retroperitoneal lymph nodes cannot be assessed through laparoscopy. Another risk associated with the surgical trauma to the patient is the risk of port-site metastases, which is caused by the disruption of the peritoneum during laparoscopy. Tumor cells are able to reach the subcutaneous and cutaneous layers and often affect patients with pain, but also psychologically, as they represent a visible manifestation of disease progression. If possible, midline port placement is encouraged so the port sites can easily be excised during any CRS and HIPEC procedure. A retrospective study of Nunez et al. [15] reported an incidence of port-site metastases of up to a third of all patients with laparoscopy performed before CRS and HIPEC, and this resulted in a significantly worse prognosis for this patient group. Obviously, diagnostic laparoscopy might miss some areas of the peritoneum, which explains the variation in PCI assessment between laparoscopy and explorative laparotomy. Nevertheless, laparoscopy is able to detect wide-

Table 4.1 Studies evaluating preoperative diagnostic tools for detection of peritoneal metastases

Study	Preoperative diagnostic regarding M category	Accuracy	Sensitivity	Specificity
Arnold	US/CT	95.9%	81.8%	100%
Blackshaw	CT	85%	88%	83%
Nakagawa	US/CT	90%	73.7%	100%
Onate-Ocana	CT	98.1%	98.5%	97.6%
Roviaro	US/CT	100%	100%	100%
Sotiropoulos	US/CT	100%	100%	100%
Tang	US	96.4%	87.5%	100%
Yano	US/CT/MRI	93.4%	86.7%	100%

spread peritoneal carcinomatosis which would preclude any benefit from CRS and HIPEC. For several reasons, this differentiation is advantageous: It helps in preventing invasive exploratory laparotomies with potential postoperative complications, such as wound infection, ileus, and damage to abdominal structures, and it minimizes time off systemic chemotherapy.

4.3 Port-Site Metastases

At the beginning of the 1990s, in the early years of laparoscopic oncologic resections, the surgical technique—still in a stage of development and improvement—contributed to a high incidence of laparoscopic port-site metastases. Some years later, after the improvement of the surgical technique and laparoscopic devices, Kim et al. [10] were able to demonstrate, in a randomized controlled trial, that the incidence of free tumor cells or port-site metastases immediately after laparoscopic resection was equal to the incidence of wound metastases or free tumor cells after open surgery. Considering the fact that almost all patients with peritoneal malignancies have free tumor cells in their abdominal cavity, the fascial and peritoneal edge represent a target of attachment for free tumor cells.

▶ Therefore, the surgeon should pay attention not only to the placement of the incision for laparoscopy but also to the immediate closure of the fascia and peritoneum after trocar removal.

Ideally, these incisions should be closed with sutures through the fascia and peritoneum.

In total, there have been four different theories describing the development of port-site metastases:

- Direct implantation of tumor cells, which attach themselves to the trocar and get implanted in the soft tissue during trocar removal
- The so called "chimney effect," in which a continuous CO_2 leakage alongside the trocar leads to tumor cells being sprayed with the gas into the muscle or subcutaneous tissue
- An indirect effect, in which tumor cells are directly forced into the subcutaneous tissue at the time of trocar removal and when the pneumoperitoneum is released
- The effect of tissue injury, in which the distinctive tissue injury leads directly to an increase in tumor growth factors, followed by a healing reaction; this reaction might lead to a better embedding and growth of tumor cells in this favorable environment [2]

According to these theories, every oncological surgeon should comply with the following advice, which is useful for diagnostic laparoscopies in patients with peritoneal metastases [7]:

Diagnostic Laparoscopy in Peritoneal Malignancies: Technique and Considerations

- Ideally, use balloon trocars in order to prevent accidental trocar removals and CO_2 leakage.
- Prevent tumor cell reflux through the port site by:
  - Complete aspiration of the ascites before trocar removal
  - Where necessary, dilution of the ascites with an abdominal lavage
  - Complete release of the pneumoperitoneum before trocar removal
  - Immediate closure of the peritoneum and the port site after trocar removal
- Reduction of tissue trauma by placing the trocar at a correct angle in order to reduce sheer forces to the tissue.
- In case of accidental removal of the trocar, try to reintroduce in the same port site.

4.4 Diagnostic Laparoscopy for Gastric Cancer

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommends the technique according to D'Ugo et al. [6] in their guidelines. After the creation of the pneumoperitoneum, an angled optic is introduced through an umbilical port. The cytological sample is either collected by aspiration of ascites or an aspirate of the abdominal fluid after the instillation of 200 ml of saline in cases without ascites. The inspection of the abdominal cavity serves three purposes:

1. Evaluation of tumor infiltration depth (T category)
2. Identification of lymph node metastases (N category)
3. Identification of peritoneal or liver metastases (M category)

The anterior surface of the stomach, as well as the perigastric area, hepatogastric area, and the liver hilum, can be inspected or biopsied after elevation of the left lateral liver lobe. Posteriorly localized tumors are accessible for evaluation after opening the omental bursa; but due to postoperative adhesions and the consequent potential difficulty differentiating between normal tissue and tumor, this maneuver is only appropriate in selected cases. For the detection and localization of liver metastases, laparoscopic ultrasound might be useful during diagnostic laparoscopy [8].

4.5 Laparoscopic Diagnosis of Peritoneal Metastases

There are several studies evaluating diagnostic laparoscopy in patients with peritoneal metastases from gastric cancer. The accuracy, sensitivity, and specificity were 93.4–100%, 73.7–100%, and 83–100%, respectively [3, 4, 14, 16, 18, 21]. According to one meta-analysis, the accuracy of CT and PET in detection of peritoneal metastases is inferior to diagnostic laparoscopy (81.2% and 88.2% vs. 89.8–100%) [19]. Laparoscopy has a significantly higher sensitivity compared with CT (28.8%), ultrasound (9%), or PET-CT (35.3%) [5, 9, 12, 20].

Regarding the laparoscopic accuracy of evaluation of the Peritoneal Cancer Index (PCI), laparoscopy might underestimate the PCI compared to open evaluation, which is the gold standard [17].

Obviously, a higher number of trocars will improve the quality of exploration, but the most recent study showed that even single-incision laparoscopic peritoneal exploration is safe and feasible in order to detect peritoneal metastases, and it remains an appropriate tool in deciding whether complete cytoreduction might be achievable [13].

4.6 Laparoscopic Diagnosis of Liver Metastases

Diagnostic laparoscopy offers no advantage in the detection of liver metastases. The diagnostic tool of choice, which is recommended in the guidelines, is contrast-enhanced CT [1].

4.7 Conclusion

Diagnostic laparoscopy provides a safe and effective diagnostic tool for the detection of peritoneal metastases and for the assessment of the possibility of complete cytoreduction. It helps to avoid unnecessary exploratory laparotomies in patients with unfavorable peritoneal spread or irresectability. It is a useful diagnostic adjunct to radiological imaging with CT or MRI.

Literature

1. Ajani JA, Barthel JS, Bekaii-Saab T, Bentrem DJ, D'Amico TA, Das P, et al. Gastric cancer. J Natl Compr Cancer Netw. 2010;8:378–409.
2. Allardyce RA, Morreau P, Bagshaw PF. Operative factors affecting tumor cell distribution following laparoscopic colectomy in a porcine model. Dis Colon Rectum. 1997;40:939–45.
3. Arnold JC, Neubauer HJ, Zopf T, Schneider A, Benz C, Adamek HE, et al. Improved tumor staging by diagnostic laparoscopy. Z Gastroenterol. 1999;37:483–38.
4. Blackshaw GR, Barry JD, Edwards P, Allison MC, Thomas GV, Lewis WG. Laparoscopy significantly

improves the perceived preoperative stage of gastric cancer. Gastric Cancer. 2003;6:225–9. https://doi.org/10.1007/s10120-003-0257-0.
5. Chen J, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, et al. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. Cancer. 2005;103:2383–90. https://doi.org/10.1002/cncr.21074.
6. D'Ugo DM, Pende V, Persiani R, Rausei S, Picciocchi A. Laparoscopic staging of gastric cancer: an overview. J Am Coll Surg. 2003;196:965–74. https://doi.org/10.1016/S1072-7515(03)00126-1.
7. Franklin ME Jr, Diaz-E JA, Balli J. Mechanical means for prevention of trocar site cancer implantation. In: Reymond MA, Bonjer GJ, Köckerling F, editors. Port-site and wound recurrences in cancer surgery. Heidelberg: Springer; 2000. p. 91–7.
8. Hori Y, SAGES Guidelines Committee. Diagnostic laparoscopy guidelines: this guideline was prepared by the SAGES Guidelines Committee and reviewed and approved by the Board of Governors of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), November 2007. Surg Endosc. 2008;22:1353–83. https://doi.org/10.1007/s00464-008-9759-5.
9. Kayaalp C, Arda K, Orug T, Ozcay N. Value of computed tomography in addition to ultrasound for preoperative staging of gastric cancer. Eur J Surg Oncol. 2002;28:540–3.
10. Kim SH, Milsom JW, Gramlich TL, Toddy SM, Shore GI, Okuda J, et al. Does laparoscopic vs. conventional surgery increase exfoliated cancer cells in the peritoneal cavity during resection of colorectal cancer? Dis Colon Rectum. 1998;41:971–8.
11. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. Gastric Cancer. 2012;15(Suppl 1):S38–47. https://doi.org/10.1007/s10120-011-0047-z.
12. Lim JS, Kim MJ, Yun MJ, Oh YT, Kim JH, Hwang HS, et al. Comparison of CT and 18F-FDG pet for detecting peritoneal metastases on the preoperative evaluation for gastric carcinoma. Korean J Radiol. 2006;7:249–56. https://doi.org/10.3348/kjr.2006.7.4.249.
13. Najah H, Malgras B, Dohan A, Gronnier C, Eveno C, Pocard M. The role of single-incision laparoscopic peritoneal exploration in the management of patients with peritoneal metastases. Surg Endosc. 2019. https://doi.org/10.1007/s00464-019-06984-8.
14. Nakagawa S, Nashimoto A, Yabusaki H. Role of staging laparoscopy with peritoneal lavage cytology in the treatment of locally advanced gastric cancer. Gastric Cancer. 2007;10:29–34. https://doi.org/10.1007/s10120-006-0406-3.
15. Nunez MF, Sardi A, Jimenez W, Nieroda C, Sittig M, MacDonald R, et al. Port-site metastases is an independent prognostic factor in patients with peritoneal carcinomatosis. Ann Surg Oncol. 2015;22:1267–73. https://doi.org/10.1245/s10434-014-4136-1.
16. Onate-Ocana LF, Gallardo-Rincon D, Aiello-Crocifoglio V, Mondragon-Sanchez R, de-la-Garza-Salazar J. The role of pretherapeutic laparoscopy in the selection of treatment for patients with gastric carcinoma: a proposal for a laparoscopic staging system. Ann Surg Oncol. 2001;8:624–31.
17. Passot G, Dumont F, Goéré D, Arvieux C, Rousset P, Regimbeau JM, Elias D, Villeneuve L, Glehen O. Multicentre study of laparoscopic or open assessment of the peritoneal cancer index (BIG-RENAPE). Br J Surg. 2018;105(6):663–7. https://doi.org/10.1002/bjs.10723.
18. Roviaro GC, Varoli F, Sonnino D, Nucca O, Rabughino G, Scarduelli A. Can routine laparoscopy help to reduce the rate of explorative laparotomies for gastric cancer? Laparoscopy in gastric cancer. Diagn Ther Endosc. 2000;6:125–31. https://doi.org/10.1155/DTE.6.125.
19. Seevaratnam R, Cardoso R, McGregor C, Lourenco L, Mahar A, Sutradhar R, et al. How useful is preoperative imaging for tumor, node, metastases (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer. 2012;15(Suppl 1):S3–S18. https://doi.org/10.1007/s10120-011-0069-6.
20. Shinohara T, Ohyama S, Yamaguchi T, Muto T, Kohno A, Kato Y, et al. Clinical value of multidetector row computed tomography in detecting lymph node metastases of early gastric cancer. Eur J Surg Oncol. 2005;3:743–8. https://doi.org/10.1016/j.ejso.2005.03.005.
21. Sotiropoulos GC, Kaiser GM, Lang H, Treckmann J, Brokalaki EI, Pottgen C, et al. Staging laparoscopy in gastric cancer. Eur J Med Res. 2005;10:88–91.
22. Tang L. Controversy and confusion in preoperative imaging precise staging of gastric cancer. Zhonghua Wei Chang Wai Ke Za Zhi. 2016;19:165–9.
23. Yano M, Tsujinaka T, Shiozaki H, Inoue M, Sekimoto M, Doki Y, et al. Appraisal of treatment strategy by staging laparoscopy for locally advanced gastric cancer. World J Surg. 2000;24:1130–5.

Scoring Systems for CRS and HIPEC

5

Jörg Pelz and Pankaj Kumar Garg

5.1 Introduction

▶ Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been a part of multimodal therapy of peritoneal metastases for many years.

In the past, there has been a lot of pessimism about the surgical management of peritoneal metastases. CRS and HIPEC have been associated with significant morbidity and mortality. In order to make this treatment modality acceptable to oncologists, patient selection criteria need to be stringent to optimize outcomes.

In 2006, PSOGI (Peritoneal Surface Oncology Group International) recommended eight clinical and radiological criteria indicating increased chances of having a complete cytoreduction [4]:

- ECOG performance status ≤2
- No evidence of extra-abdominal metastases
- Up to three resectable liver metastases
- No evidence of bile duct obstruction
- No evidence of ureteral obstruction
- No evidence of intestinal obstruction at more than one site
- No extensive involvement of the small intestine or the mesenteric root
- Only small tumor burden in the gastrohepatic ligament

These criteria were subsequently found to be lacking as effective prognosticators for successful treatment with CRS and HIPEC as they do not take into account the histological classification and the individual risk profile of patients. In the absence of large prospective trials addressing these issues, selection criteria are still largely determined by extent of disease.

5.2 Extent of Disease Scores Within the Abdomen

In recent years, many scores have been described to determine the extent of disease, the likelihood of complete cytoreduction, and the completeness of cytoreduction (CC score). Here we focus on preoperative selection criteria for CRS and HIPEC.

J. Pelz (✉)
Department of General-, Viszeral- and Oncologic Surgery, St. Bernward Hospital, Hildesheim, Germany
e-mail: prof.dr.j.pelz@bernward-khs.de

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_5

5.2.1 Sugarbaker's Peritoneal Cancer Index (PCI)

▶ The most commonly used score worldwide in clinical practice is the Peritoneal Cancer Index (PCI)

The Peritoneal Cancer Index (PCI) [6] estimates volume and location of tumor. The abdomen is divided into 13 regions: 9 regions in a grid of the abdomen, each right, center, and left in the upper abdomen, middle abdomen and lower abdomen/pelvis, and 4 regions of the small intestine (the upper and lower jejunum and the upper and lower ileum). In addition, the tumor burden of the individual regions is described depending upon the Lesion Size Score (LSS) with 0–3 points. In the absence of visible tumor, a score of 0 is assigned; in the presence of visible tumor nodules, a score of 1 is assigned if the largest tumor size is up to 2.5mm, a score of 2 if the largest tumor nodule is 2.5 mm to 2.5 cm, and a score of 3 if the largest tumor size exceeds 2.5 cm or there are confluent lesions. Every region is also assigned a number for identification: the central region is assigned the number 0, and all other regions around it are described clockwise (beginning with the right upper abdomen). PCI is calculated by adding the LSS for each of the regions. As every region may have an LSS of 0 to 3, the minimum and maximum PCI can be 0 and 39, respectively (Fig. 5.1).

▶ Several studies have shown that the extent of the PCI in a patient correlates directly with the possibility of achieving complete resection and thus has an impact on survival.

However, this classification has its own drawbacks. LSS describes only the largest tumor in the region, but not the actual extent of the tumor. For example, the presence of an isolated tumor of more than 3 cm in a region is assigned a score of 3, although it may be relatively easy to resect compared with multiple lesions with the largest tumor size of less than 3 and a lower LSS. The PCI was designed to describe colorectal peritoneal metastases and may not have similar utility for other disease types.

5.2.2 Simplified Peritoneal Cancer Index (SPCI)

Similar to PCI, the Netherlands Cancer Institute developed a Simplified Peritoneal Cancer Index (SPCI) [8, 9]. The SPCI value is also calculated by adding the scores given in a specific region based on the tumor size.

Unlike the PCI, however, the peritoneal cavity is divided into seven different regions:

- Small pelvis
- Ileocecal region
- Omentum/transverse colon
- Small bowel/mesentery
- Subhepatic region/stomach
- Left diaphragmatic region
- Right diaphragmatic region

Similar to the PCI, a score of 0 to 3 are assigned to each region based on the largest tumor size (0, no tumor; 1, tumor size up to 1 cm; 2, tumor size of 1–5 cm; 3, tumor size more than 5 cm).

5.2.3 Gilly Classification

The Gilly classification was developed by keeping in mind the location of the primary tumor and the extent of peritoneal metastases and was promoted as a prognostic factor in peritoneal carcinomatosis [1, 5]. It is used primarily in French-speaking countries. It classifies peritoneal carcinomatosis into five stages (0–4) (Table 5.1).

For peritoneal carcinomatosis of gastric or colon origin, a direct correlation between the survival and Gilly stages has been demonstrated [1]. Glehen et al. [5] also demonstrated a correlation between Gilly stages and survival. However, the Gilly staging criteria failed to inspire confidence in surgeons globally and is no longer used widely.

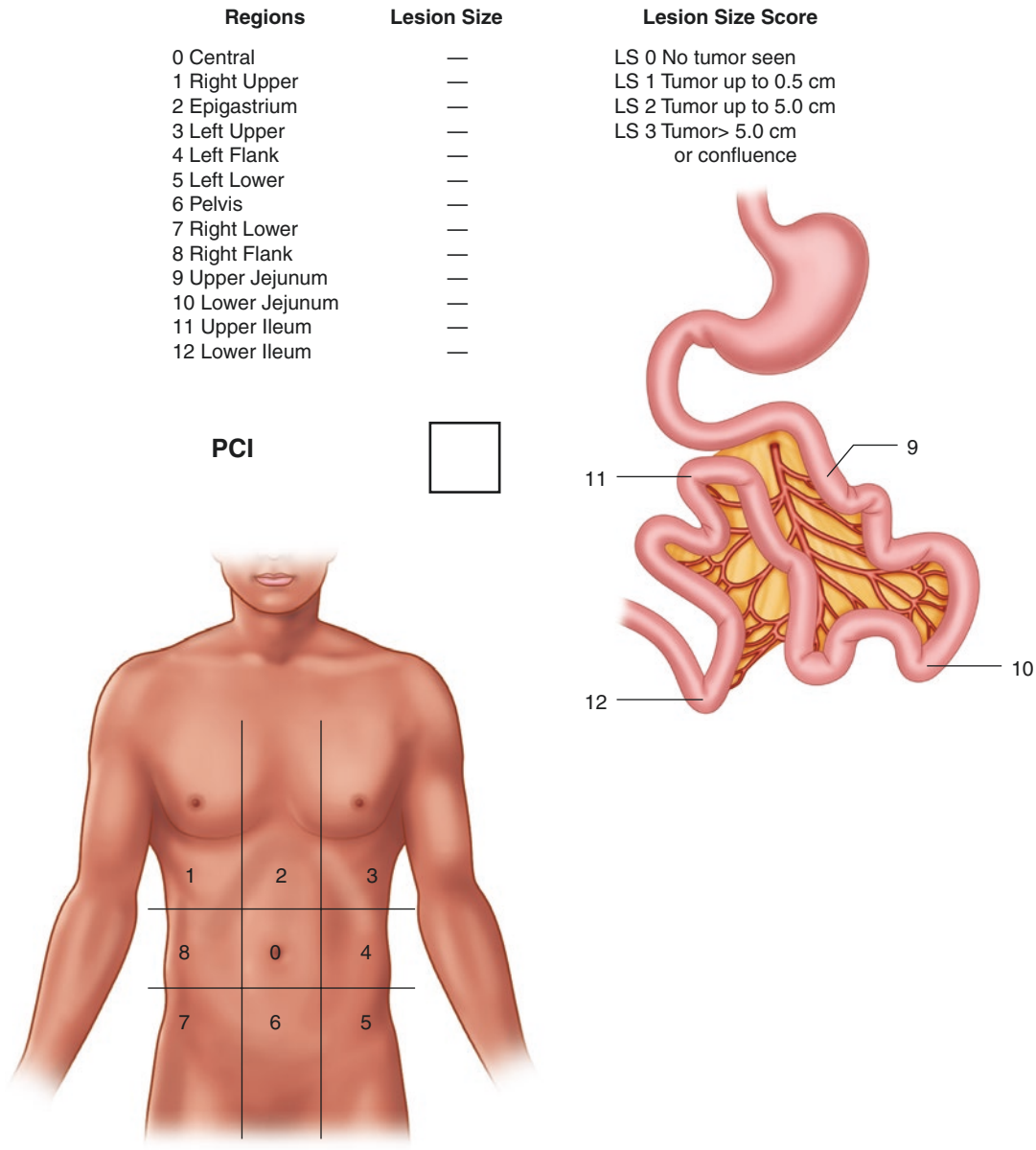


Fig. 5.1 Peritoneal Index according to Sugarbaker. (Adapted from Jacquet and Sugarbaker [6])

5.2.4 P-Score

The P-score is one of the oldest descriptions of peritoneal carcinomatosis. It was developed by the Japanese Research Society for Gastric Cancer in 1981. Notably, it is only for peritoneal metastases from gastric cancer. It describes the relative location of the peritoneal disease with respect to the position of the stomach.

The P-score is thus a relatively rough description. It does not take into account the size of the tumor or extent of the disease in a particular

Table 5.1 Gilly classification of the peritoneal carcinomatosis

Stage	Description
0	No peritoneal disease
1	Local small nodular peritoneal disease (nodules <5 mm in the vicinity of the primary tumor)
2	Widespread peritoneal disease (nodules <5 mm throughout peritoneum)
3	Widespread peritoneal disease (nodules <2 cm in the entire peritoneum)
4	Widespread peritoneal disease (nodules ≥2 cm, or confluent nodules)

Table 5.2 P-score (Japanese Research Society for Gastric Cancer)

Designation	Description
P0	No intraperitoneal metastases
P1	Disseminated metastases in the adjacent peritoneum. No further metastases in more distant peritoneum
P2	Isolated metastases in distant peritoneum
P3	Numerous metastases in distant peritoneum or all over the abdomen

region (Table 5.2). Understandably, the P-score is not used by most international working groups due to these limitations.

5.2.5 Simplified Preoperative Assessment for Appendix Tumor Score (SPAAT)

The Simplified Preoperative Assessment for Appendix Tumor Score (SPAAT) was developed by Dineen et al. in 2015. It describes the likelihood of complete cytoreduction in "low-grade" mucinous carcinomas of appendix [3]. The score is determined semi-quantitatively on a preoperative CT scan highlighting two CT imaging features: the presence of scalloping over the liver, spleen, pancreas, and portal vein (score of 0–4) and the presence of mesenteric foreshortening of the small bowel (score of 0 to 3). SPAAT can vary from a minimum of 0 to a maximum of 7. A score of <3 suggests a good possibility of complete cytoreduction.

5.3 Other Radiological Scores

5.3.1 Limitations of Scoring Systems

▶ The main problem with all scores is the fact that they are semi-quantitative and, above all, subjective.

Thus, various surgeons may come to a different conclusion based on these scores because of their subjective nature. The scores are also determined based on intraoperative findings, and this is another Achilles heel when using them. For meaningful patient selection, tumor burden should be known prior to laparotomy. Diagnostic laparoscopy has its own shortcomings and often underestimates disease extent - although - if small bowel serosal involvement is seen, this is a relative contraindication to CRS and HIPEC.

▶ Another problem is the lack of standardization of scores on different tumors of varying origin and pathology.

5.4 Combined Scores

For example, disease extent does not influence completeness of cytoreduction in pseudomyxoma peritonei of appendiceal origin. In experienced centers, the majority of these patients have complete CRS and benefit from surgery regardless of preoperative PCI.

Peritoneal metastases from a moderately differentiated colon carcinoma should have a PCI of less than 20 for an anticipated complete CRS. Moreover, PCI should be even lower if the histopathology of primary reveals G3 tumor signet ring cells or other high-grade features.

As described above, a semi-quantitative score for the sole determination of disease extent alone is not always sufficient to ensure adequate patient selection. Other factors—tumor biology, the location of the primary tumor and unfavorable

sites of disease, the general condition of the patient, prior surgical history, and response to chemotherapy—are equally important in determining the suitability of the patient for CRS and HIPEC and ultimately survival.

Recently, other combined scores, incorporating other factors than just estimating disease extent, have been described to improve patient selection for CRS/HIPEC.

5.4.1 Assessment Based on Various Clinical Criteria

The French working group led by Pocard attempted to combine a number of clinical criteria to identify definitive and relative exclusion criteria for better patient selection. The group recommended that a combination of these criteria is used as a yard stick to exclude patients who may not benefit from CRS/HIPEC.

Clinical Criteria

Definite exclusion criteria of French workgroup:
- Age >70 years
- Multiple liver metastases
- Severe comorbidities
- Disease progression despite chemotherapy
- Malnutrition
- Lung metastases

Relative exclusion criteria:
- No reduction in the levels of tumor markers following chemotherapy
- BMI > 40
- Prior intraperitoneal chemotherapy
- Clinical symptoms (e.g., ascites)
- More than four previous operations
- Obstruction
- No resection of distant metastases except the ovary

Recommendation:
- No criteria fulfilled—HIPEC indication
- One relative criteria fulfilled—expert opinion
- One absolute or two relative criteria fulfilled—chemotherapy, reassessment after 3 months
- More than one absolute or three relative criteria fulfilled—no multimodality treatment, only palliative treatment

Depending on the number of exclusion criteria, of definitive or relative criteria, and of positive factors, one can recommend either surgery, systemic chemotherapy followed by reassessment for surgery, or palliative treatment/best supportive care. However, this scoring system has its own pitfalls. Firstly, the criteria are often subjective and thus lead to varied inter-observer consistency. In addition, old age (>70 years) is considered a definite exclusion criteria, which might not be acceptable to many oncologists as these patients are being evaluated over a period of time (from months to years). So which age should be considered—the age at diagnosis or the age following chemotherapy?

Though this scoring system may have many flaws, the French workgroup clearly showed that the estimation of disease extent alone for patient selection may not work, and thus other clinical factors must also be taken into account.

5.4.2 Peritoneal Surface Disease Severity Score (PSDSS)

In patients with peritoneal dissemination originating from colorectal cancer, the Peritoneal Surface Disease Severity Score (PSDSS) provides objective criteria for patient selection [7]. In addition to tumor burden (PCI <10, 10–20, >20), PSDSS also includes clinical symptoms (weight loss, pain, and ascites) and tumor biology (well to moderately differentiated and N0, moderately differentiated, and N1 or N2, poorly differentiated or signet ring). PSDSS has been categorized into four stages: I to IV based on the summation of the arbitrary scores for the staging criteria. PSDSS stages I/II were shown to have significantly better life expectancy than stages III/IV. [2, 7].

It should be emphasized that all criteria necessary to calculate PSDSS can be assessed preoperatively. An exact value of PCI is not required in estimating PSDSS; it can be calculated radiologically, using either CT or MRI, and can be scored as low (PCI = 1–10), medium (PCI = 11–20), or high (PCI >21). This seems to be the definite advantage of using PSDSS when compared to other scores.

5.5 Conclusion

A range of scoring systems exist to aid selection of those most likely to benefit from CRS and HIPEC. These scores should not be used in isolation, but in the context of the age of the patient, comorbidities, and anticipated perioperative complications, these patients should be discussed at multidisciplinary meetings in order to select the most appropriate treatment plan.

With advances in our understanding of tumor biology, and response to systemic anticancer treatments, selection criteria for CRS and HIPEC will be refined to avoid futile surgical procedures and associated morbidity.

References

1. Beaujard AC, Glehen O, Caillot JL, et al. Intraperitoneal chemohyperthermia with mitomycin C for digestivetract cancer patients with peritoneal carcinomatosis. Cancer. 2000;88:2512–9.
2. Chua TC, Morris DL, Esquivel J. Impact of the peritoneal surface disease severity score on survival in patients with colorectal cancer peritoneal carcinomatosis undergoing complete cytoreduction and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17:1330–6.
3. Dineen SP, Royal RE, Hughes MS, Sagebiel T, Bhosale P, Overman M, Matamoros A, Mansfield PF, Fournier KF. A simplified preoperative assessment predicts complete cytoreduction and outcomes in patients with low-grade mucinous adenocarcinoma of the appendix. Ann Surg Oncol. 2015;22:3640–6.
4. Esquivel J, et al. Society of Surgical Oncology Annual Meeting: cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. Ann Surg Oncol. 2007;14:128–33.
5. Glehen O, Cotte E, Schreiber V, et al. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. Br J Surg. 2004;91:747–54.
6. Jacquet P, Sugarbaker PH. Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. J Exp Clin Cancer Res. 1996;15:49–58.
7. Fur JO, Stojadinovic A, Nissan A, et al. Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol. 2009;99:9–15.
8. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737–43.
9. Swellengrebel HA, Zoetmulder FA, Smeenk RM, Antonini N, Verwaal VJ. Quantitative intra-operative assessment of peritoneal carcinomatosis - a comparison of three prognostic tools. Eur J Surg Oncol. 2009;35(10):1078–84. https://doi.org/10.1016/j.ejso.2009.02.010.

The Natural Course of Peritoneal Carcinomatosis (PC)

6

Jürgen Tepel and Dieudonne Ajah

6.1 The Peritoneum

The peritoneum is the thin serous semi-permeable membrane that lines the walls of the abdominal and pelvic cavities and clothes the abdominal and pelvic viscera. It is the largest serous membrane of the human body and consists of a simple layer of squamous epithelial cells called the mesothelium. It has an approximate surface area of 1–2 m^2.

The peritoneum consists of two parts: (1) the parietal peritoneum lining the internal wall of abdominopelvic cavity and (2) the visceral peritoneum lining the majority of abdominal viscera.

The visceral peritoneum is served by the same blood, lymphatic vessels, and nerves as the organs it covers. The parietal peritoneum, however, shares circulation and nerve supply with the abdominal wall. The cavity formed between the parietal and visceral peritoneum is known as the peritoneal cavity.

A small amount of fluid is secreted by the mesothelium. It fills the peritoneal cavity and allows for frictionless movement between the two layers of the peritoneum. Added to this, the peritoneum also functions as a barrier to infections, and it plays an important role in suspending various organs within the abdominal cavity. It also serves as a means of conveying blood, lymph vessels, and nerves to the organs.

6.2 Peritoneal Carcinomatosis (PC)

PC represents the spread of malignancies to the parietal and visceral peritoneum [20, 21]. The emergence of PC is the result of a molecular crosstalk between cancer cells and host elements, involving several well-defined steps, known as the peritoneal metastatic cascade. Individual cells or clumps of tumor cells detach from the primary tumor and gain access to the peritoneal cavity and the regular peritoneal fluid transport [12, 29].

This spread of tumor cells occurs through several mechanisms: intraperitoneal seeding, direct invasion, and hematogenous and lymphatic dissemination. Although lymphatic dissemination plays a minor role in the spread of this disease, it is an important factor in the growth of carcinoma along the wall of the stomach or intestines. Once in the peritoneal cavity, these cells adhere to the mesothelium and invade the submesothelial connective tissues, where angiogenesis sustains proliferation and enables further metastatic growth [11, 13, 26].

J. Tepel (✉)
Surgical Department, Klinikum Osnabrueck GmbH, Osnabrück, Germany
e-mail: Juergen.Tepel@klinikum-os.de

D. Ajah
Klinik Mallersdorf, Mallersdorf-Pfaffenberg, Germany
e-mail: ajah.d@klinik-mallersdorf.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_6

It has been shown that the distribution of malignant seeding correlates with the circulation of peritoneal fluid, which is driven by a combination of gravity and diaphragmatic pressure gradients created during normal respiratory motion. Four predominant sites of metastases include: the pouch of Douglas, the right lower quadrant, the left lower quadrant along the superior border of the sigmoid mesocolon, and the right paracolic gutter lateral to the cecum and the ascending colon. Relative stasis of ascites at these sites promotes seeding of malignant cells [14, 15].

Three different patterns of peritoneal cancer spread have been described [3]:

- Random proximal distribution (RPD): leads to early peritoneal implantation due to adherent molecules on cancer cell surface, also in the presence of ascites. This pattern of spread is typical for moderate- to high-grade cancers, e.g., adenocarcinoma and carcinoid of the appendix, nonmucinous colorectal cancer, gastric cancer, and serous ovarian cancer.
- Complete redistribution (CRD): due to low biological aggressiveness of the tumor cells, there is no adhesion to the peritoneal surface close to the primary tumor. This distribution pattern is typical of the pseudomyxoma peritonei and diffuse malignant mesothelioma.
- Widespread cancer distribution (WCD): characterized by the presence of adherent molecules on the surface of cancer cells that produce large amounts of mucus, interfering with cell adherence. This is typical of aggressive and undifferentiated tumors such as G2–G3 cystadenocarcinoma of the appendix, mucinous colorectal cancer, and mucinous ovarian cancer.

An understanding of the various patterns of spread is very important for the planning of cytoreductive surgery (local parietal peritonectomy or complete/total peritonectomy).

Peritoneal malignancies could be divided into two groups:

Primary peritoneal malignancies (PPM) [31]
- Peritoneal mesothelioma
- Primary peritoneal carcinoma
- Cystic mesothelioma
- Peritoneal sarcoma
- Desmoplastic round cell tumor (DRCT)

Secondary peritoneal malignancies or metastasis

Extra-abdominal tumors:
- Lobular breast cancer
- Lung cancer
- Melanoma

Intra-abdominal tumors:
- Ovarian cancer
- GI cancer: stomach, pancreas, colon, appendix, and pseudomyxoma peritonei (PMP)

Primary malignancies of the peritoneum are rare. Most cancers of the peritoneum are metastases from carcinomas of other intra-abdominal organs. Of the different malignant processes of the peritoneal cavity, metastatic diseases of the gastrointestinal tract (stomach, colon, appendix, gallbladder, and pancreas) and the ovary are the most common primaries [1].

The presence of PC is generally associated with disease progression and poor prognosis. Though some patients may be asymptomatic, the following are a few forms of clinical presentations of this condition: abdominal pain, abdominal distension, ascites, weight loss, abdominal mass, nausea, intestinal obstruction, etc. All these are indications of the advanced stage of the condition [3, 23]. Once the diagnosis is made, the prognosis is usually poor, with 2 to 6 months median survival [25].

PC has been shown to reduce overall survival in patients with liver metastases or dissemination outside the peritoneum from gastrointestinal cancer [3].

Peritoneal metastasis is the most frequent pattern of gastric cancer recurrence [7, 10], and it develops in more than 50% of patients diagnosed

with gastric cancer [17]. For patients with PC of gastric origin, the 5-year survival rate is lower than 3%, with an overall mean and median survival of 6.5 and 3.1 months, respectively. In 5% to 20% of the diagnoses of gastric cancer, PC is identified [3, 22].

The peritoneum is one of the most frequent sites for metastasis of colorectal cancer: approximately 4% to 7% of patients with colorectal cancer already present with PC at the time of diagnosis [9, 24], and it is recognized as the second most frequent cause of death after metastatic liver disease [30]. For patients with synchronous PC and liver metastasis of colorectal origin, a median survival of 5 months—in comparison with 95 months for patients with non-metastasized diseases—has been shown [19, 28].

In a large study involving 2756 CRC patients, it was observed that about 8% and 5% of the patients presented with synchronous and metachronous PC, respectively, at the time of diagnosis [8, 9].

This typically leads to poor prognosis. The clinical presentations are often nonspecific: fatigue, cachexia, nausea, abdominal discomfort as a result of ascites, and intestinal obstruction in advanced stages.

Pseudomyxoma peritonei (PMP) is a clinical syndrome characterized by the presence of mucinous ascites ("jelly belly") within the peritoneal cavity frequently associated with perforation of an appendiceal mucinous adenoma [2, 16].

While traditionally considered benign, PMP should be at best considered a "borderline malignancy." The incidence of mucinous epithelial neoplasma of the appendix is approximated at 0.3% and a progression to PMP at 20% [6].

Overall the most common presentations were suspected appendicitis (27%), increasing abdominal distension (23%), and a new-onset hernia (14%).

Until recently, treatment was repeated operative evacuation of the mucinous tumor mass. Eventually the patients succumbed to intestinal obstructions and terminal starvation. This approach resulted in a median survival of 2.5 years, with few patients still alive after 5 years [5].

The occurrence of PC in ovarian cancer is also very common, mainly due to the fact that there are no effective screening tests for the disease, and therefore diagnosis is often made after the disease has already reached an advanced stage [4].

PC associated with ovarian malignancies—just like other PCs of other origins—also generally present with poor survival. It has been shown to present a median overall survival of 10 months with a very high decrease in the quality of life [27].

Because the overall survival of PC is only slightly influenced by systemic chemotherapy, the condition is generally considered terminal, and the presence of malignant ascites in PC is a poor prognostic indicator [18].

In conclusion, the *EVOCAPE-1 multicentric prospective study on peritoneal carcinomatosis of non-gynecologic origin* gives a detailed analysis of the known course of peritoneal carcinomatosis.

6.3 Conclusion

- There has been a constant increase in the understanding of the intraperitoneal dissemination of tumor cells, the development of peritoneal metastasis, and the effect this has on the prognosis of different tumor entities. Based on this understanding, better multimodal therapy concepts can be developed, modified, and evaluated.

References

1. Arrington A, Kim J. Diseases of the peritoneum retroperitoneum. ACS Surgery; Decker Intellectual Properties Inc. 2014. https://doi.org/10.2310/7800.225707/14.
2. Chua TC, Al-Zahrani A, Saxena A, Derek G, Liauw W, Zhao J, et al. Determining the association between preoperative computed tomography findings and postoperative outcomes cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei. Ann Surg Oncol. 2011;18(6):1582–9.

3. Coccolini F, Gheza F, Marco L, Virz S, Iusco D, Ghermandi C, et al. Peritoneal carcinomatosis. World J Gastroenterol. 2013;19(41):6979–94.
4. Dunton CJ. Management of Treatment-Related Toxicity in advanced ovarian cancer. Oncologist. 2002;7:11.
5. Esquivel J, Sugarbaker P. Clinical presentation of the pseudomyxoma peritonei syndrome. Br J Sci. 2000;87:1414.
6. Fallis SA, Moran BJ. Management of pseudomyxoma peritonei. JBUON. 2015;20:S47.
7. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Cancer. 1994;73(8):2048–52.
8. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2002;89:1545.
9. Klaver YL, Lemmens VE, Nienhuijs SW, Luyer MD, de Hingh IH. Peritoneal carcinomatosis of colorectal origin: incidence, prognosis and treatment options. World J Gastroenterol. 2012;18:5489.
10. Kobayashi D, Kodera Y. Intraperitoneal chemotherapy for gastric cancer with peritoneal metastasis. Gastric Cancer. 2016;20(1):111–21.
11. Kusamura S, Baratt D, Zaffaroni N, Villa R, Laterza B, Baestra MR. Pathophysiology and biology of peritoneal carcinomatosis. World J Gastrointest Oncol. 2010;2:12.
12. Lemoine L, Sugarbaker P, Van der Speeten K. Pathophysiology of colorectal peritoneal carcinomatosis: role of the peritoneum. World J Gastroenterol. 2016;22:7692.
13. Levy AD, et al. Primary peritoneal tumors: imaging. Radiographics. 2008;28(2):583–607.
14. McLaughlin PD, et al. Neoplastic diseases of the peritoneum and mesentery. Am J Roentgenol. 2012;200(5):W420–30.
15. Meyers MA. Distribution of intra-abdominal malignant seeding: dependency on dynamics of flow of ascitic fluid. Am J Roentgenol. 1973;119:198.
16. Moran BJ, Cecil TD. The etiology, clinical presentation, and management of pseudomyxoma peritonei. Surg Oncol Clin. 2003;12:585.
17. Nadiradze G, et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with low-dose cisplatin and doxorubicin in gastric peritoneal metastasis. J Gastrointest Surg. 2016;20(2):367–73.
18. Orgiano L, et al. The role of "closed abdomen" hyperthermic intraperitoneal chemotherapy (HIPEC) in the palliative treatment of neoplastic ascites from peritoneal carcinomatosis: report of a single-center experience. In: Support Care Cancer, vol. 24; 2016. p. 4293.
19. Pelz JO, et al. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. BMC Cancer. 2010;22(10):689.
20. Rodt AP, et al. Clinical course for patients with peritoneal carcinomatosis excluded from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg Oncol. 2013;11(1):232.
21. Royal RE. Diagnosis and management of peritoneal carcinomatosis arising from adenocarcinoma of the colon and rectum. Semin Oncol. 2007;35(2):183–91.
22. Sadeghi B, et al.. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;88(2):358–63.
23. Sano T. Is peritoneal carcinomatosis an incurable disease or a controllable locoregional condition? Challenge of surgeons with hyperthermic intraperitoneal chemotherapy. Jpn J Clin Oncol. 2001;31:571.
24. Segelman J, et al. Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2012;99:699.
25. Spratt JS, et al. Peritoneal carcinomatosis: anatomy, physiology, diagnosis, management. Curr Probl Cancer. 1986;10(11):553–84.
26. Sugarbaker P. Peritoneal carcinomatosis: principle of management: Kluwer academic publishers; 1996.
27. Tempfer CB, et al.. Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal carcinomatosis: a cohort study. Anticancer Res. 2015;35(12):6723–9.
28. Thomassen I, et al. Incidence, prognosis, and treatment options for patients with synchronous peritoneal carcinomatosis and liver metastases from colorectal origin. Dis Colon Rectum. 2013;56(12):1373–80.
29. van der Wal J, Jeekel J. Biology of the peritoneum in normal homeostasis and after surgical trauma. Color Dis. 2007;9(Suppl 2):9–13.
30. Verwaal VJ, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. Am Soc Clin Oncol. 2003;21:3737.
31. Wissam B. Peritoneal cancer. Medscape; 2016. https://emedicine.medscape.com/article/281107-print.

Part III

Treatment Option of Systemic Disease

7 Inductive Preoperative Chemotherapy for Peritoneal Metastases of Tumors of the Upper GI Tract

Prisca Bartels and Peter Thuss-Patience

7.1 Introduction

There is limited data on cytoreductive surgery (CRS) of peritoneal metastases in esophageal or hepatobiliary cancer. Likewise, for pancreatic cancer, there is only scarce data about peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) or additional chemotherapy. A Greek study [26] analyzed the effect of adjuvant gemcitabine-based HIPEC in 21 patients with pancreatic cancer. Overall, the therapy was well-tolerated. In a phase II study, 33 patients with histological or cytological evidence of peritoneal carcinomatosis of pancreatic origin received oral fluoropyrimidine derivate S1 with systemic and intraperitoneal paclitaxel [21]. Eight patients were eligible for subsequent/secondary surgery, which resulted in a favorable outcome suggesting a potential positive effect of chemotherapy. It is not clear what part is attributable to systemic or to intraperitoneal chemotherapy or surgery. However, when combined with complete tumor resection and HIPEC, distal pancreatectomy can be associated with more severe postoperative pancreatic fistula [11].

> In summary, there is insufficient evidence to recommend chemotherapy combined with CRS/HIPEC in pancreatic cancer.

Data on the combination of CRS/HIPEC with modern chemotherapy regimens, such as nab-paclitaxel + gemcitabine or FOLFIRINOX is lacking.

This chapter focuses on peritoneal metastases of gastric cancer. Current German guidelines on gastric cancer do not recommend intraperitoneal chemotherapy outside of clinical trials.

Data is accumulating that may suggest some possible improvement of prognosis following CRS and HIPEC in gastric cancer with limited peritoneal carcinomatosis; it is currently not sufficient to recommend the procedure outside of a clinical trial [19].

7.2 Peritoneal Cancer Index

- The peritoneal carcinomatosis index (PCI) is the most important factor predicting extensive surgical cytoreduction [33].

P. Bartels · P. Thuss-Patience (✉)
Medical Clinic for Hematology, Oncology and Tumor-Immunology, Campus Virchow-Klinikum, Charité – University Medicine Berlin, Berlin, Germany
e-mail: prisca.bartels@charite.de; peter.thuss@charite.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_7

A favorable prognosis was determined at varying PCI cutoff levels ranging from 6 [34], <12 [12], to <20 [29]. A meta-analysis including 748 patients identified an optimal PCI cutoff level at 12, differentiating patients with a more favorable vs. more fatal prognosis following peritonectomy [7]. Patients with a PCI above the cutoff level had a fatal prognosis despite complete surgical cytoreduction [31]. A potential PCI reduction can be attempted by preoperative chemotherapy. Here, smaller phase II trials in selected patients seem promising.

7.3 Developments of Chemotherapy in Perioperative and Palliative Setting

Preoperative chemotherapeutic PCI reduction can be achieved by either systemic or intraperitoneal chemotherapy.

Risk factors for peritoneal carcinomatosis include a grading of G3 or G4, nodal positivity, a signet ring histology, and a T3 or T4 stadium [22]. For these subgroups, there are no specific chemotherapy regimens. Instead, data on perioperative and palliative chemotherapy from patients with gastric cancer needs to be extrapolated.

The most important developments regarding preoperative chemotherapy will be discussed below. These will be complemented by findings from palliative therapy in gastric cancer.

- Perioperative chemotherapy is a recommended standard therapy for gastric and gastroesophageal junction adenocarcinoma in Europe.

Table 7.1 summarizes clinical trials on perioperative and preoperative chemotherapy in the curative setting.

The perioperative MAGIC study [8] randomized 503 patients with gastric and gastroesophageal junction adenocarcinoma to either perioperative chemotherapy (epirubicin/cisplatin/5-fluorouracil) or surgery alone. The 5-year survival rate was increased from 23% to 36% ($p = 0.009$). Postoperative morbidity was not elevated in the chemotherapy group. A French study of the FNCLCC [30] corroborated the positive effect of perioperative chemotherapy found in the MAGIC study. A total of 224 patients were randomized between perioperative chemotherapy and surgery alone. The 5-year survival rate was significantly improved from 24% to 38% ($p = 0.021$). According to these trials, perioperative therapy for gastric cancer became the standard of care. Furthermore, ECF or CF were the preferred chemotherapy regimens until the presentation of the FLOT trial (see below).

The British randomized REAL-2 trial (Table. 7.2) in patients with metastatic gastric cancer showed a comparable efficacy substituting 5-FU with capecitabine as well as cisplatin with oxaliplatin [9]. In this two-by-two factorial design study, 1002 patients were randomized to epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX) or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). Statistical analysis for the primary endpoint of overall survival showed noninferiority of both capecitabine and oxaliplatin. This suggests that, also in preoperative therapy, cisplatin can be substituted by oxaliplatin and 5-FU by capecitabine.

However, the role of epirubicin has been increasingly challenged by recent studies. A British randomized study including 897 patients with adenocarcinoma of the distal esophagus and the gastroesophageal junction compared two preoperative cycles of an epirubicin-free chemotherapy (cisplatin/5-FU) to a four-cycle ECX regimen (OE-05 trial) [4]. There was no significant benefit to the intensified therapy with epirubicin.

In contrast to the perioperative therapy, in the palliative setting docetaxel has been shown to improve the efficacy of chemotherapy in metastatic gastric cancer (Table 7.2). A randomized phase III trial including 445 patients with metastasized gastric cancer compared 5-FU/cisplatin to docetaxel/5-FU/cisplatin. The addition of docetaxel significantly improved survival ($p = 0.01$) [28]. However, this regimen was associated with more severe side effects. Therefore, nowadays docetaxel-containing triple therapies

Table 7.1 Phase III trials with neoadjuvant or perioperative chemotherapy in patients with gastric and gastroesophageal junction adenocarcinoma

Author	Year	*N*	Patients with adenocarcinoma	Gastroesophageal junction, distal esophagus	5-year overall survival		Hazard ratio	*p*	Treatment arms
					CT → SX	SX alone			
Allum et al.	2002 2009	802	66%	74%	23%	17%	0.84	0.01	2× CF vs. SX alone
Kelsen et al.	1998 2007	467	52%	N/A	35%	37%	1.04	0.53	Preop. CF vs. SX alone
Cunningham et al.	2006	503	100%	25%	36%	23%	0.75	0.009	Periop. ECF vs. SX alone
Ychou et al.	2011	244	100%	74%	38%	24%	0.69	0.02	Periop. CF vs. SX alone
Schuhmacher et al.	2010	144	100%	53%	73%[a]	70%[a]	0.84	0.47	Preop. CF vs. SX alone
Alderson et al.	2015	897	100%	100%	2,02 months[b]	2,15 months	0.92	0.858	2× CF vs. 4× ECX
Cunningham et al.	2015	1063	100%	64%	48.9%[c]	47.6%[c]	1.07	0.478	Periop. ECX vs. ECX-Beva
Al-Batran et al.	2019	716	100%	56%	36% ECF/ECX vs. 45% FLOT		0.77	0.012	Periop. ECX/ECF vs. FLOT

CT → SX chemotherapy followed by surgery, *CF* cisplatin/5-FU, *ECF* epirubicin/cisplatin/5-fluorouracil, *ECX* epirubicin/cisplatin/capecitabine, *N/A* not available

[a]2-year overall survival

[b]Median overall survival

[c]3-year overall survival

Table 7.2 Crucial trials in palliative treatment of gastric cancer (phase III)

Author	Year	*N*	Regimen	Median OS (months)	Hazard ratio	*p*	Conclusion
Cunningham et al.	2008	1002	ECF	9.9	0.86		Cape can substitute 5-FU
			ECX	9.9			
			EOF	9.3	0.92		Ox can substitute Cis
			EOX	11.2			
Van Cutsem et al.	2006	445	CF	8.6	1.29	0.02	Docetaxel improves OS
			DCF	9.2			
Bang et al.	2010	584	CF + T-mab	13.8	0.74	0.005	T-mab improves OS
			CF	11.1			

5-FU fluorouracil, *Cape* capecitabine, *CF* cisplatin/5-FU, *Cis* cisplatin, *DCF* docetaxel/cisplatin/5-FU, *ECF* epirubicin/cisplatin/5-fluorouracil, *ECX* epirubicin/cisplatin/capecitabine, *OS* overall survival, *Ox* oxaliplatin, *T-mab* trastuzumab

are commonly modified. One option is the Gastro-TAX regimen with a 14-day application of docetaxel/cisplatin/folinic acid and 5-FU [20]. A modified DCF regimen was compared to the original DCF regimen by Shah et al. [23], showing improved tolerability with sustained efficacy.

As a consequence of the improved efficacy by adding docetaxel, phase II trials also tested a combination of docetaxel/platinum and 5-FU for preoperative therapy. Three preoperative cycles of docetaxel/cisplatin and capecitabine increased the pathologic complete remission rate to 13.7% [27].

A randomized phase II/III trial (FLOT4 trial) of the AIO (Arbeitsgemeinschaft Internistische Onkologie) with 716 patients in the perioperative setting compared the FLOT regimen, which consisted of 4 pre- and 4 postoperative cycles, to the ECF regimen established in the MAGIC trial. An analysis of the phase II part, including 265 patients, showed an increase in the pathologic complete remission rate using FLOT to 16% compared to 6% when using ECF [2]. The final results from the FLOT4 trial showed an increased progression-free and overall survival in the FLOT group compared to the ECF group [3]. The overall survival improved from a median of 35 to 50 months (hazard ratio [HR] 0.77; 95% confidence interval [CI; 0.63–0.94]; $p = 0.012$). The 3-year overall survival increased from 48% to 57%, the 5-year overall survival from 36% to 45%. The perioperative morbidity and mortality rates tended to be lower in the FLOT group compared to the ECF group.

> FLOT is the new standard treatment for perioperative therapy in gastric or gastroesophageal junction adenocarcinoma. The triple combination of 5-FU/platinum and docetaxel represents one of the most effective preoperative therapies for unselected patients.

About 20% of patients with gastric cancer show tumor overexpression of HER2 receptors [5]. A randomized trial in patients with metastasized gastric cancer revealed a significantly increased efficacy of chemotherapy with fluoropyrimidine and cisplatin when adding trastuzumab, a monoclonal anti-HER2 receptor antibody. A subgroup analysis of 446 patients with marked HER2 overexpression demonstrated an increased median survival from 11.8 to 16.0 months (HR 0.65; 95% CI 0.51–0.83).

> In patients with HER2 overexpression, the addition of trastuzumab to platinum and fluoropyrimidine represents standard first-line therapy.

It remains unclear whether trastuzumab might also improve the results of perioperative therapy for localized gastric carcinomas. Recent studies evaluated the addition of trastuzumab to a triple combination therapy (FLOT) in the preoperative treatment of gastric cancer. Hofheinz et al. [14] showed a very high pathologic complete remission rate in these patients. Overall, therapy tolerability was good. However, in the perioperative setting trastuzumab should only be applied as part of clinical trials. Such trials are currently recruiting—for example, the INNOVATION trial of the EORTC (NCT02205047).

7.4 Chemotherapy for Downstaging in Peritoneal Carcinomatosis

What is the best chemotherapy for preoperative downstaging in patients with peritoneal metastasized gastric cancer?

There is no data on the most effective therapy in patients with peritoneal carcinomatosis.

> Therefore, the best-established chemotherapy should be used for treatment of peritoneal carcinomatosis.

For HER2-negative patients, this would consist of a triple combination with platinum/5-FU and docetaxel; for HER2-positive patients, adding trastuzumab is recommended either in combination with fluoropyrimidine and platinum or with docetaxel and platinum. However, as mentioned above, the latter is not approved in this combination.

Clinical experience has shown that systemic chemotherapy might also be effective in peritoneal carcinomatosis. A study by Imamoto et al. [15] addressed this question by testing intravenous paclitaxel in 64 patients who had gastric cancer with peritoneal carcinomatosis. Ascites was reduced in 39.1% of patients.

Nevertheless, patients with peritoneal carcinomatosis are characterized by a more dismal prognosis compared to patients without peritoneal carcinomatosis. For example, this was demonstrated for colorectal carcinoma in retrospective analyses of larger trials [18]. One hypothesis that would explain the unfavorable disease progression in patients with peritoneal carcinomatosis despite systemic chemotherapy is a blood-peritoneal barrier [6]. The barrier might diminish penetration of circulating systemic drugs into the peritoneal cavity. Animal studies demonstrated a substantially higher intraperitoneal concentration after intraperitoneal administration of chemotherapy compared to systemic therapy [10].

> Therefore, a number of smaller studies, especially from Asia, combine systemic chemotherapy with an intraperitoneal chemotherapy prior to CRS and HIPEC.

Yonemura et al. [34] administered intraperitoneal docetaxel and cisplatin combined with oral S1. Other studies on the so-called bidirectional intraperitoneal and systemic induction therapy similarly apply oral S1 followed by a 7-day discontinuation, followed by intraperitoneal and systemic docetaxel and cisplatin [32].

Ishigami et al. [16] report on an analysis of 40 patients with intraperitoneal paclitaxel combined with oral S1, showing a response rate of 56% and a 1-year survival of 78%.

Additional side effects are likely to occur after preoperative chemotherapy. However, there was no increase of postoperative morbidity and mortality in the randomized trials of pre- and postoperative chemotherapy vs. surgery alone in the curative treatment setting [3, 8, 30].

Whether preoperative chemotherapy is associated with elevated morbidity in patients with gastrectomy and CRS has not been studied in randomized trials.

A review by Yonemura et al. [33] suggests that neoadjuvant intraperitoneal chemotherapy combined with systemic chemotherapy could lead to an increased rate of morbidity and, potentially, mortality. Reported rates of postoperative morbidity, severe complications, and re-surgery range from 3.4% to 4%, 24–27%, and 7.6% [12, 13, 34].

7.5 Conclusion

Decisions regarding the most effective preoperative therapy for patients with intended gastrectomy and CRS can currently not be based on randomized trials. A triple combination therapy comprising fluoropyrimidine, platinum, and docetaxel seems to be most effective. The potential benefit of an additional combination of preoperative intraperitoneal chemotherapy and a systemic treatment (bidirectional intraperitoneal and systemic induction therapy) seems promising, but this should be evaluated in future trials.

In patients with HER2-overexpressing tumors, the addition of trastuzumab to chemotherapy is essential.

Outlook

New treatment strategies for preoperative therapy might hopefully emerge from already established and successful strategies in palliative therapy. These include VEGF inhibitors such as ramucirumab as well as immune checkpoint inhibitors. In a large randomized phase III trial, third-line or later anti-PD-1 monoclonal antibody nivolumab increased overall survival from 4.14 months with placebo to 5.32 months with nivolumab (HR 0.63; 95% CI 0.50–0.78, $p < 0.0001$) in an Asian population with subsequent approval in Japan [17]. Survival benefits were seen irrespective of PD-L1 expression. Pembrolizumab has been evaluated in global second- and first-line randomized trials. The phase III KEYNOTE-061 trial failed to show superiority for second-line pembrolizumab versus chemotherapy in patients with PD-L1+ (combined positive score [CPS] ≥1) tumors [24]. The randomized KEYNOTE-062 trial compared first-line pembrolizumab to chemotherapy in 763 patients in a noninferiority design [25]. In patients with CPS ≥ 1 gastric and gastroesophageal adenocarcinomas, pembrolizumab was found to be noninferior to chemotherapy (HR 0.91; 95% CI 0.69–1.18) given the prespecified noninferiority margin of the hazard ratio of 1.2. In the CPS ≥10 tumor cohort, pembrolizumab outperformed chemotherapy (HR 0.69; 95% CI 0.49–0.67). It was particularly effective in all subgroups with gastric carcinoma with microsatellite instability.

Furthermore, IMAB362, a monoclonal antibody directed against claudin 18.2, could show promising results in a phase II trial in comparison to chemotherapy alone [1].

References

1. Al-Batran S-E, Schuler MH, Zvirbule Z, et al. FAST: an international, multicenter, randomized, phase II trial of epirubicin, oxaliplatin, and capecitabine (EOX) with or without IMAB362, a first-in-class anti-CLDN18.2 antibody, as first-line therapy in patients with advanced CLDN18.2+ gastric and gast. J Clin Oncol. 2016a;34:LBA4001. https://doi.org/10.1200/jco.2016.34.18_suppl.lba4001.
2. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO). Lancet Oncol. 2016b;17:1697–708. https://doi.org/10.1016/S1470-2045(16)30531-9.
3. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. Lancet. 2019;393:1948–57. https://doi.org/10.1016/S0140-6736(18)32557-1.
4. Alderson D, Langley RE, Nankivell MG, et al. Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). J Clin Oncol. 2015;33:4002. https://doi.org/10.1200/jco.2015.33.15_suppl.4002.
5. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97. https://doi.org/10.1016/S0140-6736(10)61121-X.
6. Baron MA. Structure of the intestinal peritoneum in man. Am J Anat. 1941;69:439–97. https://doi.org/10.1002/aja.1000690305.
7. Coccolini F, Catena F, Glehen O, et al. Complete versus incomplete cytoreduction in peritoneal carcinosis from gastric cancer, with consideration to PCI cut-off. Systematic review and meta-analysis. Eur J Surg Oncol. 2015;41:911–9. https://doi.org/10.1016/j.ejso.2015.03.231.
8. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20. https://doi.org/10.1056/NEJMoa055531.
9. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46. https://doi.org/10.1056/NEJMoa073149.
10. de Bree E, Tsiftsis DD. Experimental and pharmacokinetic studies in intraperitoneal chemotherapy: from laboratory bench to bedside. Recent Results Cancer Res. 2007;169:53–73. https://doi.org/10.1007/978-3-540-30760-0_5.
11. Downs-Canner S, Ding Y, Magge DR, et al. A comparative analysis of postoperative pancreatic fistulas after surgery with and without hyperthermic intraperitoneal chemoperfusion. Ann Surg Oncol. 2015;22:1651–7. https://doi.org/10.1245/s10434-014-4186-4.
12. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal

chemotherapy. Ann Surg Oncol. 2010;17:2370–7. https://doi.org/10.1245/s10434-010-1039-7.
13. Glehen O, Schreiber V, Cotte E, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. Arch Surg. 2004;139:20–6. https://doi.org/10.1001/archsurg.139.1.20.
14. Hofheinz R, Hegewisch-Becker S, Thuss-Patience PC, et al. HER-FLOT: Trastuzumab in combination with FLOT as perioperative treatment for patients with HER2-positive locally advanced esophagogastric adenocarcinoma: a phase II trial of the AIO Gastric Cancer Study Group. J Clin Oncol. 2014;32:4073. https://doi.org/10.1200/jco.2014.32.15_suppl.4073.
15. Imamoto H, Oba K, Sakamoto J, et al. Assessing clinical benefit response in the treatment of gastric malignant ascites with non-measurable lesions: a multicenter phase II trial of paclitaxel for malignant ascites secondary to advanced/recurrent gastric cancer. Gastric Cancer. 2011;14:81–90. https://doi.org/10.1007/s10120-011-0016-6.
16. Ishigami H, Kitayama J, Kaisaki S, et al. Phase II study of weekly intravenous and intraperitoneal paclitaxel combined with S-1 for advanced gastric cancer with peritoneal metastasis. Ann Oncol. 2009;21:67–70. https://doi.org/10.1093/annonc/mdp260.
17. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:2461–71. https://doi.org/10.1016/S0140-6736(17)31827-5.
18. Klaver YLB, Simkens LHJ, Lemmens VEPP, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. Eur J Surg Oncol. 2012;38:617–23. https://doi.org/10.1016/j.ejso.2012.03.008.
19. Leitlinienprogramm Onkologie. (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF):S3-Leitlinie Magenkarzinom, Langversion 2.01 (Konsultationsfassung), 2019 AWMF Registernummer: 032/009OL, http://www.leitlinienprogrammonkologie.de/leitlinien/magenkarzinom/ (abgerufen am: 07.11.2019).
20. Lorenzen S, Hentrich M, Haberl C, et al. Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. Ann Oncol. 2007;18:1673–9. https://doi.org/10.1093/annonc/mdm269.
21. Satoi S, Fujii T, Yanagimoto H, et al. Multicenter phase II study of intravenous and intraperitoneal paclitaxel with s-1 for pancreatic ductal adenocarcinoma patients with peritoneal metastasis. Ann Surg. 2017;265:397–401. https://doi.org/10.1097/SLA.0000000000001705.
22. Seyfried F, von Rahden BH, Miras AD, et al. Incidence, time course and independent risk factors for metachronous peritoneal carcinomatosis of gastric origin - a longitudinal experience from a prospectively collected database of 1108 patients. BMC Cancer. 2015;15:73. https://doi.org/10.1186/s12885-015-1081-8.
23. Shah MA, Janjigian YY, Stoller R, et al. Randomized multicenter phase II study of modified docetaxel, cisplatin, and fluorouracil (DCF) versus DCF plus growth factor support in patients with metastatic gastric adenocarcinoma: a study of the US gastric cancer consortium. J Clin Oncol. 2015;33:3874–9. https://doi.org/10.1200/JCO.2015.60.7465.
24. Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. Lancet. 2018;392:123–33. https://doi.org/10.1016/S0140-6736(18)31257-1.
25. Tabernero J, Van Cutsem E, Bang Y-J, et al. Pembrolizumab with or without chemotherapy versus chemotherapy for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma: the phase III KEYNOTE-062 study. J Clin Oncol. 2019;37:LBA4007. https://doi.org/10.1200/jco.2019.37.18_suppl.lba4007.
26. Tentes AAK, Kyziridis D, Kakolyris S, et al. Preliminary results of hyperthermic intraperitoneal intraoperative chemotherapy as an adjuvant in resectable pancreatic cancer. Gastroenterol Res Pract. 2012;2012:506571. https://doi.org/10.1155/2012/506571.
27. Thuss-Patience PC, Hofheinz RD, Arnold D, et al. Perioperative chemotherapy with docetaxel, cisplatin and capecitabine (DCX) in gastro-oesophageal adenocarcinoma: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Ann Oncol. 2012;23:2827–34. https://doi.org/10.1093/annonc/mds129.
28. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V25 study group. J Clin Oncol. 2006;24:4991–7. https://doi.org/10.1200/JCO.2006.06.8429.
29. Yang XJ, Li Y, Yonemura Y. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy to treat gastric cancer with ascites and/or peritoneal carcinomatosis: results from a Chinese center. J Surg Oncol. 2010;101:457–64. https://doi.org/10.1002/jso.21519.
30. Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29:1715–21. https://doi.org/10.1200/JCO.2010.33.0597.
31. Yonemura Y. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from

gastric cancer. World J Gastrointest Oncol. 2010;2:85. https://doi.org/10.4251/wjgo.v2.i2.85.

32. Yonemura Y. A new bidirectional intraperitoneal and systemic induction chemotherapy (BISIC) for the peritoneal metastasis from gastric cancer in neoadjuvant setting. Integr Cancer Sci Ther. 2014;1(2):26–9. https://doi.org/10.15761/icst.1000106.
33. Yonemura Y, Canbay E, Li Y, et al. A comprehensive treatment for peritoneal metastases from gastric cancer with curative intent. Eur J Surg Oncol. 2016;42:1123–31. https://doi.org/10.1016/j.ejso.2016.03.016.
34. Yonemura Y, Endou Y, Shinbo M, et al. Safety and efficacy of bidirectional chemotherapy for treatment of patients with peritoneal dissemination from gastric cancer: selection for cytoreductive surgery. J Surg Oncol. 2009;100:311–6. https://doi.org/10.1002/jso.21324.

8 Preoperative Chemotherapy in Peritoneal Metastases of Tumors of the Lower GI Tract Including Appendix Carcinoma

Thorsten O. Götze and Salah E. Al-Batran

8.1 Peritoneal Metastatic Colorectal Cancer

8.1.1 Introduction

In a significant proportion of patients with colorectal cancer, the diagnosis is made at an advanced stage of disease when the tumor has already perforated the intestine and a peritoneal spread of tumor cells has been established. Zeng et al. [48] showed in 1992 that, in cases with completely resected colon carcinomas in a T-stage "T3 and T4," tumor cells already exist on the serosal surface of the intestine in up to 50% of the patients. In comparable reports, Pomeranz et al. [35] and Ambrose et al. [2] were able to detect free cancer cells in peritoneal lavages in up to 25% of patients with colorectal carcinomas. Newland et al. [31] showed that, due to a tumor perforation in patients without regional lymph node involvement, the 5-year survival rate was already reduced by 23%. After curative surgery, up to 40% of patients experience a recurrence of tumor progression, and, in 80–90% of these cases, the recurrence takes place within the first 2 years after surgery. More interesting is that the relapse occurs in about 40% of patients in the surgical field and/or is combined with peritoneal seeding.

Local recurrence in the area of the intestinal wall is found in only 27% of cases. In 69% of the cases, infestation occurs in neighboring structures. Tumor spread in the peritoneum was observed by Russel et al. [41] in 36% of cases and in 42% of patients with a local relapse. Peritoneal metastases are one of the main causes of death in colorectal carcinoma due to the associated complications, such as intestinal obstruction and ileus. According to Galandiuk et al. [18], this occurs in an interval of 19 months after the primary tumor resection.

According to the analysis carried out by Jayne et al. [24] on 349 patients with peritoneal metastatic colorectal carcinoma (pmCRC) from 3019 patients with colorectal carcinoma (CRC), the spontaneous survival of patients with pmCRC is only 7 months. The EVOCAPE-1 study [42] analyzed patients with non-gynecological peritoneal cancer, among whom 118 patients had colorectal cancer as the primary carcinoma. Overall survival was only 6.9 months on average (range 0.6–44.9 months); the median was 5.2 months. Chu et al. [9] showed a survival rate of 6 months between the diagnosis of peritoneal carcinomatosis and death. These data underline the very poor

T. O. Götze (✉)
Department of Surgery, Institute of Clinical Cancer Research-UCT University Cancer Center Frankfurt, Frankfurt, Germany
e-mail: Goetze.Thorsten@khnw.de

S. E. Al-Batran
Institute of Clinical Cancer Research-UCT University Cancer Center Frankfurt, Frankfurt, Germany
e-mail: Albatran.salah@khnw.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_8

prognosis in patients with peritoneal metastatic colorectal carcinoma.

Theoretically, these patients have an increased risk of both intraperitoneal and systemic treatment failure. It is therefore hypothesized that the patients could benefit from a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) as well as systemic chemotherapy. However, the role and the optimal timing of the sequence of systemic therapy in CRS-HIPEC is still a matter of debate [27]. It must also be said that there is no clearly defined clinical pathway for these patients and that further study is required.

8.1.2 Peritoneal Metastases from Colorectal Adenocarcinoma

In the group of colorectal carcinomas, the complete cytoreduction of peritoneal metastases resulted in a 5-year relapse-free survival rate of 43% (German Society for Visceral Surgery). In these patients the use of inductive chemotherapy before HIPEC in colorectal cancer will result in two distinct scenarios as shown in Fig. 8.1 following the algorithm of Glockzin et al. [21].

The first option is CRS plus HIPEC, which is necessary in a curative concept for pmCRC with the possibility of neoadjuvant chemotherapy. The second option is CRS plus HIPEC along with palliative systemic therapy in a definitely incurable situation. Another possibility is a prophylactic HIPEC in a high-risk situation, which is the subject of studies (i.e., the PROMENADE trial/COLOPEC trial) and will not be discussed further in this report. The current PROPHYLOCHIP trial failed to improve survival in this situation.

There are patients with pmCRC who can achieve a CC-0/1 (completeness of cytoreduction score) following the operation. In such cases, the S3 guidelines [36, 37] recommend cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy for patients with isolated and limited peritoneal carcinomatosis. The following conditions should be met: There should be a PCI (peritoneal cancer index) below 20, no extra-abdominal metastases, and the possibility of macroscopically complete removal or destruction of any tumor manifestation (CC-0/1).

Peritoneal metastatic colorectal patients are not comparable with hepatic metastatic patients. In the case of metastases limited to the liver and technical irresectability, the ESMO guidelines [45] propose the so-called conversion chemotherapy. In RAS wild-type, an anti-EGFR and cytostatic doublet is recommended. Treatment with the triplet FOLFOXIRI and bevacizumab is also possible, or FOLFIRI plus bevacizumab. The latter combinations are the drugs of choice for RAS-mutated patients. The maximum response is expected after 12–16 weeks. The evidence for this is substantiated by large phase III studies. In the case of resectable hepatic metastases, the data regarding inductive chemotherapy is relatively sparse. The only positive evidence for improved progression-free survival (PFS) is the data regarding FOLFOX from the EPOC trial [33] perioperatively and/or postoperatively. The

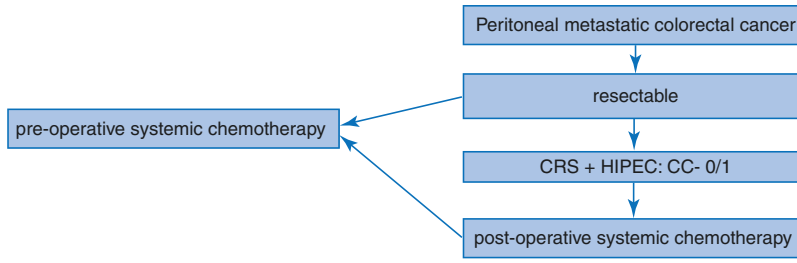


Fig. 8.1 Therapy algorithm of inductive chemotherapy as a part of the so-called quasi-curative concept in colorectal carcinoma with a manifest peritoneal carcinosis (CC completeness of cytoreduction, CRS cytoreductive surgery, HIPEC hyperthermic intraperitoneal chemotherapy)

results for the addition anti-EGFR in the New EPOC trial [38] are negative. The collectives of both studies were not comparable. In the EPOC trial, the patients were clearly resectable at the time of trial inclusion; in the New EPOC trial, some patients were clearly resectable, whereas others were less optimally resectable. In the EPOC trial, up to four patients with liver lesions were included, but in the New EPOC trial there were no such limitations [26]. The data on bevacizumab has not been sufficiently evaluated, as is obvious, for example, in the BOS 2 trial. Perioperative chemotherapy for a resectable finding confined to the liver is therefore worthy of discussion, and it remains the decision-making task of a MDT.

The data on the corresponding intravenous chemotherapy combinations used with CRS and HIPEC is even less clear, especially because the overlap between purely inductive therapy and conversion therapy, particularly in borderline situations. It is as fluent as described above for the liver. Within the framework of the recently published reviews, separation is often difficult. The decision can often be determined only in the context of laparotomy. Exceptions are patients with a prophylactic HIPEC as well as HIPEC in patients with a massive peritoneal tumor burden. However, these are not often the target groups for treatment.

8.1.3 Chemotherapy: The State of Research

In addition to the definition of the target group for preoperative chemotherapy of pmCRC, and a potentially curative HIPEC for metastatic disease, it is important to consider cytostatic substances and the cytostatic combination therapies that are effective. This is in order to choose a suitable foundation for induction therapy. Although there are a variety of prospective randomized studies as well as retrospective analyses of systemic chemotherapy in CRC, the data regarding the subgroup of pmCRC patients is sparse. Ultimately, regional intra-abdominal chemotherapy was the invention of necessity: Systemically administered chemotherapies are less effective when applied in the abdomen through the peritoneum-plasma barrier than at other localizations of the body. The peritoneal carcinosis consists of partially poorly vascularized nodes [4, 8, 14, 44], and it is therefore comparatively resistant to intravenous chemotherapy alone.

Furthermore, the group of pmCRC patients, when compared with the multiple mCRC studies with intravenous chemotherapy, still appears to be a subgroup of mCRC patients that has been disproportionately poorly evaluated.

Franko et al. [17] analyzed 364 patients with a peritoneal metastases from 2 randomized phase III studies [22, 25] from a total 2095 patients. Analysis showed a 30% relative reduction in overall survival in the pmCRC subgroup versus non-pmCRC patients. Median survival was 12.7 months vs. 17.6 months in the pmCRC group vs. the non-pmCRC group. In these studies, an advantage for a systemic FOLFOX therapy compared to an irinotecan-based regime was found. This was independent of the extent of peritoneal metastases. The subgroup analysis of the CAIRO and CAIRO-2 study showed the same results. An analysis by Adachi et al. [1] showed an advantage for an oxaliplatin-based chemotherapy compared with irinotecan-based therapy for pmCRC patients. Moreover, the addition of bevacizumab or cetuximab showed positive effects. An Asian study by Lee et al. [28] also showed the effectiveness of systemic oxaliplatin-based therapy (FOLFOX-4) for patients with pmCRC.

A national population-based study by Razenberg et al. [39] showed that, for 222 patients with metachronic pmCRC and palliative systemic chemotherapy, a median survival rate of 13 months was achieved; when bevacizumab was added, this rose to 20.3 months. Without systemic therapy, however, it was only 3.4 months. Similar survival rates were reported by Elias et al. [15] from the French Register in a similar patient population (n = 48) with a median overall survival (OS) of 23.9 months using modern combined systemic chemotherapy. These data underline the effectiveness of systemic therapy also for pmCRC.

Taking into account the promising results of first-line studies as well as established first-line

therapies with combination chemotherapy and targeted therapy in metastatic colorectal carcinoma with a median survival of 25–41.3 months [11, 23, 43, 46] and in view of the fact that, in the context of these studies, patients with pmCRC were frequently treated within these trials, patients should therefore be treated with the usual doublets or triplets as well as with targeted therapy that considers molecular biological aspects.

Data from inductive therapy of CLM ("colon liver metastases") or conversion therapy of CLM in liver-limited tumors (LLM) cannot be directly applied to pmCRC patients, since pmCRC is prognostically different. In addition, patients who receive HIPEC for pmCRC often show metastases in other organs.

A retrospective multicenter cohort study by Elias et al. [16] on 523 pmCRC patients from 23 centers, who were treated with CRS and intraperitoneal chemotherapy, defined the following independent prognostic factors for pmCRC patients: the presence of liver metastases, the experience of the center, and especially adjuvant chemotherapy after CRS with intraperitoneal chemotherapy. An additional systemic adjuvant chemotherapy in the study had a dramatic influence on the prognosis, and this underlines the concept of adding a systemic therapy to HIPEC. Retrospective data of Glehen et al. [19] on 506 pmCRC patients from 28 centers support the addition of adjuvant chemotherapy as an independent prognostic factor. In non-metastatic cases, FOLFOX/CAPOX is the reference regimen in the adjuvant therapy in node-positive colorectal carcinoma, as well as in the perioperative addition in completely resected liver metastases [30, 32]. In contrast to the retrospective data of the two studies already mentioned, one current multicenter study ($n = 221$) by Maillet et al. [29] from the BIG-RENAPE Working Group shows a significant improvement of progression-free 1-year survival ($p = 0.001$) and peritoneal recurrence-free survival (PRFSl) ($p = 0.0004$) for pmCRC patients treated with adjuvant chemotherapy after CRS and HIPEC; the overall survival, however, was not prolonged. 127 patients (55%) received an adjuvant chemotherapy, 120 (94%) of the adjuvant-treated patients had already been treated preoperatively. The authors concluded that early postoperative chemo does not improve overall survival. It must be added, however, that this only applies when chemotherapy has already been administered preoperatively.

In addition, it is important to note that, in the study by Maillet et al. [29], patients had a complete cytoreduction and that it was a series with peritoneal carcinomatosis only (including ovarian lesions) without any other metastatic sites. In the report of Elias et al. [16], which had a highly significant prognosis improvement due to adjuvant chemotherapy, the population was mixed. Adjuvant chemotherapy was applied if there was an objective response to a preoperative chemotherapy (assuming it was applied) or if unfavorable postoperative prognostic factors—such as a CCR-1 or CCR-2 status, or infested lymph nodes or liver metastases—were present. The significance of a neoadjuvant or perioperative therapy was not assessed either in the study by Elias et al. [16] or in the Maillet et al. [29] publication.

Both studies show that the data for neoadjuvant and adjuvant (additive) therapy are difficult to compare and thus also to evaluate.

In a study by Passot et al. [34], the importance of neoadjuvant therapy in mCRC before HIPEC has been evaluated in regard to both pathological remission and to its impact on the prognosis. The patients received a median of five cycles preoperatively. All patients who had been evaluated for pathological remission were CC-0 or CC-1. Among the 124 evaluated samples, 12 patients (9.7%) showed a pCR, 25 (20.2%) exhibited a major response, 79 (63.7%) a minor response, and 8 (6.4%) no response to inductive therapy. The pathologic response was related to the survival ($p = 00019$). The only significant prognostic factors on overall survival were pCR and major pathological remission after neoadjuvant therapy.

Recent data from Devilee et al. [13] supports the concept of a neoadjuvant systemic therapy. The neoadjuvant-treated group had benefits in terms of overall survival and showed a 3-year survival of almost 90%. This was significantly longer than the survival of patients in the standard

Table 8.2 Survival after cytoreductive surgery plus HIPEC

	No chemotherapy($N = 16$)	Chemotherapy($N = 55$)	P value
PFS (months)			
Median (95% CI)	4 (1–7)	15 (14–16)	
After 3 years (%)	0	37	0.024
OS (months)			
Median (95% CI)	14 (3–25)	30 (19–41)	0.015
After 3 years (%)	16	45	

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *OS* overall survival, *PFS* progression free survival, *95% CI* 95% confidence interval
Adaptiert an [27]

Table 8.1 Mode of application

Sequence of chemo application	*N* (%)
No chemotherapy	16 (23)
In front of CRS + HIPEC	14 (29)
After CRS + HIPEC	32 (45)
In front of and after CRS + HIPEC	9 (13)

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy
Adaptiert an [27]

arm with immediate CRS + HIPEC followed by adjuvant chemotherapy. This data is even more interesting because the preoperative group included patients who were initially not under consideration for CRS + HIPEC due to negative prognostic factors such as extensive peritoneal metastases that were locally too advanced, or synchronous systemic metastasis, or bad general condition. In another Dutch study by Kuijpers et al. [27], 73 patients were included with initial nodal-positive CRC and development of a peritoneal carcinomatosis after or within 1 year after diagnosis of node-positive disease. The patients in this trial where investigated regarding chemotherapy in the context of CRS + HIPEC (Tables 8.1 and 8.2). Most patients had peritoneal carcinomatosis limited to a maximum of five or seven sites. A macroscopically complete (R1) cytoreduction was possible in 87% of patients included in the study. The 55 patients with perioperative chemotherapy showed significantly better results in terms of progression-free and overall survival than the 16 patients without perioperative chemotherapy. The timing of the application—before or after CRS + HIPEC—had no significant impact on prognosis.

In their guidelines for the treatment of patients with peritoneal neoplasms using CRS plus HIPEC, the Austrian Society of Surgical Oncology [5] recommends, in particular in patients with secondary peritoneal neoplasms or advanced disease, a preoperative systemic therapy in addition to a postoperative systemic therapy with complete CRS and HIPEC should be considered.

8.2 Peritoneal Metastases from Adenocarcinoma of the Appendix

8.2.1 Introduction

Often, diseases of the appendix are those which cause pseudomyxoma peritonei syndrome. It can be a malignant or a benign form. The appendix mucocele is benign. The mucin-producing appendiceal carcinoma has a better prognosis among the colorectal carcinomas, but it changes if the peritoneum is affected.

Overall, the long-term results are better in the group of patients with appendiceal carcinoma compared with pmCRC patients. For pseudomyxoma peritonei, the 10-year disease-free survival rate is 85%. In the group of colorectal carcinomas, the complete cytoreduction of peritoneal seeding—assuming there were no other of abdominal metastases—resulted in a recurrence-free 5-year survival rate of 43% [6]. In many CRC protocols and studies, the adenocarcinoma of the appendix is not treated separately from CRC: see, for example, the retrospective evalua-

tion of the data of the University of Regensburg [20]. One should also note that the authors excluded patients with disseminated peritoneal adenomucinosis (DPAM) or peritoneal mucinous carcinomatosis with intermediate characteristics (PMCA-I) [20]. Multivariate analysis of the SEER database by Xie et al. [47] between 2004 and 2013 showed that the patients in stages IV and I–III (AJCC staging manual, 7th ed.) with mucinous adenocarcinomas had a significantly worse 5-year survival rate, indicating that mucinous appendiceal carcinomas are completely different from non-mucinous colonic types.

8.2.2 Influence of Subtypes

When talking about appendiceal carcinomas, it is essential to discuss the terminology of the histological subtypes and their differentiation as well as the term "pseudomyxoma peritonei" (PMP), since they are often the cause of peritoneal carcinomatosis stemming from an appendix tumor.

There are three generally accepted subtypes of PMP [40], with significant prognostic differences:

- The disseminated peritoneal adenomucinous carcinomatosis (DPAM)
- The peritoneal mucinous carcinomatosis (PMCA)
- The PMCA with intermediates or discordant characteristics (PMCA-I)

According to a study by Ronnett et al. [40], the most important significant prognostic factor in this disease was the achievement of CC-0/CC-1 cytoreduction in metastatic cases. Similar results have been reported in a study by Deraco et al. [12]. The specified 10-year survival rate differed significantly depending on the subtype: 67% for DPAM and 40.7% for PMCA. A new classification of peritoneal carcinomatosis caused by appendiceal carcinomas classifies patients in two groups based on histopathological characteristics.

The patients previously classified as DPAM according to the Wake Forest classification are now divided into well-differentiated mucinous carcinomatosis and low-grade differentiated mucinous appendiceal neoplasia as "low-grade mucinous carcinoma peritonei," while moderate or poorly differentiated adenocarcinomas (PMCAs) and cases with signet ring cell component are classified as "high-grade mucinous carcinoma peritonei" [7]. Asare et al. [3] recently published an analysis of 25,992 adenocarcinomas of the appendix. A total of 11,871 cases of adenocarcinoma of the appendix from the NCDB (National Cancer Database) were evaluated. Patients with stage II–III mucinous and non-mucinous showed improved survival due to additional systemic chemotherapy after appendectomy, right hemicolectomy, colectomy, or other resections. In stage IV, there was no improvement of survival due to chemotherapy in mucinous histology, whereas survival in patients with non-mucinous histology was improved by chemotherapy. Due to nature of data, one could only distinguish between patients in stage IV who had received surgery and those without surgery. A conclusion regarding cytoreductive surgery could not be made based on the data, but for patients with surgery there was a survival advantage in both the mucinous as well as in non-mucinous group. For well-differentiated mucinous histology, there was no survival benefit for chemo vs. no chemotherapy. It is important to distinguish between the histological subtypes of disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis because patients with PMCA have a less favorable prognosis, and therefore there is a need for an extra cytostatic systemic therapy [10].

8.3 Conclusion

The data show that chemotherapy in peritoneal metastasis of colorectal carcinoma is quite effective. Also, the addition of systemic therapy to CRS + HIPEC in cases with a completeness of cytoreduction score of 0/1, corresponding to a complete macroscopic cytoreduction (CC 0/1), seems to be effective. However, the data of published collectives are very heterogeneous, and

both the optimal chemotherapy combination as well the chronological order of the therapies must be examined in future studies. In appendiceal carcinomas it is important to consider the different histological subtypes in order to make a decision.

References

1. Adachi T, Hinoi T, Egi H, Shimomura M, Ohdan H. Oxaliplatin and molecular-targeted drug therapies improved the overall survival in colorectal cancer patients with synchronous peritoneal carcinomatosis undergoing incomplete cytoreductive surgery. Surg Today. 2015;45:986–92. https://doi.org/10.1007/s00595-014-1017-y.
2. Ambrose N, MacDonald F, Young J, Thompson H, Keighley M. Monoclonal antibody and cytological detection of free malignant cells in the peritoneal cavity during resection of colorectal cancer–can monoclonal antibodies do better? Eur J Surg Oncol. 1989;15:99–102.
3. Asare EA, Compton CC, Hanna NN, et al. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: analysis of the National Cancer Data Base. Cancer. 2016;122:213–21. https://doi.org/10.1002/cncr.29744.
4. Averbach A, Jacquet P, Sugarbaker P. Surgical technique and colorectal cancer: impaction on local recurrence and survival. Tumori. 1994;81(3 Suppl):65–71.
5. Bachleitner-Hofmann T, Zitt M, Jäger T, et al. (ACO-ASSO), f. d. A. P. M. d. Ö. G. f. C. O. Leitlinie zur Behandlung von Patienten mit peritonealen Neoplasmen mittels zytoreduktiver Chirurgie und hyperthermer intraperitonealer Chemotherapie in Österreich 2013. www.aco-asso.at/arbeitsgruppen/ag-peritoneale-malignome/leitlinie-zur-behandlung-von-patienten-mit-peritonealen-neoplasmen-mittels-zytoreduktiver-chirurgieund-hyperthermer-intraperitonealer-chemotherapiein-oesterreich/
6. Deutsche Gesellschaft für Viszeralchirurgie, Arbeitsgemeinschaft Chirurgische Onkologie (Hrsg) Basisprotokoll für ein multimodales chirurgisches Therapiekonzept zur Behandlung von Patienten mit Peritonealcarcinose mittels Peritonektomie/Multiviszeralresektion und hyperthermer intraperitonealer Chemotherapie. www.barmherzige--regensburg.de/fileadmin/user_upload/kh_regensburg/Kliniken/Allg_Visz_Chir/Peritoneal/Leistungen_Behandlungsprotokoll_Peritonealkarzinose.pdf
7. Bradley RF, Stewart JH t, Russell GB, et al. Pseudomyxoma peritonei of appendiceal origin: a clinicopathologic analysis of 101 patients uniformly treated at a single institution, with literature review. Am J Surg Pathol. 2006;30:551–9. https://doi.org/10.1097/01.pas.0000202039.74837.7d.
8. Carmignani CP, Sugarbaker TA, Bromley CM, Sugarbaker PH. Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. Cancer Metastasis Rev. 2003;22:465–72.
9. Chu DZ, Lang NP, Thompson C, Osteen PK, Westbrook KC. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. Cancer. 1989;63:364–7.
10. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol. 2012;30:2449–56. https://doi.org/10.1200/jco.2011.39.7166.
11. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol. 2015;16:1306–15. https://doi.org/10.1016/s1470-2045(15)00122-9.
12. Deraco M, Kusamura S, Laterza B, et al. Cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy (HIPEC) in the treatment of pseudomyxoma peritonei: ten years experience in a single center. In Vivo. 2006;20:773–6.
13. Devilee RA, Simkens GA, van Oudheusden TR, et al. Increased survival of patients with synchronous colorectal peritoneal metastases receiving preoperative chemotherapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2016;23:2841–8. https://doi.org/10.1245/s10434-016-5214-3.
14. Eggermont A, Steller EP, Sugarbaker PH. Laparotomy enhances intraperitoneal tumor growth and abrogates the antitumor effects of interleukin-2 and lymphokine-activated killer cells. Surgery. 1987;102:71–8.
15. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27:681–5. https://doi.org/10.1200/jco.2008.19.7160.
16. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28:63–8. https://doi.org/10.1200/jco.2009.23.9285.
17. Franko J, Shi Q, Goldman CD, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol. 2012;30:263–7. https://doi.org/10.1200/jco.2011.37.1039.
18. Galandiuk S, Wieand H, Moertel C, et al. Patterns of recurrence after curative resection of carcinoma

of the colon and rectum. Surg Gynecol Obstet. 1992;174:27–32.
19. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol. 2004;22:3284–92. https://doi.org/10.1200/jco.2004.10.012.
20. Glockzin G, Gerken M, Lang SA, et al. Oxaliplatin based versus irinotecan-based hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastasis from appendiceal and colorectal cancer: a retrospective analysis. BMC Cancer. 2014;14:807. https://doi.org/10.1186/1471-2407-14-807.
21. Glockzin G, Schlitt HJ, Piso P. Therapeutic options for peritoneal metastasis arising from colorectal cancer. World J Gastrointest Pharmacol Ther. 2016;7:343–52. https://doi.org/10.4292/wjgpt.v7.i3.343.
22. Goldberg RM, Sargent DJ, Morton RF, et al. NCCTG study N9741: leveraging learning from an NCI Cooperative Group phase III trial. Oncologist. 2009;14:970–8.
23. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open label, phase 3 trial. Lancet Oncol. 2014;15:1065–75. https://doi.org/10.1016/s1470-2045(14)70330-4.
24. Jayne DG, Fook S, Loi C, Seow-Choen F. Peritoneal carcinomatosis from colorectal cancer. Br J Surg. 2002;89:1545–50. https://doi.org/10.1046/j.1365-2168.2002.02274.x.
25. Kim GP, Sargent DJ, Mahoney MR, et al. Phase III noninferiority trial comparing irinotecan with oxaliplatin, fluorouracil, and leucovorin in patients with advanced colorectal carcinoma previously treated with fluorouracil: N9841. J Clin Oncol. 2009;27:2848–54.
26. Kohne CH. Is progression-free survival the right end point in trials of patients with clearly resectable, borderline resectable, and unresectable liver-limited colorectal cancer? J Clin Oncol. 2015;33:2406–7. https://doi.org/10.1200/jco.2014.60.7044.
27. Kuijpers AM, Mehta AM, Boot H, et al. Perioperative systemic chemotherapy in peritoneal carcinomatosis of lymph node positive colorectal cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Oncol. 2014;25:864–9. https://doi.org/10.1093/annonc/mdu031.
28. Lee DH, Oh SY, Lee YR, et al. A phase II study of modified FOLFOX4 for colorectal cancer patients with peritoneal carcinomatosis. Cancer Res Treat. 2011;43:225–30. https://doi.org/10.4143/crt.2011.43.4.225.
29. Maillet M, Glehen O, Lambert J, et al. Early postoperative chemotherapy after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for isolated peritoneal carcinomatosis of colon cancer: a multicenter study. Ann Surg Oncol. 2016;23:863–9. https://doi.org/10.1245/s10434-015-4914-4.
30. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. J Clin Oncol. 2008;26:4906–11.
31. Newland RC, Chapuis PH, Smyth EJ. The prognostic value of substaging colorectal carcinoma. A prospective study of 1117 cases with standardized pathology. Cancer. 1987;60:852–7.
32. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371:1007–16. https://doi.org/10.1016/s0140-6736(08)60455-9.
33. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14:1208–15. https://doi.org/10.1016/s1470-2045(13)70447-9.
34. Passot G, You B, Boschetti G, et al. Pathological response to neoadjuvant chemotherapy: a new prognosis tool for the curative management of peritoneal colorectal carcinomatosis. Ann Surg Oncol. 2014;21:2608–14. https://doi.org/10.1245/s10434-014-3647-0.
35. Pomeranz AA, Garlock JH. Postoperative recurrence of cancer of colon due to desquamated malignant cells. J Am Med Assoc. 1955;158:1434–6.
36. Pox C, Aretz S, Bischoff SC, et al. S3-guideline colorectal cancer version 1.0. Z Gastroenterol. 2013;51:753–854. https://doi.org/10.1055/s-0033-1350264.
37. Pox C et al. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Kolorektales Karzinom, Leitlinienreport, Version 2.1, 2019 AWMF Registrierungsnummer: 021/007OL 2019, http://www.leitlinienprogramm-onkologie.de/leitlinien/kolorektales-karzinom/
38. Primrose J, Falk S, Finch-Jones M, et al. Systemic chemotherapy with or without cetuximab in patients with resectable colorectal liver metastasis: the New EPOC randomised controlled trial. Lancet Oncol. 2014;15:601–11. https://doi.org/10.1016/s1470-2045(14)70105-6.
39. Razenberg LG, van Gestel YR, Lemmens VE, et al. Bevacizumab in addition to palliative chemotherapy for patients with peritoneal carcinomatosis of colorectal origin: a nationwide population-based study. Clin Colorectal Cancer. 2016;15:e41–6. https://doi.org/10.1016/j.clcc.2015.12.006.
40. Ronnett BM, Yan H, Kurman RJ, Shmookler BM, et al. Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Cancer. 2001;92:85–91.

41. Russell AH, Pelton J, Reheis CE, et al. Adenocarcinoma of the colon: an autopsy study with implications for new therapeutic strategies. Cancer. 1985;56:1446–51.
42. Sadeghi B, Arvieux C, Glehen O, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;88:358–63.
43. Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol. 2014;32:2240–7. https://doi.org/10.1200/jco.2013.53.2473.
44. Spratt JS, Adcock RA, Sherrill W, Travathen S. Hyperthermic peritoneal perfusion system in canines. Cancer Res. 1980;40:253–5.
45. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27(8):1386–422.
46. Venook AP, Niedzwiecki D, Lenz HJ, et al.. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). Paper presented at the ASCO Annual Meeting Proceedings. 2014.
47. Xie X, Zhou Z, Song Y, et al. The management and prognostic prediction of adenocarcinoma of appendix. Sci Rep. 2016;6:39027. https://doi.org/10.1038/srep39027.
48. Zeng Z, Cohen AM, Hajdu S, et al. Serosal cytologic study to determine free mesothelial penetration of intraperitoneal colon cancer. Cancer. 1992;70:737–40.

Part IV

Treatment Options of Cytoreductive Surgery

9 Procedures of Parietal and Visceral Peritonectomy of the Upper Abdomen

Hubert Leebmann and Pompiliu Piso

9.1 Dissection Techniques

The chosen dissection technique depends essentially on the preferences of the operating surgeon. Basically, one should choose a technique that allows for a swift operation with only minimal blood loss. The most widely used technique is the so-called electroevaporative surgery described by P.H. Sugarbaker [9]. The basis of this preparation technique is tissue dissection using high-frequency surgery in the so-called pure cut mode with high wattage.

In this case, temperatures of more than 100 °C arise between the electrode and the tissue. The cells are heated up so fast that they evaporate (vaporization). This leads to the separation of the tissue. The use of a 3 mm ball electrode has proved its worth. The combination of high-frequency surgery in cutting mode and a ball electrode (cutting electrode with a larger surface area) allows a smooth cut with good hemostatic effect. At the same time, superficial heat necrosis creates a narrow safety margin on the healthy tissue. This aspect is important since, in the case of peritonectomy, it is often necessary to dissect in the immediate vicinity of the tumor, so that the usual safety margins cannot be maintained. Rapid cutting movements and regular irrigation help to avoid deep tissue damages despite the high wattage used. With simultaneous tension and retraction, the described dissection technique allows rapid progression along anatomical planes.

High-frequency surgery, especially in cutting mode, *generates a considerable amount of smoke*. Smoke gases contain ultrafine particles and polycyclic aromatic hydrocarbons that are potentially carcinogenic [1, 4]. The surgery should therefore be carried out exclusively under continuous smoke evacuation.

9.2 The Extent of the Resection

▶ The extent of the resection is mainly determined by the extent of the tumor, its biology, and the existing pattern of affection.

Due to adhesion molecules on the cell surface area, moderately to poorly differentiated tumors tend to build early formation of peritoneal implants around the tumor (randomly proximally distributed, RPD). This distribution pattern is typical of *gastrointestinal carcinoma metastases*

H. Leebmann (✉) · P. Piso
Clinic for General and Visceral Surgery, Barmherzige Brüder Hospital, Regensburg, Germany
e-mail: hubert.leebmann@barmherzige-regensburg.de; Pompiliu.Piso@barmherzige-regensburg.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_9

and of *ovarian carcinoma metastases*. In the previously mentioned tumor entities, *selective parietal peritonectomy* is carried out, which means that only the areas affected by the tumor and the sites with a predilection for tumor recurrence are resected.

Free tumor cells of highly differentiated tumors and mucin-forming tumors with low biological aggressiveness are distributed over the peritoneal cavity following the peritoneal fluid and tend to develop peritoneal carcinomatosis predominantly in the typical distribution sites (complete redistribution phenomenon, CRP). Examples of tumors with such distribution patterns are the *malignant peritoneal mesothelioma* and *pseudomyxoma peritonei*. Dedifferentiated, highly aggressive tumors tend to develop disseminated peritoneal carcinomatosis (widespread cancer dissemination, WCD). In tumors whose metastatic behavior corresponds to the CRP or the WCD type, a *complete parietal peritonectomy* should always be carried out—even when there is only isolated peritoneal carcinomatosis [3].

Extensive spread into the visceral peritoneum requires visceral, often multivisceral, resection. The perioperative morbidity and mortality, as well as the postoperative quality of life, depend especially on the extent of the organ resection. Often, individual decisions must be made taking into account the patient's request expressed before the surgery. Scoring systems such as the Peritoneal Disease Severity Score can help with the risk-benefit assessment [6]. However, the clinical assessment of an experienced surgeon can never be replaced by any analytical-statistical procedure.

9.3 Access and Anterior Peritonectomy

The patients lay in a modified lithotomy position. Due to the usually long operation, a careful patient placement is essential. To avoid placement damage, positioning should be repeatedly checked during the operation. Preoperatively, a transurethral permanent catheter with integrated temperature sensor must be inserted. In cases involving women, preoperative vaginal disinfection with povidone-iodine solution must also be performed. The ensuing skin disinfection and covering should be performed so generously that an eventual installation of a chest drainage would also be possible if needed.

Due to potential environmental contamination by chemotherapeutics exiting via the laparotomy or drainage sites, the draping of the patient is carried out with disposable single-use surgical drapes.

If the operability was not clarified preoperatively by an explorative laparoscopy, the abdominal cavity must be explored via a short-distance laparotomy, especially in case of tumors whose metastatic behavior corresponds to the RPD or WCD type. After the contraindications are eliminated and the extent of the resection is established, the operation can take place as described below.

- If a complete peritonectomy is planned, it is recommended to complete the extraperitoneal dissection before opening the intraperitoneal space. This can reduce tumor cell dissemination. In addition, this systematic approach saves a considerable amount of time.

Operative access takes place by median laparotomy starting from the xiphoid process and ending at the pubic symphysis. After skin incision, the skin margins can be stretched out by a retractor using supportive sutures. The fixation of the skin margins to the retractor system improves the exposure and leaves less work for the assistants. The frequent preexisting scar is resected together with the fascial parts. In individual cases with extensive tumor formations in the upper abdomen, an en bloc resection of the scar, fascia, and xiphoid process can improve the exposure. In cases with tumor nodules close to the umbilicus, an omphalectomy should also be carried out as part of the cicatricectomy. A basic resection of the xiphoid process and the navel is not necessary.

After dissecting the fascia, the preparation is continued strictly extraperitoneally for about 5–10 cm anterolaterally with closed, intact peri-

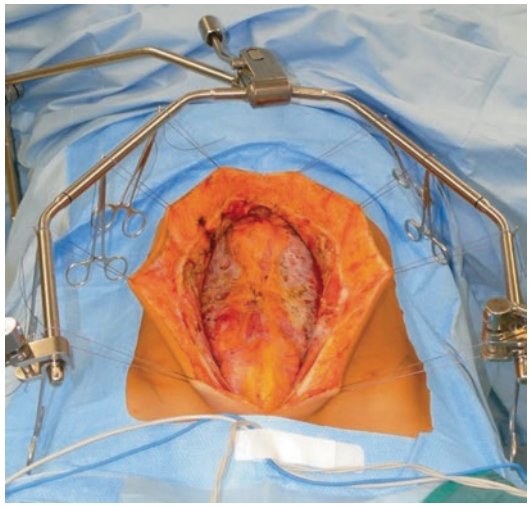


Fig. 9.1 Circular exposure of the peritoneal sac. The extraperitoneal dissection is facilitated by fixation of the skin margins to a retractor frame

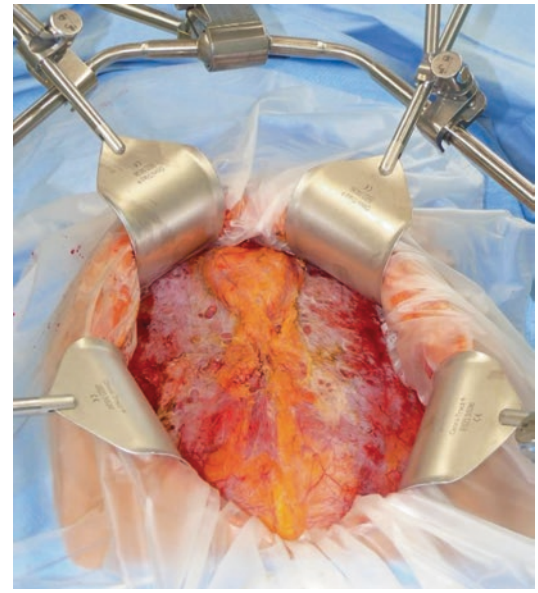


Fig. 9.2 Introduction of the wound-protecting foil and optimization of the exposure through a self-retaining retractor system

toneal sac (Fig. 9.1). The correct dissection layer in the lower abdomen can be opened relatively easily, since there are only loose adhesions between the peritoneum and the subperitoneal adipose tissue. Under continuous tension and retraction, the peritoneal sac can then be gradually opened circularly. In the lower abdomen, one progresses until reaching the top of the bladder. Here, the surgeon looks for the urachus and marks it with an Allis clamp. In the upper abdomen, the peritonectomy should be extended on both sides several centimeters in the subdiaphragmal direction. This is the first step of the upper abdominal peritonectomy. Subsequently, a ring foil is introduced in order to avoid contamination of the wound edges. The dissection into the lower aspect of the costal arch makes it necessary to use a self-retaining retractor.

The abdominal and pelvic space can thus be optimally exposed during the entire operation (Fig. 9.2). The peritoneum can then be slightly opened. In particular, for patients who have been previously operated on, it is advisable to provide this access outside the median line, in order to avoid serous lesions or transmural defects in the adhesions during the course of the former laparotomy. The abdominal cavity can be explored through this so-called peritoneal window. After contraindications, especially a multilocular small bowel involvement, are eliminated, the operation can be continued to the necessary extent.

The subperitoneal dissection beneath the posterior rectus sheath can then be easily and quickly extended to the renal fascia. After reaching the renal fascia, the avascular layer can be opened by pulling on the colon, and the left and right hemicolon can be separated from the retroperitoneum along the embryonic layers. Both ureters should then be exposed and, if necessary, separated at an early stage. An intermittent abdominal packing of the left and right retroperitoneum reduces blood and fluid loss and keeps the site clean. Retained ascites and prolapsing tumor masses or intestinal loops can interfere with the subperitoneal dissection. Dissection should continue until the retroperitoneum is reached, if possible, with a closed peritoneum. Anterolateral peritonectomy is rapidly completed and does not increase the complication rate—not even in case of a later-established inoperability.

The renal fascia should be exposed on both sides with mobilization of both the right and the left hemicolon. This is an important anatomical landmark and is the starting point for further interventions into the upper and lower abdomen.

9.4 Exploration of the Abdominal Cavity

For the next step in the surgery, the peritoneum should be divided along the four quadrants, and the abdominal cavity should be opened. Possible adhesions of intestinal loops or of the greater omentum to the peritoneum should be released. To gain a better view, the greater omentum is cut off from the transverse colon, taking the anterior mesocolon with it. If there are no major tumor formations in the so-called subpyloric space, A. and V. gastroepiploica dextra can already be transected close to its origin. After the mobilization of the left colonic flexure, the soft tissue links between the greater omentum and the spleen are gently divided and the gastrosplenic ligament can be dissected close to the spleen. The subsequent omentectomy is a compulsory part of the peritonectomy. An omentectomy with preservation of the gastroepiploic vascular arcade should be carried out only in exceptional cases, with a macroscopically clear greater omentum. As a rule, the greater omentum is dissected along with the gastroepiploic vascular arcade. This surgical procedure is successful even with extensive tumorous infiltration of the greater omentum ("omental cake"), usually preserving the transverse colon. The rest of the site becomes much cleaner and more accessible by reducing the burden caused by the tumor. In addition, the omentectomy is a prerequisite for a free and unhindered distribution of the chemotherapy solution.

After completing the adhesiolysis, the assessment of the abdominal space regarding its resectability and the extent of the resection is carried out.

▶ The decision whether an optimal cytoreduction is possible or not can usually only be made intraoperatively. The complete resection of all visible tumorous lesion is the strongest prognostic factor for all tumor entities [7].

In most cases, a preoperatively undetected multilocular small bowel involvement is the limiting factor for complete cytoreduction. Peritoneal carcinoma lesions on the small intestine and the small intestinal mesentery are an independent negative prognostic factor in many tumors. In addition, the loss of multiple intestinal segments leads to a reduction in the postoperative quality of life and to increased morbidity and mortality. Therefore, when establishing the extent of the resection, the functional consequences of the resection must always be taken into account, in addition to the completeness of cytoreduction. Especially with extensive metastases, the procedure is often like a tightrope walk between oncological necessity and negative consequences. Therefore, an organ resection should only take place after definitely establishing the surgical objective.

Also with regard to intraperitoneal chemotherapy, the dissolution of all adhesions is an essential surgical procedure. Free circulation and uniform distribution of the chemotherapy perfusion in the abdomen is possible only after complete adhesiolysis.

9.5 Right Upper Quadrant

The right upper abdomen is in many cases the main site for manifestation of a peritoneal carcinomatosis. The complex anatomy of the upper abdomen and the distribution of the tumor lesions in the immediate vicinity of vital structures explain why the peritonectomy of the right upper abdomen is the technically most demanding part of the operation.

To avoid blood loss, the preparation of the entire upper quadrant should be performed with low central venous pressure in normothermic patients who have good coagulation. This situation is most likely to occur at the beginning of an operation.

The subdiaphragmatic peritonectomy is best achieved when the peritoneum is completely

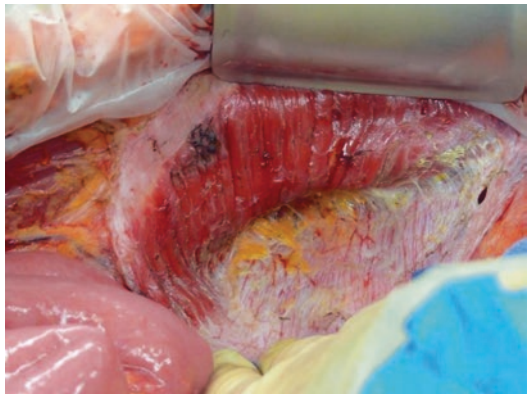


Fig. 9.3 Blunt detachment of the peritoneum from the diaphragm

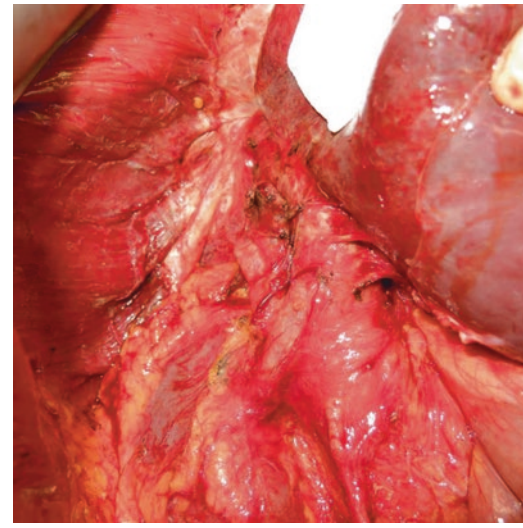


Fig. 9.4 Parietal peritonectomy of the upper right quadrants to the retrohepatic vena cava

removed by continuous traction. The entry into the correct plane of dissection is relatively simple in the area of the so-called fatty triangle. Here, the preperitoneal fat and the peritoneum can be separated bluntly from the diaphragm (Fig. 9.3). The subphrenic dissection then takes place partially bluntly, partially with a sharp detachment, until the junction of the hepatic veins and the vena cava is reached. The junction of the hepatic veins with the vena cava is usually palpable at the space between the right and middle hepatic veins. In extraperitoneal preparation, this area is usually palpable long before the vena cava becomes visible. The retrohepatic vena cava is the medial border of the right upper abdomen's parietal peritonectomy. The exposure of the central tendon of diaphragm is technically demanding, since the anatomical layers between the diaphragm and the peritoneum are almost eliminated. After reaching the central tendon of diaphragm from an anterior and medial direction, it is advisable to continue the dissection first dorsally and laterally. The peritoneum is lifted off the perirenal fat and right adrenal gland via the renal fascia. Starting laterally, the subdiaphragmatic peritonectomy can then also take place up to the central tendon of diaphragm. The remaining adhesions between the diaphragm and peritoneum are finally sharply cut off, for example, by means of bipolar scissors. Possible diaphragmatic injuries should be treated immediately to avoid the contamination of the pleural cavity. If diaphragmatic partial resection is required due to tumor infiltration, this can be carried out in most cases by a stapler. An opening of the thoracic space is thus avoided. Finally, the peritoneal envelope is cut through dorsal to the liver. After complete subdiaphragmatic peritonectomy, the retrohepatic vena cava is thus exposed in its entire length (Fig. 9.4).

The extraperitoneal exposure of the retrohepatic vena cava is especially effective in cases when the right upper quadrant is extensively involved. In such cases, primary mobilization of the liver can lead to liver lacerations where bleeding is difficult to stop.

The resection of the falciform ligament and the left triangular ligament improves the circulation of the perfusion fluid in the upper abdomen and should therefore be carried out prior to any hyperthermic intraperitoneal chemoperfusion (HIPEC). The falciform ligament is dissected from the liver capsule and remains attached to the peritoneum.

As part of a complete peritonectomy, the liver parenchyma must be cut through over the round ligament of the liver ("pont hepatique"). There are often tumor nodules behind this parenchymal bridge. The round ligament of the liver must then be dissected while protecting the left portal vein and left hepatic artery.

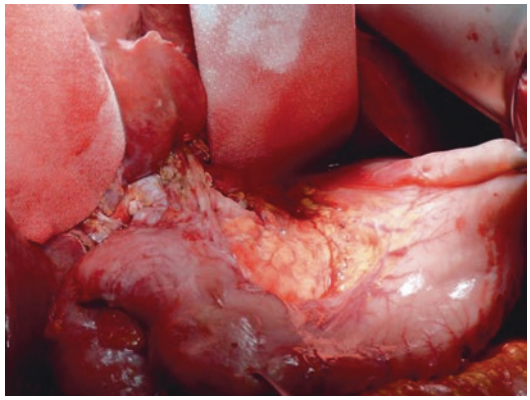


Fig. 9.5 Peritonectomy of the hepatoduodenal ligament and resection of the hepatogastric ligament

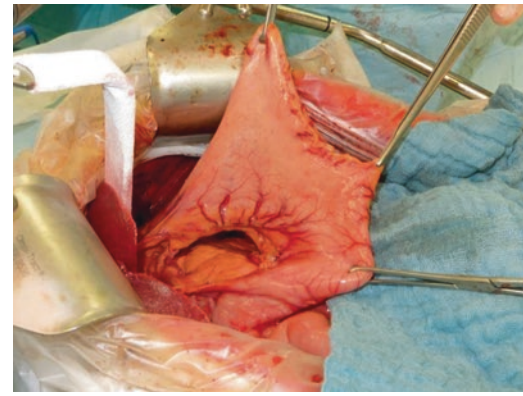


Fig. 9.6 Stomach after the resection of the greater and lesser omentum; the preserved vascular arch is at the small curvature (right and left gastric artery)

A cholecystectomy is routinely performed. The gallbladder is dissected from anterior to posterior from the liver bed; the cystic duct and the cystic artery are ligated and separated. In particular, when thick tumor layers surround the hepatoduodenal ligament, it is helpful to follow the cystic duct to where it enters the common bile duct.

Prior to the preparation of the hepatoduodenal ligament, a generous Kocher maneuver should be performed, exposing the vena cava to just below the caudate lobe. The common bile duct then serves as a lead structure for the posterior dissection of the hepatoduodenal ligament. Injuries to the common bile duct must be carefully avoided. Resection of the common bile duct due to tumor infiltration is contraindicated since reconstruction by cholangio-intestinal anastomosis results in loss of a small intestine resorption area and is risky due to HIPEC. Anteriorly, the peritoneum or the tumor is lifted off the hepatic artery. The hepatoduodenal ligament is gradually dissected circularly until the anterior and the posterior dissection meet on the medial side of the portal vein (Fig. 9.5). The right hepatic artery should—if technically possible—be protected (Fig. 9.6). In cases of extensive infiltration and tumor formations extending far into the liver hilum, this surgical procedure is time-consuming and technically demanding. The aim of the dissection of the hepatoduodenal ligament is a tumor-free hepatoduodenal ligament, a clearing of the foramen of Winslow, and a free inferior vena cava.

The hepatogastric ligament is resected between the liver segments 2/3 and the caudate lobe, along the fissure defined by the ductus venosus. The lesser omentum is a major site of peritoneal carcinomatosis.

In patients with pseudomyxoma peritonei, about 50% of patients have tumor in this area. When resecting the lesser omentum, care must be taken to protect the left gastric artery, especially after the omentectomy has already taken place and the gastroepiploic vascular arcade has been removed along with it. The left gastric vein is variable in its course and cannot always be preserved. The anterior vagal trunk cannot always be spared, especially when there are larger tumor formations in the lesser omentum. Nevertheless, gastric emptying disorders are rarely observed and are usually transient. The openness of the pylorus can be checked simply by gripping it with the thumb and index finger. A normal pylorus requires no prophylactic pyloromyotomy.

In about 20% of the cases, there is a direct infiltration of the liver capsule. Isolated small tumor lesions can be locally excised or fulgurated. In cases of widespread tumor infiltration, the affected areas should be resected en bloc along with the liver capsule [5]. After incision with the electric knife, Glisson's capsule can be held with the fingers and removed laterally start-

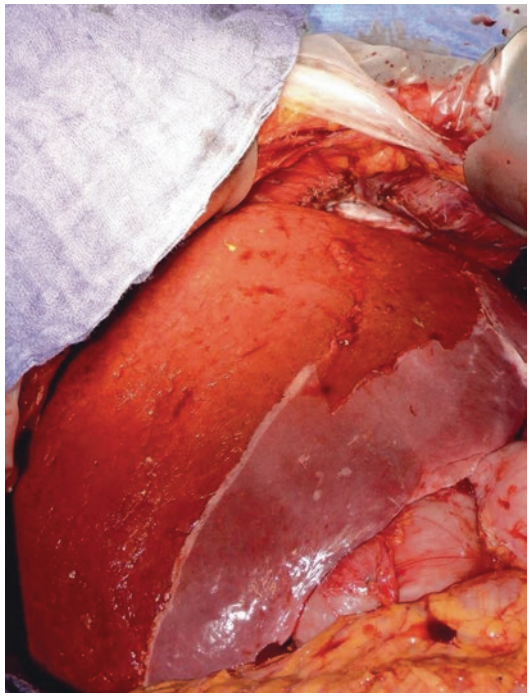


Fig. 9.7 Resection of Glisson's capsule

ing from the liver tissue (Fig. 9.7). Hemostasis of the liver is achieved by means of fulguration or bipolar forceps. It is important that the decapsulation of the liver takes place as the last operation in the right upper abdomen. Further liver manipulation, which may lead to deep parenchymal lacerations (liver fracture) after capsule resection, should be avoided as possible. The right upper abdomen can then be tamponed with abdominal towels to ensure a complete hemostasis. The capsule dissection can thus be performed with little blood loss. Biliary fistulas are a rarity even in cases of wide decapsulation.

9.6 Left Upper Quadrant

The parietal peritonectomy of the left upper quadrant is usually much easier than the peritonectomy of the right upper quadrant. The left upper quadrant usually has a significantly lower tumor load than the right. In addition, the left upper quadrant, especially after the previous omentectomy, is clean and better accessible than

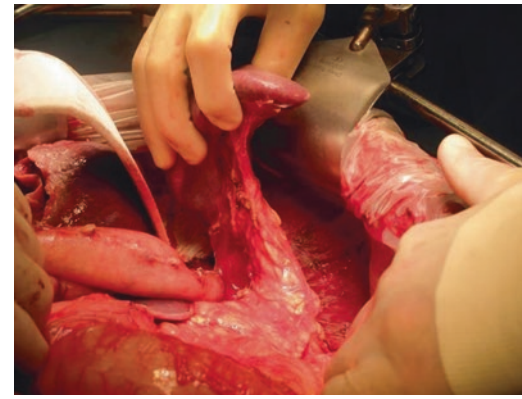


Fig. 9.8 The mobilization of spleen and pancreatic tail facilitates peritonectomy of the left upper abdomen

the right upper quadrant. The technique corresponds to the previous procedure carried out on the other side. The extensive mobilization of the left colic flexure as well as the spleen and pancreatic tail on Gerota's fascia facilitates subdiaphragmatic dissection (Fig. 9.8). The mobilization of the spleen and the pancreatic tail also allows for dorsal, extraperitoneal access to the splenic artery and vein in the spleen's hilum.

If the spleen and/or spleen hilum are infiltrated by the tumor, a splenectomy is required. Even in cases with large tumor masses in the spleen hilum, the splenic vein and artery are surrounded only by loose connective tissues, which can usually be cut off between the ligatures without damage to the pancreas. Only after transection of the hilar vessels can the tumor tissue be carefully detached from the pancreatic tail dorsally. The indication for splenectomy should be considered carefully. A splenectomy in the context of a peritonectomy with HIPEC leads to a significantly higher postoperative complication rate and should therefore only be performed in cases of tumor infestation or iatrogenic spleen injury [2].

Extensive tumor formation in the upper left abdomen requires an en bloc resection of the greater omentum, spleen, and pancreatic tail. In these cases, too, a dorsal access to the previous peritonectomy is helpful. In case of a very confusing anatomy, a ligature of the splenic vein and artery in the spleen hilum before further prepara-

tion of the pancreas and the removal of the pancreas can avoid unnecessary blood loss. The pancreas resection is performed by means of a stapler. The staples are additionally sewn over using the single stich technique. Left pancreatic resection increases the morbidity and mortality of the procedure and should therefore only be performed in strictly selected patients [8].

9.7 Gastric Resection and Gastrectomy

Starting from the so-called subpyloric space, infiltration of the gastric antrum is frequently found, especially in extensive peritoneal carcinomatosis. In these cases, a distal gastric resection is necessary. This should be done by preserving as far as possible the organs; only actually tumor-infiltrated gastric components should be removed. Gastric resection can be performed safely and does not increase morbidity. Gastrectomy should only be performed in selected cases, taking into account the patient's nutritional status, as this procedure, especially in combination with subsequent small and large bowel resections, significantly compromises the patient's quality of life.

9.8 Conclusion

For carefully selected patients, multimodal therapy—consisting of cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), and, if necessary, systemic chemotherapy—is the treatment offering the best chance for long-term tumor control. The most important component of the multimodal approach is the cytoreductive surgery. Full resection of all visible tumor sites is the strongest prognostic factor in all tumor entities. The upper abdomen represents a major challenge for the surgeon in this respect. Especially in the right upper abdomen, the extraperitoneal preparation and the demanding anatomical conditions require special visceral-surgical and oncological expertise. Only a largely standardized, systematic procedure makes it possible to perform this complex operation with low morbidity and mortality.

References

1. Andreasson SN, et al. Peritonectomy with high voltage electrocautery generates higher levels of ultrafine smoke particles. Eur J Surg Oncol. 2009;35:780–4.
2. Dagbert F, et al. Splenectomy increases postoperative complications following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2016;23:1980–5.
3. Deraco M, et al. Surgical technique of parietal and visceral peritonectomy for peritoneal surface malignancies. J Surg Oncol. 2009;100:321–8.
4. Näslund Andreasson S, et al. Polycyclic aromatic hydrocarbons in electrocautery smoke during peritonectomy procedures. J Environ Public Health. 2012;2012:929053.
5. Passot G, et al. Digital glissonectomy: a safe perihepatic peritonectomy. Ann Surg Oncol. 2016;12:3978–85.
6. Pelz JO, et al. Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol. 2009;99:9–15.
7. Piso P, et al. Multimodal treatment approaches for peritoneal carcinosis in colorectal cancer. Dtsch Arztebl Int. 2011;108:802–8.
8. Schwarz L, et al. Is the combination of distal pancreatectomy and cytoreductive surgery with HIPEC reasonable? Results of an international multicenter study. Ann Surg Oncol. 2016;263:369–75.
9. Sugarbaker PH. Dissection by electrocautery with a ball tip. J Surg Oncol. 1994;56:246–8.

10 Procedures of the Visceral and Parietal Peritonectomy in the Lower Abdomen

Philipp Horvath, Alfred Königsrainer, and Ingmar Königsrainer

10.1 Surgical Issues of the Visceral and Parietal Peritonectomy in the Lower Abdomen

The peritoneal metastasis of primary gastrointestinal and gynecological tumors requires not only the resection of the primary tumor but also the removal of the involved parietal and visceral peritoneum. The complete macroscopic removal of all tumor foci represents the basis of the peritonectomy procedure in terms of a curative treatment. The microscopic tumor cells remaining after a complete cytoreduction are treated by an application of an intraoperative hyperthermic chemotherapy. Extensive peritonectomy procedures without subsequent HIPEC (hyperthermic intraperitoneal chemotherapy) treatment can raise the recurrence rates along the peritoneal dissection areas. The underlying pathophysiological mechanisms were summarized by P.H. Sugarbaker in his "Tumor Cell Entrapment Hypothesis" [8].

10.1.1 Visceral Peritonectomy in the Lower Abdomen

The tumor infiltration of the visceral peritoneum represents a substantially bigger challenge because of the need for multivisceral resections to achieve a high-quality radical resection. It should be noted beforehand that the visceral peritonectomy is subject to other technical principles than the parietal peritonectomy. In the latter case, it is possible to obtain an exact dissection by using mono- and bipolar electrical current, which thermally improves the margins of resection and simultaneously achieves adequate hemostasis. This is not possible when the tumors infiltrate the visceral peritoneum of the small intestine and the colon.

Anatomic sites at increased risk are peritoneal recesses and anatomical structures, which show a peritoneal involvement in many patients because of their decreased/reduced peristalsis and their substantial/extensive fixation on the surrounding structures (e.g., on the retroperitoneum). Among

P. Horvath (✉)
Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany
e-mail: Philipp.horvath@med.uni-tuebingen.de

A. Königsrainer
Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany

Department of Surgery, University of Tübingen, Tübingen, Germany
e-mail: alfred.koenigsrainer@med.uni-tuebingen.de

I. Königsrainer
Department of General, Visceral and Thoracic Surgery, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
e-mail: ingmar.koenigsrainer@lkhf.at

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_10

Table 10.1 Types of peritoneal affection of the visceral peritoneum and its therapies

Type	Extent	Therapy recommendations
I	Noninvasive tumor nodes at the visceral peritoneum	Local excision in taking along/entrainment of the peritoneum and suture of the defect
II	Minimally invasive tumor nodes in antimesenterial localization	Resection and entrainment of deeper intestinal wall structures and suture
III	Moderate invasive tumor nodes in antimesenterial localization	Solid wall resection and suture
IV	Gross invasive tumor nodes	Bowel resection
V	Mesenterially situated large tumor nodes	Bowel resection

Modified from Sugarbaker et al. [8]

them are, especially, the rectosigmoidal transition, the ligament of Treitz, the pylorus, the ileocecal transition, and the so-called hepatic bridge (*pont hepatique*). The necessity for a visceral resection depends on the extent of the invasive tumor nodes as well as the localization. Sugarbaker et al. [8] categorized five types of peritoneal tumor infestation overall with the corresponding therapy suggestions and recommendations (see Table 10.1). The classification focuses on a peritoneal involvement infestation of the mesentery of the small intestine and the small intestine itself but also can be used for the rectosigmoidal mesentery.

10.1.2 Visceral Resection in the Lower Abdomen

To achieve sufficient tumor clearance, large resections are necessary if the visceral peritoneum is extensively affected in the lower abdomen. The peritoneum in the lower abdomen adjacent to the rectum also partially covers the urinary bladder and, in women, the uterus. All these anatomical structures except the urinary bladder can be resected in order to achieve a R0- or CC-0 resection (Fig. 10.1). Attention should

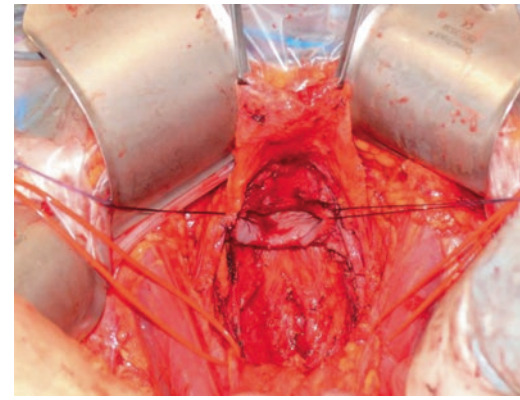


Fig. 10.1 Female pelvis after a total peritonectomy. The rectum is dorsally stapled, the root of the vagina is pulled cranially with the strands. The bladder is still in situ

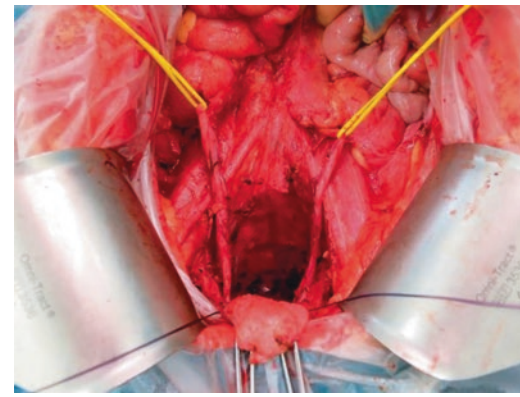


Fig. 10.2 Pelvic space following complete exenteration

be paid to the fact that extensive resections result in high morbidity and in a limited quality of life. Thus the patients have to be informed preoperatively about the possible level of resection and the resulting limitations. The maximum surgical approach would be the complete exenteration of the pelvis. This includes the removal of the rectum, the urinary bladder, and, in women, the uterus (Fig. 10.2).

The reason for such a radical surgical approach is usually a local relapse of a rectal or sigmoid cancer, or even an ovarian cancer, but with limited peritoneal metastasis. In the majority of cases, these patients have already been treated with systemic chemotherapy and sometimes even radiotherapy.

10.1.3 Parietal Peritonectomy in the Lower Abdomen

The midline laparotomy is carried out in the lithotomy position, starting from the xiphoid process and continuing to the symphysis. All preexisting scars must be excised in recurrent interventions. Self-retaining retractors are used to optimize the visualization of the peritoneal surfaces, especially the surfaces of the small pelvis and the diaphragm.

The resection line of the peritoneum from beneath the posterior rectus sheath can be joined on both sides with the resection lines of the peritonectomy beneath both paracolic sulci. The peritoneum of the urinary bladder and the underlying fatty tissue are incised and resected on both sides. This step can be facilitated substantially by a retrograde filling of the urinary bladder as it is performed before an ureterocystostomy during a kidney transplantation. The distal anatomic border for the parietal peritonectomy of the small pelvis in women is the cervix uteri and in men the seminal vesicles. The resection of the round ligament of the uterus in the opening of the deep inguinal ring and the transection of the ovarian vein completes the parietal peritonectomy in women.

10.2 Technical Issues in Men

In the case of an extensive tumor involvement within the range of the lower abdomen, radical surgery should always be preoperatively discussed. The possible resection of the inguinal canal with all the corresponding structures (ductus deferens, testicular vessels, nerves) and the expected postoperative complications (infertility, atrophy of the testicles, and loss of sensitivity) should always be explained to the patient. The possible rectum-sparing resection procedure should always be intraoperatively considered. Proximal separation of the peritoneum can shift the necessary rectal resection into the middle third of the rectum so that an extirpation can be avoided. Simultaneously existing inguinal hernias can result in a tumor involvement of the prolapsing parts of the peritoneum through the deep inguinal ring and in the accumulation of mucus in the hernia sac or the tunica vaginalis.

10.3 Technical Issues in Women

It is necessary to perform a hysterectomy and a salpingoovariectomy in the case of an expanded tumorous infestation of the lower female abdomen in order to achieve a complete cytoreduction. Both of the round ligaments of the uterus are primarily divided, and, if possible, the uterus under the cervix and underneath the peritoneal folding is resected. Attention should be paid to perfusion in long-duration ureterolysis. Especially the anterior rectal wall requires careful attention within the pouch of Douglas.

10.3.1 Oophorectomy *per Principe*?

There is still no consensus on recommending or requiring preventive ovariectomy in cases of peritoneal metastasis of gastrointestinal origin. This is especially true for premenopausal women with uninvolved ovaries. A general consensus seems to be reached on preventive oophorectomy in premenopausal women to reduce the relapse rates [1, 3, 4]. To date, only one retrospective analysis from the Netherlands studied the incidence of ovarian cancer metastasis in patients with colorectal peritoneal metastasis or with pseudomyxoma peritonei [5]. In the collective patient population, 52% of the women had histopathologically detected ovarian metastases. A macroscopically and a microscopically suspicion of tumor involvement provided the indication for an ovariectomy in this study. Interestingly, 21 of the 65 patients with colorectal cancer showed only microscopically a tumor involvement of the ovaries. The study does not mention how many of the ovaries showed no signs of pathology intraoperatively. Furthermore, in 75% of the premenopausal women under age 40, ovarian metastases could be detected. However, this study could not show a significant difference between women with or without synchronous ovarian metastases

regarding their disease-free and disease-specific survival. Nevertheless these data do recommend a preventive oophorectomy for premenopausal women with macroscopically inconspicuous ovaries.

In a randomized controlled trial in the USA, 1 out of 77 women with colorectal cancer in Dukes' stages B and C showed microscopic tumor involvement after preventive oophorectomy [9]. However, a statistically nonsignificant improvement in their survival rate after 2 years, and even after 3 years, could be shown for patients following preventive oophorectomy, although this benefit could no longer be detected after 5 years.

Another retrospective analysis evaluated the justification for preventive oophorectomy in the context of a primary tumor resection in patients with rectal cancer or carcinoma of the rectosigmoidal transition [7]. A preventive oophorectomy was indicated in cases of cystic ovarian lesions, in cases of an adherence to the primary tumor, and of ascites in the lesser pelvis. The preventive oophorectomy was performed on a total of 64 patients whenever one of the abovementioned criteria applied. In 15 patients (23%), micrometastases were found. As in other studies [1, 2, 6, 9], a preventive oophorectomy ovariectomy did not significantly affect overall survival when performed during primary surgery on patients with colorectal cancer without synchronous peritoneal metastasis. In conclusion, to sum up, it is recommendable to perform a preventive ovariectomy oophorectomy in premenopausal women even with uninvolved ovaries if a colorectal peritoneal metastasis is being treated.

References

1. Banerjee S, Kapur S, Moran BJ. The role of prophylactic oophorectomy in women undergoing surgery for colorectal cancer. Color Dis. 2005;7:214–7.
2. Birnkrant A, Sampson J, Sugarbaker PH. Ovarian metastases from colorectal cancer. Dis Colon Rectum. 1986;29:767–71.
3. Boa P, Bartlett D. Surgical techniques in visceral resection and peritonectomy procedures. Cancer J. 2009;15:204–11.
4. Deraco M, Baratti D, Kusamura S, et al. Surgical technique of parietal and visceral peritonectomy for peritoneal surface malignancies. J Surg Oncol. 2009;100:321–8.
5. Evers DJ, Verwaal VJ. Indication for oophorectomy during cytoreduction for intraperitoneal metastatic spread of colorectal or appendiceal origin. Br J Surg. 2010;98:287–92.
6. Hanna NN, Cohen AM. Ovarian neoplasms in patients with colorectal cancer: understanding the role of prophylactic oophorectomy. Clin Colorectal Cancer. 2004;3:215–22.
7. Liang JT, Lai HS, Wu CT, et al. Laparoscopic prophylactic oophorectomy plus N3 lymphadenectomy for advanced rectosigmoid cancer. Ann Surg Oncol. 2007;14:1991–9.
8. Sugarbaker PH, Deraco M, Glehen O, et al. Cytoreductive surgery & perioperative chemotherapy for peritoneal surface malignancy: textbook and video atlas. Woodbury: Cine-Med; 2013.
9. Young-Fadok TM, Wolff BG, Nivatvongs S, et al. Prophylactic oophorectomy in colorectal carcinoma: preliminary results of a randomized, prospective trial. Dis Colon Rectum. 1998;41:277–83.

11 Parietal and Visceral Peritonectomy

Beate Rau, Wieland Raue, and Pankaj Kumar Garg

11.1 Introduction

An essential operational step in the surgical treatment of peritoneal metastases is cytoreductive surgery with parietal and visceral peritonectomy.

- The peritonectomy can be carried out in various ways, depending on the type and extent of the Metastasis.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-62640-2_11) contains supplementary material, which is available to authorized users. The videos can be accessed by scanning the related images with the SN More Media App.

B. Rau (✉)
Department of Surgery, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität of Berlin, Berlin, Germany
e-mail: beate.rau@charite.de

W. Raue
Department of Surgery, AKH-Group, Hospital of Celle, Celle, Germany

Allgemeines Krankenhaus Celle, Klinik für Allgemein-, Viszeral- und Thoraxchirurgie, Celle, Germany

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

11.2 Methods of Peritonectomy

In the case of small nodular infiltrating carcinomatosis (Fig. 11.1), as found, for example, in gastric or pancreatic carcinoma, the approach is different from that for the mucinous, slimy variant of peritoneal tumor nodules observed in ovarian cancer (Fig. 11.2).

In small nodular infiltrating carcinomas, there is often confluent metastases, especially in the upper abdomen, which can be removed en bloc as an area with a low overall peritoneal carcinomatosis index (PCI), making complete resection possible. Additional isolated foci should be removed individually or can also be destroyed by thermocoagulation.

- If there is confluent metastases of an aggressive tumor present all over the abdomen (high PCI), its complete removal is likely to be futile and will not improve survival.

With low-grade mucinous peritoneal tumors, on the other hand, even with a high tumor load and high PCI, peritonectomy with removal of all tumor nodules is a central component of cytoreductive surgery and likely to improve survival.

As a rule, if complete peritonectomy is contemplated in patients with a high PCI, it is important to mobilize the peritoneum right at the beginning. All attempts must be made not to make any hole in the peritoneum in the initial part

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_11

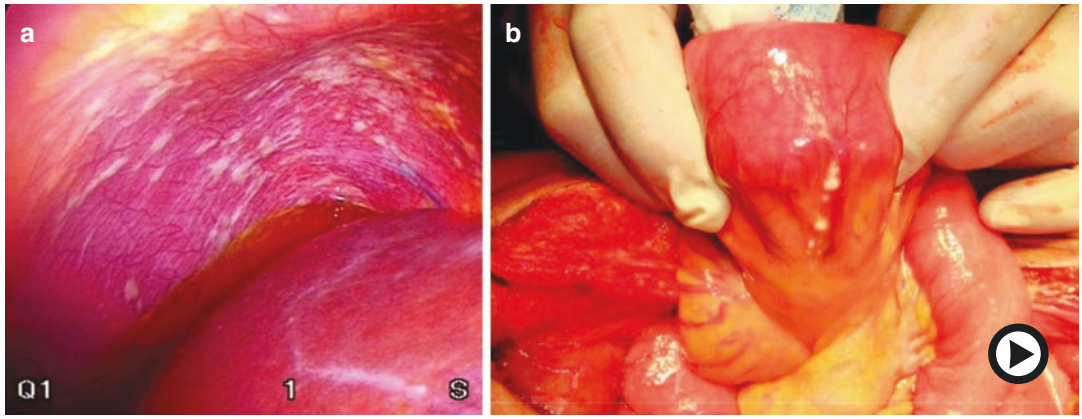


Fig. 11.1 (**a** and **b**) Small nodular, partly confluent and infiltrating peritoneal metastases
Video 11.1 Extraperitoneal anterior rectal resection: The video presents a posterior pelvic exenteration with en bloc bladder peritonectomy. This is often necessary when mucinous tumor masses have spread in the pouch of Douglas area. To facilitate the operative procedure, the bladder is filled up and the peritoneum is completely detached from the pelvic wall up to the vesicouterine or vesicorectal pouch. Thereafter, the entire pelvic peritoneum over the pouch of Douglas can be stripped off while thus preserving about 5 cm of the middle rectum

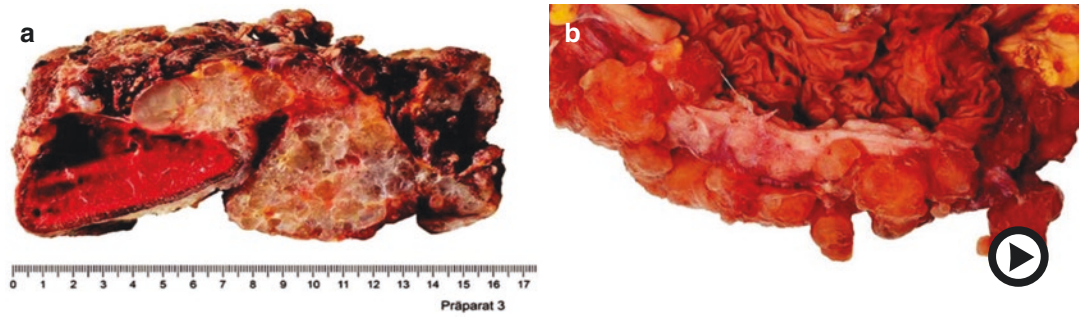


Fig. 11.2 (**a** and **b**) Mucinous peritoneal metastases
Video 11.2 Insight into Douglas's area: The video presents the already resected extraperitoneal anterior rectal specimen. When you incise the peritoneal surface you can see the mucinous tumor mass in the cul de sac

of parietal peritonectomy. Mobilization is a very useful technique to achieve a complete parietal peritonectomy especially in patients with ascites, as it keeps the two compartments—intraperitoneal from preperitoneal—separated (Fig. 11.3).

If peritoneum is injured in the initial part of parietal peritonectomy, ascetic fluid makes the operative field difficult to work in and also it affects the functioning of electrocautery.

11.3 Colonic Involvement

The "omental cake" is a term that describes the complete tumor infiltration of the greater omentum and is a metaphor for a pronounced, usually mucinous, peritoneal metastases. The omentum lies on the transverse colon and is supplied with blood by the gastroepiploic arcade. As a rule, the greater omentum is removed with or without preserving the gastroepiploic arcade. The gastroepiploic arcade may be safely sacrificed without any effect on gastric emptying depending upon the extent of the tumor [8].

If possible, the omentum should be removed while preserving the transverse colon. This is not always possible, especially if the tumor nodules over the omentum deeply infiltrate the colonic serosa, necessitating repeated colonic resection during cytoreduction (Fig. 11.4). However, individual tumor nodules that lie on the small or large bowel serosa can often be dissected tangentially [2].

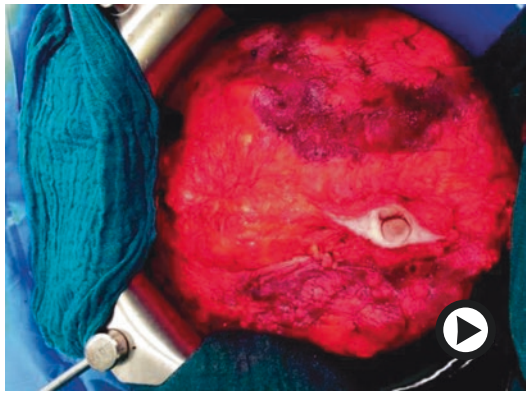


Fig. 11.3 Complete peritonectomy with omphalectomy for trocar metastasis
Video 11.3 Resection of a tumor nodule: the video presents subtle removement of small bowel nodules. In addition, coagulation of very small lesion is possible. Please be aware that you can harm your eyes; please wear glasses for eye protection during this procedure

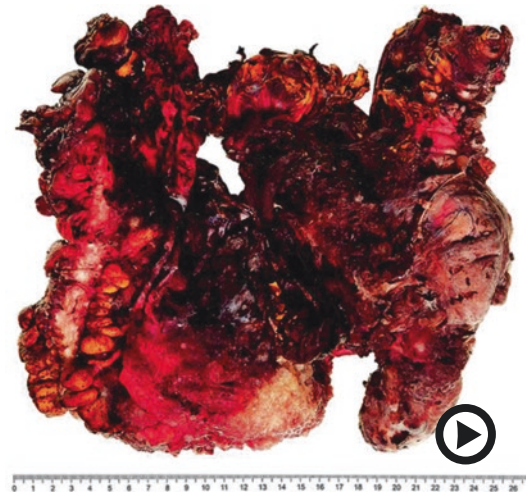


Fig. 11.4 Colectomy with omentectomy and extraperitoneal anterior rectal resection
Video 11.4 Stitch for deserosation of small bowel: every single small deserosation should be stitched to prevent small bowel fistula as a severe postoperative complication

11.4 Pelvic Peritonectomy

If complete cytoreduction cannot be achieved with a pelvic peritonectomy in the small pelvis, an extraperitoneal anterior rectal resection in men and posterior pelvic exenteration with en bloc hysterectomy and salpingo-oophorectomy in women should be considered. This is often necessary when mucinous tumor masses have spread in the pouch of Douglas area. To facilitate the operative procedure, the bladder is filled up and the peritoneum is completely detached from the pelvic wall up to the vesicouterine or vesicorectal pouch. Thereafter, the entire pelvic peritoneum over the pouch of Douglas can be stripped off while thus preserving about 5 cm of the middle rectum (Video 11.1 – Extraperitoneal anterior rectal resection and Video 11.2 – Insight into Douglas's area at www.springermedizin.de/vzb-peritoneale-tumoren).

After removal of the rectum, a stapled colorectal anastomosis is performed after careful hemostasis. Depending upon the level of the anastomosis, the creation of a protective ileostomy may be considered.

- Barring primary tumors of the rectum, as a rule the pelvic peritonectomy, necessitates an anastomosis in the upper or middle third of the rectum, and thus total mesorectal excision is not warranted. Usually, a protective diversion is not required following colorectal anastomosis.

In order to avoid bowel- and bladder-related deterioration in quality of life of the patients, it is necessary to preserve the hypogastric nerves while performing pelvic peritonectomy.

11.5 Indications for Oophorectomy

Often, bilateral oophorectomy is performed as a part of cytoreduction. The decision to preserve or remove the ovaries depends upon the anticipated future risk of ovarian cancer or ovarian metastasis. It is imperative to consider the consequences of surgical menopause, which can significantly affect the quality of life in premenopausal women.

Krukenberg tumors are rare (approx. 1–2%) and are most often found in association with gastric cancer (32%) or colorectal cancer (45%). They are associated with poor prognosis [16]. In a study of 4566 women with colorectal cancer, Segelman et al. [14] reported the presence of

synchronous or metachronous ovarian metastases in colon cancer to be 1.1% each and 0.6% or 0.1% in rectal cancer, respectively. In a retrospective analysis, 43 of 267 patients with stage II and III colon carcinoma had a bilateral oophorectomy. In both univariate and multivariate analyses, there was no survival benefit associated with bilateral oophorectomy [5]. The tumor stage and the administration of adjuvant chemotherapy were found to be prognostic factors. An advantage of bilateral oophorectomy could only be demonstrated in patients who did not receive adjuvant chemotherapy [5].

However, the risks of serious illnesses that can develop in the course of bilateral oophorectomy due to the hormone deficiency should be taken into account. Early menopause can lead to osteoporosis, bone fractures, and cardiovascular diseases, thereby increasing the risk of mortality [11].

Hormonal substitution can reduce the symptoms; however, it can also be associated with thromboembolism, stroke, and gallbladder disease [10]. Therefore, a bilateral oophorectomy should always be carefully considered and discussed with the patient in advance. In postmenopausal women with an intact uterus, estrogen and progesterone are recommended to reduce the risk of endometrial hyperplasia following bilateral oophorectomy [9].

11.6 Small Bowel Involvement

In principle, the use of various aids is conceivable for peritonectomy. These include scissors or electrical scissors, bipolar electrocoagulation, lasers, plasma beamers, etc. The aim of all instruments is to remove the tumor-bearing peritoneum from the fat layer of the small intestine mesentery without damaging the vessels. After the parietal peritonectomy has been performed, if necessary, the intra-abdominal recess is examined to find and remove hidden foci. In the area of the ligament of Treitz, the small intestine is systematically examined from both sides in a thorough search for tumor nodules.

The area around the duodenojejunal junction, the adhesions of the small intestine, the folds of the duodenum, and the transition from the mesentery to the small intestine should also be thoroughly inspected. The following methods are available for isolated foci:

- Extensive peritonectomy (Fig. 11.5)
- Resection of a tumor nodule (Video 11.3, www.springermedizin.de/VZB-peritoneal-tumors)
- Coagulation of tumor sites (Fig. 11.6)
- Immediately stitching of deserosation (Video 11.4, www.springermedizin.de/VZB-peritoneal-tumors)

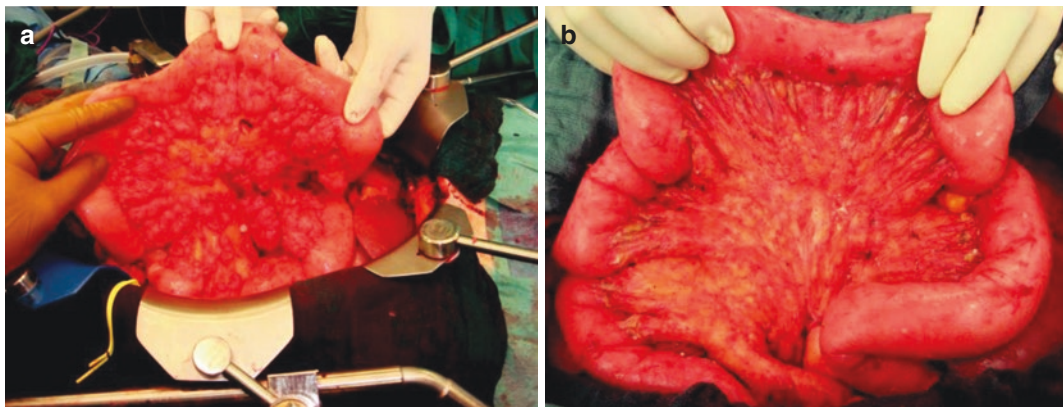


Fig. 11.5 (**a** and **b**) Extensive peritonectomy (**a**) with confluent tumor mass, (**b**) after removal of the visceral peritoneum on the small intestine mesentery

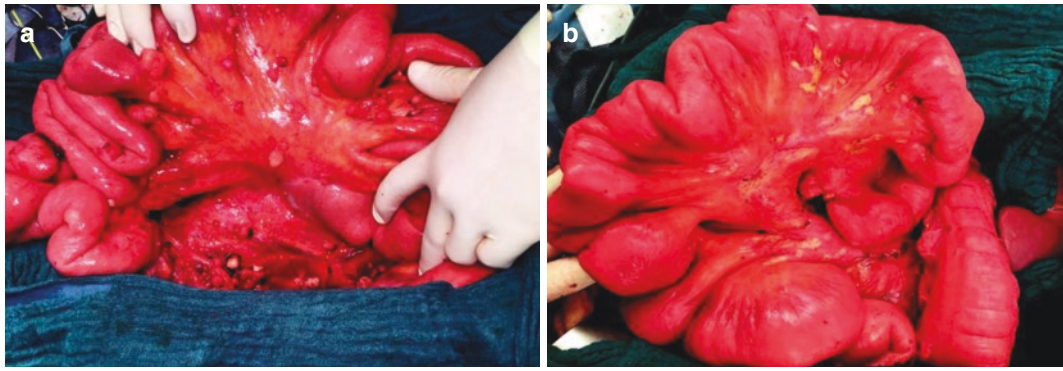


Fig. 11.6 (**a** and **b**) Coagulation of tumor nodules

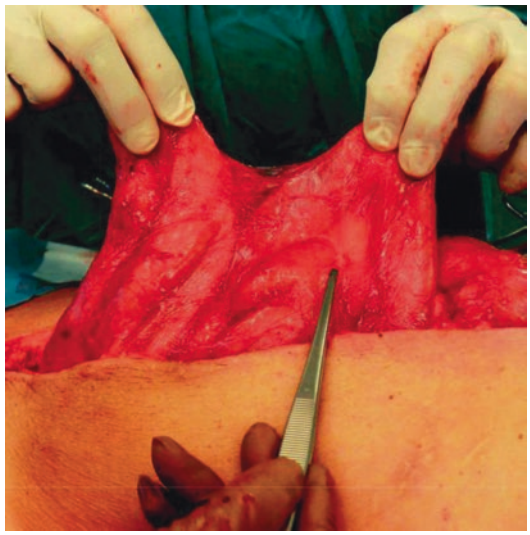


Fig. 11.7 Tumor nodules anchored in the fibrin that can be removed with the covering

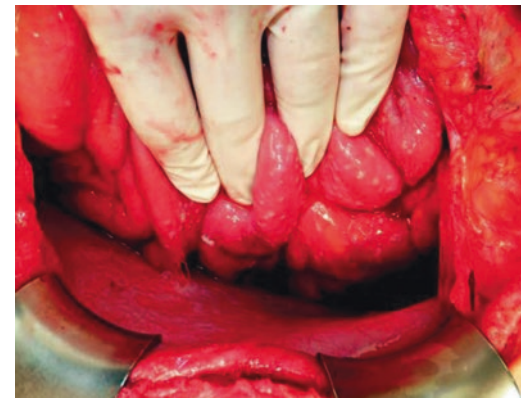


Fig. 11.8 Disseminated infiltrating peritoneal metastases to the small intestine

When coagulating a tumor nodule, the surgical team members should wear glasses for their own protection, as electrocoagulation may lead to diffuse spray due to the high water content of the tumor nodules.

If the tumor nodules are present on the surface of the small intestine, it may be possible to remove them using sharp scissors or a knife without injuring the bowel wall (Fig. 11.7). If the serosa is infiltrated and removed along with tumor nodules, it must be repaired using seromuscular sutures in order to avoid the risk of bowel perforation in the postoperative period (Fig. 11.8). In some cases, tumor nodules are limited to the terminal ileum and the ascending colon, and they may necessitate a right hemicolectomy to achieve complete cytoreduction. If there is extensive involvement of the small bowel or deep infiltration of the serosa with tumor nodules at multiple places, it may not be worthwhile to proceed with cytoreduction, and one must abort the surgery (Fig. 11.9).

- Bowel resection (small intestine, possibly also large intestine) is justified if it leads to complete macroscopic removal of the tumor nodules.

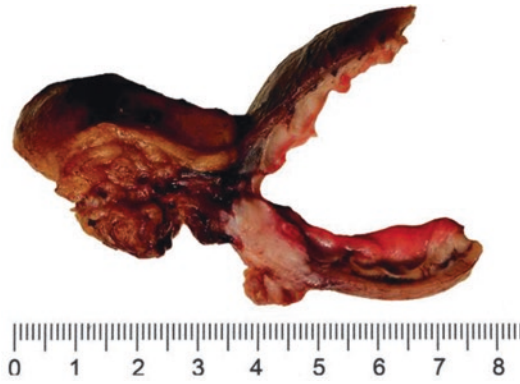


Fig. 11.9 Tumor implants at the mesenteric border

11.7 Indications for Cholecystectomy

A cholecystectomy (Fig. 11.10) is often necessary when small tumor nodules over the serosa of the gallbladder cannot be removed, as is also the case with the small bowel. Removal of the tumor nodules over the serosa of the gallbladder and then subsequent serosal repair is associated with a very high risk of postoperative biliary fistula and is thus not recommended.

Even if there are no tumor nodules over the gallbladder, a cholecystectomy is still recommended, since either hyperthermic or normothermic intraperitoneal chemotherapy can severely irritate the gallbladder serosa and can cause severe cholecystitis.

11.8 Indication for Splenectomy

The indication for splenectomy is evident if mucinous tumor masses can only be completely removed from the left upper abdomen by taking the spleen with them (Fig. 11.11). The risk must be weighed against its anticipated benefits as patients undergoing splenectomy have a significantly high postoperative mortality risk of up to 50% due to progressive sepsis [13, 15].

The splenectomized patient must therefore be clearly informed about the life-threatening risk of any infectious disease with or without a fever.

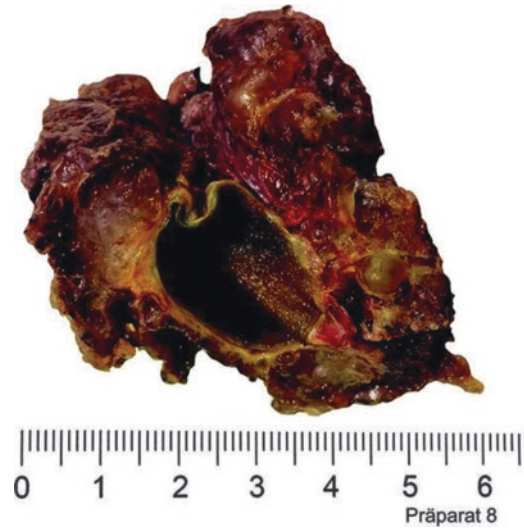


Fig. 11.10 Cholecystectomy for tumor nodules

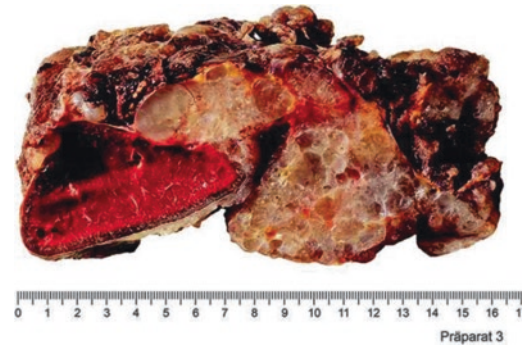


Fig. 11.11 Splenectomy and omental cake

▶ Therefore, patients should follow post-splenectomy vaccination guidelines—they must undergo vaccination against pneumococci, type B *Haemophilus influenzae*, and meningococcal disease within 2–4 weeks after surgery and have regular vaccinations against seasonal influenza viruses [12, 13].

It is essential to start appropriate antimicrobial therapy as soon as a patient who has undergone splenectomy develops any feature of infection that could be associated with fever. Lifelong prophylaxis is provided for asplenic patients who have had an episode of post-splenectomy sepsis or OPSI ("overwhelming post-splenectomy infection").

The risk of developing post-splenectomy sepsis depends upon various factors such as the patient's age, general condition, immune status, interval of the spleen-free period (highest risk in the first year after splenectomy), reason for splenectomy (traumatic, carcinoma, etc.), and the cause of bacteremia (associated with catheter infection) [13, 15]. In children with an increased risk, penicillin V is also recommended for the first 3–5 years. In cases of penicillin intolerance, a suitable alternative can be macrolides or oral cephalosporins [1].

11.9 Avoiding Complications

It is not surprising that extensive cytoreductive surgery followed by intraperitoneal chemotherapy results in postoperative complications. Serious complications are usually accompanied by higher reoperation rates and are reported as 20% in the literature. The risk of postoperative complications essentially increases with poor preoperative nutritional status, the length of the operation, the administration of blood products, and the number of anastomoses [6].

Complications can be avoided, for example, by improving preoperative alimentation [3, 4] and preoperative intestinal irrigation [7]. The interval between the last day of neoadjuvant chemotherapy and the day of the operation should be between 4 and 6 weeks.

11.10 Conclusion

The technique of cytoreduction must be adapted to the existing tumor load and the characteristics of the peritoneal metastasis. When planning to undertake extensive surgical cytoreduction, the likelihood of achieving complete cytoreduction and the risk of long-term restrictions in quality of life must be considered. Organ resections in particular are associated with an increased risk of postoperative complications. Even following an extraperitoneal rectal resection, a protective diversion stoma is usually not required. After splenectomy and oophorectomy, the recommendations of the relevant specialist societies should be followed to reduce the risk of postoperative long-term complications.

References

1. AWMF. Leitlinien der Deutschen Gesellschaft für Kinderchirurgie: Traumatische Milzruptur im Kindesalter. 2015. www.awmf.org/uploads/tx_szleitlinien/006-112l_S1_Traumatische_Milzruptur_Kindesalter_2015-02.pdf
2. Bijelic L, Yan TD, Sugarbaker PH. Failure analysis of recurrent disease following complete cytoreduction and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. Ann Surg Oncol. 2007;14:2281–8.
3. Burden S, Todd C, Hill J, Lal S. Pre-operative nutrition support in patients undergoing gastrointestinal surgery. Cochrane Database Syst Rev. 2012;11:CD008879. https://doi.org/10.1002/14651858.CD008879.pub2.
4. Burden ST, Gibson DJ, Lal S, Hill J, Pilling M, Soop M, Ramesh A, Todd C. Pre-operative oral nutritional supplementation with dietary advice versus dietary advice alone in weight-losing patients with colorectal cancer: single-blind randomized controlled trial. J Cachexia Sarcopenia Muscle. 2017;8(3):437–46.
5. Cai GX, Xu Y, Tang DF, Lian P, Peng JJ, Wang MH, Guan ZQ, Cai SJ. Interaction between synchronous bilateral prophylactic oophorectomy and adjuvant chemotherapy in female patients with locally advanced colorectal cancer. Color Dis. 2011;13:414–9.
6. Chua TC, Saxena A, Schellekens JF, Liauw W, Yan TD, Fransi S, Zhao J, Morris DL. Morbidity and mortality outcomes intraperitoneal chemotherapy at a single tertiary institution: towards a new perspective of this treatment. Ann Surg. 2010;251:101–6.
7. Daneman N, Sarwar S, Fowler RA, Cuthbertson BH. Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13:328–41.
8. Evers DJ, Smeenk RM, Bottenberg PD, van Werkhoven ED, Boot H, Verwaal VJ. Effect of preservation of the right gastro-epiploic artery on delayed gastric emptying after cytoreductive surgery and HIPEC: a randomized clinical trial. Eur J Surg Oncol. 2011;37:162–7.
9. Furness S, Roberts H, Marjoribanks J, Lethaby A, Hickey M, Farquhar C. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2009;(2):CD000402.
10. Marjoribanks J, Farquhar C, Roberts H, Lethaby A. Trial does not change the conclusions of Cochrane review of long term hormone therapy for perimenopausal and postmenopausal women. BMJ.

2012;345:e8141; author reply e8164. https://doi.org/10.1136/bmj.e8141.
11. Orozco LJ, Salazar A, Clarke J, Tristan M. Hysterectomy versus hysterectomy plus oophorectomy for premenopausal women. Cochrane Database Syst Rev. 2008;(3):CD005638.
12. Robert Koch Institut. Empfehlungen der Ständigen-Impfkommission (STIKO) am Robert Koch-Institut. Epid Bull. 2016;34:301–40.
13. Rubin LG, Schaffner W. Clinical practice. Care of the asplenic patient. N Engl J Med. 2014;371:349–56.
14. Segelman J, Floter-Radestad A, Hellborg H, Sjovall A, Martling A. Epidemiology and prognosis of ovarian metastases in colorectal cancer. Br J Surg. 2010;97:1704–9.
15. Theilacker C, Ludewig K, Serr A, Schimpf J, Held J, Bogelein M, Bahr V, Rusch S, Pohl A, Kogelmann K, Frieseke S, Bogdanski R, Brunkhorst FM, Kern WV. Overwhelming post splenectomy infection: a prospective multicenter cohort study. Clin Infect Dis. 2016;620:871–8.
16. Wu F, Zhao X, Mi B, Feng LU, Yuan NA, Lei F, Li M, Zhao X. Clinical characteristics and prognostic analysis of Krukenberg tumor. Mol Clin Oncol. 2015;3:1323–8.

Cytoreduction Preparation Devices

12

Horst Günter Rau, Peter Busch,
Pankaj Kumar Garg, and Igor Yakubov

12.1 Introduction

Cytoreduction is usually a time-consuming procedure and is associated with large areas of raw wound surfaces. In addition to the peritonectomy, often multivisceral resections may also be required to achieve complete cytoreduction. The technical details of the specific procedure are described in detail in different chapters of this book.

The parietal peritoneum is mostly separated from the abdominal wall layers using blunt dissection. In addition to blunt dissection, a swab (Fig. 12.1), scissors, or bipolar scissors (Fig. 12.2c) can be helpful. The water jet dissector (Fig. 12.2a) or argon beamer (Fig. 12.2b) can likewise be useful implements to separate densely adherent peritoneum from the diaphragm or to dissect the liver capsula.

H. G. Rau (✉)
Krankenhaus Martha Maria, Munich, Germany
e-mail: HorstGuenter.Rau@Martha-Maria.de

P. Busch
Funktionsoberarzt Chirurgie, Krankenhaus Agatharied, Hausham, Germany
e-mail: Peter.Busch@kh.agatharied.de

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

I. Yakubov
Facharzt Viszeralchirurgie, Chirurgische Praxis, Fürstenfeldbruck, Germany

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_12

Vessel-sealing instruments are particularly useful to minimize the blood loss and reduce the duration of the surgery; these instruments include bipolar scissors, Ultracision®, and LigaSure™ as well as a combination of these two methods: THUNDER BEAT® (Fig. 12.2d). The principles of these instruments and their preferred uses are discussed below.

12.2 High-Frequency Surgery

The use of high-frequency current in surgery dates back to Christian Heinrich Erbe from Tübingen. In the early twentieth century, he presented the first high-frequency surgery generator to the professional world in 1923. AC heat (150–400 °C) is generated in high-frequency surgery (HF surgery). The heat leads to destruction of the tissues and the sealing of smaller vessels.

Using alternating current with a frequency range between 300 and 4000 kHz in the electrosurgical unit avoids or reduces nerve irritation and electrolysis.

12.2.1 Monopolar Coagulation

A monopolar diathermy is commonly used during cytoreduction surgery. In this mode, the current flows from a small area of contact with the active electrode toward a large area of contact

with the neutral electrode. Due to the current density, the thermal effect at the active electrode is greatest, whereas it is practically unnoticeable at the neutral electrode.

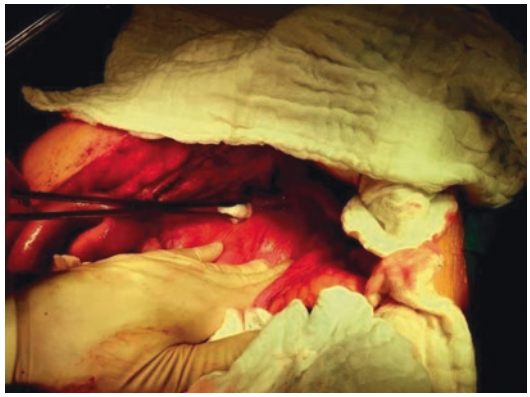


Fig. 12.1 Blunt dissection

The monopolar RF devices allow a faster dissection when they are used in cytoreduction—for example, in colon resection while dissecting a vascular layer. They are also quite effective while doing peritonectomy. One should also note that monopolar devices result in the largest lateral thermal damage to the tissues. An application of 40 W of monopolar diathermy for 10 seconds may cause temperatures to rise to 59.2 °C in the tissues located even 1 cm away from the tip of the instrument [23].

Though there is risk of lateral tissue damage, monopolar diathermy is generally used for entering the abdominal cavity. Small vessels (<1 mm) may be tackled with monopolar diathermy quickly without much consequence. These small vessels must be gripped with surgical forceps and the current is applied carefully. One has to be careful while dissecting the ureter with monopolar dia-

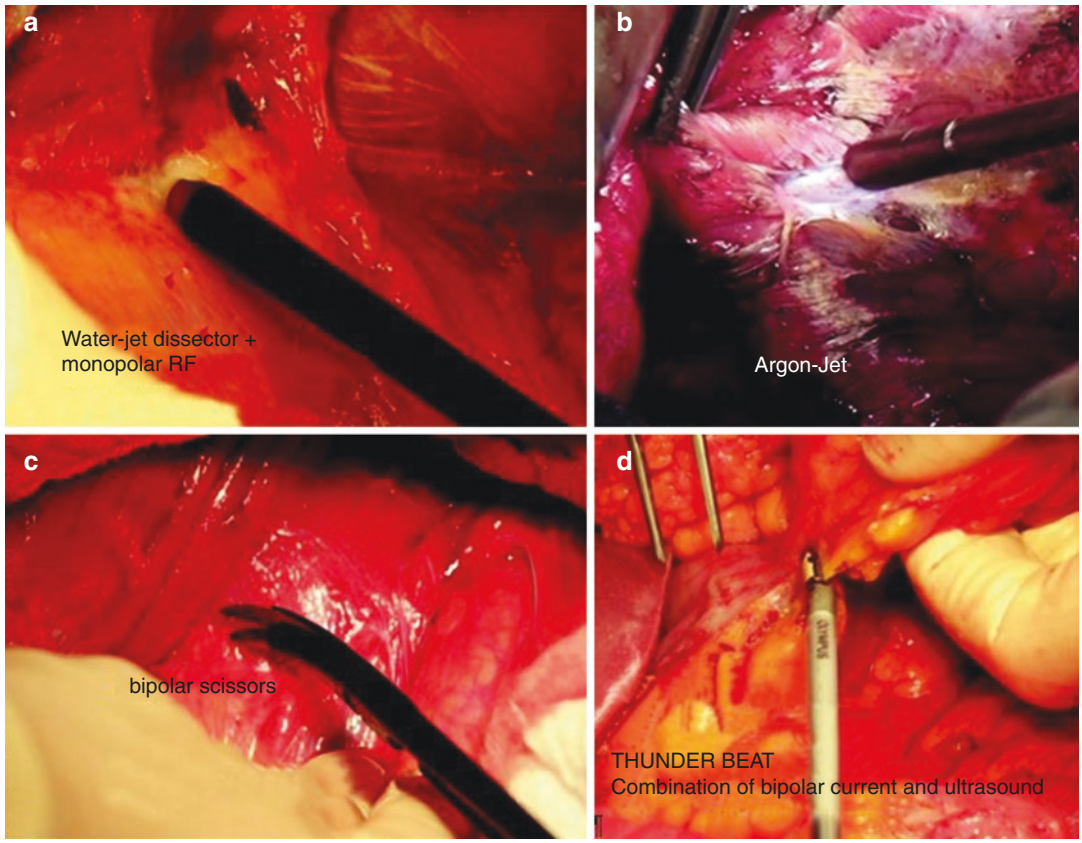


Fig. 12.2 (**a**–**d**) Examples of dissection: (**a**) Water jet dissector and monopolar radio frequency (RF), (**b**) Argon-Jet, (**c**) bipolar scissors, (**d**) THUNDER BEAT: combination of bipolar current and ultrasound

thermy as current may get localized at places in the ureter due to the presence of urine. Unfortunately, this may go unnoticed during the surgery and the patient may present with urinary leak or stricture in the late postoperative period [17, 20].

12.2.2 Bipolar Coagulation

In the bipolar instruments, the current flows through the tissue held between the two surfaces of the forceps- or scissor-shaped instrument (Fig. 12.3). As the current does not flow laterally in the surrounding tissues, thermal damage does not spread laterally. Moreover, a neutral electrode is not required.

Thus, the advantages of using bipolar coagulation devices over monopolar diathermy are obvious: no or minimal thermal injury to surrounding tissues, and no interference to external monitoring devices such as the ECG or to internal stimulating devices such as a pacemaker.

With bipolar scissors, dissection can be performed swiftly and cleanly. Bipolar scissors serve as our main instrument while doing dissection in open surgery (Fig. 12.4). A bipolar device is capable of addressing the small vessels; its use in peritonectomy or in lymphadenectomy leads to an almost complete vascular dissection (Fig. 12.5). However, large vessels must be tackled differently.

Fig. 12.3 The workstation manufactured by Erbe Elektromedizin GmbH (with permission of Erbe)

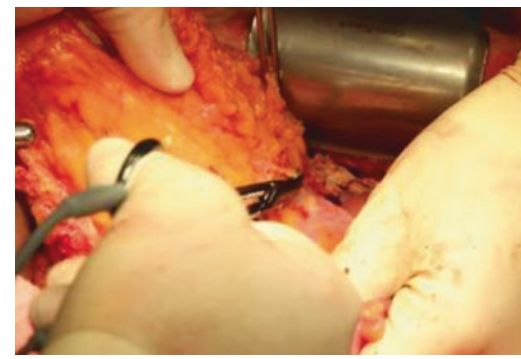


Fig. 12.4 Omentectomy with bipolar scissors

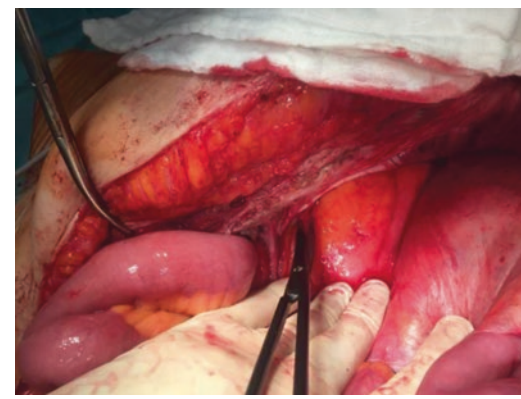


Fig. 12.5 Peritonectomy with bipolar scissors

12.2.3 Bipolar Sealing Instruments with Impedance Measurement (Electrothermal Bipolar Vessel Sealing)

Example: LigaSure™ (Covidien)

An evolutionary technique in bipolar diathermy was developed by Covidien in 1998. The company introduced LigaSure, an Electrothermal Bipolar Vessel Sealing System (EBVS). This new technique uses a combination of pressure and bipolar thermal energy controlled by impedance measurements. Using direct pressure to compress the vessels and tissues, EBVS leads to a safe closure of arteries of up to 7 mm in diameter and veins of up to 12 mm in diameter [10, 11].

Compared to the conventional approach, the EBVS can lead to a significant reduction in the duration of surgery and the amount of blood loss [11]. The same has been demonstrated in thyroidectomies [2], in hysterectomies [22], and in splenectomies [7]. Currently, other manufacturing companies have also developed their own EBVS: for example, Erbe, Ethicon, BOWA, Olympus, and KLS Martin. ◄

The authors use the EBVS during cytoreduction, for example, when performing an omentectomy, a gastric resection, or in the division of mesentery, in order to reduce the duration of surgery and the amount of blood loss.

12.3 Ultrasound-Based Instruments

Example: Harmonic Scalpel Ultracision® (Ethicon)

Ultrasonic scalpel ("Harmonic") is a surgical instrument that can be used to simultaneously cauterize and cut tissues (Fig. 12.6). Its

Fig. 12.6 Handpiece Ultracision (with permission of company (Johnson & Johnson))

mechanism of action lies in the fact that the active blade converts vibrational energy into mechanical energy, resulting in a surgical dissection and simultaneous hemostasis. The active blade cuts through tissue by vibrating in the range of 20,000–60,000 Hz. The vibration cuts through the tissue and seals it using protein denaturation rather than heat. A good analogy is whisking an egg white: another example of denaturation of protein through vibration rather than heat.

This method is used in abdominal surgery, for example, when performing partial liver resections [5, 14, 24], rectal resections [1], colon resections [8], and gastrectomies [4] as well as in ENT procedures [13].

The vibration of the active blade (55.5 kHz) results in volume changes in tissue, which leads to the formation of vapor bubbles at body temperature. In connective tissue, the formation of bubbles results in the dissection of the tissue layers. In addition, the high-frequency vibration of the active blade also leads to the defragmentation of protein compounds and thus to hemostasis. This effect can already be observed at a low-temperature range from 37 °C to a maximum of 63 °C. Prolonged exposure to locally applied energy leads to a rise in temperature, which releases water vapor (at 63–100 °C) and later to the denaturation of protein at a maximum temperature of 150 °C. As is the case with defragmentation, the denaturation also leads

to hemostasis [12]. Thus, the tissue dissection offers simultaneous hemostasis without any current flowing through the patient. Ultrasonic-based instruments do not produce any burns, electric shocks, or tissue damage related to the leakage of current. The tissue damage through heat extends up to a maximum depth of 50–150 μm [21]. Studies by Meurisse et al. [16] showed that the postoperative analgesic consumption following thyroid resections using an ultrasonic scalpel was significantly lower in comparison to analgesic consumption when monopolar diathermy was used. This was probably due to the reduction in tissue damage in the operating area. And there are other advantages of using an ultrasonic scalpel: they produce no smoke and afford a better view of the operating area by comparison with monopolar diathermy or laser applications. Moreover, many studies have also demonstrated a shorter operation time [15].

The authors have had a positive experience when using the ultrasonic scalpel. Especially in laparoscopic procedures, the ultrasonic scalpel results in better hemostasis, more precise tissue dissection, and shorter duration of surgery. However, while using the ultrasonic scalpel, vessels larger than 5 mm in diameter must be either ligated or clipped [25]. During cytoreduction, the ultrasonic scalpel is particularly helpful for small and large bowel resection, omentectomy, and lymphadenectomy (Fig. 12.7). ◄

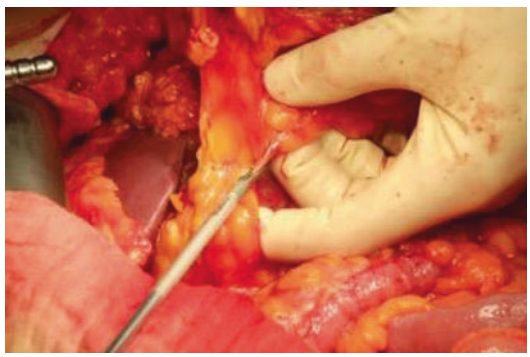


Fig. 12.7 Omentectomy with Ultracision

12.4 Water Jet Dissection

Example: Hydro-Jet (Euromed Medizintechnik)

Using a high-pressure water jet for cutting was initially developed in the industrial field. For its application in surgery, a number of modifications were carried out in the nozzles and pressure parameters before it could be used safely for cutting and dissection.

Initial experiments were carried out by Papachristou and Bengmark in 1982. They did the initial clinical research to implement this technology. Since 1996, many commercial devices have become available: two among them are the Handy-Jet (Saphir Medical S.A., Dardilly, France) and Hydro-Jet (Euromed Medizintechnik, A. Pein, Schwerin, Germany).

The jet cutter uses a high-pressure water jet dissector with pressures ranging between 20 and 50 bar and a nozzle with a diameter of 0.1–0.2 mm. A water jet of this quality allows for liver resection, separating the parenchyma from the biliary and vessels according to their degree of hardness. The remaining vessels and biliary structures can then be selectively clipped and divided.

This technique has been mainly used during liver resections [18, 19]. Its use has also been described in other parenchymatous organs such as the brain [9] and the kidney [26]. We usually use the water jet dissector in liver resections and in peritonectomy (Figs. 12.8 and 12.9). Because the vessels can be easily identified and ligated or clipped, the blood loss is minimal. The peritoneum can also be stripped off easily with the help of a water jet dissector. ◄

12.4.1 Argon Plasma Coagulation (APC)

In argon plasma coagulation (e.g., Argon Plasma Coagulator 2 from ERBE; PlasmaJet® from Plasma Surgical Ltd. or the KLS-Martin Argon

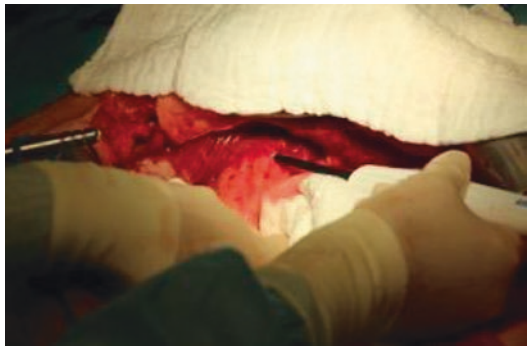


Fig. 12.8 Deperitonealization with Hydro-Jet

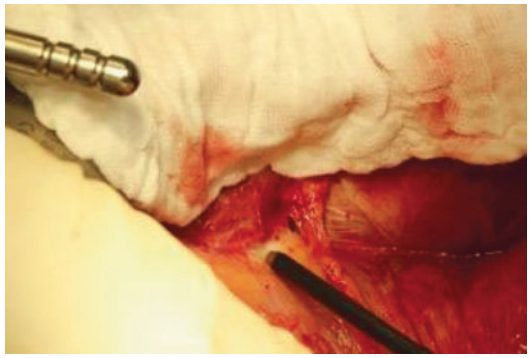


Fig. 12.9 Peritonectomy with Hydro-Jet ®: thermal dissection

Beam System), electrical energy is transmitted through conductive (ionized) gaseous argon over the tissue from a distance. The energy transfer takes place without direct contact to the tissues. One has to be very careful while doing so, since the probe is brought close to the tissues and the ionized gas is applied in short pulses. The sensitive and the deeper structures are spared and preserved in this technique. A quick hemostasis can be achieved over a large raw area because it coagulates the capillaries and small blood vessels. Since there is no flow of electric current, there is no risk of electric burns. Another advantage of APC is the absence of muscular fasciculation—this is especially beneficial while stripping the peritoneum from the diaphragmatic surfaces. The single-use handpieces with a diameter of 5 mm are also available in a length of 7, 12, or 28 cm for laparoscopic use.

This principle can be applied, for example, in the peritonectomy. Depending on the high-frequency power and the application time, APC can cut tissue while simultaneously coagulating smaller superficial bleeding. The argon plasma technology thus facilitates deperitonealization and transection of the liver parenchyma with minimal bleeding. But due to the higher cost and the problematic application of argon plasma in poorly visible areas, we generally prefer to use blunt dissection or preparation with bipolar scissors in deperitonealization.

12.4.2 Nd:YAG Laser

Another recent method of tissue-parenchymal division using the principle of thermally induced tissue destruction is the YAG laser (neodymium-doped yttrium aluminum garnet laser) with a wavelength of 1064 nm. The laser is delivered through a glass fiber of about 400–600 microns in diameter, which is placed in a special handle. The target acquisition takes place using a pilot laser beam. It is operated with a laser beam of up to 50 watts and a pulse duration of 1 to 2 seconds. In order to minimize the risk of bowel perforation, strictly adhering to the safe distance of about 1 cm from the tissues is essential. Our experience in peritonectomy with the laser procedure is limited to a few interventions.

12.5 Conclusion

Currently, the surgical armamentarium is full of various electrosurgical and other devices which can be of immense use while performing cytoreductive surgeries. There are no studies available in the medical literature to suggest which one is ideal for a particular operative step. The decision to use a device is usually based on its availability and the operating surgeons' experience and comfort in using it.

Table 12.1 Advantages, disadvantages, and application examples of the preparation devices

	Advantages	Disadvantages	Heat-induced lateral damage	Application
Monopolar	Fast cutting and coagulation	Risk of cautery plate injury, no closure of large vessels, disturbances in ECG readings and in pacemaker	3.5 mm (60 W, 1 s) >20 mm (60 W, 2 s)	Entering the abdominal cavity, preparation of avascular layer peritonectomy
Bipolar	Fast cutting and coagulation; no disturbances in ECG and in pacemaker	No closure of large vessels	2.2 mm (60 W, 1 s) 3.6 mm (60 W, 2 s)	During lymphadenectomy and peritonectomy
Electrothermal bipolar device (e.g., LigaSure)	Safe sealing of vessels up to 7 mm	Two step approach—sealing and cutting	2.8 mm (automatic)	Cutting vascular structures like mesentery, during lymphadenectomy
Ultrasound-based instruments (Ultracision)	Fast, easy, can be used for layer dissection	No secure close of vessels >3 mm	1.3 mm (level 3, 1 s) 1.8 mm (level 5, 1 s) 1.6 mm (level 3, 2 s)	Laparoscopic peritonectomy
Water jet dissection (e.g., Hydro-Jet dissection)	Gentle dissection of the tissues from delicate structures like vessels	Time-consuming	None	Parenchymal transection of the liver and kidney; peritonectomy
Argon plasma coagulation (APC)	Contact-less action	Expensive device; distance from the tissues crucial	Depending upon the distance from the tissues	Good hemostasis
Nd: YAG laser	Contact-less action	No tactile feel, nonselective dissection of the tissues, safety concerns	Depending upon the distance from the tissues	Peritonectomy

Generally, there remains a risk of lateral damage to the surrounding tissues while using these electrosurgical devices during surgery. This lateral damage depends upon the duration of the exposure and the strength of the effect. The risk of lateral damage is significantly higher with monopolar current, whereas it is comparatively very low when using an electrothermal bipolar device (e.g., LigaSure) or ultrasound-based instruments (Ultracision) (Table 12.1) [3, 6].

The authors use the following devices while performing cytoreductive surgeries:

- Peritonectomy: Blunt dissection, bipolar scissors, and Hydro-Jet
- Liver resection: Bipolar scissors, Hydro-Jet, argon beam, and Nd:YAG laser
- Resection of the omentum, stomach, small intestine, colon: Bipolar scissors, Ultracision, and LigaSure

References

1. Balogh A, et al. Total mesorectal excision with ultrasonic coagulation knife ("ULTRACISION") in surgery of rectal cancer. Orv Hetil. 2000;141:379–83.
2. Chavez V, et al. Comparative analysis between a bipolar vessel sealing and cutting device and the tie and suture technique in thyroidectomy: a randomized clinical trial. Surgery. 2016;161:477–84.
3. Druzijanic N, et al. Comparison of lateral thermal damage of the human peritoneum using monopolar diathermy, harmonic scalpel and LigaSure. Can J Surg. 2012;55:317–21.
4. Hang C, et al. Gastrectomy and D2 lymphadenectomy for gastric cancer: a meta-analysis comparing the harmonic scalpel to conventional techniques. Int J Surg Oncol. 2015;2015:397,260.
5. Hanyong S, et al. A prospective randomized controlled trial: comparison of two different methods of hepatectomy. Eur J Surg Oncol. 2014;41:243–8.
6. Hefermehl L, et al. Lateral temperature spread of monopolar, bipolar and ultrasonic instruments for robot-assisted laparoscopic surgery. BJUI Int. 2014;114:245–52.

7. Hou SY, et al. Randomized clinical trial of vessel sealing system (LigaSure) in esophagogastric devascularization and splenectomy in patients with portal hypertension. Am J Surg. 2011;202:82–90.
8. Hubner M, et al. Prospective randomized study of monopolar scissors, bipolar vessel sealer and ultrasonic shears in laparoscopic colorectal surgery. BJS. 2008;95:1098–104.
9. Jacob S, et al. Endoscopic use of the water jet dissector in the cerebral ventricle system—an experimental study. Zentralbl Neurochir. 2000;61:14–21.
10. Kennedy JS, et al. High-burst strength, feedback-controlled bipolar vessel sealing. Surg Endosc. 1998;12:876–8.
11. Landman J, et al. Evaluation of a vessel sealing system, bipolar electrosurgery, harmonic scalpel, titanium clips, endoscopic gastrointestinal anastomosis vascular staples and sutures for arterial and venous ligation in a porcine model. J Urol. 2003;169:697–700.
12. Lee SJ. Ultrasonic energy in endoscopic surgery. Yonsei Med J. 1999;40:545–9.
13. Leonard DS, et al. Evaluation of the ultracision ultrasonic dissector in head and neck surgery. Oper Tech Otolayngol Head Neck Surg. 2008;19:59–66.
14. Manasa DM, et al. Expert opinion on advanced techniques for hemostasis in liver surgery. EJSO. 2016;42:1597–607.
15. Matthews B, et al. Ultrasonic and nonultrasonic instrumentation: a systematic review and meta-analysis. Arch Surg. 2008;143:592–600.
16. Meurisse M, et al. Evaluation of the Ultracision ultrasonic dissector in thyroid surgery. Prospective randomized study. Ann Chir. 2000;125:468–72.
17. Parpala-Spårman, et al. Increasing numbers of ureteric injuries after the introduction of laparoscopic surgery. Scand J Urol Nephrol. 2008;42:422–7.
18. Rau HG, et al. Liver resection with the water jet: conventional and laparoscopic surgery. Chirurg. 1996;67:546–51.
19. Rau HG, et al. The use of water-jet dissection in open and laparoscopic liver resection. HPB (Oxford). 2008;10:275–80.
20. Selli C, et al. Delayed-onset ureteral lesions due to thermal energy: an emerging condition. Arch Ital Urol Androl. 2014;86:152–3.
21. Sherman JA, et al. Ultracision®: the harmonic scalpel and its possible uses in maxillofacial surgery. Br J Oral Maxillofac. 2000;38:530–2.
22. Silva F-L, et al. Randomized study of bipolar vessel sealing system versus conventional suture ligature for vaginal hysterectomy. Eur J Obstet Gynecol Reprod Biol. 2009;146:200–3.
23. Sutton PA, et al. Comparison of lateral thermal spread using monopolar and bipolar diathermy, the harmonic scalpel and the LigaSure. Br J Surg. 2010;97:428–33.
24. Takeshi A, et al. Skeletonization and isolation of the Glissonean and venous branches in liver surgery with an ultrasonic scalpel technology. Int Surg. 2015;100:1048–53.
25. Timm RW, et al. Sealing vessels up to 7 mm solely with ultrasonic technology. Med Devices Evidence Res. 2014;70:263–71.
26. Yi G, et al. Hydro-jet assisted laparoscopic partial nephrectomy with no renal arterial clamping: a preliminary study in a single center. Int Urol Nephrol. 2014;46:1289–93.

Part V

Treatment Option of Intraperitoneal Treatment and Experimental Approach

13 Application of IPC, HIPEC, and PIPAC

Kurt Van der Speeten, Maik Kilian, and Lieselotte Lemione

13.1 Introduction

In the past, oncologists assumed peritoneal carcinomatosis (PC) was identical to distant metastases and, as such, regarded it as an incurable component of intra-abdominal malignancy only open to palliative treatment options. Since the 1980s, different treatment hypotheses for patients with isolated peritoneal metastases and primary peritoneal malignancies have emerged, based on the revised hypothesis that PC is a local-regional disease, which therefore warrants a local-regional therapeutic approach [64, 101, 103]. These new treatment protocols are based on a combination of cytoreductive surgery (CRS) and hyperthermic intraperitoneal perioperative chemotherapy (HIPEC). In this setting, CRS aims at removing all macroscopic tumor, whereas the subsequent intraperitoneal (IP) chemotherapy seeks to eliminate all residual microscopic tumor [81]. CRS and HIPEC have evolved over three decades and have demonstrated encouraging clinical results in several phase II and III trials [6, 41, 47, 76, 95, 102, 127–129, 133]. The combined treatment modality is now the standard of care for peritoneal metastases from appendiceal epithelial cancers, colorectal cancer, and peritoneal mesothelioma [24, 42, 115]. Promising results have also been published for HIPEC in recurrent ovarian cancer [5, 102]. Although there is now a near universal standardization regarding CRS, based on the work by Sugarbaker et al. [108, 117], no standardized IP chemotherapy treatment modalities exist. This chapter reviews the different treatment modalities for IP chemotherapy, with a special focus on the pharmacologic variables.

13.2 Pharmacology

Pharmacology of IP chemotherapy can be subdivided into pharmacokinetics and pharmacodynamics (Table 13.1). Whereas pharmacokinetics describes what the body does to the drug, pharmacodynamics looks at what the drug does to the body. Pharmacokinetics of IP chemotherapy studies the alterations between the moment of administration of the IP chemotherapy and the cancer chemotherapy drug showing up at the level of the tumor nodule. The basic way of depicting pharmacokinetic data is by a concentration x

K. Van der Speeten (✉)
Ziekenhuis Oost-Limburg, Genk, Belgium

Faculty of Life Sciences, University Hasselt, Hasselt, Belgium
e-mail: Kurt.Vanderspeeten@zol.be

M. Kilian
Department of Surgery, Evangelische Elisabeth Klinik, Berlin, Germany

Evangelic Elisabeth Hosipital, Berlin, Germany
e-mail: maik.kilian@pgdiakonie.de

L. Lemione
Ziekenhuis Oost-Limburg, Genk, Belgium
e-mail: Lieselotte.Lemione@zol.be

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_13

Table 13.1 Pharmacokinetic and pharmacodynamic variables of intraperitoneal chemotherapy

Pharmacokinetic VR	Pharmacodynamic VR
Dose	Tumor nodule size
Volume	Density
Duration	Vascularity
Carrier solution	Interstitial fluid pressure
Pressure	Binding
Molecular weight	Temperature

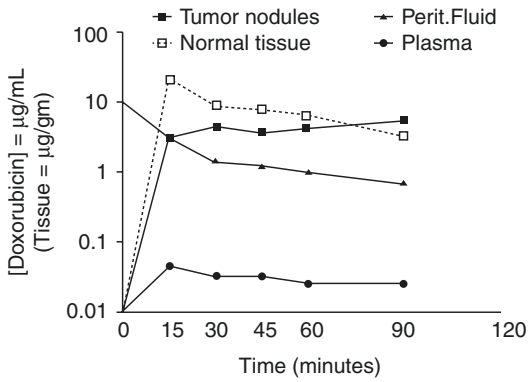


Fig. 13.1 Concentration-time graph of intraperitoneal doxorubicin during HIPEC. Doxorubicin concentration in plasma, peritoneal fluid, tumor nodules, and normal adjacent tissue. Data obtained from a single patient. (Adapted from [124])

time graph (Fig. 13.1). Pharmacodynamics subsequently looks into the effect of that cancer chemotherapy drug on the tumor. Pharmacodynamic data is depicted in a concentration x effect graph. Pharmacokinetic research seeks to deliver the chemotherapy in the most efficient way possible at the front door of the tumor.

13.3 Dose Intensification

The pharmacokinetic rationale of perioperative IP cancer chemotherapy is based on the dose intensification provided by the peritoneal-plasma barrier [13]. From peritoneal dialysis research, Dedrick et al. [15] concluded that the peritoneal permeability of a number of hydrophilic anticancer drugs may be considerably less than the plasma clearance of the same drug after IP administration. The peritoneal clearance is inversely proportional to the square root of its

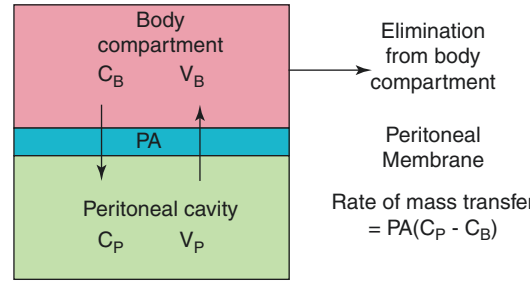


Fig. 13.2 The traditional two-compartment model of peritoneal transport; transfer of a drug from the peritoneal cavity to the blood occurs across the "peritoneal membrane." The permeability area result (PA) governs this transfer. PA is calculated by measuring the rate of drug disappearance from the cavity, which is divided by the overall concentration difference between the peritoneal cavity and the blood (or plasma). C_B = the free drug concentration in the blood (or plasma); V_B = volume of distribution of the drug in the body; C_p = the free drug concentration in the peritoneal fluid; V_p = volume of the peritoneal cavity [14, 54]

molecular weight and results in a higher concentration in the peritoneal cavity than in the plasma after IP administration [16, 31]. This dose intensification over the peritoneal membrane is merely an application of Fick's basic law of diffusion to transperitoneal transport. A simplified mathematical diffusion model considers the plasma to be a single compartment separated from another single compartment, the peritoneal cavity, by an effective membrane (Fig. 13.2).

This results in Eq. (13.1):

$$\text{Rate of mass transfer} = \text{PA}\left(C_{\text{Per}} - C_{\text{Bl}}\right) \qquad (13.1)$$

where PA = permeability area (PA = effective peritoneal contact area A × permeability P), C_{Per} = concentration in peritoneal cavity, and C_{Bl} = concentration in the blood [33]. This simple conceptual model indicates the importance of the effective contact area [32]. Although the equation permits calculation of the pharmacokinetic advantage, the model does not reveal anything about the specific penetration of the cancer chemotherapy drug into the tissue or tumor nodule [34], nor does it predict the value of the effective contact area. The model simply describes the transfer between two compartments. After CRS, this concentration difference increases the pos-

sibility of exposing residual tumor cells to high doses of chemotherapeutic agents with reduced systemic concentrations and lower systemic toxicity. This advantage is expressed by the area under the curve (AUC) ratios of intraperitoneal (IP) versus plasma (IV) exposure. Already at this point, one should realize that the pharmacokinetic advantage does not automatically translate into better pharmacodynamics and thus effect.

13.4 Timing of Cancer Chemotherapy in Relation to Timing of Surgical Intervention

In the clinical application of intraperitoneal chemotherapy in PC patients, IP chemotherapy can occur at four points in relation to the time of surgery.

13.4.1 Neoadjuvant Bidirectional Chemotherapy

First, neoadjuvant bidirectional chemotherapy uses both the intraperitoneal and intravenous routes of chemotherapy administration prior to the CRS. It has been suggested as an option for reducing dissemination to the extra-abdominal space, for testing the tumor biology, and for reducing the extent of small PC nodules. Theoretically, this approach, which is called neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), may facilitate definitive CRS after initial exploratory laparoscopy or laparotomy [137]. Radiological and clinical responses with NIPS have been reported by several groups [113, 137, 138, 141]. However, although NIPS may reduce the tumor load to be addressed by CRS, it has several disadvantages. Adhesions from prior surgical interventions may interfere with adequate intraperitoneal drug distribution, and, as complete responses are unusual, further cytoreduction-chemotherapy is necessary if the approach is to be curative. NIPS is reported to add to morbidity and mortality of further surgical treatment [25]. Furthermore, extensive fibrosis, as a response to chemotherapy, may occur and render judgments concerning the extent of PC difficult or impossible.

13.4.2 Hyperthermic Intraperitoneal Perioperative Chemotherapy (HIPEC)

Hyperthermic intraperitoneal perioperative chemotherapy is the most widely explored modality that has consistently clinically improved outcomes in many phase II and III trials [9, 19, 21, 35, 43, 51, 61, 127–129, 131, 132, 134].

13.4.3 Normothermic Intraperitoneal Preoperative Chemotherapy (NIPEC)

Over the past years, several experimental studies have been conducted to investigate what exactly is the added benefit of combining hyperthermia to the CRS alone [8, 45, 63, 80, 100, 140]. In vitro experiments performed by Michalakis et al. [80] indicate that short-term treatment of carcinoma cells with high concentrations of paclitaxel in both normothermic and hyperthermic settings is equally effective for cell growth arrest. Klaver et al. [63] used a rodent model of colorectal PC to demonstrate that the effectiveness of intraoperative intraperitoneal perfusion after CRS is not dependent on hyperthermia. Sørensen et al. [100] showed that NIPEC provided high intraperitoneal mitomycin C concentrations and increased bioavailability in extraperitoneal tissue, while hyperthermia at 41 °C did not modify the mitomycin C pharmacokinetics. On the other hand, Glehen et al. [45] evaluated the effect of hyperthermia on the pharmacokinetics and tissue distribution of intraperitoneal melphalan in a rodent model. They report that hyperthermia resulted in a decreased area under the curve (AUC) of melphalan in the peritoneal fluid, without increasing the plasma AUC, and increased intra-abdominal tissue concentrations.

Also, several clinical trials addressed the question regarding the additional effect of hyperthermia [105]. In a meta-analysis of the randomized controlled trials on adjuvant IP chemotherapy for resectable gastric cancer, Yan et al. [132] observed a trend toward survival improvement in patients receiving NIPEC. However, this was not significant with patients receiving early postoperative chemotherapy (EPIC) or delayed postoperative IP chemotherapy. A more recent meta-analysis comparing different methods of intraoperative and IP chemotherapy for patients with gastric cancer [53] showed that both HIPEC and NIPEC were associated with significant improvement in overall survival and that hyperthermia had no additional effect. In a retrospective analysis determining the risk factors of anastomotic leak after low colorectal resection, Averbach et al. [4] reported that anastomotic leakage was not compromised by NIPEC. Additional hyperthermia was associated with high leak rate when extensive colon resection was performed.

A randomized phase II clinical trial is currently ongoing at Ghent University Hospital. This trial compares normothermic versus hyperthermic IP perioperative chemotherapy after optimal CRS in patients diagnosed with PC from colorectal origin, including appendiceal mucinous neoplasms and the pseudomyxoma syndromes (https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-000701-77). Initial results from this trial indicate no difference in its morbidity or mortality between normothermic and hyperthermic oxaliplatin-based IP intraoperative chemotherapy [48].

13.4.4 Early Postoperative Intraperitoneal Chemotherapy (EPIC)

Early postoperative intraperitoneal chemotherapy has some conceptual advantages. It is administered shortly after CRS at the time of minimal residual tumor burden. Moreover, IP treatments initiated before wound healing occurs can minimize nonuniform drug distribution and eliminate residual cancer cell entrapment in postoperative fibrin deposits.

EPIC does not involve hyperthermia and is administered postoperatively (typically day 1 to day 4/5) through both an inflow catheter and outflow drains inserted during CRS, and it can be applied with or without HIPEC [109]. The proper selection of chemotherapy agents based on pharmacologic principles suggests the use of cell cycle-specific drugs such as 5-fluorouracil and the taxanes [112, 126]. This implies administrating multiple cycles, each with a dwell time of around 23 hours before renewal. This ensures that all the residual tumor cells are susceptible to the cell cycle-specific drug.

Disadvantages associated with EPIC are the increased risks of infection and postoperative complications. Vaillant et al. [122] performed a prospective multicenter phase III trial randomizing patients with stage III colon cancer to either resection with IV 5-fluorouracil during surgery and IP administration of 5-fluorouracil for 6 days thereafter or resection alone. They report that the addition of IP chemotherapy during a short period of time after resection did not significantly reduce the risk of morbidity. However, the results suggested that it should be associated with IV chemotherapy to reduce both local and distant recurrences. Lam et al. [69] compared the overall and the recurrence-free survival of patients treated with HIPEC with mitomycin C and EPIC with 5-fluorouracil versus patients treated with HIPEC alone using oxaliplatin and simultaneous IV infusion of 5-fluorouracil. They reported that survival did not differ between the two groups. However, patients that received the combination of HIPEC and EPIC experienced more grade III/IV complications. A randomized phase II trial is currently ongoing at the Memorial Sloan Kettering Cancer Center. This study compares the efficacy and toxicity of EPIC and HIPEC after optimal CRS in patients with neoplasms of the appendix, colon, or rectum with isolated PC (https://clinicaltrials.gov/ct2/show/NCT01815359).

13.4.5 Long-Term Combined Intraperitoneal and Systemic Chemotherapy

A number of randomized phase III trials demonstrate that intravenous plus intraperitoneal chemotherapy improves survival in patients with optimally debulked stage III ovarian cancer, compared to intravenous chemotherapy alone [1, 3, 38, 59, 77, 87, 135]. This approach may be used as a "chemotherapeutic bridging" between incomplete initial surgery and definitive cytoreduction or second-look surgery. This type of chemotherapy is an adjuvant and not a perioperative use of chemotherapy. However, failure analysis for CRS plus perioperative chemotherapy indicates recurrent cancer occurs most frequently within the abdominal and pelvic cavity [10]. Although systemic metastases occur, treatment failures rarely occur in the liver, the lungs, or other systemic sites.

In order to optimize the treatment of patients with PC, the greatest benefit will probably result from a combination of the four treatment strategies.

13.5 Intraperitoneal Perioperative Chemotherapy

13.5.1 Selection of Chemotherapy Drugs for IP Administration

Perhaps the most crucial aspect of an optimal IP chemotherapy treatment modality is the selection of a chemotherapy drug for use within the peritoneal space. The ideal drug for IP chemotherapy has a high peritoneal tissue concentration, because of direct IP administration, and a high penetration into the cancer nodule. This should occur in conjunction with slow diffusion of the chemotherapy solution through the capillary endothelium and deep into the subperitoneal space. Pharmacologic variables that should be taken into account are the route of administration—either intraperitoneal only or intraperitoneal combined with intravenous administration. The use of naked drugs versus nanoparticles, and single drugs versus multiple drugs, should also be considered. Table 13.2 summarizes the pharmacologic properties of the chemotherapy drugs most frequently selected for IP application [110].

To select a chemotherapy drug, one must know the response expected with this drug in patients with metastatic disease. The AUC ratio is important in that it estimates the dose intensity expected in the treatment of peritoneal metastases as compared to the toxicity experienced as a result of the systemic effects of the drug. As depicted in Table 13.2, many of the drugs selected for IP administration have a respectable AUC ratio. The drugs with the most favorable AUC ratios are mitomycin C, doxorubicin, gemcitabine, and pegylated liposomal doxorubicin.

The drugs that are used in the operating room are acute-phase drugs that can exert their effects in the absence of cell proliferation [126]. Those drugs that are used for EPIC are selected because they require cell division for their optimal effects. Such drugs are 5-fluorouracil and paclitaxel [112, 126].

The retention of the IP chemotherapy drug is crucial in drug selection in that a response of the peritoneal metastasis is dependent upon the time over which a particular concentration of drug is present at the surface of the nodule. Slow clearance of the intraperitoneal drug and prolonged hyperthermia would be expected to cause a maximal response. The heat-augmented drugs that have a prolonged retention are gemcitabine, pegylated liposomal doxorubicin, and ifosfamide.

Another strategy for prolonged exposure of peritoneal nodules to chemotherapy requires the continuous infusion of the drug. By combining intraoperative IV and intraoperative IP cancer chemotherapy, a bidirectional diffusion gradient is created through the intermediate tissue layer, which contains the tumor nodules, as depicted in Fig. 13.3. The best-studied intravenous chemotherapy agent targeted to peritoneal surfaces is ifosfamide. Continuous infusion of ifosfamide during HIPEC will result in cytotoxic levels of this drug within the peritoneal nodule over the 90 minutes

Table 13.2 Dosimetry and pharmacologic characteristics of cancer chemotherapy drugs used for intraperitoneal chemotherapy application

Drug	Type	Molecular weight(Daltons)	Dose	Exposure time	AUC ratio	Penetration depth	Thermal augmentation	Remarks
Cisplatin	Alkylator	300,1	50 mg/m^2–250 mg/m^2	30 minutes–20 hours	7,8–21	1–5 mm	Yes	Dose-limiting nephrotoxicity
Carboplatin	Alkylator	371,25	200 mg/m^2–800 mg/m^2	30 minutes–20 hours	1,9–10	0,5–9 mm	Yes	
Oxaliplatin	Alkylator	397,3	360 mg/m^2–460 mg/m^2	30 minutes–20 hours	3,5–16	1–2 mm	Yes	Dextrose-based carrier
Melphalan	Alkylator	305,2	50 mg/m^2–70 mg/m^2	90 minutes–120 minutes	93		Yes	Rapid degradation
Mitomycin C	Antitumor antibiotic	334,3	15 mg/m^2–35 mg/m^2	90 minutes–150 minutes	10–23,5	2 mm	Yes	
Doxorubicin	Antitumor antibiotic	579,99	15 mg/m^2–75 mg/m^2	90 minutes	162–579	4–6 cell layers	Yes	
Docetaxel	Antimicrotubule agent	861,9	45 mg/m^2–150 mg/m^2	30 minutes–23 hours	552	NA	Conflicting data	Cell cycle specific
Paclitaxel	Antimicrotubule agent	853,9	20 mg/m^2–180 mg total dose	30 minutes–23 hours	1000	> 80 layers	Conflicting data	Cell cycle specific
5-Fluorouracil	Antimetabolite	130,08	650 mg/m^2 for 5 days (EPIC)	23 hours	250	0,2 mm	Yes, mild	Cell cycle specific
Gemcitabine	Antimetabolite	299,5	50 mg/m^2–1000 mg/m^2	60 minutes–24 hours	500	NA	NA	Cell cycle specific
Pemetrexed	Antimetabolite	471,4	500 mg/m^2	24 hours	19,2	NA	NA	Cell cycle specific

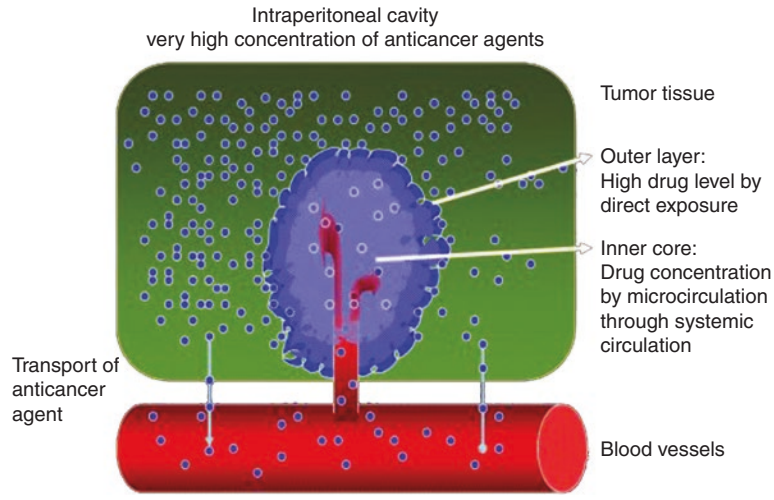


Fig. 13.3 Pharmacological concept of bidirectional intravenous and intraperitoneal chemotherapy. (Adapted from Fujiware K. et al. 2007, with permission)

of HIPEC [125]. Also, 5-fluorouracil has been used as a bolus infusion to augment the effect of hyperthermic intraperitoneal oxaliplatin [19].

A third mechanism for increased drug retention within the peritoneal space during HIPEC is repeated dosing of the chemotherapy agents. Verwaal et al. [128] used a triple dosing schedule for mitomycin C in order to increase the intraperitoneal exposure of this drug. They used half the drug dose at the initiation of HIPEC, one-quarter of it at 30 minutes, and another one-quarter of the dose at 60 minutes for a total of 90 minute HIPEC. By their calculation, this increased the effective dose of the mitomycin C.

In line with findings in systemic oncology, one can expect that the real question is not what the ideal drug is for IP chemotherapy, but rather what is the ideal drug for IP chemotherapy in this specific patient. The molecular heterogeneity within one tumor type of PC is staggering. These molecular subtypes have relevance for diagnosis, staging, prognosis, but increasingly so also for the choice of chemotherapeutic agent.

13.5.2 Dosage

The current dosing regimens of IP chemotherapy can be divided into body surface area (BSA)-based and concentration-based. Most groups use a drug dose based on calculated BSA (mg/m^2) in analogy to systemic chemotherapy regimens (Table 13.2). These regimens take BSA as a measure for the effective peritoneal contact area: the peritoneal surface area in the Dedrick formula. However, Rubin et al. [91] demonstrate that there is an imperfect correlation between actual peritoneal surface area and calculated BSA, and there may be sex differences in peritoneal surface areas, which in turn affects absorption characteristics. BSA-based IP chemotherapy will result in a fixed dose (BSA-based) diluted in varying volumes of perfusate—and thus different concentrations depending on substantial differences in the body composition of patients and differences in the HIPEC technique (open versus closed abdomen). From the Dedrick formula above, we know that peritoneal concentration and not peritoneal dose is the driving diffusion force. The importance of this has been discussed by Elias and Sideris [22]. In a clinical investigation where 2, 4, and 6 liters of perfusate solution was administered with a constant dose of chemotherapy, the more diluted intraperitoneal chemotherapy concentration retarded the clearance of chemotherapy and resulted in less systemic toxicity [111]. Therefore, it can be assumed that, with the diffusion model, less concentrated chemotherapy would penetrate less into the cancer nodules and into normal tissues. Concentration-based chemotherapy offers a more predictable exposure of the tumor nodules to the IP chemotherapy [78] and

thus more efficacy. Unfortunately, the price to be paid for a better prediction of the efficacy of the intraperitoneal chemotherapy is the high unpredictability of the plasmatic cancer chemotherapy levels and thus toxicity. Indeed, according to the abovementioned Dedrick formula of transport over the peritoneal membrane, an increase in the volume of concentration-based IP chemotherapy solution will cause an increase in both diffusion surface and the amount of drug transferred from peritoneal space to plasma [123]. These theoretical assumptions have since been validated; both in a preclinical PC rat model and in randomized clinical trial in humans [73, 74].

13.5.3 Carrier Solution

Hypotonic, isotonic, and hypertonic solutions with both low- and high-molecular-weight chemotherapy molecules have been explored. Salt-based, dextrose-based, hetastarch, or icodextrin solutions have been used [20, 67, 82–84, 86]. Moreover, the stability of the chemotherapeutic agent in the chosen carrier should also be considered. Mehta et al. [79] investigated the stability of oxaliplatin in both chloride-containing and chloride-deficient carrier solutions. They report that oxaliplatin concentration remained stable over a 2-hour period in a 5% dextrose-based solution. Increasing degradation rates of oxaliplatin were associated with increasing chloride concentrations, but this degradation was limited to a maximum of 10% after 30 minutes (the standard peritoneal perfusion time during HIPEC). Moreover, chloride seemed to promote the formation of the active cytotoxic drug form of oxaliplatin ($Pt(dach)Cl_2$) and therefore could enhance its cytotoxic effect. The ideal carrier solution should enhance the exposure of the peritoneal surface and residual tumor cells to the chemotherapeutic agent. This is especially important in the setting of EPIC, where maintenance of a high dwell volume of perfusate over a prolonged time period improves the distribution of the drug and the effectiveness of the treatment. In a HIPEC setting with a relatively short dwell time, one could theoretically expect a pharmacodynamic advantage of a hypotonic carrier through the mechanism of increased tissue and tumor absorption. Contrary to experimental studies supporting this hypothesis, Elias et al. [20] showed no increase in tumor penetration in humans. A concomitant high incidence (50%) of postoperative peritoneal bleeding and severe thrombocytopenia has contraindicated the further clinical use of hypotonic carriers.

13.5.4 Volume of Chemotherapy Solution

Since peritoneal metastases and free-floating tumor cells can be present anywhere on the peritoneal surface, the entire surface of the abdominal and pelvic cavity is the target. Substantial differences in the body composition of patients and differences in the actual HIPEC technique will result in a wide variety of perfusate volumes. In current practice, the volume of the perfusate is chosen quite arbitrarily. Based upon the above-stated equation concerning the mass transfer over the peritoneal-plasma membrane, increasing the solution-contact area A improves the mass transfer. Keshaviah et al. [57] demonstrated a linear rise in mass transfer in ten patients who were dialyzed with different volumes ranging from 0.5 up to 3 liters. Elias first published the importance of the volume of chemotherapy in determining systemic exposure to the drug [22]. Sugarbaker et al. [111] carried out a clinical investigation where 2 versus 4 versus 6 liters of chemotherapy solution were administered. The dose of chemotherapy solution in these studies was constant. They showed that a more diluted intraperitoneal chemotherapy concentration retarded the clearance of chemotherapy and led to a lesser systemic toxicity. It also must be assumed that the less concentrated chemotherapy would, according to the diffusion model, penetrate less into the cancer nodules and into normal tissues. These authors determined that it was necessary to regulate not only the chemotherapy dose but also the volume of chemotherapy solution to match the patient's BSA. A consistent drug dose and chemotherapy solution volume may be the optimal method to predict a maximal treatment in the abdomen with

a predictable bone marrow toxicity. Sugarbaker and colleagues suggested that variable volume is a dangerous practice with unpredictable systemic toxicities [111]. If the chemotherapy solution is administered until the abdomen is full, the contact area will increase. If the contact area is variable, the total absorption of drug cannot be predicted.

13.5.5 Temperature

Adding hyperthermia to IP chemotherapy will theoretically increase the tumor response by several mechanisms. First, heat alone has some direct antitumor effects. Although potentially important, the extent of the temperature elevation within the core of a tumor nodule is extremely limited. Selective cytotoxicity of malignant cells by heat is related to impaired DNA repair, increased protein denaturation, increased acidity, lysosomal activation, and increased apoptotic cell death [106].

A second and perhaps more important augmentation for hyperthermia is increased cytotoxicity with heat. Synergy between heat and cancer chemotherapy drugs is a complex pharmacological event. Augmented effects have been demonstrated for doxorubicin, cisplatin, mitomycin C, melphalan, oxaliplatin, and gemcitabine [116].

A third mechanism for increased cell kill of peritoneal metastases with hyperthermia is related to the increased depth of penetration of the cancer chemotherapy into tumor nodules. Jacquet et al. [55] reported increased tissue penetration of doxorubicin when the cancer chemotherapy solution was administered intraperitoneally at 43 °C. This increase in tissue concentration did not affect the pharmacokinetic advantages of the intraperitoneal administration. The elevated interstitial fluid pressure in tumor nodules compared to normal tissue is an acknowledged phenomenon [139]. A thermal dose-dependent decrease in interstitial fluid pressure in experimental solid tumors in an animal model has been reported by Leunig et al. [71] .

However, the level of hyperthermia must be matched to the intraperitoneal cancer chemotherapy drug. With cisplatin, the higher the temperature, the greater the increase in cytotoxicity. In addition, those chemotherapy drugs that function as prodrugs may have a temperature threshold for maximal augmentation of cytotoxicity. Mitomycin C and gemcitabine are included in this category. It has been shown that gemcitabine, when heated to 43 °C, is impaired in its cytotoxicity. It is postulated that the conversion of gemcitabine triphosphate (the active agent) may be inhibited intracellularly at higher temperatures. Therefore, with this drug intraperitoneal heat should be limited to 41–42 °C [107]. The same situation is likely to exist with mitomycin C.

Urano et al. [121] identified the cancer chemotherapy drugs that are augmented by moderate hyperthermia of 41 °C. The drugs with the largest increase in cytotoxicity were cisplatin, melphalan, ifosfamide, and cyclophosphamide. These "super drugs" for hyperthermia are not all appropriate for intraperitoneal administration. Ifosfamide and cyclophosphamide are prodrugs which are expected to show little cytotoxicity when present with cancer cells in a chemotherapy solution. However, cisplatin and melphalan are said to enter the peritoneal metastases well, and the hyperthermia at 43–44 °C augments their expected therapeutic effect considerably.

As hyperthermia is the main logistical challenge hindering the widespread use of IP chemotherapy, the assumed increased cytotoxicity of adding hyperthermia to IP chemotherapy suggested by basic science needs urgent validation in clinical trials.

13.5.6 Pressure

Dedrick et al. [15] postulated that the penetration distance is equal to the square root of the ratio of the tissue diffusivity and the rate constant for drug removal from the tissue $(D/k)^{1/2}$. Using a rat model, Flessner et al. [30] showed a doubling of the extracellular space in the anterior abdominal wall of rats when the pressure of intra-abdominal peritoneal dialysis solution was raised from 0 to 4 cm H_2O. An increased effective diffusivity was postulated.

Animal experiments confirmed the increased intratumoral accumulation and antitumor effect of intraperitoneal doxorubicin and cisplatin when the intra-abdominal pressure was raised [23, 56]. Using a pig model, Facy et al. [27] report that high pressure (25 cm H_2O) enhances diffusion of oxaliplatin in the visceral and parietal peritoneum. The combination of high pressure and hyperthermia resulted in the highest tissue concentration of oxaliplatin. Increased intra-abdominal pressure is thought to generate a convective flux that forces the drug from the peritoneal cavity into the subperitoneal tissue. At the same time, intra-abdominal pressure may counteract the hydraulic capillary pressure and slow the outflow of the drug to the body compartment. Measurement of local cisplatin concentrations along the radii of peritoneal tumor nodules showed platinum penetration far beyond the 1 mm limit advocated by Los et al. [75]. The clinical limit of usable intra-abdominal pressure enhancement is dictated by respiratory and hemodynamic tolerance [93]. Clinical applications of HIPEC in intra-abdominal pressure settings have so far been limited to palliation of debilitating malignant ascites with laparoscopic HIPEC at 10–15 mm Hg [26, 40].

A novel approach involving pressurized intraperitoneal aerosol chemotherapy (PIPAC) takes advantage of the physical properties of pressure by using capnoperitoneum at a pressure of 12 mmHg to enhance drug uptake [120]. PIPAC is a laparoscopic method for repetitive delivery of low-dose intraperitoneal chemotherapy as a pressurized aerosol, claiming enhanced tumor penetration, homogeneous intraperitoneal drug distribution, and limited local and systemic toxicity. Due to these promising initial results, PIPAC is currently increasingly implemented in multiple centers worldwide.

13.5.7 Duration

A wide variation in the duration (ranging from 30 to 120 minutes) of IP chemotherapy protocols are reported (Table 13.2). The dose-response curves and their dependency on exposure time have been mathematically modeled by Gardner [39]; according to this model, a plateau in tumor cell kill is reached, after which prolonged exposure time offers no further cytotoxic advantage. Theoretically, the most advantageous exposure time for cytotoxic effects in PC patients should be carefully weighed against systemic exposure and bone marrow toxicity and degradation processes. Duration of perioperative chemotherapy regimens should be pharmacology-driven and not arbitrary.

Of all variables, duration of IP chemotherapy is next to the choice of the drug the most important one. The best example for this is the combined negative randomized controlled trials (PRODIGE 7, COLOPEC, PROPHYLOCHIP) [46, 62, 88]. All three of them used a non-validated and flawed 30 minutes HIPEC with oxaliplatin. Already at the time of the study design, translational data were available demonstrating that oxaliplatin at 30 minutes was greatly inferior to oxaliplatin at 120 minutes [60]. Our group used apoptosis studies (activated caspase) to evaluate tumor cell death in PC nodules after CRS and HIPEC, once again both in a preclinical rat PC model and in human colorectal PC patients [73, 74]. In both instances the amount of apoptosis after 30 minutes of oxaliplatin-based HIPEC was very disappointing.

13.5.8 Irrigation Techniques

Although HIPEC has received the greatest attention in the search for eradication of the cellular component of peritoneal metastases following CRS, other mechanisms may be of value or less toxic. The mechanical removal of residual cancer cells through intraoperative irrigation prior to HIPEC may assist in the maximal eradication of cancer cells. Even after performing CRS for peritoneal metastases, large numbers of cancer cells will undoubtedly still be present within the ascites fluid: they will have been dislodged from the peritonectomy specimens or released from traumatized tumor nodules or the primary tumor [72]. In order to remove them, frequently throughout the CRS, dissection sites should be irrigated copiously and subsequently aspirated.

This frequent irrigation is to remove blood, tissue debris, and stray cancer cells as well as to clarify the anatomy for safe subsequent dissection. As a parietal peritonectomy procedure is completed, a large volume of warm saline irrigation should flood the peritonectomy site and the fluid should be vigorously manipulated to remove biologic fluids and cells. After the complete removal of the irrigation fluid, laparotomy pads or sterile towels should be placed in the peritonectomy site to prevent cancer cells from implanting within the raw surfaces as additional cytoreduction proceeds [94].

Upon completion of the cytoreduction but prior to HIPEC, an irrigation with a cytotoxic but non- chemotherapeutic agent should occur. Peroxide at 0.24% in 3 L of warm saline is used by Sugarbaker and colleagues [50]. Others have used 3 L of warm distilled water. Still others have utilized a diluted povidone-iodine solution [70]. Kuramoto et al. [66] have shown the value of mechanical cleansing of the peritoneal space with a large volume of fluid. They have used extensive intraperitoneal lavage (EIPL) to improve the survival of patients with gastric cancer and a high risk for implantation of gastric cancer cells. His strategy is to use 10 L of warm saline, 1 liter at a time in order to maximally irrigate away cancer cells that may be present.

13.6 Modes of Perfusion

Several different methodologies for administering HIPEC have been developed at centers experienced in the management of peritoneal surface malignancy.

13.6.1 Open Abdomen Technique

The open abdomen technique with a vapor barrier created by smoke evacuators has been used extensively at the MedStar Washington Hospital Center (Fig. 13.4) [108].

During the open coliseum technique (Fig. 13.5), the abdominal cavity is expanded after CRS by applying traction sutures on the skin, which elevates the skin edge and provides the so-called coliseum [114]. This technique assures that the chemotherapy solution reaches all abdominal recesses. A heater circulator is used to maintain moderate hyperthermia (41–43 °C) within the abdomen and pelvis. Most treatment centers use a single inflow catheter that is moved in a clockwise direction from the right upper quadrant to beneath the left hemidiaphragm, to the left paracolic sulcus, to the pelvis, to the right paracolic sulcus, and then back to the right upper quadrant. Direct inflow within the small bowel regions is avoided. To remove the chemotherapy solution from the peritoneal space, one or more outflow catheters are placed in separate abdominal areas. The flow of the chemotherapy solution is usually set between 1 and 1.5 L/min. During the open abdomen technique, the abdomen is covered with a plastic sheet. A cruciate incision is made within the sheet to provide an access for manipulation of the abdominal viscera and to allow the heated chemotherapy solution to access all dependent parts of the abdomen and pelvis to ensure good drug distribution. A smoke evacuator is used to clear aerosolized chemotherapy liberated during the procedure.

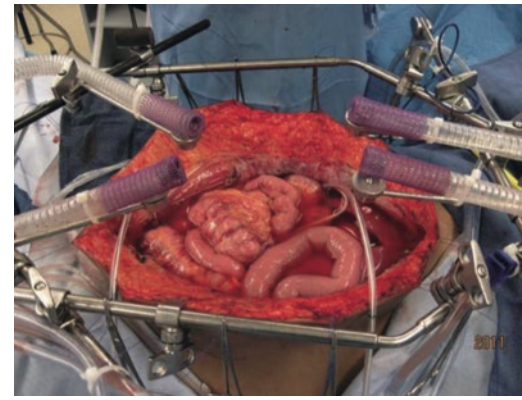


Fig. 13.4 The open abdomen technique to administer hyperthermic intraperitoneal perioperative chemotherapy (HIPEC). A vapor barrier is created by smoke evacuators [108]. (© 2017 with permission, Ciné-Med, Inc)

The concern with the open abdomen technique is the potentially hazardous occupational exposure: i.e., exposing the operating room staff to the chemotherapy solution in liquid or vaporized form. Several studies have been per-

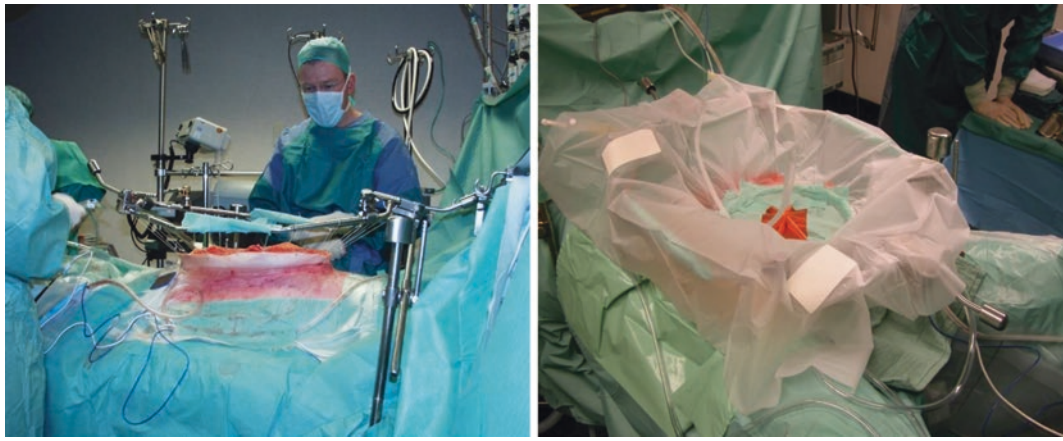


Fig. 13.5 During the open coliseum technique, the abdominal cavity is expanded after CRS by applying traction sutures on the skin, which elevates the skin edge and provides the so-called coliseum. The abdomen is covered with a plastic sheet. A cruciate incision is made within the sheet to provide an access for manipulation of the abdominal viscera and to allow the heated chemotherapy solution to access all dependent parts of the abdomen and pelvis in order to ensure good drug distribution. A smoke evacuator is used to clear aerosolized chemotherapy liberated during the procedure

formed to address this issue by measuring platinum levels in the blood and urine of healthcare workers and environmental (air and surfaces) samples during HIPEC [65, 92, 130]. They report that there is no risk of platinum exposure during the open coliseum technique when safety considerations are followed. Capron et al. [12] reported that double gloving can be used safely during HIPEC, as there was no detectable permeation of chemotherapy drugs during tests performed at 43 °C. These studies emphasize the need for a standardized protocol concerning HIPEC procedures with specific recommendations regarding environmental contamination risk management, personal protective equipment, and occupational health supervision [29].

13.6.2 Closed Abdomen Technique

Some groups close the abdomen prior to the HIPEC administration and then, following HIPEC, open the abdomen to perform anastomoses and to repair seromuscular tears, thereafter closing the abdominal incision. In this closed technique, the skin is only closed in a watertight fashion so that all of the structures of the anterior abdominal wall are thoroughly treated by the chemotherapy solution. Some use a totally closed technique. In this methodology, the CRS is performed, and the abdomen is irrigated prior to the performance of intestinal anastomoses and the closure of the abdominal incision. Tubes and drains are positioned prior to the definitive closure of the abdomen. After closure of the abdomen, the perfusion of the heated chemotherapy solution is started [44, 68].

Advantages associated with the closed abdomen technique are the ability to rapidly achieve and to maintain hyperthermia in addition to the increased safety for operating staff. Another advantage believed to be associated with the closed HIPEC technique is that increased intra-abdominal pressure may increase the chemotherapy penetration into tissue. However, Ortega-Deballon et al. [85] report, in an experimental study, that the open technique had higher systemic absorption and abdominal tissue penetration of oxaliplatin than the closed technique. Facy et al. [28] used a pig model to demonstrate that tissue concentration of oxaliplatin was higher in the open technique even when high pressure was used in the closed abdomen technique. They conclude that the use of high pressure during the

closed abdomen technique does not outweigh the drawbacks. These drawbacks include the risk of recurrence along the abdominal incision and suture lines and lack of uniform distribution of the heated solution [18, 104]. Preferential flow circuits exist and some peritoneal surfaces are underexposed, which increases the risk of recurrence in these undertreated recesses. An attempt to better distribute the chemotherapy can be made by manually agitating the abdominal wall during the perfusion.

In a clinical study including patients diagnosed with PC of different origins, Halkia et al. [49] evaluated the differences in intraoperative parameters in patients receiving either the closed or open HIPEC technique. They concluded that both methods are safe and efficient in the treatment of PC with equal morbidity and mortality. They recommend the closed technique as the method of choice for frail patients due to more stable hemodynamic parameters.

13.6.3 Semi-open/Semi-closed Abdomen Techniques

The peritoneal cavity expander (PCE) was first described by Fuijmura et al. [37]. During this technique, an acrylic cylinder is secured over the wound. This cylinder contains inflow and outflow catheters, is large enough to allow the small intestine to float in the heated perfusate, and allows manual manipulation of the perfusate. When compared with the closed perfusion technique, a more uniform drug distribution is achieved by temporarily increasing the volume of the peritoneal cavity. This method was mostly used for the treatment of gastric PC [52, 136].

The abdominal cavity expander, also referred to as the Landager technique, is a semi-closed abdomen technique with open abdomen, which ensures protection against potential hazardous occupational exposure and allows permanent access to the whole abdomen cavity, ensuring uniform drug distribution [7]. During this method, the skin edges are stapled watertight to a soft "abdominal cavity expander" supported by a Thompson self-retaining retractor positioned over the abdomen. In this way, the level of the liquid can be widely raised above the level of the skin edges. The anterior abdominal wall and the wall edges are constantly exposed to the liquid [89]. The abdominal cavity expander has been recently used by Frøysnes et al. [36] in the treatment of colorectal PC.

13.7 Novel Approaches: PIPAC

PIPAC (Fig. 13.6) is a novel approach to deliver IP chemotherapy to patients diagnosed with PC [120]. During PIPAC, a normothermic capnoperitoneum (at a pressure of 12 mmHg) is established through a laparoscopic access in an operating room equipped with a laminar airflow. A cytotoxic solution is nebulized into the abdominal cavity during 30 minutes and thereafter removed through a closed suction system [97, 98]. The hypothesis underlying this technique is that intraabdominal application of chemotherapy under pressure will enhance tumor drug uptake and that aerosolizing and spraying chemotherapy will enhance the area of peritoneal surface covered by the drug.

Several experimental and clinical studies have been conducted to test the abovementioned hypothesis [96–99, 119]. Solass et al. [98] used a pig model to evaluate the stain distribution and direct penetration into the peritoneum during nebulization of methylene blue. They report that the stained peritoneal surface was larger and that the direct penetration of the stain into the peritoneum was enhanced after aerosol application when compared to conventional peritoneal lavage. They also performed PIPAC with cisplatin and doxorubicin in three end-stage patients with advanced PC of gastric, appendiceal, and ovarian origin. They report that PIPAC required only 1/10 of the doxorubicin dose to achieve higher tumor concentrations as compared to HIPEC. Doxorubicin was not only detected in tumor nodules, but nuclear staining was also demonstrated throughout the peritoneum, penetrating deeply into the retroperitoneal fatty tissue. They concluded that PIPAC was well tolerated with excellent local exposure and low

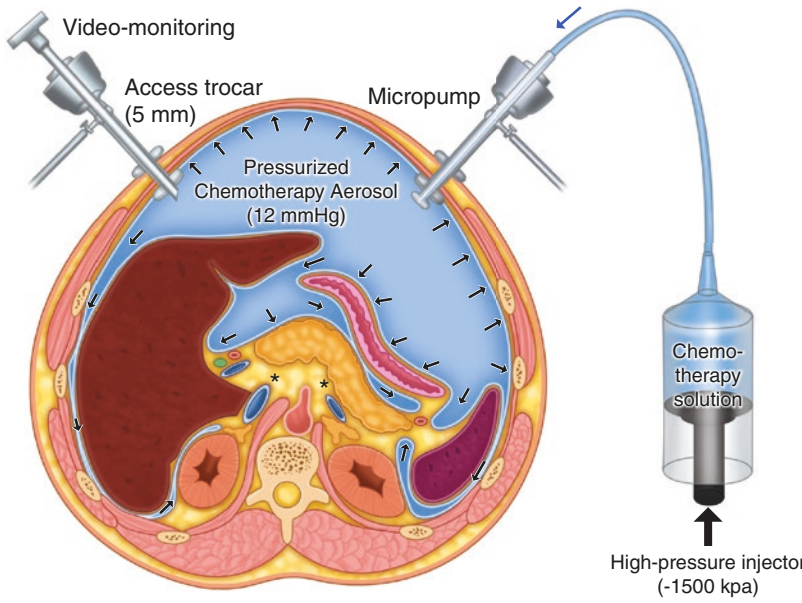


Fig. 13.6 During pressurized intraperitoneal aerosol chemotherapy (PIPAC), a normothermic capnoperitoneum (pressure of 12 mmHg) is established through a laparoscopic access in an operating room equipped with a laminar airflow. A cytotoxic solution is nebulized into the abdominal cavity during 30 minutes and thereafter removed through a closed suction system. (Adapted from [99])

systemic exposure [99]. Khosrawipour et al. [58] in 2019 also reported increased tissue penetration with doxorubicin-based PIPAC. Moreover, PIPAC appeared to be associated with very limited hepatic and renal toxicity even after repeated PIPAC [11, 90]. In a phase II study conducted by Tempfer et al. [119], 64 patients with recurrent ovarian, fallopian, or peritoneal cancer with PC were treated with three courses doxorubicin- and cisplatin-based PIPAC. PIPAC was well tolerated, easy to perform, and associated with an increased quality of life as compared to systemic chemotherapy, with the absence of grade IV toxicities. Demtröder et al. [17] performed a retrospective analysis including 17 patients with pretreated (surgery alone or combined with systemic chemotherapy) colorectal peritoneal metastases, who had received up to six cycles of oxaliplatin-based PIPAC. Repeated PIPAC with oxaliplatin induced regression of the peritoneal metastases, with low toxicities. However, it should be taken into account that patients included in these trials are highly selected and often have had extensive surgery and were already heavily pretreated with several lines of systemic chemotherapy. The potential limited access of the aerosolized chemotherapy due to the presence of adhesions is not considered. Moreover, incomplete responses warrant further cytoreduction. However, it has been reported that PIPAC should not be combined with CRS due to the potential of increased local toxicity [118].

Delivering chemotherapy as an aerosol might cause an increased risk of exposure to healthcare workers. The potentially hazardous occupational exposure when using PIPAC with cisplatin has been tested. The results indicated that PIPAC is in compliance with the labor safety laws and regulations of the European Community [96]. Further investigations are however needed to test the occupational safety and logistics when PIPAC is used with other cytostatic drugs.

Currently, there are two ongoing trials assessing PIPAC in women with gynecologic and gastric malignancies. The first ongoing trial is entitled: "A phase I, single-arm (non-randomized), open-label, dose escalation study with cisplatin and doxorubicin applied as pressurized intraperitoneal aerosol chemotherapy (PIPAC) in patients with recurrent ovarian cancer and peritoneal

carcinomatosis (PIPAC-OV2)" (EudraCT-Nr. 2014-001034-28). In this trial, safety and tolerability of doxorubicin- and cisplatin-based PIPAC in a dose escalation scheme will be investigated until dose-limiting toxicity is reached. Moreover, pharmacologic studies will be included regarding hematological, liver, and renal function as well as the determination of cisplatin and doxorubicin plasma levels. The second ongoing trial is entitled "Feasibility, efficacy and safety of pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in women with recurrent gastric cancer: an open-label, single-arm phase II clinical trial (PIPAC-GA1)" (https://clinicaltrials.gov/ct2/show/NCT01854255). In this trial, patients with recurrent gastric cancer will be treated with three cycles of doxorubicin- and cisplatin-based PIPAC. The primary outcome measure will be the clinical benefit rate according to the Response Evaluation Criteria in Solid Tumors (RECIST) after three cycles of PIPAC. Efficacy of this treatment will further be assessed by CT, tumor marker studies, survival, and safety.

In 2019, Alyami et al. [2] performed a systematic review of available data. They reported PIPAC to be feasible and safe. Data on objective response and quality of life were encouraging. Therefore, they propose PIPAC to be considered as a treatment option for refractory, isolated peritoneal metastasis of various origins. However, it needs to be validated by prospective studies.

Today, there is no phase III trial data available for PIPAC, emphasizing that this is still an experimental treatment that should be further investigated within the context of controlled clinical trials. This data will be important in identifying the role of PIPAC in the treatment of peritoneal surface malignancy patients. Today, PIPAC can play a role as a new palliative treatment option in highly selected patients with PC. Therefore, PIPAC cannot be directly compared with CRS and HIPEC, since the patient population and the intention to treat are different: palliative versus curative. Other potential roles of PIPAC should be explored—for example, in the neoadjuvant setting, to test tumor biology.

13.8 Conclusion

The combination of CRS and IP chemotherapy is now the standard of care for peritoneal metastases from appendiceal epithelial cancers, colorectal cancer, and peritoneal mesothelioma. Although there is a near universal standardization regarding CRS, there is still a much-needed standardization among the various IP chemotherapy treatment modalities used today in clinical practice. Pharmacologic evidence should be provided to answer important questions raised by the myriad of variables associated with IP chemotherapy. Tumor nodule apoptosis emerges as a valid pharmacologic endpoint in IP chemotherapy basic science. Furthermore, new and innovative IP chemotherapy concepts, like PIPAC, should be investigated in well-designed and adequately powered phase III clinical trials.

References

1. Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, Franklin EW, Clarke-Pearson DL, Malviya K, DuBeshter B. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med. 1996;335:1950–1955 [PMID: 8960474]. https://doi.org/10.1056/NEJM199612263352603.
2. Alyami M, Hübner M, Grass F, Bakrin N, Villeneuve L, Laplace N, Passot G, Glehen O, Kepenekian V. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol. 2019;20(7):e368–77. https://doi.org/10.1016/S1470-2045(19)30318-3.PMID: 31267971.
3. Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA. Gynecologic oncology G. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354:34–43 [PMID: 16394300]. https://doi.org/10.1056/NEJMoa052985.
4. Averbach AM, Chang D, Koslowe P, Sugarbaker PH. Anastomotic leak after double-stapled low colorectal resection. Dis Colon Rectum. 1996;39:780–787 [PMID: 8674371].
5. Bakrin N, Bereder JM, Decullier E, Classe JM, Msika S, Lorimier G, Abboud K, Meeus P, Ferron G, Quenet F, Marchal F, Gouy S, Morice P, Pomel C, Pocard M, Guyon F, Porcheron J, Glehen O. Group F. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal

Chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. Eur J Surg Oncol: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2013;39:1435–1443 [PMID: 24209430]. https://doi.org/10.1016/j.ejso.2013.09.030.

6. Baratti D, Kusamura S, Cabras AD, Bertulli R, Hutanu I, Deraco M. Diffuse malignant peritoneal mesothelioma: long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC). Eur J Cancer. 2013;49:3140–3148 [PMID: 23831335]. https://doi.org/10.1016/j.ejca.2013.05.027.
7. Benoit L, Cheynel N, Ortega-Deballon P, Giacomo GD, Chauffert B, Rat P. Closed hyperthermic intraperitoneal chemotherapy with open abdomen: a novel technique to reduce exposure of the surgical team to chemotherapy drugs. Ann Surg Oncol. 2008;15:542–546 [PMID: 17929098 PMCID: PMC2887654]. https://doi.org/10.1245/s10434-007-9635-x.
8. Bespalov VG, Kireeva GS, Belyaeva OA, Senchik KY, Stukov AN, Gafton GI, Soloviev LA, Vasilchenko MV, Guseinov KD, Alexeev VV, Belyaev AM. Intraoperative intraperitoneal chemoperfusion treatment with cisplatin and dioxadet on a model of peritoneal carcinomatosis in ovarian cancer: safety and efficacy evaluation. Vopr Onkol. 2015;61:647–652 [PMID: 26571838].
9. Bijelic L, Jonson A, Sugarbaker PH. Systematic review of cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy for treatment of peritoneal carcinomatosis in primary and recurrent ovarian cancer. Ann Oncol. 2007a;18:1943–1950 [PMID: 17496308]. https://doi.org/10.1093/annonc/mdm137.
10. Bijelic L, Yan TD, Sugarbaker PH. Failure analysis of recurrent disease following complete cytoreduction and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. Ann Surg Oncol. 2007b;14:2281–2288 [PMID: 17503156]. https://doi.org/10.1245/s10434-007-9410-z.
11. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). Ann Surg Oncol. 2013;20:2311–2316 [PMID: 23377563 PMCID: PMC3675273]. https://doi.org/10.1245/s10434-012-2840-2.
12. Capron A, Destree J, Jacobs P, Wallemacq P. Permeability of gloves to selected chemotherapeutic agents after treatment with alcohol or isopropyl alcohol. Am J Health Syst Pharm. 2012;69:1665–1670 [PMID: 22997120]. https://doi.org/10.2146/ajhp110733.
13. Ceelen WP, Flessner MF. Intraperitoneal therapy for peritoneal tumors: biophysics and clinical evidence. Nat Rev Clin Oncol. 2010;7:108–115 [PMID: 20010898]. https://doi.org/10.1038/nrclinonc.2009.217.
14. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst. 1997;89(7):480–7. [PMID: 9086004 Review]. https://doi.org/10.1093/jnci/89.7.480.
15. Dedrick RL, Myers CE, Bungay PM, DeVita VT Jr. Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep. 1978;62:1–11 [PMID: 626987].
16. Dedrick RL. Theoretical and experimental bases of intraperitoneal chemotherapy. Semin Oncol. 1985;12:1–6 [PMID: 4048968].
17. Demtroder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Color Dis. 2016;18:364–371 [PMID: 26400556]. https://doi.org/10.1111/codi.13130.
18. Elias D, Antoun S, Goharin A, Otmany AE, Puizillout JM, Lasser P. Research on the best chemohyperthermia technique of treatment of peritoneal carcinomatosis after complete resection. Int J Surg Investig. 2000;1:431–439 [PMID: 11341599].
19. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, Pignon JP, Drouard-Troalen L, Ouellet JF, Ducreux M. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol. 2002a;13:267–272 [PMID: 11886004].
20. Elias D, El Otmany A, Bonnay M, Paci A, Ducreux M, Antoun S, Lasser P, Laurent S, Bourget P. Human pharmacokinetic study of heated intraperitoneal oxaliplatin in increasingly hypotonic solutions after complete resection of peritoneal carcinomatosis. Oncology. 2002b;63:346–352 [PMID: 12417789]. https://doi.org/10.1159/000066229.
21. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, Ferron G, Guilloit JM, Meeus P, Goere D, Bonastre J. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27:681–685 [PMID: 19103728]. https://doi.org/10.1200/JCO.2008.19.7160.
22. Elias DM, Sideris L. Pharmacokinetics of heated intraoperative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis. Surg Oncol Clin N Am. 2003;12:755–769, xiv [PMID: 14567029].
23. Esquis P, Consolo D, Magnin G, Pointaire P, Moretto P, Ynsa MD, Beltramo JL, Drogoul C, Simonet M, Benoit L, Rat P, Chauffert B. High intra-abdominal pressure enhances the penetration and antitumor effect of intraperitoneal cisplatin on experimental peritoneal carcinomatosis. Ann Surg. 2006;244:106–112 [PMID: 16794395 PMCID: PMC1570583]. https://doi.org/10.1097/01.sla.0000218089.61635.5f.

24. Esquivel J, Piso P, Verwaal V, Bachleitner-Hofmann T, Glehen O, Gonzalez-Moreno S, Deraco M, Pelz J, Alexander R, Glockzin G. American Society of Peritoneal Surface Malignancies opinion statement on defining expectations from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer. J Surg Oncol. 2014;110:777–778 [PMID: 25043759]. https://doi.org/10.1002/jso.23722.
25. Esquivel J, Vidal-Jove J, Steves MA, Sugarbaker PH. Morbidity and mortality of cytoreductive surgery and intraperitoneal chemotherapy. Surgery. 1993;113:631–636 [PMID: 8506520].
26. Facchiano E, Scaringi S, Kianmanesh R, Sabate JM, Castel B, Flamant Y, Coffin B, Msika S. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of malignant ascites secondary to unresectable peritoneal carcinomatosis from advanced gastric cancer. Eur J Surg Oncol: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2008;34:154–158 [PMID: 17640844. https://doi.org/10.1016/j.ejso.2007.05.015.
27. Facy O, Al Samman S, Magnin G, Ghiringhelli F, Ladoire S, Chauffert B, Rat P, Ortega-Deballon P. High pressure enhances the effect of hyperthermia in intraperitoneal chemotherapy with oxaliplatin: an experimental study. Ann Surg. 2012;256:1084–1088 [PMID: 22634898]. https://doi.org/10.1097/SLA.0b013e3182582b38.
28. Facy O, Combier C, Poussier M, Magnin G, Ladoire S, Ghiringhelli F, Chauffert B, Rat P, Ortega-Deballon P. High pressure does not counterbalance the advantages of open techniques over closed techniques during heated intraperitoneal chemotherapy with oxaliplatin. Surgery. 2015;157:72–78 [PMID: 25027716]. https://doi.org/10.1016/j.surg.2014.06.006.
29. Ferron G, Simon L, Guyon F, Glehen O, Goere D, Elias D, Pocard M, Gladieff L, Bereder JM, Brigand C, Classe JM, Guilloit JM, Quenet F, Abboud K, Arvieux C, Bibeau F, De Chaisemartin C, Delroeux D, Durand-Fontanier S, Goasguen N, Gouthi L, Heyd B, Kianmanesh R, Leblanc E, Loi V, Lorimier G, Marchal F, Mariani P, Mariette C, Meeus P, Msika S, Ortega-Deballon P, Paineau J, Pezet D, Piessen G, Pirro N, Pomel C, Porcheron J, Pourcher G, Rat P, Regimbeau JM, Sabbagh C, Thibaudeau E, Torrent JJ, Tougeron D, Tuech JJ, Zinzindohoue F, Lundberg P, Herin F, Villeneuve L, Group B-RW. Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): a French multicentric survey. Eur J Surg Oncol the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015;41:1361–1367 [PMID: 26263848]. https://doi.org/10.1016/j.ejso.2015.07.012.
30. Flessner M, Henegar J, Bigler S, Genous L. Is the peritoneum a significant transport barrier in peritoneal dialysis? Perit Dial Int: journal of the International Society for Peritoneal Dialysis. 2003;23:542–549 [PMID: 14703194].
31. Flessner MF, Fenstermacher JD, Dedrick RL, Blasberg RG. A distributed model of peritoneal-plasma transport: tissue concentration gradients. Am J Phys. 1985;248:F425–435 [PMID: 3919596].
32. Flessner MF, Lofthouse J, Williams A. Increasing peritoneal contact area during dialysis improves mass transfer. J Am Soc Nephrol. 2001;12:2139–2145 [PMID: 11562413].
33. Flessner MF. The transport barrier in intraperitoneal therapy. Am J Physiol Renal Physiol. 2005;288:F433–442 [PMID: 15692055]. https://doi.org/10.1152/ajprenal.00313.2004.
34. Flessner MF. Intraperitoneal drug therapy: physical and biological principles. Cancer Treat Res. 2007;134:131–152 [PMID: 17633051].
35. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh HJ 3rd. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer. 2010;116:3756–3762 [PMID: 20564081]. https://doi.org/10.1002/cncr.25116.
36. Froysnes IS, Larsen SG, Spasojevic M, Dueland S, Flatmark K. Complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastasis in Norway: prognostic factors and oncologic outcome in a national patient cohort. J Surg Oncol. [PMID: 27173150]. 2016; https://doi.org/10.1002/jso.24290.
37. Fujimura T, Yonemura Y, Fushida S, Urade M, Takegawa S, Kamata T, Sugiyama K, Hasegawa H, Katayama K, Miwa K, et al. Continuous hyperthermic peritoneal perfusion for the treatment of peritoneal dissemination in gastric cancers and subsequent second-look operation. Cancer. 1990;65:65–71 [PMID: 2104572].
38. Gadducci A, Carnino F, Chiara S, Brunetti I, Tanganelli L, Romanini A, Bruzzone M, Conte PF. Intraperitoneal versus intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin in optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologico Nord-Ovest. Gynecol Oncol. 2000;76:157–162 [PMID: 10637064]. https://doi.org/10.1006/gyno.1999.5677.
39. Gardner SN. A mechanistic, predictive model of dose-response curves for cell cycle phase-specific and -nonspecific drugs. Cancer Res. 2000;60:1417–1425 [PMID: 10728708].
40. Garofalo A, Valle M, Garcia J, Sugarbaker PH. Laparoscopic intraperitoneal hyperthermic chemotherapy for palliation of debilitating malignant ascites. Eur J Surg Oncol: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2006;32:682–685 [PMID: 16631341]. https://doi.org/10.1016/j.ejso.2006.03.014.

41. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D. Association Francaise de C. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010a;17:2370–2377 [PMID: 20336386]. https://doi.org/10.1245/s10434-010-1039-7.
42. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer. 2010b;116:5608–5618 [PMID: 20737573]. https://doi.org/10.1002/cncr.25356.
43. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, Barone R, Yonemura Y, Cavaliere F, Quenet F, Gutman M, Tentes AA, Lorimier G, Bernard JL, Bereder JM, Porcheron J, Gomez-Portilla A, Shen P, Deraco M, Rat P. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol. 2004a;22:3284–3292 [PMID: 15310771]. https://doi.org/10.1200/JCO.2004.10.012.
44. Glehen O, Osinsky D, Cotte E, Kwiatkowski F, Freyer G, Isaac S, Trillet-Lenoir V, Sayag-Beaujard AC, Francois Y, Vignal J, Gilly FN. Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. Ann Surg Oncol. 2003;10:863–869 [PMID: 14527903].
45. Glehen O, Stuart OA, Mohamed F, Sugarbaker PH. Hyperthermia modifies pharmacokinetics and tissue distribution of intraperitoneal melphalan in a rat model. Cancer Chemother Pharmacol. 2004b;54:79–84 [PMID: 15048586]. https://doi.org/10.1007/s00280-004-0779-0.
46. Goéré D, Glehen O, Quenet F, et al. Second-look surgery plus hyperthermic intraperitoneal chemotherapy versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP-PRODIGE 15): a randomised, phase 3 study. BIG-RENAPE group. Lancet Oncol. 2020;21(9):1147–1154. https://doi.org/10.1016/S1470-2045(20)30322-3. Epub 2020 Jul 24.
47. Gonzalez Bayon L, Steiner MA, Vasquez Jimenez W, Asencio JM, Alvarez de Sierra P, Atahualpa Arenas F, Rodriguez del Campo J, Garcia Sabrido JL. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for the treatment of advanced epithelial ovarian carcinoma: upfront therapy, at first recurrence, or later? Eur J Surg Oncol: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2013;39:1109–1115 [PMID: 23870278]. https://doi.org/10.1016/j.ejso.2013.06.022.
48. Gremonprez F, Gossye H, Ceelen W. Use of hyperthermia versus normothermia during intraperitoneal chemoperfusion with oxaliplatin for colorectal peritoneal carcinomatosis: a propensity score matched analysis. Eur J Surg Oncol. 2019;45(3):366–70. https://doi.org/10.1016/j.ejso.2018.08.023. Epub 2018 Sep 6. PMID: 30243468.
49. Halkia E, Tsochrinis A, Vassiliadou DT, Pavlakou A, Vaxevanidou A, Datsis A, Efstathiou E, Spiliotis J. Peritoneal carcinomatosis: intraoperative parameters in open (coliseum) versus closed abdomen HIPEC. Int J Surg Oncol. 2015;2015:610597 [PMID: 25785194 PMCID: PMC4345051]. https://doi.org/10.1155/2015/610597.
50. Harrison LE, Tiesi G, Razavi R, Wang CC. A phase I trial of thermal sensitization using induced oxidative stress in the context of HIPEC. Ann Surg Oncol. 2013;20:1843–1850 [PMID: 23354567]. https://doi.org/10.1245/s10434-013-2874-0.
51. Helm CW, Richard SD, Pan J, Bartlett D, Goodman MD, Hoefer R, Lentz SS, Levine EA, Loggie BW, Metzinger DS, Miller B, Parker L, Spellman JE, Sugarbaker PH, Edwards RP, Rai SN. Hyperthermic intraperitoneal chemotherapy in ovarian cancer: first report of the HYPER-O registry. Int J Gynecol Cancer. 2010;20:61–69 [PMID: 20130504]. https://doi.org/10.1111/IGC.0b013e3181c50cde.
52. Hirose K, Katayama K, Iida A, Yamaguchi A, Nakagawara G, Umeda S, Kusaka Y. Efficacy of continuous hyperthermic peritoneal perfusion for the prophylaxis and treatment of peritoneal metastasis of advanced gastric cancer: evaluation by multivariate regression analysis. Oncology. 1999;57:106–114 [PMID: 10461056 DOI: 12016].
53. Huang JY, Xu YY, Sun Z, Zhu Z, Song YX, Guo PT, You Y, Xu HM. Comparison different methods of intraoperative and intraperitoneal chemotherapy for patients with gastric cancer: a meta-analysis. Asian Pac J Cancer Prev. 2012;13:4379–4385 [PMID: 23167347].
54. Jackman DM. Current options for systemic therapy in mesothelioma. Semin Thorac Cardiovasc Surg. 2009;21:154–158 [PMID: 19822287]. https://doi.org/10.1053/j.semtcvs.2009.06.010.
55. Jacquet P, Averbach A, Stuart OA, Chang D, Sugarbaker PH. Hyperthermic intraperitoneal doxorubicin: pharmacokinetics, metabolism, and tissue distribution in a rat model. Cancer Chemother Pharmacol. 1998;41:147–154 [PMID: 9443628].
56. Jacquet P, Stuart OA, Dalton R, Chang D, Sugarbaker PH. Effect of intraperitoneal chemotherapy and fibrinolytic therapy on tumor implantation in wound sites. J Surg Oncol. 1996;62:128–134 [PMID: 8649039]. https://doi.org/10.1002/(SICI)1096-9098(199606)62:2<128::AID-JSO9>3.0.CO;2-A.
57. Keshaviah P, Emerson PF, Vonesh EF, Brandes JC. Relationship between body size, fill volume, and mass transfer area coefficient in peritoneal dialysis. J Am Soc Nephrol. 1994;4:1820–1826 [PMID: 8068881].

58. Khosrawipour V, Reinhard S, Martino A, Khosrawipour T, Arafkas M, Mikolajczyk A. Increased tissue penetration of doxorubicin in pressurized intraperitoneal aerosol chemotherapy (PIPAC) after high-intensity ultrasound (HIUS). Int J Surg Oncol. 2019;2019:6185313. https://doi.org/10.1155/2019/6185313. eCollection 2019. PMID: 31915548.
59. Kirmani S, Braly PS, McClay EF, Saltzstein SL, Plaxe SC, Kim S, Cates C, Howell SB. A comparison of intravenous versus intraperitoneal chemotherapy for the initial treatment of ovarian cancer. Gynecol Oncol. 1994;54:338–344 [PMID: 8088611].
60. Kirstein MN, Root SA, Moore MM, Wieman KM, Williams BW, Jacobson PA, Marker PH, Tuttle TM. Exposure-response relationships for oxaliplatin-treated colon cancer cells. Anti-Cancer Drugs. 2008;19(1):37–44. PMID: 18043128. https://doi.org/10.1097/CAD.0b013e3282f07791.
61. Klaver CE, Musters GD, Bemelman WA, Punt CJ, Verwaal VJ, Dijkgraaf MG, Aalbers AG, van der Bilt JD, Boerma D, Bremers AJ, Burger JW, Buskens CJ, Evers P, van Ginkel RJ, van Grevenstein WM, Hemmer PH, de Hingh IH, Lammers LA, van Leeuwen BL, Meijerink WJ, Nienhuijs SW, Pon J, Radema SA, van Ramshorst B, Snaebjornsson P, Tuynman JB, Te Velde EA, Wiezer MJ, de Wilt JH, Tanis PJ. Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial. BMC Cancer. 2015;15:428 [PMID: 26003804 PMCID: PMC4492087. https://doi.org/10.1186/s12885-015-1430-7.
62. Klaver CEL, Wisselink DD, Punt CJA, Snaebjornsson P, Crezee J, Aalbers AGJ, Brandt A, Bremers AJA, Burger JWA, Fabry HFJ, Ferenschild F, Festen S, van Grevenstein WMU, Hemmer PHJ, de Hingh IHJT, Kok NFM, Musters GD, Schoonderwoerd L, Tuynman JB, van de Ven AWH, van Westreenen HL, Wiezer MJ, Zimmerman DDE, van Zweeden AA, Dijkgraaf MGW, Tanis PJ. COLOPEC collaborators group. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open-label, randomised trial. Lancet Gastroenterol Hepatol. 2019;4(10):761–70. https://doi.org/10.1016/S2468-1253(19)30239-0. Epub 2019 Jul 29. PMID: 31371228.
63. Klaver YL, Hendriks T, Lomme RM, Rutten HJ, Bleichrodt RP, de Hingh IH. Hyperthermia and intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis: an experimental study. Ann Surg. 2011;254:125–130 [PMID: 21502859]. https://doi.org/10.1097/SLA.0b013e3182197102.
64. Koga S, Maeta M, Shimizu N, Osaki Y, Hamazoe R, Oda M, Karino T, Yamane T. Clinical effects of total-body hyperthermia combined with anticancer chemotherapy for far-advanced gastrointestinal cancer. Cancer. 1985;55:1641–1647 [PMID: 3978559].
65. Konate A, Poupon J, Villa A, Garnier R, Hasni-Pichard H, Mezzaroba D, Fernandez G, Pocard M. Evaluation of environmental contamination by platinum and exposure risks for healthcare workers during a heated intraperitoneal perioperative chemotherapy (HIPEC) procedure. J Surg Oncol. 2011;103:6–9 [PMID: 20886552]. https://doi.org/10.1002/jso.21740.
66. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, Yonemura Y, Baba H. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg. 2009;250:242–246 [PMID: 19638909]. https://doi.org/10.1097/SLA.0b013e3181b0c80e.
67. Kusamura S, Dominique E, Baratti D, Younan R, Deraco M. Drugs, carrier solutions and temperature in hyperthermic intraperitoneal chemotherapy. J Surg Oncol. 2008;98:247–252 [PMID: 18726886]. https://doi.org/10.1002/jso.21051.
68. Kusamura S, Younan R, Baratti D, Costanzo P, Favaro M, Gavazzi C, Deraco M. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique. Cancer. 2006;106:1144–1153 [PMID: 16456817]. https://doi.org/10.1002/cncr.21708.
69. Lam JY, McConnell YJ, Rivard JD, Temple WJ, Mack LA. Hyperthermic intraperitoneal chemotherapy + early postoperative intraperitoneal chemotherapy versus hyperthermic intraperitoneal chemotherapy alone: assessment of survival outcomes for colorectal and high-grade appendiceal peritoneal carcinomatosis. Am J Surg. 2015;210:424–430 [PMID: 26051744]. https://doi.org/10.1016/j.amjsurg.2015.03.008.
70. Lang-Lazdunski L, Bille A, Papa S, Marshall S, Lal R, Galeone C, Landau D, Steele J, Spicer J. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine, prophylactic radiotherapy, and systemic chemotherapy in patients with malignant pleural mesothelioma: a 10-year experience. J Thorac Cardiovasc Surg. 2015;149:558–565; discussion 565-556 [PMID: 25726878]. https://doi.org/10.1016/j.jtcvs.2014.10.041.
71. Leunig M, Goetz AE, Dellian M, Zetterer G, Gamarra F, Jain RK, Messmer K. Interstitial fluid pressure in solid tumors following hyperthermia: possible correlation with therapeutic response. Cancer Res. 1992;52:487–490 [PMID: 1728421].
72. Lloyd JM, McIver CM, Stephenson SA, Hewett PJ, Rieger N, Hardingham JE. Identification of early-stage colorectal cancer patients at risk of relapse post-resection by immunobead reverse transcription-PCR analysis of peritoneal lavage fluid for malignant cells. Clin Cancer Res. 2006;12:417–423 [PMID: 16428481]. https://doi.org/10.1158/1078-0432.CCR-05-1473.
73. Lemoine L, Thijssen E, Carleer R, Geboers K, Sugarbaker P, van der Speeten K. Body surface area-based vs concentration-based perioperative intraperitoneal chemotherapy after optimal cyto-

reductive surgery in colorectal peritoneal surface malignancy treatment: COBOX trial. J Surg Oncol. 2019a;119(7):999–1010. https://doi.org/10.1002/jso.25437. Epub 2019 Mar 5.
74. Lemoine L, Thijssen E, Carleer R, Cops J, Lemmens V, Eyken PV, Sugarbaker P, der Speeten KV. Body surface area-based versus concentration-based intraperitoneal perioperative chemotherapy in a rat model of colorectal peritoneal surface malignancy: pharmacologic guidance towards standardization. Oncotarget. 2019b;10(14):1407–24. https://doi.org/10.18632/oncotarget.26667. eCollection 2019 Feb 15. PMID: 30858926.
75. Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. Cancer Chemother Pharmacol. 1991;28:159–165 [PMID: 1855272].
76. Marcotte E, Dube P, Drolet P, Mitchell A, Frenette S, Leblanc G, Leclerc YE, Sideris L. Hyperthermic intraperitoneal chemotherapy with oxaliplatin as treatment for peritoneal carcinomatosis arising from the appendix and pseudomyxoma peritonei: a survival analysis. World J Surg Oncol. 2014;12:332 [PMID: 25380618 PMCID: PMC4233099]. https://doi.org/10.1186/1477-7819-12-332.
77. Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, Wadler S, Sickel J. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol. 2001;19:1001–1007 [PMID: 11181662].
78. Mas-Fuster MI, Ramon-Lopez A, Nalda-Molina R. Importance of standardizing the dose in hyperthermic intraperitoneal chemotherapy (HIPEC): a pharmacodynamic point of view. Cancer Chemother Pharmacol. 2013;72:273–274 [PMID: 23736155]. https://doi.org/10.1007/s00280-013-2204-z.
79. Mehta AM, Van den Hoven JM, Rosing H, Hillebrand MJ, Nuijen B, Huitema AD, Beijnen JH, Verwaal VJ. Stability of oxaliplatin in chloride-containing carrier solutions used in hyperthermic intraperitoneal chemotherapy. Int J Pharm. 2015;479:23–27 [PMID: 25535649]. https://doi.org/10.1016/j.ijpharm.2014.12.025.
80. Michalakis J, Georgatos SD, de Bree E, Polioudaki H, Romanos J, Georgoulias V, Tsiftsis DD, Theodoropoulos PA. Short-term exposure of cancer cells to micromolar doses of paclitaxel, with or without hyperthermia, induces long-term inhibition of cell proliferation and cell death in vitro. Ann Surg Oncol. 2007;14:1220–1228 [PMID: 17206477]. https://doi.org/10.1245/s10434-006-9305-4.
81. Mirnezami R, Mehta AM, Chandrakumaran K, Cecil T, Moran BJ, Carr N, Verwaal VJ, Mohamed F, Mirnezami AH. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. Br J Cancer. 2014;111:1500–1508 [PMID: 25225906 PMCID: PMC4200082]. https://doi.org/10.1038/bjc.2014.419.
82. Mohamed F, Marchettini P, Stuart OA, Yoo D, Sugarbaker PH. A comparison of hetastarch and peritoneal dialysis solution for intraperitoneal chemotherapy delivery. Eur J Surg Oncol: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2003a;29:261–265 [PMID: 12657237].
83. Mohamed F, Stuart OA, Sugarbaker PH. Pharmacokinetics and tissue distribution of intraperitoneal docetaxel with different carrier solutions. J Surg Res. 2003b;113:114–120 [PMID: 12943819].
84. Mohamed F, Sugarbaker PH. Carrier solutions for intraperitoneal chemotherapy. Surg Oncol Clin N Am. 2003;12:813–824 [PMID: 14567033].
85. Ortega-Deballon P, Facy O, Jambet S, Magnin G, Cotte E, Beltramo JL, Chauffert B, Rat P. Which method to deliver hyperthermic intraperitoneal chemotherapy with oxaliplatin? An experimental comparison of open and closed techniques. Ann Surg Oncol. 2010;17:1957–1963 [PMID: 20143265]. https://doi.org/10.1245/s10434-010-0937-z.
86. Pestieau SR, Schnake KJ, Stuart OA, Sugarbaker PH. Impact of carrier solutions on pharmacokinetics of intraperitoneal chemotherapy. Cancer Chemother Pharmacol. 2001;47:269–276 [PMID: 11320672].
87. Polyzos A, Tsavaris N, Kosmas C, Giannikos L, Katsikas M, Kalahanis N, Karatzas G, Christodoulou K, Giannakopoulos K, Stamatiadis D, Katsilambros N. A comparative study of intraperitoneal carboplatin versus intravenous carboplatin with intravenous cyclophosphamide in both arms as initial chemotherapy for stage III ovarian cancer. Oncology. 1999;56:291–296 [PMID: 10343192]. https://doi.org/10.1159/000011980.
88. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. J Clin Oncol. 2018;36:LBA3503.
89. Rat P, Benoit L, Cheynel N, Osmak L, Favoulet P, Peschaud F, Chauffert B, Favre JP. Intraperitoneal chemo-hyperthermia with "overflow" open abdomen. Ann Chir. 2001;126:669–671 [PMID: 11676240].
90. Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. World J Surg Oncol. 2016;14:128 [PMID: 27125996 PMCID: PMC4850728. https://doi.org/10.1186/s12957-016-0892-7.
91. Rubin J, Clawson M, Planch A, Jones Q. Measurements of peritoneal surface area in man

and rat. Am J Med Sci. 1988;295:453–458 [PMID: 3287918].
92. Schenk KE, Schierl R, Angele M, Burkhart-Reichl A, Glockzin G, Novotny A, Nowak D. Cisplatin and oxaliplatin surface contamination in intensive care units (ICUs) and hospital wards during attendance of HIPEC patients. Int Arch Occup Environ Health [PMID: 27142971]. 2016; https://doi.org/10.1007/s00420-016-1137-3.
93. Schluermann CN, Hoeppner J, Benk C, Schmidt R, Loop T, Kalbhenn J. Intra-abdominal pressure, cardiac index and vascular resistance during hyperthermic intraperitoneal chemotherapy: a prospective observational study. Minerva Anestesiol. 2016;82:160–169 [PMID: 25971283].
94. Sethna KS, Sugarbaker PH. New prospects for the control of peritoneal surface dissemination of gastric cancer using perioperative intraperitoneal chemotherapy. Cancer Chemother. 2004;2:79–84.
95. Sideris L, Mitchell A, Drolet P, Leblanc G, Leclerc YE, Dube P. Surgical cytoreduction and intraperitoneal chemotherapy for peritoneal carcinomatosis arising from the appendix. Can J Surg. 2009; 52:135–141 [PMID: 19399209 PMCID: PMC2663512].
96. Solass W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. Ann Surg Oncol. 2013;20:3504–3511 [PMID: 23765417 PMCID: PMC3764316]. https://doi.org/10.1245/s10434-013-3039-x.
97. Solass W, Herbette A, Schwarz T, Hetzel A, Sun JS, Dutreix M, Reymond MA. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. Surg Endosc. 2012b;26:847–852 [PMID: 22042585 PMCID: PMC3271218]. https://doi.org/10.1007/s00464-011-1964-y.
98. Solass W, Hetzel A, Nadiradze G, Sagynaliev E, Reymond MA. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg Endosc. 2012a;26:1849–1855 [PMID: 22580869]. https://doi.org/10.1007/s00464-012-2148-0.
99. Solass W, Kerb R, Murdter T, Giger-Pabst U, Strumberg D, Tempfer C, Zieren J, Schwab M, Reymond MA. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21:553–559 [PMID: 24006094] PMCID: PMC3929768. https://doi.org/10.1245/s10434-013-3213-1.
100. Sørensen O, Andersen AM, Kristian A, Giercksky KE, Flatmark K. Impact of hyperthermia on pharmacokinetics of intraperitoneal mitomycin C in rats investigated by microdialysis. J Surg Oncol. 2014;109:521–526 [PMID: 24347444]. https://doi.org/10.1002/jso.23527.
101. Speyer JL, Myers CE. The use of peritoneal dialysis for delivery of chemotherapy to intraperitoneal malignancies. Recent Results Cancer Res. 1980;74:264–269 [PMID: 7444143].
102. Spiliotis J, Halkia E, Lianos E, Kalantzi N, Grivas A, Efstathiou E, Giassas S. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol. 2015;22:1570–1575 [PMID: 25391263]. https://doi.org/10.1245/s10434-014-4157-9.
103. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res. 1980;40:256–260 [PMID: 6766084].
104. Stephens AD, Alderman R, Chang D, Edwards GD, Esquivel J, Sebbag G, Steves MA, Sugarbaker PH. Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique. Ann Surg Oncol. 1999;6:790–796 [PMID: 10622509].
105. Stephens AD, Belliveau JF, Sugarbaker PH. Intraoperative hyperthermic lavage with cisplatin for peritoneal carcinomatosis and sarcomatosis. Cancer Treat Res. 1996;81:15–30 [PMID: 8834572].
106. Sticca RP, Dach BW. Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents. Surg Oncol Clin N Am. 2003;12:689–701 [PMID: 14567025].
107. Sugarbaker PSO, Bijelic L, et al. Hyperthermic intraperitoneal gemcitabine chemotherapy for patients with resected pancreatic cancer: clinical pharmacologic data. CurrTopic Pharmacol. 2014;18:81–92.
108. Sugarbaker P. An overview of peritonectomy, visceral resections, and perioperative chemotherapy for peritoneal surface malignancy. In: Deraco M, et al., editors. Cytoreductive Surgery & Perioperative Chemotherapy for peritoneal surface malignancy: textbook and video atlas, 2012; 2012a. p. 1–30.
109. Sugarbaker PH, Graves T, DeBruijn EA, Cunliffe WJ, Mullins RE, Hull WE, Oliff L, Schlag P. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: pharmacological studies. Cancer Res. 1990;50:5790–5794 [PMID: 2118420].
110. Sugarbaker PH, Mora JT, Carmignani P, Stuart OA, Yoo D. Update on chemotherapeutic agents utilized for perioperative intraperitoneal chemotherapy. Oncologist. 2005;10:112–122 [PMID: 15709213]. https://doi.org/10.1634/theoncologist.10-2-112.
111. Sugarbaker PH, Stuart OA, Carmignani CP. Pharmacokinetic changes induced by the volume of chemotherapy solution in patients treated with hyperthermic intraperitoneal mitomycin C. Cancer Chemother Pharmacol. 2006;57:703–708 [PMID: 16096789]. https://doi.org/10.1007/s00280-005-0074-8.
112. Sugarbaker PH, Welch LS, Mohamed F, Glehen O. A review of peritoneal mesothelioma at the Washington Cancer Institute. Surg Oncol Clin N Am. 2003;12:605–621, xi [PMID: 14567020].

113. Sugarbaker PH. Treatment of peritoneal carcinomatosis from colon or appendiceal cancer with induction intraperitoneal chemotherapy. Cancer Treat Res. 1996;82:317–325 [PMID: 8849959].
114. Sugarbaker PH. Peritonectomy procedures. Surg Oncol Clin N Am. 2003;12:703–727, xiii [PMID: 14567026].
115. Sugarbaker PH. New standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome? Lancet Oncol. 2006;7:69–76 [PMID: 16389186]. https://doi.org/10.1016/S1470-2045(05)70539-8.
116. Sugarbaker PH. Laboratory and clinical basis for hyperthermia as a component of intracavitary chemotherapy. Int J Hyperth. 2007;23:431–442 [PMID: 17701534]. https://doi.org/10.1080/02656730701455318.
117. Sugarbaker PH. Parietal peritonectomy. Ann Surg Oncol. 2012b;19:1250 [PMID: 22322950]. https://doi.org/10.1245/s10434-012-2229-2.
118. Tempfer CB, Solass W, Buerkle B, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with cisplatin and doxorubicin in a woman with pseudomyxoma peritonei: a case report. Gynecol Oncol Rep. 2014;10:32–35 [PMID: 26076000 PMCID: PMC4434151]. https://doi.org/10.1016/j.gore.2014.10.001.
119. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, Rezniczek GA, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol. 2015;137:223–228 [PMID: 25701703]. https://doi.org/10.1016/j.ygyno.2015.02.009.
120. Tempfer CB. Pressurized intraperitoneal aerosol chemotherapy as an innovative approach to treat peritoneal carcinomatosis. Med Hypotheses. 2015;85:480–484 [PMID: 26277656]. https://doi.org/10.1016/j.mehy.2015.07.001.
121. Urano M, Kuroda M, Nishimura Y. For the clinical application of thermochemotherapy given at mild temperatures. Int J Hyperth. 1999;15:79–107 [PMID: 10323618].
122. Vaillant JC, Nordlinger B, Deuffic S, Arnaud JP, Pelissier E, Favre JP, Jaeck D, Fourtanier G, Grandjean JP, Marre P, Letoublon C. Adjuvant intraperitoneal 5-fluorouracil in high-risk colon cancer: a multicenter phase III trial. Ann Surg. 2000;231:449–456 [PMID: 10749603 PMCID: PMC1421018].
123. Van der Speeten K, Stuart OA, Chang D, Mahteme H, Sugarbaker PH. Changes induced by surgical and clinical factors in the pharmacology of intraperitoneal mitomycin C in 145 patients with peritoneal carcinomatosis. Cancer Chemother Pharmacol. 2011a;68:147–156 [PMID: 20857115]. https://doi.org/10.1007/s00280-010-1460-4.
124. Van der Speeten K, Stuart OA, Mahteme H, Sugarbaker PH. A pharmacologic analysis of intraoperative intracavitary cancer chemotherapy with doxorubicin. Cancer Chemother Pharmacol. 2009;63:799–805 [PMID: 18654746]. https://doi.org/10.1007/s00280-008-0800-0.
125. Van der Speeten K, Stuart OA, Mahteme H, Sugarbaker PH. Pharmacokinetic study of perioperative intravenous Ifosfamide. Int J Surg Oncol. 2011b;2011:185092 [PMID: 22312496 PMCID: PMC3263669]. https://doi.org/10.1155/2011/185092.
126. Van der Speeten K, Stuart OA, Sugarbaker PH. Pharmacology of perioperative intraperitoneal and intravenous chemotherapy in patients with peritoneal surface malignancy. Surg Oncol Clin N Am. 2012;21:577–597 [PMID: 23021717]. https://doi.org/10.1016/j.soc.2012.07.013.
127. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, de Hingh IHJT, van der Velden J, Arts HJ, Massuger LFAG, Aalbers AGJ, Verwaal VJ, Kieffer JM, Van de Vijver KK, van Tinteren H, Aaronson NK, Sonke GS. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230–240. PMID: 29342393. https://doi.org/10.1056/NEJMoa1708618.
128. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol. 2008;15:2426–2432 [PMID: 18521686]. https://doi.org/10.1245/s10434-008-9966-2.
129. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737–3743 [PMID: 14551293]. https://doi.org/10.1200/JCO.2003.04.187.
130. Villa AF, El Balkhi S, Aboura R, Sageot H, Hasni-Pichard H, Pocard M, Elias D, Joly N, Payen D, Blot F, Poupon J, Garnier R. Evaluation of oxaliplatin exposure of healthcare workers during heated intraperitoneal perioperative chemotherapy (HIPEC). Ind Health. 2015;53:28–37 [PMID: 25327298 PMCID: PMC4331192]. https://doi.org/10.2486/indhealth.2014-0025.
131. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol. 2006;24:4011–4019 [PMID: 16921055]. https://doi.org/10.1200/JCO.2006.07.1142.
132. Yan TD, Black D, Sugarbaker PH, Zhu J, Yonemura Y, Petrou G, Morris DL. A systematic review and

meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol. 2007a;14:2702–2713 [PMID: 17653801]. https://doi.org/10.1245/s10434-007-9487-4.

133. Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Gilly FN, Levine EA, Shen P, Mohamed F, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol. 2009;27:6237–6242 [PMID: 19917862]. https://doi.org/10.1200/JCO.2009.23.9640.
134. Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. Ann Oncol. 2007b;18:827–834 [PMID: 17130182]. https://doi.org/10.1093/annonc/mdl428.
135. Yen MS, Juang CM, Lai CR, Chao GC, Ng HT, Yuan CC. Intraperitoneal cisplatin-based chemotherapy vs. intravenous cisplatin-based chemotherapy for stage III optimally cytoreduced epithelial ovarian cancer. Int J Gynaecol Obstet. 2001;72:55–60 [PMID: 11146078].
136. Yonemura Y, Bandou E, Kinoshita K, Kawamura T, Takahashi S, Endou Y, Sasaki T. Effective therapy for peritoneal dissemination in gastric cancer. Surg Oncol Clin N Am. 2003;12:635–648 [PMID: 14567022].
137. Yonemura Y, Bandou E, Sawa T, Yoshimitsu Y, Endou Y, Sasaki T, Sugarbaker PH. Neoadjuvant treatment of gastric cancer with peritoneal dissemination. Eur J Surg Oncol: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2006;32:661–665 [PMID: 16621433]. https://doi.org/10.1016/j.ejso.2006.03.007.
138. Yonemura Y, Elnemr A, Endou Y, Ishibashi H, Mizumoto A, Miura M, Li Y. Effects of neoadjuvant intraperitoneal/systemic chemotherapy (bidirectional chemotherapy) for the treatment of patients with peritoneal metastasis from gastric cancer. Int J Surg Oncol. 2012;2012:148420 [PMID: 22900159 PMCID: PMC3415092]. https://doi.org/10.1155/2012/148420.
139. Young JS, Lumsden CE, Stalker AL. The significance of the tissue pressure of normal testicular and of neoplastic (Brown-Pearce carcinoma) tissue in the rabbit. J Pathol Bacteriol. 1950;62:313–333 [PMID: 14784896].
140. Zeamari S, Floot B, van der Vange N, Stewart FA. Pharmacokinetics and pharmacodynamics of cisplatin after intraoperative hyperthermic intraperitoneal chemoperfusion (HIPEC). Anticancer Res. 2003;23:1643–1648 [PMID: 12820435].
141. Zylberberg B, Dormont D, Janklewicz S, Darai E, Bretel JJ, Poncelet C, Guillet JL, Madelenat P. Response to neo-adjuvant intraperitoneal and intravenous immunochemotherapy followed by interval secondary cytoreduction in stage IIIc ovarian cancer. Eur J Gynaecol Oncol. 2001;22:40–45 [PMID: 11321492].

14 Cytokine-Induced Senescence: An Experimental Treatment of Peritoneal Tumors

Thomas Wieder, Ellen Brenner, Heidi Braumüller, Pankaj Kumar Garg, and Martin Röcken

14.1 Introduction

With the introduction of immune checkpoint inhibitors, immunotherapy has become the fourth pillar of cancer treatment—the other three being surgery, chemotherapy, and radiotherapy. The success of immunotherapy is not only related to the destruction of cancer cells but also to a whole gamut of new biological processes. One of these biological processes is cellular senescence, which is the permanent growth arrest of the tumor cells.

Immune cells monitor the senescent tumor cells. In addition to direct contact, various soluble factors, including cytokines, play an active role. In this chapter, we will introduce the concept of cellular senescence and how this can be potentially used in the management of peritoneal metastasis.

T. Wieder (✉) · E. Brenner · H. Braumüller
M. Röcken
Department of Dermatology, University Medical Center Tübingen, Tübingen, Germany
e-mail: thomas.wieder@med.uni-tuebingen.de; ellen.brenner@med.uni-tuebingen.de; heidi.braumueller@med.uni-tuebingen.de; martin.roecken@med.uni-tuebingen.de

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

14.2 The Concept of Senescence

Cellular senescence actually means cell aging and has been implicated in some physiological and pathophysiological factors such as aging of the organism, age-related diseases, tissue homeostasis, and embryogenesis [1–4].

▶ In the context of aging, cellular senescence is one of the nine hallmarks of aging. Besides telomeric shortening, other notable stimuli that trigger senescence are non-telomeric DNA damage and de-repression of the INK4/ARF locus [9].

Cellular senescence is recognized as a potent autonomous tumor-suppressive mechanism. p53 and p16INK4a/pRB pathways, the two most powerful tumor-suppressor pathways, are critical for cellular senescence. Various stimuli for the activation of the p53 and p16INK4a/pRB pathways to establish and maintain the senescence growth arrest include dysfunctional telomeres, non-telomeric DNA damage, disruptions to chromatin organization, the expression of certain activated oncogenes, strong or persistent mitogenic signals, and several types of cellular stress, including oxidative stress.

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_14

These tissue-resorbing properties of senescence are driven, at least in part, by the senescence-associated secretory phenotype (SASP) of aging single cells, with senescent cells delivering a large number of specific signaling molecules, such as interleukins, chemokines, and growth factors to the surrounding tissue [5].

In addition to the pathophysiological relevance of senescence in connection with the aging of the organism described above, it has recently been described that the biological principle of permanent cell-cycle arrest with subsequent removal of the arrested cells also plays a crucial role in the development of the organism during the period of embryogenesis. This "developmental senescence" is a physiologically programmed senescence-signaling pathway that has recently become one of the mechanisms of embryonic development besides apoptosis (programmed cell death) [12, 17]. In contrast, both oncogene and therapy-induced senescence are understood to be purely stress-response mechanisms that counteract excessive cell growth.

14.3 Cellular Senescence as an Antitumor Mechanism

▶ Premature senescence of tumor cells is an intrinsic antitumoral mechanism that can be triggered by various genetic or epigenetic disorders.

These include the expression of hyperactive oncogenes [10], the influence of cytotoxic drugs on DNA [6, 15], or the loss of the tumor-suppressor gene PTEN—the "phosphatase and tensin homologue deleted on chromosome 10" [1]. These changes in the genetic information or disorders in the regulation of genetic information transduction in the tumor cells ultimately result in the irreversible cell-cycle arrest of these cells. Premature senescence can best be described as a cellular emergency brake, which intervenes when the cells threaten to run out of control.

However, for this mechanism of intrinsic cancer protection to be effective, it is likely that the arrested tumor cells will eventually have to be removed from the tissue and ultimately from the organism—a process that is mainly done by specialized macrophages. This complete senescence monitoring of tumors [8] complements the strategy of cytotoxic immune defense based on tumor-cell apoptosis and tumor-cell lysis, thus contributing substantially to the antitumor defense system of the immune system. The linkage of the permanent proliferation arrest of the tumor cells with the elimination of these cells by the immune system seems to be essential for the antitumoral effect of this defense mechanism. In the long run, senescent cells result in the formation of a SASP, which leads to the secretion of chemokines, growth factors, etc., and they thus have a pro-inflammatory, tumor-fostering effect [4]. However, the exact mechanisms by which senescent cells are cleared off in the body need to be further investigated and elucidated.

Since senescent cells are typically characterized by a very much flattened and extensive morphology (Fig. 14.1), which strongly resembles the shape of a sunny-side-up fried egg, it is also conceivable that they first disintegrate into smaller components before removal—or they go through a kind of secondary apoptosis or another kind of subordinate cell death.

14.4 The Cytokine-Induced Senescence as Part of Immune Surveillance of Tumors

With the description of the immune surveillance of tumors [7] and the characterization of cellular senescence as an endogenous barrier against the unrestricted growth of tumors [10], two biological mechanisms have been identified that are not directly cytotoxic. Both of the mechanisms are in conformity with the concept of tumor dormancy. This state of a tumor can also be induced by the

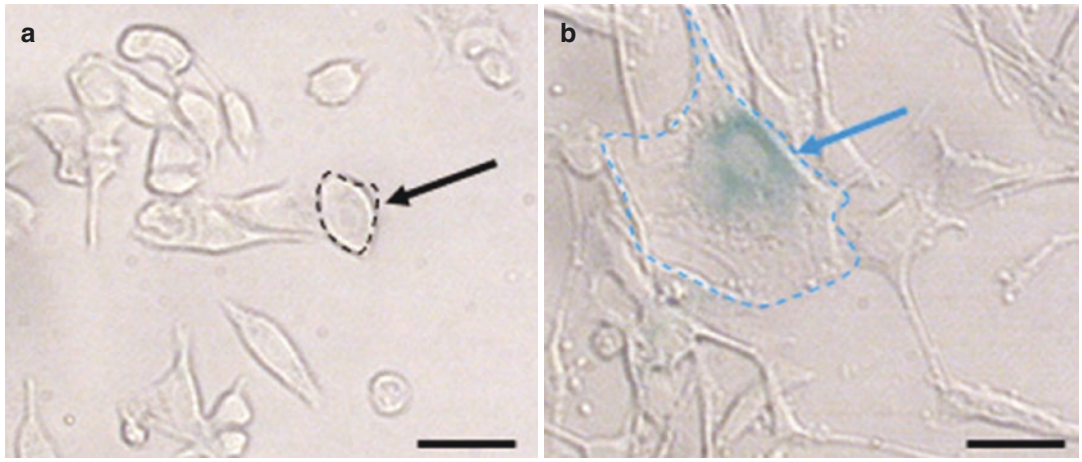


Fig. 14.1 (**a**, **b**) Comparison of the morphology of proliferating versus senescent cells. A light-microscopic image of a proliferating cell population (**a**) as compared to a growth-arrested cell population of WM-115 melanoma cells (**b**) is shown

administration of cytokine-producing T-helper-1 (TH1) cells, as shown in the tumor model of an endogenous β-cell carcinoma in transgenic RIP-Tag2 mice [11].

These "sleeping" tumors may stay in the body for many years without causing any damage. However, immune surveillance of the tumors, which is absolutely necessary for this purpose, has long been described as a balance between proliferating and dying tumor cells [16]. This concept has recently been supplemented with immune senescence monitoring. Immune senescence surveillance attains its tumor-suppressive effect mainly by suppressing the cell cycle and less by killing of the malignant cells. Senescent cells may then be disposed of by the immune system, similar to apoptosis [8]. Senescence monitoring clearly has the potential to permanently counteract cancer growth. In this context, it has now been clearly demonstrated that the TH1 cytokines interferon-γ (IFN-γ) and tumor necrosis factor (TNF) can drive cancer cells directly into premature senescence [3]. The induction of senescence was demonstrated both in vitro and in vivo by different methods: for example, by the determination of senescence-associated β-galactosidase (SA-β-Gal), by the detection of senescence-associated heterochromatin foci (SAHF), by immunochemical detection of cell-cycle inhibitors p16Ink4a and retinoblastoma protein (Rb), by detection of a G0/G1 arrest by flow cytometric cell-cycle analysis, and by various growth-arrest assays [3, 14]. In turn, the cytokines necessary for the therapeutic effect are released by the TH1 cells in the immediate vicinity of the murine β-cell tumors after stimulation by antigen-presenting cells [18, 19] and arrest the growth of the malignant cells. The concept was further successfully tested ex vivo on various human cancer cell lines and on primary tumor-cell preparations from cancer patients. These experiments showed that more than 50% of the investigated tumor-cell

populations respond to IFN-γ and TNF with a durable cell-cycle arrest [3]. In addition, it has been demonstrated in a mouse model that an IL-12-/IFN-γ-triggered immune response in vivo can also induce secretion-associated changes in human rhabdomyosarcoma cancer cells [14]. These are astounding findings, as senescence has so far been described only as an intrinsic cellular program elicited by oncogenes in human cancer cells in vivo [10].

▶ The fact that senescence can be elicited via membranous receptors by certain extracellular signaling molecules is a prerequisite for a possible application of the concept in cancer therapy and thus has far-reaching practical consequences.

The signaling pathways leading to senescence of the tumor cells following stimulation by the interferon/TNF cocktail described above have been partially elucidated. Thus, cytokine-induced senescence (CIS) is dependent on the cytokine receptors IFN-γ receptor1/IFN-γ receptor2 (IFN-GR1/IFNGR2) and TNF receptor1 (TNFR1), on the transcription factor signal transducer and activator of transcription1 (STAT1), and on the cell-cycle inhibitor p16Ink4a [3]. Receptor stimulation leads to an IFN-γ-dependent upregulation of Schlafen-1 and to a TNF-dependent upregulation of $p16^{Ink4a}$—the most important molecule that can arrest tumor cells [3]. Together, these signals lead to Rb hypophosphorylation and subsequent cell-cycle arrest by suppression of important cell-cycle genes such as cyclin E and E2F2 (Fig. 14.2).

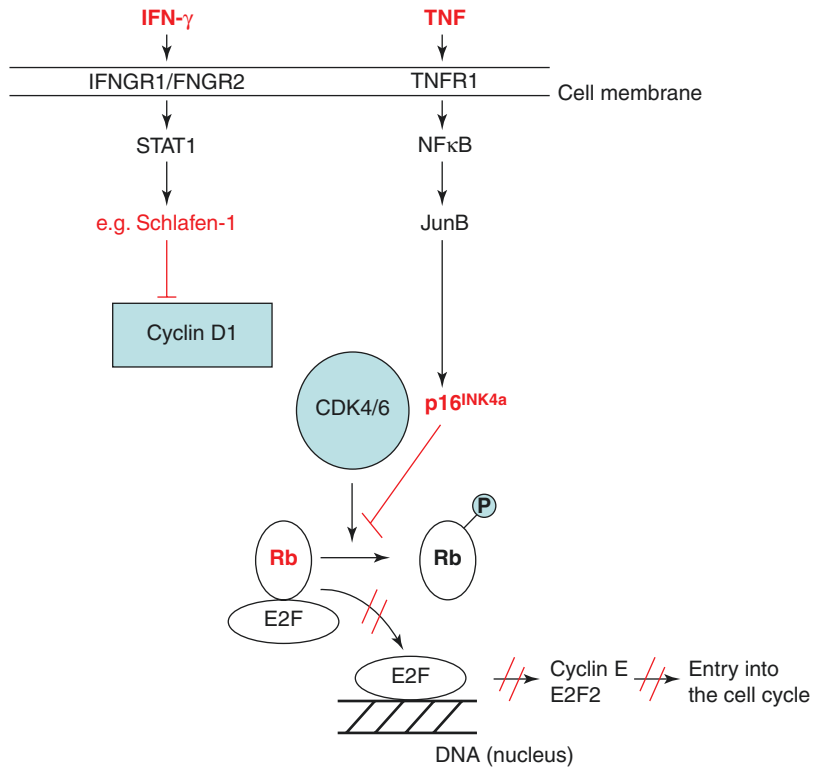


Fig. 14.2 Signal pathways of cytokine-induced senescence (CIS). The stimulation of tumor cells with IFN-γ and TNF possibly via upregulation of Schlafen-1 (left) and upregulation of $p16^{Ink4a}$ (right) leads to stabilization of hypophosphorylated Rb. Hypophosphorylated Rb in turn prevents, via binding of the transcription factor E2F, the expression of the cell-cycle genes cyclin E and E2F2 and thus inhibits the active entry of cells into the cell cycle. CDK4/6 cyclin-dependent kinase 4/6, E2F transcription factor E2F, IFNGR1/2 interferon-γ receptor 1/2, JunB transcription factor JunB, NF-kB nuclear factor kappa B, TNFR1 tumor necrosis factor receptor 1. (Modified and updated from [18])

14.5 Possible Application of Interferons in the Treatment of Ascites-Causing Tumors

IFN-γ and TNF induce growth arrest in different cancer cells, which continues beyond the actual exposure time of the cytokines [3]. This is how the cytokine-induced senescence differs fundamentally from other mechanisms of action such as cytokine-induced apoptosis, which destroys the cells in a defined time window immediately after stimulation of the receptors.

▶ Since CIS also shows effects on the cancer cells that last longer than the treatment, it represents a suitable mechanism to curb highly metastatic or micro-metastatic tumors.

This new mechanism of action may thus be relevant for melanoma therapy and, in this context, for the reduction of malignant ascites. Analyses in our laboratory have shown that melanoma cell lines can also be converted into a CIS by the combination of IFN-γ with TNF (unpublished data). However, the type II interferon used by us in vitro, IFN-γ, is rarely used clinically because of its strong side effects. It is thus all the more important that type I interferon, IFN-α, is a cytokine commonly used in melanoma therapy with a more moderate toxicity profile, and that it has, in vitro, effects on proliferation, cell cycle, and in vitro expression of important senescence markers of melanoma cells that are similar to IFN-γ (unpublished data). Building on these in vitro data, the relevance of CIS in vivo should now be developed. In order to do this, the use of cytokines in cases of malignant ascites would be particularly suitable for three reasons:

- In this disease, cancer cells can be isolated from the ascites following paracentesis and then examined for senescence induction in vitro.
- The application of the cytokines could be carried out directly following paracentesis, whereby the direct accessibility of the cancer cells by the cytokine combination is similar to that given in the in vitro experiments.
- Due to the presence of inflammation-induced endogenous TNF in detectable amounts, the external administration of TNF could be omitted.

In advance, the effect of cytokines in a peritoneal carcinoma model should be investigated in immunodeficient NOD-SCIDxIL2Rcγ$^{-/-}$ mice. For this, cytokine-sensitive A204 cells [3, 14] and melanoma cells (WM115, Fig. 14.1) are implanted intraperitoneally. After 1 week of tumor establishment, multiple intraperitoneal IFN-α plus TNF applications are performed for a maximum treatment period of 40 days. Then, the number of tumor cells in peritoneal lavage is investigated. Furthermore, in the absence of cytokines, growth curves of the isolated peritoneal tumor cells are recorded, and important senescent markers such as p16^{Ink4a} and the heterochromatin protein pHP1-γ are determined. On the other hand, the induction of senescence on primary cancer cells obtained from the ascites of patients can be analyzed ex vivo. For this purpose, the melanoma cells are isolated, cultured, and characterized by means of various melanoma markers (S100, HMB45) from a part of the therapeutically produced ascites. Subsequently, the melanoma cells are treated ex vivo with cytokines and investigated for the initiation of CIS by creating growth curves as well as through the measurement of SA-β-galactosidase activity and the immunofluorescence detection of p16^{Ink4a} and pHP1-γ.

14.6 Conclusion

In summary, non-toxic, antitumoral mechanisms such as immune senescence monitoring and CIS play a crucial role in the treatment of metastatic tumors. Harnessing these mechanisms for the treatment of malignant ascites will be one of the most urgent tasks in the near future.

References

1. Alimonti A, Nardella C, Chen Z, et al. A novel type of cellular senescence did can be enhanced in mouse models and human tumor xenografts to suppress prostate tumorigenesis. J Clin Invest. 2010;120:681–93.
2. Baker DJ, Wijshake T, Tchkonia T, et al. Clearance of senescent cells delays p16Ink4a-positive aging-associated disorders. Nature. 2011;479:232–6.
3. Braumüller H, Wieder T, Brenner E, et al. T-helper cell-1 cytokines drive cancer into senescence. Nature. 2013;494:361–5.
4. Campisi J. Aging, cellular senescence, and cancer. Annu Rev. Physiol. 2013;75:685–705.
5. Campisi J, Andersen JK, Kapahi P, et al. Cellular senescence: a link between cancer and age-related degenerative disease? Semin Cancer Biol. 2011;21:354–9.
6. Chang BD, Broude EV, Dokmanovic M, et al. A senescence-like phenotype distinguishes tumor cells did undergo terminal proliferation arrest after exposure to anti-cancer agents. Cancer Res. 1999;59:3761–7.
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
8. Kang TW, Yevsa T, Woller N, et al. Senescence surveillance of pre-malignant hepatocytes limits liver cancer development. Nature. 2011;479:547–51.
9. Lopez-Otin C, Blasco MA, Partridge L, et al. The hallmarks of aging. Cell. 2013;153:1194–217.
10. Michaloglou C, Vredeveld LC, Soengas MS, et al. BRAFE600-associated senescence-like cell cycle arrest of human nevi. Nature. 2005;436:720–4.
11. Müller-Hermelink N, Braumüller H, Pichler B, et al. TNFR1 signaling and IFN-gamma signaling deterministic mine whether T cells induce tumor dormancy or promote multistage carcinogenesis. Cancer Cell. 2008;13:507–18.
12. Muñoz-Espín D, Canamero M, Maraver A, et al. Programmed cell senescence during mammalian embryonic development. Cell. 2013;155:1104–18.
13. Perez-Mancera PA, Young AR, Narita M. Inside and out: the activities of senescence in cancer. Nat Rev Cancer. 2014;14:547–58.
14. Schilbach K, Alkhaled M, Welker C, et al. Cancer-targeted IL-12 controls human rhabdomyosarcoma by senescence induction and myogenic differentiation. OncoImmunology. 2015;4:e1014760.
15. Schmitt CA, Fridman JS, Yang M, et al. A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. Cell. 2002;109:335–46.
16. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. Science. 2011;331:1565–70.
17. Storer M, Mas A, Robert Moreno A, et al. Senescence is a developmental mechanism did contributes to embryonic growth and patterning. Cell. 2013;155:1119–30.
18. Wieder T, Braumüller H, Brenner E, et al. Changing T-cell enigma: cancer killing or cancer control? Cell Cycle. 2013;12:3146–53.
19. Wieder T, Brenner E, Braumüller H, et al. Immunotherapy of melanoma: efficacy and mode of action. J Dtsch Dermatol Ges. 2016;14:28–36.

15 Mode of Action and Experimental and Clinical Data of Regional Hyperthermia

Peter Wust and Pirus Ghadjar

15.1 Introduction

Both in vitro and in vivo data suggest that temperature elevation (hyperthermia) is associated with a cytotoxic and sensitizing effect. The definition of a thermal dose is possible. Sensitization is detectable with temperatures above 39 °C in the presence of cytostatic drugs (cisplatinum, ifosfamide) and above 40 °C in conjunction with radiation therapy. Regional hyperthermia is being conducted using annular phased array (APA) techniques (70–120 MHz) and capacitive systems (8–13 MHz). Standard systems are available (Pyrexar with SIGMA applicators or Thermotron/Oncotherm with capacitive techniques), with which clinical trials were successfully conducted in patients with cervical cancer and high-risk soft tissue sarcoma. In a hybrid system, noninvasive MR thermometry has been clinically established. An advancement toward a novel MR-guided, online-optimized, regional hyperthermia is the goal currently aspired to. Additional clinical trials in abdominal tumors (pancreatic cancer) and pelvic tumors (bladder cancer, prostate cancer, anal cancer) have been initiated.

P. Wust (✉) · P. Ghadjar
Charité Universitätsmedizin, Clinic for Radiation Oncology, Berlin, Germany
e-mail: peter.wust@charite.de; pirus.ghadjar@charite.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_15

15.2 Biological Preconditions

Temperature elevation (hyperthermia) above 43 °C can cause cell death (cytotoxicity) by denaturation of important biomolecules. A family of heat shock proteins have a protective role against various kinds of cell stress, including heat. During temperature elevation (e.g., 42 °C), and especially after a heat shock (>43 °C), heat shock proteins will be induced. This reduces the cell sensitivity to heat during several days (thermotolerance). In order to quantify the cytotoxic influence, heat-dose-effect curves for several cell types have been measured. Cell survival is dependent on temperature and exposition time. With these two parameters (temperature multiplied by time), a thermal dose concept was developed [4].

- While the cytotoxic effect can significantly vary from cell type to cell type, parameterized dose-effect curves contain a principle serving as the basis for the introduction of the thermal dose: A temperature of 43 °C over 60 min will be survived by (only) 10% of the cells (reduction of cell count by one log). The thermal dose is regarded as the reference dose and provides an empirical formula for the cytotoxic effect.
- For tumor elimination, 9 logs must be destroyed, which is unrealistic using temperatures of around 43 °C. Thermal tolerance is one of the key resistance mechanisms in this

context. Therefore, within the typical temperature range for clinical hyperthermia (39–44 °C), heat alone is not able to result in local tumor control.

- The effect curves over different temperatures show that every temperature elevation of 1 °C above 43 °C leads to a bisection of the exposition time to reach the same cell survival (isoeffect). For example, the use of 43 °C over 60 min is equivalent to 30 min at 44 °C and 15 min at 45 °C. However, below 43 °C, for every 1 °C of temperature reduction, the exposition time needs to be quadrupled to maintain isoeffectiveness.
- The conversion to a thermal dose provides an estimation for the temperature at which local tumor control (e.g., a cytotoxic effect of 9 logs) can be reached. A cell kill of 9 logs will be accomplished using 47 °C over 40 min or with 50 °C over only 5 min. For the therapeutic use of temperatures above 50 °C, which are, in principal, well suited for tumor elimination, the expression *thermoablation* has been introduced.

Hyperthermia can also improve the effectiveness of other cancer therapies. These effects are related to temperature-dependent alterations of biomolecules and cellular pathways.

In preclinical studies, a synergistic effect was described with radiation therapy and several cytostatic drugs (Table 15.1). The exact cellular mechanisms for this effect are not always known. Regarding the synergistic effect of temperature elevation and radiation, for instance, several different repair enzyme systems have been identified that are potentially involved in this.

For the *synergism of hyperthermia and radiation therapy*, other rules apply, which are of practical importance:

- The thermal dose for a significant increase of radiation effectiveness is significantly lower than the values applicable to cytotoxicity. Likewise, also temperatures around 41 °C are associated with a thermal enhancement ratio (TER) of 1.1. A TER of 1.1 represents a net increase of 10% of radiation dose effect.
- Thermal tolerance impacts upon the sensitization effect, but to a lesser extent as compared to cytotoxicity. Therefore, when radiation therapy and hyperthermia are combined, more frequent hyperthermia treatments are justifiable (e.g., two treatments a week).
- The sensitization effect is maximal when radiation and hyperthermia are applied simultaneously, according to preclinical studies, and it decreases when applied sequentially after a 2–4 h time interval between hyperthermia and radiation therapy. The optimal sequence cannot be identified with the current data, which is a pity. It can be regarded as one valid standard that hyperthermia is commonly performed within 1-4 h after radiation therapy.

Table 15.1 Eligibility of common cytostatic drugs in combination with hyperthermia (if applicable): + standard substances with proven synergism (also for moderate temperatures); (+) complex interaction, sequence and obtained temperatures are important, antagonistic effects are possible; – no synergism proven

Substance	Interaction	Sequence	Synergism
Cisplatin, carboplatin	Linear	Simultaneous	+
Alkylating substances (ifosfamide, cyclophosphamide)	Linear	Simultaneous	+
Nitrosourea (ACNU, BCNU, CCNU)	Linear	Simultaneous	+
Anthracyclines (doxorubicin, epirubicin)	Threshold	Directly before	(+)
Antibiotics (bleomycin, mitomycin C, mitoxantrone)	Threshold	Directly before	(+)
Gemcitabine	43 °C	24 h before	(+)
Taxanes (paclitaxel)	42 °C	>15 h before	(+)
Antimetabolites (5-FU, methotrexate)	Unknown	–	–
Vinca alkaloids (vincristine)	No	–	–
Trabectedin	41.8 °C	Before	(+)
Topotecan, irinotecan	No	–	–
Etoposide (VP-16)	Unknown	Before	–

This scheme employs disruption of repair of double-strand breaks in addition to the reoxygenation effects of the heat sessions.

The *combination of hyperthermia and chemotherapy* is especially promising for the following reasons:

- A simultaneous treatment (and every other desired sequence) is possible for the combination of chemotherapy and hyperthermia.
- Established cytostatic drugs consist especially of cisplatin and alkylating substances (ifosfamide), for which significant improvements in effectiveness could be observed even at moderate temperatures of 39–41 °C.
- However, only a few cytostatic drugs are suitable for combined therapy (Table 15.1). Unfortunately, testing has never been performed for many newer cytostatic drugs or novel systemic agents.

Additional temperature-dependent effects have been found and should serve as a rationale for the use of hyperthermia alone (within the moderate temperature of 39–40 °C). Especially modulation/stimulation of the immune system is thought to be an interesting issue. Likewise, frequency shifts were observed for lymphocyte populations. Comparable effects are, however, also observed after stress situations or after physical exertion.

▶ Further hyperthermia effects in addition to cytotoxicity and sensitization:

▶ Perfusion can be increased or decreased. Exact dose-response relations are often not known. Validation of these mechanisms within clinical trials has not been performed yet.

- Increase in perfusion: cytostatic drug accumulation, reoxygenation
- Decrease in perfusion: vascular breakdown, coronary steal syndrome
- Alterations of the microenvironment: acidosis, oxygenation
- Stimulation of the immune system: antigen presentation, activation of NK cells
- Gene expression: triggering of molecular processes
- Antiangiogenesis: synergism with angiogenesis inhibitors
- Inhibition of cytokine release: less late effects

Of special interest are increased antigen presentations (e.g., heat shock protein HSP70), which were observed after hyperthermia [18]. The increased antigenicity of tumor cells could have systemic effects (e.g., with respect to micrometastasis) comparable to the abscopal effect.

However, immunological effects due to hyperthermia alone (possibly with lower temperatures) have not been proven by clinical examinations. There is therefore no straightforward rationale for using hyperthermia alone to achieve immune stimulation. More research in this direction is required.

Under equilibrium conditions on a macroscopic scale of some centimeters, the temperature rise ΔT (in °C) within tissue can be expressed in a simple relationship to the energy transfer per time SAR (specific absorption rate W/kg) and the perfusion w (ml/100 g/min):

$$T = 1.5 \times SAR / w \qquad (15.1)$$

The coefficient 1.5 can be deduced from the bioheat transfer equation, describing the relation between temperature, SAR, and perfusion in a given organism (for more information compare [27]).

The physiological requirements favor hyperthermia for human tumors. On the one hand, normal human tissues have a high capability for thermal regulation resulting from a regulatory increase of perfusion, which can be many times higher compared to the basal perfusion (Table 15.2). In contrast, the potential for thermal regulation in tumors is significantly lower, due to impaired vascularization. This can result in selective tumor heating despite the fact that the power density distribution SAR does not reflect this.

According to Eq. 15.1, a SAR of 30 W/kg—a value commonly achieved with available technological solutions (compare below)—and a

Table 15.2 Perfusion parameters for temperature calculation. We differentiate between basal perfusion and reactive perfusion during hyperthermia. Thermal regulation leads to a significantly increased perfusion. Maximal values are also listed (right column)

Gewebe	Basal perfusion [ml/100 g/min]	Hyperthermic perfusion [ml/100 g/min]	Maximal perfusion [ml/100 g/min]
Muscle	5	20	80
Fat	5	20	20
Bone	5	10	10
Abdomen	20	20	120
Liver	100	100	400
Kidneys	400	400	400
Rectum	5	20	20
Perirectal tissue	5	20	20
Vagina	5	20	20
Bladder	5	20	20
Tumor	2–5	5–10	15

perfusion of 10 ml/100 g/min (during hyperthermia) will lead to 4.5 °C increase in heat of a given tumor. The 4.5 °C will be added to the systemic temperature of 37.5 °C, resulting in a tumor temperature of 42 °C. This represents effective hyperthermia.

On the other hand, one can extrapolate from Eq. 15.1 that a tumor with higher perfusion (e.g., >20 ml/100 g/min) or with tissue comparable to the liver (100 ml/100 g/ml) cannot be effectively treated using available hyperthermia techniques.

15.3 Technological Approaches

Regional hyperthermia can heat large and deeply located areas of the body. The dimensions are commonly larger than 10 cm and are either located in the pelvis (cervical, prostate, bladder, rectal, and anal cancer), in the abdomen (pancreatic cancer, sarcomas), or in the extremities (mostly sarcomas). For certain indications, ideally the whole abdomen should be heated (abdominal hyperthermia for peritoneal or gastrointestinal tumors). These regions can be treated with standard applicators of the SIGMA family (Pyrexar Medical, Salt Lake City, UT 84119, USA; Dr. Sennewald Medizintechnik GmbH, 81,829 München, Germany) or adjustable waveguide applicators of the ALBA-4D or AMC-8 system (MED-LOGICS S.R.L., 00131 Roma, Italy).

The temperature elevation in the tissue is caused by the power deposition pattern SAR (compare above) and can, within certain limits, be spatially controlled by adapting the SAR distribution. Phase-controlled three-dimensional multi-antenna systems provide the highest potential for the controlled application of power (Fig. 15.1). Planning studies showed that at least two rings of antennas (see AMC-8), and preferably three rings (see SIGMA Eye), are required for three-dimensional control.

One important parameter is the frequency of the RF radiation. Common frequencies for pelvic and abdominal tumors range from 70 to 100 MHz. With these frequencies and standard settings (e.g., in phase control of all antennas), in addition to the usual cross sections, a sufficient deposition of power in deep body areas appears to be possible (30–40 W/kg, [28]). The prerequisites for an effective power distribution are comparably favorable for the abdomen because it consists of a quasi-homogeneous medium.

In the pelvis there are significant disturbances of the SAR distribution due to bony structures, leading to maxima (e.g., hot spots) and shielding effects (e.g., cold spots). In the presence of complex 3D heterogeneities, suitable phase control can lead to resolution of these interface phenom-

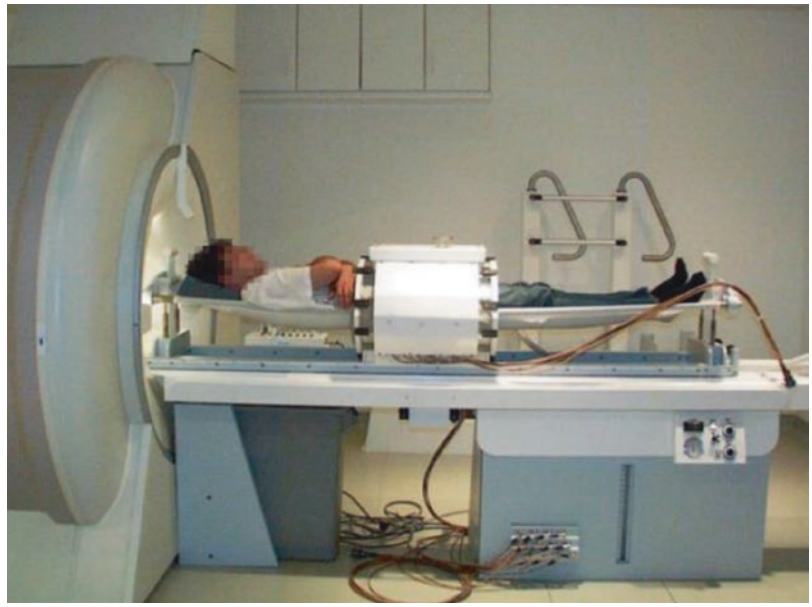


Fig. 15.1 Hybrid system with proband in the SIGMA EYE MR applicator, consisting of three antenna rings. The applicator is shifted with the patient in the gantry of the MR tomograph, where the radiofrequency hyperthermia is conducted in conjunction with MR-based temperature measurements (combination of the BSD-2000 3D MRI, Pyrexar Inc., Salt Lake City, UT, with a 1.5 T Magnetom Symphony, Siemens AG, Erlangen, Germany)

ena and therefore contribute to a higher energy transfer within the tumor [28]. Especially in such complex situations, an increase of the frequency to 200–300 MHz can be advantageous [21] since with the higher frequency and lower wave length (e.g., 10 cm with 300 MHz), the control/focus increases.

However, with such complex control mechanisms, the demands for precision are also higher. Inaccuracies, coupling effects and disturbances of the radiation behavior of the antennas have inhibited the clinical application of these planning studies [28]. Therefore, regional hyperthermia is still being performed with the standard settings of the SIGMA applicators.

Improvements can be obtained with MR-guided hyperthermia. A hybrid system (use of MR-compatible SIGMA applicators within a 1.5-T cryo-MRI) has been installed, established, and clinically evaluated by Charité – Universitätsmedizin Berlin for the first time [28]. Noninvasive MR-thermometry was established using 3D-phantoms [7, 8] and successfully clinically applied and validated in rectal cancer recurrences and soft tissue sarcomas [7–9]. Using this hybrid system, Weihrauch et al. [23] demonstrated in a phantom study that online-control via MRI effectively allows for optimization of the SAR distribution.

Another advancement in technology was obtained by Winter et al. [24] with the so-called integrated system. Biconical dipole antennas were developed, which served both as hyperthermia antennas (radiating electric fields) as well as MR-antennas (sending/receiving of magnetic fields) using the resonance frequency of 298 MHz (at 7.0 T). On an anatomical model, the controlled energy transfer (focus, focus shifting) and the intermittent MR-thermometry was demonstrated. The high frequency is especially suited for treatments in the head and neck area.

Abdominal hyperthermia is a special application of regional hyperthermia, which is used for abdominal tumors and peritoneal carcinomatosis. Here, a volume of 5–10 L, extending from the liver down to the small pelvis, is required to be preferably homogenously illuminated by a sufficiently high SAR. Available technology (SIGMA-applicators) can achieve this only rudimentarily [1]. A dedicated applicator for abdominal hyperthermia is required to target a large volume using an appropriate array of antennas (SIGMA applicator) or waveguides (ALBA). A solution without water bolus (e.g., coupling via

air) would be preferable, which might be possible according to recent research [19]. The optimal frequency is not known yet, but it is probably in the range of <100 MHz. The development of a suitable (MR-compatible) applicator for abdominal hyperthermia remains a significant challenge that should be addressed with high priority.

For a broad and accepted clinical use, the development of a noninvasive abdominal MR thermometry is necessary because invasive temperature measurements in the abdomen are problematic and not feasible in clinical practice. MR thermometry of the liver would be a solution, because the temperature elevation in the liver provides information regarding the mean abdominal temperature (elevation). For the liver, special acquisition and analysis tools are required that would also factor in respiratory motion [25]. For abdominal hyperthermia, solutions within a 3 T MR system (using 128 MHz) appear to be feasible.

An optimal use of regional hyperthermia is only possible when there is a coincidence of hyperthermia planning [16] and online MR thermometry. Weihrauch et al. demonstrated in [23] that, for correct hyperthermia planning in a specific situation, an adaption of the antenna function would be required. For online optimization of regional hyperthermia, a different time constant for SAR distributions and temperature distribution has to be considered.

While the SAR distribution can vary within seconds, when control parameters (e.g., phases) are changed, the difference in temperature distribution takes minutes to establish a new balance. Under clinical conditions, optimization of the temperature distribution can be achieved only as an interplay between simulation calculations and MR thermometry [28].

15.4 Clinical Data

Hyperthermia, especially regional hyperthermia (RHT) using APA technique (BSD 2000 or BSD-2000/D, ALBA-4D) as well as capacitive systems (Thermotron, Oncotherm), has been validated in multiple prospective randomized trials [26, 28].

Van der Zee [22] and Harima [10, 11] showed that, for locally *advanced cervical cancer* (FIGO IIB-IIIB), there was an improvement in *local control* after adding hyperthermia (HT) to radiotherapy (RT) or radiochemotherapy (RCT). After 12 years of follow-up, the *overall survival* had improved for RT + HT when compared to RT (37% vs. 20%, [6]). Cisplatin chemotherapy (CT) also improves results of RT and is available everywhere. However, in cases where CT with cisplatin is contraindicated, RT + HT can be used as an equivalent treatment to RT + CT.

Recently, Minnaar [17] showed an improvement in *response* and *pelvic local control* for *advanced cervical cancer* (in the majority with pelvic and retroperitoneal lymph node metastases) when comparing RCT and RCT plus HT. The researchers used the capacitive system EHY 2020 (Oncotherm GmbH, Troisdorf, Germany) at 13.56 MHz with an additional amplitude modulation (AM) by audio frequencies, i.e., kHz range (called modulated electro-hyperthermia (mEHT)). Minnaar [17] applied a total power of only 130 W for AM RF radiation, while Van der Zee [22] applied 500–800 W using 70–100 MHz RF radiation (APA technology), and Harima [10, 11] even 800–1500 W using 8 MHz RF radiation (capacitive device). These clinical data are consistent with preclinical data and suggest that AM might add a nonthermal effect to RF radiation [29]. Further research is required on this interesting issue.

Regional hyperthermia should also be used in cases where the obligatory brachytherapy cannot be performed as part of RT.

For muscle-invasive *bladder cancer*, a higher response rate has been shown for RT + HT when compared to RT alone [22], and organ preserving strategies using RT + HT + CT are being explored in an ongoing clinical trial.

In patients with *rectal cancer*, there is currently no data available showing a benefit for additional hyperthermia, even though a phase II trial initially demonstrated good results with a higher response rate (downstaging) in the preoperative setting [20]. After long-term follow-up, no improvement of disease-specific survival could be obtained by hyperthermia [22]. An

important, perhaps decisive, reason is the fact that rectal cancers of the middle or proximal third of the rectum, since they are located in the presacral space, are hard to heat. With available techniques only rectal cancers of the distal third as well as anal cancer can be sufficiently heated [28], and we recommend patient selection for future trials accordingly.

In another trial, neoadjuvant chemotherapy plus hyperthermia was tested in patients with high-risk *soft tissue sarcoma* and compared to neoadjuvant chemotherapy alone [13]. Sarcomas of the abdominopelvic region and the extremities were included, both in the primary setting and recurrences, or after incomplete resection. According to the protocol, whenever feasible, a postoperative radiation therapy was conducted. Both local progression-free survival (81% vs. 70% after 2 years) and disease-free survival (58% vs. 44% after 2 years) were significantly improved with the addition of hyperthermia [13]. In long-term follow-up, overall survival after hyperthermia also improved to 60% vs. 50% after 6 years [14].

The additional use of hyperthermia is especially interesting in patients with sarcomas for the following reasons:

- Sarcomas are easy to heat due to their impaired vascularization, especially in tumors of the extremities.
- Regional hyperthermia can improve the local effectiveness of chemotherapy.
- Neoadjuvant radiation therapy is effective but can also be associated with prolonged wound healing after surgery (and radiation therapy might therefore be preferred after surgery).

Preoperative hyperthermic chemotherapy followed by postoperative radiation therapy has, however, not yet been compared with maximally effective preoperative chemoradiation. Such a trial would be important to further clarify the role of hyperthermia in the multimodal treatment of high-risk soft tissue sarcoma.

The HEAT (Hyperthermia European Adjuvant Trial) trial randomizes patients after resection for pancreatic cancer to receive either adjuvant chemotherapy alone (gemcitabine and capecitabine) or combined chemotherapy (consisting of gemcitabine and capecitabine and cisplatinum) and abdominal hyperthermia—in this case, not only heating up the tumor bed, but preferably the whole peritoneal cavity including the liver [1] to temperatures of >40–41 °C. Cisplatin was chosen additionally in the experimental arm because the synergistic effect with hyperthermia is already present with temperatures >39 °C.

In a pilot study, abdominal hyperthermia was used for patients with recurrent therapy-refractory ovarian cancer [5].

▶ Abdominal hyperthermia for gastrointestinal tumors (pancreatic cancer, stomach cancer, colorectal cancer) and for ovarian cancer is a promising treatment option that needs to be evaluated in novel trials because not only the primary tumor but also the areas commonly affected by distant metastasis—e.g., the liver and peritoneal cavity—are being treated.

Clinical trials to examine abdominal hyperthermia and chemotherapy in patients with peritoneal carcinomatosis are lacking. A clinical trial in this setting should also be considered.

For pelvic tumors, there are ongoing trials for patients with muscle-invasive bladder cancer (RT + CT + HT), anal cancer (RT + CT + HT), and biochemically recurrent prostate cancer (RT + HT).

Also for superficial tumors (local breast cancer recurrences) and for middle-deep tumors (inoperable tumors of the head and neck region), several clinical trials have demonstrated the superiority of combined RT + HT over RT alone (meta-analyses of [2, 3, 15]). In addition to local hyperthermia (using microwave applicators), capacitive hyperthermia also appears to be well suited in such cases.

Capacitive hyperthermia has been widely used in Japan, and it has been demonstrated in randomized trials that capacitive hyperthermia, when combined with radiation therapy, improved outcomes when compared to radiation therapy alone in patients with head and neck cancer [2, 12] as well as with cervical cancer [10, 17].

15.5 Conclusion

Hyperthermia can improve the effectiveness of chemotherapy and/or radiation therapy. There are positive randomized trials for soft tissue sarcoma, cervical cancer, bladder cancer, head and neck cancer, and several superficially located tumors. For the application of hyperthermia, phase-controlled multi-antenna systems have been developed; capacitive treatment systems have also been developed and are commercially available. For gastrointestinal and peritoneal tumors, abdominal hyperthermia is being applied, but still needs methodological improvement, including availability of MR-based temperature monitoring.

References

1. Beck M, Ghadjar P, Weihrauch M, Burock S, Budach V, Nadobny J, Sehouli J, Wust P. Regional hyperthermia of the abdomen, a pilot study towards the treatment of peritoneal carcinomatosis. Radiat Oncol. 2015;10:157.
2. Datta NR, Rogers S, Gómez Ordóñez S, Puric E, Bodis S. Hyperthermia and radiotherapy in the management of head and neck cancers: a systematic review and meta-analysis. Int J Hyperth. 2016a;32(1):31–40.
3. Datta NR, Puric E, Klingbiel D, Gomez S, Bodis S. Hyperthermia and radiation therapy in locoregional recurrent breast cancers: a systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2016b;94(5):1073–87.
4. Dewhirst MW, Viglianti BL, Lora-Michiels M, Hanson M, Hoopes PJ. Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. Int J Hyperth. 2003;19(3):267–94.
5. Fotopoulou C, Cho CH, Kraetschell R, Gellermann J, Wust P, Lichtenegger W, Sehouli J. Regional abdominal hyperthermia combined with systemic chemotherapy for the treatment of patients with ovarian cancer relapse: results of a pilot study. Int J Hyperth. 2010;26(2):118–26.
6. Franckena M, Stalpers LJA, Koper PCM, Wiggenraad RGJ, Hoogenraad WJ, van Dijk JDP, Wárlám-Rodenhuis CC, Jobsen JJ, van Rhoon GC, van der Zee J. Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: an update of the Dutch Deep Hyperthermia Trial. Int J Radiat Oncol Biol Phys. 2008;70(4):1176–82.
7. Gellermann J, Wlodarczyk W, Ganter H, Nadobny J, Fähling H, Seebass M, Felix R, Wust P. A practical approach to thermography in a hyperthermia/magnetic resonance hybrid system: validation in a heterogeneous phantom. Int J Radiat Oncol Biol Phys. 2005a;61(1):267–77.
8. Gellermann J, Wlodarczyk W, Hildebrandt B, Ganter H, Nicolau A, Rau B, Tilly W, Fähling H, Nadobny J, Felix R, Wust P. Noninvasive magnetic resonance thermography of recurrent rectal carcinoma in a 1.5 Tesla hybrid system. Cancer Res. 2005b;65(13):5872–80.
9. Gellermann J, Hildebrandt B, Issels R, Ganter H, Wlodarczyk W, Budach V, Felix R, Tunn PU, Reichardt P, Wust P. Noninvasive magnetic resonance thermography of soft tissue sarcomas during regional hyperthermia: correlation with response and direct thermometry. Cancer. 2006;107(6):1373–82.
10. Harima Y, Nagata K, Harima K, Ostapenko VV, Tanaka Y, Sawada S. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma. Int J Hyperth. 2001;17:97–105.
11. Harima Y, Ohguri T, Imada H, Sakurai H, Ohno T, Hiraki Y, Tuji K, Tanaka M, Terashima H. A multicenter randomised clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer. Int J Hyperth. 2016;32(7):801–8.
12. Huilgol N, Gupta S, Sridhar C. Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: a report of randomized trial. J Cancer Res Therap. 2010;6(4):492.
13. Issels RD, Lindner LH, Verweij J, Wust P, Reichardt P, Schem BC, Abdel-Rahman S, Daugaard S, Salat C, Wendtner CM, Vujaskovic Z, Wessalowski R, Jauch KW, Dürr HR, Ploner F, Baur-Melnyk A, Mansmann U, Hiddemann W, Blay JY, Hohenberger P. European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG); European Society for Hyperthermic Oncology (ESHO). Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol. 2010;11(6):561–70.
14. Issels RD, Lindner LH, Verweij J, Wessalowski R, Reichardt P, Wust P, Ghadjar P, Hohenberger P, Angele M, Salat C, Vujaskovic Z, Daugaard S, Mella O, Mansmann U, Dürr HR, Knösel T, Abdel-Rahman S, Schmidt M, Hiddemann W, Jauch KW, Belka C, Gronchi A. European Organization for the Research and Treatment of Cancer-soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: the EORTC 62961-ESHO 95 randomized clinical trial. JAMA Oncol. 2018;4(4):483–92.
15. Jones EL, Oleson JR, Prosnitz LR, Samulski TV, Vujaskovic Z, Yu D, Sanders LL, Dewhirst MW. Randomized trial of hyperthermia and radiation for superficial tumors. J Clin Oncol. 2005;23(13):3079–85.

16. Kok HP, Wust P, Stauffer PR, Bardati F, van Rhoon GC, Crezee J. Current state of the art regional hyperthermia treatment planning: a review. Radiat Oncol. 2015;10:196.
17. Minnaar CA, Kotzen JA, Ayeni OA, Naidoo T, Tunmer M, Sharma V, Vangu E, Baeyens A. The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: early results from a phase III randomized controlled trial. PLoS One. 2019;14(6):e0217894.
18. Multhoff G. Activation of natural killer cells by heat shock protein 70. Int J Hyperth. 2002;8(6):576–85.
19. Oberacker E, Kuehne A, Oezerdem C, Nadobny J, Weihrauch M, Beck M, Sebastian Zschaeck S, Diesch C, Eigentler TW, Waiczies H, Ghadjar P, Wust P, Winter L, Niendorf T. Radiofrequency applicator concepts for thermal magnetic resonance of brain tumors at 297 MHz (7.0 Tesla). Int J Hyperth. 2019;37(1):549–63.
20. Rau B, Wust P, Tilly W, Gellermann J, Harder C, Riess H, Budach V, Felix R, Schlag PM. Preoperative radiochemotherapy in locally advanced or recurrent rectal cancer: regional radiofrequency hyperthermia correlates with clinical parameters. Int J Radiat Oncol Biol Phys. 2000;48(2):381–91.
21. Seebass M, Beck R, Gellermann J, Nadobny J, Wust P. Electromagnetic phased arrays for regional hyperthermia: optimal frequency and antenna arrangement. Int J Hyperth. 2001;17(4):321–36.
22. Van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JDP, van Putten WLJ, Hart AAM. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective, randomised, multicentre trial. Lancet. 2000;355:1119–25.
23. Weihrauch M, Wust P, Weiser M, Nadobny J, Eisenhardt S, Budach V, Gellermann J. Adaptation of antenna profiles for control of MR guided hyperthermia (HT) in a hybrid MR-HT system. Med Phys. 2007;34(12):4717–25.
24. Winter L, Özerdem C, Hoffmann W, Santoro D, Müller A, Waiczies H, Seemann R, Graessl A, Wust P, Niendorf T. Design and evaluation of a hybrid radiofrequency applicator for magnetic resonance imaging and RF induced hyperthermia: electromagnetic field simulations up to 14.0 Tesla and proof-of-concept at 7.0 Tesla. PLoS One. 2013;8(4):e61661.
25. Winter L, Oberacker E, Paul K, Ji Y, Oezerdem C, Ghadjar P, Thieme A, Budach V, Wust P, Niendorf T. Magnetic resonance thermometry: methodology, pitfalls and practical solutions. Int J Hyperth. 2016;32(1):63–75.
26. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM. Hyperthermia in combined treatment of cancer. Lancet Oncol. 2002;3(8):487–97.
27. Wust P, Cho CH, Hildebrandt B, Gellermann J. Thermal monitoring: invasive, minimal-invasive and non-invasive approaches. Int J Hyperth. 2006;22(3):255–62.
28. Wust P. Thermotherapy in oncology UNI-MED Verlag Bremen. London, Boston: International Medical Publishers; 2016.
29. Wust P, Ghadjar P, Nadobny J, Beck M, Kaul D, Winter L, Zschaeck S. Physical analysis of temperature-dependent effects of amplitude-modulated electromagnetic hyperthermia. Int J Hyperth. 2019;36(1):1246–54.

HIPEC in Pediatric Patients

16

Guido Seitz, Jörg Fuchs, and Stefan Beckert

16.1 Introduction

The introduction of chemotherapy itself and the combination of chemotherapy, radiotherapy, and surgery as multimodal therapy approaches have increased the survival rates of children with solid tumors from 0–20% in the 1970s to 75–80% today. Certainly also the centralized treatment of patients in the context of oncologic, therapy-optimized clinical trials contributed to this development.

▶ Despite the apparent improvement of the treatment results for children with solid tumors, the outcome still depends on the tumor entity as well as the tumor stage.

Still, the treatment of children with advanced and, in particular, with metastasized tumor stages represents a major challenge because, despite very intensive therapies, no significant improvement in the survival rates is achieved for these patients. Peritoneal carcinomatosis/peritoneal sarcomatosis is very rare in children and mostly appears in colorectal carcinomas, desmoplastic small round cell tumors (DSRCT), and rhabdomyosarcomas.

16.2 Peritoneal Carcinomatosis

The incidence of peritoneal carcinomatosis (PC) in children is unknown. Regarding peritoneal mesotheliomas, an incidence of 2/1,000,000 is assumed in the USA [16]. For other tumor entities, mostly only single case reports are available. The largest trial published to date includes 50 cases of patients aged between 3 and 21 years with PC and peritoneal sarcomatosis (PS) [5]. In children, PC develops in particular in the context of colorectal and ovarian cancer. The current therapy for these children generally consists in systemic chemotherapy. Usually, the prognosis is very unfavorable.

16.3 Peritoneal Sarcomatosis

One particularity is peritoneal sarcomatosis that may occur in cases of soft tissue sarcomas (desmoplastic small round cell tumors,

G. Seitz (✉)
Department of Pediatric Surgery, University Hospital Giessen-Marburg, Marburg, Germany
e-mail: Guido.seitz@med.uni-marburg.de

J. Fuchs
Department of Pediatric Surgery and Urology, University Children's Hospital, Tübingen, Germany
e-mail: joerg.fuchs@med.uni-tuebingen.de

S. Beckert
Department of General and Visceral Surgery, Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Germany
e-mail: stefan.beckert@sbk-vs.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_16

rhabdomyosarcomas, GIST, liposarcomas, and leiomyosarcomas). The risk of developing local recurrences is very high in these patients. The current treatment consists of systemic chemotherapy and, if possible, radiation of the entire abdomen. In general, the prognosis of the patients is very poor.

16.3.1 Relevance of Cytoreductive Surgery and HIPEC in Pediatric Patients

The significance of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in pediatric patients has not been ultimately clarified due to the low number of cases. The largest trial of patients younger than 21 years was published by Hayes-Jordan et al. [4] from Houston, USA. It revealed the following:

- Taking into account that a major part of these patients additionally underwent radiation of the abdomen, CRS and HIPEC were able to improve the survival rates of children and adolescents suffering from DSRCT.

The survival rates of patients with other tumor entities than rhabdomyosarcomas and gastrointestinal carcinomas were significantly poorer compared to DSRCT patients.

- In addition to tumor histology, another crucial factor for the survival is the extent of radical surgery.

Here, it has been shown that patients with an extent of resection of CC-0 or CC-1 had a longer median survival than patients with CC-2 resections. Another factor is the level of the peritoneal tumor load, which is defined by means of the peritoneal carcinomatosis index (PCI) [5]. The trial of the team in Houston revealed that patients with a PCI below 16 had a significantly better outcome compared to patients with a higher PCI: In the first group, the median survival achieved 34 months; in the second group, it was only 19.9 months ($p = 0.047$) [5].

16.4 Indication

To date, no larger case series are available that would allow evidence-based statements on the significance of CRS and HIPEC in pediatric patients. Based on the current data, the following indications seem to be suitable:

- Desmoplastic small round cell tumors (DSRCT)
- Rhabdomyosarcomas
- Colorectal cancer

Other entities that have been described in single case reports and that have already been treated by means of CRS and HIPEC are nephroblastomas (Wilms' tumors), chemotherapy-sensitive non-RMS-like sarcomas, histiocytic sarcoma, and germ cell tumors of the ovary [7, 11].

The decisions regarding therapy should be made by an interdisciplinary pediatric tumor board with expertise in the fields of pediatric oncological surgery as well as CRS and HIPEC. In addition, surgeons of the Cooperative Weichteilsarkom-Studie (CWS, Cooperative Soft Tissue Sarcoma Trial) of the Society for Pediatric Oncology and Hematology (GPOH,; www.gpoh.de) for patients treated in Europe or the Soft Tissue Sarcoma Committee of the Childrens Oncology Group (www.childrensoncologygroup.org) for North America may be consulted.

The following criteria should be taken into account and fulfilled in the context of indication [12]:

- Age of more than 1 year because chemotherapy may be associated with important systemic side effects in younger children
- Peritoneal tumors (sarcomas, DSRCT, carcinomas) limited to the peritoneal cavity
- Exclusion of distant metastases; however, liver metastases that can be entirely resected are not considered as distant metastases
- Achievement of complete tumor resection of CC-0/CC-1
- Compensated renal function (creatinine clearance of more than 50 ml/min/1.73 m^3)

The following contraindications should be excluded prior to CRS and HIPEC in children [12]:

- Poor physical condition that makes extensive abdominal surgery impossible
- Presence of distant metastases
- Presence of grade 3 neurotoxicity
- CRS and HIPEC during the previous 6 months
- Histologically confirmed diagnosis of liposarcoma

16.5 HIPEC in Young Children

There is currently not much data on CRS and HIPEC in young children. Nevertheless, this age group is important for this treatment approach since there are several contraindications for abdominal radiotherapy and relevant toxicity in young children. In a case series of six patients younger than 5 years of age, Gesche and colleagues have demonstrated that CRS and HIPEC are feasible in this age group with only low-grade side effects and only grade 1 and 2 toxicities. Additionally, the authors did not observe any complications even when a combination treatment with cisplatin and doxorubicin was used [2].

16.6 Neoadjuvant Therapy

Depending on the tumor entity, pediatric patients are generally treated with neoadjuvant therapy according to the current recommendations of the therapy protocols of the treatment optimization trials of the appropriate cooperative group. These recommendations also include a complete staging of the patients at the beginning of therapy. It encompasses, among other things, a whole-body MRI, a CT scan of the thorax, and a bone marrow examination of the child in order to exclude involvement of the bone marrow. For soft tissue sarcomas, we use the current protocol of the CWS trial of the GPOH [9]. Hereby, a histology-dependent neoadjuvant therapy is performed (embryonal RMS, "high-risk group"/alveolar RMS, "very high-risk group"). Neoadjuvant therapy consists of three cycles and includes a combination of ifosfamide, vincristine, and actinomycin D. In the "very high-risk group," the therapy regimen is extended with doxorubicin. Tumors of the family of non-RMS-like sarcomas are treated like tumors of the abovementioned "very high-risk group." After completion of neoadjuvant chemotherapy, reevaluation of the tumor region is performed by means of contrast-enhanced MRI. For patients with PS, it might be helpful to perform computed tomography of the abdomen to better assess PS. The level of radiation exposure should be adapted to the age of the pediatric patient; however, according to the authors, considering the severity of the disease, this risk may be neglected. Depending on the response of the tumor, an individual decision must be made on whether further reduction of the PS may be expected by cytostatic therapy and thus if neoadjuvant chemotherapy should be extended. However, the nephrotoxicity has to be taken into account in order not to jeopardize the later intraperitoneal application of platinum derivatives. An exception is colorectal carcinomas in pediatric and adolescent patients who do not receive neoadjuvant therapy and should directly undergo cytoreductive surgery and HIPEC. Secondary HIPEC after primary tumor surgery (e.g., hemicolectomy) should be performed within 10 days in order to avoid extensive adhesiolysis.

16.7 Cytostatics Applicable for HIPEC in Pediatric Patients

As is well-known, the intraperitoneal application of cytostatics in the context of HIPEC allows the best possible exposition of the peritoneal tumors and combines it with additional cytotoxic effects due to local hyperthermia. Similar to adults, the choice of the cytostatics for children depends on several factors. Determining factors are the tumor entity, the patient's age, as well as possible previous diseases [12].

Currently, mostly the application of cisplatin for HIPEC in children is described in the

literature. It seems to be appropriate as a relatively large water-soluble substance because it can hardly overcome the peritoneal barrier and enter the systemic circulation. Hayes-Jordan et al. [3] used concentrations of up to 100 mg/m^2 body surface. The clearly dose-limiting toxicity was the grade 3 nephrotoxicity, which could be reduced by the application of sodium thiosulfate, or whereby the dose could be increased to 100 mg/m^2 [3]. Severe chemotherapy-associated side effects have not been observed. In our own series, we were able to confirm that concentrations of 75 mg/m^2 body surface without application of sodium thiosulfate could lead to significant proteinuria, so concentrations of 50–75 mg/m^2 were used. Due to possible adverse effects (shock, impairment of consciousness, hypersensitivity reactions), sodium thiosulfate is currently not applied for nephroprotection in children and HIPEC in Germany. A combination of cisplatin with doxorubicin (15 mg/m^2 body surface) is also suitable and can also be used when relapse occurs [2, 12]. If the origin of peritoneal carcinomatosis is a colorectal carcinoma, mitomycin C (35 mg/m^2) over 90 minutes may be applied.

16.8 Preoperative Preparation

The necessity of preoperative imaging and staging of the patients was already depicted in Sect. 16.7. The patients are hospitalized on the day before surgery at the latest, and intestinal cleansing is performed with suitable substances (e.g., Macrogol). The dosage should be adjusted to the patient's age. Preoperative laboratory tests include blood count, prothrombin time, PTT, electrolytes, creatinine, urea, transaminases, overall/direct bilirubin, alkaline phosphatase, and albumin. Furthermore, the creatinine clearance is examined by means of 24-hour urine collection. Other preoperatively required examinations include echocardiography, ECG, audiometry, as well as a pregnancy test in female patients after menarche.

16.9 Surgery

The surgical technique and the details of the procedure were described by Sugarbaker [14, 15]. For pediatric patients, individual modifications are necessary. The surgical strategy should be CC-0/CC-1 resection, which may also require multi-visceral resection depending on the tumor entity and growth. Preoperative laparoscopy might be used in unclear cases as in adults to clarify diagnosis, but normally PC or PS is diagnosed on preoperative imaging. In children, we perform a median laparotomy from the epigastric region to the symphysis. In this way, an optimal exploration of the abdomen is possible. The transverse upper laparotomy, which is often used in smaller children as a possible approach, does not seem to be suitable because of the poorer exploration of the small pelvis. Following laparotomy, the entire abdomen is explored, and the PCI is determined and documented. The peritonectomy includes tumor-suspected regions and is performed with application of monopolar current, cutting from the periphery into the center. Organs are resected if they are infiltrated by the tumor. Prophylactic removal of non-infiltrated organs (splenectomy, cholecystectomy), as it had been performed when CRS and HIPEC was just being developed, is not indicated and can be omitted. Regarding the vessels, the decision must be made whether vascular resection with/without vascular graft or vessel-preserving resection with microscopic tumor residuals is possible. In cases of vascular grafts in pediatric patients, one must consider the fact that surgery is being performed in a still-growing organism and that the vascular graft cannot be left there for longer periods. Regarding the nerves, an individual decision must be reached if resection is required. In case of bowel resections, a hand-sewn, double-rowed end-to-end anastomosis is carried out with absorbable sutures due to bowel size in smaller children and the preference of the authors in older children. A stapled anastomosis might also be carried out in older children. Protective

stoma formation is omitted whenever possible due to appropriate wound healing in children in order to avoid redo-laparotomy. After completion of the tumor resection, HIPEC is prepared in the closed system. About 30 minutes prior to HIPEC, the patient has to be cooled down with the objective of maintaining central normothermia. The target parameter should be a core body temperature below 38.5 °C. For HIPEC, five drainages (two for the inflow, three for the outflow) are inserted in the abdominal cavity, and the abdomen is closed with a running suture. Then the test filling of the abdomen with warmed-up glucose 5% solution (41.5–42 °C) follows. The maximum filling volume of the abdominal cavity depends on the patient's age and weight, and it varies between 1.5 and 5 l.

- Parameters for filling are a moderate distension of the abdomen, the level of the tolerable ventilation pressure, and the maintenance of the patient's self-diuresis of 2–3 ml/kg body weight per hour.

The sufficient self-diuresis has to be verified by the surgical team before actually starting HIPEC. Afterward, the respective cytostatics are added in the predefined dosages via the HIPEC pump, similar to the procedure in adults (see Sect. 16.8). The cytostatic treatment is performed over 60 minutes at a temperature of 41.5–42 °C. After these 60 minutes, the abdominal cavity is first rinsed in the closed system and then openly. Finally, the abdominal wall is definitively closed [12]. The perioperative pain therapy is performed via a peridural catheter that is described in the literature as the analgesic procedure of choice [10].

16.10 Postoperative Treatment

Postoperatively, the patient is observed and cared for in the pediatric intensive care unit with 16–24 hours of ventilation. During this time, a PEEP of 8–10 is best to achieve.

- The postoperative supply of fluids amounts at least to 1.5 times the normal liquid quantity with the aim of a minimum diuresis of 1–2 ml/kg body weight per hour in order to avoid prerenal kidney failure [12].

The application of catecholamine varies individually. Skin clips should be removed on the 14th postoperative day at the earliest. Laboratory controls should be performed every day due to possible leukopenia.

16.11 Perioperative Complications

In single-case series, the morbidity and mortality of children and adolescents is considered to be lower than among adults [12]. Significant problems seem to be possible renal insufficiency and wound-healing impairment. In the largest HIPEC trial published to date, with 50 children and young adults, the rate of major complications amounted to 28% and included complications such as intestinal obstruction, pancreatitis, micturition disturbances, and wound-healing impairments [5]. In a trial conducted in France with nine patients, the complication rate was 78% [1].

16.12 Prevention of Complications

A definitive prevention of complications does not seem to be possible. Strict patient selection and indication may potentially reduce the number of complications. Important aspects in this context are the determination of the operability, the sufficient renal function, and the adequate dosage of the cytostatic agents.

16.13 Treatment Results

Extended peritoneal carcinomatosis in pediatric patients is very rare. Peritoneal sarcomatosis, however, occurs more frequently. To date, an international comparison with adults revealed

only few children and adolescents that have been treated. The largest trial published so far included 50 patients aged between 3 and 21 years: 21 patients suffered from DSRCT, 7 patients from RMS, 4 patients from mesotheliomas, and 21 from carcinomas. A multivariate analysis showed that patients with incomplete cytoreductive surgery and HIPEC had a significantly poorer outcome (5-year overall survival, 7.1 months) compared to patients with complete cytoreductive surgery and HIPEC (5-year overall survival, 31.4 months, $p = 0.012$). In addition, the level of the peritoneal carcinomatosis index played an important role for the survival of the patients [5]. The best treatment results were achieved for DSRCT. Here, a significant improvement in overall survival was revealed in combination with abdominal radiation [4]. A phase 2 trial demonstrated that complete CRS and HIPEC are effective in selected DSRCT patients, but patients with hepatic or portal metastasis have a poorer outcome [8]. Additionally, it was shown that the cytoreductive surgery itself seems to be the most effective local control modality in DSRCT [6]. In a retrospective trial of 187 DSRCT patients, including both children and adults, it has been shown that there was an improved 3- and 5-year OS following combined chemotherapy, cytoreductive surgery, and radiation therapy, but there was no improvement in survival in patients treated with additional HIPEC [13]. Therefore, the significance of HIPEC in DSRCT remains unclear. In a trial with nine patients in France, four out of nine patients survived after a median follow-up of 4.9 years [1]. In our own series of four children aged between 1 and 16 years with abdominal RMS, we observed complete tumor remission in all patients after a follow-up of 22.5 months. Treatment results are summarized in Table 16.1.

Table 16.1 Overview of CRS and HIPEC in children, adolescents and young adults in series with five or more patients. Case series with mixed patients populations (children/adults), in which a clear discrimination between these groups is not feasible are not shown

Author	Year	Patients (n)	Age (J)	Diagnosis	Survivors (n)	Complications (n)	Radiotherapy (n)
Stiles	2020	9	10–24	DSRCT	5	4	Yes (7/9)
Anghelescu	2019	9	10–24	DSRCT	9	4	No data
Gesche	2019	6	2–4	RMS	5	1	No
Zmora	2018	9	4–16	RMS Mesothelioma Sertoli-Leydig DSRCT Colonic cancer Wilms´ tumor	7	4 (minor)	3/9
Scalabre	2018	21	4–17	Mesothelioma DSRCT Others	6	14	Yes (4/21)
Hayes-Jordan	2015	50	3–21	DSRCT RMS Mesothelioma Carcinoma	25	28	No data
Seitz	2014	5	1–16	RMS Colonic cancer DSRCT	4	None	No
Bautista	2014	9	8–16	Ovarian tumors Mesothelioma HCC Pseudopapillary pancreatic tumor Adenocarcinoma	4	7	No data

16.14 Conclusion

Cytoreductive surgery and HIPEC in pediatric patients offer a new and innovative treatment approach that might be curative for abdominal rhabdomyosarcomas and DSRCT in children. To date, the best treatment outcomes have been achieved in patients with DSRCT [5], but it remains unclear whether cytoreductive surgery alone or combined with HIPEC is most effective [13]. The treatment of the patients requires high surgical efforts and intensive care, as well as the excellent interdisciplinary cooperation of pediatric anesthesiologists, pediatric surgeons, pediatric intensive care specialists, and pediatric oncologists. However, the relevance of the treatment cannot be ultimately assessed because of the low number of cases. Due to the rare occurrence of the diseases, patients should be treated and analyzed in international multicenter study protocols.

References

1. Bautista F, Elias D, Pasqualini C, Valteau-Couanet D, Brugieres L. Hyperthermic intraperitoneal chemotherapy after cytoreductive surgery for the treatment of peritoneal carcinomatosis in pediatric solid malignancies: a single institution experience. J Pediatr Surg. 2014;49:1276–9.
2. Gesche J, Beckert S, Neunhoeffer F, Kachanov D, Königsrainer A, Seitz G, Fuchs J. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: a safe treatment option for intraperitoneal rhabdomyosarcoma in children below 5 years of age. Pediatr Blood Cancer. 2019;66(2):e27517.
3. Hayes-Jordan A, Green H, Ludwig J, Anderson P. Toxicity of hyperthermic intraperitoneal chemotherapy (HIPEC) in pediatric patients with sarcomatosis/carcinomatosis: early experience and phase 1 results. Pediatr Blood Cancer. 2012;59:395–7.
4. Hayes-Jordan A, Green HL, Lin H, Owusu-Agyemang P, Fitzgerald N, Arunkumar R, Mejia R, Okhuysen-Cawley R, Mauricio R, Fournier K, Ludwig J, Anderson P. Complete cytoreduction and HIPEC improves survival in desmoplastic small round cell tumor. Ann Surg Oncol. 2014;21:220–4.
5. Hayes-Jordan A, Green H, Lin H, Owusu-Agyemang P, Mejia R, Okhuysen-Cawley R, Cortes J, Fitzgerald NE, McAleer MF, Herzog C, Huh WW, Anderson P. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for children, adolescents, and young adults: the first 50 cases. Ann Surg Oncol. 2015;22:1726–32.
6. Hayes-Jordan A. Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy in DSRCT: Progress and pitfalls. Curr Oncol Rep. 2015;17:38.
7. Hayes-Jordan A, Lopez C, Green HL, Xiao LC, Huh W, Herzog CE. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in pediatric ovarian tumors: a novel treatment approach. Pediatr Surg Int. 2016;32:71–3.
8. Hayes-Jordan A, Coakley BA, Green HL, Xiao LC, Fournier KF, Herzog CE, Ludwig JA, McAleer MF, Anderson PM, Huh WW. Desmoplastic small round cell tumor treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: results of a phase 2 trial. Ann Surg Oncol. 2018;25(4):872–7.
9. Koscieliniak E, Klingebiel T. CWS-guidance for risk adapted treatment of soft tissue sarcoma and soft tissue tumors in children, adolescents, and young adults. Stuttgart: Own Publication of the Cooperative Weichteilsarkom-Studiengruppe (CWS); 2014.
10. Owusu-Agyemang P, Soliz J, Hayes-Jordan A, Harun N, Gottumukkala V. Safety of epidural analgesia in the perioperative care of patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2014;21:1487–93.
11. Sandler G, Franklin A, Hayes-Jordan A. Histiocytic sarcoma in a child – successful management and long-term survival with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Pediatr Blood Canc. 2018;65:e27054.
12. Seitz G, Fuchs J, Königsrainer I, Warmann SW, Königsrainer A, Beckert S. Zytoreduktive Chirurgie und HIPEC bei peritoneal-metastasierten Tumoren im Kindesalter. Zentralbl Chir. 2014;139:607–12.
13. Subbiah V, Lamhamedi-Cherradi SE, Cuglievan B, Menegaz BA, Camacho P, Huh W, Ramamoorthy V, Anderson PM, Pollock RE, Lev DC, Qiao W, McAleer MF, Benjamin RS, Patel S, Herzog CE, Daw NC, Feig BW, Lazar AJ, Hayes-Jordan A, Ludwig JA. Multimodality treatment of desmoplastic small round cell tumor: chemotherapy and complete cytoreductive surgery improve patient survival. Clin Cancer Res. 2018;24(19):4865–73.
14. Sugarbaker PH. Peritonectomy procedures. Ann Surg. 1995;221:29–42.
15. Sugarbaker PH. Partial Pertonectomy. Ann Surg Oncol. 2012;19:1250.
16. Thomas A, Chen Y, Yu T, Gill A, Prasad V. Distinctive clinical characteristics of malignant mesothelioma in young patients. Oncotarget. 2015;6:16766–73.

Part VI

Potential Curative Treatment Attempt

17 Significance of Prophylactic Hyperthermic Intraperitoneal Chemotherapy After Curative Resection of Gastrointestinal Cancers

Philipp Horvath, Can Yurttas, Stefan Beckert, Florian Struller, Alfred Königsrainer, and Ingmar Königsrainer

17.1 Carcinomas of the Stomach and the Gastroesophageal Junction

The peritoneal cavity is the most common site of metastases of gastric cancer. 20% of patients planned for curative gastrectomy are diagnosed with peritoneal metastases at the time of exploration [8]. Despite cytoreductive surgery with HIPEC, survival rates are ranging between 9 and 21 months and depend on the completeness of cytoreduction [4–6]. This is also shown by the fact that the identification of risk factors for development of metachronous peritoneal carcinomatosis is emerging. To date, there is no clinical or diagnostic score that clearly identifies patients at risk. Serosal invasion and cytological detection of free tumor cells within the peritoneal cavity are generally accepted as risk factors [7].

In 2016, a meta-analysis of one randomized and two nonrandomized trials investigating the need for therapy of patients with detection of free peritoneal tumor cells without signs of macroscopic peritoneal metastases was published [2]. Patients with Cy+/PC- (positive cytology without peritoneal metastases) had a prolonged 2- and 5-year overall survival as well as a reduced incidence of metachronous peritoneal metastases when HIPEC was performed. An even bigger advantaged for both factors—2- and 5-year overall survival and reduction of metachronous peritoneal recurrences—was shown for a combination of HIPEC with extensive peritoneal lavage (7 to 10 liters of Ringer solution, depending on the trial). The only ran-

P. Horvath (✉) · C. Yurttas · A. Königsrainer
Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany
e-mail: Philipp.horvath@med.uni-tuebingen.de; can.yurttas@med.uni-tuebingen.de; alfred.koenigsrainer@med.uni-tuebingen.de

S. Beckert
Department of General and Visceral Surgery, Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Germany
e-mail: Stefan.Beckert@sbk-vs.de

F. Struller
Department of General, Visceral and Transplant Surgery, University Hospital Erlangen, Erlangen, Germany
e-mail: florian.struller@uk-erlangen.de

I. Königsrainer
Department of General, Visceral and Thoracic Surgery, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
e-mail: ingmar.koenigsrainer@lkhf.at

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_17

domized trial in this meta-analysis [10] with 88 patients randomized in three treatment groups (1. surgery; 2. surgery plus HIPEC; 3. surgery plus HIPEC and extensive peritoneal lavage) led to a median survival of 35 months for the third treatment group compared with 15 months in group 1 and 16 months in group 2. The multivariate analysis identified the peritoneal lavage as the only statistically significant prognostic factor. The EXPEL trial, an international multicenter randomized controlled trial evaluating the impact of extensive peritoneal lavage after curative gastrectomy, did not show an oncological benefit with a 3-year cumulative incidence of peritoneal recurrence of 6.6% for the therapy group and 7.9% for the control group (hazard ratio [HR] = 1.33; $p = 0.347$). [14] Limitations are caused by the low sensitivity (53%) but high specificity (90%) [7] of the cytological diagnostic and accuracy of T classification, which is mainly made by CT scan or endosonography. A proactive management justifies performance of HIPEC for patients without peritoneal metastases (PCI = 0) but with high-risk features. The National German ProPEC trial, which will evaluate the impact of prophylactic HIPEC in Cy+/PC- patients after curative gastrectomy, has not yet started recruitment. Graziosi et al. [7] treated 11 patients with locally advanced gastric cancer at risk for the development of metachronous peritoneal metastases (T4 cancer with either detected tumor cells or mRNA of CEA by quantitative PCR in peritoneal cytology) with gastrectomy including D2 lymphadenectomy and prophylactic HIPEC with cisplatin and mitomycin C [7].

- Only one patient after gastrectomy in combination with HIPEC was diagnosed with peritoneal metastasis after 12 months, whereas the other patients had a median survival of 29.6 months and a disease-free survival of 20 months.

The prospective and randomized GASTRICHIP trial is designed to investigate the effect of an additional prophylactic HIPEC for patients at risk of peritoneal carcinomatosis (e.g., serosal invasion, lymph node metastasis, cytological detection of tumor cells) after curative gastrectomy with D2 lymphadenectomy.

Comparable to Craziosi's trial but with a longer follow-up, Kang et al. [9] were able to show a benefit to prophylactic HIPEC for patients with pre- or intraoperative diagnosis of serosal invasion (3-year disease-free survival 29% vs. 66%). There was also no statistically significant difference in perioperative complications. Similarly, Saladino et al. [12] were able to show a survival benefit for 12 patients with a median survival of 24 months. During follow-up, only one patient developed peritoneal carcinomatosis.

- In summary, highly selected patients at risk of peritoneal metastasis should be offered a treatment consisting of prophylactic HIPEC in addition to the resection with an acceptable mortality rate.

17.2 Colorectal Cancer

Peritoneal metastasis is the second most common site of metastatic disease of colorectal cancer. In comparison with gastric cancer, fewer colorectal cancer patients (4.3–7.1%) are diagnosed with peritoneal metastases at the primary operation [1]. The fraction of patients who develop metachronous peritoneal metastasis is reported to be as high as 50% in some publications [13]. Three trials, one of which is randomized and two nonrandomized, were able to show a survival benefit for cytoreductive surgery with HIPEC compared to standard resection combined with systemic chemotherapy. Selected patients may reach 5-year survival rates of 45%. Such results are

only applicable for patients with initially low tumor burden and complete cytoreduction.

Preventive procedures have been established in almost all areas of medicine and have contributed to prolongation of overall survival. This approach has also been evaluated for patients with colorectal cancer.

▶ Sugarbaker [15] defined parameters that justify a prophylactic approach.

The following summary shows an overview:

▶ Indications for a prophylactic HIPEC in colorectal cancer (modified according to [15])

- T4 tumors
- Peritoneal biopsy showing peritoneal metastasis or suspicious ovary mass
- R1 situation
- Spontaneous or iatrogenic tumor rupture
- Tumor cells in cytology
- Tumor infestation of neighboring organs or fistulation
- Metastatic infestation of lymph vessels at the resection site

Sammartino et al. [13] performed a monocentric case-control trial enrolling only patients with advanced tumor stages (T3 and T4) and mucinous or signet-cell histology in order to investigate the effect of a prophylactic HIPEC on overall survival and disease-free survival. The surgical therapy was extended by omentectomy, appendectomy, and bilateral adnexectomy for postmenopausal women in the therapy group.

▶ This aggressive approach during primary resection led to a statistically significant improvement of disease-free survival (36.8 vs. 21.9 months), while the overall survival remained equal.

The morbidity was similar in both groups. After a follow-up of 37.8 months, there was only one patient with peritoneal recurrence in the therapy group, whereas 11 patients in the control group experienced metachronous peritoneal recurrence. HIPEC had no effect on the incidence of systemic disease. However, as a possible bias, it is worth noting that surgical therapy differed in both treatment groups. Although there were no peritoneal metastases in the additionally resected specimens, it is questionable whether the reduced rate of peritoneal recurrences is due to the extended resection of predilection sites for peritoneal metastases or due to HIPEC. This proactive approach is further confirmed by data from Elias et al. [3]. Patients with tumor perforation, ovary metastases, or synchronous peritoneal metastasis had second look surgery. At the time of second look surgery, there were no clinical or radiological signs of peritoneal recurrence. 55% of patients had peritoneal metastases at the time of second operation after 12 months. Following cytoreductive surgery with HIPEC, after a follow-up of 24 months, 50% of patients were free of recurrence. In patients with high-risk features after primary tumor resection, diagnostic laparoscopy is a viable option for detecting asymptomatic and radiologically undetected peritoneal recurrence.

17.3 Pancreatic Cancer

Despite radical surgery and standardized adjuvant chemotherapy for pancreatic ductal adenocarcinoma, prognosis remains poor though. At primary diagnosis, only 10–20% of patients qualify for curative resection, of which 15% are still alive after 5 years.

▶ Failure of therapy is due to a high rate of local (50%) and peritoneal (40–60%) recurrences despite curative R0 resection [17].

These high recurrence rates are thought to arise from tumor-cell spillage from the tumor or its lymphatic or blood vessels. These free tumor cells are entrapped by fibrin or adhesions at the

resection site and may contribute to local or peritoneal recurrences. To date there are two phase I/II trials that investigate a clinical benefit of 60 minutes of HIPEC with 1000 mg/m^2 gemcitabine after R0 or R1 resection of ductal pancreatic adenocarcinoma [16, 17]. The idea behind using intraperitoneal gemcitabine is the 200- to 500-fold increase in intraperitoneal concentration by comparison with systemic levels [16]. Pharmacological studies by Sugarbaker et al. [16] showed that 68% of gemcitabine is resorbed after 60 minutes and that the plasma peak of 4.03 µg/ml is reached after 15 minutes. After intravenous application of gemcitabine, the optimal plasma level of gemcitabine is reported to be 5.26 µg/ml [11].

This very similar plasma level with higher local exposition at the predilection sites for recurrences makes gemcitabine HIPEC an attractive treatment option. Tentes et al. [17] were able to show a clinical benefit for 21 patients in a monocentric phase I/II trial of gemcitabine HIPEC.

- With rates of morbidity and mortality of 33% or 9.5%, respectively, the 5-year overall survival was 23%. The overall recurrence rate was 50%. However, no patient had a local recurrence.

Of 21 patients in total, 17 patients had duodenopancreatectomy (Whipple's procedure). There was only one insufficiency of the pancreaticojejunal anastomosis, which was treated in a conservative manner. Although the number of patients was low, a remarkable tumor control was achieved. Likewise, Sugarbaker et al. [16] were able to demonstrate the benefit of gemcitabine HIPEC in a phase II clinical trial. In this trial, an intraperitoneal port system was implanted in order to facilitate the intraperitoneal application of gemcitabine postoperatively. For 6 months in total, the normothermic intraperitoneal chemotherapy with gemcitabine continued. Without grade 3 or grade 4 toxicities, this treatment was well tolerated. At this time point, results concerning long-term survival have not yet been reported. The german monocentric phase I/II trial (PanHIPEC) investigating the effect of additional gemcitabine HIPEC after R0 or R1 resection of pancreatic ductal adenocarcinoma has currently been finished in Tuebingen, and its results are about to be published.

As is the case for gastric cancer, the impact of extensive peritoneal lavage on peritoneal recurrence after curative resection of pancreatic cancer has also been evaluated. Yamamoto et al. [18] compared a non-EIPL (extensive intraoperative peritoneal lavage) group to an EIPL group, and the performance of EIPL was statistically significantly associated with reduced peritoneal recurrences. As a small number of patients were included, no definite conclusions can be drawn from these results, but EIPL after curative resection of pancreatic cancer should be further evaluated.

17.4 Conclusion

- Despite curative resection of gastrointestinal carcinomas, many patients experience peritoneal recurrences. Prophylactic HIPEC after curative resection is still experimental, but might be offered to selected patients at risk of developing peritoneal metastases. Although the numbers of treated patients are low, the latest data show that prophylactic HIPEC may reduce the incidence of peritoneal recurrences in gastric, colorectal, and pancreatic cancer.

References

1. Baratti D, Kusamura S, Deraco M. Prevention and early treatment of peritoneal metastases from colorectal Cancer: second-look laparotomy or prophylactic HIPEC? J Surg Oncol. 2014;109:225–6.
2. Coccolini F, Catena F, Glehen O, et al. Effect of intraperitoneal chemotherapy and peritoneal lavage in positive peritoneal cytology in gastric cancer. Systematic review and meta-analysis. Eur J Surg Oncol. 2016;42:1261–7.
3. Elias D, Goéré D, Di Pietrantonio D, et al. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2008;247:445–50.

4. Glehen O, Schreiber V, Cotte, et al. Cytoreductive surgery and intraperitoneal chemohyperthermia for peritoneal carcinomatosis arising from gastric cancer. Arch Surg. 2004;139:20–6.
5. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17:2370–7.
6. Glehen O, Passot G, Villeneuve L, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. BMC Cancer. 2014;14:183.
7. Graziosi L, Cantarella F, Mingrone E, et al. Preliminary results of prophylactic HIPEC in patients with locally advanced gastric cancer. Ann Ital Chir. 2013;84:551–6.
8. Hioki M, Gotohoda N, Konishi M, et al. Predictive factors improving survival after gastrectomy in gastric cancer patients with peritoneal carcinomatosis. World J Surg. 2010;34:555–62.
9. Kang LY, Mok KT, Liu SI, et al. Intraoperative hyperthermic intraperitoneal chemotherapy as adjuvant chemotherapy for advanced gastric cancer patients with serosal invasion. JCMA. 2012;76:425–31.
10. Kuramoto M, Shimada S, Ikeshima S, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg. 2009;250:242–6.
11. Sabbatini P, Aghajanian M, Leitao, et al. Intraperitoneal cisplatin with intraperitoneal gemcitabine in patients with epithelial ovarian cancer: results of a phase I/II trial. Clin Cancer Res. 2004;10:2962–7.
12. Saladino E, Fleres F, Mazzeo C, et al. The role of prophylactic hyperthermic intraperitoneal chemotherapy in the management of serosal involved gastric cancer. Anticancer Res. 2014;34:2019–22.
13. Sammartino P, Sibio S, Biacchi D, et al. Prevention of peritoneal metastases from Colon cancer in high-risk patients: preliminary results of surgery plus prophylactic HIPEC. Gastroenterol Res Pract. 2012;2012:141585.
14. So J, Ji J, Han SU, et al. Extensive peritoneal lavage after curative gastrectomy for gastric cancer study (EXPEL): an international multicenter randomized controlled trial. Abstract ASCO 2020. 2020.
15. Sugarbaker PH. Update on the prevention of local recurrence and peritoneal metastases in patients with colorectal cancer. World J Gastroenterol. 2014;20:9286–91.
16. Sugarbaker PH, Stuart A, Bijelic L. Intraperitoneal gemcitabine chemotherapy treatment for patients with resected pancreatic Cancer: rationale and report of early data. Int J Surg Oncol. 2011;2011:161862.
17. Tentes AAK, Kyziridis D, Kakolyris S, et al. Preliminary results of Hyperthermic intraperitoneal intraoperative chemotherapy as an adjuvant in Resectable pancreasstic cancer. Gastroenterol Res Pract. 2012;2012:506571.
18. Yamamoto K, Shimada S, Hirota M, et al. EIPL (extensive intraoperative peritoneal lavage) therapy significantly reduces peritoneal recurrence after pancreatectomy in patients with pancreatic cancer. Int J Oncol. 2005;27:1321–8.

18 Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Pseudomyxoma Peritonei

Florian Struller, Stefan Beckert, Ingmar Königsrainer, Alfred Königsrainer, and Faheez Mohamed

18.1 Introduction

Pseudomyxoma peritonei (PMP) is an uncommon malignancy with an estimated incidence of 1–2 per million people worldwide and a complex biological behavior. The term describes a clinical macroscopic diagnosis; most cases arise from a perforated primary appendix tumor.

The disease is characterized by an intra-abdominal, partially adherent mucus accumulation and slimy ascites in characteristic sites of the abdominal cavity, often with sparing of the small bowel. Symptoms can progress slowly over many years and are nonspecific with abdominal distension from intra-abdominal accumulation of mucinous ascites or "jelly belly" that make it difficult to eat and drink which results in weight loss and ultimately bowel obstruction (see Fig. 18.1) [6].

18.2 The Origin of Pseudomyxoma Peritonei: The Mucinous Appendiceal Neoplasm

According to the consensus conference (modified Delphi consensus process) under the auspices of the Peritoneal Surface Oncology Group International (PSOGI), mucinous neoplasms are subdivided into [5]:

F. Struller (✉)
Department of General and Transplant Surgery, University Hospital Erlangen, Erlangen, Germany
e-mail: florian.struller@uk-erlangen.de

S. Beckert
Department of General Surgery, Hospital Schwarzwald-Baar, Villingen-Schwenningen, Germany
e-mail: stefan.beckert@sbk-vs.de

I. Königsrainer
Department of General and Thoracic Surgery, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
e-mail: ingmar.koenigsrainer@lkhf.at

A. Königsrainer
Department of General and Transplant Surgery, University of Tübingen, Comprehensive Cancer Center, Tübingen, Germany
e-mail: Alfred.koenigsrainer@med.uni-tuebingen.de

F. Mohamed
Peritoneal Malignancy Institute, Basingstoke and North Hampshire Hospital, Basingstoke, UK

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_18

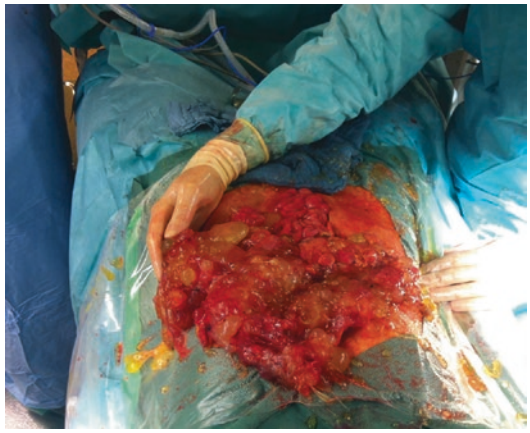


Fig. 18.1 Intra-abdominal slimy ascites, so-called jelly-belly

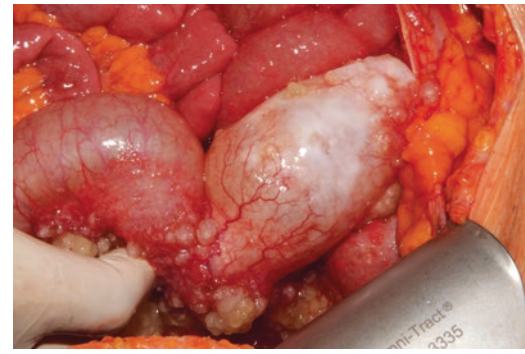


Fig. 18.2 Low-grade appendiceal mucinous neoplasm (LAMN) with pseudomyxoma peritonei

(a) Low-grade appendiceal mucinous neoplasms (LAMN)
(b) High-grade appendiceal mucinous neoplasms (HAMN)
(c) Mucinous adenocarcinoma

The assessment of biological behavior of LAMN has been discussed in the literature. On the one hand, this neoplasm displays benign features as there is no destructive invasion of organs. On the other hand, LAMN shows histomorphological similarity to adenomas of the colon [14]. Macroscopically, the appendix can appear normal or may be distended . The appendiceal wall is often fibrotic and calcified with intramural mucin (see Fig. 18.2). Patients often present with symptoms of acute appendicitis. In cases where the appendiceal wall is intact, without any signs of rupture and negative resection margins, the appendectomy may be curative [1].

However, the rupture or perforation of LAMNs will cause intraperitoneal dissemination of mucin. Despite the lack of infiltration with slow progression in terms of a diffuse peritoneal adenomucinosis (DPAM), the mucinous accumulation does not exhibit any malignant potential but can result in death from bowel obstruction and terminal starvation.

LAMNs usually show KRAS mutation but generally do not show microsatellite instability or BRAF mutation. GNAS mutations have been detected which are uncommon in colorectal neoplasms.

HAMN do not exhibit infiltrative invasion, but, in contrast to LAMN, they display high-grade dysplasia. The macroscopic and histomorphological changes of the appendiceal wall are the same as those observed in LAMN. So far, there is little evidence regarding the behavior of HAMN. Some authors suggest that HAMN exhibit a more aggressive course than LAMN or they are more likely associated with epithelial cells in the extra-appendiceal mucin.

In contrast, the mucinous adenocarcinoma of the appendix displays malignant properties such as invasive tumor growth with desmoplastic stroma and high-grade atypia, which may include signet-ring cell histology and the potential development of distant metastases.

Besides appendiceal tumors, other perforated tumors of the gastrointestinal tract can very rarely cause a pseudomyxoma peritonei—for instance, the mucinous carcinoma of the colon or pancreatic carcinoma.

Rarely pseudomyxoma peritonei arises from an urachal or ovarian carcinoma. The ovaries are often involved and commonly incorrectly identified as the primary tumour. The ovaries are the primary tumor site in well-differentiated mucinous adenocarcinoma of an intestinal type, arising within a cystic teratoma [13].

18.3 Pseudomyxoma Peritonei: A Clinical Term

As already mentioned, the term "pseudomyxoma peritonei" reflects a macroscopic description of intra-abdominal mucinous accumulation rather than a histological diagnosis.

According to the classification of Carr et al. within the framework of the consensus conference, the cellularity of the mucin as well as the degree of dysplasia is differentiated into acellular, low-, high-grade and high-grade with signet ring cells (see Table 18.1) [5].

In cases where perforation of LAMN has occurred, tumor cells enter freely into the abdominal cavity and circulate with the peritoneal fluid, resulting in following predilection sites:

- The paracolic gutters
- The greater omentum
- The undersurfaces of the diaphragm
- The pouch of Douglas [12]

Typically, pseudomyxoma peritonei does not show distant metastasis and only limited involvement of the small bowel serosa, and it is characterized by slow but progressive tumor growth.

Table 18.1 Classification of pseudomyxoma peritonei

Lesion	Criteria
Acellular mucin	Mucin containing non-neoplastic epithelial cells
Low-grade mucinous carcinoma peritonei/DPAM	Epithelial component Minimal cytological atypia Sporadic mitosis Pushing type invasion
High-grade mucinous carcinoma peritonei/PMCA	Relatively more cellular High-grade atypia Numerous mitosis Destructive infiltrative invasion
High-grade mucinous carcinoma peritonei with signet ring cells/PMCA-S	Any lesion containing signet ring cells

Modified according to Carr et al. [5]
DPAM disseminated peritoneal adenomucinosis, *PMCA* peritoneal mucinous carcinomatosis, *PMCA-S* peritoneal mucinous carcinomatosis

These characteristics fulfill the definition of a locoregional tumour making it ideally suited for cytoreductive surgery and HIPEC [17].

For the most part, the grade of dysplasia of the appendiceal neoplasm correlates with the grade of dysplasia of the PMP, implying that LAMN is not necessarily but mostly associated with a low-grade pseudomyxoma peritonei, whereas a high-grade appendiceal neoplasm is associated with a high-grade pseudomyxoma peritonei [2].

18.4 Who Can Undergo Surgery? Patient Selection and Indications

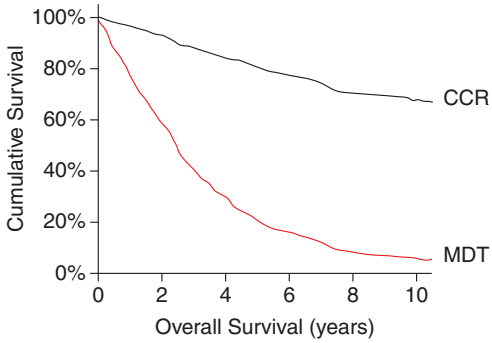
In 1980, the very first patient who successfully underwent cytoreductive surgery and HIPEC performed by Spratt et al. was a 35-year-old male suffering from pseudomyxoma peritonei with unknown primary [15].

These often time-consuming surgeries with corresponding morbidity and mortality as well as postoperative intensive care are a great burden for the patient. Thus, one is reluctant to perform cytoreduction on patients with cardiopulmonary comorbidity and poor nutritional status. These patients have an increased risk of postoperative complications with prolonged intensive care therapy and with corresponding poor quality of life [18].

Crucial factors influencing patient's survival and hence the indication for surgery are not only the histology of PMP, but also the prior surgical score, the peritoneal cancer index (PCI), and the completeness of cytoreduction score (CC score) [9] (see Fig. 18.4).

Ten-year overall survival of patients with low- and high-grade PMP after complete cytoreduction combined with HIPEC is ca. 75% compared to 5% with maximal tumor debulking (CC-2/−3). (see Fig. 18.3)

Overall survival of patients with low-grade PMP and complete cytoreduction (CC-0/−1) combined with HIPEC is significantly higher, with a 20-year survival rate of ca. 78% compared to a 54% 10-year survival in patients with high-grade histology ([7]).



Number at Risk

CCR	1102	890	650	447	227	169
MDT	338	175	80	32	12	8

Fig. 18.3 Survival curve for patients with PMP treated at Peritoneal Malignancy Institute, Basingstoke, with CRS and HIPEC. CCR = complete cytoreductive surgery; MDT = maximal debulking of tumor. (With kind approval of K. Chandrakumaran)

There is little evidence to support the use of the peritoneal cancer index (PCI) in selecting patients with PMP who might benefit from CRS and HIPEC. Some authors defined the cutoff as a PCI of 20 [3, 7]. The critical question is how well one can effectively select patients preoperatively using computer tomography (CT)—the standard imaging for detecting peritoneal metastases—and what the actual influence of the radiological PCI is on resectability.

Flicek et al. [8] demonstrated that the radiological PCI underestimated by 7.8 points the intraoperative PCI in 62% of patients. Of the remaining 42 patients, the actual intraoperative PCI was overestimated by 5.5 points on average. The main reasons for the preoperative underestimation of the intraoperative PCI were the dissemination of tumor growths smaller than 1 cm and the concealment of tumor by ascites. The radiological overestimation of the actual PCI was based on mucinous ascites mimicking an incorrect tumor burden. Overall, the radiological PCI showed a sensitivity of 76% and a specificity of 69%, with a positive and negative predictive power of 85% and 56%, respectively.

In this study, the PCI cutoff of 20 was not an effective parameter for predicting complete cytoreduction. For almost half of the patients whose radiological PCI was greater than 20, complete cytoreduction was achieved. In contrast, for 7% of patients whose PCI was lower than 20, complete cytoreduction could not be achieved .

Benhaim et al. [4] evaluated the difference in survival and mortality according to the extent of PMP. Extensive PMP was defined as an PCI >28, whereas non-extensive PMP as an PCI < 28. The 5-year overall survival was 70% in the extensive PMP group and 90% in the non-extensive group ($p < 0.0001$). Patients in the extensive PMP group experienced more complications (46% vs. 23%, $p < 0.001$), but the post-operative mortality was not significantly different (8% vs. 3%, $p = 0.1$).

Based on our own clinical experience, the PCI level alone is not an accurate parameter for determining suitability for surgery (Fig. 18.4).

Rather, the PCI must be considered together with the histology and the performance status of the patient. In cases of low-grade pseudomyxoma, a complete cytoreduction can be achieved despite high intra-abdominal tumor burden. However, in cases of a high-grade pseudomyxoma peritonei with invasive tumor growth together with a high intra-abdominal tumor burden, the likelihood of complete cytoreduction is lower (see Fig. 18.5). The crucial fact for the prognosis of the patient is the achievement of complete cytoreduction, which can be achieved in cases of low-grade histology despite a high PCI for most patients. The comorbidities of the patient can, however, be limiting if extensive surgery is likely.

▶ Thus, the PCI itself should not be the only parameter for indication to surgery but should always be considered together with the patient's condition as well as the histology.

Complete cytoreduction and HIPEC are critical for patient survival. For low-grade PMP, the 20-year survival rate following incomplete cytoreduction (CC-2/−3) without HIPEC drops to

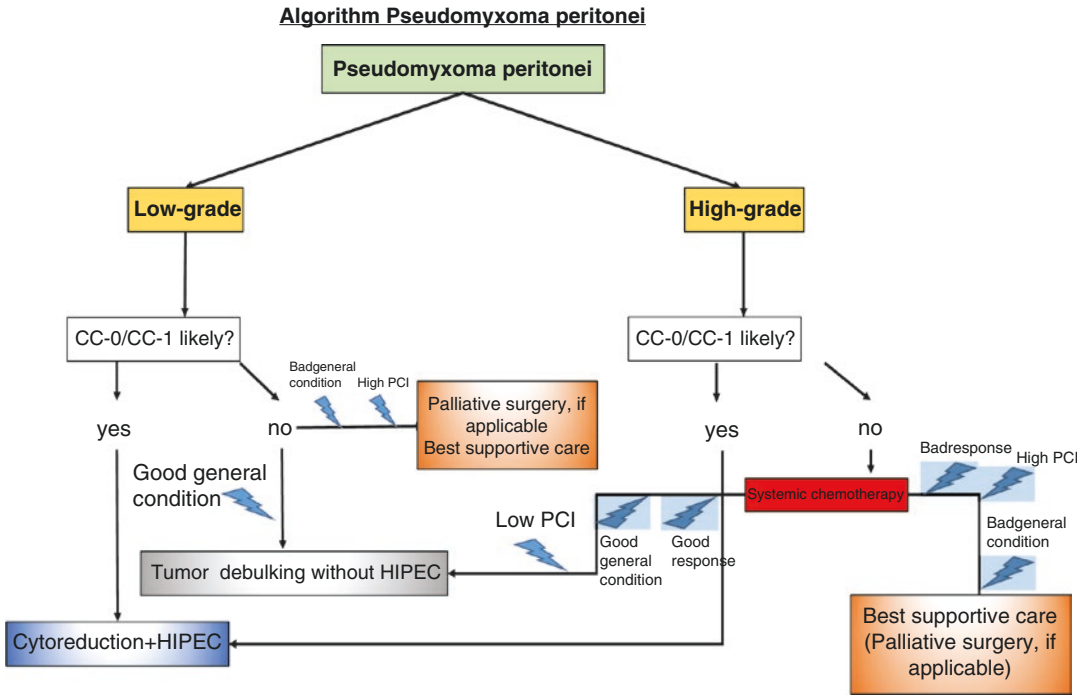


Fig. 18.4 Treatment algorithm for pseudomyxoma peritonei

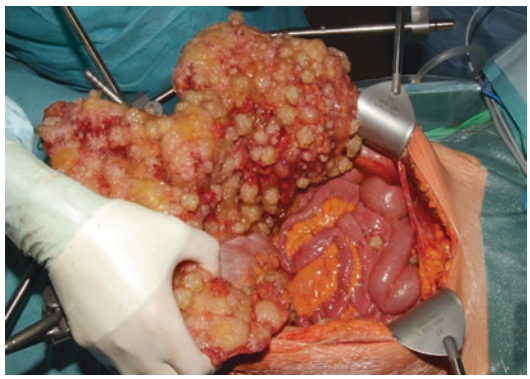


Fig. 18.5 Omental cake in high-grade pseudomyxoma peritonei

26% (compared with 78% for CC-0/−1). In cases of high-grade PMP, the data is even worse. Only 10% of patients are alive after 10 years following incomplete cytoreduction (compared with 54% after complete cytoreduction).

Despite this, survival rates after incomplete cytoreduction are acceptable so that tumor debulking with or without HIPEC is justified in some cases, in particular for low-grade histology. In a retrospective analysis of Dayal et al. [19], an overall survival rate at 3, 5, and 10 years of 47%, 30%, and 22% was achieved in case of maximal tumor debulking in PMP.

18.5 Where to Refer Patients? Surgical Centers

Prolonged survival is seen in patients with complete cytoreduction, low-grade histology without prior extensive surgery, no lymph node involvement, and minimal small intestinal involvement.

It is crucial to select these kinds of patients early enough and to send them to a surgical center that is specialized in the treatment of peritoneal metastases. The learning curve for cytoreductive surgery in PMP is steep and significantly longer than other surgical procedures [11]. Benhaim et al. [4] were able to demonstrate this impressively, particularly in cases of extensive PMP with a high PCI. The experienced surgeon is the best guarantor of a CC-0 resection. This

emphasizes the importance of choosing an experienced surgical center for this complex disease.

- All patients with PMP should be referred to a surgical center specialized in the treatment of peritoneal metastases.

18.6 Inoperable Patients: Systemic Chemotherapy?

The role of systemic chemotherapy is unclear for patients in whom no surgical solution is available. Chua et al. [7] showed that neoadjuvant chemotherapy worsened the outcome of patients.

Data regarding the outcome of palliative systemic chemotherapy for patients with advanced PMP are not available. Overall, response rates of approximately 29% have been demonstrated with progression-free survival of approximately 7 months. However, disease progression rates of up to 50% were seen [10, 16].

- Systemic chemotherapy is only justified in patients with unresectable disease of an aggressive histological subtype. Here, chemotherapy could improve survival compared to purely palliative therapy in terms of best supportive care. The decision should be made on an individual basis.

18.7 Conclusion

A complete cytoreduction is the most important determinant of long-term survival following CRS and HIPEC for PMP. Patient selection should utilize tools that allow an accurate estimation of the likelihood that complete tumor removal will be achieved. Preoperative radiology in the form of an abdominal CT scan with positive oral and intravenous contrast remains one of the most effective methods of identifying suitable patients. Although radiological PCI can aid in surgical planning, it is not a sensitive indicator of the surgeon's ability to achieve complete cytoreduction. High-volume centers have the best outcomes following CRS and HIPEC with an institutional learning curve ensuring morbidity and mortality are minimized. Although complete cytoreduction is desirable, tumor debulking can be beneficial. Due to the protracted surgery and corresponding morbidity, the patient's general condition is the critical factor regarding indications for surgery.

The gold standard of treatment for pseudomyxoma peritonei thus represents, with a few exceptions, complete cytoreduction in combination with HIPEC. In any case, the decision on therapy should be made by a multidisciplinary team.

References

1. Arnason T, Kamionek M, Yang M, Yantiss RK, Misdraji J. Significance of proximal margin involvement in low-grade appendiceal mucinous neoplasms. Arch Pathol Lab Med. 2015;139(4):518–21.
2. Baratti D, Kusamura S, Milione M, Bruno F, Guaglio M, Deraco M. Validation of the recent PSOGI pathological classification of Pseudomyxoma Peritonei in a single-center series of 265 patients treated by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2018;25(2):404–13.
3. Barrios P, Losa F, Gonzalez-Moreno S, Rojo A, Gomez-Portilla A, Bretcha-Boix P, et al. Recommendations in the management of epithelial appendiceal neoplasms and peritoneal dissemination from mucinous tumours (pseudomyxoma peritonei). Clin Transl Oncol. 2016;18(5):437–48.
4. Benhaim L, Honore C, Goere D, Delhorme JB, Elias D. Huge pseudomyxoma peritonei: surgical strategies and procedures to employ to optimize the rate of complete cytoreductive surgery. Eur J Surg Oncol. 2016;42(4):552–7.
5. Carr NJ, Bibeau F, Bradley RF, Dartigues P, et al. Histopathological classification, diagnosis and differential diagnosis of mucinous appendiceal neoplasms, appendiceal adenocarcinomas and pseudomyxoma peritonei. Histopathology. 2017;71(6):847–58.
6. Chira RI, Nistor-Ciurba CC, Mociran A, Mircea PA. Appendicular mucinous adenocarcinoma associated with pseudomyxoma peritonei, a rare and difficult imaging diagnosis. Med Ultrason. 2016;18(2):257–9.
7. Chua TC, Moran BJ, Sugarbaker PH, Levine EA, Glehen O, Gilly FN, et al. Early- and long-term

outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol. 2012;30(20):2449–56.
8. Flicek K, Ashfaq A, Johnson CD, Menias C, Bagaria S, Wasif N. Correlation of radiologic with surgical peritoneal cancer index scores in patients with pseudomyxoma peritonei and peritoneal carcinomatosis: how well can we predict Resectability? J Gastrointest Surg. 2016;20(2):307–12.
9. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74.
10. Lieu CH, Lambert LA, Wolff RA, Eng C, Zhang N, Wen S, et al. Systemic chemotherapy and surgical cytoreduction for poorly differentiated and signet ring cell adenocarcinomas of the appendix. Ann Oncol. 2012;23(3):652–8.
11. Ansari N, Chandrakumaran K, Dayal S, Mohamed F, Cecil TD, Moran BJ. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1000 patients with perforated appendiceal epithelial tumours. Eur J Surg Oncol. 2016;42(7):1035–41.
12. Raptopoulos V, Gourtsoyiannis N. Peritoneal carcinomatosis. Eur Radiol. 2001;11(11):2195–206.
13. Reiter E. Muzinöse Appendixtumoren und Pseudomyxoma peritonei: Ein aktueller Überblick. Interdisziplinäre Onkologie. Ann Oncol. 2012;23:652–8.
14. Reu S, Neumann J, Kirchner T. Mucinous neoplasms of the vermiform appendix, Pseudomyxoma peritonei, and the new WHO classification. Pathologe. 2012;33(1):24–30.
15. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res. 1980;40(2):256–60.
16. Sugarbaker PH, Bijelic L, Chang D, Yoo D. Neoadjuvant FOLFOX chemotherapy in 34 consecutive patients with mucinous peritoneal carcinomatosis of appendiceal origin. J Surg Oncol. 2010;102(6):576–81.
17. Sugarbaker PH. Cytoreductive surgery and perioperative intraperitoneal chemotherapy as a curative approach to pseudomyxoma peritonei syndrome. Eur J Surg Oncol. 2001;27(3):239–43.
18. Vashi PG, Gupta D, Lammersfeld CA, Braun DP, Popiel B, Misra S, et al. The relationship between baseline nutritional status with subsequent parenteral nutrition and clinical outcomes in cancer patients undergoing hyperthermic intraperitoneal chemotherapy. Nutr J. 2013;12:118.
19. Dayal S, Taflampas P, Riss S. Complete cytoreduction for pseudomyxoma peritonei is optimal but maximal tumor debulking may be beneficial in patients in whom complete tumor removal cannot be achieved. Dis Colon Rectum. 2013;56(12):1366–72.

19 The Role of CRS and HIPEC in the Management of Diffuse Malignant Peritoneal Mesothelioma (DMPM)

Beate Rau, Marianne Sinn, Pankaj Kumar Garg, Marcello Deraco, and Andreas Brandl

19.1 Epidemiology and Frequency of DMPM

Malignant mesothelioma (MM) is an aggressive malignant disease of the mesothelium that can involve the pleura, peritoneum, pericardium, and tunica vaginalis and is associated with a dismal long-term prognosis. Diffuse malignant peritoneal mesothelioma (DMPM) is a malignant neoplasm originating from the mesothelium of the peritoneum. It has a morphological similarity to pleural mesothelioma and is associated with asbestos and erionite exposure. Asbestos is a collective name for several naturally occurring fibrous crystallized silicate minerals. In 50–80% of cases, prior asbestos exposure is present, and the likelihood of DMPM increases exponentially with the duration of exposure. The role of the SV40 virus in the etiopathogenesis of MM is still being debated. Similarly, the role of genetic predisposition is still unclear, as familial asbestos contamination (e.g., through contact with contaminated clothing) cannot be ruled out [28].

The Germline BAP1 (BRCA1-associated protein 1) mutation that causes an autosomal-dominant inherited cancer syndrome characterized by MM and uveal melanoma was first reported after an investigation was conducted into a mesothelioma epidemic in Cappadocia, Turkey [17]. In a Consensus Report of the 2015 Weinman International Conference on Mesothelioma, BAP1 screening was recommended for the patients with MM occurring in the setting of a high-risk family history of MM, UM, cutaneous melanoma, renal cell carcinoma, cholangiocarcinoma, and basal cell carcinoma and/or a high family incidence of multiple cancers and patients with MM carrying melanocytic

B. Rau (✉)
Department of Surgery, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität of Berlin, Berlin, Germany
e-mail: beate.rau@charite.de

M. Sinn
Universitäres Cancer Center, Hamburg-Eppendorf, Hamburg, Germany

Universitätsklinikum Hamburg-Eppendorf, II. Medizinische Klinik und Poliklinik- Onkologie, Hämatologie, Knochenmarktransplantation mit der Sektion Pneumologie, Hamburg, Germany
e-mail: ma.sinn@uke.de

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

M. Deraco
Fondazione IRCCS Istituto Nazionale Dei Tumori di Milano, Peritoneal Surface Malignancies Unit, Milan, Italy
e-mail: marcello.deraco@istitutotumori.mi.it

A. Brandl
Digestive Unit, Champalimaud Foundation, Lisbon, Portugal
e-mail: andreas.brandl@fundacaochampalimaud.pt

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_19

BAP1-mutated atypical intradermal tumors known as MBAITs [10].

With an incidence rate in industrialized countries of 0.5 to 3 cases per 1,000,000 inhabitants in men and 0.2 to 2 cases per 1,000,000 in women, abdominal mesothelioma is a rare disease [1, 9, 44]. Compared with pleural mesothelioma, it is ten times rarer, with fewer than 100 new cases per year reported in Germany. Despite the ban on using asbestos-containing building materials, the incidence of asbestos-related illnesses continues to rise. This can be explained by the long latency period of 15 to 60 years following asbestos exposure for the development of MM [44]. Accordingly, the majority of the patients are in the sixth decade of their life or older [7].

In particular, asbestos fibers of >5 μm in length are considered to play a relevant role in the mesothelioma formation. Due to their length, the fibers cannot be taken up and degraded by the macrophages. Instead, they get into the interstitium, where they have the opportunity to interact with the mesothelial cells. Several cell-damaging processes are to be considered: First, the mechanical irritation leads to an increased regeneration of the mesothelium. Due to their steric properties, the asbestos fibers can interact with the mitotic spindle and thus lead to errors in cell division resulting in aneuploidy. On the other hand, they indirectly damage the DNA of the mesothelial cells by inducing the formation of reactive oxygen species (ROS) and free radicals. Furthermore, local inflammation promotes the formation of cytokines and growth factors with phosphorylation of proteins (including MAP kinases) involved in cell-cycle regulation; this leads to increased proliferative capacity [14]. All these described patho-mechanisms cause an increased degeneration of the mesothelial cells with an increased risk of developing malignant mesothelioma [37]. An exposure-threshold dose for the development of DMPM is unknown. Even short and low asbestos exposure can induce mesothelioma after a latency period. Approximately 90% of the DMPMs recorded in the German Register are asbestos-associated [28].

- Diffuse malignant peritoneal mesothelioma (DMPM) is a malignant neoplasm originating from the peritoneal mesothelium.
- DMPM is associated with asbestos or erionite exposure.
- BAP1 screening in patients with MM and familial clustering is recommended.
- DMPM has no pathognomonic symptoms in 90% of the advanced mesothelioma and presents with non-specific clinical features such as ascites, abdominal pain, asthenia, weight loss, and anorexia.
- Staging laparoscopy is used to describe the peritoneal carcinomatosis index (PCI) and histology.

19.2 Diagnosis of DMPM

19.2.1 Symptoms

Abdominal mesothelioma is relatively difficult to diagnose because it has no pathognomonic clinical features. Manzini et al. categorized the patients with DMPM into three different clinical groups: (a) patients with massive ascites and large tumor nodules associated with weight loss and abdominal pain (Fig. 19.1), (b) patients with acute problems requiring emergency surgical treatment, and (c) patients with unexplained fever, weight loss, and a clinical picture resembling inflammatory bowel disease [34].

Symptoms such as fatigue, loss of appetite, loss of weight, and unclear fever (B symptoms) occur at an early stage. Dyspnea, abdominal pain, nausea, vomiting, diarrhea, and ascites indicate an advanced stage. Ninety percent of advanced mesotheliomas show malignant ascites [6, 37]. About 10% of patients are diagnosed with DMPM as part of an umbilical hernia repair [27, 37].

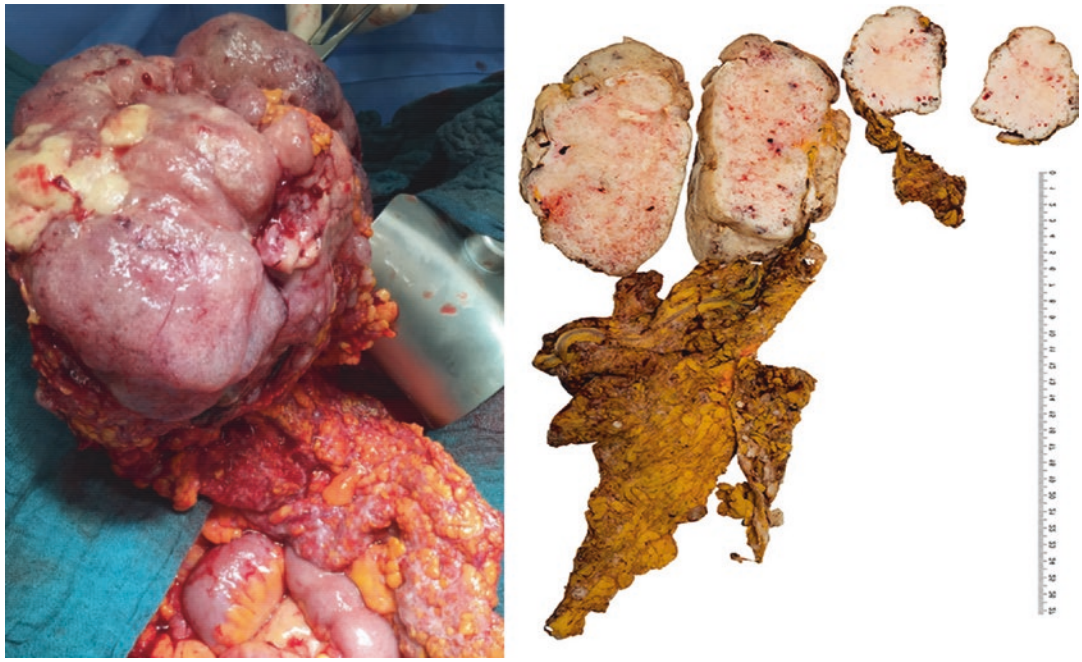


Fig. 19.1 Large solid tumor nodule of an adenomatoid malignant mesothelioma in the omentum

Non-specific findings such as anemia, thrombocytosis, and eosinophilia are often detectable later. Occasionally, paraneoplastic formation of antidiuretic hormones (ADH), growth hormones, adrenocorticotropic hormones (ACTH), insulin-like substances, and parathyroid hormone-like peptides occurs. In addition, an elevated level of hyaluronic acid is found in the blood, which is directly related to tumor progression [6].

At advanced stages of the disease, significant bowel thickening resulting in bowel obstruction may occur (Fig. 19.2). Infiltration of the neoplastic cells into the wall of the stomach or bowel, continuing up to the submucosa or even the mucosa, may take place. Often the tumor cells may also spread into the subcutaneous fatty tissue along the incisions, which is why previous incisions or puncture sites should be resected during the surgery.

19.3 Conventional Cross-Sectional Diagnosis

DMPM is a rare condition and difficult to differentiate macroscopically from other common causes of peritoneal carcinomatosis, which must be excluded before a diagnosis of DMPM is considered. These include gastrointestinal cancer with peritoneal dissemination (such as gastric, colon, rectal carcinoma, etc.), advanced ovarian cancer, and special forms of mesothelioma such as WDPM (well-differentiated papillary mesothelioma) and MPM (multicystic peritoneal mesothelioma). In addition, an adenomatoid tumor and a primary carcinoma of the peritoneum should also be considered in the differential diagnosis of DMPM [38].

An initial abdominal ultrasound examination followed by a computed tomography (CT) scan of the thorax, abdomen, and pelvis is the standard

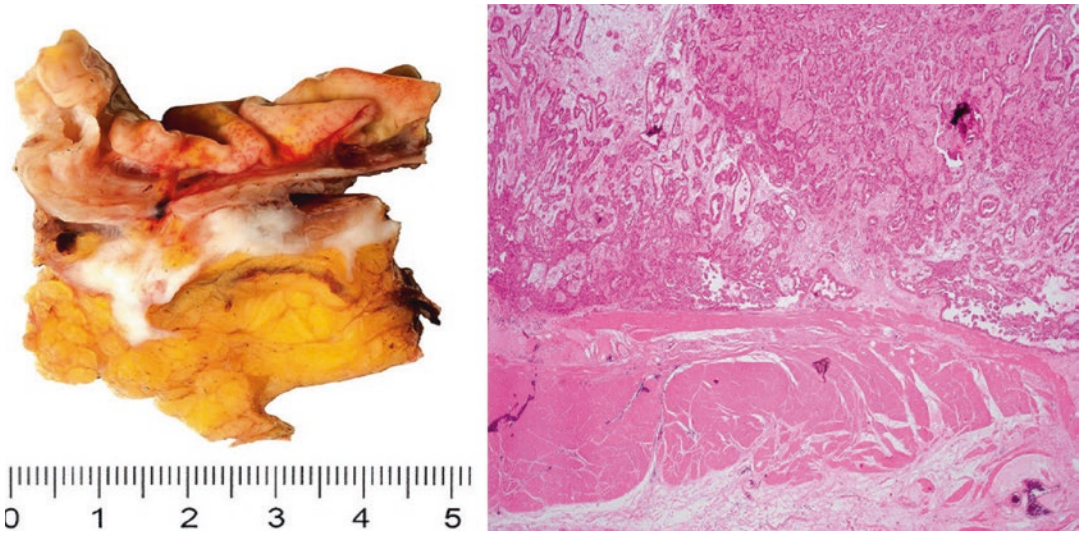


Fig. 19.2 Highly differentiated papillary mesothelioma with infiltration of the serosa

radiological imaging for a patient with suspected DMPM. CT scans usually show multiple nodular lesions over the peritoneum, an omental cake, and a thickening of the mesenteric root in DMPM. In some cases, MRI offers interesting results with special protocols and may in the future have a greater role in the diagnosis of peritoneal tumors [25]. The amount of ascites, the maximum diameter of individual lesions, number of tumor nodules, and the thickness of the peritoneum and mesenteric root are very common in malignant peritoneal mesothelioma and can be used as parameters for differential diagnosis [23, 48].

The role of PET-CT in the diagnosis of DMPM is not well defined. According to some authors, PET-CT does not lead to a significantly better informative value due to the presence of small tumor nodules over the peritoneal surface [26, 40]. However, PET-CT has been considered by others a valuable imaging modality in the pre-surgical evaluation, management, and prognosis [18].

A reliable assessment of tumor dissemination and a histopathological diagnosis can be achieved by laparoscopy [35, 41]. In addition, staging laparoscopy can be used to determine the peritoneal cancer index (PCI) and to visualize the morphology of the tumor nodules. Therefore, laparoscopy may be useful in the diagnostic workup of a patient with DMPM. Abdominal paracentesis is usually non-contributory due to the low cellularity in the peritoneal fluid; moreover, it carries the risk of tumor-cell implantation in the needle track.

19.4 Tumor Markers

In DMPM, there are currently no reliable tumor markers (e.g., CEA, Ca19–9, CA 125) that could be considered as diagnostic markers. Recently, a high specificity for and a high positive predictive value of serum mesothelin has been reported in the differential diagnosis between DMPM and peritoneal dissemination of unknown origin. Additionally, osteopontin correlates with survival, and consequently it might predict prognosis [8].

19.5 Staging, TNM System

There is currently no validated staging system for DMPM. The TNM system was developed for pleural mesotheliomas only, but it is rarely used as it has little prognostic value [38].

The Peritoneal Surface Oncology Group International (PSOGI) pooled the prospective

Table 19.1 Grouping of a TNM system for diffuse malignant peritoneal mesothelioma (DMPM)

Stage	T category	N category	M category	5-year survival
I	T 1	N 0	M 0	87%
II	T 1–3	N 0	M 0	53%
III	T 4	N 0–1	M 0–1	29%
	T 1–4	N 1	M 0–1	
	T 1–4	N 0–1	M 1	

Modified from Yan et al. [47]

data of patients with DMPM undergoing cytoreductive surgery and receiving HIPEC in eight international institutions in order to formulate a clinico-pathological staging system through the identification of significant prognostic parameters [47]. A total of 294 complete patient datasets were evaluated. The PCI was categorized into 4 sections and served as equivalent to the T-category. A PCI of 1–10 corresponds to T1, a PCI of 11–20 corresponds to T2, a PCI of 21–30 corresponds to T3, and a PCI of 30–39 corresponds to T4. An abdominal lymph-node involvement was classified as N1. Though it is still debatable which regional lymph-node stations need to be removed, the intraabdominal lymph nodes most commonly involved are iliac and paracolic [4]. Distant metastasis is considered as extra-abdominal metastasis. This has led to the development of a staging system which provides a meaningful prognosis for an appropriately staged patient (Table 19.1).

19.6 Histopathological Diagnosis

The diagnosis of DMPM is based on both macroscopic and microscopic findings. Morphologically, MM can present either as a diffuse or a localized type, both consisting of white and moderately firm tissues. Most common are the diffusely growing tumors, which initially present as isolated nodules, but, later on, coalesce and spread out over the area. The localized tumors occur predominantly in the lower abdomen as well as in the greater omentum, and they are usually 2 cm or less in size; however, they may grow to attain a significant size in some cases (e.g., omental cake).

Microscopically, peritoneal mesothelioma can be broadly divided into three types: epithelioid, sarcomatoid, and mixed (biphasic) types. The epithelioid type is the most common type, present in approximately 90% of cases, whereas the mixed and sarcomatoid type constitute the remaining 10% of cases [20].

As no single test for diagnosing MM exists, a combination of techniques—histological, immunohistochemical, and molecular—is employed to confirm the diagnosis. MM must be differentiated from other benign tumors or reactive changes. Different diagnostic markers are used for different tumor subtypes [36].

Positive markers that have also been recommended in various international guidelines are calretinin (nuclear and cytoplasmic), D2–40 (membrane-bound), MNF116, CK 5/6, WT1 (nuclear), and podoplanin. The negative markers include MOC31, BerEP4, and TTF1. In addition, antibodies against CDX2, CK20, CK7, S100, desmin, actin, AE1 / 3, CD56, and PAX8 are also used in the differential diagnosis. Furthermore, MIB1/Ki67 are recommended to better define tumor aggressiveness. Molecular-biological markers also play a role in the diagnosis, including the p16 deletion or SYT translocation [21, 43]. Also important is the description of existing tissue infiltrations that can reach the stroma, adipose tissue, or neighboring structures [30, 31]. The detection of the asbestos fibers in a lung-tissue sample may additionally be useful when it comes to the recognition of peritoneal mesothelioma as an occupational disease [39].

The checkpoint inhibitors PDL-1 and PD1 are increasingly playing a role in the management of MM. Though these checkpoint inhibitors are reported to be present in 20% of pleural MM, similar data is lacking for DMPM [12].

19.7 Treatment of DMPM

DMPM is a rare and locally aggressive tumor with a poor prognosis. Traditionally treated with systemic palliative chemotherapy, the treatment of DMPM has radically evolved over the last two decades. Over time, a gradual affirmation

of surgical treatment has been observed, while the role of traditional chemotherapy, due to its lack of effectiveness, is usually limited to inoperable cases. Surgical approaches range from conservative surgery to more radical treatment with cytoreductive surgery (CRS) and intraperitoneal chemotherapy. Every case of DMPM needs to be discussed by a multidisciplinary team of doctors at a specialized center to arrive at an individualized treatment plan for a given patient.

Currently, the best available therapy incorporates complete cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC). This regimen has been shown to achieve a 5-year overall survival rate of up to 68% [5].

Systemic chemotherapy is contemplated as a palliative treatment for patients with extraperitoneal involvement, non-operable tumors, and with poor prognostic cases in view of their biology subtype (sarcomatoid and biphasic histology), their high PCI, or the residual disease after CRS.

The patients who are advised palliative care have a median survival of 1 to 2 years. However, the median survival improves to more than 50 months, with a 5-year survival of more than 50%, after curative-intent treatment (CRS and HIPEC) for appropriately selected patients. Left untreated, patients with DMPM have a dismal prognosis with a median survival of 6 months [37].

- Untreated DMPM has a dismal prognosis with a median survival of 6 months.
- Chemotherapy alone is recognized as a palliative treatment for DMPM.
- Currently, the treatment strategy with the best survival outcomes combines complete cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC).
- The commonly used chemotherapeutic drugs in HIPEC are a combination of cisplatin, doxorubicin, and mitomycin for DMPM.

19.8 Systemic Chemotherapy

Due to the rarity of DMPM compared to pleural mesothelioma, there are currently no randomized studies confirming the survival benefit of chemotherapy. Systemic chemotherapy is classically used as a palliative therapy in DMPM.

The response rates with systemic cisplatin chemotherapy were reported as 11–28%. The use of pemetrexed has significantly improved the response rates up to 37%. Simon et al. integrated mericitabine into the combination therapy and achieved a median survival of 26.8 months, though there was a higher incidence of grade 3–4 neutropenia in 60% of patients [42]. Carteni et al. supported the efficacy of pemetrexed in a non-randomized study and recommended the use of pemetrexed with or without cisplatin-containing chemotherapy (Table 19.2) [11].

Table 19.2 Outcome of a non-randomized treatment study that used and compared different chemotherapy regimens in peritoneal mesothelioma

	PEM + CIS	PEM + CARBO	PEM
Evaluable patients	*n* = 37/37	*n* = 32/34	*n* = 35/38
Response	10 (27%)	12 (35%)	4 (11%)
No change	8 (22%)	7 (21%)	6 (16%)
Tumor progression	7 (19%)	2 (6%)	9 (24%)
Toxicity grade 3–4			
Anemia	3%	22%	11%
Leukopenia	14%	25%	31%
Thrombocytopenia	11%	38%	40%

Modified from Carteni et al. [11]
PEM pemetrexed, *CIS* cisplatin, *CARBO* carboplatin

A randomized study of pleural mesothelioma assessed the effect of adding bevacizumab to systemic chemotherapy: PCB vs. PC (pemetrexed 500 mg/m^2, cisplatin 75 mg/m^2, bevacizumab 15 mg/kg). A total of 448 patients were randomized into two groups. The overall survival was significantly higher in the PCB group compared to the PC group (18.8 vs. 16.1 months). However, chemotherapy-induced grade 3 and 4 adverse events were also higher: 71% in the PCB group and 62% in the PC group. There were also higher risks of hypertension and thrombosis in the PCB group compared to the PC arm [49].

Due to the positive response rates to combined chemotherapy (cisplatin and pemetrexed) of 71.2% and an acceptable side effect rate of 35% grade 3 or 4 toxicity (predominantly neutropenia, anemia), this chemotherapy regimen has established its role in the preoperative or postoperative setting in DMPM [22].

19.9 The Role of Surgery

Cytoreductive surgery (CRS) is recognized as a standard surgical procedure for peritoneal mesothelioma (Fig. 19.3). As the aim of the surgery is to remove all tumor nodules in DMPM, it essentially amounts to performing a complete peritonectomy to achieve a complete gross extirpation of the disease. The extent to which complete peritonectomy should be performed, especially in cases where there are areas of disease-free peritoneum, was addressed by Baratti et al. The authors compared selective peritonectomy (SPP) with complete peritonectomy (CPP) in a group of 30 patients each. The 5-year overall survival was significantly better in the CPP group compared to the SPP group (63.9% vs. 40%, p value 0.027). Interestingly, 12 out of 24 patients in the CPP group had tumor nodules on the parietal peritoneum that the surgeon had missed because these lesions were not grossly conspicuous [2]. Based on this data, a complete parietal peritonectomy is recommended even in cases of limited tumor seeding of the peritoneum.

The completeness of cytoreduction (CC) can be assessed in terms of a score: a CC score of 0 corresponds to complete removal of all the peritoneal tumor nodules, while a CC score of 1 to 3 indicates incomplete removal (a CC score of 1 indicates remaining nodules of size less than

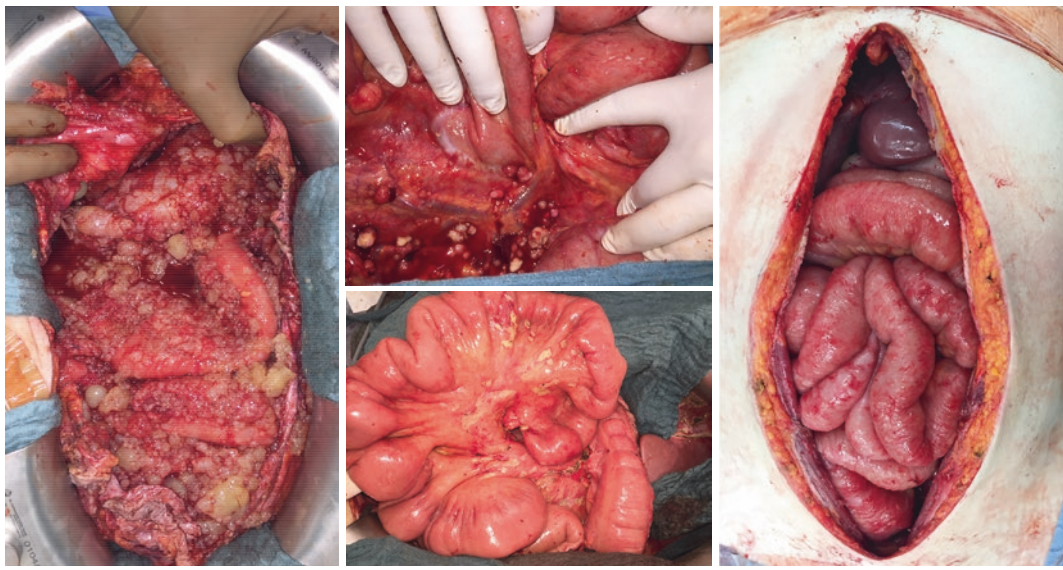


Fig. 19.3 Epithelioid malignant mesothelioma PCI 39. Treatment entailed an excision of the umbilicus, total peritonectomy (on both sides subphrenic, interenteric, lateral, and pelvic); right hemicolectomy and ileocolic anastomosis; cholecystectomy, extraperitoneal anterior resection with colorectal anastomosis, infragastric omentectomy, Baud auditory drainage, and HIPEC with CDDP 163.5 mg ip and doxorubicin 32.7 mg ip CCR 00/1

0.5 mm; a CC score of 2 for remaining nodules of size 0.5 mm–2.5 cm; a CC score of 3 for remaining nodules of size more than 2.5 cm or confluent foci). In a meta-analysis, patients with CRS and HIPEC with a median PCI of 19 achieved a CC score of 0–1 in 67% of patients [20].

In order to achieve a CC score of 0–1, the visceral organs other than the parietal peritoneum may also need to be resected if they are found to be involved by the tumor. This may lead to multivisceral resections, such as partial gastric resection, splenectomy, colon resection, pelvic exenteration, etc., resulting in a higher postoperative morbidity and mortality. In several centers, a postoperative complication rate of 8–90% and a mortality of up to 5% are reported following multivisceral resection [20]. However, the high rate of postoperative morbidity and mortality following multivisceral resection may be an expression of the learning curve of a given center.

19.10 Role of HIPEC and EPIC

Within the last 10 years, CRS and HIPEC have become increasingly established for DMPM. Unfortunately, as DMPM patients are diagnosed very late, the disease is relatively advanced, with an average life expectancy of 4–12 months if not treated [13]. Systemic chemotherapy, which was adapted from the experience with pleural mesothelioma, achieved a median survival of 10–27 months in peritoneal mesothelioma [22, 42].

In a recent literature review, 6528 articles from 20 papers were extracted and evaluated. There were 15 retrospective analyses, 4 clinical studies, and a prospective cohort study. A total of 1047 patients underwent CRS and HIPEC +/− EPIC (early postoperative chemotherapy). During HIPEC, the most common chemotherapy combination—cisplatin, doxorubicin, and mitomycin—was used in 71% of the patients. With this multimodal therapy, a median overall survival of 19–92 months was achieved. The average progression-free interval was 11–28 months and disease-free interval was 7–40 months. The status of early postoperative intraperitoneal chemotherapy (EPIC) is still unclear, although the 5-year overall survival in patients treated with EPIC was 45 months versus 39 months without EPIC [20].

19.11 Role of Perioperative Chemotherapy

In a retrospective study of 116 patients, it was demonstrated that preoperative chemotherapy had no effect on the rate of complete resections or serious postoperative complications. The overall survival was not significantly influenced [15].

In another retrospective multicenter study, a total of 126 patients with DMPM were evaluated. They were divided into four groups: only preoperative chemotherapy (PreChemo $n = 40$); only postoperative chemotherapy (PostChemo $n = 16$); perioperative chemotherapy (PeriChemo $n = 16$); and no chemotherapy (NoChemo $n = 4$). All patients underwent cytoreductive surgery. After a follow-up period of 61 months, the 5-year overall survival was 40% in the PreChemo group, 67% in the PostChemo group, 62% in the PeriChemo group, and 56% in the NoChemo group [24]. It can be concluded that postoperative chemotherapy may be useful. However, there are many limitations in this analysis, so a prospective study with a large sample size is urgently needed.

19.12 Re-resection Following CRS and HIPEC

It is estimated that more than 50% of the patients with DMPM develop tumor recurrence after CRS and HIPEC. In most of the recurrent cases, re-resection of the tumor nodules is unlikely to benefit the patient (Fig. 19.4). However, re-resection may be contemplated in the symptomatic patients with radiological evidence of recurrence.

The interval between the first and the second CRS is 14 months in a large series with a range of 3–102 months [32]. The median survival of these patients, calculated from the first CRS, was 61.5 months, with a 5-year survival rate of 41.6% [32]. In the patients without clinical abnormali-

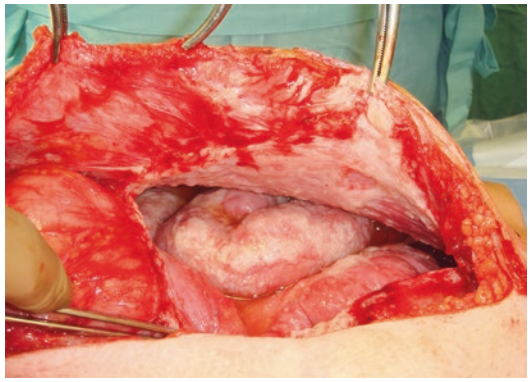


Fig. 19.4 Papillary mesothelioma recurring at 16 months after CRS and HIPEC. Here there is no remaining option for tumor removal

ties, sometimes after planned second-look surgery, the median survival was 83 months [32]. The second relapse developed in 74% of patients within the first 2 years [32].

19.13 Prognostic Factors

Within a median follow-up period of 43 months, 38 patients experienced a progression of their disease. Eighty percent showed peritoneal progression, 71% in the wall lining of the small intestine [3].

Feldman et al. searched various publications for prognostic parameters in DMPM. The following prognostic parameters were determined in a multivariate analysis of the publications: age >60 years, tumor infiltration, previous debulking operation, detection of lymph node metastases, biphasic or sarcomatoid DMPM in histology, and more than 5 mitoses/50 HPF [19].

A multi-institutional study of 294 patients with DMPM revealed that women had a significant survival advantage over the men. The 5-year survival of women was 68% and that of men was only 39%. The difference may be hormone-dependent, as younger women under 55 have a survival advantage compared to older women ($p = 0.0019$) [9].

Deraco et al. determined the role of proliferation index Ki67 in DMPM [16]. Kusamura et al. determined the growth fraction with Ki67 in 117 patients, which ranged from 5% to 60% (median 5%) [29]. Unfavorable independent prognostic factors were a Ki67 of >9%, a PCI >17, and the histological type (biphasic/sarcomatoid).

Magge et al., in a study of 65 patients, highlighted that the most important prognostic parameters were <60 years, PCI <15, resection success with CC score CC-0/1, and the histological type (epithelioid, papillary, multicystic) [33].

In a study of 401 patients, Yan et al. identified 10 important parameters associated with prolonged survival in a univariate analysis: (a) age ≤50 years, (b) women, (c) histologically epithelial subtype, (d) no lymph-node metastasis, (e) no distant metastases, (f) PCI ≤20, (g) CC score of 0/1, (h) utilization of HIPEC, (i) blood transfusion ≤5, and (j) exclusion of cardiac complications [46]. The multivariate analysis was limited to the histological subtype, N0 situation, complete resection, and HIPEC. The key forecast factors are summarized in Table 19.3.

19.14 Summary

Diffuse malignant peritoneal mesothelioma (DMPM) is a heterogeneous disease. Etiology, sex, histopathology, tumor mass, and therapeutic procedures are the relevant factors that influence the course of the disease.

Germline mutations of the BAP 1 gene seem to have a predisposition to malignant mesothelioma. In cases of familial disease, screening is recommended.

Cytological examination of the ascitic fluid alone is not enough. A biopsy and a determination of PCI should be done as a part of a laparoscopy.

Aggressive cytoreductive surgery with the goal of complete tumor resection is the cornerstone of therapy with the best long-term survival benefit. In selected cases, 5-year overall survival

Table 19.3 Prognostic factors in DMPM

Factors	Cut-off value	Author	*N*	Univariate analysis (univ. *P* value)	Multivariate analysis (univ. *P* value)
Age	54 years	Baratti [4]	83	0.04	0.15
	n	Kusamura [29]	117	<0.001	NS
	<60 years	Magge [33]	65	kA	0.02
	<55	Tudor [45]	20	0.006	kA
	<50	Yan [46]	401	0.003	kA
Gender	Female	Yan [46]	401	<0.001	kA
ECOG	>2	Deraco [15]	116	<0.01	NS
Preoperative thrombocytosis	400,000/ mm^3	Deraco [15]	116	<0.01	<0.01
Alcohol consumption	No	Tudor [45]	20	0.003	kA
PCI	<20	Baratti [4]	83	0.027	NS
	<20	Deraco [15]	116	0.01	NS
	<17	Kusamura [29]	117	<0.001	<0.001
	<15	Magge [33]	65	0.002	kA
	<20	Yan [46]	401	0.002	n/a
CC score	0/1	Baratti [4]	83	0.018	0.001
	CC0 / 1 vs 2/3	Deraco [15]	116	<0.01	0.01
	CC0 / 1 vs 2/3	Magge [33]	65	kA	0.01
	CC0 / 1 vs 2/3	Tudor [45]	20	0.02	kA
	CC0	Yan [46]	401	<0.001	kA
Blood transfusion	≤5	Yan [46]	401	0.003	kA
Histology	Epithelial	Baratti [4]	83	0.024	0.015
	Epithelial	Deraco [15]	116	0.02	0.01
	Epithelial	Kusamura [29]	117	0.04	0.013
	Epithelial	Magge [33]	65	kA	0.001
	Epithelial	Tudor [45]	20	0.01	kA
	Epithelial	Yan [46]	401	0.006	kA
Growth fraction (Ki67)	<9%	Kusamura [29]	117	<0.001	<0.001
Pos. lymph nodes	N pos	Baratti [4]	83	0.005	0.027
	N pos	Yan [46]	401	0.008	kA
Mitoses	5/50 HPF	Baratti [4]	83	0.001	0.001
Progression-free time	9 months	Baratti [3]	38	<0.001	0.009

rates of 30–85% are reported, depending upon the stage.

Pemetrexed in combination with cisplatin-containing chemotherapy currently achieves a long-term stable disease in 10% and 35% of cases with an acceptable toxicity.

Prior Surgical Score (PSS)

References

1. Baas P, Fennell D, Kerr KM, Van Schil PE, Haas RL, Peters S. Malignant pleural mesothelioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(Suppl 5):v31–9. https://doi.org/10.1093/annonc/mdv199. Epub 2015 Jul 28. v31–v39
2. Baratti D, Kusamura S, Cabras AD, Deraco M. Cytoreductive surgery with selective versus complete parietal peritonectomy followed by hyperther-

mic intraperitoneal chemotherapy in patients with diffuse malignant peritoneal mesothelioma: a controlled study. Ann Surg Oncol. 2012;19(5):1416–24.
3. Baratti D, Kusamura S, Cabras AD, Dileo P, Laterza B, Deraco M. Diffuse malignant peritoneal mesothelioma: failure analysis following cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol. 2009;16(2):463–72.
4. Baratti D, Kusamura S, Cabras AD, Laterza B, Balestra MR, Deraco M. Lymph node metastases in diffuse malignant peritoneal mesothelioma. Ann Surg Oncol. 2010;17(1):45–53.
5. Baratti D, Kusamura S, Deraco M. Diffuse malignant peritoneal mesothelioma: systematic review of clinical management and biological research. J Surg Oncol. 2011;103(8):822–31.
6. Baumann F, Buck BJ, Metcalf RV, McLaurin BT, Merkler DJ, Carbone M. The presence of Asbestos in the natural environment is likely related to mesothelioma in young individuals and women from southern Nevada. J Thorac Oncol. 2015;10(5):731–7.
7. Baumann F, Carbone M. Environmental risk of mesothelioma in the United States: an emerging concern-epidemiological issues. J Toxicol Environ Health B Crit Rev. 2016;19(5–6):231–49.
8. Bruno F, Baratti D, Martinetti A, Morelli D, Sottotetti E, Bonini C, Guaglio M, Kusamura S, Deraco M. Mesothelin and osteopontin as circulating markers of diffuse malignant peritoneal mesothelioma: a preliminary study. Eur J Surg Oncol. 2018;44:792–8.
9. Cao C, Yan TD, Deraco M, Elias D, Glehen O, Levine EA, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. Importance of gender in diffuse malignant peritoneal mesothelioma. Ann Oncol. 2012;23(6):1494–8.
10. Carbone M, Kanodia S, Chao A, Miller A, Wali A, Weissman D, Adjei A, Baumann F, Boffetta P, Buck B, de PM, Dogan AU, Gavett S, Gualtieri A, Hassan R, Hesdorffer M, Hirsch FR, Larson D, Mao W, Masten S, Pass HI, Peto J, Pira E, Steele I, Tsao A, Woodard GA, Yang H, Malik S. Consensus report of the 2015 Weinman international conference on mesothelioma. J Thorac Oncol. 2016;11(8):1246–62.
11. Carteni G, Manegold C, Garcia GM, Siena S, Zielinski CC, Amadori D, Liu Y, Blatter J, Visseren-Grul C, Stahel R. Malignant peritoneal mesothelioma—results from the international expanded access program using pemetrexed alone or in combination with a platinum agent. Lung Cancer. 2009;64(2):211–8.
12. Cedres S, Ponce-Aix S, Zugazagoitia J, Sansano I, Enguita A, Navarro-Mendivil A, Martinez-Marti A, Martinez P, Felip E. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). PLoS One. 2015;10(3):e0121071.
13. Chua TC, Yan TD, Morris DL. Outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal mesothelioma: the Australian experience. J Surg Oncol. 2009;99(2):109–13.
14. Clin B, Morlais F, Dubois B, Guizard AV, Desoubeaux N, Marquignon MF, Raffaelli C, Paris C, Galateau-Salle F, Launoy G, Letourneux M. Occupational asbestos exposure and digestive cancers—a cohort study. Aliment Pharmacol Ther. 2009;30(4):364–74.
15. Deraco M, Baratti D, Hutanu I, Bertuli R, Kusamura S. The role of perioperative systemic chemotherapy in diffuse malignant peritoneal mesothelioma patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2013;20(4):1093–100.
16. Deraco M, Cabras A, Baratti D, Kusamura S. Immunohistochemical evaluation of Minichromosome maintenance protein 7 (MCM7), topoisomerase IIα, and Ki-67 in diffuse malignant peritoneal mesothelioma patients using tissue microarray. Ann Surg Oncol Dec. 2015;22(13):4344–51.
17. Dogan AU, Baris YI, Dogan M, Emri S, Steele I, Elmishad AG, Carbone M. Genetic predisposition to fiber carcinogenesis causes a mesothelioma epidemic in Turkey. Cancer Res. 2006;66(10):5063–8.
18. Domènech-Vilardell A, Rasiej MJ, Taub RN, Ichise M. Clinical utility of 18F-FDG positron emission tomography in malignant peritoneal mesothelioma. Q J Nucl Med Mol Imaging. 2016;60(1):54–61. Epub 2014 Apr 14
19. Feldman AL, Libutti SK, Pingpank JF, Bartlett DL, Beresnev TH, Mavroukakis SM, Steinberg SM, Liewehr DJ, Kleiner DE, Alexander HR. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. J Clin Oncol. 2003;21(24):4560–7.
20. Helm JH, Miura JT, Glenn JA, Marcus RK, Larrieux G, Jayakrishnan TT, Donahue AE, Gamblin TC, Turaga KK, Johnston FM. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. Ann Surg Oncol. 2015;22(5):1686–93.
21. Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, Borczuk AC, Butnor K, Cagle PT, Chirieac LR, Churg A, Dacic S, Fraire A, Galateau-Salle F, Gibbs A, Gown A, Hammar S, Litzky L, Marchevsky AM, Nicholson AG, Roggli V, Travis WD, Wick M. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2013;137(5):647–67. https://doi.org/10.5858/arpa.2012-0214-OA. PMID: 22929121.
22. Janne PA, Wozniak AJ, Belani CP, Keohan ML, Ross HJ, Polikoff JA, Mintzer DM, Taylor L, Ashland J, Ye Z, Monberg MJ, Obasaju CK. Open-label study of pemetrexed alone or in combination with cisplatin for the treatment of patients with peritoneal mesothelioma: outcomes of an expanded access program. Clin Lung Cancer. 2005;7(1):40–6.

23. Kato K, Gemba K, Fujimoto N, Aoe K, Takeshima Y, Inai K, Kishimoto T. Computed tomographic features of malignant peritoneal mesothelioma. Anticancer Res. 2016;36(3):1067–72.
24. Kepenekian V, Elias D, Passot G, Mery E, Goere D, Delroeux D, Quenet F, Ferron G, Pezet D, Guilloit JM, Meeus P, Pocard M, Bereder JM, Abboud K, Arvieux C, Brigand C, Marchal F, Classe JM, Lorimier G, De CC, Guyon F, Mariani P, Ortega-Deballon P, Isaac S, Maurice C, Gilly FN, Glehen O. Diffuse malignant peritoneal mesothelioma: evaluation of systemic chemotherapy with comprehensive treatment through the RENAPE database: multi-institutional retrospective study. Eur J Cancer. 2016;65:69–79. https://doi.org/10.1016/j.ejca.2016.06.002. Epub 2016 Jul 26. 69-79
25. Klumpp B, Schwenzer NF, Gatidis S, Koenigsrainer I, Koenigsrainer A, Beckert S, Mueller M, Claussen CD, Pfannenberg C. Assessment of relapse in patients with peritoneal carcinomatosis after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy using F-18-FDG-PET/CT. Rofo. 2014;186(4):359–66.
26. Klumpp BD, Schwenzer N, Aschoff P, Miller S, Kramer U, Claussen CD, Bruecher B, Koenigsrainer A, Pfannenberg C. Preoperative assessment of peritoneal carcinomatosis: intraindividual comparison of 18F-FDG PET/CT and MRI. Abdom Imaging. 2013;38(1):64–71.
27. Konstantinova AM, Michal M, Kacerovska D, Kazakov DV. Multilocular mesothelial proliferation involving the skin of the umbilicus. Am J Dermatopathol. 2013;35(8):856–8.
28. Krismann M, Muller KM. Malignant mesothelioma of the pleura, pericardium and peritoneum. 1: etiology, pathogenesis, pathology (German). Chirurg. 2000;71(8):877–86.
29. Kusamura S, Torres Mesa PA, Cabras A, Baratti D, Deraco M. The role of Ki-67 and pre-cytoreduction parameters in selecting Diffuse Malignant Peritoneal Mesothelioma (DMPM) patients for Cytoreductive surgery (CRS) and Hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol. 2016;23(5):1468–73.
30. Lee M, Alexander HR, Burke A. Diffuse mesothelioma of the peritoneum: a pathological study of 64 tumours treated with cytoreductive therapy. Pathology. 2013;45(5):464–73.
31. Liu S, Staats P, Lee M, Alexander HR, Burke AP. Diffuse mesothelioma of the peritoneum: correlation between histological and clinical parameters and survival in 73 patients. Pathology. 2014;46(7):604–9.
32. Llanos MD, Sugarbaker PH. Symptoms, signs and radiologic findings in patients having reoperative surgery for malignant peritoneal mesothelioma. Eur J Surg Oncol. 2016;43:10.
33. Magge D, Zenati MS, Austin F, Mavanur A, Sathaiah M, Ramalingam L, Jones H, Zureikat AH, Holtzman M, Ahrendt S, Pingpank J, Zeh HJ, Bartlett DL, Choudry HA. Malignant peritoneal mesothelioma: prognostic factors and oncologic outcome analysis. Ann Surg Oncol. 2014;21(4):1159–65.
34. Manzini VP, Recchia L, Cafferata M, Porta C, Siena S, Giannetta L, Morelli F, Oniga F, Bearz A, Torri V, Cinquini M. Malignant peritoneal mesothelioma: a multicenter study on 81 cases. Ann Oncol. 2010;21(2):348–53.
35. Marmor RA, Kelly KJ, Lowy AM, Baumgartner JM. Laparoscopy is safe and accurate to evaluate peritoneal surface metastasis prior to cytoreductive surgery. Ann Surg Oncol. 2016;23(5):1461–7.
36. Mesotheliomregister (2016) Jahresbericht Mesotheliomregister 2014.
37. Mirarabshahii P, Pillai K, Chua TC, Pourgholami MH, Morris DL. Diffuse malignant peritoneal mesothelioma—an update on treatment. Cancer Treat Rev. 2012;38(6):605–12.
38. Neumann V, Loseke S, Nowak D, Herth FJ, Tannapfel A. Malignant pleural mesothelioma: incidence, etiology, diagnosis, treatment, and occupational health. Dtsch Arztebl Int. 2013;110(18):319–26.
39. Neumann V, Loseke S, Tannapfel A. [Medical insurance aspects of peritoneal tumors with particular attention to peritoneal mesotheliomas] (German). Med Klin (Munich). 2009;104(10):765–71.
40. Porcel JM, Hernandez P, Martinez-Alonso M, Bielsa S, Salud A. Accuracy of fluorodeoxyglucose-PET imaging for differentiating benign from malignant pleural effusions: a meta-analysis. Chest. 2015;147(2):502–12.
41. Rau B, Hunerbein M. Diagnostic laparoscopy: indications and benefits. Langenbecks Arch Surg. 2004;390:187–96.
42. Simon GR, Verschraegen CF, Janne PA, Langer CJ, Dowlati A, Gadgeel SM, Kelly K, Kalemkerian GP, Traynor AM, Peng G, Gill J, Obasaju CK, Kindler HL. Pemetrexed plus gemcitabine as first-line chemotherapy for patients with peritoneal mesothelioma: final report of a phase II trial. J Clin Oncol. 2008;26(21):3567–72.
43. Tischoff I, Neid M, Neumann V, Tannapfel A. Pathohistological diagnosis and differential diagnosis. Recent Results Cancer Res. 2011;189:57–78. https://doi.org/10.1007/978-3-642-10862-4_5.
44. Tischoff I, Tannapfel A. [Pathologic and anatomic evidence of peritoneal metastases] (German). Chirurg. 2007;78(12):1085–90.
45. Tudor EC, Chua TC, Liauw W, Morris DL. Risk factors and clinicopathological study of prognostic factors in the peritoneal mesothelioma. Am Surg. 2010;76(4):400–5.
46. Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Gilly FN, Levine EA, Shen P, Mohamed F, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol. 2009;27(36):6237–42.

47. Yan TD, Deraco M, Elias D, Glehen O, Levine EA, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database*. Cancer. 2011;117(9):1855–63.
48. Yin WJ, Zheng GQ, Chen YF, Chen DQ, Sun NN, Yang YX, Sun XY, Kang LQ. CT differentiation of malignant peritoneal mesothelioma and tuberculous peritonitis. Radiol Med. 2016;121(4):253–60.
49. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, Molinier O, Corre R, Monnet I, Gounant V, Riviere F, Janicot H, Gervais R, Locher C, Milleron B, Tran Q, Lebitasy MP, Morin F, Creveuil C, Parienti JJ, Scherpereel A. Bevacizumab for newly diagnosed pleural mesothelioma in the mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2015;15:10–6736.

20 Indication of CRS and HIPEC in Gastric Cancer-Related Peritoneal Metastasis

Beate Rau, Eva Pachmayr, Peter Thuss-Patience, Pankaj Kumar Garg, Olivier Glehen, and Andreas Brandl

20.1 Epidemiology of Gastric Cancer-Related Peritoneal Metastasis

Gastric cancer is the fifth most common cancer in the world with nearly one million new cases per year. More than two-thirds of the patients come from countries with so-called emerging economies. Korea, Japan, and Mongolia have the highest incidence rates [52]. There are also epidemiological differences in the incidence of gastric cancer in eastern and western parts of the world.

There has been a constant reduction in the incidence and mortality of gastric cancer. Between the years 1990 and 2012, the Robert Koch Institute registered a decline in age-standardized incidence of 38% in women and 30% in men [49].

In Germany in 2012, 15,640 patients were diagnosed with gastric cancer, out of whom 58% were men. The mean age for diagnosis of gastric cancer was 75 years in women and 72 years in men. Though there has been a substantial improvement in the treatment of gastric cancer patients, their 5-year survival still remains dismal at 30% [49]. The majority of the patients succumb to systemic metastasis. Almost 40% of the patients with gastric cancer have synchronous metastasis at the time of diagnosis. The median survival of patients with stage IV gastric cancer is only 3 months without treatment [57, 58].

Diffuse liver and lung metastases are common and present in 11% and 1% of synchronous metastatic gastric cancer, respectively. The prognosis for these patients is extremely poor [36, 44].

B. Rau (✉)
Department of Surgery, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität of Berlin, Berlin, Germany
e-mail: beate.rau@charite.de

E. Pachmayr
Department of Surgery, Campus Virchow-Klinikum and Charité Campus Mitte, Charité – Universitätsmedizin Berlin, Berlin, Germany
e-mail: eva.pachmayr@charite.de

P. Thuss-Patience
Head of Upper GI Oncology, Charité-University Medicine Berlin, Berlin, Germany
Medical Clinic for Hematology, Oncology and Tumor-Immunology, Campus Virchow-Klinikum, Charité – Universitätsmedizin Berlin, Berlin, Germany
e-mail: peter.thuss@charite.de

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

O. Glehen
Department of Surgical Oncology, Centre Hospitalier Lyon-Sud, Lyon, France
e-mail: olivier.glehen@chu-lyon.fr

A. Brandl
Digestive Unit, Champalimaud Foundation, Lisbon, Portugal
e-mail: andreas.brandl@fundacaochampalimaud.pt

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_20

Metastasectomy in patients with diffuse metastasis currently plays no role in treatment [2].

Peritoneal metastasis—34% of the patients—is significantly higher with gastric cancer [57, 58]. The median survival without chemotherapy is around 3.4 months and may increase to 7.7 months with chemotherapy. Even newer chemotherapeutic drugs have not been able to affect the prognosis significantly.

20.2 Risk of Peritoneal Metastases

>> New results of molecular and genomic research on the development of the gastric cancer have led to complete genomic profiling of 295 cases, which are divided into four different subtypes.

As per the Cancer Genome Atlas [6, 10], the four subtypes of gastric cancer are:

- EBV-infected carcinomas
- MSI carcinomas
- Genomically stable carcinomas
- Chromosomally unstable carcinomas

EBV-positive carcinomas were detected in 9%, microsatellite unstable carcinomas in 21%, genomically stable carcinomas in 20%, and chromosomally unstable carcinomas in 50% of gastric cancers. These subtypes may be found in any region of the stomach—cardia, fundus, body, or antrum—in varied frequency [6]).

73% of the diffuse adenocarcinomas of the stomach were genomically stable. Cardiac carcinomas were often chromosomally unstable, and EBV-positive carcinomas were increasingly analyzed in the fundus and corpus [6].

Currently we know that, although chromosomally unstable cancers have a worse prognosis, they respond better to a platinum-based chemotherapy [45]. To what extent these genomic characteristics can be attributed to the accumulated occurrence and development of peritoneal metastasis remains to be seen. Even after curative resection, around 7% of the early gastric cancers (T1–T2) present with disease recurrence within the first 3 years [7]. There may be a number of reasons for this. A positive peritoneal cytology prior to a curative resection is observed in 4–25% of the patients and places the patients at higher risk of peritoneal metastasis [5]. In distal gastric cancers, the risk factors for peritoneal metastasis are serosal infiltration, diffuse adenocarcinomas (according to the Lauren classification), lymph-node metastases, and T4 lesions [8, 62].

Kanda et al. [33] showed that the infiltrative growth pattern is associated with 91% of cases with peritoneal metastasis compared to expansive or intermediate types of gastric cancer (as per Japanese Classification).

>> Peritoneal involvement in gastric cancer is a poor prognostic marker and leads to significantly poorer survival.

While the 5-year survival is around 37% following curative gastrectomy in patients without peritoneal metastasis, it decreases to 24% in the presence of microscopic peritoneal disease and further drops to 6–13% in the presence of obvious peritoneal metastasis [23, 38].

These are the risk factors known to be associated to peritoneal metastasis (Table. 20.1):

- Young patients aged ≤60 years [34]
- Locally advanced tumor depth of infiltration (T3/T4) [34]
- Diffuse type according to Lauren [15]
- Signet-ring cell adenocarcinoma
- Lymph-node metastases

The Lauren classification divided gastric cancers into diffuse, intestinal, and mixed types. The diffuse type is more prone to peritoneal metastasis: While up to 81% of the patients with diffuse type have peritoneal involvement, it is only about 38% in the intestinal type [15].

20.3 Diagnosis of Peritoneal Metastatic Gastric Cancer

Gastroscopy is used in the diagnostic investigation of a patient with suspected gastric cancer, whereas biopsy confirms the diagnosis. It also describes the tumor and documents the correct site, size, and extent of the tumor. Endosonography helps in the differentiation between early (T1/2)

Table 20.1 Risk factors for peritoneal tumor recurrence

Factors	Cut-off value	Author	n (%)	Hazard ratio	95 -% - CI	Univariate analysis (*P*-value)	Hazard ratio	95 – % – CI	Multivariate analysis (*P*-value)
Location of gastric cancer	Distal carcinoma	Chang et al. [8]	707/1090 (64.9%)	0.62	From 0.46 to 0.84	0.002	0.71	0.51 to 0.98	0.036
Perineural invasion	Yes	Chang et al. [8]	535/1090 (49.1%)	2.76	2.12 to 3.58	<0.001	1.78	1.32 to 2.40	<0.001
Lauren classification	Diffuse	Chang et al. [8]	555/1090 (50.9%)	2.46	1.85 to 3.26	<0.001	1.62	1.18 to 2.24	<0.001
	Signet-ring cell adenocarcinoma	Seyfried et al. [50]	NN / 550	3.88	1.56 to 9.71	0.004	NA	NA	NA
Type of growth	Infiltrative	Kanda et al. [33]	23/243 (11.5%)	NA	NA	0.001	2.31	1.02 to 5.39	0.045
Tumor grade	G 3/4	Seyfried et al. [50]	NN / 550	2.03	1.13 to 3.65	0.018	NA	NA	NA
T category	T4	Chang et al. [8]	627/1090 (57.5%)	12.04	4.96 to 29.25	<0.001	4.67	1.84 to 11.89	<0.001
	T3 / T4	Seyfried et al. [50]	NN/550	2.35	1.35 to 4.12	0.003	NA.	NA	NA
Tumor size	> 50 mm	Kanda et al. [33]	28/243 (11.5%)	NA	NA	<0.001	2.91	1.20 to 7.83	0.017
N category	N2	Chang et al. [8]	276/1090 (25.3%)	1.41	0.85 to 2.35	0.19	2.52	1.48 to 4.29	<0.001
	N3a	Chang et al. [8]	232/1090 (21.3%)	2.79	1.71 to 4.55	<0.001	3.92	2.35 to 6.52	<0.001
	N3b	Chang et al. [8]	137/1090 (12.6%)	4.63	2.80 to 7.65	<0.001	5.75	3.38 to 9.78	<0.001
	npos	Seyfried et al. [50]	NN/550	2.39	1.34 to 4.26	0.003	k. A.	k. A.	k. A.

95% CI 95% confidence interval, *NA* not available

vs. advanced (T3/4) gastric cancers. Endosonography can also be used additionally for the detection of perigastric nodes and ascites (an indication of peritoneal metastasis). Levy et al. demonstrated that sensitivity, specificity, and accuracy of EUS-FNA compared to CT/magnetic resonance imaging (MRI) is 91% versus 28%, 100% versus 85%, and 94% versus 47%, respectively. In newly diagnosed cancer patients, peritoneal FNA may cause upstaging in almost one fourth of patients.

After histological confirmation of the primary tumor, computed tomography (CT) of the chest and abdomen/pelvis should be done to assess the local extent of the tumor, regional lymph nodes, and distant metastasis.

Cross-sectional imaging of the abdomen and pelvis may indicate the presence of peritoneal disease. The sensitivity of CT for the diagnosis of peritoneal disease varies between 60% and 90% [13, 30]. A significant limitation of the CT scan is its inability to detect small peritoneal tumor nodules. Jacquet et al. [30] highlighted that the accuracy of the CT in detecting peritoneal nodules is related to their size: the sensitivity is only 28% if the tumor nodules are less than <0.5 cm, and it increases to 72% for the tumors between 0.5 and 5 cm, while for the tumors of more than 5 cm in size, it further increases to more than 90%. Other additional features such as ascites or "omental cake" also increase the accuracy of CT scans in diagnosing peritoneal disease. The sensitivity and specificity of CT for estimating the peritoneal carcinomatosis index (PCI) is dependent upon the tumor type. Chang-Yun et al. [9] reported that the detection rate of peritoneal metastasis was highest in the appendix and lowest in the stomach (84% and 47%, respectively).

In a multicenter study by Esquivel et al. [16], when compared to the intra-operatively measured PCI, the infestation level was correctly determined with CT in 65% of patients, underestimated in 33% of patients, and overestimated in 2% of patients.

Moreover, the accuracy also depends on the anatomical localization of tumor involvement. In a study of colorectal cancers with peritoneal metastasis, Esquivel et al. [16] showed that there were inaccuracies in the CT-based assessment of lesion sizes with respect to the abdominal region: RUQ ($P = 0.004$), LLQ ($P < 0.0005$), RLQ ($P = 0.003$), distal jejunum ($P = 0.004$), and distal ileum ($P < 0.0005$). Furthermore, the authors suggested that CT underestimated PCI in 33% cases: 21% were upstaged from low to moderate, 8% from low to severe, and 4% from moderate to severe.

Dromain et al. [13] showed that CT and PET/CT imaging are not accurate enough to assess the extent of peritoneal carcinomatosis. Though the presence of peritoneal carcinomatosis was correctly determined on CT and PET/CT in 82% and 57% of patients, respectively, both the investigations understaged the extent of peritoneal metastasis in 90% patients.

Conventional magnetic resonance imaging (MRI) has a sensitivity of 52–92% and specificity of 90–92% in the diagnosis of peritoneal metastasis [35, 39].

> *>> Much more efficient for the diagnosis and assessment of the extent of peritoneal metastasis is diagnostic laparoscopy. It is the gold standard for the evaluation of peritoneal metastasis.*

Important parameters such as the PCI, involvement of the small intestine or the colon, involvement of the bowel mesentery, presence of ascites, and consistency of the metastases (slimy, adherent, etc.) should be described (Fig. 20.1) during laparoscopy. A biopsy for histological confirmation of the diagnosis is important and must always be done.

The following parameters should be recorded:

- Peritoneal carcinomatosis index (PCI)
- Consistency (slimy, coarse, adherent)
- Ascites

In a study of 197 cases of peritoneal metastasis, Garofalo and Valle [22] were able to achieve full laparoscopic assessment of PCI in 196 of 197 (99.49%) cases, and only 4 of 197 (2.03%) cases were understaged before the routine use of laparoscopic ultrasound. The detection of peritoneal metastases in gastric cancer patients using laparoscopy achieves a sensitivity of 74–100% and a specificity of 83–100% [37].

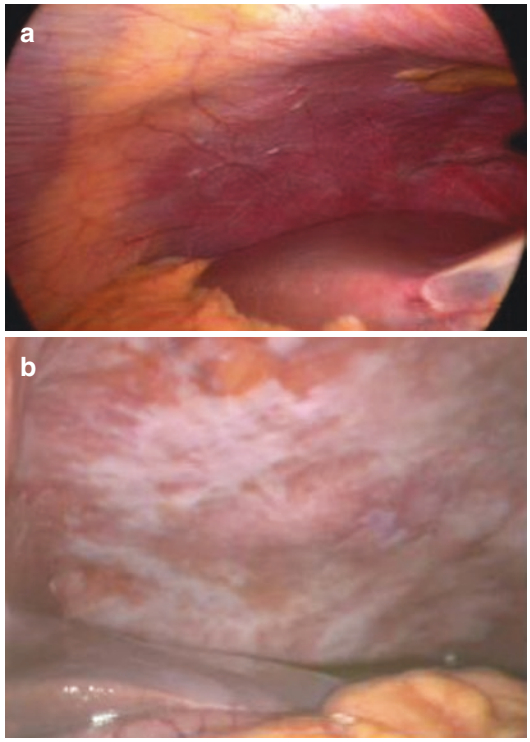


Fig. 20.1 (**a**) Low volume peritoneal metastasis in the right upper abdomen, (**b**) diffuse and confluenting peritoneal metastasis in the left upper abdomen with ascites

As diagnostic laparoscopy has distinct advantages in the diagnosis of peritoneal metastasis, its use must be considered in patients planned for curative resection.

>> *There is consensus that diagnostic laparoscopy is recommended in patients with locally advanced gastric cancers (T3, T4) as it may detect unexpected peritoneal metastasis in 30% of patients.*

Although diagnostic laparoscopy is recommended in the assessment of gastric cancer, there are certain disadvantages: relatively invasive, difficult access in previous abdominal surgery, failure to access retroperitoneal space, trocar-site metastasis, and the cost of the procedure [41]. Presence of adhesions due to prior abdominal surgery may make the laparoscopic assessment technically difficult and inaccurate. It may not even be possible to find access for the insertion of the trocars, and it carries the potential risk of visceral injury. Tumor seeding may occur along the trocar route, and it is advisable to incorporate trocar sites into the expected laparotomy incision (Fig. 20.2). In a retrospective study of 65 patients undergoing laparoscopy before CRS/HIPEC, 144 port-sites were resected: 41 (29%) ports were positive for malignancy in a total of 22 (34%) patients. Port-site metastasis was an independent predictor of survival with an HR of 3.462 (95% CI 1.19–10.0). Mean overall survival at 1, 3, and 5 years was 73, 35, and 23%, respectively, in patients with PSM [42].

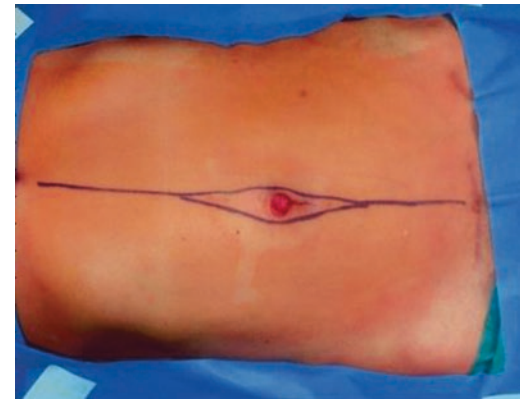


Fig. 20.2 Port site metastasis of the umbilicus, which was excised during laparotomy

>> *Diagnostic laparoscopy may supplement imaging modalities to allow direct visualization of the peritoneal metastasis [63].*

In gastric cancer, the prognosis is dismal in the presence of peritoneal metastasis. The NCCN guidelines [1] as well as the German S3 guidelines [41] indicate that these patients should be treated with palliative therapy with "best supportive care." Palliative chemotherapy may be given in the settings of research trials. Surgical treatment should be reserved for tumor-related complications like bleeding, perforation, or obstruction [31].

The median survival of these patients with gastric cancer and associated peritoneal metastasis is 3–5 months with best supportive care in the absence of systemic chemotherapy. Moreover, there has not been any substantial increase in median survival in metastatic gastric cancer with systemic chemotherapy as well.

In a meta-analysis, the GASTRIC Group showed that systemic chemotherapy did produce

a survival benefit, but not beyond 12 months [43]. In a select group where the gastric tumor overexpresses human epidermal growth factor receptor 2 (HER2), the addition of antibody therapy (trastuzumab) may further increase the median survival to 14 months [3]. These considerations led to the use of intraperitoneal chemotherapy to further increase the survival in patients with gastric cancer with peritoneal metastasis. In the context of the limited experience of emergency palliative gastric resection in the presence of peritoneal metastasis, survival was observed to be better with systemic chemotherapy.

In a Surveillance, Epidemiology, and End Results (SEER) database-analysis of 8429 patients with stage IV gastric cancer treated between 1998 and 2009, the median survival for patients who underwent palliative gastrectomy (N = 1445, 17.4%) and for patients who did not undergo palliative gastrectomy (N = 6804, 82.4%) was 7 and 3 months, respectively. However, the palliative gastrectomy rate dropped from 18.8 to 10.2% (P = 0.004) in this time period [14].

In order to clarify the role of palliative gastrectomy in metastatic gastric cancer, Fujitani et al. [21] conducted an open-label, randomized, metacentric phase III trial (REGATTA trial) including patients with advanced gastric cancer with a single non-curable factor confined to either the liver, peritoneum, or para-aortic lymph nodes, who underwent chemotherapy alone or gastrectomy followed by chemotherapy. The trial did not show any survival benefit of palliative gastrectomy. Overall survival at 2 years for all randomly assigned patients was 31.7% (95% CI 21.7–42.2) for patients assigned to chemotherapy alone compared with 25.1% (16.2–34.9) for those assigned to gastrectomy plus chemotherapy. Median overall survival was 16.6 months (95% CI 13.7–19.8) for patients assigned to chemotherapy alone and 14.3 months (11.8–16.3) for those assigned to gastrectomy plus chemotherapy (hazard ratio 1.09, 95% CI 0.78–1.52; one-sided p = 0.70). Interestingly, among the 86 patients assigned to chemotherapy alone, five underwent gastrectomy with curative intent because of complete disappearance of all non-curable factors during chemotherapy.

However, based on these results, the gastrectomy alone appears futile in the absence of excision of isolated metastatic sites. Presently, another randomized trial is ongoing: the GYMSSA trial, in which gastrectomy plus metastasectomy followed by systemic treatment is being compared with systemic therapy alone in terms of overall survival and adverse events, with a planned enrolment of 136 patients.

Perhaps the best strategy to address gastric cancer with isolated peritoneal metastasis is the removal of the primary tumor and peritonectomy.

When the PCI index is less than 10, an aggressive multimodal treatment including cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) should be offered if complete tumor resection is possible.

In a study to assess the role of multimodality therapy (including CRS and HIPEC) in 38 patients with gastric cancer and peritoneal metastasis, the median survival time after gastrectomy was similar between patients receiving CRS-HIPEC and matched control patients operated for advanced gastric cancer without PM (8.1 months, 95% CI 10.1–26.0 versus 21.8 months, 95% CI 8.0–35.5 months) resulting in a comparable 5-year survival (11.9% vs. 12.1%) [4]. Other authors have also shown that better survival results can be expected in selected patients with a PCI <10 and complete tumor removal [26, 28, 32, 65]. Glehen et al. [25] highlighted the fact that a PCI of less than 6 is associated with best survival rates among the patients with gastric cancer-related peritoneal metastasis. In a study of 95 gastric cancer patients with a PCI <6, 91% patients had a CCR of 0/1, while only 42% of the patients with PCI >7 were able to receive complete cytoreduction [47, 48, 67].

20.3.1 Synchronous and Metachronous Peritoneal Metastatic Gastric Cancer

Spratt and Sugarbaker are the pioneers of the surgical treatment of isolated peritoneal metastases. As a part of multidisciplinary treatment, they performed cytoreductive surgery with the aim of

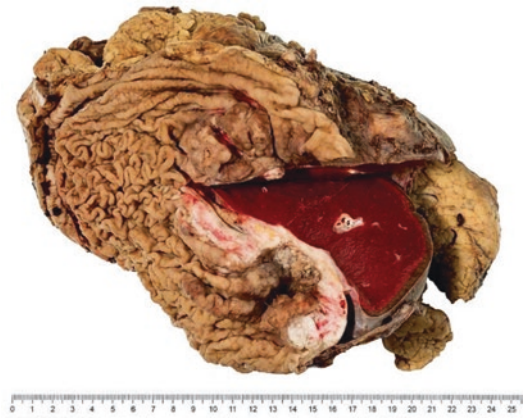


Fig. 20.3 Multivisceral en-bloc resection including the stomach and spleen in a patient with gastric cancer with infiltration of the spleen

complete tumor removal and subsequent hyperthermic intraperitoneal chemotherapy, and achieved excellent survival results in these patients [51, 53–55]. For advanced gastric carcinoma, most of the literature was generated by Fujimoto from Japan [20].

The rationale for the aggressive surgical procedure is based on the complete macroscopic removal of peritoneal tumor nodes and the oncological resection of the primary tumor (no tumor residue larger than 0.25 cm). In some cases, complete cytoreduction involves a total peritonectomy with multiple visceral resections, which can include an omentectomy, cholecystectomy, and even segments of the small and large intestine, the stomach, the spleen, the uterus, and the ovaries (Fig. 20.3).

20.4 CRS Without Intraperitoneal Chemotherapy

>> *There is general consensus that complete tumor removal of a non-metastatic gastric cancer represents the only curative option. However, the extent of the disease may warrant preoperative chemotherapy* [41].

There is lot of controversy in the management of metastatic gastric carcinoma. As complete resection is not possible in most of the cases and there is a high risk of postoperative complications, palliative chemotherapy has been the traditional treatment. However, with the refinement in the surgical techniques and various advancements in technology, surgery has again come back to the forefront of treatment of metastatic gastric cancer with isolated peritoneal metastasis. With a perioperative mortality of 1–3%, a significant improvement in the 5-year survival rates has been achieved. This improvement in surgical methods is not only related to better surgical techniques but is also attributed to the adoption of multimodality treatment [50]. Synchronous peritoneal metastasis has a better survival outcome compared to metachronous when treated with CRS and HIPEC.

In a study to evaluate the outcomes of patients who underwent palliative gastrectomy for incurable gastric carcinoma, the median survival of patients undergoing non-curative gastrectomy was significantly longer than that of patients without gastrectomy (12.4 vs. 7.1 months, $p = 0.003$). There was 21% morbidity and 1.2% mortality among the 162 patients who underwent palliative gastrectomy. The patients who received postoperative chemotherapy also showed significantly better survival than those without chemotherapy (13.2 vs. 4.3 months, $p < 0.001$). The authors concluded that primary tumor resection and postoperative chemotherapy are the most important prognostic factors for incurable gastric carcinoma. Median survival in patients receiving non-curative gastrectomy combined with postoperative chemotherapy was 13.9 months, which was significantly longer than gastrectomy alone (5.4 months), chemotherapy alone (9.6 months), and no treatment (3.2 months) [31].

A meta-analysis of 14 studies and 3003 patients showed that palliative gastrectomy is associated with a significant improvement in overall survival (HR 0.56; 95% CI 0.39–0.80; $p < 0.002$) compared with that of patients treated without palliative gastrectomy [56].

Similar data also exist for the peritoneal metastatic gastric carcinoma. Following complete resection of the primary tumor (often with multivisceral resections) and removal of all peritoneal nodules (complete cytoreduction, CC 0), significant survival benefit can be expected compared to

incomplete cytoreduction [23, 24]. The success of complete cytoreduction depends on the extent of tumor dissemination as measured by the peritoneal carcinomatosis Index (PCI) [29]. With a high PCI, extensive carcinomatosis usually involves the small bowel mesentery and mesocolon; this makes it highly unlikely to achieve a CC score of 0 and provide survival benefit to the patients. Therefore, it is not recommended to consider CRS and HIPEC in patients with a PCI of more than 12 [24].

20.5 Preoperative Intraperitoneal Chemotherapy for Tumor Reduction

Preoperative chemotherapy may be required to downstage the disease in order to achieve complete cytoreduction. Moreover, downstaging of the disease with preoperative chemotherapy also allows testing in vivo chemosensitivity of chemotherapeutic drugs. Various randomized trials have also shown the survival benefit of preoperative chemotherapy in advanced non-metastatic gastric cancer [46]. The same can be extrapolated to metastatic gastric cancer if chemotherapy can also be given locally (intraperitoneally) in addition to systemic administration. Intraperitoneal chemotherapy has the advantage of directly affecting the tumor cells without causing significant systemic toxicity.

Yonemura et al. [68] reported their experience of treating 96 patients according to the neoadjuvant intraperitoneal-systemic chemotherapy protocol (NIPS) followed by CRS. Complete cytoreduction (by gastrectomy + D2 dissection + peritonectomy) was achieved in 82 patients. Complete pathologic response was observed in 30 (36.8%) patients [68].

Whether CRS and HIPEC should be performed upfront on patients who are diagnosed with occult peritoneal metastasis during diagnostic laparoscopy or whether these patients should first be subjected to systemic chemotherapy is a common dilemma faced by the surgeons. A retrospective analysis of 26 such patients revealed that median survival is better in patients first undergoing CRS and HIPEC compared to patients who are given systemic chemotherapy followed by CRS and HIPEC (28.2 versus 25.0 months). The treatment complications were also similar in both the groups [61].

20.6 Hyperthermic Intraperitoneal Chemotherapy (HIPEC) After CRS

After a successful complete cytoreduction, there is enough literature to suggest that intraperitoneal chemotherapy in a high concentration can kill the microscopic residual tumor cells in the peritoneal cavity. A systematic review of non-metastatic advanced gastric cancer patients suggested that there is a significant difference in mortality in the patients receiving intraperitoneal adjuvant chemotherapy versus surgery alone (OR 0.65; 95%CI 0.52, 0.81; $P < 0.005$) [18]. Additional heating of intraperitoneal chemotherapy to over 40 °C serves to enhance the effectiveness of killing tumor cells. This may be due to several reasons:

- The haphazardly arranged microcirculation of tumor cells does not allow them to cool down as quickly as a "normal cell" with normal microcirculation. The tumor cells cannot dissipate heat as effectively. When the desired temperature is reached, the accumulation of heat changes the oxygenation and leads to a hyperacidity of the milieu [27].
- Heat acts to augment the toxicity of some chemotherapeutic agents [12].
- Heat allows better tumor penetration of the chemotherapy [64].

These are the reasons for the widespread use of HIPEC in advanced gastric cancer, and with good results.

A combination of CRS and HIPEC can improve the median survival to 15 months compared to 3 months with best supportive care in selected patients with gastric cancer and peritoneal metastasis. The perioperative

mortality is about 5%. Postoperative complications (including abscesses, fistulas, and anastomosis leak) occur in approximately 21.5% of the cases [23]. However, early diagnosis is crucial for successful treatment and good prognosis.

Though there are many retrospective studies supporting the role of CRS and HIPEC in gastric cancer, it is always questioned as the survival benefit may be related to a bias in selecting patients with good prognostic factors. Currently, a German Cancer Aid funded phase III multicenter GASTRIPEC trial is being conducted to assess the role of CRS and HIPEC following preoperative chemotherapy in gastric cancer and esophagogastric junction tumors. In this study, patients with histologically proven peritoneal metastasis (and no other distant metastasis except ovaries) are being included. Preoperative chemotherapy is similar in both groups. An EOX (epirubicin, oxaliplatin, and capecitabine) chemotherapeutic regimen is prescribed to HER-2 negative patients, while CCT (cisplatin, capecitabine, and trastuzumab) is given to HER-2 positive patients. The preoperative chemotherapy is followed by surgical cytoreduction in both groups. Patients randomized into the HIPEC group are treated with an intraperitoneal (abdominal cavity) chemoperfusion with mitomycin C and cisplatin. Postoperatively, both receive three more cycles of postoperative chemotherapy. Due to the semi-curative approach to primary metastatic gastric carcinoma, whether postoperative chemotherapy should be given is a controversial topic in view of aggressive CRS and HIPEC. All landmark studies for gastric and esophagogastric junction tumors have recommended postoperative chemotherapy in advanced tumors [11, 66]. There is a likely possibility that microscopic free tumor cells may persist in the peritoneal cavity even after extensive complete cytoreduction and HIPEC. These data support the use of postoperative chemotherapy.

>> *Though systemic chemotherapy is primarily palliative, providing symptomatic relief, it may also lead to prolongation of survival [19, 40, 59].*

20.6.1 Palliative Treatment of Progressive Peritoneal Metastasis

As a rule, progressive peritoneal metastasis leads to ascites, which significantly affects the patients' quality of life. The expected survival of these patients is usually just weeks to very few months. Any radical operation in this setting is not justified and would only lead to further deterioration in quality of life. Often the patient just needs periodic paracentesis to reduce the intraabdominal pressure. Frequent paracentesis is fraught with the risk of intraabdominal infection and the development of abdominal metastases through the insertion channel. The alternative intraperitoneal cetuximab therapy is also not free of side effects and usually requires repeated hospital stays.

Retrospective studies have shown that laparoscopic HIPEC could significantly reduce such repeated punctures. In a study of 12 patients undergoing laparoscopic HIPEC for the palliation of refractory malignant ascites in patients who were unsuitable for cytoreductive surgery, a complete and definitive disappearance of ascites was observed in 10 patients. Two patients (17%) developed recurrent MA 124 days and 283 days post-HIPEC. None of the patients had high-grade morbidity or mortality. The median OS was 57 days [60].

A systematic review of eight studies and 183 patients also highlighted that laparoscopic HIPEC appears to be a safe and effective procedure (almost 95%) when performed to treat malignant ascites refractory to less aggressive treatments [17].

20.7 Conclusion

The locally advanced gastric carcinoma is associated with poor survival rates. Presence of peritoneal metastasis is a poor prognostic factor and results in a median survival of 3–5 months in the absence of any anticancer treatment. Radiological imaging such as computed tomography and

magnetic resonance imaging have their own limitations in the diagnosis of peritoneal metastasis.

Diagnostic laparoscopy is considered the gold standard for the diagnosis of peritoneal metastasis, histopathological confirmation, and assessment of the extent of the disease. In a patient with low volume peritoneal disease (low PCI), complete cytoreduction and hyperthermic intraperitoneal chemotherapy is shown to improve survival. Much published literature has confirmed the survival benefit of CRS and HIPEC, though controversy still exists. Patients should be selected carefully for low PCI and other good prognostic factors for a curative-approach treatment. Many randomized controlled trials are under way to better define the selection criteria and to generate a high level of evidence in favor of CRS and HIPEC. Laparoscopic HIPEC may be beneficial in controlling ascites in progressive peritoneal metastasis in patients who are not fit for CRS.

References

1. Ajani JA, Bentrem DJ, Besh S, D'Amico TA, The P Denlinger C, Fakih MG, Fuchs CS, Gerdes H, Glasgow RE, Hayman JA, Hofstetter WL, Ilson DH, Keswani RN, Kleinberg LR, Grain WM, Lockhart AC, Meredith K, Mulcahy MF, Orringer MB, YES P, Sasson AR, Scott WJ, Strong VE, Varghese TK Jr, Warren G, Washington MK, Willett C, Wright CD, NR MM, Sundar H. Gastric cancer, version 2.2013: featured updates to the NCCN guidelines. J Natl Compr Cancer Netw. 2013;11:531–46.
2. Aurello P, Petrucciani N, Giulitti D, Campanella L, D'Angelo F, Ramacciato G. Pulmonary metastases from gastric cancer: is there any indication for lung metastasectomy? A systematic review. Med Oncol. 2016;33:9.
3. Bang YJ, Van CE, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, pen-KOV E, Hill J, Lehle M, Ruschoff J, Kang YK. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet. 2010;376:687–97.
4. Boerner T, Graichen A, Jeiter T, Zemann F, Renner P, Marz L, Soeder Y, Schlitt HJ, Piso P, Dahlke MH. CRS-HIPEC prolongs survival but is not curative for patients with peritoneal carcinomatosis of gastric cancer. Ann Surg Oncol. 2016;23:3972–7.
5. Burke EC, Karpeh MS Jr, Conlon KC, Brennan MF. Peritoneal lavage cytology in gastric cancer: an independent predictor of outcome. Ann Surg Oncol. 1998;5:411–5.
6. The Cancer Genome Atlas Research Network, bass A, et al. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513:202–9.
7. Cao L, Selby LV, Hu X, Zhang Y, Janjigian YY, Tang L, Coit DG, Brennan MF, Strong VE. Risk factors for recurrence in T1-2N0 gastric cancer in the United States, China. J Surg Oncol. 2016;113:745–9.
8. Chang JS, Kim KH, Keum KC, Noh SH, Lim JS, Kim HS, Rha SY, Lee YC, Hyung WJ, Koom WS. Recursive partition analysis of peritoneal and systemic recurrence in patients with gastric cancer who underwent D2 gastrectomy: implications for neoadjuvant therapy consideration. J Surg Oncol. 2016;114:859–64.
9. Chang-Yun L, Yonemura Y, Ishibashi H, Sako S, Tsukiyama G, Kitai T, Matsuki N. Evaluation of preoperative computed tomography in estimating peritoneal cancer index in peritoneal carcinomatosis. Gan To Kagaku Ryoho. 2011;38:2060–4.
10. Cui J, Yin Y, Ma Q, Wang G, Olman V, Zhang Y, Chou WC, Hong CS, Zhang C, Cao S, Mao X, Li Y, Qin S, Zhao S, Jiang J, Hastings P, Li FXY. Comprehensive characterization of the genomic alterations in human gastric cancer. Int J Cancer. 2015;137:86–95.
11. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, Magic TP. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
12. Dewey WC. Interaction of heat with radiation chemotherapy. Cancer Res. 1984;44:4714–20.
13. Dromain C, Leboulleux S, Auperin A, Goere D, Malka D, Lumbroso J, Schumberger M, Sigal R, Elias D. Staging of peritoneal carcinomatosis: enhanced CT vs. PET/CT. Celiac Imaging. 2008;33:87–93.
14. Ebinger SM, Warschkow R, Tarantino I, Smith BM, Guller U, Schiesser M. Modest overall survival improvements from 1998 to 2009 in metastatic gastric cancer patients: a population-based SEER analysis. Gastric Cancer. 2016;19:723–34.
15. Esaki Y, Hirayama R, Hirokawa K. A comparison of patterns of metastasis in gastric cancer by histologic type and age. Cancer. 1990;65:2086–90.
16. Esquivel J, Chua TC, Stojadinovic A, Melero JT, Levine EA, Gutman M, Howard R, Piso P, Nissan A, Gomez-Portilla A, Gonzalez-Bayon L, Gonzalez-Moreno S, Shen P, Stewart JH, Sugarbaker PH, Barone RM, Hoefer R, Morris DL, Sardi A, Sticca RP. Accuracy and clinical relevance of computed tomography scan interpretation of peritoneal cancer index in colorectal cancer peritoneal carcinomatosis: a multi-institutional study. J Surg Oncol. 2010;102:565–70.
17. Facchiano E, Risio D, Kianmanesh R, Msika S. Laparoscopic hyperthermic intraperitoneal che-

motherapy: indications, aims, and results: a systematic review of the literature. Ann Surg Oncol. 2012;19:2946–50.
18. Feingold PL, Kwong ML, Davis JL, Rudloff U. Adjuvant intraperitoneal chemotherapy for the treatment of gastric cancer at risk for peritoneal carcinomatosis: a systematic review. J Surg Oncol. 2016;115:192–201.
19. Ford HE, Marshall A, Bridgewater YES, Janowitz T, Coxon FY, Wadsley J, Mansoor W, Fyfe D, Madhusudan S, Middleton GW, Swinson D, Falk S, Chau I, Cunningham D, Kareclas P, Cook N, Blazeby JM, Dunn JA. Doce taxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomized controlled trial. Lancet Oncol. 2014;15:78–86.
20. Fujimoto S, Shrestha RD, Kokubun M, et al. Intra peritoneal perfusion Hyperthermic combined with surgery effective for gastric cancer patients with peritoneal seeding. Ann Surg. 1988;208:36–41.
21. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, Iwasaki Y, Hyung WJ, Takagane A, Park DJ, Yoshi Kawa T, Hahn S, Nakamura K, Park CH, Kurokawa Y, Bang YJ, Park BJ, Sasako M, Tsujinaka T. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (RACING): a phase 3, randomized controlled trial. Lancet Oncol. 2016;17:309–18.
22. Garofalo A, Valle M. Laparoscopy in the management of peritoneal carcinomatosis. Cancer J. 2009;15:190–5.
23. Gill RS, Al-Adra DP, Nagendran J, Campbell S, Shi X, Haase E, Schiller D. Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. J Surg Oncol. 2011;104:692–8.
24. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients Treated by cyto reductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010a;17:2370–7.
25. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, Mansvelt B, Lorimier G, Msika S, Elias D. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer. 2010b;116:5608–18.
26. Goere D, Grass Chaput N, Auperin A, Flament C, Mariette C, Glehen O, Zitvogel L, Elias D. Treatment of gastric peritoneal carcinomatosis by combining complete surgical resection of lesions and intraperitoneal immunotherapy using catumaxomab. BMC Cancer. 2014;14:148. https://doi.org/10.1186/1471-2407-14-148.
27. Hall EJ, Brenner DJ. The radiobiology of radiosurgery: rational for different treatment regimes for AVMs and malignancies [see comments]. Int J Radiat Oncol Biol Phys. 1993;25:381–5.
28. Hultman B, Lind P, Glimelius B, Sundbom M, Nygren P, Haglund U, Mahteme H. Phase II study of patients with peritoneal carcinomatosis from gastric Treated cancer with preoperative systemic chemotherapy therapy Followed by peritonectomy and intraperitoneal chemotherapy. Acta Oncol. 2013;52:824–30.
29. Jacquet P, Sugar Baker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–74.
30. Jacquet P, Jelinek JS, Steve MA, Sugar Baker PH. Evaluation of computed tomography in patients with peritoneal carcinomatosis. Cancer. 1993;72:1631–6.
31. Jeong O, Park YK, Choi WY, Ryu SY. Prognostic significance of non-curative gastrectomy for gastric carcinoma incurable. Ann Surg Oncol. 2014a;21:2587–93.
32. Jeong O, Park YK, Choi WY, Ryu SY. Prognostic significance of non-curative gastrectomy for gastric carcinoma incurable. Ann Surg Oncol. 2014b;21:2587–93.
33. Kanda M, Mizuno A, Fujii T, Shimoyama Y, Yamada S, Tanaka C, Kobayashi D, Koike M, Iwata N, Niwa Y, Hayashi M, Takami H, Nakayama G, Sugimoto H, Fujiwara M, Kodera Y. Tumor infiltrative pattern predicts sites of recurrence after curative gastrectomy for stages 2 and 3 gastric cancer. Ann Surg Oncol. 2016;23:1934–40.
34. Kim KW, Chow O, Parikh K, Blank S, Jibara G, Kadri H, Labow DM, Hiotis SP. Peritoneal carcinomatosis in patients with gastric cancer, and the role for surgical resection, cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy. Am J Surg. 2014;207:78–83.
35. Klumpp B, Schwenzer NF, Gatidis S, Koenig Rainer I, Koenig Rainer A, Beckert S, Mueller M, Claussen CD, Pfannenberg C. Assessment of relapse in patients with peritoneal carcinomatosis after cytoreductive surgery and hyperthermic intraperitoneal Chemotherapy using F-18-FDG-PET/CT. Rofo. 2014;186:359–66.
36. Kong X, Wang JL, Chen HM, Fang JY. Comparison of the clinicopathological characteristics of young and elderly patients with gastric carcinoma: a meta-analysis. J Surg Oncol. 2012;106:346–52.
37. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, Rowsell C, Coburn NG. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Gastric Cancer. 2012;(15 Suppl 1):27–37.
38. Liu X, Cai H, Sheng W, Wang Y. Long-term results and prognostic factors of gastric cancer patients with peritoneal carcinomatosis micro scopic. PLoS One. 2012;7:e37284.
39. Low RN, Barone RM, Lee MJ. Surveillance MR imaging is superior to serum tumor markers for Detecting early tumor recurrence in patients with appendiceal cancer Treated with surgical cytoreduction and HIPEC. Ann Surg Oncol. 2013;20:1074–81.

40. Mirza A, Pritchard S, Welch I. The postoperative component of MAGIC chemotherapy is associated with improved prognosis Following surgical resection in gastric and gastroesophageal junction adenocar cinomas. Int J Surg Oncol. 2013. 2013: doi 781,742th:10.1155 / 2013/781742.
41. Moehler M, Baltin CT, Ebert M, Fischbach W, Gockel I, Grenacher L, Holscher AH, Lordick F, Malfertheiner P, Messmann H, Meyer HJ, Palmqvist A, Distaff C, Shoe Maker C, Steel M, Stuschke M, Vieth M, Wittekind C, Wagner D, Monig SP. International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus. Gastric Cancer. 2015;18:550–63.
42. Nunez MF, Sardi A, Jimenez W, Nieroda C, Sittig M, Mac Donald R, Aydin N, Milovanov V, Gushchin V. Port-site metastases is an independent prognostic factor in patients with peritoneal carcinomatosis. Ann Surg Oncol. 2015;22:1267–73.
43. Oba K, Paoletti X, Alberts S, Bang YJ, Benedetti J, Bleiberg H, Catalano P, Lordick F, Michiels S, Morita S, Ohashi Y, Pignon JP, Rougier P, Sasako M, Sakamoto J, Sargent D, Shitara K, Cutsem EV, Buyse M, Burzykowski T. Disease-free survival as a surrogate for overall survival in adjuvant trials of gastric cancer: a meta-analysis. J Natl Cancer Inst. 2013;105:1600–7.
44. Okano K, Maeba T, Ishimura K, Karasawa Y, Goda F, Wakabayashi H, Usuki H, Maeta H. Hepatic resection for metastatic tumors from gastric cancer. Ann Surg. 2002;235:86–91.
45. Ott K, Vogelsang H, Mueller J, Becker K, Muller M, Fink U, Siewert JR, Hofler H, Keller G. Chromosomal instability rather than p53 mutation is associated with response to neoadjuvant cisplatin-based chemotherapy therapy in gastric carcinoma. Clin Cancer Res. 2003;9:2307–15.
46. Pasquali S, Yim G, Vohra RS, Mocellin S, Nyanhongo D, Marriott P, Go JI, Griffiths EA. Survival after neoadjuvant and adjuvant treatments compared to surgery alone for esophageal carcinoma resectable: a network meta-analysis. Ann Surg. 2016;265:481–91.
47. Rau B, Brandl A, Piso P, Pelz J, Busch P, Demtroder C, Schule S, Schlitt HJ, Roitman M, Tepel J, Sulkowski U, Uzunoglu F, Hunerbein M, Horbelt R, Strohlein M, Beckert S, Konigsrainer I, Konigsrainer A. Peritoneal metastasis in gastric cancer: results from the German database. Gastric Cancer. 2020;23(1):11–22.
48. Rau B, Brandl A, Thuss-Patience P, Bergner F, Raue W, Arnold A, Horst D, Pratschke J, Biebl M. The efficacy of treatment options for patients with gastric cancer and peritoneal metastasis. Gastric Cancer. 2019;22(6):1226–37.
49. RKI. Prevalence of cancers in Germany: Robert Koch Institute; 2016. p. 1–181.
50. Seyfried F, of Rahden bra, Miras AD, Gasser M, Maeder U, Kunzmann V, Germer CT, Fur J, Kerscher AG. Incidence, time course and independent risk factors for metachronous peritoneal carcinomatosis of gastric origin – a longitudinally experience from a prospectively collected database of 1,108 patients. BMC Cancer. 2015;15 https://doi.org/10.1186/s12885-015-1081-8.73-1081.
51. Spratt JS, Adcock RA, Sherrill W, Travathen S. Hyperthermic peritoneal perfusion system in canines. Cancer Res. 1980;40:253–5.
52. Stewart B, Wild CP. International Agency for Research on Cancer. In: Stew B, Wild CP (eds) IARC Nonserial Publication; 2014.
53. Sugarbaker PH. Intraperitoneal chemotherapy and cytoreductive surgery for the prevention and treatment of peritoneal carcinomatosis and sarcomatosis. Semin Surg Oncol. 1998;14:254–61.
54. Sugarbaker PH, Jablonski KA. Prognostic features of colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreduc tive surgery and intraperitoneal chemotherapy. Ann Surg. 1995;221:124–32.
55. Sugarbaker PH, Cunliffe WJ, Belliveau J, de Bruijn EA, Graves T, Mullins RE, Impact P. Rationale for integra ting early postoperative intraperitoneal chemotherapy into the surgical treatment of gastrointestinal cancer. Semin Oncol. 1989;16:83–97.
56. Sun J, Song Y, Wang Z, Chen X, Gao P, Xu Y, Zhou B, Xu H. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis. BMC Cancer. 2013;13(577) https://doi.org/10.1186/1471-2407-13-577.577-13.
57. Thomassen I, Bernards N, van Gestel YR, Creemers GJ, Jacobs EM, Lemmens VE, de Hingh IH. Chemotherapy as a palliative treatment for peritoneal carcinomatosis of gastric origin. Acta Oncol. 2014a;53:429–32.
58. Thomassen I, van Gestel YR, Aalbers AG, van Oudheusden TR, Wegdam YES, Lemmens VE, de Hingh IH. Peritoneal carcinomatosis is less frequently diagnosed during laparoscopic surgery compared to open surgery in patients with colorectal cancer. Eur J Surg Oncol. 2014b;40:511–4.
59. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, Dogan Y, Gebauer B, Schumacher G, Reichardt P. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – a randomized phase III study of the Arbeitsgemeinschaft Medical oncology (AIO). Eur J Cancer. 2011;47:2306–14.
60. Valle SJ, Alzahrani NA, Alzahrani SE, Liauw W, Morris DL. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for refractory malignant ascites in patients unsuitable for cytoreductive surgery. Int J Surg. 2015;23:176–80.
61. Wu X, Li Z, Li Z, Jia Y, Shan F, Ji X, Bu Z, Zhang L, Wu A, Ji J. Hyperthermic intraperitoneal chemotherapy plus simultaneous versus staged cytoreductive surgery for gastric cancer with occult peritoneal metastasis. J Surg Oncol. 2015;111:840–7.
62. Xie D, Liu L, Osaiweran H, Yu C, Sheng F, Gao C, Hu J, Gong J. Detection and characterization of meta-

static cancer cells in the mesogastrium of gastric cancer patients. PLoS One. 2015;10:e0142970.
63. Yan TD, Morris DL, Shigeki K, Dario B, Marcello D. Preoperative investigations in the management of peritoneal surface malignancy with cytoreductive surgery and perioperative intraperitoneal chemotherapy: expert consensus statement. J Surg Oncol. 2008;98:224–7.
64. Yan TD, Cao CQ, Munkholm-Larsen S. A pharmacological review on intraperitoneal chemotherapy for peritoneal malignancy. World J Gastrointest Oncol. 2010;2:109–16.
65. Yarema RR, Ohorchak MA, Zubarev GP, Mylyan YP, Oliynyk YY, Zubarev MG, Gyrya PI, Kovalchuk YJ, Safiyan VI, Fetsych TG. Hyperthermic intraperitoneal chemoperfusion in combined treatment of locally advanced and disseminated gastric cancer: results of a single-center retrospective study. Int J Hyperth. 2014;30:159–65.
66. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Geneve J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for RESEC-table gastroesophageal adenocarcinoma: to FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29:1715–21.
67. Yonemura Y, Elnemr A, Endou Y, Hirano M, Mizumoto A, Takao N, Ichinose M, Miura M, Li Y. Multidisciplinary therapy for treatment of patients with peritoneal carcinomatosis from gastric cancer. World J Gastro intest Oncol. 2010;2:85–97.
68. Yonemura Y, Elnemr A, Endou Y, Ishibashi H, Mizumoto A, Miura M, Li Y. Effects of neoadjuvant intraperitoneal/systemic chemotherapy (bidirectional chemotherapy) for the treatment of patients with peritoneal metastasis from gastric cancer. Int J Surg Oncol. 2012, 2012. 148,420th: 10.1155 / 2012/148420.

21 Indications for CRS and HIPEC in Peritoneal Metastases from Colorectal Carcinoma

Loreen März, Francois Quenet, and Pompiliu Piso

For many years, an aggressive locoregional treatment for peritoneal metastases appeared experimental. When Yan et al. published their study back in 2008, performing cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) as a treatment for peritoneal metastases from colorectal cancer, this still was the question. Since then, both procedures have grown to be an essential part of the therapy of metastatic colorectal cancer. Several countries, in Europe and worldwide, have added CRS and HIPEC to their national treatment guidelines. In 2013 (and in the revised version of 2017), CRS and HIPEC were introduced into the German S3-Guidelines, although at low evidence grade (Grade 0, nonbinding recommendation) [16].

Choosing the right patients is the major task when aiming for the best possible outcome (Fig. 21.1) [13]. Patients who will benefit most from CRS and HIPEC are those with a complete resection of metastatic tissue (CCR 0), which is only possible in 25% of all patients [10].

The main three questions to be answered are:

1. Can we remove all visible disease – CC?
2. What is the tumor load and extent – PCI?
3. How is the tumor biology (signet ring cells, progression under chemotherapy, biomolecular markers)?

Our main selection tools are as follows:

21.1 Peritoneal Cancer Index

In order to quantify peritoneal metastases, most surgeons use the PCI (Peritoneal Cancer Index) [18]. There is still a need for clarification regarding the cut-off values for CRS and HIPEC, which ranged from under 20 in the beginning to 17 based on an analysis of 180 patients with peritoneal metastatic colorectal carcinoma by Goere et al. [7]. The latest findings from 2018's PRODIGE 7 study by Quenet et al. [17] fail to show an additional clinical benefit from the use of oxaliplatin-based hyperthermic intraperitoneal chemotherapy (HIPEC) over complete surgical cytoreduction only in patients with colorectal cancer. As an incidental result, median overall survival of patients with a PCI of 11–15 was significantly higher in the CRS + HIPEC group compared to the group with CRS alone

L. März
Germany Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany
e-mail: LoreenMaerz@gmx.de

F. Quenet
IC Val d'Aurelle, Montpellier, France
e-mail: Francois.Quenet@icm.unicancer.fr

P. Piso (✉)
Klinik für Allgemein- und Viszerachirurgie, Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany
e-mail: Pompiliu.Piso@barmherzige-regensburg.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_21

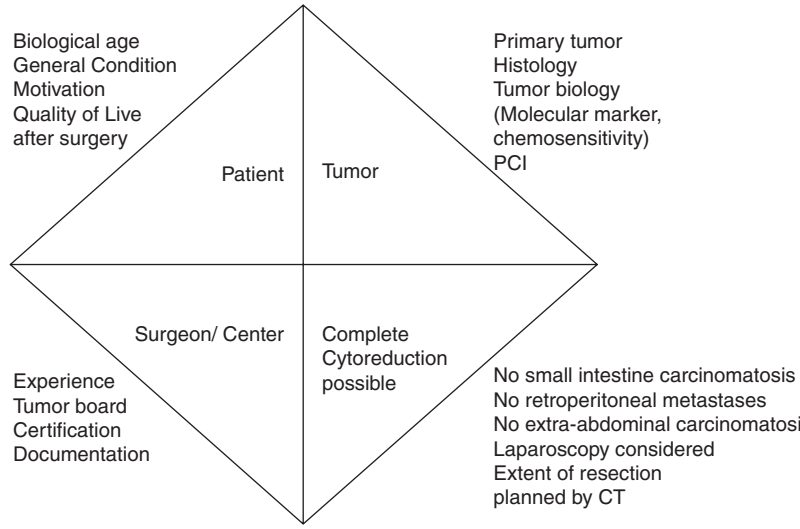


Fig. 21.1 Important factors for patient selection. [13]

(41.6 months versus 32.7 months), while patients with a PCI of less than 11 or 16–24 did not differ. However, since this was an unplanned analysis in a very small sample, results have to be looked upon with caution; further investigation is needed to confirm findings.

21.2 Distribution of Peritoneal Metastases

In addition to the PCI, tumor spreading should be considered when opting for CRS. Limitations to CRS include a disseminated tumor spreading to the small intestine and its mesentery, since extensive small bowel resection can cause short bowel syndrome and should be avoided. Involvement of the lymphatic system and carcinoma with low grade histology also limit the success of CRS and HIPEC [11].

21.3 Histology

Histopathologic tissue diagnosis is another key point in patient selection. Tumors with signet-ring cell carcinoma tend to be less sensitive to CRS and HIPEC, which leads to a restricted mean survival time (approximately 1 year) after HIPEC [19]. Therefore, signet-ring cell carcinoma should be regarded as a contraindication.

21.4 Liver Metastases

Liver metastases, on the other hand, don't categorically exclude CRS and HIPEC. Up to three hepatic metastases can be removed while performing CRS if they are located at the liver's margin and well accessible to resection. Prognosis worsens, however, in the presence of an extensive infiltration of the parietal peritoneum [12]. If the tumor extends beyond the abdominal cavity or spreads to the retroperitoneal space due to an aggressive tumor biology, patients should undergo a systemic palliative chemotherapy instead of CRS and HIPEC [5].

21.5 Biology

Biological sex, location of the primary tumor, a prior neoadjuvant chemotherapy, and a mucinous tumor histology, however, do not seem to have a major effect on the outcome [11]. Some authors call for a certain chemosensitivity in the treated tissue [2, 4]. In a small phase II trial, the feasibility of a multimodality concept including 3 months neoadjuvant therapy has been investigated with

no mortality and long-term survival similar to the Prodige 7 trial [6].

21.6 Comorbidity and Risk Assessment

With careful patient selection that takes into consideration the patient's general condition and valid indications for surgery, the morbidity and mortality of CRS and HIPEC appear to be acceptable. If surgery is performed at a certified center, Grade 3 and 4 complications are below 30%, and mortality is below 5% [2]. In addition to the preceding criteria, the general condition of the patient should be examined carefully. Patients suffering from severe cardiovascular, pulmonary, or hepatorenal diseases should not undergo CRS and HIPEC. As to this point, some authors call for an ECOG Performance Status of up to 2 or a Karnovsky Index below 70 [8].

21.7 Learning Curve and Centralization

As patient selection is a very complex issue, an interdisciplinary tumor board should be involved in the decision. Plenty of selection criteria have to be considered, with complete macroscopic cytoreduction, PCI, and histopathology foremost among them. Perioperative morbidity and mortality have to be balanced against the achievable oncologic advantage. These two points are important topics to be discussed with the patient.

The learning curve is long, and the results regarding not only morbidity and mortality but also the prognosis are better in centers and in particular in certified centers. In a nationwide German analysis, the mortality and the reoperation rate was significantly lower in centers that have performed more than 100 procedures [14].

21.8 HIPEC Controversy

Many data from past studies have been performed investigating the role of HIPEC with MMC in patients with colorectal studies [9]. These suggested an improved survival as compared to systemic chemotherapy alone. Direct comparisons between oxaliplatin and mitomycin C have shown that MMC is associated with less complications and comparable long-term survival data [3, 20]. Therefore the German Association for Surgical Oncology has recommended, as several other international groups, to continue performing HIPEC however, not with the regimen used in the Prodige 7 study. Instead, MMC should be preferred (Fig. 21.2).

In a population-based analysis of eastern Bavaria in Germany, the Prodige 7 has been reproduced with a median survival of 44 months, whereas the majority of the patients received a MMC-based HIPEC [15].

Message 1: Cytoreductive surgery is indicated and improves the median survival up to **42 mos** in patients with limited and isolated PM from CRC

Message 2: HIPEC for **30 Min** with high-dose Oxaliplatin should **not** be performed anymore.

Message 3: HIPEC for CRC should be performed for 90 min with **mitomycin c** (25-35 mg/m^2)

Message 4: CRS and HIPEC should be performed in (ceritified) experienced centers

Fig. 21.2 Recommendations of the German Association for Surgical Oncology with respect to the immediate impact of the Prodige 7 trial. (http://aco-chirurgie.de/wp-content/uploads/2019/01/Prodige-7-Studie-Statement-revidiert_final.pdf)

21.9 Re-CRS and HIPEC

Should a patient be submitted to evaluation for Re-CRS and HIPEC, the same selection criteria as for initial procedure can be used with similar prognosis, as shown in an analysis of an international PSOGI register [1].

Getting back to the main three questions, the answers would be:

1. Can we remove all visible disease? Yes
2. What is the tumor load and extent – PCI? PCI-15
3. How is the tumor biology? No signet ring cells, good response after chemotherapy, favorable constellation of biomolecular markers, e.g., RAS wild type, BRAF wild type

21.10 Conclusions and Perspectives

CRS and HIPEC have great potential when it comes to treating peritoneal metastases from colorectal cancer. If patients are selected carefully by an interdisciplinary tumor board, and if their preoperative general condition is examined critically, risks of surgery regarding morbidity is acceptable and mortality is low. Especially in cases of complete tumor removal (CCR-0) and low tumor load (PCI < 15), the outcome improves significantly compared to chemotherapy alone. The median survival exceeds 40 months, and the survival probability at 5 years may be around 40%. Nevertheless, a further improvement might be achieved regarding the intraperitoneal chemotherapy as the present regimens are old and the technique of HIPEC delivery can be optimized. Some aspects may include new drugs or combinations, new carrier solutions, longer time of exposure, less complications related to therapy, combination with i. p. immunotherapy, more experimental data provided prior to clinical use, less ambitioned end-points for studies, e.g., peritoneal DFS, and last but not the least better selection based on molecular marker. This was the clue for the personalized systemic chemotherapy and will for certain play a role in the locoregional treatment as well.

References

1. Alzahrani NA, Valle SJ, Fisher OM, Sugarbaker PH, Yonemura Y, Glehen O, Goere D, Honore C, Brigand C, de Hingh I, Verwaal VJ, Deraco M, Baratti D, Kusamura S, Pocard M, Piso P, Maerz L, Marchal F, Moran B, Levine EA, Dumont F, Pezet D, Abboud K, Kozman MA, Liauw W, Morris DL. Iterative cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases: a multi-institutional experience. Peritoneal Surface Oncology Group International (PSOGI) and Big-RENAPE groups. J Surg Oncol. 2019;119(3):336–46. https://doi.org/10.1002/jso.25277.
2. Arjona-Sánchez A, Medina-Fernández FJ, Muñoz-Casares FC, Casado-Adam A, Sánchez-Hidalgo JM, Rufián-Peña S. Peritoneal metastases of colorectal origin treated by cytoreduction and HIPEC: an overview. World J Gastrointest Oncol. 2014;6:407–12.
3. Bakkers C, et al. Long-term survival after hyperthermic intraperitoneal chemotherapy using mitomycin C or oxaliplatin in colorectal cancer patients with synchronous peritoneal metastases: a nationwide comparative study. Eur J Surg Oncol. 2020;46(10 Pt A):1902–7.
4. Cotte E, Passot G, Gilly FN, Glehen O. Selection of patients and staging of peritoneal surface malignancies. World J Gastrointest Oncol. 2010;2:31–5.
5. Elias D, Mariani A, Cloutier AS, et al. Modified selection criteria for complete cytoreductive surgery plus HIPEC based on peritoneal cancer index and small bowel involvement for peritoneal carcinomatosis of colorectal origin. Eur J Surg Oncol. 2014;40:1467–73.
6. Glockzin G, Zeman F, Croner RS, Königsrainer A, Pelz J, Ströhlein MA, Rau B, Arnold D, Koller M, Schlitt HJ, Piso P. Perioperative systemic chemotherapy, cytoreductive surgery, and hyperthermic intraperitoneal chemotherapy in patients with colorectal peritoneal metastasis: results of the prospective multicenter phase 2 COMBATAC trial. Clin Colorectal Cancer. 2018;17(4):285–96. https://doi.org/10.1016/j.clcc.2018.07.011. Epub 2018 Jul 31
7. Goere D, Souadka A, Faron M, et al. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. Ann Surg Oncol. 2015;22:2958–64.
8. Helderman RFCPA, Löke DR, Kok HP, Oei AL, Tanis PJ, Franken NAPK, Crezee J. Variation in clinical application of hyperthermic intraperitoneal chemotherapy: a review. Cancers. 2019;11(1):78.
9. Huang CQ, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy improves survival for peritoneal carcinomatosis from colorectal cancer: a systematic review and meta-analysis of current evidence. Oncotarget. 2017;8(33):55657–83. https://doi.org/10.18632/oncotarget.17497.
10. Klaver YL, Lemmens VE, Nienhuijs SW, Luyer MD, de Hingh IH. Peritoneal carcinomatosis of colorectal origin: incidence, prognosis and treatment options. World J Gastroenterol. 2012;18:5489–94.
11. Kwakman R, Schrama AM, van Olmen JP, et al. Clinicopathological parameters in patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer metastases: a meta-analysis. Ann Surg. 2016;263:1102–11.
12. Maggiori L, Goere D, Viana B, et al. Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent? A case-control study. Ann Surg. 2013;258:116–21.
13. Piso P, Glockzin G, von Breitenbuch P, Sulaiman T, Popp F, Dahlke M, Esquivel J, Schlitt HJ. Patient selection for a curative approach to carcinomatosis. Cancer J. 2009;15:236–42.
14. Piso P, Nedelcut SD, Rau B, Königsrainer A, Glockzin G, Ströhlein MA, Hörbelt R, Pelz J. Morbidity and mortality following cytoreductive surgery and hyperthermic intraperitoneal che-

motherapy: data from the DGAV StuDoQ registry with 2149 consecutive patients. Ann Surg Oncol. 2019;26(1):148–54. https://doi.org/10.1245/s10434-018-6992-6. Epub 2018 Nov 19

15. Piso P, Stierstorfer K, Gerken M, Klinkhammer-Schalke M. Benefit of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy in patients with isolated peritoneal metastases from colorectal cancer. Int J Colorectal Dis. 2018;33(11):1559–67. https://doi.org/10.1007/s00384-018-3146-z. Epub 2018 Aug 21. Int J Colorectal Dis. 2018. PMID: 30132068.
16. Pox C, Aretz S, Bischoff SC, et al. S3-guideline colorectal cancer version 1.0. Z. Gastroenterol. 2013;51:753–854.
17. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. J Clin Oncol. 2018;36(suppl; abstr LBA 3503)
18. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg. 1995;221:124–32.
19. van Oudheusden TR, Braam HJ, Nienhuijs SW, et al. Poor outcome after cytoreductive surgery and HIPEC for colorectal peritoneal carcinomatosis with signet ring cell histology. J Surg Oncol. 2015;111:237–42.
20. Woeste, et al. Optimal perfusion chemotherapy: a prospective comparison of mitomycin C and oxaliplatin for hyperthermic intraperitoneal chemotherapy in metastatic colon cancer. J Surg Oncol. 2020;121(8):1298–305.

The Role of HIPEC in the Treatment of Ovarian Cancer

22

Thomas Boerner, Anton Oseledchyk, and Oliver Zivanovic

For decades, hyperthermic intraperitoneal chemotherapy (HIPEC), administered at the time of cytoreductive surgery, has been a subject of debate in the oncological community. Recently, HIPEC made its first appearance in the National Comprehensive Cancer Network (NCCN) Guidelines for ovarian cancer.

Because ovarian cancer is a classic peritoneal malignancy, some have proposed that HIPEC should be added to its cytoreductive surgical management. This proposal was, until recently, based on mostly retrospective data and expert opinions in a disease which has been heavily studied in practice-changing randomized clinical trials, resulting in improved outcomes for patients with ovarian cancer over the past decades. More recently, molecular markers of homologous recombination deficiency have been identified, predicting pivotal vulnerability and substantial treatment response to oral PARP inhibitors. This has resulted in prolonged progression-free survival and overall survival, with durable responses in up to 50% of all patients with ovarian cancer.

T. Boerner · O. Zivanovic (✉)
Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA
e-mail: boernert@mskcc.org; zivanovo@mskcc.org

A. Oseledchyk
Department of Medical Oncology, Helios Klinikum Berlin-Buch, Berlin, Germany

22.1 Rationale for Peritoneal Chemotherapy in Patients with Ovarian Cancer

In 1978, Dedrick et al. introduced the theoretical model of a peritoneal/blood barrier allowing for high intraperitoneal doses of chemotherapeutic agents with limited systemic toxicity, for the treatment of peritoneal malignancies [14]. In order for a drug to be effective, it must penetrate via passive or active transport mechanisms into the cancer cell and/or the nucleus and interact with its substrate (e.g., DNA or disruption of microtubules function) [31].

Local cytotoxic drugs expose tumors within the peritoneal cavity to concentrations several times greater than that attained with intravenous drug administration. There is a theoretical pharmacological advantage for intraperitoneal chemotherapy delivery with improved tumor cell access, prolonged drug exposure, increased dose intensity, slow peritoneal clearance, and the potential to overcome chemoresistance [43].

When selecting a drug for intraperitoneal administration, pharmacokinetic characteristics play an important role [20, 21, 35, 42]. The molecular size of the drug correlates with drug levels in the peritoneal cavity and the plasma. For example, peak peritoneal paclitaxel concentrations exceed plasma concentrations by 1000-fold and persist in the peritoneal cavity for over 24 hours due to the large size of the paclitaxel

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_22

molecule compared with cisplatin; the latter shows a 12-fold higher concentration in the peritoneal compartment compared with the serum. Preclinical models have shown that high intraperitoneal drug concentrations may overcome drug resistance by overriding drug efflux and DNA repair mechanisms of cancer cells [31].

Intraperitoneal (IP) drugs such as cisplatin and paclitaxel, administered postoperatively through an intraperitoneal port (not heated, and not delivered in the operating room during the cytoreductive procedure) have been studied in several clinical trials ([1, 36] [3]). The Gynecologic Oncology Group (GOG protocol 172) randomly assigned patients—after primary debulking of stage III ovarian, fallopian tube, or peritoneal cancer with postoperative residual tumor <1 cm—to receive either IV paclitaxel at 135 mg/m^2 over 24 hours on day 1 and IV cisplatin at 75 mg/m^2 on day 2, or IV paclitaxel at 135 mg/m^2 over 24 hours on day 1 and IP cisplatin at 100 mg/m^2 over 24 hours on day 2, followed by IP paclitaxel at 60 mg/m^2 on day 8 of a 3-week cycle. Only 42% of patients randomized to postoperative IV/IP treatment completed all 6 planned postoperative cycles, due to toxicity, and continued with IV treatment only. 58% of the patients discontinued IP therapy due to increased hematologic and gastrointestinal toxicity; inadequate hydration or inadequate antiemetic therapy; or IP port complications, including obstruction, leakage, and infection. The progression-free survival and overall survival were improved in favor of IP treatment. The investigators showed a significantly increased progression-free and overall survival of 23.8 months versus 18.3 months, and 65.5 months versus 49.7 months, respectively, in favor of the IV/IP treatment arm (Table 22.1). Based on these results, the National Cancer Institute issued an alert to include postoperative normothermic IP therapy in the care of women with optimally debulked stage III ovarian cancer. Longer follow-up data from GOG protocols 114 and 172 were retrospectively analyzed, and the advantage of IP over IV treatment is measurable beyond 10 years [45].

Table 22.1 Postoperative intraperitoneal chemotherapy in primary ovarian cancer

Study	Treatment		PFS (months)	OS (months)	Literature
GOG 104	i.v. Cyclophosphamide 600 mg/m^2 + i.v. Cisplatin 100 mg/m^2		N/A	41	[1]
	i.v. Cyclophosphamide 600 mg/m^2 + i.p. Cisplatin 100 mg/m^2		N/A	49	
GOG 114	i.v. Paclitaxel 135 mg/m^2 (for 24 h) + i.v. Cisplatin 75 mg/m^2		22	52	[36]
	2x i.v. Paclitaxel (AUC 9, every 4 weeks), then i.v. Paclitaxel 135 mg/m^2 (for 24 h) + i.v. Cisplatin 100 mg/m^2		28	63	
GOG 172	i.v. Paclitaxel 135 mg/m^2 (for 24 h, Day 1) + i.v. Cisplatin 75 mg/m^2 (Day 2)		18.3	49.7	[3]
	i.v. Paclitaxel 135 mg/m^2 (for 24 h, Day 1) + i.p. Cisplatin 100 mg/m^2 (for 24 h, Day 2) + i.p. Paclitaxel 60 mg/m^2 (Day 8)		23.8	65.5	
GOG 252	i.v. Carboplatin (AUC 6) + i.v. Paclitaxel 80 mg/m^2 (Day 1, 8, and 15)	All therapeutic regimen included additional treatment with Bevacizumab 15 mg/kg (every 3 weeks) starting at cycle 2 for a total of 21 courses	24.9	N/A	Walker et al. 2017
	i.p. Carboplatin (AUC 6) + i.v. Paclitaxel 80 mg/m^2 (Day 1, 8, and 15)		27.3	N/A	
	i.v. Paclitaxel 135 mg/m^2 (Day 1) + i.p. Cisplatin 75 mg/m^2 (Day 2) + i.p. Paclitaxel 60 mg/m^2 (Day 8)		26	N/A	

PFS progression-free survival, *OS* overall survival, *i.v.* intravenous, *i.p.* intraperitoneal, *N/A* not available
[a]Unless otherwise noted, treatment arms consisted of six 3-weekly therapy cycles

The major challenges for healthcare providers of postoperative IP chemotherapy are the increased toxicity and the complex logistical management of patients and side effects, the need for additional home care to ensure adequate IV hydration, longer treatment times, and intensified nursing involvement. These challenges have resulted in a general underuse of the IP approach [47, 48].

For this reason, the most recent GOG 252 trial used a modified outpatient IP regimen:

- Arm 1: intravenous carboplatin AUC (area under the curve) 6/intravenous weekly paclitaxel at 80 mg/m^2
- Arm 2: intraperitoneal carboplatin AUC 6/intravenous weekly paclitaxel at 80 mg/m^2
- Arm 3: intravenous paclitaxel at 135 mg/m^2 on day 1/intraperitoneal cisplatin at 75 mg/m^2 on day 2/intraperitoneal paclitaxel at 60 mg/m^2 on day 8

In addition, patients in each arm received intravenous bevacizumab at 15 mg/kg with cycles 2 through 6 of chemotherapy and then as maintenance for cycles 7 through 22.

GOG 252 failed to show a progression-free and overall survival advantage associated with IP cisplatin/IP paclitaxel or IP carboplatin over dose-dense IV paclitaxel and carboplatin. Given the results of GOG 252, postoperative IP treatment has fallen out of favor.

22.2 Rationale for HIPEC

Hyperthermic intraperitoneal chemotherapy (HIPEC) is a single treatment of intraoperative chemotherapy after cytoreductive surgery [25, 44]. The drug is diluted in normal saline and warmed to 42 °C before perfusing the peritoneal cavity. The solution is either introduced via the open technique or the closed abdomen technique. No prospective studies have compared the different methods of administration [40]. Thus, there is not enough evidence to favor one technique over the other.

The cytotoxic mechanisms of hyperthermia are unclear. Temperatures in the range of 42–45 °C for 10–60 minutes were shown to be cytotoxic [22], with alterations in the cell membrane and nucleus, protein denaturation, and changes in calcium permeability. Hyperthermia disproportionately affects hypoxic tumor cells due to their relatively poor perfusion and acidotic state [26]. Hyperthermia increases sensitivity to chemotherapeutics, especially cisplatin, in ovarian cancer cell lines [26]. In vitro studies have shown that treatment of the tumor cells with both hyperthermia and platinum lead to an increase in the number of platinum-DNA adducts and an additive cytotoxic effect [32, 34, 39].

There is interest in combining surgical cytoreduction and HIPEC in the management of ovarian cancer:

The rationale for HIPEC is as follows:

(a) Ovarian cancer is confined to the peritoneal cavity in the majority of patients.
(b) Postoperative IP chemotherapy trials in patients with ovarian cancer have shown survival benefit in favor of IP regimens [1, 3, 36].
(c) Barriers of postoperative adhesions can be avoided. Intraoperatively, the chemotherapy can be delivered under anesthesia and the perfusate can be drained from the peritoneal cavity.
(d) There is no interval between cytoreduction and chemotherapy [29, 41].
(e) Hyperthermia alone has been associated with cytotoxic effects. In addition, hyperthermia has been shown to increase the cytotoxic effect of many chemotherapeutic agents [27, 28, 33].

22.3 Phase I/II Studies, Pharmacokinetics, Toxicity, Morbidity, and Mortality

Several phase I/II studies have been performed in the primary and recurrent disease settings. Zivanovic et al. [49] reported their experience using dose-escalated cisplatin during secondary

cytoreductive surgery in 12 patients with platinum-sensitive, recurrent ovarian cancer. The median operative time, including the 90-minute HIPEC procedure, was 463 minutes. No perioperative deaths or grade 4 adverse events were observed. Most adverse events were mild-to-moderate and appeared related to surgery. Pharmacokinetic measurements showed high intraperitoneal and low systemic exposure of cisplatin. The limited rate of observed chemotherapy-related side effects in this study was confirmed by the very low systemic exposure of cisplatin measured during and after HIPEC. Tumor samples before and after HIPEC were frozen for detection of cisplatin-induced DNA adducts. The visualization and quantification of cisplatin-induced intrastrand crosslinks in nuclear DNA were confirmed in tumor biopsies after 90 minutes of HIPEC. HIPEC did not compromise the ability to postoperatively administer standard systemic chemotherapy.

Paclitaxel has recently been investigated in the setting of HIPEC. De Bree et al. [13] performed a pharmacokinetic study on 13 patients administering 175 mg/m^2 paclitaxel for 2 hours. Mean maximal intraperitoneal paclitaxel concentration was 101 mg/L, which was an average of 1178 times higher than the peak plasma levels. Cytotoxic drug concentrations were detected in peritoneal fluid for a mean period of 2.7 days, despite drainage of the drug solution after 2 hours of treatment. The delivery of paclitaxel at 175 mg/m^2 showed an acceptable morbidity of 38% (minor and major complications), with no postoperative deaths. Ansaloni et al. [2] evaluated 11 patients who received cisplatin and paclitaxel as HIPEC. Cisplatin was administered at a dose of 100 mg/m^2, and paclitaxel was administered at a dose of 175 mg/m^2 for 90 minutes. In this study, superficial penetration of paclitaxel into the tissue was seen with ionization imaging mass spectrometry. Grade 3–4 surgical complications were recorded in four patients; in addition, five patients experienced grade 3 and two patients experienced grade 4 hematological complications (thrombocytopenia and anemia). No mortality was reported.

22.4 Retrospective Studies

The majority of data evaluating HIPEC in patients with ovarian cancer is based on retrospective research.

Multiple studies including 30 or more patients have reported the use of HIPEC for advanced-stage ovarian cancer, both in the upfront [4, 5, 7, 16, 37] and recurrent disease settings [5, 12, 15] for platinum-sensitive [7, 19, 37] or platinum-resistant disease. The studies include both heterogeneous groups of patients and drugs. A great variation is seen in the chemotherapy agents used, with single agent platinum and single agent paclitaxel being the most common, followed by combination therapies. Even within a single study, variation in the agents and doses used, and perfusion times, is commonly present.

Progression-free survival for patients with primary advanced-stage ovarian cancer treated with HIPEC is reportedly between 12 [5] and 24 months [37], while overall survival varies from 42 [5] to 57 months [37]. Progression-free survival for patients with recurrent disease ranges from 11 [15] to 27 months [38], and reported overall survival varies from 28 to 63 months [38]. In one of the largest retrospective studies of persistent and recurrent ovarian cancer, Bakrin et al. [5] described survival and morbidity in 246 patients over a period of 17 years and showed both acceptable morbidity (12%) and a median overall survival of 49 months. In this retrospective study patients with platinum-resistant and platinum-sensitive disease were included. Interestingly, two studies have found no difference in survival between platinum-sensitive and platinum-resistant recurrences treated with HIPEC [5, 12]. One study observed improved survival for platinum-sensitive disease, yet this study used 12 months to define platinum sensitivity instead of the usual 6 months. While the favorable outcomes of patients with platinum-resistant disease are encouraging, the criteria for surgery are likely the result of selection bias. This should be considered carefully when interpreting these retrospective findings.

Two studies compared the use of HIPEC in patients with a platinum-sensitive recurrence to

controls. One found that fewer patients treated with HIPEC recurred (66% vs. 100%, $p = 0.001$) or died from disease (23% vs. 62%, $p = 0.003$), while the other found no significant difference in survival (3-year progression-free survival 45% HIPEC vs. 23% surgery alone, $p = 0.078$). The only study that compared HIPEC in the upfront setting to standard care found that the 3-year PFS was higher in patients treated with HIPEC than controls (63% vs. 18%, $p < 0.01$).

Another area of interest is the rate of complications and mortality associated with the use of HIPEC. Reported rates of serious (grade 3 or higher) complications range from 8.6% to 35.7%, while the rates of 30-day mortality range from a reported 0% to 7.1%. The reported rates of major complications are comparable to those of other large retrospective studies evaluating surgical complication after cytoreductive surgery without the use of HIPEC [10, 30].

The surgical outcomes of patients in multiple retrospective studies mimic those of studies without the use of HIPEC, suggesting the safety and feasibility of this approach in centers with expertise. At the same time, the survival outcomes are difficult to interpret outside the setting of a randomized trial. Multiple retrospective studies in patients selected to undergo cytoreductive surgery without HIPEC report outcomes similar to or not inferior to the outcomes reported by many studies including HIPEC [6, 8, 9, 11, 17, 18, 50].

22.5 Prospective Studies

A single institution, randomized phase III trial comparing conventional secondary cytoreductive surgery with or without HIPEC in patients with recurrent ovarian cancer was published in 2015 (Spiliotis et al.). This study included 120 patients with both platinum-sensitive and platinum-resistant disease. Cisplatin at 100 mg/m^2 and paclitaxel at 175 mg/m^2 were administered in patients with platinum-sensitive disease, while doxorubicin at 35 mg/m^2 and paclitaxel at 175 mg/m^2 or mitomycin at 15 mg/m^2 were administered in patients with platinum-resistant disease. The authors reported a mean survival of 27 months for patients randomized to HIPEC versus 13 months for patients in the standard group, with the greatest effect seen in patients with platinum-resistant disease. However, significant shortcomings in the trial design, preoperative randomization process, inclusion of heterogeneous patient cohorts and chemotherapeutic regimens, lack of specification of postoperative chemotherapy and follow-up are seen in this study [23, 24].

More recently, van Driel et al. [46] published the first randomized trial evaluating the use of HIPEC with cisplatin at the time of interval debulking surgery for patients with stage III ovarian cancer who underwent neoadjuvant intravenous chemotherapy. In this study, 245 patients who had at least stable disease after 3 cycles of intravenous neoadjuvant paclitaxel and carboplatin chemotherapy were randomly assigned to undergo interval debulking surgery with or without HIPEC with cisplatin at a dose of 100 mg/m^2. Randomization was performed before surgery. Three additional cycles of carboplatin and paclitaxel were administered postoperatively. The median progression-free survival, which was the primary endpoint, was 10.7 months in patients in the standard arm versus 14.2 months in patients treated with HIPEC (hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.50 to 0.87; $P = 0.003$). At the time of analysis, 44% of patients were alive, with a significant improvement in median overall survival favoring HIPEC (45.7 vs. 33.9 months; HR, 0.67; 95% CI, 0.48 to 0.94, $P = 0.02$). The number of patients with grade 3–4 adverse events was similar in both treatment arms (27% vs. 25%, $p = 0.76$). There was no delay in postoperative chemotherapy treatment and no compromise in completing the additional 3 cycles of chemotherapy in the postoperative setting in patients who received HIPEC. In addition, there was no difference in health-related quality of life.

This is the first reported randomized trial in which the only intervention that differs between groups is the use of a single 90-minute perfusion of cisplatin after surgical cytoreduction. The dose of cisplatin was determined at 100 mg/m^2, which had been established in previous phase I/II and

multiple retrospective studies. Protocol-specific standardized surveillance measures—including the defined CA125 measurements and CT-scans—were used to assess the primary endpoint of progression-free survival. Safety assessments were included in the study and were addressed adequately. In addition, the median progression-free survival and overall survival in the control group is reproducible and identical to previously reported outcomes from randomized clinical trials that included patients with similar inclusion criteria. A major weakness of this trial is the timing of randomization, which occurred before surgery. Another weakness is that, in patients randomized to the control arm, more unusual or unfavorable histologies are observed. Costs of treatment—including longer OR time, longer hospitalization, and higher rates of diverting ostomies in the HIPEC arm—were not addressed. The higher rate of diverting ileostomies and colostomies is concerning and must be communicated to patients, especially because its use is based on concerns over higher anastomotic leak rates in the HIPEC group; this may not be justified, as there is no clear evidence that HIPEC is associated with higher leak rates.

22.6 Conclusion

Locoregional treatment strategies provide decreased systemic toxicity and a high pharmacological advantage for tumors confined to a single organ or body cavity. While intraperitoneal chemotherapy for patients with advanced ovarian cancer has been accepted as part of standard care, HIPEC administered at the time of cytoreductive surgery has been the subject of debate and reservation, and doubts about it remain prevalent.

Over the past 10 years, multiple phase I/II trials and sizable retrospective studies have been reported. The incorporation of pharmacokinetic analyses into these studies confirmed very high concentrations of chemotherapeutic agents in the peritoneal cavity, with minimal systemic exposure and overall minimal systemic toxicity. In addition, tissue penetration and DNA adduct formation of platinum- and taxane-based compounds have been confirmed, and the efficacy of cisplatin at a dose of 100 mg/m^2 has been reproduced in multiple settings. Moreover, the vast majority of adverse events observed at experienced centers is related to the surgical procedure itself and does not appear to be higher than in studies evaluating the role of cytoreductive surgery without HIPEC. The results of the recently published randomized trial demonstrating clinical efficacy of 100 mg/m^2 cisplatin over 90 minutes of HIPEC during interval cytoreductive surgery are encouraging, but legitimate questions remain about how to best apply this technique in routine care.

In an evolving environment of molecular diagnostics, novel targeted therapies, and a persistent underuse of postoperative IP treatment, HIPEC may serve as a complementary treatment at the time of cytoreductive surgery and may improve outcomes for women with ovarian cancer in the future.

References

1. Alberts DS, et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med. 1996;335(26):1950–5.
2. Ansaloni L, et al. Pharmacokinetics of concomitant cisplatin and paclitaxel administered by hyperthermic intraperitoneal chemotherapy to patients with peritoneal carcinomatosis from epithelial ovarian cancer. Br J Cancer. 2015;112(2):306–12.
3. Armstrong DK, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med. 2006;354(1):34–43.
4. Bakrin N, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: a multicenter, prospective study of 246 patients. Ann Surg Oncol. 2012;19(13):4052–8.
5. Bakrin N, et al. Peritoneal carcinomatosis treated with cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. Eur J Surg Oncol. 2013;39(12):1435–43.
6. Bristow RE, et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002;20(5):1248–59.
7. Cascales-Campos PA, et al. Treatment of microscopic disease with hyperthermic intraoperative intraperitoneal chemotherapy after complete cyto-

reduction improves disease-free survival in patients with stage IIIC/IV ovarian cancer. Ann Surg Oncol. 2014;21(7):2383–9.
8. Chi DS, et al. Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer. 2006b;106(9):1933–9.
9. Chi DS, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol. 2009;114(1):26–31.
10. Chi DS, et al. The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas. Gynecol Oncol. 2010;119(1):38–42.
11. Chi DS, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol. 2006a;103(2):559–64.
12. Classe JM, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for first relapse of ovarian cancer. Anticancer Res. 2015;35(9):4997–5005.
13. de Bree E, et al. Cytoreductive surgery and intraoperative hyperthermic intraperitoneal chemotherapy with paclitaxel: a clinical and pharmacokinetic study. Ann Surg Oncol. 2008;15(4):1183–92.
14. Dedrick RL. Theoretical and experimental bases of intraperitoneal chemotherapy. Semin Oncol. 1985;12(3 Suppl 4):1–6.
15. Deraco M, et al. Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study. BJOG. 2012;119(7):800–9.
16. Di Giorgio A, et al. Cytoreduction (peritonectomy procedures) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in advanced ovarian cancer: retrospective Italian multicenter observational study of 511 cases. Ann Surg Oncol. 2017;24(4):914–22.
17. Eisenhauer EL, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. Gynecol Oncol. 2006;103(3):1083–90.
18. Eisenkop SM, et al. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol. 2003;90(2):390–6.
19. Fagotti A, et al. Cytoreductive surgery plus HIPEC in platinum-sensitive recurrent ovarian cancer patients: a case-control study on survival in patients with two year follow-up. Gynecol Oncol. 2012;127(3):502–5.
20. Francis P, et al. Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: a Gynecologic Oncology Group pilot Study. J Clin Oncol. 1995;13(12):2961–7.
21. Fujiwara K, et al. Principles and practice of intraperitoneal chemotherapy for ovarian cancer. Int J Gynecol Cancer. 2007;17(1):1–20.
22. Giovanella BC, Stehlin JS, Morgan AC. Selective lethal effect of supranormal temperatures on human neoplastic cells. Cancer Res. 1976;36(11 part 1):3944–50.
23. Harter P, et al. Brief report about the role of hyperthermic intraperitoneal chemotherapy in a prospective randomized phase 3 study in recurrent ovarian cancer from Spiliotis et al. Int J Gynecol Cancer. 2017;27(2):246–7.
24. Harter P, et al. Statement of the AGO Kommission Ovar, AGO Study Group, NOGGO, AGO Austria and AGO Switzerland Regarding the Use of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer. Geburtshilfe Frauenheilkd. 2016;76(2):147–9.
25. Helm CW. The role of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer. Oncologist. 2009;14(7):683–94.
26. Hettinga JV, Konings AW, Kampinga HH. Reduction of cellular cisplatin resistance by hyperthermia—a review. Int J Hyperth. 1997a;13(5):439–57.
27. Hettinga JV, et al. Mechanism of hyperthermic potentiation of cisplatin action in cisplatin-sensitive and -resistant tumour cells. Br J Cancer. 1997b;75(12):1735–43.
28. Hildebrandt B, et al. The cellular and molecular basis of hyperthermia. Crit Rev Oncol Hematol. 2002;43(1):33–56.
29. Hofstetter G, et al. The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - analysis of patient data in the prospective OVCAD study. Gynecol Oncol. 2013;131(1):15–20.
30. Kehoe SM, et al. Incidence and management of pancreatic leaks after splenectomy with distal pancreatectomy performed during primary cytoreductive surgery for advanced ovarian, peritoneal and fallopian tube cancer. Gynecol Oncol. 2009;112(3):496–500.
31. Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer. 2007;7(8):573–84.
32. Los G, et al. Effects of temperature on the interaction of cisplatin and carboplatin with cellular DNA. Biochem Pharmacol. 1993;46(7):1229–37.
33. Los G, et al. Optimisation of intraperitoneal cisplatin therapy with regional hyperthermia in rats. Eur J Cancer. 1991;27(4):472–7.
34. Los G, van Vugt MJH, Pinedo HM. Response of peritoneal solid tumours after intraperitoneal chemohyperthermia treatment with cisplatin or carboplatin. Br J Cancer. 1994;69(2):235–41.
35. Markman M, et al. Phase I trial of intraperitoneal taxol: a gynecoloic oncology group study. J Clin Oncol. 1992;10(9):1485–91.
36. Markman M, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the gynecologic oncology group, southwestern oncology group, and eastern cooperative oncology group. J Clin Oncol. 2001;19(4):1001–7.

37. Munoz-Casares FC, et al. Peritonectomy procedures and HIPEC in the treatment of peritoneal carcinomatosis from ovarian cancer: long-term outcomes and perspectives from a high-volume center. Eur J Surg Oncol. 2016;42(2):224–33.
38. Petrillo M, et al. Long-term survival for platinum-sensitive recurrent ovarian cancer patients treated with secondary cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol. 2016;23(5):1660–5.
39. Reed E, et al. Platinum-DNA adduct in leukocyte DNA of a cohort of 49 patients with 24 different types of malignancies. Cancer Res. 1993;53(16):3694–9.
40. Rodriguez Silva C, et al. Are there intra-operative hemodynamic differences between the Coliseum and closed HIPEC techniques in the treatment of peritoneal metastasis? A retrospective cohort study. World J Surg Oncol. 2017;15(1):51.
41. Seagle BL, et al. Chemotherapy delay after primary debulking surgery for ovarian cancer. Gynecol Oncol. 2017;144(2):260–5.
42. Speyer JL, Sorich J. Intraperitoneal carboplatin: rationale and experience. Semin Oncol. 1992;19(1 Suppl 2):107–13.
43. Stordal B, Davey M. Understanding cisplatin resistance using cellular models. IUBMB Life. 2007;59(11):696–9.
44. Sugarbaker PH. Peritonectomy procedures. Ann Surg. 1995;221(1):29–42.
45. Tewari D, et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a gynecologic oncology group study. J Clin Oncol. 2015;33(13):1460–6.
46. van Driel WJ, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med. 2018;378(3):230–40.
47. Walker JL, et al. Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: a gynecologic oncology group study. Gynecol Oncol. 2006;100(1):27–32.
48. Wright AA, et al. Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. J Clin Oncol. 2015;33(26):2841–7.
49. Zivanovic O, et al. HIPEC ROC I: a phase I study of cisplatin administered as hyperthermic intraoperative intraperitoneal chemoperfusion followed by postoperative intravenous platinum-based chemotherapy in patients with platinum-sensitive recurrent epithelial ovarian cancer. Int J Cancer. 2015;136(3):699–708.
50. Zivanovic O, et al. The effect of primary cytoreduction on outcomes of patients with FIGO stage IIIC ovarian cancer stratified by the initial tumor burden in the upper abdomen cephalad to the greater omentum. Gynecol Oncol. 2010;116(3):351–7.

23 Indication of CRS and HIPEC in Peritoneal Metastases of NET and Small Intestine Carcinomas

Hubert Leebmann and Pompiliu Piso

23.1 Preamble

Malignant tumors of the small intestine are very rare, with an incidence rate of 1.1 per 100,000/year [5].

With a length of about 3 m, the small intestine accounts for about 75% of the overall length and nearly 90% of the surface area of the gastrointestinal tract's mucosa.

Despite its length and anatomical position between two regions of high cancer risk—the stomach and the colon—the small bowel is the site of only about 2% of all gastrointestinal malignancies [30]. The malignant tumors of the small intestine, with about 40 diverse histological subtypes, constitute a very heterogeneous disease group. Adenocarcinoma (36.9%) and neuroendocrine tumors (NET) (37.4%) are the predominant subtypes [4].

The malignant tumors of the small intestine are diagnosed mainly at an advanced stage. Clinical presentation of small bowel tumors is rather nonspecific. A diagnostic delay of 16 to 32 weeks after symptom development is common, primarily due to technical limitations of standard endoscopy and imaging techniques [26]. In 30% of the patients, the correct diagnosis is established by laparotomy [7].

The significant co-occurrence of small intestine malignancies and synchronous or metachronous secondary tumors is remarkable [27]. In a recent epidemiological study, secondary tumors were observed in one third of patients with malignant small bowel tumors [5]. Overall, prognosis remains poor for malignant small bowel tumors, with 5-year survival rates between 37% and 54% [2]. Due to the very limited therapeutic progress, survival has remained disappointingly unchanged throughout the last 20 years [4].

23.2 Adenocarcinomas of the Small Bowel

With an incidence rate of up to 0.55 per 100,000 per year, adenocarcinomas appear mostly in the sixth or seventh decade of life. In more than half of the cases, the tumor is localized in the duodenum [5]. Carcinomas of the small bowel are typically diagnosed in an advanced stage. In a study of the M. D. Anderson Cancer Center, three quarters of the patients had lymph node or distant metastases at the time of diagnosis, and in only 24% of the cases was diagnosis established at an

H. Leebmann (✉)
Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany
e-mail: hubert.leebmann@barmherzige-regensburg.de

P. Piso
Klinik für Allgemein- und Viszerachirurgie, Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany
e-mail: Pompiliu.Piso@barmherzige-regensburg.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_23

earlier tumor stage. The 5-year survival rate among all patients amounted to 26%, and median survival time was 20 months [7].

Due to the rarity of small bowel carcinomas, randomized studies are lacking. Treatment occurs prevalently in analogy to the therapeutic recommendations for colorectal carcinoma.

Total resection of the primary tumor including the lymphatic drainage is the treatment of choice for all locoregional tumors (stage I through III). In most series, resection rates varied between 40% and 65% with 5-year survival rates between 36% and 81% for resected tumors and 12–30% for non-resected tumors [30]. The benefit of adjuvant chemotherapy is still not conclusively clarified. The limited data of former retrospective studies could not prove any benefit from adjuvant therapy [7, 14, 15].

However, recent data support the use of adjuvant therapy in stage III small bowel adenocarcinoma (median survival time, 42.4 vs. 26.1 months; 5-year survival rate, 25.0% vs. 17%) [9].

35% of the patients with small bowel carcinomas are diagnosed at a metastasized stage [7]. Patients with metastasized carcinomas or tumor recurrence have an extremely poor prognosis, with a median survival of only 6.6 months and 5-year survival rates between 0% and 5% [1, 17, 20]. The role of palliative chemotherapy for small bowel adenocarcinomas still remains unproven. However, unlike adjuvant chemotherapy, there seems to be evidence of a benefit for the use of palliative systemic chemotherapy for patients with unresectable or metastatic disease (median survival time: 11.8 vs. 4.1 months [20].

A large retrospective multicenter study regarding palliative chemotherapy for advanced adenocarcinoma of the small intestine was published by Zaanan et al. in 2010. This study indicates that small bowel adenocarcinoma is sensitive to platinum-based chemotherapy (FOLFOX) (median survival time: 17.8 months).

Like carcinomas of the large bowel, adenocarcinomas of the small intestine metastasize mostly to the liver and the peritoneum.

>> Synchronous peritoneal carcinomatosis occurs in approximately 25% of the patients with stage IV tumors.

Recurrence after curative resection occurs in 40–70%. The most common sites after recurrence are liver and lung (67%) and the peritoneum (24%) [1, 7].

At present, there are only a few case reports regarding peritoneal carcinomatosis of small intestine adenocarcinomas treated by cytoreductive surgery and intraperitoneal chemotherapy [6, 11, 18, 22, 23, 28, 29].

Table 23.1 provides an overview of the literature.

One retrospective multicenter study reports the results of combined treatment (complete cytoreductive surgery and intraperitoneal chemotherapy) for four different digestive adenocarcinomas (small bowel, appendix, colon, and rectum) [11].

Among 440 patients with peritoneal carcinomatosis, 341 originated from the colon, 27 from the rectum, 41 from appendiceal cancer without pseudomyxoma peritonei, and 31 from the small bowel. Neither patient characteristics (gender, age, tumor extension and distribution, presence of liver metastases, histological differentiation of the tumors, and lymph node involvement) nor the type of treatment differed between the patients according to the tumor origin. All patients received intraperitoneal chemotherapy either in form of HIPEC or as EPIC. The 5-year overall survival rate for all patients was 33%, and the 5-year disease-free survival rate was 18%. The median overall survival for patients with colon carcinoma (32.4 months), rectum carcinoma (34 months), and small bowel carcinoma (47 months) was similar. A better survival rate

Table 23.1 Publications published to date on small intestine carcinomas given multimodal therapy

	Acquisition period	N	Median survival time (months)
Marchettini et al.		6	12
Sun et al.	1995–2011	17	18.4
Chua et al.	1997–2009	7	25
Elias et al.	1989–2007	31	47
van Oudheusden et al.	2005–2014	16	30.8
Liu et al.	2006–2014	31	36

was achieved for carcinomatosis originating from the appendix (89 months).

> *>> Until specific selection parameters for the combined treatment of small bowel adenocarcinoma are defined, patient selection should be oriented toward the well-established selection criteria for colorectal carcinoma.*

By extrapolating the established selection criteria for colorectal carcinoma to small bowel carcinoma, long-term survival could be achieved with cytoreductive surgery and intraperitoneal chemotherapy [22, 29].

> *>> Overall survival can be doubled by adequate multimodal treatment of carcinomatosis originating from the small bowel, in comparison to sole use of palliative chemotherapy.*

However, the data should be interpreted very cautiously. The good results following cytoreductive surgery and intraperitoneal chemotherapy are also based on a substantial selection bias. Negative prognostic factors such as multilocal metastatic spread, advanced age, and reduced general condition are exclusion criteria for multimodal therapy. In addition, there is an underrepresentation of duodenal adenocarcinoma in comparison to jejunal or ileal carcinoma in most studies. In the studies of Liu et al. [22] and van Oudheusden et al. [29], among 25 and 16 patients, respectively, with adenocarcinoma of the small bowel, there is only one case of duodenal carcinoma in each study. Elias et al. [11] provide no data on the distribution of tumors. Duodenal carcinomas require considerably more complex surgical therapy than carcinomas at further distal locations. In addition, due to their anatomical properties, they have a poorer prognosis even at early stages.

23.3 Neuroendocrine Tumors

Neuroendocrine neoplasms arise in the neuroendocrine organs as well as from the cells of the diffuse neuroendocrine system. The diffuse neuroendocrine system is located, isolated or in small groups, in nearly every organ. Despite a considerable increase in the incidence rate by a factor of 2.4 to 5–6 cases per 100,000 per year, the neuroendocrine neoplasms are still very rare tumors (merely 0.46% of all bronchopulmonary and gastrointestinal tumors). The most frequent primary tumor sites are the lungs and the small bowel (25% and 18% of the cases, respectively) [16].

Neuroendocrine neoplasms are classified according to WHO criteria. Epithelial neuroendocrine neoplasms are divided into well- and poorly differentiated neoplasms. The well-differentiated neuroendocrine neoplasms of the gastrointestinal tract are also called neuroendocrine tumors (NET). They show a lower mitotic and proliferation rate (<20%). The term carcinoid, previously used for designating these tumors, is obsolete. The poorly differentiated neuroendocrine carcinomas (G3, Ki67-index 20–50%) are treated—similar to small cell bronchial carcinoma—mostly by chemotherapy. The operative therapy of the neuroendocrine neoplasms is usually restricted to well-differentiated NETs (G2–3, Ki67-Index <20%). In addition to surgery, the treatment options include local ablative procedures, chemotherapy, somatostatin analogues, radioligand therapy, and targeted substances that can be applied as neoadjuvant, adjuvant, or palliative treatment. Due to the rarity of the tumors, in most cases, the therapy recommendations are based on expert opinion and are not validated by prospective randomized studies. Owing to the heterogeneity of the tumors, to the vast number of therapy strategies, and to the often individual complex disease courses, each patient should be discussed individually—especially, if surgery is taken into account—in a multidisciplinary tumor conference.

At the time of the diagnosis, about 20% of all patients with NET show synchronous distant metastatic spread. 38% of the patients develop metachronous metastases during the further course of the disease. Metastatic status is associated with a worse prognosis. Furthermore, overall survival differs significantly according to the primary tumor site. NETs of the rectum and the small intestine present the highest 5-year survival rates (87% and 73%, respectively), while the prognosis of NETs with pancreatic origin is worse (49% 5-year survival rate) [16].

NETs of the midgut typically progress slowly. The 5-year survival rate for all stages reaches between 50% and 60%. In NETs with only local disease, the 5-year survival rate is 80–90%. For regional growth (positive locoregional lymph nodes), 5-year survival rate is between 70% and 80%. Moreover, even stage IV tumors have a good prognosis (5-year survival rate: 35–60%) [13]. The liver is the most common metastatic site (50–60%). In 20–30% of cases, metastatic lymph nodes occur beyond the primary drainage area. Lungs and bones are affected by metastatic disease in 3–5% and 1–6%, respectively. In 10–33% of the patients, peritoneal carcinomatosis can be expected [8]. There is an association between the location of the primary NET and the metastatic pattern. NET-derived peritoneal carcinomatosis arises mainly from the small intestine [3, 10].

In contrast to older studies, a recent Swedish study identified peritoneal carcinomatosis as an independent negative prognostic factor for patients with NET [25]. Five- and ten-year survival rates for patients with peritoneal carcinomatosis were 52 and 32%, respectively, whereas five- and ten-year survival rates for patients with non-peritoneal metastases were 79% and 54%, respectively.

Whether a complete cytoreduction with or without HIPEC results in prolongation of overall survival was examined by Elias et al. [12]. Among 189 patients with well-differentiated NET, 17 patients underwent complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. The median peritoneal carcinomatosis index of Sugarbaker (PCI) was 18 (range 4–26). Liver metastasis was present in all but one patient. Liver metastases were treated by either simultaneous liver resection or arterial hepatic chemoembolization. A comparison group of 20 patients underwent only a palliative surgical resection due to the peritoneal and/or hepatic tumor extension.

The 5-year survival rate of the multimodal therapy group was better than the survival rate of the comparison group (62.2% and 40.9%, respectively). In the multimodal therapy group, only one death was attributed directly to the peritoneal carcinomatosis (17%), whereas bowel obstruction due to progression of carcinomatosis was the direct cause of death for six patients in the comparison group (40%).

In a second study, Elias et al. [10] attempted to answer the question whether there is a benefit of adding HIPEC to cytoreductive surgery. The data of 41 patients receiving therapy from 1994 to 2012 were collected. The inclusion criterion was an "optimal operation," that is, complete resection or ablation of all macroscopically visible tumor. Complete cytoreduction was defined as resection of all nodules >1 mm. 28 patients treated between 1994 and 2007 received additional HIPEC (HIPEC group). The comparison group (10 patients, non-HIPEC group) was treated without HIPEC between 2008 and 2012. There was no significant difference regarding their peritoneal carcinomatosis index, distribution and extension of the liver metastasis, Ki67-index, lymph node metastases, and the extent of resection between the two groups. The 5-year and 10-year survival rate for all patients was 69% and 52%, respectively. There was no statistically significant difference regarding overall survival and the rate of peritoneal recurrence between the HIPEC and non-HIPEC group.

> >> *Well-selected patients may benefit from an aggressive surgical approach. The role of intraperitoneal chemotherapy in addition to cytoreductive surgery is still unclear.*

Patients with low tumor burden, favorable tumor distribution, and the possibility of complete cytoreduction are the most eligible.

> >> *Peritoneal carcinomatosis of NET is nearly always associated with extensive multicentric disease (especially liver metastasis). Surgery should be performed in specialized centers for the treatment of peritoneal carcinomatosis and also liver metastases.*

The primary therapeutic purpose of peritonectomy consists in the therapy and/or prophylaxis of local complications. Specific symptoms in a functionally active NET do not constitute an indication for a cytoreductive operation. In any event, the hepatic metastasis in cases of carcinoid

Table 23.2 Scoring system of the European Society of Neuroendocrine Tumors (ENETS) for gastroenteropancreatic NET

	0 points	1 point	2 points	3 points
Lymph node metastases	Local	Regional	Distant	Extraabdominal
Liver metastases	None	One liver lobe <5 metastases	Both liver lobes 5–10 metastases	Both liver lobes >10 metastases
Peritoneal carcinomatosis	None	Gilly I–II resectable	Gilly III–IV resectable	Gilly I-IV nonresectable
GPS grade "A": 0–3 points, GPS grade "B": 4–6 points, GPS grade "C": 7–9 points				

syndrome is often so advanced that operative/ablative therapy is no longer viable.

The "abdominal gravity PC score" (GPS) may offer assistance in establishing the indication (Table 23.2) [19]. Patients with grade "A" GPS seem to be suitable for cytoreductive surgery. Grade "C" GPS is an exclusion criterion for an aggressive surgical procedure. A multidisciplinary tumor board should take "B" an individual decision.

23.4 Goblet Cell Carcinoids

The so-called goblet cell carcinoids represent a distinct entity; due to their pathological characteristics and tumor biology, they should be ranged between the well-differentiated neuroendocrine tumors and the appendix carcinomas. In advanced stages, the goblet cell carcinoids tend to spread peritoneal and metastasize to the ovaries. In almost all patients with distant metastases, there is also peritoneal carcinomatosis [21].

> *>> A 3-year survival rate of 63.4% can be achieved with CRS and HIPEC for patients with peritoneally metastasized goblet cell carcinoids [24].*

Survival rates for goblet cell carcinoids after CRS and HIPEC are better than for high-grade mucinous appendix tumors and appendix carcinomas (40.4% and 52.2%, respectively). The most important positive prognostic factors include the possibility of a complete cytoreduction and a peritoneal carcinosis index <20.

23.5 Conclusions

The results published for adenocarcinomas of the small intestine to date are promising and indicate a prognosis benefit for patients receiving multimodal therapy. Until specific selection criteria for small intestine carcinoma are established, the selection should be oriented toward the criteria of colorectal carcinomas. The role of an additional adjuvant chemotherapy has not been definitively clarified. A clear therapy recommendation for peritoneal metastasis of small bowel carcinomas cannot be made at this point due to the small number of cases and to the lack of prospective randomized trials.

Only very few publications deal with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for neuroendocrine tumors. In selected cases, the concept may be helpful for peritoneal metastasis, when a complete cytoreduction at low tumor burden can be achieved. The subgroup of patients with goblet cell carcinoid of the appendix seems to particularly benefit.

References

1. Agrawal S, McCarron EC, Gibbs JF, Nava HR, Wilding GE, Rajput A. Surgical management and outcome in primary adenocarcinoma of the small bowel. Ann Surg Oncol. 2007;14(8):2263–9.
2. Anderson LA, Tavilla A, Brenner H, Luttmann S, Navarro C, Gavin AT, et al. (2015) Survival for oesophageal, stomach and small intestine cancers in Europe 1999–2007: results from EUROCARE-5. Eur J Cancer, 51(15):2144–21457.

3. Bhosale P, Shah A, Wei W, Varadhachary G, Johnson V, Shah V, et al. Carcinoid tumours: predicting the location of the primary neoplasm based on the sites of metastases. Eur Radiol. 2013;23(2):400–7.
4. Bilimoria KY, Bentrem DJ, Wayne JD, Ko CY, Bennett CL, Talamonti MS. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009;249(1):63–71.
5. Bojesen RD, Andersson M, Riis LB, Nielsen OH, Jess T. Incidence of, phenotypes of and survival from small bowel cancer in Denmark, 1994–2010: a population-based study. J Gastroenterol. 2016;51(9):891–9.
6. Chua TC, Koh JL, Yan TD, Liauw W, Morris DL. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from small bowel adenocarcinoma. J Surg Oncol. 2009;100(2):139–43.
7. Dabaja BS, Suki D, Pro B, Bonnen M, Ajani J. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer. 2004;101(3):518–26.
8. de Mestier L, Lardiere-Deguelte S, Brixi H, O'Toole D, Ruszniewski P, Cadiot G, et al. Updating the surgical management of peritoneal carcinomatosis in patients with neuroendocrine tumors. Neuroendocrinology. 2015;101(2):105–11.
9. Ecker BL, McMillan MT, Datta J, Mamtani R, Giantonio BJ, Dempsey DT, et al. Efficacy of adjuvant chemotherapy for small bowel adenocarcinoma: a propensity score-matched analysis. Cancer. 2016;122(5):693–701.
10. Elias D, David A, Sourrouille I, Honore C, Goere D, Dumont F, et al. Neuroendocrine carcinomas: optimal surgery of peritoneal metastases (and associated intra-abdominal metastases). Surgery. 2014;155(1):5–12.
11. Elias D, Glehen O, Pocard M, Quenet F, Goere D, Arvieux C, et al. A comparative study of complete cytoreductive surgery plus intraperitoneal chemotherapy to treat peritoneal dissemination from colon, rectum, small bowel, and nonpseudomyxoma appendix. Ann Surg. 2010;251(5):896–901.
12. Elias D, Sideris L, Liberale G, Ducreux M, Malka D, Lasser P, et al. Surgical treatment of peritoneal carcinomatosis from well-differentiated digestive endocrine carcinomas. Surgery. 2005;137(4):411–6.
13. Fendrich V, Bartsch DK. Surgical treatment of gastrointestinal neuroendocrine tumors. Langenbeck's Arch Surg/Deutsche Gesellschaft fur Chirurgie. 2011;396(3):299–311.
14. Fishman PN, Pond GR, Moore MJ, Oza A, Burkes RL, Siu LL, et al. Natural history and chemotherapy effectiveness for advanced adenocarcinoma of the small bowel: a retrospective review of 113 cases. Am J Clin Oncol. 2006;29(3):225–31.
15. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg. 2010;199(6):797–803.
16. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121(4):589–97.
17. Howe JR, Karnell LH, Menck HR, Scott-Conner C. The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985–1995. Cancer. 1999;86(12):2693–706.
18. Jacks SP, Hundley JC, Shen P, Russell GB, Levine EA. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis from small bowel adenocarcinoma. J Surg Oncol. 2005;91(2):112–7. discussion 8–9
19. Kianmanesh R, Ruszniewski P, Rindi G, Kwekkeboom D, Pape UF, Kulke M, et al. ENETS consensus guidelines for the management of peritoneal carcinomatosis from neuroendocrine tumors. Neuroendocrinology. 2010;91(4):333–40.
20. Koo DH, Yun SC, Hong YS, Ryu MH, Lee JL, Chang HM, et al. Systemic chemotherapy for treatment of advanced small bowel adenocarcinoma with prognostic factor analysis: retrospective study. BMC Cancer. 2011;11:205.
21. Lamarca A, Nonaka D, Lopez Escola C, Hubner RA, O'Dwyer S, Chakrabarty B, et al. Appendiceal goblet cell carcinoids: management considerations from a reference peritoneal tumour service centre and ENETS centre of excellence. Neuroendocrinology. 2016;103(5):500–17.
22. Liu Y, Ishibashi H, Takeshita K, Mizumoto A, Hirano M, Sako S, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal dissemination from small bowel malignancy: results from a single specialized center. Ann Surg Oncol. 2016;23(5):1625–31.
23. Marchettini P, Sugarbaker PH. Mucinous adenocarcinoma of the small bowel with peritoneal seeding. Eur J Surg Oncol. 2002;28(1):19–23.
24. McConnell YJ, Mack LA, Gui X, Carr NJ, Sideris L, Temple WJ, et al. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: an emerging treatment option for advanced goblet cell tumors of the appendix. Ann Surg Oncol. 2014;21(6):1975–82.
25. Norlen O, Edfeldt K, Akerstrom G, Westin G, Hellman P, Bjorklund P, et al. (2014) Peritoneal carcinomatosis from small intestinal neuroendocrine tumors: clinical course and genetic profiling. Surgery, 156(6):1512–1521; discussion 21–2.
26. Rangiah DS, Cox M, Richardson M, Tompsett E, Crawford M. Small bowel tumours: a 10 year experience in four Sydney teaching hospitals. ANZ J Surg. 2004;74(9):788–92.
27. Scelo G, Boffetta P, Hemminki K, Pukkala E, Olsen JH, Andersen A, et al. Associations between small intestine cancer and other primary cancers: an international population-based study. Int J Cancer/Journal international du cancer. 2006;118(1):189–96.

28. Sun Y, Shen P, Stewart JH, Russell GB, Levine EA. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from small bowel adenocarcinoma. Am Surg. 2013;79(6):644–8.
29. van Oudheusden TR, Lemmens VE, Braam HJ, van Ramshorst B, Meijerink J, te Velde EA, et al. Peritoneal metastases from small bowel cancer: results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in The Netherlands. Surgery. 2015;157(6):1023–7.
30. Zouhairi ME, Venner A, Charabaty A, Pishvaian MJ. Small bowel adenocarcinoma. Curr Treat Options in Oncol. 2008;9(4–6):388–99.

24 Indication for CRS and HIPEC for Peritoneal Metastases of Pancreatic Cancer

Can Yurttas, Florian Struller, Philipp Horvath, Ingmar Königsrainer, Alfred Königsrainer, and Stefan Beckert

24.1 Epidemiology and Prognosis of Ductal Pancreatic Adenocarcinoma

In 2010 more than 16,000 people in Germany were diagnosed with pancreatic cancer. Nearly identical numbers of incidence and mortality indicate that almost all patients being diagnosed with pancreatic cancer die of their disease. Despite medical progress, age-adapted incidence and mortality have remained constant since the 1990s. Higher numbers of cases are expected additionally due to the aging of our society [19].

Radical surgical resection of the tumor with its adjacent lymph nodes still remains the only potential curative therapy.

According to the location of the tumor, either pancreaticoduodenectomy (Whipple procedure) including resection of the head of the pancreas, duodenum, and distal bile duct, with gallbladder and gastric antrum, or, if located in the tail of the pancreas, a so-called distal pancreas resection is required. Such extensive visceral resections are related to non-eligible morbidity and mortality. Constant improvement of surgical techniques, procedures in anesthesia, and postoperative intensive care have led to a reduction of mortality rate to less than 5% [1, 4, 11].

Unfortunately, long time survival even after complete tumor resection is uncommon.

C. Yurttas (✉) · P. Horvath
Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany
e-mail: can.yurttas@med.uni-tuebingen.de; philipp.horvath@med.uni-tuebingen.de

F. Struller
Department of General, Visceral and Transplant Surgery, University Hospital Erlangen, Erlangen, Germany
e-mail: florian.struller@uk-erlangen.de

I. Königsrainer
Department of General, Visceral and Thoracic Surgery, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
e-mail: ingmar.koenigsrainer@lkhf.at

A. Königsrainer
Department of General, Visceral and Transplant Surgery, University Hospital of Tübingen, Comprehensive Cancer Center, Tübingen, Germany

Department of Surgery, University of Tübingen, Tübingen, Germany
e-mail: alfred.koenigsrainer@med.uni-tuebingen.de

S. Beckert
Department of General and Visceral Surgery, Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Germany
e-mail: stefan.beckert@sbk-vs.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_24

Five-year survival rates of less than 20% and median survival rates of 17–28 months are reported in the literature [5, 17]. Even after curative (R0) resection, 50% of patients experience local recurrence, 40–60% peritoneal metastases, and 50–60% metastases to the liver [28]. In cases with simultaneous peritoneal metastases at the time of initial diagnosis, the possibility for long-term survival is dramatically low [16]. The exact mechanisms determining how frequent local recurrences and metastasis develop remain unclear. However, there is indication that tumor growth exceeds beyond anatomic borders at the time of diagnosis in 90% of all patients or that free tumor cells are detectable in the fluid of the peritoneal cavity [3, 13], although this has never been objectified during preoperative staging diagnostics. Owing to its close proximity to vital anatomic structures (e.g., the hepatic artery and portal vein), which makes wide safety margins for resections technically difficult, histopathological examination of resection margins may show infiltration of tumor, resulting in a so-called R1-resection. Another possible explanation for the frequent local recurrences and distant metastases might be tumor-cell spillage during the surgical resection of the primary tumor [24].

24.2 Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

In the 1980s, Professor Paul Sugarbaker popularized the technique of cytoreductive surgery with HIPEC for the therapy of peritoneal metastases originating from gastrointestinal malignancies. Following a complete macroscopic resection of all peritoneal metastases, HIPEC is used to eliminate potential free or minimal residual tumor cells within the peritoneal cavity [22, 23]. Using this method, patients suffering from peritoneal metastases of colorectal cancer had a better overall survival compared to patients receiving systemic therapy only [27]. The prognosis may be improved especially for those patients who have little intra-abdominal tumor burden or in which complete cytoreduction, meaning a removal of all macroscopic tumor tissue, is possible [6, 7]. This oncological benefit, however, may be accompanied by higher rates of morbidity and mortality. Dependent on the extent of surgery, the morbidity is reported to be 35% and the mortality up to 5% [10].

24.3 CRS and HIPEC for Peritoneal Metastases of Pancreatic Cancer

Both synchronous and metachronous metastases from pancreatic cancer reduce the probability of survival substantially [16].

> *According to the German S3 guidelines, surgery is not indicated in the metastasized state of pancreatic cancer as the potential oncological benefit does not justify the postoperative morbidity and mortality* [20].

In 2018, an approach to treat synchronous or metachronous peritoneal metastasis from pancreatic adenocarcinoma by pancreatic resection, cytoreductive surgery, and HIPEC was published. Six patients with pancreatic adenocarcinoma originating from the tail of the organ and with a PCI ranging from 3 to 25 were treated in eight cytoreductive operations. A CC0 status was achieved in five and CC1 status in two cases. One patient had palliative surgery only. Two patients died during their hospital stay. Four patients survived for more than 12 months with signs of recurrence. Five patients had recurrent disease, of which three had local recurrence and two distant metastases. [25].

24.4 Prophylactic HIPEC for Locally Advanced Pancreatic Cancer

The facts regarding the prognosis of pancreatic cancer may be summarized as follows:

The probability for long-term survival is low if there are any synchronous or metachronous distant or peritoneal metastases.

In up to 50% of cases, there is local recurrence following curative surgery because a radical

resection is not possible due to anatomical limitations and because there are often free abdominal tumor cells present already at the time of resection.

Taking these two facts together, it seems reasonable to investigate a simultaneous local intraoperative therapy that would be able to control both peritoneal metastases and local recurrence. Comparable approaches that could provide such local control over colorectal cancer (ProphyloCHIP, NCT01226394) or locally advanced gastric cancer (GASTRICHIP, NCT01882933) [9] using adjuvant HIPEC were tested in clinical phase III trials.

Paul Sugarbaker was able to show that intraperitoneal gemcitabine at 1000 mg/m^2 of body-surface area for 60 min creates a concentration-gradient from the peritoneal cavity to the blood of 210. This indicates that a high intraperitoneal concentration of gemcitabine may be established with low systemic concentrations at the same time, accounting for the lack of toxicity [24]. Gamblin et al. [8] also report about the good tolerance of postoperatively applied gemcitabine via abdominal port catheter system. Remarkably, concentration of gemcitabine decreased quickly within the peritoneal fluid, whereas the systemic concentration remained constantly low, suggesting almost complete uptake of gemcitabine by the peritoneal tissue. In Tübingen, Germany, we therefore initiated a phase I/II study to investigate the toxicity of HIPEC with gemcitabine at 1000 mg/m^2 of body surface area dissolved in a 1.5% dextrose-solution, which was administered at 42.0 °C in closed technique after macroscopic complete resection (R0 or R1) of histologically proven pancreatic cancer. HIPEC was performed according to the technique of H. G. Becker, using two inflow and three outflow catheters as well as polyurethane sponges to avoid suction of tissue [2]. The study has been completed and showed that the combination of pancreatic resection and HIPEC with gemcitabine is feasible and safe with acceptable morbidity and/or mortality (unpublished data).

Tentes and colleagues designed a comparable study treating 33 patients with resectable pancreatic cancer by complete surgical resection followed by 60 minutes of gemcitabine HIPEC. Within a postoperative observation period of 45 days, the mortality was 6.1% and the morbidity 24.2%. 18 patients received adjuvant systemic chemotherapy with gemcitabine. The median survival was 13 months, the 5-year overall survival 24% and the median disease-free survival 9 months. Those patients who received systemic chemotherapy showed a median survival of 25 months compared to 11 months median survival of patients with adjuvant gemcitabine treatment [26].

24.5 Approaches

In the recent literature there are reports about novel strategies to approach peritoneal metastasis of pancreatic cancer.

Noninvasive abdominal heating in combination with systemic chemotherapy is currently under investigation as an alternative to cytoreductive surgery with HIPEC in patients with peritoneal metastasis of pancreatic cancer [18]. Convincing data are however missing for this indication.

In a case report of three malignant intraductal papillary mucinous neoplasms (IPMN) with peritoneal dissemination cytoreductive surgery with HIPEC could improve survival outcomes to median 44.3 months. In selected cases this might therefore be a therapeutic approach for this entity [21].

PIPAC has been suggested for the treatment of peritoneal metastasis originating from pancreatic cancer. Early results indicate safety and feasibility with histological signs of tumor regression [12, 14, 15]. However evidence proving effectiveness in terms of oncological benefit is missing.

24.6 Conclusion

Currently, there is no indication for cytoreductive surgery with HIPEC for synchronous or metachronous peritoneal metastases of pancreatic cancer. However, the objective of recent clinical

studies is to find out whether their prophylactic HIPEC is of value to reduce the incidence of local recurrences and metachronous peritoneal metastases of pancreatic cancer.

References

1. Adam U, Makowiec F, Riediger H, Schareck WD, Benz S, Hopt UT. Risk factors for complications after pancreatic head resection. Am J Surg. 2004;187:201–8.
2. Becker HG, Gassmann B, Hoffmann C, Steurer W. Towards more efficacy in HIPEC—optimization of fluid mechanics. Eur J Cancer. 2011;1:47.
3. Beger HG, Rau B, Gansauge F, Leder G, Schwarz M, Poch B. Pancreatic cancer—low survival rates. Deutsches Arzteblatt international. 2008;105:255–62.
4. Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg. 2015;220:530–6.
5. Cleary SP, Gryfe R, Guindi M, Greig P, Smith L, Mackenzie R, Strasberg S, Hanna S, Taylor B, Langer B, Gallinger S. Prognostic factors in resected pancreatic adenocarcinoma: analysis of actual 5-year survivors. J Am Coll Surg. 2004;198:722–31.
6. da Silva RG, Sugarbaker PH. Analysis of prognostic factors in seventy patients having a complete cytoreduction plus perioperative intraperitoneal chemotherapy for carcinomatosis from colorectal cancer. J Am Coll Surg. 2006;203:878–86.
7. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dube P, Glehen O. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28:63–8.
8. Gamblin TC, Egorin MJ, Zuhowski EG, Lagattuta TF, Herscher LL, Russo A, Libutti SK, Alexander HR, Dedrick RL, Bartlett DL. Intraperitoneal gemcitabine pharmacokinetics: a pilot and pharmacokinetic study in patients with advanced adenocarcinoma of the pancreas. Cancer Chemother Pharmacol. 2008;62:647–53.
9. Glehen O, Passot G, Villeneuve L, Vaudoyer D, Bin-Dorel S, Boschetti G, Piaton E, Garofalo A. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. BMC Cancer. 2014;14:183.
10. Glockzin G, Ghali N, Lang SA, Schlitt HJ, Piso P. Results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal cancer. J Surg Oncol. 2009;100:306–10.
11. Gooiker GA, van Gijn W, Wouters MW, Post PN, van de Velde CJ, Tollenaar RA. Systematic review and metaanalysis of the volume-outcome relationship in pancreatic surgery. Br J Surg. 2011;98:485–94.
12. Graversen M, Detlefsen S, Bjerregaard JK, Pfeiffer P, Mortensen MB. Peritoneal metastasis from pancreatic cancer treated with pressurized intraperitoneal aerosol chemotherapy (PIPAC). Clin Exp Metastasis. 2017;34(5):309–14.
13. Heeckt P, Safi F, Binder T, Buchler M. Free intraperitoneal tumors cells in pancreatic cancer–significance for clinical course and therapy. Chirurg. 1992;63:563–7.
14. Horvath P, Beckert S, Struller F, Konigsrainer A, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases of pancreas and biliary tract cancer. Clin Exp Metastas. 2018;35(7):635–40.
15. Khosrawipour T, Khosrawipour V, Giger-Pabst U. Pressurized Intra Peritoneal Aerosol Chemotherapy in patients suffering from peritoneal carcinomatosis of pancreatic adenocarcinoma. PLoS One. 2017;12(10):e0186709.
16. Kim HW, Lee JC, Paik KH, Lee YS, Hwang JH, Kim J. Initial metastatic site as a prognostic factor in patients with stage IV pancreatic ductal adenocarcinoma. Medicine (Baltimore). 2015;94:e1012.
17. Klempnauer J, Ridder GJ, Bektas H, Pichlmayr R. Surgery for exocrine pancreatic cancer–who are the 5- and 10-year survivors? Oncology. 1995;52:353–9.
18. Kok HP, Beck M, Loke DR, Helderman RFCPA, van Tienhoven G, Ghadjar P, Wust P, Crezee H. Locoregional peritoneal hyperthermia to enhance the effectiveness of chemotherapy in patients with peritoneal carcinomatosis: a simulation study comparing different locoregional heating systems. Int J Hyperther. 2020;37(1):76–88.
19. RKI, editor. Krebsregisterdaten. Pankreaskarzinom. Berlin: Robert Koch Institut; 2014.
20. Seufferlein T, Porzner M, Becker T, Budach V, Ceyhan G, Esposito I, Fietkau R, Follmann M, Friess H, Galle P, Geissler M, Glanemann M, Gress T, Heinemann V, Hohenberger W, Hopt U, Izbicki J, Klar E, Kleeff J, Kopp I, Kullmann F, Langer T, Langrehr J, Lerch M, Lohr M, Luttges J, Lutz M, Mayerle J, Michl P, Moller P, Molls M, Munter M, Nothacker M, Oettle H, Post S, Reinacher-Schick A, Rocken C, Roeb E, Saeger H, Schmid R, Schmiegel W, Schoenberg M, Siveke J, Stuschke M, Tannapfel A, Uhl W, Unverzagt S, van Oorschot B, Vashist Y, Werner J, Yekebas E. S3-guideline exocrine pancreatic cancer. Z Gastroenterol. 2013;51:1395–440.
21. Sirisai C, Yonemura Y, Ishibashi H, Wakama S, Mizumoto A. Hyperthermic intraperitoneal chemotherapy in management of malignant intraductal papillary mucinous neoplasm with peritoneal dissemination: case report. Int J Surg Case Rep. 2019;63(2210–2612 (Print)):85–8.
22. Sugarbaker PH. Peritonectomy procedures. Ann Surg. 1995;221:29–42.

23. Sugarbaker PH. Parietal peritonectomy. Ann Surg Oncol. 2012;19:1250.
24. Sugarbaker PH, Stuart OA, Bijelic L. Intraperitoneal gemcitabine chemotherapy treatment for patients with resected pancreatic cancer: rationale and report of early data. Int J Surg Oncol. 2011;2011:161862.
25. Tentes AA, Pallas N, Karamveri C, Kyziridis D, Hristakis C. Cytoreduction and HIPEC for peritoneal carcinomatosis of pancreatic cancer. J BUON. 2018;23:482–7.
26. Tentes AA, Stamou K, Pallas N, Karamveri C, Kyziridis D, Hristakis C. The effect of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) as an adjuvant in patients with resectable pancreatic cancer. Int J Hyperth. 2016;32:895–9.
27. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737–43.
28. Warshaw AL, Fernandez-del Castillo C. Pancreatic carcinoma. N Engl J Med. 1992;326:455–65.

25 Indications of CRS and HIPEC in Incidentally Detected Peritoneal Carcinomatosis

Stefan Benz and Pankaj Kumar Garg

25.1 Introduction

Peritoneal carcinomatosis (PC) that occurs as a metastasis of a colorectal carcinoma significantly worsens the prognosis. However, this can be significantly improved by cytoreductive surgery (CRS) and hyperthermic intraoperative chemoperfusion (HIPEC) [14]. This applies particularly to the early stage of peritoneal carcinosis (peritoneal carcinomatosis index <6), in which a 5-year survival of between 40% and 50% can be achieved and a curative therapeutic approach is possible [6]. However, CRS with HIPEC is a very complex procedure and is only available at comparatively few centers. In contrast, colorectal cancer is currently operated on in almost every hospital with basic visceral surgery. In addition, limited peritoneal cancer often escapes routine preoperative diagnosis. This raises the question of the optimal procedure if peritoneal carcinomatosis is found as a surprise during the planned resection of a primary tumor.

25.2 Incidence of Peritoneal Carcinomatosis

According to a French population-based study [12], peritoneal carcinomatosis is present in colorectal cancer at the time of initial diagnosis in approximately 7% of cases (synchronous peritoneal carcinosis). A somewhat lower incidence of simultaneous PC was reported in a population-based survey by Lemmens et al. [10].

> *>> The risk is highest in tumors of the right colon and appendix and drops as the site changes over the left colon to the rectum.*

Women are affected more often than men. Histologically, mucinous differentiation is a significant risk factor for the development of peritoneal carcinomatosis. Another risk factor is diagnosis after obstruction or perforation (Quere et al. 2015). In the course of the disease, the incidence of peritoneal carcinomatosis rises to 30–40% (metachronous peritoneal carcinomatosis).

25.3 Prognostic Factors for CRS and HIPEC

The best prognosis after CRS and HIPEC for peritoneal carcinomatosis of colorectal cancer origin is found in patients with a peritoneal cancer index (PCI) of <6. This has been shown

S. Benz (✉)
Klinik für Allgemein- VIszeral- und Kinderchirurgie, Boeblingen, Germany

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_25

in all the studies with long-term results. However, the extent of peritoneal carcinomatosis also plays a significant role in perioperative morbidity [3].

>> *Even in patients with a high probability of having good prognosis following HIPEC, one will find intraoperative surprises.*

It is therefore of particular importance that those patients with limited disease preoperatively as identified on preoperative imaging are treated with a standard algorithm of CRS with HIPEC.

25.4 Avoiding Surprises

The S3 guidelines on colorectal carcinoma provide a rather limited preoperative diagnosis for colon carcinoma. Accordingly, distant metastases are clarified by means of sonography and a chest X-ray examination. In addition, many clinics routinely perform a contrast-enhanced computer tomography of the abdomen. This improves the diagnostic accuracy with regard to the detection of liver metastases. Moreover, the primary tumor can usually be localized and a T4 situation recognized or at least suspected. Furthermore, the surgeon can adjust to anatomical variants in the mesenteric root, for example, for the complete mesocolic excision (CME).

>> *CT is of great importance in the detection of peritoneal carcinomatosis [5], in patients with colorectal cancer.*

In early stage disease, there are usually tiny peritoneal deposits around the tumor, in the mesentery, in the subphrenic area, or in the omentum. These tiny peritoneal deposits are usually missed on CT examination as maximum attention is diverted to assess the extent of the primary tumor or to diagnose liver metastasis.

One must look for these tiny peritoneal deposits diligently in the presence of risk factors like large tumors on the right side or mucinous differentiation. A targeted sonography may also be helpful at times to diagnose limited peritoneal carcinomatosis. However, despite diligent preoperative assessment, peritoneal carcinomatosis is not diagnosed accurately in more than half of the patients [7].

>> *If there is clear preoperative evidence of peritoneal disease in a patient with colorectal cancer, one should not only concentrate on excision of the primary tumor.*

If there is suspicion of peritoneal carcinomatosis and there are no clear contraindications (age, comorbidity, diffuse metastasis) for CRS with HIPEC, the next step should be a diagnostic laparoscopy [9]. The extent of the peritoneal carcinomatosis should be assessed and duly recorded. It is important to pay attention to any suspicious changes in the ovaries. Assessment of the extent of peritoneal carcinomatosis is critical in determining the effectiveness of CRS and HIPEC, if it is available locally, or in discussing with the patient a possible transfer to an expert center and in planning the availability of resources.

25.5 Intraoperative Diagnosis of Peritoneal Carcinomatosis of Colorectal Cancer

There is a good evidence to suggest that complete cytoreduction must be performed in patients with colorectal cancer and limited peritoneal disease. However, this is a complex decision in view of the significant postoperative morbidity and mortality associated with cytoreduction. A number of factors must be taken into account when opting for cytoreduction: the age of the patient, the presence of comorbidities, the symptoms of the primary tumor, the resectability of the primary tumor, and the extent of peritoneal disease.

There is potential risk of tumor cells seeding the retroperitoneal and subperitoneal spaces following peritonectomy. However, its real impact on future local or regional recurrences is currently not well defined.

>> *In a potentially curative condition of colorectal cancer with limited peritoneal disease, it is advisable to perform single-stage complete cytoreductive surgery with HIPEC to improve survival.*

Sugarbaker and Glehen recently proposed an algorithm that reflects the current status of cytoreductive surgery in patients with colorectal cancer and limited peritoneal carcinomatosis (PCI <20) [13]. They have presented a good algorithm to follow in challenging clinical situations.

25.5.1 Scenario 1: Peritoneal Carcinomatosis with Asymptomatic Primary Tumor

This is a potentially curative situation.

> >> *Surgery should be aborted after thorough exploration and histological confirmation of the disease.*

A diligent exploration should be undertaken to determine an accurate peritoneal carcinomatosis index. The paracolic gutters, the omentum, the entire small bowel along with its mesentery, the subdiaphragmatic surfaces, and the falciform ligament should be thoroughly inspected for tiny peritoneal deposits. Attempts should be made to avoid dissecting the peritoneum. A thorough examination of the pelvis with special emphasis on the ovaries in females must be performed. Irrespective of the whether the exploration is through an open approach or laparoscopic, the assessment should be complete.

After a thorough assessment, definite surgery should be aborted, and patients should be subjected to a "short course" of systemic chemotherapy (e.g., FOLFOX). Further addition of bevacizumab may be advantageous [4]. The case should be discussed in a multidisciplinary tumor board after three to four cycles of chemotherapy for a possible cytoreductive surgery and HIPEC in good responders. CRS and HIPEC should be carried out approximately 12 weeks after the primary intervention.

The role of second-look surgery to detect peritoneal carcinomatosis in patients with normal imaging but at high risk of peritoneal carcinomatosis was first elucidated in 2008 by Elias [7].

The authors reported that performing second-look surgery at 1 year in selected patients at high risk of developing PC allowed the early detection and treatment of PC in 55% of cases. With this procedure, 10 of the 16 patients were free of recurrence after a median follow-up period of 27 months. Three of them had isolated organ metastases or a relapse of peritoneal carcinomatosis. These results were confirmed in a follow-up publication in 2011 with 25 patients with minimal PC [8]. From these results it can be concluded that good long-term results can be achieved if HIPEC is integrated into the therapy regime for limited peritoneal carcinomatosis. On the other hand, it must also be pointed out that even with minimal peritoneal carcinomatosis, complete resection, and adjuvant chemotherapy, recurrence occurs in more than 50% within 1 year. In addition, 5 of the 10 patients with a relapse of peritoneal carcinomatosis after CRS and HIPEC were relapse-free in the further course. It can therefore be assumed that even more favorable results could have been achieved with CRS and HIPEC as a primary procedure, which also corresponds to the observation in a case series of Sugarbaker [11].

> >> *Termination of the exploration followed by systemic chemotherapy and CRS/HIPEC is a better approach in a patient with asymptomatic primary tumor and limited peritoneal metastasis compared to upfront surgery and systemic chemotherapy followed by second-look surgery.*

If, however, resection of the primary tumor has already been performed, a second-look operation with HIPEC should be carried out if possible—after interim systemic chemotherapy—even if there is no clinical evidence of progression of peritoneal carcinomatosis.

25.5.2 Scenario 2: Symptomatic Resectable Primary Tumor (Bleeding, Obstruction)

Here, intervention needs to be done in view of the symptomatic primary tumor. The tumor must be resected. The peritoneal covering should not be opened much, and minimum planes should be opened in order to remove only the primary with

a peripheral arcade—safe R0 resection. No radical surgery should be attempted [13].

Whether, in order to achieve intestinal continuity, a stoma needs to be fashioned depends upon the general condition of the patient and local factors. However, it should be kept in mind that an anastomotic leak can make subsequent CRS with HIPEC almost impossible. CRS and HIPEC must be considered after a few cycles of systemic chemotherapy. In the case of a previously performed limited resection, a complete mesocolic excision must be performed as a part of CRS.

25.5.3 Scenario 3: Symptomatic Irresectable Primary Tumor

In this situation, a diverting stoma needs to be fashioned in order to control symptoms. Accordingly, a bypass method can also be used where possible. However, a bypass should only be carried out under otherwise optimal conditions, since, as already mentioned, if an anastomotic leak occurs, it is very likely that the patient will not be eligible for any definitive surgery later. This also creates new peritoneal scars, which in turn have a predilection for peritoneal tumor deposits. Thereafter, neoadjuvant chemotherapy is initiated, which should continue until the maximum response is attained. If the response is sufficient, the primary tumor can be resected with CRS and HIPEC [13]. In this scenario, there are usually large tumors in the right upper abdomen or at the pelvic inlet, in which the questionable resectability in preoperative diagnostics has usually already been noticed preoperatively. In this scenario, the intraoperative diagnosis of the extent of peritoneal carcinomatosis is critical in deciding the future course of surgical management.

>> In cases with an initially unresectable primary tumor, the patient may not be immediately considered for CRS and HIPEC. However, it is critical to assess the patient diligently and plan the future course of surgical management if the patient responds well to systemic chemotherapy.

For the first time, Sugarbaker formulated a comprehensible algorithm for the management of the unexpected intraoperative diagnosis of peritoneal carcinomatosis in a patient with colorectal carcinoma [13].

It must be emphasized that this is based on comprehensible assumptions, but, of course, it is not completely evidence-based. Moreover, certain issues that are of immense importance while considering CRS and HIPEC are not explicitly mentioned. This is particularly true for assessing the extent of peritoneal carcinomatosis (peritoneal carcinomatosis index, PCI) for a possible complete cytoreduction. In the majority of cases, the patient is initially operated on in a hospital where a CRS program is not fully adopted; thereafter, it becomes difficult for the next surgeon who is planning CRS later to understand the PCI. Here, it is essential that she talks to the first surgeon and asks for the most exact description possible. In addition to PCI, it is also critical to take into account other patient-related factors such as age, presence of comorbidity, etc. There is definitely a higher risk for postoperative complications in a patient of the same age and comorbidities if he presents in scenario 3 compared to when he is in scenario 1.

One scenario that is not explicitly included in the aforementioned algorithm is the finding of isolated ovarian metastases from a colorectal cancer without macroscopic PC. This situation is associated with a very high incidence of subsequent peritoneal metastasis and overall poor prognosis.

>> Pathophysiologically, ovarian metastases also represent peritoneal carcinomatosis because the malignant cells reach the ovaries via ascites.

Accordingly, isolated ovarian metastases are also an indication for HIPEC [14]. The problem with this situation is that it becomes difficult to differentiate, on a frozen-section examination, whether the ovarian mass is a primary ovarian neoplasm or a metastasis from colorectal cancer. This means that the operation cannot be terminated without resection of the primary tumor, as suggested in scenario 1. Therefore, the primary

tumor should first be resected, and then, as described above, a second-look operation should be carried out after few cycles of systemic chemotherapy [7, 8].

In the case of carcinoma of the appendix, the surgical procedure depends upon the histology. Therefore, the primary intervention after adequate exploration and histology acquisition should be stopped if possible. Appendicular carcinomas which have intestinal differentiation can be treated with the already discussed algorithm [2]. However, systemic chemotherapy is almost ineffective in mucinous histology [1]. The indication for CRS with HIPEC depends on the histological subtype and the extent. This issue is dealt with elsewhere in this book.

Another scenario is intraoperative diagnosis of unsuspected peritoneal disease in a patient with colorectal cancer who is being operated on at a center with expertise in CRS and HIPEC. The situation is still not very rosy, since the patient might have not given consent for CRS and HIPEC; there may also be logistical issues in performing HIPEC immediately. In scenario 1, however, one can certainly discuss whether the intervention will be carried out in the following days without neoadjuvant chemotherapy. Resection during the primary operation and performing HIPEC in the second procedure appears to be unjustified and unfavorable. The argument presented above that the peritoneum should not be opened without the immediately following HIPEC [13] suggests surgery should be terminated after the exploration in this situation and the CRS with HIPEC should be carried out together as the second procedure.

25.6 Unexpected Peritoneal Malignancies of Non-colorectal Origin

Unexpected peritoneal carcinomatosis of non-colorectal origin may be encountered during surgery as an incidental finding in following two scenarios.

In a rare scenario, peritoneal carcinomatosis can be incidentally diagnosed when laparoscopy or laparotomy is performed for an absolutely different clinical condition (e.g., laparoscopic hernia repair). In this case, histological confirmation should be carried out, and an exact diagnosis should be made. This not only includes assessment of the extent of peritoneal carcinomatosis but also inspection of the possible primary tumor locations (ovary, appendix, stomach, and colon). The procedure—either laparoscopy or laparotomy—should only be continued if a life-threatening condition is being dealt with; otherwise, it should be terminated. Further management depends upon the histology and the primary tumor site. Early pseudomyxoma peritonei deserves mention here—there may be only a few milliliters of slimy liquid which should be preserved. It is particularly important not to overlook this finding as the prognosis is very good. In the second scenario, the symptoms of peritoneal carcinomatosis, usually intestinal obstruction, lead to laparotomy. Apart from colorectal tumors, common primary tumors in peritoneal carcinomatosis are previously undiagnosed tumors in the stomach, pancreas, or ovary. In this situation, the cause of the symptoms should first be remedied followed by histological confirmation and assessment for the primary tumor. Radical tumor resections in the presence of intestinal obstruction are not justified in the absence of histopathological diagnosis.

25.7 Conclusion

Cytoreductive surgery with HIPEC has the potential to achieve a rather good prognosis in some malignancies with peritoneal carcinomatosis. If peritoneal carcinomatosis is detected unexpectedly during surgery, the surgical procedure should be terminated in an asymptomatic colorectal cancer as soon as histopathological confirmation and a thorough assessment of the extent of peritoneal involvement have been completed. A limited R0 resection or the creation of a diversion stoma should be done in a patient with a symptomatic primary tumor. The case should be discussed at a multidisciplinary meeting with the involvement of a center of excellence for

peritoneal malignancies in order to determine the potential indication for CRS and HIPEC after neoadjuvant chemotherapy.

References

1. Asare EA, Compton CC, Hanna NN, Kosinski LA, Washington MK, Kakar S, Weiser MR, Overman MJ. The impact of stage, grade, and mucinous histology on the efficacy of systemic chemotherapy in adenocarcinomas of the appendix: analysis of the National Cancer Data Base. Cancer. 2016;122:213–21.
2. Barrios P, Losa F, Gonzalez-Moreno S, Rojo A, Gomez-Portilla A, Bretcha-Boix P, Ramos I, Torres-Melero J, Salazar R, Benavides M, Massuti T, Aranda E. Recommendations in the management of epithelial appendiceal neoplasms and peritoneal dissemination from mucinous Tumors (pseudomyxoma the peritoneum). Clin Transl Oncol. 2016;18:437–48.
3. Cascales-Campos PA, Lopez-Lopez V, Munoz-Casares FC, Feliciangeli E, Torres Melero J, Barrios P, Morales R, Ramos I, Ortega G, Camps B, Gonzalez-Bayon L, Bretcha-Boix P, Farre-Alegre J, Gonzalez-Moreno S, Gil J. Morbidity and mortality outcomes after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients aged 75 years and over: Spanish group of peritoneal cancer surgery (GECOP) multicenter study. Surg Oncol. 2016;25:111–6.
4. Ceelen W, Van Nieuwenhove Y, Putte DV, Pattyn P. Neoadjuvant chemotherapy with bevacizumab may improve outcome after cytoreduction and intraperitoneal Hyperthermic chemoperfusion (HIPEC) for colorectal carcinomatosis. Ann Surg Oncol. 2014;21:3023–8.
5. Duhr CD, Kenn W, Kickuth R, Kerscher AG, Germer CT, Hahn D, Pelz JO. Optimizing of preoperative computed tomography for diagnosis in patients with peritoneal carcinomatosis. World J Surg Oncol. 2011;9:171.
6. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, Lorimier G, Dube P, Glehen O. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28:63–8.
7. Elias D, Goere D, Di Pietrantonio D, Boige V, Malka D, Kohneh-Shahri N, Dromain C, Ducreux M. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2008;247:445–50.
8. Elias D, Honore C, Dumont F, Ducreux M, Boige V, Malka D, Burtin P, Dromain C, Goere D. Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2011;254:289–93.
9. Jayakrishnan TT, Zacharias AJ, Sharma A, Pappas SG, Gamblin TC, Turaga KK. Role of laparoscopy in patients with peritoneal metastases considered for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). World J Surg Oncol. 2014;12:270.
10. Lemmens VE, Klaver YL, Verwaal VJ, Rutten HJ, Coebergh JW, de Hingh IH. Predictors and survival of synchronous peritoneal carcinomatosis of colorectal origin: a population-based study. Int J Cancer. 2011;128:2717–25.
11. Pestieau SR, Sugarbaker PH. Treatment of primary colon cancer with peritoneal carcinomatosis: comparison of concomitant vs. delayed management. Color Dis. 2000;43:1341–6; discussion 1347–1348.
12. Quere P, Facy O, Manfredi S, Jooste V, Faivre J, Lepage CAM. Bouvier epidemiology, management, and survival of peritoneal carcinomatosis from colorectal cancer: a population-based study. Dis Colon Rectum. 2015;58(8):743–52. https://doi.org/10.1097/DCR.0000000000000412.
13. Sugarbaker P, Glehen O. Management of unexpected peritoneal metastases with primary colorectal cancer using second-look surgery with HIPEC. Cancer Surg. 2016;1:1–5.
14. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol. 2008;15:2426–32.

Part VII

Palliative Treatment Attempt of Advanced Peritoneal Metastasis

26 Importance of Systemic Chemotherapy in Advanced Peritoneal Metastasis

Thomas Golombek, Andreas Brandl, and Florian Lordick

26.1 Introduction

▶ The occurrence of peritoneal metastasis (PM) of solid tumors represents an interdisciplinary challenge and often requires individually adapted concepts in therapy.

A secondary tumor spread in the peritoneum *per continuitatem* occurs especially in gynecological and gastrointestinal cancers. This event is usually associated with a profound worsening of the prognosis and—with a few exceptions—the loss of curative treatment options. The median overall survival of these patients treated with purely supportive therapy lies between 3 (gastric cancer) and 6 (colorectal cancer) months (see, for example, [38]).

The peritoneal involvement can unfortunately lead to severe abdominal pain, pronounced weight loss, and serious complications such as mechanical ileus, pre- and postrenal kidney failure due to low fluid intake as well as encirclement of ureters, and ascites, which leads to a progressive impairment of quality of life. In several studies, malignant ascites repeatedly proved to be an unfavorable prognostic factor for overall survival (median overall survival [mOS] in gastrointestinal tumors approx. 3 months) [5].

Regarding the feasibility of systemic therapies, these complications often pose a challenge or even sometimes prohibit a potentially effective drug treatment.

26.2 Selection of Systemic Therapy

▶ In general, systemic chemotherapy is effective in the treatment of peritoneal metastasis.

The response rate of systemic chemotherapy in patients with PM seems to be reduced in comparison to the treatment of hepatic metastasis [16]. One explanation, among other theories, is the reduced blood vessel supply of the peritoneum and accordingly of the PM. In general, preclinical data underline the importance of angioneogenesis in tumor growth and dissemination (e.g., [30]).

▶ A specific therapeutic regimen that is tailored to "peritoneal metastasis" does not exist.

T. Golombek (✉) · F. Lordick
University Cancer Center Leipzig (UCCL), University Hospital Leipzig, Leipzig, Germany
e-mail: thomas.golombek@medizin.uni-leipzig.de; florian.lordick@medizin.uni-leipzig.de

A. Brandl
Digestive Unit, Champalimaud Foundation, Lisbon, Portugal
e-mail: andreas.brandl@fundacaochampalimaud.pt

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_26

Indication for systemic chemotherapy as an important component of a multimodal oncological concept depends on primary tumor, the extent of peritoneal manifestation and the option for a cytoreductive procedure, as well as the performance status and comorbid conditions of the patient. In general, the importance of systemic chemotherapy increases as the extent of PM rises, or with the occurrence of extraperitoneal metastases, when loco-regional concepts (Sect. 26.6) become less important. In the following paragraphs, the current systemic therapeutic regimens in patients with peritoneal metastases from gastrointestinal tract will be illustrated and discussed. According to its clinical relevance, this chapter focuses on gastric, pancreatic, and colorectal cancer. Of note, drug approval status and availability of drugs differ among healthcare systems. The organ chapters therefore are generally adjusted to the current European Society for Medical Oncology (ESMO) guidelines (reference: https://www.esmo.org/guidelines, accessed 3 August 2020).

26.3 Gastric Cancer

The rate of gastric cancer compared to all malignant disease is about 5% in Western industrialized regions like Central Europe. There is an evident shift in epidemiology with an increasing incidence of proximal gastric cancer and adenocarcinomas of the gastroesophageal junction, while the total number of new cases with gastric cancer is constantly declining. Patients with adenocarcinomas of the gastroesophageal junction in stage IV are treated similar to gastric cancer. The presence of synchronous peritoneal metastasis is high, with an incidence of approximately 30% [35].

In cases where a patient is not suitable for a clinical trial for the purpose of a curative-intended multimodal therapy (e.g., cytoreductive surgery in combination with intraperitoneal chemotherapy), palliative chemotherapy allows for an extension of overall survival and improvement of quality of life through symptom control [24]. Nevertheless, patients diagnosed with a UICC stage IV gastric cancer still have a very poor prognosis (3-year survival <5%).

26.3.1 First-Line Therapy

The only established molecular parameter for treatment selection in patients with metastatic gastric cancer is the HER2 expression and/or amplification status. The first-line therapy should be chosen accordingly (Fig. 26.1). Approximately 16% of all patients present with an overexpression of human epidermal growth factor receptor (HER2) and benefit from the addition of trastuzumab to chemotherapy including 5-fluorouracil (5-FU) or the oral 5-FU derivate capecitabine and a platinum compound, classically cisplatin (mOS 13.8 vs. 11.1 months, hazard ratio [HR] 0.74; [6]). Efforts to introduce further HER2-targeted therapies (lapatinib, T-DM-1) in the treatment of metastatic, HER2-positive gastric cancer have unfortunately failed so far. The effectiveness of the HER2-directed antibody pertuzumab in the treatment of HER2-overexpressing gastric cancer was also lower than expected. The randomized JACOB trial did not reach the expected risk reduction of the primary endpoint death (HR 0.84, 95% confidence interval [CI] 0.71–1.00; $p = 0.0565$; [43]). Therefore, pertuzumab is not available for the treatment of HER2-positive gastric cancer.

In patients without HER2 overexpression, a combination of a fluoropyrimidine and a platinum derivate is recommended. In many regions, FOLFOX-like regimens are commonly used (Table 26.1) (mOS 10.7 months, median progression-free survival [mPFS] 5.8 months; [1]). The use of triplet regimens in stage IV gastric cancer is currently not recommended but can be considered in selected individual cases.

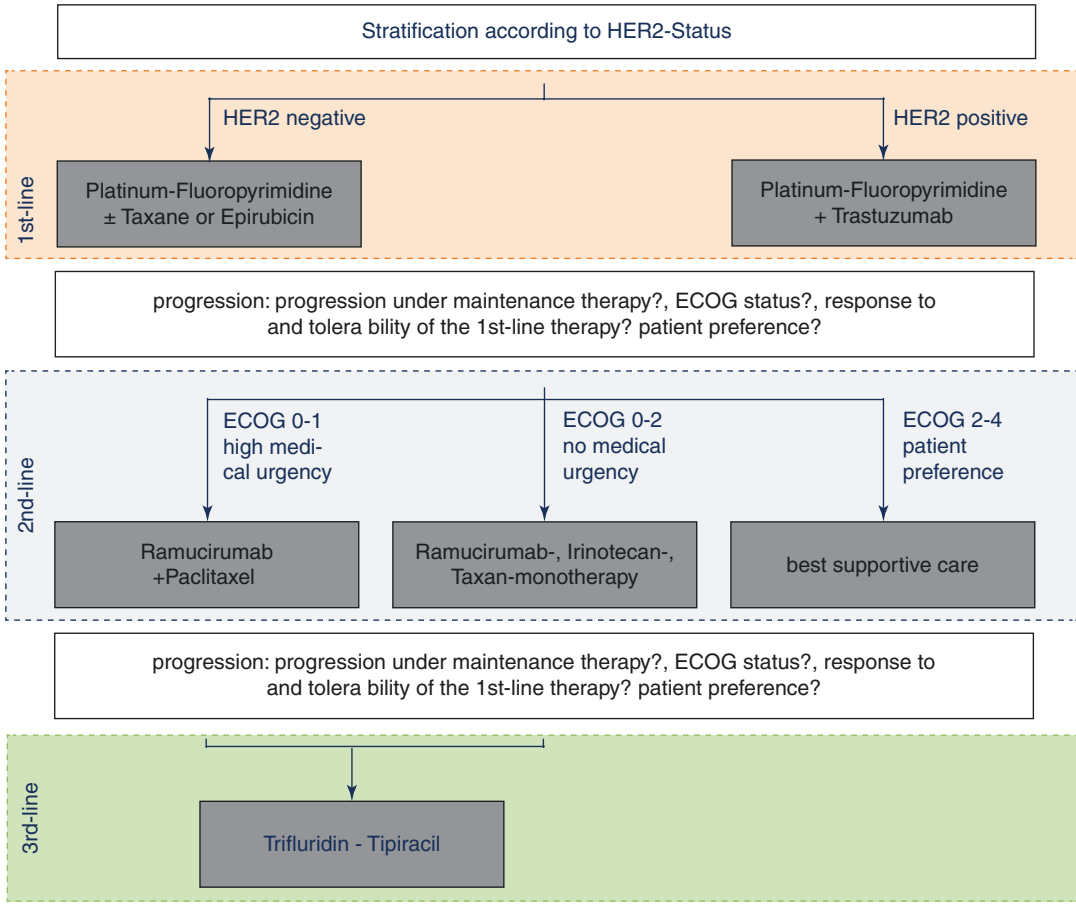


Fig. 26.1 First- and second-line therapy algorithm for stage IV stomach tumors and adenocarcinomas of the gastroesophageal junction. HER2-positivity is defined as an immunohistochemistry (IHC) score of 3 or an IHC score of 2 in combination with a positive in situ hybridization (ISH). Please note that outside of Europe immunotherapy may be approved in the second and/or third line of therapy

▶ The additional side effects of docetaxel, such as neuropathy, taste and skin disorders, nail changes, and fatigue have to be critically counterbalanced with the potential benefit for these patients.

The use of anthracyclines has declined in recent years. In addition to the higher toxicity rate, several studies did not demonstrate a benefit in patients treated with anthracyclines (e.g., [53]).

26.3.2 Second-Line Therapy

Since 2014, the combination of paclitaxel and ramucirumab has been approved as a second-line therapy (mOS 9.6 vs. 7.4 months [vs. paclitaxel mono]; HR 0.807; [52]).

The use of the antiangiogenic, monoclonal antibody ramucirumab was associated with mostly manageable toxicity (especially neutropenia, leukopenia, hypertension, and fatigue).

Table 26.1 Chemotherapeutic regimens for stage IV gastric and gastroesophageal junction tumors

Day	Drug	Dose	Application
XP + trastuzumab			
1	*Herceptin*	8 mg/kg bodyweight i. v.	i. v. in 250 ml NaCl 0.9% (30 min)
	Cisplatin	80 mg/m^2	i. v. in 500 ml NaCl 0.9% (60 min)
1–14	*Capecitabine*	2 × 1000 mg/m^2	p. o., 30 min after meals
Repetition day 22, Herceptin from 2nd cycle with 6 mg/kg i. v.			
FLO			
1	*Oxaliplatin*	85 mg/m^2	i. v. in 250 ml G5% (2 h)
	Folinic acid	200 mg/m^2	i. v. in 250 ml G5% (2 h)
	5-Fluorouracil	2600 mg/m^2	i. v. in 250 ml G5% (24 h)
Repetition day 15			
FLOT			
1	*Docetaxel*	50 mg/m^2	i. v. in 250 ml G5% (60 min)
	FLO (↑)		
Repetition day 15			
Ramucirumab (+paclitaxel)			
1, 15	*Ramucirumab*	8 mg/kg bodyweight	i. v. in 250 ml NaCl 0.9% (60 min)
1, 8, 15	*Paclitaxel*	80 mg/m^2	i. v. in 250 ml NaCl 0.9% (60 min)
Repetition day 29			
Irinotecan monotherapy			
1	*Irinotecan*	150 mg/m^2	i. v in 250 ml NaCl 0.9% (60 min)
Repetition day 15			
1	*Irinotecan*	250 mg/m^2	i.v in 250 ml 0 NaCl 0.9% (60 min)
Repetition day 22			
Docetaxel monotherapy			
1	*Docetaxel*	60 mg/m^2	i. v. in 250 ml NaCl 0.9% (60 min)
Repetition day 22			
Trifluridine/tipiracil			
1–5 8–12	*Trifluridine/tipiracil*	35 mg/m^2 (max. 80 mg abs.)	Twice daily per os
Repetition day 29			

▶ As the combination of ramucirumab and paclitaxel is currently the most effective scheme for second-line therapy, it should be used in patients with good general condition and high remission pressure.

Alternatively, monotherapies such as ramucirumab (mOS 5.2 vs. 3.8 months [best supportive care, BSC], HR 0.776, improved quality of life [QoL]; [18]), irinotecan (mOS 4.0 vs. 2.4 months [vs. BSC], HR 0.48, improvement of tumor-associated symptoms 50% vs. 7%; [45]), or docetaxel (mOS 5.2 vs. 3.6 months [vs. BSC], $p = 0.001$, improved symptom control; [15]) may be considered.

However, the efficacy of currently recommended therapies is still unsatisfactory [2], and the majority of patients who receive second-line treatment fail to achieve a response [8]. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) can be a treatment option for these patients after more than one line or even in addition to palliative intravenous chemotherapy in case of a disease limited to the peritoneum [42].

26.3.3 Third-Line Therapy

In case of treatment failure after at least two lines of systemic therapy, trifluridine/tipiracil is an orally available option with the potential to prolong survival in this heavily pretreated population (median overall survival 5.7 months (95% CI 4.8–6.2) vs. 3.6 months (95% CI 3.1–4.1; hazard ratio 0.69 [95% CI 0.56–0.85]; one-sided

p = 0.00029, two-sided p = 0.00058)) [40]. Immunotherapy with PD-1 checkpoint inhibitors is approved in some countries, but not yet in EU countries.

26.4 Pancreatic Cancer

Despite the fact that early detection of precancerous lesions (mucinous-cystic neoplasm, intraductal papillary mucinous neoplasm, pancreatic intraepithelial neoplasia) has progressed significantly in recent years, approximately 80% of patients are diagnosed in an incurable stage, such as locally advanced and inoperable or metastasized stage [23, 27]. In total, 5–10% of all patients are diagnosed with synchronous peritoneal metastasis [35]. For these patients a secondary resection after induction chemotherapy can only be considered in highly selected cases after complete histological response diagnosed via laparoscopy. At the moment, there is limited evidence for a tailored approach of systemic chemotherapy.

Nevertheless, new treatment options for advanced pancreatic cancer patients (median overall survival in metastatic stage 5–8 months) have been developed in recent years (Fig. 26.2).

The median age of onset is about 69 (men) or 76 (women) years. Therefore, the evaluation of the performance status as well as relevant comorbidities is of importance before choosing the therapeutic regimen. Particularly, liver function must be critically examined if irinotecan or taxanes can be part of the selected combination.

26.4.1 First-Line Therapy

Palliative chemotherapy should always be administered in combination with best supportive care (BSC) and can thus provide a significant extension of overall survival with an improved quality of life [19].

- After many years of negative study results, a combination therapy has recently been established that has proven to be superior in overall and progression-free survival as well as tumor response compared to monotherapy with gemcitabine (Table 26.2).

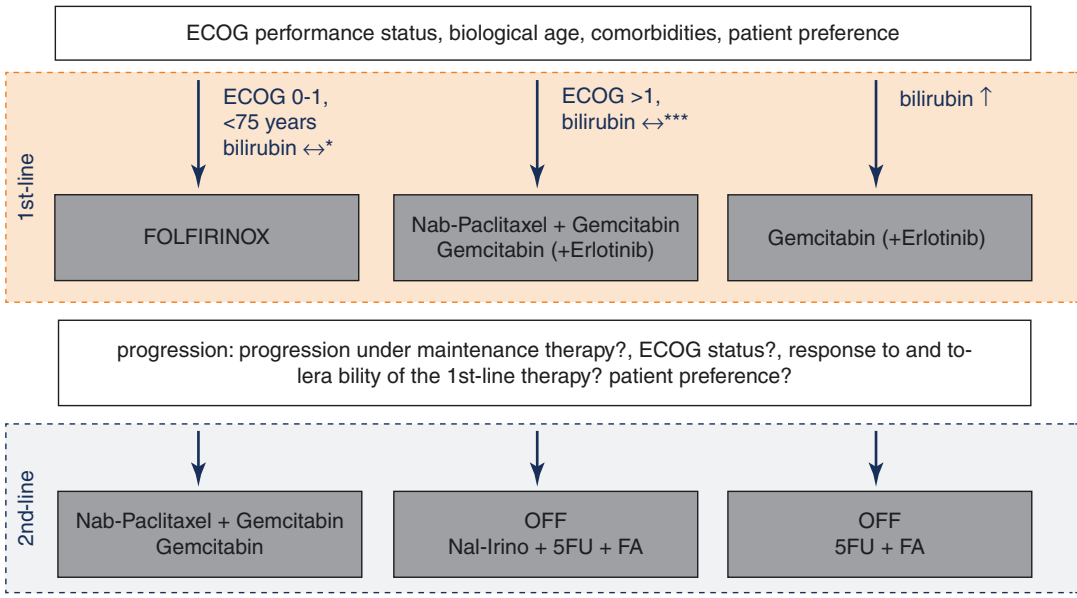


Fig. 26.2 Therapy algorithm for pancreatic carcinoma stage IV. *Bilirubin in the preliminary study maximum 1.5 times the upper norm limit; **bilirubin in the preliminary study for nab-paclitaxel + gemcitabine as well as nal-irinotecan + 5-FU + FS normative. Adequate bile drainage should be ensured before starting chemotherapy. (FS folinic acid, 5-FU 5-fluorouracil, FOLFIRINOX 5-FU + folinic acid + irinotecan + oxaliplatin, nal-Irino nanoliposomal irinotecan, OFF oxaliplatin + 5-fluorouracil + folinic acid)

Table 26.2 Chemotherapeutic regimens for stage IV pancreatic cancer

Day	Drug	Dose	Application
FOLFOXIRI			
1	*Oxaliplatin*	85 mg/m²	i. v. in 500 ml G5% (2 h)
	Folinic acid	400 mg/m²	i. v. in 500 ml G5% (2 h)
	Irinotecan	180 mg/m²	i. v. in 250 ml G5% (60 min)
	5-Fluorouracil	400 mg/m²	i. v. 100 ml G5% (15 min)
	5-Fluorouracil	2400 mg/m²	i. v. in 500 ml G5% (46 h)
Repetition day 15			
Nab-paclitaxel + gemcitabine			
1, 8, 15	*Nab-paclitaxel*	125 mg/m²	i. v. (30 min)
	Gemcitabine	1000 mg/m²	i. v. in 250 ml NaCl 0.9% (30 min)
Repetition day 29			
OFF			
1, 15	*Folinic acid*	200 mg/m²	i. v. in 250 ml G5% (30 min)
	5-Fluorouracil	2000 mg/m²	i. v. in 250 ml G5% (24 h)
8, 22	*Oxaliplatin*	85 mg/m²	i. v. in 500 ml G5% (2 h)
	Folinic acid	200 mg/m²	i. v. in 250 ml G5% (2 h)
	5-Fluorouracil	2000 mg/m²	i. v. in 250 ml G5% (24 h)
Repetition day 43			
Nal-irinotecan + 5-FU + FA			
1	*Nal-irinotecan*	80 mg/m²	i. v. (90 min)
	Folinic acid	400 mg/m²	i. v. in 500 ml NaCl 0.9% (30 min)
	5-Fluorouracil	2400 mg/m²	i. v. in 500 ml NaCl 0.9% (46 h)
Repetition day 15			

FA folinic acid, *5-FU* 5-fluorouracil, *G5%* glucose 5%

Patients in good general condition (ECOG 0-1), younger than 75 years and with compensated liver function (bilirubin <1.5× of the upper limit), can be considered for treatment with FOLFIRINOX. In a randomized controlled study, this regimen has been shown to offer a significant improvement of overall survival (median 11.1 vs. 6.8 months; HR 0.57) as well as progression-free survival (median 6.4 vs. 3.3 months; HR 0.47) compared to gemcitabine monotherapy [10]. Although the patients more frequently developed grade 3 and 4 toxicities (i.e., hematotoxicity, diarrhea, sensory polyneuropathy), an increase of quality of life was observed in patients under FOLFIRINOX therapy compared to gemcitabine monotherapy [21].

For patients with good general condition who do not qualify for FOLFIRINOX, the combination of nab-paclitaxel and gemcitabine is available. An improved overall survival (8.7 vs. 6.6 months; HR 0.72) and progression-free survival (5.5 vs. 3.7 months; HR 0.69) have been demonstrated in a phase III study [50]. This effect can be explained by a synergism of both compounds: nab-paclitaxel ensures a remodeling and depletion of the tumor stromal, which plays a key role in pancreatic cancer regarding tumor invasion, growth, and resistance to chemotherapy. Additionally, nab-paclitaxel inhibits the degradation of the effective gemcitabine metabolite (difluordesoxycytidin-triphosphate).

The expected toxicity with this combination therapy is higher compared to gemcitabine monotherapy (especially fatigue, hematotoxicity, sensory polyneuropathy), but with a generally lower expected toxicity compared to FOLFIRINOX.

The latter, however, has not been tested so far in a direct head-to-head comparison against nab-paclitaxel/gemcitabine.

Recent study data demonstrate a significant advantage in progression-free survival for patients who are treated with a platinum-based combination chemotherapy for a minimal duration of 4 months, are not progressive after this time period, and have a germline BRCA1 or BRCA2 mutation, if the poly-ADP-ribose polymerase (PARP) inhibitor olaparib is given as a maintenance therapy instead of placebo (7.4 months vs. 3.8 months; hazard ratio for disease progression or death, 0.53; 95% confidence interval [CI], 0.35 to 0.82; $P = 0.004$) [20].

26.4.2 Second-Line Therapy

The choice of second-line therapy depends on previous first-line or adjuvant therapies, their toxicities, the performance status of the patient, and comorbidities. Nanoliposomal irinotecan (nal-irinotecan) following a first-line therapy with gemcitabine has been approved in the EU. This pegylated recombinant human hyaluronidase-containing compound can help to reduce the relevant tumor stroma especially in patients with therapy-resistant pancreatic cancer. The combination of nal-irinotecan with 5-FU + leucovorin was able to increase the median overall survival in a phase III trial compared to 5-FU + leucovorin alone (6.1 vs. 4.2 months; [51]). Still, many combination therapies including 5-FU/leucovorin, oxaliplatin, and irinotecan are commonly used after first-line therapy containing gemcitabine (e.g., OFF scheme: mOS 4.8 vs. 2.3 months [vs. BSC]; [32]). Impressive data was provided by a prospective cohort study using a combination therapy with gemcitabine/nab-paclitaxel as a second-line therapy after FOLFIRINOX, in the first-line, had failed, with a reported median overall survival of 8.8 months (mOS since the beginning of first-line therapy 18 months). These results were achieved with a significant toxicity rate of approximately 40% grade 3 and 4 (especially hematotoxicity and sensory polyneuropathy) [36].

26.5 Colorectal Cancer

Colorectal cancer (CRC) is one of the most common cancer diagnoses in the Western world. In total, 35–45% of patients present with distant metastasis or in an inoperable stage of the primary at diagnosis.

- The advancements of systemic chemotherapy during the last two decades have brought a median overall survival of 2–3 years in this cohort of patients.

About every third to fourth patient survives 5 years or longer.

Only a few studies are solely focused on peritoneal metastasis of CRC. An isolated peritoneal metastasis is expected in 2–15% of all patients. The group of Franko et al. [16] described peritoneal metastasis as an independent, negative prognostic factor irrespective of further distant metastasis. In his cohort of patients treated with systemic chemotherapy, overall survival (median 12.7 vs. 17.6 months) and progression-free survival (median 5.8 vs. 7.2 months) were significantly reduced in patients with peritoneal metastasis. In this extensively analyzed cohort, though retrospective, the factor of peritoneal metastasis did not seem to influence the effectiveness of systemic chemotherapy.

- The presence of peritoneal metastasis could not be identified as a factor influencing the decision for a certain chemotherapeutic regimen.

Combination therapy used in palliative intention has the potential to improve overall and progression-free survival as well as to improve the quality of life. Patients with a sufficiently preserved performance status (ECOG ≤2) should be treated with a doublet or triplet combination, as long as toxicities are manageable.

In order to make the right therapeutic decision, several factors—such as expected side effects of the treatment, the performance status and comorbidities of the patient, as well as the therapeutic pressure (rapid progression, major complaints by symptoms), tumor location, and molecular characteristics (especially *RAS* and *BRAF* mutation status and microsatellite instability)—have to be taken into consideration.

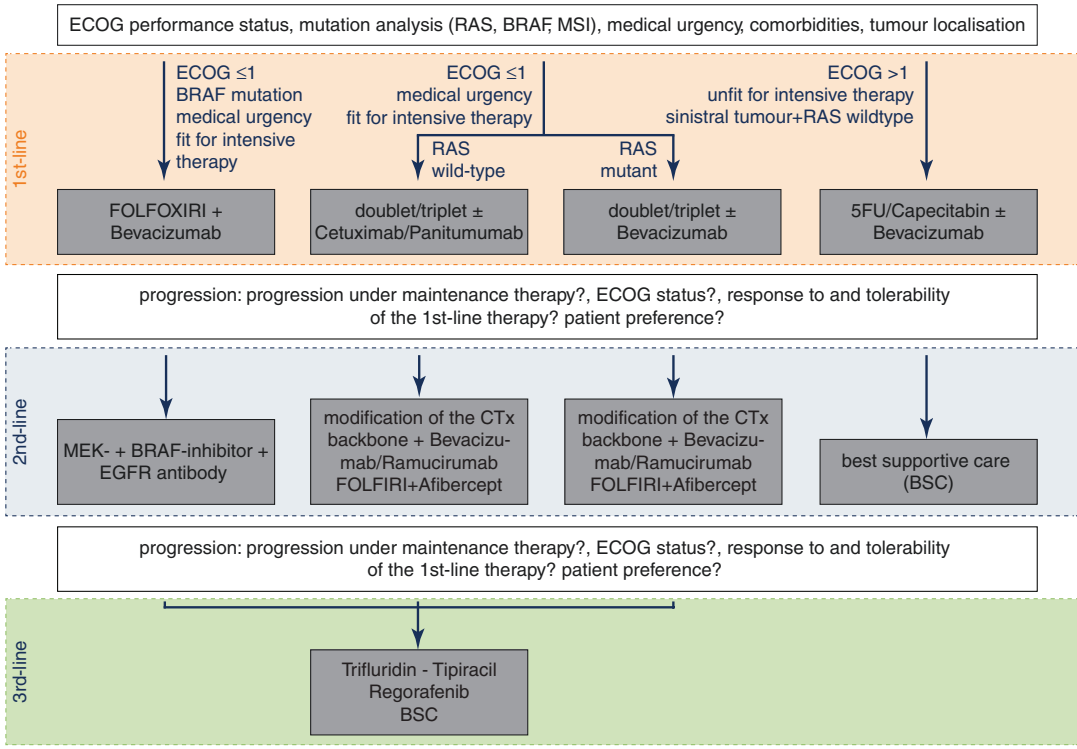


Fig. 26.3 Therapy algorithm for stage IV colorectal carcinoma. The left hemicolon is defined as the distal/aboral colon of the flexura coli sinistra. (RAS Wt RAS wildtype, FS folinic acid, 5-FU 5-fluorouracil, FOLFIRI 5-FU + FS + irinotecan, FOLFOXIRI 5-FU + FS + oxaliplatin + irinotecan, CT chemotherapy, BSC best supportive care). Please note for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors, pembrolizumab monotherapy is a promising therapeutic option in the first line and is approved in some countries

An overview of the therapeutic decisions as well as the approved regimens for patients with stage IV without the possibility of a secondary resectability is provided in Fig. 26.3 and Table 26.3.

26.5.1 First-Line Therapy

5-FU and leucovorin is the established backbone of chemotherapy for CRC, which is often combined with oxaliplatin or irinotecan. These are classified as equivalent regarding their effectiveness (i.e. [9]) and regardless of the sequence of application [46]. The addition of an antibody with an antiangiogenic or an EGF-receptor inhibitor has been established in the palliative setting.

Combination Therapy with Antiangiogenesis

The reported median overall survival of the doublet chemotherapy (FOLFOX or FOLFIRI) in combination with the VEGF antibody bevacizumab is approx. 2 years (FOLFOX + beva: mOS 21.3 months [39]; FOLFIRI + beva: mOS 20.3 months, [[25], [34]]). The combination therapy FOLFOXIRI + bevacizumab attained a further increase in median overall survival of 29.8 months [11].

- The combination therapy with FOLFOXIRI is currently the maximum therapy reserved for patients with excellent performance status especially when the treatment goal is secondary resectability.

Table 26.3 Chemotherapeutic regimens for stage IV colorectal cancer

Day	Drug	Dose	Application
FOLFIRI			
1	*Folinic acid*	200 mg/m^2	i. v. in 500 ml NaCl 0.9% (2 h)
	Irinotecan	180 mg/m^2	i. v. in 250 ml NaCl 0.9% (1 h)
	5-Fluorouracil	400 mg/m^2	i. v. 100 ml in 15 min
	5-Fluorouracil	2400 mg/m^2	i. v. in 500 ml NaCl 0.9% (46 h)
Repetition day 15			
FOLFIRI + cetuximab			
1	*Cetuximab*	400 mg/m^2	i. v. in 250 ml NaCl 0.9% (2 h)
	FOLFIRI (↑)		
8	*Cetuximab*	250 mg/m^2	i. v. in 250 ml NaCl 0.9% (1 h)
Repetition day 15; from 2nd cycle cetuximab dose 250 mg/m^2 weekly			
FOLFIRI + bevacizumab			
1	*Bevacizumab*	5 mg/kg bodyweight	i. v. in 100 ml NaCl 0.9% (90–30 min)
	FOLFIRI (↑)		
Repetition day 15			
FOLFIRI + aflibercept			
1	*Aflibercept*	4 mg/kg bodyweight	i. v. in 100 ml NaCl 0.9% (60 min)
	FOLFIRI (↑)		
Repetition day 15			
FOLFIRI + panitumumab			
1	*Panitumumab*	6 mg/kg bodyweight	i. v. in 100 ml NaCl 0.9% (60 min)
	FOLFIRI (↑)		
Repetition day 15			
mFOLFOX6			
1	*Oxaliplatin*	85 mg/m^2	i. v. in 250 ml G5% (2 h)
	Folinic acid	200 mg/m^2	i. v. in 500 ml G5% (2 h)
	5-Fluorouracil	400 mg/m^2	i. v. 100 ml in 15 min
	5-Fluorouracil	2400 mg/m^2	i. v. in 500 ml G5% (46 h)
Repetition day 15			
mFOLFOX6 + bevacizumab			
1	*Bevacizumab*	5 mg/kg bodyweight	90–30 min in 100 ml G5%
	mFOLFOX6 (↑)		
Repetition day 15			
XELOX + bevacizumab			
1	*Bevacizumab*	7.5 mg/kg bodyweight	90–30 min in 100 ml NaCl 0.9%
	Oxaliplatin	130 mg/m^2	i. v. in 250 ml Glucose (2 h)
1–14	*Capecitabine*	2 × 1000 mg/m^2	p. o. 30 min after meals
Repetition day 22			
FOLFOXIRI			
1	*Irinotecan*	165 mg/m^2	i. v. in 250 ml G5% (1 h)
	Oxaliplatin	85 mg/m^2	i. v. in 250 ml G5% (2 h)
	Folinic acid	200 mg/m^2	i. v. in 500 ml G5% (2 h)
	5-Fluorouracil	3200 mg/m^2	i. v. in 500 ml G5% (48 h)
Repetition day 15			
FOLFOXIRI + bevacizumab			
1	*Bevacizumab*	5 mg/kg bodyweight	90–30 min in 100 ml NaCl 0.9%
	FOLFOXIRI (↑)		
Repetition day 15			
Regorafenib			
1–22	*Regorafenib*	160 mg in total	4 tablets of 40 mg daily

(continued)

Table 26.3 (continued)

Day	Drug	Dose	Application
Repetition day 29			
TAS-102			
1–14	*TAS-102*	2 × 35 mg/m²	p. o. after meals 5 days taking – 2 days pause
Repetition day 29			
Irinotecan + cetuximab			
1	*Cetuximab*	400 mg/m²	i. v. in 250 ml NaCl 0.9% (2 h)
	Irinotecan	125 mg/m²	i. v. in 250 ml NaCl 0.9% (1 h)
8, 15, 22	*Cetuximab*	250 mg/m²	i. v. in 250 ml NaCl 0.9% (1 h)
	Irinotecan	125 mg/m²	i. v. in 250 ml NaCl 0.9% (1 h)
29	*Cetuximab*	250 mg/m²	i. v. in 250 ml NaCl 0.9% (1 h)
Repetition day 36, cetuximab from 2nd cycle 250 mg/m²			
Panitumumab			
1	*Panitumumab*	6 mg/kg bodyweight	i. v. in 100 ml NaCl 0.9% (60 min)
Cetuximab/encorafenib/binimetinib			
1	*Cetuximab*	400 mg/m²	i. v. in 250 ml NaCl 0.9% (2 h)
8, 15, 22	*Cetuximab*	250 mg/m²	i. v. in 250 ml NaCl 0.9% (1 h)
1–28	*Encorafenib*	75 mg	4 × 75 mg/d p.o.
1–28	*Binimetinib*	45 mg	2 × 45 mg/d p.o.
Repetition day 29, cetuximab from 2nd cycle 250 mg/m²			

In addition, there is evidence that patients with a prognostically unfavorable *BRAF* mutation especially benefit from FOLFOXIRI [11]. The precise clinical scenario for the use of this combination therapy remains still to be determined through further clinical studies. Compared to FOLFIRI and bevacizumab, patients treated with FOLFOXIRI increasingly report diarrhea, stomatitis, hematotoxicity, and neurotoxicity.

Combination Therapy with EGF-Receptor Antibodies

According to current evidence, the mutation rate in one of the relevant *RAS* oncogenes (KRAS exons 2, 3, and 4 or NRAS exons 2, 3, and 4) is between 35% and 45%. In this situation, treatment with an EGF-receptor antibody such as cetuximab or panitumumab is not indicated due to immanent pathway resistance. The humanized receptor antibody panitumumab is approved in combination with FOLFOX and FOLFIRI as first-line therapy and showed a lower rate of intolerance reactions (<0.5% vs. 2%), and has the benefit of a biweekly vs. weekly application compared to cetuximab with the same efficacy [37].

The question of the preferred therapy regimen for patients with RAS wildtype was addressed by the randomized control trial CALGB. These patients received a combination therapy with antiangiogenesis or EGF-receptor antibody. The results showed no significant difference between the two groups [49]. Recently, the question of the treatment sequence, however, has moved to the background in comparison to the question of tumor location. Several publications as well as a meta-analysis have just recently demonstrated that patients in stage IV with a right-sided CRC (cecum including appendix up to and including transverse colon), even with RAS-wildtype, do not benefit from a EGF-receptor antibody (cetuximab, panitumumab), whereas for patients with a left-sided CRC and RAS wildtype, a doublet chemotherapy plus EGF-receptor antibody as a first-line therapy is recommended (e.g., [4, 41]).

Recently (June 2020) the FDA approved pembrolizumab for first-line treatment of patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient (dMMR) colorectal cancer based on the data of the Keynote-177 study which showed an impressive benefit of immunotherapy vs. chemotherapy (PFS 16.5 months vs. 8.2 months; HR 0.60, 95% CI 0.45, 0.80; two-sided p-value = 0.0004). Data

for OS are not yet published [3, 13]. Approval in Europe is currently pending (June 2020).

26.5.2 Second-Line Therapy

The choice of second-line therapy is mainly based on previous therapies and the BRAF and RAS mutation status. In patients who have already received a bevacizumab-containing therapy, the chemotherapy backbone should be changed in favor of oxaliplatin or irinotecan while bevacizumab can be maintained beyond progression [7]. Another possibility is the change of the antiangiogenic agent to aflibercept or ramucirumab in combination with FOLFIRI after a progression on FOLFOX ± bevacizumab. Patients treated with aflibercept showed an increased median overall and progression-free survival (mOS 13.5 vs. 12.1 months; HR 0.82, mPFS 6.9 vs. 4.7 months; HR 0.75; [48]), or ramucirumab (mOS 13.3. vs. 11.7 months; HR 0.84; mPFS 5.7 vs. 4.5 months; HR 0.79; [44]) compared to a placebo in the corresponding approval trials. However, a switch from bevacizumab to aflibercept did not show a significant difference regarding overall survival.

Patients who have progressed with FOLFOX and haven't received an EGF-receptor antibody can be treated with the approved combination of FOLFIRI and panitumumab. In this situation, the addition of panitumumab increased the median PFS from 3.9 to 5.9 months [33].

In case of an underlying BRAF V600E mutation, standard chemotherapy is typically not effective and patients progress very fast. Recently the combination of encorafenib, cetuximab, and binimetinib showed prolonged overall survival and a higher response rate than standard therapy in the second- and third-line therapy [28].

Patients who were deescalated to a 5-FU-based maintenance therapy (e.g., 5-FU + bevacizumab) after an initial good response to first-line combination therapy (induction therapy), and who have recently progressed, should be treated with the reimplementation of the scheme of the first-line therapy, if adequately tolerated at previous exposure.

26.5.3 Third-Line Therapy

The median overall survival of patients in whom the first- and second-line therapy failed is approx. 6 months. A treatment option for patients with *RAS* wildtype who have not received an EGF-receptor antibody is either the combination of cetuximab-irinotecan [12] or panitumumab monotherapy [47].

The multi-tyrosine-kinase inhibitor regorafenib, which is approved in Europe, was able to increase the median overall survival by approximately 1.5 months in its approval trial (mOS 6.4 vs. 5.0 months; HR 0.44; [22]). Commonly observed side effects of this treatment are hand-foot syndrome, fatigue, arterial hypertension, diarrhea, and rash. The pharmaceutical company closed the distribution in Germany after a reevaluation of the clinical benefit of regorafenib performed by the G-BA, which certified no additional benefit. Recently, the monotherapy with the nucleoside analogue and thymidine-phosphorylase inhibitor trifluridine/tipiracil was approved in Europe for patients with progression after two lines of chemotherapy according to a phase III approval trial (mOS 7.1 vs. 5.3 months; HR 0.68; [31]).

26.6 Conclusion

Gastric Cancer

The choice of the first-line combination chemotherapy for patients with gastric cancer and peritoneal metastasis depends upon the patient's performance, the HER2 receptor status, and other paraclinical parameters. Ramucirumab, especially in combination with paclitaxel, has proven its efficacy against progressive disease. Currently, a variety of clinical trials for patients with advanced, inoperable, or metastatic gastric and gastroesophageal-junction cancer are being carried out. Recently, immunotherapy such as PD-1 inhibitors (e.g., pembrolizumab, nivolumab) has shown promising results in phase II trials depending on the PD-L1 expression status, with higher response rates for patients with higher expression (e.g., [17]). Furthermore, microsatellite-instable

carcinomas seemed to be especially responsive to immunotherapy, which appears to be a cross-entity effect [29]. Therefore, testing for microsatellite instability, or the mismatch repair deficiency syndrome, is recommended for all advanced, incurable cancers—not only for gastric cancer.

Pancreatic Cancer

Physicians have several different systemic chemotherapeutic options for the treatment of metastatic pancreatic cancer. The feasibility is particularly dependent upon the general condition of the patient and his/her liver function. The decision should be taken with a sense of proportion especially in patients with limited functional status. Combination therapies, namely, FOLFIRINOX and nab-paclitaxel/gemcitabine, still have the potential to improve the quality of life despite increased toxicity. Some new approaches in the therapy of metastatic pancreatic cancer are in development. Examples are the Janus-kinase-inhibitor ruxolitinib and vaccine trials. Similar to nal-irinotecan, ruxolitinib addresses the stroma of the tumor, regulating inflammatory reactions. First studies of the application in combination with capecitabine revealed efficacy in patients with elevated CRP [26]. The currently recruiting ECLIPSE trial examines the increase of antitumoral immune response through vaccination with allogenic, devitalized pancreatic cancer cells.

Colorectal Cancer

Metastatic colorectal cancer is an excellent example of the relevance of precise patient selection. New standardized methods for the most sensitive and selective analysis of *RAS* and *BRAF* status will be facilitated in the future. Many promising concepts such as BRAF and MEK inhibition for BRAF mutant tumors as well as immunotherapy for MSI-high tumors are being transferred into clinical practice. Further prognostic markers such as MSI, HER2, and MET status or the methylation status of CpG islands are in evaluation. The Cancer Genome Atlas Network published a comprehensive molecular characterization of the colorectal carcinoma in 2012. Many of the 24 identified altered genes or signaling pathways can be principally addressed with medication, including "programmed cell death protein 1" (PD1), HER2 and the anaplastic lymphoma kinase, and the c-ros oncogene (ALK/ROS, C.G.A.N. 2012). In particular for immune checkpoint inhibitors, there is growing evidence that the extent of genetic aberration of the tumor correlates with the response to the therapy. Therefore, especially microsatellite instable tumors can be treated with these therapies [29]. Furthermore, resistance mechanisms are the focus of research [14].

References

1. Al-Batran SE, Hartmann JT, Hofheinz R, Homann N, Rethwisch V, Probst S, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol. 2008a;19(11):1882–7. https://doi.org/10.1093/annonc/mdn403.
2. Al-Batran SE, Hartmann JT, Probst S, Schmalenberg H, Hollerbach S, Hofheinz R, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: a study of the Arbeitsgemeinschaft Internistische Onkologie. J Clin Oncol. 2008b;26(9):1435–42. https://doi.org/10.1200/JCO.2007.13.9378.
3. Andre T, Shiu K-K, Kim TW, Jensen BV, Jensen LH, Punt CJA, et al. Pembrolizumab versus chemotherapy for microsatellite instability-high/mismatch repair deficient metastatic colorectal cancer: the phase 3 KEYNOTE-177 study. J Clin Oncol. 2020;38(18_suppl):LBA4. https://doi.org/10.1200/JCO.2020.38.18_suppl.LBA4.
4. Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol. 2017;28(8):1713–29. https://doi.org/10.1093/annonc/mdx175.
5. Ayantunde AA, Parsons SL. Pattern and prognostic factors in patients with malignant ascites: a retrospective study. Ann Oncol. 2007;18(5):945–9. https://doi.org/10.1093/annonc/mdl499.
6. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet.

2010;376(9742):687–97. https://doi.org/10.1016/S0140-6736(10)61121-X.
7. Bennouna J, Sastre J, Arnold D, Osterlund P, Greil R, Van Cutsem E, et al. Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. Lancet Oncol. 2013;14(1):29–37. https://doi.org/10.1016/S1470-2045(12)70477-1.
8. Choi IS, Choi M, Lee JH, Kim JH, Suh KJ, Lee JY, et al. Treatment patterns and outcomes in patients with metastatic gastric cancer receiving third-line chemotherapy: a population-based outcomes study. PLoS One. 2018;13(6):e0198544.
9. Colucci G, Gebbia V, Paoletti G, Giuliani F, Caruso M, Gebbia N, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol. 2005;23(22):4866–75. https://doi.org/10.1200/JCO.2005.07.113.
10. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011;364(19):1817–25. https://doi.org/10.1056/NEJMoa1011923.
11. Cremolini C, Loupakis F, Antoniotti C, Lupi C, Sensi E, Lonardi S, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. Lancet Oncol. 2015;16(13):1306–15. https://doi.org/10.1016/S1470-2045(15)00122-9.
12. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004;351(4):337–45. https://doi.org/10.1056/NEJMoa033025.
13. Diaz LA, Le DT, Yoshino T, Andre T, Bendell JC, Koshiji M, et al. KEYNOTE-177: randomized phase III study of pembrolizumab versus investigator-choice chemotherapy for mismatch repair-deficient or microsatellite instability-high metastatic colorectal carcinoma. J Clin Oncol. 2017;35(4_suppl):TPS815.
14. Fakih MG. Metastatic colorectal cancer: current state and future directions. J Clin Oncol. 2015;33(16):1809–24. https://doi.org/10.1200/JCO.2014.59.7633.
15. Ford HE, Marshall A, Bridgewater JA, Janowitz T, Coxon FY, Wadsley J, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78–86. https://doi.org/10.1016/S1470-2045(13)70549-7.
16. Franko J, Shi Q, Goldman CD, Pockaj BA, Nelson GD, Goldberg RM, et al. Treatment of colorectal peritoneal carcinomatosis with systemic chemotherapy: a pooled analysis of north central cancer treatment group phase III trials N9741 and N9841. J Clin Oncol. 2012;30(3):263–7. https://doi.org/10.1200/JCO.2011.37.1039.
17. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol. 2018;4(5):e180013. https://doi.org/10.1001/jamaoncol.2018.0013.
18. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9. https://doi.org/10.1016/S0140-6736(13)61719-5.
19. Glimelius B, Hoffman K, Sjoden PO, Jacobsson G, Sellstrom H, Enander LK, et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. Ann Oncol. 1996;7(6):593–600. https://doi.org/10.1093/oxfordjournals.annonc.a010676.
20. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hallet MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019;381:317–27.
21. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouche O, Guimbaud R, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. J Clin Oncol. 2013;31(1):23–9. https://doi.org/10.1200/JCO.2012.44.4869.
22. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303–12. https://doi.org/10.1016/S0140-6736(12)61900-X.
23. Haberland J, Bertz J, Wolf U, Ziese T, Kurth BM. German cancer statistics 2004. BMC Cancer. 2010;10:52. https://doi.org/10.1186/1471-2407-10-52.
24. Hacker U, Lordick F. Current standards in the treatment of gastric cancer. Dtsch Med Wochenschr. 2015;140(19):1417. https://doi.org/10.1055/s-0041-106868.
25. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42. https://doi.org/10.1056/NEJMoa032691.
26. Hurwitz HI, Uppal N, Wagner SA, Bendell JC, Beck JT, Wade SM 3rd, et al. Randomized, double-blind, phase II study of ruxolitinib or placebo in combination with capecitabine in patients with metastatic pancreatic cancer for whom therapy with gemcitabine has failed. J Clin Oncol. 2015;33(34):4039–47. https://doi.org/10.1200/JCO.2015.61.4578.

27. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277–300. https://doi.org/10.3322/caac.20073.
28. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med. 2019;381(17):1632–43. https://doi.org/10.1056/NEJMoa1908075.
29. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357(6349):409–13. https://doi.org/10.1126/science.aan6733.
30. Masoumi Moghaddam S, Amini A, Morris DL, Pourgholami MH. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer Metastasis Rev. 2012;31(1–2):143–62. https://doi.org/10.1007/s10555-011-9337-5.
31. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med. 2015;372(20):1909–19. https://doi.org/10.1056/NEJMoa1414325.
32. Oettle H, Riess H, Stieler JM, Heil G, Schwaner I, Seraphin J, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014;32(23):2423–9. https://doi.org/10.1200/JCO.2013.53.6995.
33. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28(31):4706–13. https://doi.org/10.1200/JCO.2009.27.6055.
34. Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Maspero F, et al. FOLFIRI-bevacizumab as first-line chemotherapy in 3500 patients with advanced colorectal cancer: a pooled analysis of 29 published trials. Clin Colorectal Cancer. 2013;12(3):145–51. https://doi.org/10.1016/j.clcc.2013.04.006.
35. Piso P, Arnold D. (2011) Multimodal treatment approaches for peritoneal carcinosis in colorectal cancer. Dtsch Arztebl Int. 2011;108(47):802–8. https://doi.org/10.3238/arztebl.2011.0802.
36. Portal A, Pernot S, Tougeron D, Arbaud C, Bidault AT, de la Fouchardiere C, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort. Br J Cancer. 2015;113(7):989–95. https://doi.org/10.1038/bjc.2015.328.
37. Price TJ, Peeters M, Kim TW, Li J, Cascinu S, Ruff P, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014;15(6):569–79. https://doi.org/10.1016/S1470-2045(14)70118-4.
38. Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer. 2000;88(2):358–63. https://doi.org/10.1002/(sici)1097-0142(20000115)88:2<358::aid-cncr16>3.0.co;2-o.
39. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26(12):2013–9. https://doi.org/10.1200/JCO.2007.14.9930.
40. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet Oncol. 2018;19(12):e668]. Lancet Oncol. 2018;19(11):1437–48. https://doi.org/10.1016/S1470-2045(18)30739-3.
41. Stintzing S, Modest DP, Rossius L, Lerch MM, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab for metastatic colorectal cancer (FIRE-3): a post-hoc analysis of tumour dynamics in the final RAS wild-type subgroup of this randomised open-label phase 3 trial. Lancet Oncol. 2016;17(10):1426–34. https://doi.org/10.1016/S1470-2045(16)30269-8.
42. Struller F, Horvath P, Solass W, Weinreich F-J, Strumberg D, Kokkalis MK, et al. Pressurized intraperitoneal aerosol chemotherapy with low-dose cisplatin and doxorubicin (PIPAC C/D) in patients with gastric cancer and peritoneal metastasis: a phase II study. Ther Adv Med Oncol. 2019;11:1758835919846402.
43. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2018;19(10):1372–84. https://doi.org/10.1016/S1470-2045(18)30481-9.
44. Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol. 2015;16(5):499–508. https://doi.org/10.1016/S1470-2045(15)70127-0.
45. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47(15):2306–14. https://doi.org/10.1016/j.ejca.2011.06.002.

46. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004;22(2):229–37. https://doi.org/10.1200/JCO.2004.05.113.
47. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol. 2007;25(13):1658–64. https://doi.org/10.1200/JCO.2006.08.1620.
48. Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausova J, Macarulla T, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol. 2012;30(28):3499–506. https://doi.org/10.1200/JCO.2012.42.8201.
49. Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA. 2017;317(23):2392–401. https://doi.org/10.1001/jama.2017.7105.
50. von Hoff D, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369(18):1691–703. https://doi.org/10.1056/NEJMoa1304369.
51. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016;387(10018):545–57. https://doi.org/10.1016/S0140-6736(15)00986-1.
52. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014;15(11):1224–35. https://doi.org/10.1016/S1470-2045(14)70420-6.
53. Yun J, Lee J, Park SH, Park JO, Park YS, Lim HY, et al. A randomised phase II study of combination chemotherapy with epirubicin, cisplatin and capecitabine (ECX) or cisplatin and capecitabine (CX) in advanced gastric cancer. Eur J Cancer. 2010;46(5):885–91. https://doi.org/10.1016/j.ejca.2009.12.015.

PIPAC for Advanced Peritoneal Metastasis

27

Kuno Lehmann, Wiebke Solass, Lilian Roth, Joshua R. Kapp, Clemens B. Tempfer, and Marc A. Reymond

27.1 Introduction

Cytoreductive surgery (CRS) combined with hyperthermic intraoperative peritoneal chemotherapy (HIPEC) has become an important tool in the cancer therapy toolbox for peritoneal metastasis. However, due in part to the invasiveness of this combined therapeutic approach, it is associated with significant postoperative mortality, morbidity, and a long convalescence period. In the treatment of aggressive peritoneal metastasis, it has become increasingly well recognized that the aforementioned risks need to be carefully weighed against the potential benefit for the patient. For example, in colorectal peritoneal metastasis, an international consensus has stipulated a 30-month target survival rate following CRS/HIPEC; however, in many cases this cannot be achieved [9]. Consequently, any treatment decision must be taken very carefully. To this end, multiple national registries have clearly defined negative selection criteria. These include diffuse intraabdominal metastases involving multiple quadrants (peritoneal cancer index >15) or histology demonstrating signet-ring cell differentiation [3, 8]. To further aid decision making, prognostic scores have been developed that enable compilation of prognostic patient-risk profiles [4, 34] toward a better selection of patients for CRS/HIPEC or other treatment options.

27.2 Advances in Systemic Therapy

Invasive therapeutic approaches such as CRS/HIPEC must be carefully assessed in terms of potential benefit for each patient, particularly in light of modern advances in systemic therapy. For example, novel combination therapies for colorectal cancer such as FOLFIRINOX and bevacizumab [22] or PD-1 checkpoint inhibitors

K. Lehmann (✉) · L. Roth · J. R. Kapp
Department of Surgery and Transplantation, University Hospital Zurich, Zurich, Switzerland
e-mail: kuno.lehmann@usz.ch; lilian.Roth@usz.ch; joshua.kapp@doctors.org.uk

W. Solass
Institute of Pathology, University of Tübingen, Tübingen, Germany
e-mail: wiebke.solass@med.uni-tuebingen.de

C. B. Tempfer
Department of Obstetrics and Gynecology, Marien Hospital Herne, Ruhr-Universität Bochum, Herne, Germany
e-mail: clemens.tempfer@marienhospital-herne.de

M. A. Reymond
Department of General, Visceral and Transplant Surgery, University of Tübingen, Tübingen, Germany

National Center for Pleura and Peritoneum (NCPP), University of Tübingen, Tübingen, Germany
e-mail: marc.reymond@med.uni-tuebingen.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_27

such as pembrolizumab [21] are expected to achieve new improvements in patient outcomes. To reflect these expected improvements, a hypothetical randomized clinical trial would have to adjust the life expectancy of its non-CRS/HIPEC control group upward of the current 30-month median survival for colorectal cancer.

It remains to be seen whether the recent developments in systemic therapy will also be effective for patients with peritoneal metastasis, or whether we will continue to see poor prognosis for these patients, which is several months shorter compared to patients with liver and lung metastases [10]. Regardless of these developments, the responsiveness of peritoneal metastatic disease to neoadjuvant systemic therapy continues to be of prognostic relevance and is therefore a good indicator for determining subsequent radical treatment with CRS/HIPEC [26]. Recent improvements in understanding the biology of peritoneal metastatic disease have consequently led to a reduction in the number of patients who would appreciably benefit from invasive surgery [34]. The future of radical surgical management of patients with peritoneal metastases lies in developing more sensitive prognosticators for patient stratification. To this end, diagnostic laparoscopy and histological analysis will play an increasingly important role in monitoring patient progression, as well as determining the optimal timing for CRS/HIPEC if indicated.

27.3 Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

The development of PIPAC has brought with it new possibilities for the local management of peritoneal metastatic disease. PIPAC is a new and innovative therapeutic technique; its underlying principles are twofold:

– Analogous to branches of respiratory medicine, where aerosols have been used to treat the tracheobronchial tree for decades, PIPAC utilizes a specially adapted vaporizer to deliver therapy inside the abdomen.
– PIPAC utilizes the physical and chemical properties of CO2 pneumoperitoneum through the establishment of a hydrostatic pressure gradient [27] and/or through electrostatic charging of the therapeutic aerosol molecules, permitting subsequent electro-precipitation [6, 19].

During the PIPAC procedure, multiple biopsies can be sampled, permitting an objective assessment of the patient's response to therapy over time. The importance of this cannot be overestimated when it comes to small-volume peritoneal nodes, where the diagnostic power of modern radiological imaging techniques continues to be insufficient [17]. In a similar vein, the RECIST criteria continue to be unreproducible using modern imaging techniques [50]. In order to facilitate the histological assessment of therapeutic response, an international congregation of pathologists recently proposed a new grading standard (Fig. 27.1) [39]. In addition to histological analysis, assessment of therapeutic concen-

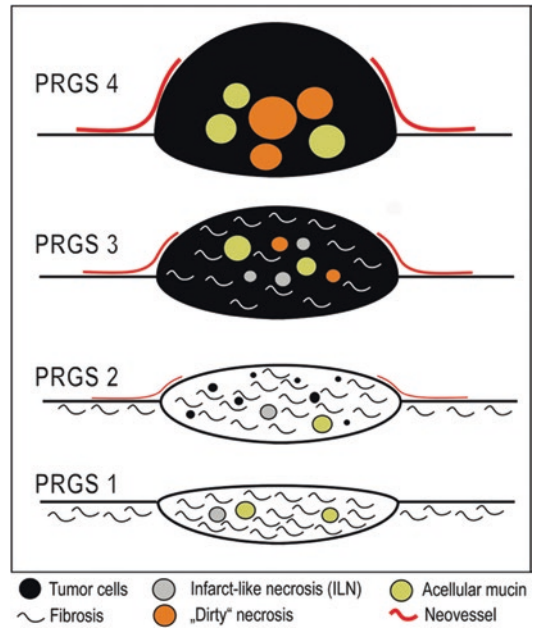


Fig. 27.1 Schematic representation of the Peritoneal Regression Grading Score (PRGS), which facilitates objective assessment of the response of peritoneal metastases to therapy. (Reproduced from Solass et al. [39]. Creative Commons Attribution License)

tration in tissue or ascites can be used to further optimize PIPAC dosage for individual patients. This approach is akin to dose-ranging studies performed according to pharmaceutical regulations [43, 44]. Finally, molecular analysis of peritoneal nodes between consecutive treatments may also help guide treatment [29].

- With the advent of PIPAC, the surgical oncologist is cast in a new role in which he or she must navigate therapy according to chemical, physical, and pharmacological parameters. The goal, as always, is to improve patient outcome.

In contrast to HIPEC, where fluid is circulated inside the abdomen, intraabdominal pressure and volume remains stable during PIPAC, similar to conditions found in a boiler. The low resistance of the peritoneal membranes for macromolecules permits high concentrations of cytostatic therapy in the peritoneal cavity, while reducing overall systemic exposure [38]. The dosages required for PIPAC are therefore on average tenfold lower than those used for HIPEC. Consequently, there is almost no evidence of organ toxicity associated with HIPEC [2, 30]. Despite lower dosages, the concentration and penetration of chemotherapy in the peritoneal tissues is considerably higher following PIPAC as compared to HIPEC. This effect has been exemplified using a 3D colorectal tumor-cell model treated with oxaliplatin. The percentage of apoptotic cells in models treated with PIPAC was considerably higher, despite a 20% dose reduction compared to the control group. Additionally, penetration of cytostatic therapy, measured as the concentration gradient between oxaliplatin in the tumor periphery and tumor center, was considerably higher in the PIPAC group. Finally, the concentration of oxaliplatin measured beyond the peritoneal membrane was significantly higher after HIPEC as compared to PIPAC. These findings represent a clear disadvantage associated with HIPEC in terms of systemic toxicity [15]. The aforementioned observational results were confirmed following initial human trials, demonstrating considerably lower concentrations of doxorubicin in the peripheral blood (approximately 1% AUC of a systemic dose), but with a 200-fold increase in local-tissue concentrations as compared to HIPEC [38].

27.4 Surgical Technique

From a technical perspective, PIPAC is a straightforward procedure resembling a staging laparoscopy (Fig. 27.2). The first part of the procedure

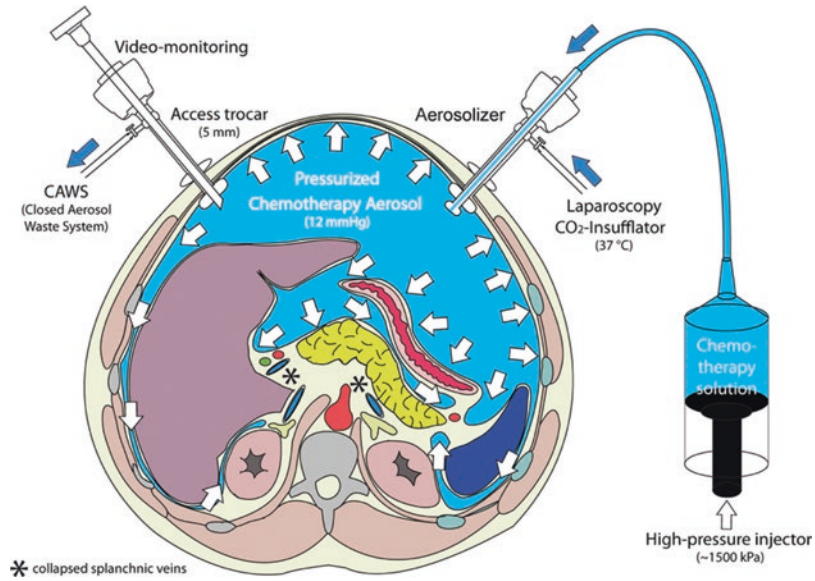


Fig. 27.2 Technically speaking, the PIPAC procedure is relatively simple and closely resembles a staging laparoscopy. (Reproduced from Solass et al. [38]. Creative Commons Attribution License)

involves a diagnostic laparoscopy performed using two ports (one 10 mm and one 5 mm port). Peritoneal biopsies are subsequently obtained from the affected parietal peritoneum. Next, the vaporizer and camera are positioned appropriately. All cables, connections, as well as the density and stability of the CO2 pneumoperitoneum are now checked according to a checklist protocol. At this point, the surgical team leaves the operating theater and the chemotherapy is aerosolized and applied intraabdominally over a period of 30 minutes. Finally, the intraabdominal gas is released via the anesthetic-contaminated air circuit, thereby ensuring that the procedure can be delivered in accordance with stringent health and safety standards [14, 25, 28, 36]. The biggest difference in PIPAC compared to CRS/HIPEC is the absence of surgical resection. To date, PIPAC has not been combined with surgical resection, owing to the increased penetration of cytotoxic therapy in the tissues and subsequent associated risk for impaired wound healing. Accordingly, performance of adhesiolysis is also avoided during PIPAC.

27.5 Critical Steps in Accessing the Abdominal Cavity

Many patients undergoing PIPAC have already been operated on, making surgical access to the abdomen more complicated than usual. The proportion of patients for whom sufficient intraabdominal working space cannot be created is estimated to be as high as 17% according to one gynecological case series.

- Iatrogenic bowel injury caused while accessing the abdominal cavity is an uncommon, yet potentially serious complication. In most cases the application of PIPAC should be aborted in cases where an iatrogenic bowel injury is suspected.

Single-port access PIPAC has recently been suggested as a potential solution in cases where surgical access is challenging [49]. Despite these potential challenges, PIPAC is a minimally invasive technique which is generally well tolerated [24]. It has been associated with significantly reduced rates of organ toxicity [2] and has been performed successfully on over 2000 patients to date.

27.6 Indications and Contraindications

As for every therapy, PIPAC can be successful or unsuccessful, and it carries with it a clear set of indications and contraindications. At present, PIPAC is indicated for cases of non-resectable peritoneal carcinomatosis where systemic therapy has failed. Specific examples include colorectal cancer, ovarian cancer, gastric cancer, primary peritoneal mesothelioma, and advanced, unresectable pseudomyxoma peritonei [1]. In such cases, early instigation of PIPAC can achieve high local response rates, which has been extensively reported in the literature [31–33, 40]. The current role for PIPAC was summarized by the 2015 Australian Health Policy Advisory Committee on Technology as follows:

- PIPAC has been used in patients who are quite ill and have already failed multiple treatment regimes, but it may not be limited to that group of patients in the future.

27.7 Clinical Studies

- Every indication for PIPAC should, in theory, stem from a rigorously conducted clinical trial.

PIPAC is not a therapy as such. Strictly speaking, it is a drug delivery system. Consequently, numerous clinical trials are theoretically required to determine the optimal chemotherapy, dose, and timing for every tumor type. Until such studies are completed, existing cancer guidelines based on tumor type should be prudently followed. Table 27.1 summarizes some current series for several tumor types. In practice, PIPAC is usually started when palliative systemic che-

Table 27.1 Clinical studies on PIPAC

Tumor type	*N*	Study type	Chemo lines before	Objective tumor response	mOS (months)
Gastric cancer	20	Prospective (II)	>1	72%	11.5[a]
Malignant mesothelioma	29	Prospective (II)	1–3	75%	26.6[b]
Colorectal and appendix cancer	18	Prospective (II)	1–2	57%	10.1[c]
Ovarian cancer	99	Retrospective	2–3	76%	14.1[d]

[a]Bremholm Ellebaek Y, Gaversen M, Detlefsen S, et al. (2020) Pressurized intraperitoneal aerosol chemotherapy (PIPAC) of peritoneal metastasis from gastric cancer: a descriptive cohort study, Clinical and Experimental Metastasis
[b]Giger-Papst U, Demtröder C, Falkenstein T A, et al. (2018) Pressurized Intra Peritoneal Aerosol Chemotherapy (PIPAC) for the treatment of malignant mesothelioma, BMC Cancer.
[c]Gockel I, Jansen-Winklen B, Haase L, et al. (2019) Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in patients with peritoneal metastasized colorectal, appendiceal and small bowel cancer, Tumori Journal.
[d]Trempfer C B, Rezniczek G A, Ende P, Solass W & Reymond M A (2015) Pressurized Intraperitoneal Aerosol Chemotherapy with Cisplatin and Doxorubicin in Women with Peritoneal Carcinomatosis: A Cohort Study, Anticancer Research

motherapy has been completed. Since only regulatorily approved chemotherapies are used for PIPAC, these agents can be used off-label without performing additional clinical studies in cases where treatment is formally recommended by an interdisciplinary board. In this vein, the regulatory context for PIPAC does not vary considerably to that for HIPEC. HIPEC also utilizes regulated cytotoxic agents which are approved for intravenous administration but not for intraperitoneal application. Similarly, PIPAC is not very different from the systemic chemotherapy deployed in medical oncology. Experts already predicted more than 10 years ago that off-label drug use in oncology would reach 60% of cases [11]. Rapid development of novel therapies combined with shrinking indications for approval, increasing prevalence of cancers that are difficult to treat, and expanding sub-classifications of cancer types are likely to increase the prevalence of off-label use. Taken together, referring to PIPAC as "experimental therapy" is inaccurate because the intention of PIPAC is neither curative nor compassionate; instead, PIPAC represents the off-label use of regulatorily approved cancer treatments, something which in the field of oncology is not uncommon (2016 Recommendations from the German Federal Institute for Drugs and Medical Devices).

27.8 Pitfalls Associated with a Decision to Treat

The fact that PIPAC is only introduced in advanced stages of peritoneal carcinomatosis implies considerable risk.

- Should the advanced stage of peritoneal metastases lead to significant bowel obstruction, the decision to treat with PIPAC should only be made with extreme caution, since the full effect of PIPAC is typically delayed and can lead to clinical deterioration of the patient.

In cases of advanced peritoneal metastases, PIPAC is unable to stop or delay the process of dying. There is strictly no role for PIPAC in such cases as a measure of "last resort" where alternatives have been exhausted. The principal reason for this is that the remaining life expectancy in such cases is too short for PIPAC to be effective. Generally, three applications with 6-week intervals over 3 months are required for a therapeutic effect. Secondly, should PIPAC be used as a last resort, it could easily be construed as the cause of death in such cases, particularly when clinical evidence for such a causality is currently lacking.

27.9 High Response Rates in the Context of Platinum Resistance

Pilot studies have demonstrated objective response rates between 60% and 80% in patients receiving PIPAC following successful palliative, platinum-based systemic chemotherapy (Fig. 27.3). These response rates have been demonstrated in patients with peritoneal carcinomatosis stemming from ovarian cancer [41], gastric cancer [23], colorectal cancer [7], and malignant peritoneal mesothelioma [37]. Should these response rates be confirmed in larger follow-up series, they would be highly compelling when compared to existing figures for established systemic therapy delivered in the same stage of the disease [16]. Currently, several studies are being conducted according to ICH-GCP standards at the US National Institutes of Health [43–48] in order to more clearly establish the limits and possibilities of PIPAC. Broader additional studies are currently under appraisal. Recurrent, platinum-resistant peritoneal carcinomatosis of ovarian origin has been the most common indication for PIPAC, now accounting for over 40% of PIPAC applications. Results from a prospective Phase II clinical trial involving 69 patients with peritoneal carcinomatosis of ovarian origin, who already received second-line chemotherapy, were recently published. PIPAC was administered to 58 (84%) of the patients. Clinical improvement was observed in 30 (52%) patients receiving PIPAC. Tumor progression was observed in 12 patients. A total of 39 patients received 3 cycles of PIPAC, of which 20 (51%) demonstrated histological evidence of regression of the peritoneal carcinomatosis. Moderate side effects were observed in eight patients. No patients developed severe side effects (CTCAE 4) and there were no recorded deaths (CTCAE 5) [42].

27.10 Introducing PIPAC in Earlier Stages of Tumor Progression

In addition to considering a role for PIPAC earlier in the palliative treatment pathway, the potential for PIPAC as a pretreatment for patients with resectable peritoneal carcinomatosis may also be

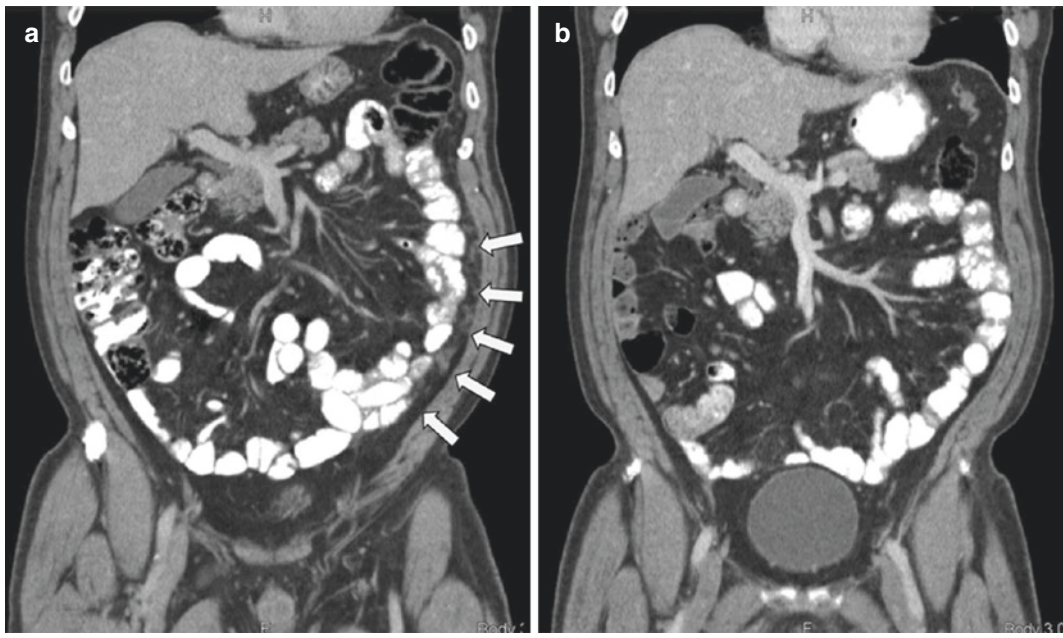


Fig. 27.3 (**a** and **b**) An example of objective radiological regression in a case of colorectal peritoneal metastasis managed with platinum-based PIPAC. (Reproduced from Demtröder et al. [7]. Creative Commons Attribution-NonCommercial-NoDerivs License)

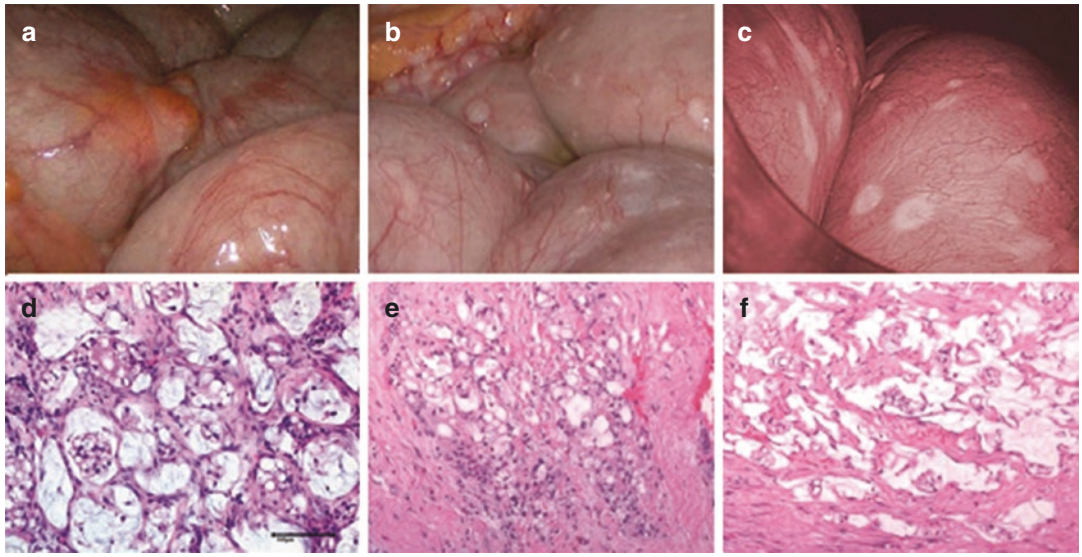


Fig. 27.4 (**a**–**d**) Macroscopic and histological regression following PIPAC C/D. 45-year-old male with diffuse peritoneal metastases (PCI = 16) originating from a signet-ring carcinoma of the appendix, presenting initially with bowel obstruction. Macroscopic images showing **a** before and **b** after first PIPAC and **c** after the third PIPAC cycle with regression of peritoneal tumor nodes affecting the small bowel. Histology confirms a high-grade tumor regression: **d** after systemic chemotherapy (PRGS-4); **e** inflammation with nodular sclerosis following the first PIPAC (PRGS 3); and **f** large, non-vital tumor regions after the third PIPAC cycle with regions of individual tumor cells (PRGS 2). Scale 100 µm. (Reproduced from Solass et al. [38]. Creative Commons Attribution License)

considered. This approach would avoid the problem posed by adhesions when PIPAC is administered after cytoreductive surgery. Furthermore, this approach would reduce the number of general anesthetics undergone by the patient since the PIPAC pretreatment can be administered during the routine staging laparoscopy. The plausibility of this approach is further exemplified in a recent retrospective case series, where the authors suggest PIPAC could be adopted as a neoadjuvant therapy prior to CRS/HIPEC. This kind of pretreatment could be particularly effective for patients with peritoneal metastases of colorectal origin [12]. Furthermore, a Phase II study of peritoneal carcinomatosis of gastric origin was recently published: 31 patients with synchronous or metachronous peritoneal carcinomatosis were treated with a combination of systemic chemotherapy (XELOX) and PIPAC with low-dose cisplatin and doxorubicin – so-called bidirectional chemotherapy [20]. The rate of complete or partial histological regression was 60% in 15 patients who had received at least 2 PIPAC cycles. The median survival rate for all patients involved in the study was 13 months. Even though a selection bias cannot be ruled out, these are promising results since they exceed not only median survival for palliative systemic chemotherapy but also the median survival rate of 9.2 months following CRS/HIPEC as published by the largest prospective multicenter study to date [13]. Bidirectional chemotherapy maintains the patient's quality of life and is significantly less traumatic, thus posing a significant challenge to the role of CRS/HIPEC in the treatment of peritoneal carcinomatosis of gastric origin (Fig. 27.4).

27.11 Conclusion

The various advantages and disadvantages associated with systematic chemotherapy, CRS/HIPEC, and PIPAC are summarized in Table 27.2. The three methods complement one another; however, PIPAC demonstrates advantages in efficacy, safety, and feasibility. The generic nature of PIPAC itself makes it an attractive approach, in terms of the broad spectrum of cytotoxic

Table 27.2 Treatment modalities for peritoneal metastases: advantages and disadvantages of systemic chemotherapy vs. CRS/HIPEC vs. PIPAC

	Systemic chemotherapy	CRS/ HIPEC	PIPAC
Efficacy			
Versatility of cytotoxic agents (chemotherapy, antibodies, nanoparticles, gene therapy)	limited	✓	✓
Repeatability	✓	limited	✓
Homogenous distribution of cytotoxic agent	✗	✗	✓
Deep tissue penetration	✗	✗	✓
Curative intent	✗	✓	✗
Maintains quality of life	+/–	✗	✓
Objective assessment of therapeutic effect	✗	✗	✓
Safety			
Non-invasive or minimally invasive	✓	✗	✓
Minimal systemic toxicity	✗	+/–	✓
Minimal local toxicity	✗	✗	✓
Feasibility			
Feasible for the majority of patients	✓	✗	✓
Effective for diffuse small-bowel involvement	✓	✗	✓
Combination with systemic chemotherapy possible	N/A	✓	✓

substances (small molecules, antibodies, gene therapy [35], and nanotherapy [5]), which can be delivered locally. Further improvement can be expected in terms of the physical and chemical conditions under which PIPAC is performed. Specifically, the feasibility of hyperthermic PIPAC (hPIPAC) [18] as well as electrostatic precipitation of therapeutic aerosols [19] has already been demonstrated. Additionally, owing to interval histological and molecular tumor testing between cycles, PIPAC can help facilitate a more personalized treatment for peritoneal metastases. The possibility that PIPAC may develop into a more definitive solution for the treatment of peritoneal carcinomatosis is exemplified by the increasing number of requests for second opinions from patients and physicians alike. This is underscored by the rapid pace at which PIPAC technology has been adopted by medical centers around the world. Taken together, the advent of a minimally invasive, local treatment for peritoneal carcinomatosis is a significant advancement in itself. Whether it might fill a gap in treatment by significantly improving the prospects for patients with peritoneal carcinomatosis remains to be seen.

References

1. Alyami M, Hübner M, Grass F, et al. Pressurized intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. Lancet Oncol. 2019;20:e368–77.
2. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy PIPAC. Ann Surg Oncol. 2013;20:2311–6.
3. Chua TC, Pelz JO, Kerscher A, Morris DL, Esquivel J. Critical analysis of 33 patients with peritoneal carcinomatosis secondary to colorectal and appendiceal signet ring cell carcinoma. Ann Surg Oncol. 2009;16:2765–70.
4. Chua TC, Morris DL, Esquivel J. Impact of the peritoneal surface disease severity score on survival in patients with colorectal cancer peritoneal carcinomatosis undergoing complete cytoreduction and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17:1330–6.
5. Dakwar GR, Shariati M, Willaert W, Ceelen W, De Smedt SC, Remaut K. Nanomedicine-based intraperitoneal therapy for the treatment of peritoneal carcinomatosis – Mission possible? Adv Drug Deliv Rev. 2016;108:13–24.
6. Demtröder C, Solass W, Winnekendonk G, Tempfer C, Reymond MA. Electrostatic Precipitation Pressurized IntraPeritoneal Aerosol Chemotherapy (ePIPAC): first in-human application. Pleura Peritoneum. 2016a;1:109–16.

7. Demtröder C, Solass W, Zieren J, Strumberg D, Giger-Pabst U, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with oxaliplatin in colorectal peritoneal metastasis. Color Dis. 2016b;18:364–71.
8. Elias D, Faron M, Iuga BS, et al. Prognostic similarities and differences in optimally resected liver metastases and peritoneal metastases from colorectal cancers. Ann Surg. 2015;261:157–63.
9. Esquivel J, Piso P, Verwaal V, et al. American Society of Peritoneal Surface Malignancies opinion statement on defining expectations from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with colorectal cancer. J Surg Oncol. 2014;110:777–8.
10. Franko J, Shi Q, Meyers JP, et al. Prognosis of patients with peritoneal metastatic colorectal cancer given systemic therapy: an analysis of individual patient data from prospective randomised trials from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. Lancet Oncol. 2016;17:1709–19.
11. Freund M. On-label – off-label. Gibt es eine sicherheitsgarantie durch regulation? GGW. 2006;2006(4):22–30.
12. Girshally R, Demtröder C, Albayrak N, Zieren J, Tempfer C, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as a neoadjuvant therapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg Oncol. 2016;14:253–9.
13. Glehen O, Gilly FN, Arvieux C, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. Ann Surg Oncol. 2010;17:2370–7.
14. Graversen M, Pedersen PB, Mortensen MB. Environmental safety during the administration of pressurized IntraPeritoneal aerosol chemotherapy (PIPAC). Pleura Peritoneum. 2016;1:203–8.
15. Haidara A, El Balkhi S, Le Marchand, et al. Délivrer la chimiothérapie par pression et aérosol (PIPAC) est supérieure à la CHIP au plan experimental. Poster 198. Journées Francaises d'Onco-Hématologie Digestive, Paris 2016.
16. Hübner M, Teixeira H, Boussaha T, Cachemaille M, Lehmann K, Demartines N. PIPAC–pressurized intraperitoneal aerosol chemotherapy. A novel treatment for peritoneal carcinomatosis. Rev Med Suisse. 2015;11:1325–30.
17. Jensen CT, Vicens-Rodriguez RA, Wagner-Bartak NA, et al. Multidetector CT detection of peritoneal metastases: evaluation of sensitivity between standard 2.5 mm axial imaging and maximum-intensity-projection (MIP) reconstructions. Abdom Imaging. 2015;40:2167–72.
18. Jung DH, Son SY, Oo AM, et al. Feasibility of hyperthermic pressurized intraperitoneal aerosol chemotherapy in a porcine model. Surg Endosc. 2016;30:4258–64.
19. Kakchekeeva T, Demtröder C, Herath NI, et al. In vivo feasibility of electrostatic precipitation as an adjunct to pressurized intraperitoneal aerosol chemotherapy (ePIPAC). Ann Surg Oncol. 2016;23(Suppl 5):592–8.
20. Khomyakov V, Ryabov A, Ivanov A, et al. Bidirectional chemotherapy in gastric cancer with peritoneal metastasis combining intravenous XELOX with intraperitoneal chemotherapy with low-dose cisplatin and doxorubicin administered as a pressurized aerosol: an open-label, Phase-2 study (PIPAC-GA2). Pleura Peritoneum. 2016;1:159–66.
21. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20.
22. Loupakis F, Cremolini C, Masi G, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014;371:1609–18.
23. Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) with low-dose cisplatin and doxorubicin in gastric peritoneal metastasis. J Gastrointest Surg. 2016;20:367–73.
24. Odendahl K, Solass W, Demtröder C, et al. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Eur J Surg Oncol. 2015;41:1379–85.
25. Oyais A, Solass W, Zieren J, Reymond MA, Giger-Pabst U. Occupational health aspects of pressurised intraperitoneal aerosol chemotherapy (PIPAC): confirmation of harmlessness. Zentralbl Chir. 2016;141:421–4.
26. Passot G, You B, Boschetti G, et al. Pathological response to neoadjuvant chemotherapy: a new prognosis tool for the curative management of peritoneal colorectal carcinomatosis. Ann Surg Oncol. 2014;21:2608–14.
27. Reymond MA, Hu B, Garcia A, et al. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. Surg Endosc. 2000;14:51–5.
28. Reymond L, Solass W, Tempfer CB, Reymond MA. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): occupational health and safety management. Adv Exp Med Biol. 2015;87
29. Rezniczek GA, Jüngst F, Jütte H, et al. Dynamic changes of tumor gene expression during repeated pressurized intraperitoneal aerosol chemotherapy (PIPAC) in women with peritoneal cancer. BMC Cancer. 2016;16:654–9.
30. Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. World J Surg Oncol. 2016;14:128.
31. Roulin D, Hübner M, Allemann P, Demartines N. New developments of surgery in 2015. Rev Med Suisse. 2016;13:23–5.
32. Sabaila A, Fauconnier A, Huchon C. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): a new way of administration in peritoneal carcinomatosis of ovarian cancer. Gynecol Obstet Fertil. 2015;43:66–7.

33. Schmid BC, Oehler MK. New perspectives in ovarian cancer treatment. Maturitas. 2014;77:128–36.
34. Schneider MA, Eden J, Pache B, Laminger F, Lopez-Lopez V, Steffen T, Hübner M, Kober F, Roka S, Campos PC, Roth L, Gupta A, Siebenhüner A, Kepenekian V, Passot G, Gertsch P, Glehen O, Lehmann K. Mutations of RAS/RAF proto-oncogenes impair survival after cytoreductive surgery and HIPEC for peritoneal metastasis of colorectal origin. Ann Surg. 2018;268(5):845–53.
35. Solass W, Herbette A, Schwarz T, et al. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: proof of concept. Surg Endosc. 2012;26:847–52.
36. Solass W, Giger-Pabst U, Zieren J, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC): occupational health and safety aspects. Ann Surg Oncol. 2013;20:3504–11.
37. Solass W, Giger-Pabst U, Demtröder C, Strumberg D, Zieren J, Reymond MA. Pressurized IntraPeritoneal aerosol chemotherapy (PIPAC) in mesothelioma. In: Reymond MA, Solass W, editors. PIPAC pressurized intra-peritoneal aerosol chemotherapy – Cancer under pressure. Berlin Boston: De Gruyter; 2014a. p. 171–3.
38. Solass W, Kerb R, Mürdter T, et al. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014b;21:553–9.
39. Solass W, Sempoux C, Carr NY, Detlefsen S, Bibau F. Peritoneal sampling procedures and histological assessment of therapeutic response: Proposal of the Peritoneal Regression Grading Score (PRGS). Pleura Peritoneum. 2016;1:99–107.
40. Tanis PJ. Is prevention of peritoneal dissemination the next step in the treatment of T4 colon cancer? Color Dis. 2016;18:125–6.
41. Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal carcinomatosis: a cohort study. Anticancer Res. 2015a;35:6723–9.
42. Tempfer CB, Winnekendonk G, Solass W, et al. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol. 2015b;137:223–8.
43. U.S. National Institutes of Health. (A) A study with intraperitoneal cisplatin and doxorubicin in recurrent ovarian cancer and peritoneal carcinomatosis (NCT024757729). 2016a. www.clinicaltrials.gov. Accessed 15 Oct 2016.
44. U.S. National Institutes of Health. (B) Study with intraperitoneal cisplatin and doxorubicin in recurrent ovarian cancer and peritoneal carcinomatosis, NCT02475772. 2016b. www.clinicaltrials.gov. Accessed 15 Oct 2016.
45. U.S. National Institutes of Health. (C) Intraperitoneal aerosol chemotherapy in gastric cancer (PIPAC-GA01), NCT01854255. 2016c. www.clinicaltrials.gov. Accessed 15 Oct 2016.
46. U.S. National Institutes of Health. (D) Pressurized intraperitoneal aerosol chemotherapy (PIPAC) applied to platinum-resistant recurrence of ovarian tumor (PARROT), NCT02735928. 2016d. www.clinicaltrials.gov. Accessed 15 Oct 2016.
47. U.S. National Institutes of Health. (E) Study of efficacy and safety of laparoscopic intra-abdominal chemotherapy (PIPAC) performed in patients with peritoneal carcinomatosis from colorectal, ovarian, gastric cancer and primary peritoneal tumors (PI-CaP), NCT02604784. 2016e. www.clinicaltrials.gov. Accessed 15 Oct 2016.
48. U.S. National Institutes of Health. (F) Treating peritoneal carcinomatosis with PIPAC, NCT02320448. 2016f. www.clinicaltrials.gov. Accessed 15 Oct 2016.
49. Vaira M, Robella M, Borsano A, De Simone M. Single-port access for pressurized IntraPeritoneal aerosol chemotherapy (PIPAC): technique, feasibility and safety. Pleura Peritoneum. 2016;142:2275–80.
50. Zhao B, Lee SM, Lee HJ, et al. Variability in assessing treatment response: metastatic colorectal cancer as a paradigm. Clin Cancer Res. 2014;20:3560–8.

Part VIII

Complications of Peritoneal Metastasis and Treatment Options

28 Complications in the Palliative Chemotherapy of Peritoneal Cancer

Marianne Sinn

Summary
Peritoneal cancer and its complications remain among the greatest challenges in oncology. Complications can occur at various time points in the course of malignant metastatic peritoneal disease with different causes, whereby the underlying neoplasia and its typical complications are major determinants of prognosis. The most important clinical symptoms, which can be divided into two main subgroups, are as follows: (1) mechanical disorders of the digestive tract, mechanical ileus/subileus, constipation, paradoxical diarrhea, pain, and compression of intra-abdominal organs (e.g., renal congestion), and (2) disorders of the autonomic nervous system of the abdomen, neuropathic pain, difficulties emptying bowels, feeling of fullness, and paralytic ileus/subileus. Further, it is necessary to determine whether these symptoms were present on initial diagnosis or occurred in the course of the malignant disease and which treatments have already been administered. Other essential factors are how extensive the peritoneal cancer is, the overall prognosis, and the general condition of the patient.

28.1 Introduction

Peritoneal cancer and its complications remain among the greatest challenges in oncology. Complications can occur at various time points in the course of malignant metastatic peritoneal disease with different causes, whereby the underlying neoplasia and its typical complications are major determinants of prognosis.

The most important clinical symptoms, which can be divided into two main subgroups, are listed below:

- Mechanical disorders of the digestive tract: mechanical ileus/subileus, constipation, paradoxical diarrhea, pain, compression of intra-abdominal organs (e.g., renal congestion)
- Disorders of the autonomic nervous system of the abdomen: neuropathic pain, difficulties emptying bowels, feeling of fullness, paralytic ileus/subileus

Further, it is necessary to determine whether these symptoms were present on initial diagnosis or occurred in the course of the malignant disease and which treatments have already been administered. Other essential factors are how extensive the peritoneal cancer is, the overall prognosis, and the general condition of the patient [5].

M. Sinn (✉)
Universitäres Cancer Center, Hamburg-Eppendorf, Hamburg, Germany

Universitätsklinikum Hamburg-Eppendorf, II. Medizinische Klinik und Poliklinik- Onkologie, Hämatologie, Knochenmarktransplantation mit der Sektion Pneumologie, Hamburg, Germany
e-mail: ma.sinn@uke.de; https://www.uke.de/

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_28

Almost all patients with peritoneal cancer receive systemic treatment in the course of their disease, generally chemotherapy with classical cytostatic substances or newer targeted therapy.

In addition to the disorders associated with the disease, complaints and side effects associated with the treatment are particularly relevant to clinical care, whereby the strict separation of these terms is not always possible or necessary.

In order to gain an overview of the various symptoms and the overall condition of a patient with advanced cancer, performing a palliative care assessment (PCA) has been found beneficial. Initially developed for patients on palliative wards, the use of standardized measurement tools can be useful in the development of individualized care plans for many patients [1, 6].

This involves an analysis of the patient's current condition and social situation and the determination of the potential need for care from the multidisciplinary team's perspective. The points outlined in the overview below should be systematically addressed.

28.1.1 Overview Start

Palliative care assessment

- Pain history
- Current physical symptoms and their intensity (including nausea/vomiting, constipation/diarrhea, dyspnea, weakness, fatigue, exhaustion, lymphedema)
- Mobility
- Level of independence
- Ability to perform activities of daily living (ADLs)
- Nutritional status
- Current mental health symptoms and their intensity (including mood, resilience)
- quality of life
- Psychosocial factors
- Social situation

28.1.2 Overview End

The standardized and validated measurement tools that can be implemented include, among others, the MIDOS sum score [15], the ECOG performance status or rather the so-called Karnofsky index [3], and the Distress Thermometer [12]. Further information on palliative care assessment is provided in Chap. 41.

The following side effects and complications are associated with chemotherapy and will be explored in greater detail (in addition, please also refer to [2] Supportive Therapie bei onkologischen PatientInnen):

- Nausea and vomiting, also known as the anorexia-nausea-emesis (ANE) syndrome
- Diarrhea
- Constipation
- Infectious complications
- Fatigue

28.2 Nausea/Vomiting, ANE Syndrome

Nausea and vomiting, or the anorexia-nausea-emesis (ANE) syndrome [14], are among the most common complaints of patients undergoing a tumor treatment program. Emesis is differentiated into acute (onset within 24 hours of treatment begin) and delayed (onset 2–5 days after treatment begin).

The following (potential) causes should be explored with differential diagnosis, whereby the chronology in relation to chemotherapy is of particular importance:

- Inflammations, mechanical obstructions, or toxic irritations of the GI tract
- Central vomiting due to an irritation of the vomiting center in the dorsal portion of the lateral reticular formation or the chemoreceptor trigger zone in the area postrema of the fourth ventricle
- Psychogenic vomiting due to conditioning [17]

The various cytostatics and targeted substances demonstrate very different emetogenic potential; an overview of selected medications is provided in Table 28.1 [17].

The following substances are generally available for the prophylaxis and treatment of nausea and vomiting [8]:

- Glucocorticoids: dexamethasone (4 mg or 8 mg p.o. or i.v.)
- Dopamine antagonists (central blockage of the D2 receptor, peripheral antiemetic effect due to increased gastrointestinal motility: metoclopramide (2–3 × 10 mg p.o. or i.v.); alizapride (2–3 × 50 mg i.v. or 1 × 150 mg p.o.); domperidone (only peripherally effective; 3 × 10–20 mg p.o.)
- Serotonin (5-HT3) antagonists (setrons), e.g., ondansetron (8–16 mg i.v./day, 12–16 mg p.o./day); granisetron (1 mg i.v./day, 2 mg p.o./day).
- Neurokinin-1 (NK1) receptor antagonists, e.g., aprepitant (125 mg p.o. day 1, 80 mg p.o. day 2, 3; or 150 mg i.v. day 1)
- Olanzapine (atypical neuroleptic): 1 × 5–10 mg p.o./day
- Dimenhydrinat (H1-receptor antagonist): 50–400 mg dimenhydrinate p.o./day, 100–300 mg i.v./day

Table 28.1 Overview of selected antineoplastic medications

Vomiting	Selected cytostatics
Stage 5: >90%	Cisplatin ≥50 mg/m^2 Cyclophosphamide ≥1.5 g/m^2
Stage 4: 60–90%	Carboplatin Cisplatin <50 mg/m^2 Cyclophosphamide 0.75–1.5 g/m^2 Doxorubicin ≥60 mg/m^2 Epirubicin >90 mg/m^2 Methotrexate >1 g/m^2
Stage 3: 30–60%	Cyclophosphamide ≤750 mg/m^2 Cyclophosphamide (oral) Doxorubicin 20–60 mg/m^2 Epirubicin <90 mg/m^2 Etoposide (oral) Ifosfamide Irinotecan Methotrexate 250–1000 mg/m^2 Oxaliplatin >75 mg/m^2 Vinorelbine (oral)
Stage 2: 10–30%	Capecitabine Cetuximab Docetaxel Doxorubicin <20 mg/m^2 Doxorubicin liposomal Etoposide Fluorouracil <1000 mg/m^2 Gemcitabine Methotrexate 50–250 mg/m^2 Mitomycin C Paclitaxel, nab-paclitaxel Pemetrexed Topotecan Trastuzumab
Stage 1: <10%	Bevacizumab Erlotinib Gefitinib (oral) Interferon α Methotrexate ≤50 mg/m^2 Sorafenib Sunitinib

28.3 Diarrhea

Severity is categorized according to the National Cancer Institute's Common Toxicities for Adverse Events (NCI CTCAE version 5.0) in five grades (U[18]):

Grade 1: 1–3 stools more per day than prior to treatment
Grade 2: 4–6 stools more per day or nocturnal bowel movements, some abdominal cramps
Grade 3: ≥7 stools more per day, incontinence, severe abdominal cramps—hospitalization required
Grade 4: life-threatening, urgent intervention required
Grade 5: death

Possible causes are typically treatment-related in association with particular substances such as:

- Cytostatics: 5FU or capecitabine, irinotecan, topotecan
- Antibodies: bevacizumab, cetuximab, panitumumab
- Tyrosine kinase inhibitors: erlotinib, sorafenib

However, radiation therapy or operations resulting in short bowel syndrome can also

cause diarrhea. Intake of laxatives or medications to increase motility are also possible explanations, and their administration and potential benefit should therefore be checked regularly.

First-line treatment involves avoidance of certain foods such as dairy products or coffee in addition to adequate hydration and light diet.

Available medications include loperamide, a non-centrally effective antagonist of the μ-opioid receptors of the myenteric plexus. It is given orally in an initial dose of 2–4 mg after each unformed stool to a maximum dose of 16 mg/day. Other medication options are the synthetic somatostatin octreotide (100–150 mg s.c. up to 3 × daily) or a primarily locally effective opium tincture.

Those with persistent, severe diarrhea should be hospitalized to enable the administration of i.v. fluids and the performance of further diagnostic tests (such as investigation for *Clostridium difficile*, colonoscopy, etc.; [11]).

28.4 Constipation

There is no standardized definition of constipation, and the objectivity of symptoms is problematic; therefore, subjective complaints and changes in individual stool habits are the primary focus.

The following diagnostic and medical history steps should be undertaken: record of stool frequency and consistency; imaging to rule out the possibility of mechanical obstruction; and record of medications and accompanying symptoms [1].

Possible causes of constipation are listed below [4]:

- The primary disease itself via gastrointestinal obstruction or neurogenic disorders due to tumor spread
- Side effects of medications (opioids, antidepressants, sedatives, antacids, diuretics, antihistamines, antihypertensives, anticonvulsants, etc.)
- Further consequences of the disease in conjunction with restricted mobility and resulting inactivity, in addition to confusion and depression
- Altered dietary habits as a result of restricted oral nutrition or nausea and vomiting
- Other pre-existing comorbidities such as diabetes mellitus, diverticulitis, hemorrhoids
- The first line of treatment should be dietary changes, such as increased fiber and/or fluid intake
- Laxatives are an essential medication in the treatment of constipation, whereby the following substance classes are available for tumor patients [11]:
- Bulk-forming agents (methylcellulose, dietary fiber)
- Anthraquinone (senna)
- Emollients (docusate)
- Opioid agonists (naloxone, methylnaltrexone, etc.)
- Contrast agents
- Stimulants (senna, bisacodyl, etc.)
- Prokinetic agents
- Prostaglandins
- Serotonin agonists

28.5 Prophylaxis and Treatment of Infections

Infections are known to be one of the commonest causes of death in cancer patients [10]. Febrile neutropenia is a feared complication of chemotherapy. It can be defined as a single incidence of a temperature >38.5 °C or ≥38.0 °C for 1 hour concurrent with a leukocyte count of <1000 cells per microliter or an absolute neutrophil count (ANC) of <500 cells per microliter. For the purposes of prophylaxis and treatment, patients are grouped according to three levels of risk (low, standard, and high risk), whereby patients with solid tumors are more frequently in the low-risk group, for whom the duration of neutropenia is not likely to exceed 5 days. These patients do not require primary prophylaxis with antibiotics or growth factors such as granulocyte colony-stimulating factor (GCSF).

Should fever occur, investigation should be undertaken immediately to identify an underlying

neutropenia and if possible the underlying reason. A calculated antibiotic therapy has to be started immediately. Patients in a stable general condition who are able to tolerate oral food intake can be prescribed oral antibiotics as per guidelines with a penicillin and beta-lactamase inhibitor (e.g., amoxicillin/clavulanic acid 875/125 mg TDS) and a quinolone (e.g., ciprofloxacin 2 × 500 mg; Possinger and Regierer 2012). Prerequisites for this treatment are the absence of signs of a CNS infection, severe pneumonia, or catheter infection. In addition, the patient must have care available and the possibility of immediate transfer to a cancer center if necessary. The effectiveness of the antibiotic regime is to be checked on day 2–3 so that, if symptoms persist, adjustment or intensification of treatment is possible [10, 14, 19].

The Multinational Association of Supportive Care in Cancer (MASCC) score also includes the following factors as relevant for categorization in the low-risk group: outpatient treatment; age <60; minimal signs of disease; and absence of hypotension, COPD, and dehydration [9].

Primary intravenous antibiotic treatment is indicated in severe cases (e.g., with piperacillin/Combactam or carbapenem; [19]; 5).

28.6 Fatigue

Fatigue is defined as an abnormal level of tiredness and exhaustion not justified by the activities leading up to it and which only marginally improves with sleep or not at all.

Patients suffering from fatigue experience permanent physical and emotional exhaustion, which affects physical, mental, and social aspects of life and therefore significantly reduces quality of life [20].

The prevalence in patients with malignant disease undergoing antitumor therapy is around 90%, whereby the pathophysiology has not yet been fully explained. Proinflammatory cytokines, disorders of the hypothalamic-pituitary-adrenal axis, disorders of the circadian rhythm, and wasting of the skeletal muscles are all considered possible causes [13].

Diagnosis is based on the subjective experience of fatigue. Treatable causes should be eliminated: anemia, thyroid disorders, poor diet, and depression are all potential differential diagnoses, whereby overlap with fatigue is possible and common [7].

A visual analogue scale (VAS) can be used to quantify the severity (0 = no fatigue, 10 = worst imaginable fatigue), whereby scores ≥4 are considered moderate to severe fatigue requiring treatment [16].

A standard fatigue treatment does not exist; pharmacological interventions (e.g., antidepressants, steroids, erythropoietin analogues) have no consistent effect. The best evidence is for regular sport activities, such as (Nordic) walking, treadmill, cycling, or ergometer training. Depending on the situation, nutritional or psycho-oncological support may be advisable. In addition, patients can be counseled to keep a fatigue journal and plan activities in advance [7].

The involvement of psycho-oncologists and the social network are important aspects of care for this complex syndrome.

28.7 Summary

In summary, the treatment of patients with peritoneal cancer necessitates not only interdisciplinary cooperation among the various disciplines but also the various professions involved in care, along with the patient's social network, in order to achieve the optimal treatment result and reduce the rate of side effects and complications.

References

1. AWMF (ed). S3-Leitlinie Palliativmedizin für Patienten mit einer nicht heilbaren Krebserkrankung. www.awmf.org/uploads/tx_szleitlinien/128–001OLl_S3_Palliativmedizin_2015–07.pdf (Zugriff 11.08.2017).
2. AWMF Leitlinie Supportive Therapie bei onkologischen PatientInnen; Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Supportive Therapie bei onkologischen PatientInnen - Langversion 1.3, 2020, AWMF Registernummer: 032/054OL, https://www.leitli-

nienprogrammonkologie.de/leitlinien/supportive-therapie/ (Zugriff am 08.06.2020).
3. Blagden SP, Charman SC, Sharples LD, Magee LRA, Gilligan D. Performance status score: do patients and their oncologists agree? Br J Cancer. 2003;89:1022–7.
4. Clark K, Lam L, Currow DC, Agar M. A Prospective Study to Investigate Contributory Factors That Lead to Constipation in Palliative Care Patients. J Pain Symptom Manage. 2014;47:e1–4.
5. Coccolini F, Gheza F, Lotti M, Virzì S, Iusco D, Ghermandi C, Melotti R, Baiocchi G, Giulini SM, Ansaloni L, Catena F. Peritoneal carcinomatosis. World J Gastroenterol. 2013;19:6979–94.
6. Deutsche Gesellschaft für Palliativmedizin (ed) Palliativmedizinisches Basisassessment. www.dgpalliativmedizin.de/images/DGP_Palliativmedizinisches_Basisassessment_2016.pdf. (Zugriff 11.08.2017).
7. Gerber LH. Cancer-related fatigue: persistent, pervasive, and problematic. Phys Med Rehabil Clin N Am. 2017;28:65–88.
8. Onkopedia Antiemese bei medikamentöser Tumortherapie; 2019; Jordan K, et al. https://www.onkopedia.com/de/onkopedia/guidelines/antiemese-bei-medikamentoeser-tumortherapie/@@guideline/html/index.html; Lambert LA. Looking up: recent advances in understanding and treating peritoneal carcinomatosis. CA Cancer J Clin. 2015;65:284–298.
9. MASCC – Multinational Association of Supportive Care in Cancer (ed). Identifying patients at low risk for FN complications: development and validation of the MASCC risk index score; 2017. www.mascc.org/mascc-fn-risk-index-score (Zugriff 24.08.2017).
10. Maschmeyer G für die Arbeitsgemeinschaft Infektionen in der Hämatologie und Onkologie (AGIHO) der DGHO (ed). Infektionen bei hämatologischen und onkologischen Patienten – Übersicht; 2014. www.onkopedia.com/de/onkopedia/guidelines/infektionen-bei-haematologischen-und-onkologischen-patienten-uebersicht (Zugriff 11.08.2017).
11. McQuade RM, Stojanovska V, Abalo R, Bornstein JC, Nurgali K. Chemotherapy-induced constipation and Diarrhea: pathophysiology, current and emerging treatments. Front Pharmacol. 2016;7:414.
12. NCCN – National Comprehensive Cancer Network (ed). NCCN Distress Thermometer and Problem List for Patients; 2016. www.NCCN.org/patients/resources/life_with_cancer/pdf/NCCN_distress_thermometer.pdf (Zugriff 11.08.2017).
13. NCCN – National Comprehensive Cancer Network (ed). Patient and Caregiver Resources; 2017. www.NCCN.org/patients/resources/life_with_cancer/managing_symptoms/fatigue.aspx (Zugriff 11.08.2017).
14. Possinger K, Regierer AC. Facharzt Hämatologie Onkologie, 2. Aufl. München: Elsevier; 2012.
15. Radbruch L, Sabatowski R, Loick G, Jonen-Thielemann I, Elsner F, Hörmann E. MIDOS--validation of a minimal documentation system for palliative medicine. Schmerz. 2000;14:231–9.
16. Reisenegger I, Weis J. Die Erfassung tumorbedingter Fatigue: Übersicht über Messinstrumente und methodische Probleme. Basel: Karger; 2000.
17. Späth-Schwalbe E. Antiemetische Behandlung bei zytostatischer Chemotherapie. Dtsch Arztebl 98 [Internet]; 2001.
18. U.S. Department of Health and Human Services (ed) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010–06–14_QuickReference_5x7.pdf (Zugriff 11.08.2017).
19. Onkopedia Fieber unbekannter Genese. 2018; Heinz W, et al. https://www.onkopedia.com/de/onkopedia/guidelines/fieber-unbekannter-genese-fuo-bei-neutropenischen-patienten/@@guideline/html/index.html
20. Lambert LA. Looking up: recent advances in understanding and treating peritoneal carcinomatosis. CA Cancer J Clin. 2015;65(4):284–98. https://doi.org/10.3322/caac.21277.

29 Cytoreductive Surgery for Complications of Peritoneal Carcinomatosis

Wolfgang Steurer and Marina Münch

29.1 Introduction

Peritoneal carcinomatosis (PC) results from dissemination and growth of malignant gynecological, gastrointestinal, and peritoneal tumor cells in the abdominal cavity and is considered as an advanced tumor disease with poor prognosis. Due to the impaired response to systemic chemotherapy in the majority of cases, the overall survival is only marginally influenced, with best supportive care as alternative option.

PC is detectable in 15–20% of patients with colorectal cancer (CRC) and up to 40% in patients with stage II–III gastric cancer at the time of the initial diagnosis. In CRC and gastric cancer, manifestation of disease relapse is seen in up to 50% of patients exclusively as tumor progression in the peritoneal space without distant metastasis, and it ultimately leads to death due to loco-regional complications [2].

Recent findings on the physiology of the peritoneum and its central role as a transport membrane for fluids and cells via the serosal surface, as a sliding layer for frictionless mobility of the integument, as an immunological barrier, and finally as regards its function for the repair of surface defects are in strong concert with the notion of PC as a loco-regional disease of the peritoneum [7]. In the initial treatment of a malignant disease of the abdominal cavity, the surgeon's role as key factor for the initiation and promotion of PC according to the "tumor cell entrapment" hypothesis discussed by Sugarbaker is essential, whereas the "natural" course of PC is independent of iatrogenic factors. The clinical presentation and extent of PC in this case is determined exclusively by the biology of the underlying malignant disease and the time of diagnosis. In the following chapter, the most frequent complications in the "natural" course of PC are summarized and the treatment is discussed, which is mostly based on the experience of the authors, since clinical studies are sparse and published data mostly rely on retrospective analyses with inadequate patient numbers. Complications in the "natural course" of PC also include complications during systemic chemotherapy without prior relevant surgical interventions.

W. Steurer (✉)
Department of General and Visceral Surgery, Leonberg Hospital, Leonberg, Germany
e-mail: w.steurer@klinikverbund-suedwest.de

M. Münch
Department of General and Visceral Surgery, Robert-Bosch Hospital, Stuttgart, Germany
e-mail: marina.muench@rbk.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_29

29.2 Clinical Presentation of Peritoneal Carcinomatosis Depending on Tumor Biology

The classical high-risk tumor diseases for developing PC have been covered in detail in previous chapters, so only relevant aspects regarding clinical presentation and the natural course should be mentioned here. A classification including the clinical presentation and/or imaging results depending on the histological subtype does not exist to date. The gastrointestinal mucinous adenocarcinomas include pseudomyxoma peritonei (PMP) and mucinous colorectal adenocarcinomas (MCA). Both tumor entities metastasize almost exclusively into the peritoneal cavity with a similar distribution pattern. PMP is characterized by excessive extracellular mucin production, which eventually leads to maldigestion and death by increasing intraabdominal pressure, enteroenteric fistula formation, or infection. Mucinous colorectal adenocarcinomas are classified as a subtype in 5.1–20% of CRC [9]. Mucus production and deposits correlate histologically for well to moderately differentiated tumors with pools of mucus between atypical glandular structures and with interstitial deposits for poorly differentiated tumors. In contrast, signet-ring cell carcinomas typically appear with intracytoplasmic mucus formation and the known high malignancy potential. MCAs are characterized by a greater likelihood of lymphogenic metastasis and peritoneal dissemination. So far, the prognostic relevance of several subtype classifications is largely unclear [6]. While the AJCC rates the mucinous subtype as prognostically not relevant, other publications show a significantly higher metastasis rate and local relapse probability, especially in stage III and IV rectal cancer. The serous-differentiated carcinomas of the female genital tract and the peritoneum are comparably malignant tumors based on their clinical course. Their diagnosis is, however, delayed and patients typically present at advanced stages due to complications related to tumor growth. The differentiation from mucin-producing tumors is important because of different therapeutic approaches and the better prognosis for serous-differentiated tumors.

29.3 Complications in the Natural Course of Peritoneal Carcinomatosis

The initial phase of peritoneal migration of malignant cells is clinically asymptomatic. Indirect evidence of the presence of peritoneal-disseminated tumor disease is nonspecific and, in most cases, not pathognomonic for a tumor entity. In many cases, fatigue, weight loss, and B-symptoms are misinterpreted initially, and a targeted clarification is frequently delayed. Only local complications of the primary tumor such as pain, intestinal bleeding, obstruction, perforation, and compression or infiltration of adjacent organs accompanied by increase in abdominal circumference due to ascites and mucin production confirm the usually advanced extent of the disease [13]. The primary goal of surgical treatment is therefore not necessarily a potentially curative intervention but the control of acute life-threatening complications, taking into account the possible yet realistic chance for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the further course of the disease (Fig. 29.1).

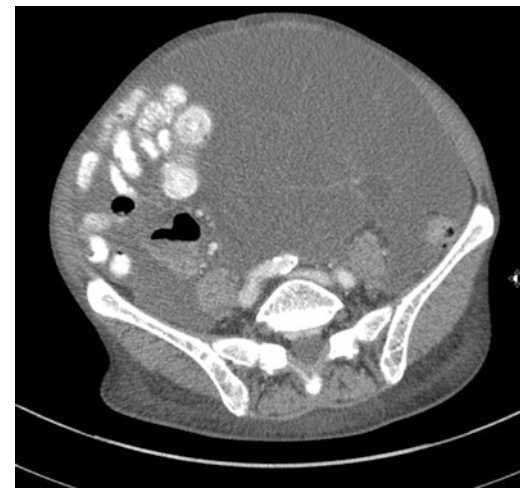


Fig. 29.1 Natural course of PMP: an 87-year-old female patient with the diagnosis of a PMP originating from a "low-grade" mucinous neoplasm of the appendix. Palliative HIPEC with parietal peritonectomy to control mucin formation

Literature on the management of complications in the natural course of the disease and case reports of surgical procedures are extremely rare. CRS contraindications include extensive tumor masses in the peritoneal cavity, the small intestine, and the mesentery; stenoses in the tracts of the small and large intestine; confluent tumor infiltration in the omental bursa and along the hepatoduodenal ligament; infiltration of the ureters and the bile duct; and para-aortic lymph-node infiltration [12]. Inoperability is detected during surgical exploration in about one-quarter of patients with planned CRS. Whether the explorative laparotomy is terminated as such or additional palliative interventions are performed does not appear to adversely affect patient morbidity and mortality. Likewise, an interrupted CRS does not prolong the time interval to initiate chemotherapy. Thus, there is no urgent need to pursue an extended operative strategy in the event of inoperability or PC-associated complications, as this may miss the chance of reoperation with successful CRS. Whether partial cytoreduction aiming for limited tumor debulking in combination with HIPEC is beneficial in the further course of the disease is also questionable. A representative literature review by Heaney and colleagues in 2015 analyzed a total of 19 studies with 2790 cases and CRS +/− HIPEC in PC of colorectal cancer [4]. Of these, 62% had CC0/1 resection (group I) and 35% had incomplete cytoreduction (group II). The median survival of patients with complete cytoreduction ranged between 11 and 62 months compared to 2.4 and 32 months for incompletely resected patients in group II. Patients did not benefit from either incomplete cytoreduction or additional HIPEC in terms of overall survival. However, in most cases, HIPEC resulted in a palliative effect in terms of reduction of ascites, abdominal distension, inappetence, and pain [11].

In summary, the indication for surgical "proactivism" in advanced findings of PC and any associated complications have to be critically discussed. Our own strategy is based on maintaining close communication with our oncologists during operative exploration, paving the way for "pseudoneoadjuvant" chemotherapy with the option of surgical reevaluation of CRS and HIPEC (Fig. 29.2).

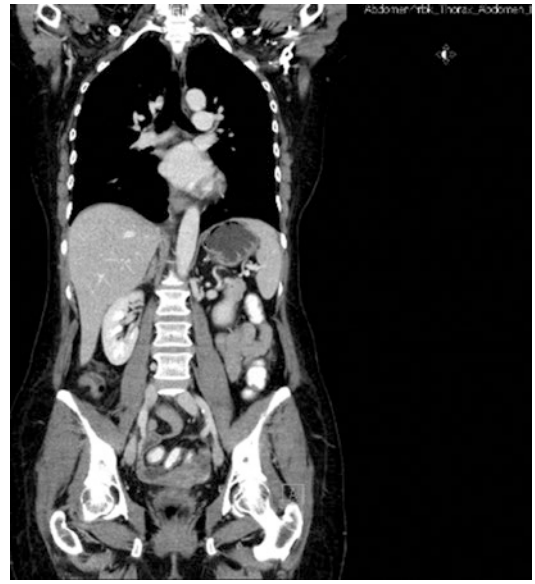


Fig. 29.2 A 53-year-old patient with an incidental finding of advanced peritoneal carcinomatosis in the context of an emergency intervention for suspected perforated appendicitis. Staging CT after laparoscopic right hemicolectomy and histologically verified ovarian cancer

29.4 Management of Peritoneal Carcinomatosis-Associated Intestinal Obstruction

Bowel obstruction due to advanced malignancy is a common complication of disease progression in up to 28% of patients with gastrointestinal tumors and up to 51% of patients with ovarian cancer. In localized or intraluminal processes, surgical intervention is successful in the majority of cases. However, the chance for success is considerably diminished in the case of advanced peritoneal carcinomatosis. Options for treatment include draining procedures of the gastric and small intestinal contents via PEG/PEJ tube (percutaneous endoscopic gastrostomy/jejunostomy), antiemetic and antisecretory concomitant medication in combination with steroids, endoscopic stent placement, or a surgical procedure usually with palliative intent. In 2014, Olson et al.

published a systematic literature review of more than 2000 publications on the significance of surgical interventions in malignant bowel obstruction with regard to palliative success, quality of life and mortality, and complication rate [10]. After appropriate selection, 18 publications with 17 studies remained for the analysis. The spectrum of postoperative complications is characteristic for patients with advanced tumors and is consistent with the expected complications of CRS and HIPEC: With an incidence between 7% and 44%, enterocutaneous fistulas, wound infections, wound dehiscence, early restenosis, high-output stoma, anastomotic leakage, as well as cardiovascular events, such as myocardial infarction, heart insufficiency, deep venous thrombosis, pulmonary embolism, and pneumonia, were observed. Re-obstruction occurred in 6–47% of patients after a short interval of symptom improvement in most of the cases. As expected, the success of a repeated surgical intervention was limited, resulting in permanent inpatient treatment in more than half of the patients (54%). The association with ascites, palpable tumor masses, and chronic obstruction is prognostically unfavorable and has patient survival between 26 and 36 days, which is comparable to palliative measures alone with gastrostomy tube in terms of patient survival (Fig. 29.3).

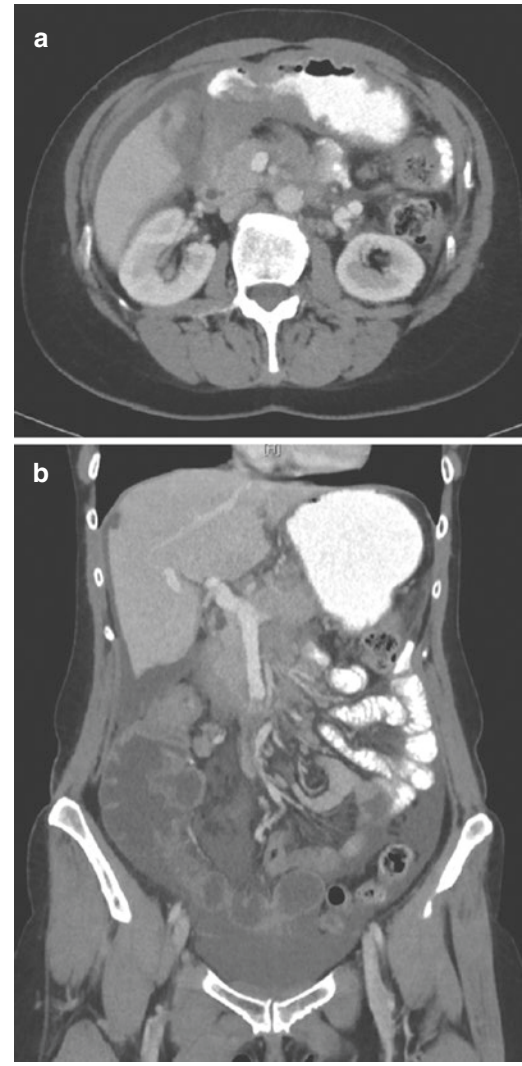


Fig. 29.3 (**a** and **b**) Intestinal obstruction due to gastric cancer with peritoneal carcinomatosis: a 51-year-old patient with advanced peritoneal carcinomatosis of gastric-cancer origin with small and large bowel obstruction as primary manifestation of the disease. An emergency laparotomy followed. Intestinal bypasses with gastro-jejunostomy and ileo-transversostomy were performed

29.5 Peritoneal Carcinomatosis-Associated Intestinal Perforation

Perforations of the gastrointestinal tract due to tumor perforation or perforation of secondary metastasis occur in varying numbers depending on the biology of tumor. The risk of perforation in colorectal tumors is low (1.6%), whereas gynecological malignancies, in particular, are associated with a significantly higher risk [1]. Several factors may be potentially causative: invasive growth of secondary tumor manifestations in the small and large intestine, radiation-related damage to the intestine after primary radiotherapy, and intestinal perforations as a result of anti-angiogenic antibody therapy in the event of a relapse (anti-VEGF mAb bevacizumab). The diagnosis of bowel perforation represents an emergency indication for laparotomy or laparoscopy in the vast majority of cases. A

watch-and-wait approach, however, may well be effective for covered perforation with localized abscess or peritonitis. Adequate therapeutic algorithms are missing at this point, so mostly retrospective data from experienced centers are the basis for decision-making. An analysis of 43 gynecological patients from the Washington University in St. Louis with intestinal perforation identified the total tumor mass as an essential predictor for survival after intestinal perforation [3]. Out of 22 patients with PC or distant metastases, only 4 survived for more than 3 months, regardless of whether a surgical or conservative procedure was taken. The expectedly high complication rate in this patient population and the elevated duration of the hospital stay would argue against an aggressive surgical procedure. 15% of the perforations were classified as a result of anti-VEGF therapy. Although the evidence speaks for a clear survival advantage in anti-angiogenic therapy in the relapse setting, only one patient with intestinal perforation survived longer than 6 months, where a conservative therapeutic regimen was applied despite a lack of PC or distant metastases. Other prognostically unfavorable factors are high ECOG status and low albumin levels at the time of diagnosis [8].

Intestinal perforations related to chemotherapy are observed as a rare complication in the treatment of other tumor entities. In a series of more than 1800 patients with advanced gastric cancer, perforations have occurred in 1.7% of cases [5]. Depending on the degree of tumor differentiation and the response to chemotherapy, median patient survival was limited to 4 months after perforation. The surgical approach (laparoscopic exploration vs. laparotomy) depends on the initial clinical presentation and imaging. In our experience, we prefer a minimally invasive approach to identify perforations, especially in the upper GI tract, even in the case of previously open abdominal interventions, in order to minimize the risk of tumor spreading into the abdominal wall in cases of PC and to minimize wound healing disorders under chemotherapy (Fig. 29.4).

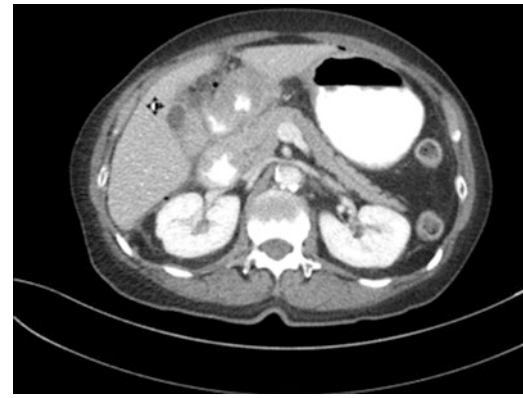


Fig. 29.4 Gastric perforation under neoadjuvant chemotherapy: a 68-year-old patient with a tumor perforation of gastric cancer under chemotherapy. Laparoscopic exploration and closure via mini-laparotomy

29.6 Peritoneal Carcinomatosis-Associated Malignant Ascites and Other Rare Complications

Ascites as the main symptom becomes clinically relevant in about one-third of patients in the natural course of peritoneal metastatic tumor disease. As a result of the increase in intraabdominal pressure due to tumor growth, progressive constipation, weight loss, abdominal pain, nausea, vomiting, and respiratory insufficiency may occur. If the indication for CRS and HIPEC is clear after diagnosis, the presence of ascites is regarded as a negative predictive factor. A retrospective analysis of 1000 cases with CRS and HIPEC showed that ascites production was stopped after 3 months of follow-up in 93% of patients. A complete cytoreduction could be achieved in only 15% of patients with ascites compared to 59% of cases without ascites. Thus, patients with incomplete cytoreduction also benefited from reduced ascites production by undergoing CRS/HIPEC [14].

The rare complications of peritoneal carcinomatosis that we have observed in our patient population include venous thrombosis in the portal system (mesenteric vein thrombosis) and scleros-

ing differentiation of the peritoneum similar to encapsulating sclerosis under chemotherapy. Both changes are detectable with CT imaging before planned surgical exploration and are manifestations of advanced peritoneal metastasis with poor prognosis.

29.7 Conclusion

The utilization of CRS/HIPEC in the management of PC complications is largely dependent on the surgeon's experience and the support from the referring oncologist since controlled trials to establish guidelines are lacking due to the complexity of the disease. The typical complications of peritoneal carcinomatosis, such as intestinal obstruction, perforation, and ascites, are indicative of an advanced stage of the disease with poor prognosis. As part of a multimodal therapeutic concept, the role of surgical therapy, taking into account all therapeutic options, especially modern chemotherapy, should be considered with restraint.

References

1. Cheynel N, Cortet M, Lepage C, Ortega-Debalon P, Faivre J, Bouvier AM. Incidence, patterns of failure, and prognosis of perforated colorectal cancers in a well-defined population. Dis Colon Rectum. 2009;52:406–11.
2. Coccolini F, Gheza F, Lotti M, et al. Peritoneal carcinomatosis. World J Gastroenterol. 2013;19:6979–94.
3. Garg G, Massad LS, Pourabolghasem S, et al. Intestinal perforation in gynecologic oncology: do all patients benefit from surgical management? Gynecol Oncol. 2013;129:538–43.
4. Heaney RM, Shields C, Mulsow J. Outcome following incomplete surgical cytoreduction combined with intraperitoneal chemotherapy for colorectal peritoneal metastases. World J Gastrointest Oncol. 2015;7:445–54.
5. Kang MH, Kim SN, Kim NK, et al. Clinical outcomes and prognostic factors of metastatic gastric carcinoma patients who experience gastrointestinal perforation during palliative chemotherapy. Ann Surg Oncol. 2010;17:3163–72.
6. Lee NK, Kim S, Kim HS, et al. Spectrum of mucin-producing neoplastic conditions of the abdomen and pelvis: cross-sectional imaging evaluation. World J Gastroenterol. 2011;17:4757–71.
7. Lemoine L, Sugarbaker P, Van der Speeten K. Pathophysiology of colorectal peritoneal carcinomatosis: role of the peritoneum. World J Gastroenterol. 2016;22:7692–707.
8. Ng DW, Teo MC, Yee AC, Ng KH, Wong TH. Surgery for the palliation of intestinal perforation from secondary metastases in advanced malignancies. Asia Pac J Clin Oncol. 2016;12:453–9.
9. Numata M, Shiozawa M, Watanabe T, et al. The clinicopathological features of colorectal mucinous adenocarcinoma and a therapeutic strategy for the disease. World J Surg Oncol. 2012;10:109.
10. Olson TJP, Pinkerton C, Brasel KJ, Schwarze ML. Palliative surgery for malignant bowel obstruction from carcinomatosis: a systematic review. JAMA Surg. 2014;149:383–92.
11. Randle RW, Swett KR, Swords DS, et al. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. Ann Surg Oncol. 2014;21:1474–9.
12. Rodt AP, Svarrer RO, Iversen LH. Clinical course for patients with peritoneal carcinomatosis excluded from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg Oncol. 2013;11:232.
13. Spiliotis J, Halkia E, de Bree E. Treatment of peritoneal surface malignancies with hyperthermic intraperitoneal chemotherapy-current perspectives. Curr Oncol. 2016;23:e266–75.
14. Terzi C, Arslan NC, Canda AE. Peritoneal carcinomatosis of gastrointestinal tumors: where are we now? World J Gastroenterol. 2014;20:14371–80.

30 IPEC, HIPEC, Bidirectional Chemotherapy, and Immunotherapy in Aggressive Peritoneal Metastasis

Michael A. Ströhlein

30.1 Complications in the Natural Course of Peritoneal Carcinomatosis

The typical complications in the natural course of peritoneal carcinomatosis include increased suffering and significant deterioration in the quality of life. They are the obvious result of tumor spread in the peritoneal cavity or on the peritoneal surface and cause characteristic complications:

- Malignant ascites
- Intestinal obstruction – ileus
- Chronic pain

30.2 Malignant Ascites

The occurrence of malignant ascites is a symptom of a far advanced disease and can also be seen as a complication of progression of peritoneal carcinomatosis. In the clinical data of our institution, malignant ascites occurs in 35% of all patients with peritoneal carcinomatosis. Interestingly, in 50% of all patients the malignancy is first diagnosed by evidence of malignant ascites.

M. A. Ströhlein (✉)
Department of Abdominal, Cancer, Vascular and Transplant Surgery, Cologne Merheim Medical Center, Witten/Herdecke University, Cologne, Germany
e-mail: stroehleinm@kliniken-koeln.de

The additional intraabdominal volume caused by the ascites causes typical problems such as dyspnea, chronic pain, nausea, and constipation. Direct symptom-oriented treatment can be achieved by paracentesis, which can promptly reduce intraabdominal pressure or displacement of the intraperitoneal structures. Nevertheless, no prolonged therapeutic effect can be achieved. Systemic chemotherapy may lead to a decrease in ascites, but overall clinical efficacy is low.

From a pathogenetic point of view, several causes are discussed for the occurrence of malignant ascites:

- The peritoneal irritation by tumor cells leads to an increase in secretory activity of the peritoneum.
- Peritoneal carcinomatosis interrupts the physiological circulation of the peritoneal fluid, causing it to accumulate.
- The secretion of peritoneal fluid at the peritoneum is increased by cancer-induced neoangiogenesis and mediators such as vascular endothelial growth factor (VEGF).

The exact causality has not yet been clarified. However, in all theories cancer cell seeding on the peritoneal surface is the central factor. Consequently, effective therapy of peritoneal carcinosis should be localized at the peritoneum and directed against the cancer cells of peritoneal carcinomatosis.

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_30

30.2.1 IPEC, HIPEC, and PIPAC in Malignant Ascites

Basically, there is no contraindication to perform surgical cytoreduction (CRS) and subsequent hyperthermic intraoperative chemoperfusion (HIPEC) in patients with malignant ascites [5, 12, 19]. However, malignant ascites is associated with a high PCI score and/or with far advanced peritoneal carcinomatosis and thus a particularly poor prognosis. Accordingly, in studies on CRS/HIPEC therapy, the efficacy against malignant ascites is not investigated as a defined endpoint. Nevertheless, the performance of classical cytoreduction followed by HIPEC in peritoneal metastatic carcinomas seems to be associated with a therapeutic or preventive effect against malignant ascites. At our institution, in patients with peritoneal carcinomatosis from colorectal cancer, malignant ascites occurred in only 4.8% of patients after CC-0 CRS/HIPEC.

Intraperitoneal chemotherapy (IPEC) has been studied as a treatment for malignant ascites. In a Chinese phase I study, 18 patients with malignant ascites due to gynecological carcinoma underwent intraperitoneal chemotherapy with docetaxel. This leads to a decline in the incidence of paracentesis in addition to demonstrating general clinical feasibility [27]. Docetaxel was also used in patients with gastric carcinoma and peritoneal carcinomatosis and showed intraperitoneal efficacy following intraperitoneal administration in combination with S1 [8]. However, so far no intraperitoneal chemotherapy has been established as the sole therapeutic approach against malignant ascites.

In 2016, a study from China investigated the approach of laparoscopic HIPEC therapy against malignant ascites in patients with nonresectable gastric carcinoma. In this study, a total of 38 patients were treated with three different chemotherapeutic regimens. Hyperthermic chemoperfusion was performed for 120 min. Because of the small size of the treatment groups, some effectiveness against ascites could be assumed, but not conclusively demonstrated.

The overpressure therapy with aerosolized chemotherapy (PIPAC) is currently being investigated as a new intraperitoneal therapy concept. Treatment of malignant ascites has not yet been the focus of studies.

30.2.2 Immunotherapy for Malignant Ascites

The best results for the treatment of malignant ascites were achieved by the clinical establishment of an immunotherapy with the trifunctional antibody catumaxomab. Catumaxomab was approved by the European authorities in 2009 for the intraperitoneal treatment of malignant ascites in peritoneal carcinomatosis by EpCAM (epithelial cell adhesion molecule)-positive carcinoma.

The peritoneal cavity is generally an immunologically privileged space in which all the prerequisites for the induction of a successful immune response are present. In particular, the peritoneum includes macrophages with the potential for antigen processing and presentation as well as T lymphocytes that can mediate specific cytotoxicity [23].

The second prerequisite for effective immunotherapy is the characterization of a defined antigen as an immunological target. For intraperitoneal immunotherapies, the epithelial cell adhesion molecule (EpCAM, CD326) was used [16]. EpCAM is a membrane protein that mediates cell-adhesion effects. EpCAM is overexpressed in carcinomas of the stomach, colon, lung, and prostate and other carcinomas [28, 29]. EpCAM-negative tissues include bone marrow, lymphocytes, endothelium, muscle, and mesenchymal tissue. Due to this property, immunotherapy in the peritoneal cavity has a favorable effect: The peritoneum is of mesenchymal origin and thus does not express any epithelial antigens. This means that cells with the EpCAM antigen on the surface in the peritoneum can be specifically identified and attacked as tumor cells.

This effect was exploited in the concept of immunotherapy of peritoneal carcinomatosis with catumaxomab, since catumaxomab has a binding site against EpCAM.

Catumaxomab is a trifunctional antibody consisting of a mouse immunoglobulin G (IgG) 2a

chain and a rat IgG2b chain [14]. Catumaxomab has three functional binding sites: The IgG2a arm binds the human EpCAM antigen. The IgG2b arm binds the human antigen CD3. The third binding site is located on the Fc portion of the antibody and activates Fcγ receptor type I (CD64)-, type IIa-, and type III-positive accessory cells. The simultaneous binding of these three cell types leads to a very effective destruction of tumor cells. The integration and activation of accessory cells results in the processing of tumor antigens with subsequent antigen presentation. This interaction leads to the expression of costimulatory molecules and cytokines, resulting in a physiological "second signal" of T cell activation. This leads to the proliferation of the T lymphocytes and avoids the physiological apoptosis that would occur without re-stimulation. The resulting destruction of the tumor cells occurs via different mechanisms: cell-mediated cytolysis via perforin and granzyme B, cytotoxicity by TNFα and IFNγ, and phagocytosis via the activation of accessory cells [15, 21, 30].

Catumaxomab has been studied as an intraperitoneal immunotherapy in pilot studies in patients with peritoneal carcinomatosis and malignant ascites. The extremely effective tumor-cell destruction in malignant ascites was associated with a clinical effect of a reduction or disappearance of malignant ascites [11]. After confirming this clinical effect in an additional study of ovarian cancer [2], a randomized phase II/III study was performed. The study investigated patients with symptomatic ascites in EpCAM-positive carcinomas, stratifying between patients with ovarian cancer and non-ovarian carcinoma. Patients in the treatment group received four intraperitoneal catumaxomab applications, whereas in the control group only paracenteses were performed. Puncture-free survival was defined as the primary endpoint of the study. In total, 258 patients were enrolled. The largest subgroup of the study were patients with gastric carcinoma (51.2%). Catumaxomab therapy significantly prolonged puncture-free survival (37 days versus 14 days) and time to next paracentesis (80 days versus 15 days). In patients with gastric carcinoma, a significant improvement in overall survival was also demonstrated (71 days versus 44 days, $p = 0.03$) [12]. In 2009, catumaxomab was approved by the European Medicines Agency (EMA) for the indication of malignant ascites in peritoneal carcinomatosis EpCAM-positive carcinoma based on these study results.

Catumaxomab remains the only drug therapy with a license for the treatment of peritoneal carcinomatosis with malignant ascites.

30.3 Intestinal Obstruction

Intestinal obstruction in peritoneal carcinomatosis is a major problem in the treatment of peritoneal carcinomatosis. The incidence in patients with peritoneal carcinomatosis is 10–30% in colon cancer and 20–50% in ovarian cancer [6, 7]. In the patient collective of our clinic, the incidence of an ileus situation is 32%. Intestinal obstruction may have either a mechanical or a functional cause. The mechanical obstruction results from an intestinal obstruction by peritoneal carcinomatosis and is a major problem in the treatment of peritoneal carcinomatosis. Functional obstruction results from a motility disorder due to neoplasia of the tumor or secondary mechanisms due to local infections or neuropathies. Another functional problem may be generalized edema of the mucosa of the small and large intestine, resulting in a significant reduction of the bowel lumen.

The few patients who will benefit from surgical treatment are difficult to select. An adequate diagnostic assessment can be made with CT scans: If a clearly localized obstruction can be visualized, which can be surgically resected, there is an indication for surgical therapy. The goal here is to improve the quality of life, as surgical resection cannot be expected to improve survival [13, 20].

Intraperitoneal chemotherapy and HIPEC therapy do not show any direct efficacy against intestinal obstruction without surgical resection. For surgical cytoreduction with HIPEC, there is also a relative contraindication in patients with ileus because of the high perioperative risk.

As a palliative drug alternative, the somatostatin preparation lanreotide is available, which was able to achieve a certain clinical efficacy in a phase II study [17].

30.4 Chronic Pain

The chronic pain syndrome in patients with peritoneal carcinomatosis is a clinical problem with multifactorial causes. The direct tumor infiltration of nerves, the chronic irritation of the peritoneum, chronic swelling of the mucosa, and chronic ileus contribute to a pain syndrome that is difficult to control. Ultimately, therapy takes place in palliative situations using high-dose morphine preparations, which lead to constipation and functional intestinal obstruction.

30.5 Complications after IPEC, HIPEC, PIPAC, Bidirectional Chemotherapy, and Immunotherapy

Regarding complications in and after intraperitoneal therapy, a distinction should be made between the complications of the actual therapy and the complications of surgical procedures such as catheter implantation, laparoscopy, or surgical cytoreduction.

Laparoscopy is a common and safe surgical procedure in patients with peritoneal carcinoma that allows both accurate diagnosis and implantation of intraperitoneal delivery catheters [18]. Nevertheless, there is a risk of intestinal injury with resulting peritonitis, which may hinder or prevent the planned therapy.

30.5.1 HIPEC and IPEC

HIPEC and IPEC lead to side effects and complications due to the inclusion of chemotherapeutic substances in the systemic circulation, which are mainly caused by the side effect profile of the cytotoxic agents used. A wide range of nausea, alopecia, bone marrow depression, etc. may be found. Chemical peritonitis due to the application of chemotherapy to the peritoneal cavity is also possible and has been observed by our group in two patients after HIPEC therapy [10].

Since HIPEC therapy is usually used in combination with extensive cytoreductive surgery, outlining a specific HIPEC-associated complication is very difficult. Ultimately, with HIPEC therapy, almost every form of complication is possible in addition to the "classic" complications such as short bowel syndrome, bleeding, and fistulas. Paul Sugarbaker described pulmonary, cardiovascular, urogenital, neurotoxic, hematological, and infectious complications in a series of 356 patients with peritonectomy and HIPEC [26]. The exact causality with respect to the hyperthermic chemoperfusion is difficult to prove. In this context, it must be stated that extensive cytoreductive surgery alone induces an extensive systemic inflammatory response (SIRS). This situation is then compounded by hyperthermia. However, according to the experience of our HIPEC center, serious complications are mainly determined by the surgical morbidity. In recent publications, morbidity after splenectomy and pancreatic resection was examined as a special surgical problem. Splenectomy was associated with an increased rate of postoperative complications [3]; therefore, spleen preservation should be attempted during cytoreductive surgery. Similar results could be shown with regard to resection of the pancreatic tail. It was also found that the necessity of a pancreatic left resection to achieve a complete tumor resection should not be an exclusion criterion for cytoreduction and HIPEC [4, 22].

30.5.2 PIPAC

Currently, the problem of specific complications as a result of PIPAC therapy cannot be conclusively assessed, as the procedure has so far only been described in a few case series. As a direct consequence of therapy, limited hepatotoxicity and nephrotoxicity have been described [1]. In a small case series, the concept was used as a neo-

adjuvant therapy for cytoreduction and HIPEC [9]. The publication did not describe any special complications.

30.5.3 Intraperitoneal Immunotherapy

Intraperitoneal immunotherapies are primarily associated with a systemic immune response in the sense of a systemic inflammatory response syndrome (SIRS), which determines the toxicity of the therapy [24, 25]. The observed side effects are short-lived and reversible. Long-term complications do not arise after intraperitoneal immunotherapy. In individual cases a laparoscopy or a laparotomy after catumaxomab therapy was performed at our center. There were no special intraperitoneal problems here. In particular, the fear of adhesions after intraperitoneal immunotherapy could not be confirmed.

30.6 Summary

Typical complications in the natural course of peritoneal carcinomatosis include malignant ascites, intestinal obstruction, and chronic pain. Paracentesis is the symptomatic therapy for malignant ascites. HIPEC seems to be therapeutic and preventive. The best results could be shown for intraperitoneal catumaxomab therapy. Intestinal obstruction is difficult to treat. Surgical indications arise only with localized stenoses. The chronic pain problem requires multidisciplinary palliation.

References

1. Blanco A, Giger-Pabst U, Solass W, Zieren J, Reymond MA. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). Ann Surg Oncol. 2013;20:2311–6.
2. Burges A, Wimberger P, Kumper C, et al. Effective relief of malignant ascites in patients with advanced ovarian cancer by a trifunctional anti-EpCAM x anti-CD3 antibody: a phase I/II study. Clin Cancer Res. 2007;13:3899–905.
3. Dagbert F, Thievenaz R, Decullier E, et al. Splenectomy increases postoperative complications following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2016;23:1980–5.
4. Downs-Canner S, Ding Y, Magge DR, et al. A comparative analysis of postoperative pancreatic fistulas after surgery with and without hyperthermic intraperitoneal chemoperfusion. Ann Surg Oncol. 2015;22:1651–7.
5. Esquivel J, Elias D, Baratti D, Kusamura S, Deraco M. Consensus statement on the loco regional treatment of colorectal cancer with peritoneal dissemination. J Surg Oncol. 2008;98:263–7.
6. Feuer DJ, Broadley KE. Systematic review and meta-analysis of corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancers. Systematic Review Steering Committee. Ann Oncol. 1999;10:1035–41.
7. Feuer DJ, Broadley KE, Shepherd JH, Barton DP. Systematic review of surgery in malignant bowel obstruction in advanced gynecological and gastrointestinal cancer. The Systematic Review Steering Committee. Gynecol Oncol. 1999;75:313–22.
8. Fujiwara Y, Takiguchi S, Nakajima K, et al. Intraperitoneal docetaxel combined with S-1 for advanced gastric cancer with peritoneal dissemination. J Surg Oncol. 2012;105:38–42.
9. Girshally R, Demtroder C, Albayrak N, Zieren J, Tempfer C, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as a neoadjuvant therapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Surg Oncol. 2016;14:253.
10. Gupta DR, Sangha H, Khanna R. Chemical peritonitis after intraperitoneal sodium thiosulfate. Perit Dial Int. 2012;32:220–2.
11. Heiss MM, Strohlein MA, Jager M, et al. Immunotherapy of malignant ascites with trifunctional antibodies. Int J Cancer. 2005;117:435–43.
12. Heiss MM, Murawa P, Koralewski P, et al. The trifunctional antibody catumaxomab for the treatment of malignant ascites due to epithelial cancer: results of a prospective randomized phase II/III trial. Int J Cancer. 2010;127:2209–21.
13. Laval G, Marcelin-Benazech B, Guirimand F, et al. Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manag. 2014;48:75–91.
14. Lindhofer H, Mocikat R, Steipe B, Thierfelder S. Preferential species-restricted heavy/light chain pairing in rat/mouse quadromas. Implications for a single-step purification of bispecific antibodies. J Immunol. 1995;155:219–25.
15. Lindhofer H, Menzel H, Gunther W, Hultner L, Thierfelder S. Bispecific antibodies target operationally tumor-specific antigens in two leukemia relapse models. Blood. 1996;88:4651–8.
16. Litvinov SV, Velders MP, Bakker HA, Fleuren GJ, Warnaar SO. Ep-CAM: a human epithelial antigen is

a homophilic cell-cell adhesion molecule. J Cell Biol. 1994;125:437–46.
17. Mariani P, Blumberg J, Landau A, et al. Symptomatic treatment with lanreotide microparticles in inoperable bowel obstruction resulting from peritoneal carcinomatosis: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol. 2012;30:4337–43.
18. Marmor RA, Kelly KJ, Lowy AM, Baumgartner JM. Laparoscopy is safe and accurate to evaluate peritoneal surface metastasis prior to cytoreductive surgery. Ann Surg Oncol. 2016;23:1461–7.
19. Pelz JO, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J. Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol. 2009;99:9–15.
20. Romeo M, de Los LGM, Cuadra Urteaga JL, et al. Outcome prognostic factors in inoperable malignant bowel obstruction. Support Care Cancer. 2016;24:4577–4586293.
21. Ruf P, Lindhofer H. Induction of a long-lasting antitumor immunity by a trifunctional bispecific antibody. Blood. 2001;98:2526–34.
22. Schwarz L, Votanopoulos K, Morris D, et al. Is the combination of distal pancreatectomy and cytoreductive surgery with HIPEC reasonable?: results of an international multicenter study. Ann Surg. 2016;263:369–75.
23. Ströhlein MA, Heiss MM. Immunotherapy of peritoneal carcinomatosis. Cancer Treat Res. 2007;134:483–91.
24. Ströhlein MA, Heiss MM. The trifunctional antibody catumaxomab in treatment of malignant ascites and peritoneal carcinomatosis. Future Oncol. 2010;6:1387–94.
25. Ströhlein M, Heiss M. Catumaxomab treatment of peritoneal carcinomatosis from EpCAM-positive cancer: identification of biomarkers with relevance for improved efficacy and survival. J Clin Oncol. 2011;29(15):e13003.
26. Sugarbaker PH, Alderman R, Edwards G, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. Ann Surg Oncol. 2006;13:635–44.
27. Tsubamoto H, Takeuchi S, Ito K, et al. Feasibility and efficacy of intraperitoneal docetaxel administration as salvage chemotherapy for malignant gynaecological ascites. J Obstet Gynaecol. 2015;35:69–73.
28. Went P, Lugli A, Meier S, et al. Frequent EpCam protein expression in human carcinomas. Hum Pathol. 2004;35:122–8.
29. Went P, Vasei M, Bubendorf L, et al. Frequent high-level expression of the immunotherapeutic target Ep-CAM in colon, stomach, prostate and lung cancers. Br J Cancer. 2006;94:128–35.
30. Zeidler R, Mysliwietz J, Csanady M, et al. The Fc-region of a new class of intact bispecific antibody mediates activation of accessory cells and NK cells and induces direct phagocytosis of tumour cells. Br J Cancer. 2000;83:261–6.

Part IX

Perioperative Treatment and Prophylaxis of Treatment-Related Complications

31 Preoperative Management: Risk Assessment, Conditioning, Nutritional Aspects, Special Preparation Including Bowel

Arved Weimann and Luisa Mantovani-Löffler

31.1 Introduction

Nowadays Enhanced Recovery after Surgery (ERAS) should be considered the standard of care even in extended surgery like cytoreduction and intraoperative HIPEC. Therefore, an ERAS program should be followed or may be adapted. First of all it needs cooperation of the well-informed patient. Good adherence to the ERAS protocol (>70%) has shown significantly increased long-term survival in patients undergoing surgery for colorectal cancer [1, 2].

From a metabolic point of view, the challenge is the severe surgical trauma with intraoperative chemotherapy in a patient with diminished immune defense by tumor burden and/or previous chemotherapy.

31.2 Risk Assessment

From the American College of Surgeons database (ACS-NSQIP) impairment of physical function and patient dependency are the main risk factors for postoperative complications and mortality [3]. Therefore, candidates for HIPEC should present with no more than ECOG (Eastern Cooperative Study Group) status 2 [4] (see Table 31.1). Risk assessment can be performed according to the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) or American College of Surgeons National Surgical Quality Improvement Program Surgical Risk Calculator (ACS-NSQIP) [5]. Organ function should be assessed on a regular base:

Table 31.1 Eastern Cooperative Study Group Performance status according to Oken et al. [4]

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

A. Weimann (✉)
Department of General and Visceral Surgery and Surgical Oncology, St. George Hospital, Leipzig, Germany
e-mail: Arved.Weimann@sanktgeorg.de

L. Mantovani-Löffler
Department of Medical Oncology and Hematology, St. George Hospital, Leipzig, Germany
e-mail: Luisa.Mantovani@sanktgeorg.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_31

- Pulmonary: spirometry
- Cardiac: echocardiography
- Liver: liver enzymes, and serum bilirubin including INH and cholinesterase
- Kidney: Split renal clearance, estimated glomerular filtration rate (EGF)

31.3 Metabolic Risk

The disease-related nutritional risk can be easily screened and assessed with the Nutritional Risk Score (NRS) [6] (see Fig. 31.1). This screening tool has been also validated for surgical patients. An observational study in a German tertiary care university center has shown in patients undergoing abdominal surgery diminished food intake in the week before hospital admission a significant risk predictor for postoperative complications [7]. The prognostic impact of preoperative serum albumin for postoperative complications has been shown many times [8]. Therefore, serum albumin should be determined and has been recommended in addition to NSQIP score [9]. Without evidence for hepatic or renal insufficiency, low serum albumin (<35 g/l) is frequently associated with malnutrition. A serum albumin <30 g/l has to be considered critical suggesting to postpone surgery [10].

In 2018, the Gobal Leadership Initiative on Malnutrition (GLIM) has presented a new consensus for the definition of malnutrition endorsed by the major clinical nutrition societies worldwide [11]. As a two-step approach, phenotypic and etiologic criteria have to be fulfilled.

Phenotypic criteria: Nonvolitional weight loss, low body mass index, reduced muscle mass Etiologic criteria: Reduced food intake or assimilation, inflammation, disease burden

Measurement of body composition including skeletal muscle and adipose tissue from a single cross section (L3) in routine computerized tomography has been established and will be most appropriate for high-risk patients [12]. So far, it has not been really implemented in clinical practice.

Recommendations for clinical practice:

- Screening for malnutrition according to NRS on hospital admission or at first contact in the outpatient clinic
- Definition of severe metabolic risk in case of at least one of the following criteria. Weight loss of >10–15% within 6 months, BMI <18.5 kg/m^2, NRS >5, serum albumin of <30 g/l (no hepatic, no renal insufficiency)
- Observation and documentation of food intake
- Monitoring of weight and BMI

Oral supplementation or even enteral/parenteral nutrition therapy may be indicated even in patients without obvious malnutrition, if it is anticipated that the patient will be unable to eat for more than 5 days or have intake of less than 50% of caloric need for seven days [10].

31.4 Prehabilitation

In case of obvious functional and nutritional deficits "prehabilitation" offers a new concept of conditioning in order to make the patient fit for ERAS. Prehabilitation is especially appropriate in the time interval between chemotherapy and surgery. This time period for recovery before surgery is usually about 2–6 weeks and opens a window for well-structured conditioning of the patient in a prehabilitation program [13, 14]. Prehabilitation modules are endurance and resistance exercise training, as well as nutrition therapy and psychological coaching [13]. First results showed significant improvement of cardiopulmonary parameters with diminished oxygen consumption and improvement of quality of life. Regarding postoperative complications and outcome in colorectal cancer patients and those undergoing liver resection no significant benefit could be found [13, 15]. However, in colorectal cancer patients' prehabilitation significantly reduced the surgical stress-induced loss of lean body mass when compared with rehabilitation interventions starting after surgery [16]. A randomized blinded controlled trial investigated per-

Initial screening		
BMI < 20,5 kg/m^2	Yes	No
Weight loss within the last 3 months	Yes	No
Reduced dietary intake within the last week	Yes	No
Severity of the disease	Yes	No

Final screening

Nutritional status	Score	Severity of the disease (metabolic stress)	Score
No or minor weight loss	0	no disease	0
Weight loss > 5% within 3 months, 50 –75% of normal food intake within the last week	1	minor surgery e.g. diagnostic laparoscopy	1
Weight loss > 5% within 2 months *or* BMI =18,5 - 20,5 kg/m^2 *and* impaired general condition *or* 20 – 50% of normal food intake within the last week	2	major abdominal surgery e.g. cytoreductive surgery/HIPEC	2
Weight loss > 5 % within 1 month *or* BMI < 18,5 kg/m^2 and impaired general condition *or* < 25 % of normal food intake within the last week	3	intensive care patient with sepsis (APACHE >10)	3
Age > 70 years	1		

Total score	
0 – 2 No risk for malnutrition	3–7 Risk for malnutrition

Score ≥ 3: the patient is nutritionally at-risk and a nutritional care plan is initiated
Score < 3: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan has to be considered in order to avoid surgery associated weight loss

Fig. 31.1 Nutritional Risk Score (NRS) according to Kondrup et al. [6]

sonalized prehabilitation in 125 high-risk patients undergoing elective major abdominal surgery. Inclusion criteria were age >70 years and/or ASA score III/IV. Patients suffering from postoperative complications, number of complications per patient, and medical complications were significantly lower in the prehabilitation group [17].

Therefore, evidence is growing that prehabilitation may decrease complications and shorten hospital length of stay. This is illustrated by recent systematic reviews and meta-analyses [18, 19]. Summarizing these results there is significant heterogeneity between studies. Suitable target populations and optimum protocols including appropriate supervision have to be defined. Long-term results are missing. Most likely, high-risk patients with functional and nutritional impairment will benefit most. It remains to be elucidated whether other modules should be added whenever appropriate. Results from ongoing trials have to be awaited. Appropriate outpatient modalities in the framework of interprofessional cooperation reimbursed by the healthcare insurances are pending.

31.5 Nutritional Aims

Regarding the severity of trauma and inflammation, optimal conditioning of the patient should be realized in the preoperative period:

The aims are:

- Decrease of catabolism and attenuation of inflammation
- Stimulation of immune defense
- Preservation of the microbiome

31.6 Preoperative Substitution of Caloric Deficiency

The benefits of preoperative enteral or parenteral nutrition therapy for 7–14 days are only evident in patients with severe metabolic risk in agreement with the GLIM criteria (BMI <18.5 kg/m^2, weight loss 10–15%, NRS >5, serum albumin <30 g/l) prior to major gastrointestinal surgery [10].

When parenteral nutrition is given for 10 days preoperatively and continued for 9 days postoperatively, the rate of complications is 30% lower and there is a reduction in mortality [10].

Aiming on the recovery of physiological function and total body protein, a considerable increase can be achieved within 7 days of parenteral nutrition. However, further significant improvement will be obtained within the second week [10].

31.7 Metabolic Conditioning

Hyperglycemia and insulin resistance in inflammatory stress make the concept of preoperative glucose intake based on physiology. Metabolic conditioning – so-called carbohydrate loading – focuses on perioperative normoglycemia with special regard to the avoidance of postoperative insulin resistance and the reduction of perioperative discomfort [2, 10]. In case of normal gastric emptying 2 hrs before surgery, intake of clear fluids may be without harm for the risk of aspiration during anesthesia [10].

While a former Cochrane analysis had found a reduction in hospital length of stay for the glucose drink [20], a more recent meta-analysis including 43 trials with 3110 patients showed a small reduction of hospital length of stay in comparison with fasting only. No benefit was observed in comparison with water and placebo. No reduction in postoperative complication rate was found [21]. It has to be argued that a considerable number of studies had included patients with minor surgery and very short hospital length of stay.

The most recent multicentric randomized study included 662 patients. While significantly less patients had the requirement of 1 dose insulin/day and blood glucose levels >140 mg/dl, no difference in clinical complications could be found [22].

In the guidelines carbohydrate loading is recommended for patients undergoing major surgery in the night before (200 ml) and 2 hrs before surgery (100 ml) [10].

31.8 Immunologic Conditioning

The stimulation of immune defense by appropriate nutritional therapy – so-called immunonutrition – is a challenging concept focusing on the inflammatory and immune responses of patients undergoing major cancer surgery [23]. Stimulation of T-cell antitumoral activity has been experimentally shown for arginine [24]. For the combination of arginine, omega-3-fatty acids, and ribonucleotides, numerous prospective randomized controlled studies and meta-analyses had been performed investigating the pre-, peri-, and postoperative use. Significant benefits were found for the reduction of infectious complications and hospital length of stay [25, 26]. Significant advantages regarding the cost-benefit analysis were shown as well [27].

A more recent meta-analysis focused on patients undergoing gastrointestinal cancer surgery and included data from 16 randomized controlled trials with 1387 ($n = 715$ immunonutrition and $n = 672$ control group). In this meta-analysis the sole use of immunonutrition before surgery again led to a significant decrease of infectious complications when compared with normal diet but also with isonitrogenous standard nutritional supplement (OR 0.52; 95% CI 0.38–0.71, $p < 0.0001$). For the hospital length of stay a significant reduction was found for immunonutrition vs. hospital diet, and a tendency vs. standard nutritional supplement [28].

Immunonutrition was also investigated within an ERAS program. In a randomized controlled study in 264 patients undergoing colorectal surgery, a diet enriched with immunonutrients was compared with a standard oral nutritional supplement and administered 7 days before surgery and continued for 5 days postoperatively. In the immunonutrition group a significant decrease in the rate of infectious complications was found (23.8% vs. 10.7%; $p = 0.0007$) [29]. These results are in favor for the integration of immunonutrition in an ERAS protocol. In the future nutrigenomics may even increase the impact of metabolic and immunologic conditioning according to the anticipated inflammatory response.

The ESPEN guideline recommends the intake of oral nutritional supplements before major surgery, while immunomodulating substrates should be preferred for 5–7 days [26, 30]. Patient compliance may be encouraged. Aiming on the decrease of postoperative infection rate the available data also emphasize continuation of immunonutrition after surgery for 5–7 days [10].

31.9 Special Preparation for Surgery

Stoma
Psychological aspects of potential stoma perception and management have to be communicated before surgery. Counseling by the ostomy therapist should be performed routinely. Appropriate skin areas will be marked preoperatively.

Urological counseling
Related to the foreseen type of surgery urological examination and placement of ureteral stents may be protective.

Bowel preparation
The impact of hyperthermia and chemotherapy on the wall of the bowel and the function of the intestinal barrier has to be taken into account regarding anastomotic healing and the development of septic complications.

Present concepts for the prevention focus on the preservation of the microbiome in the bowel, the maintenance of the intestinal barrier, and immune defense [31]. The shift from physiological microbiome to pathobiome will lead to the loss of bacteria diversity and predominance of virulent species. This shift has been also considered the initiator of local complications in the bowel like anastomotic leakage.

There is an ongoing discussion regarding the impact of mechanical bowel preparation before colorectal surgery [32]. The recent US–ERAS guideline recommends isosmotic bowel preparation in combination with oral antibiotics before elective surgery [33]. A recent meta-analysis of 36 studies (23 randomized, 13

observational) including 21568 patients did not find significant advantages regarding the frequency of anastomotic leakage and hospital length of stay. The conclusion was that mechanical bowel preparation should not be administered routinely prior to elective colorectal surgery [34].

In our patients bowel preparation will be performed slowly within the last week before surgery including nutritional advice for liquid diet like oral nutritional supplements. In many cases a single enema may avoid mechanical bowel preparation the day before surgery.

31.10 Conclusion

Consent exists to make the indication for cytoreductive surgery and HIPEC only in patients with appropriate general and nutritional status. Risk assessment is mandatory using validated tools. In case of functional impairment, the potential of individualized prehabilitation should be considered. Next to functional assessment serum albumin level which is mostly associated with the nutritional status is a prognostic predictor for postoperative complications. In case of serum albumin <30 g/l indication for cytoreductive surgery and HIPEC should be revisited, and surgery should be delayed in favor of conditioning the patient for several weeks. This is especially relevant for the period between the end of systemic chemotherapy and surgery. Supplementing nutritional therapy is required in all patients who are unable to eat more than 50% of caloric needs for more than 7 days before surgery.

References

1. Gustafsson UO, Oppelstrup H, Thorell A, Nygren J, Ljungqvist O. Adherence to the ERAS protocol is associated with 5-year survival after colorectal cancer surgery: a retrospective cohort study. World J Surg. 2016;40:1741–7.
2. Ljungqvist O. Enhanced recovery after surgery – knowing not guessing. JAMA Surg. 2019;154(8):736–7.
3. Meguid RA, Bronsert MR, Juarez-Colunga E, Hammermeister KE, Henderson WG, et al. Surgical Risk Preoperative Assessment System (SURPAS): I. Parsimonious, clinically meaningful groups of postoperative complications by factor analysis. Ann Surg. 2016;264:23–31.
4. Oken MM, Creech RH, Tomey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649–55.
5. Bilimoria KY, Liu Y, Paruchi JL, Zhou L, Knieczik TE, Ko CY, Cohen ME. Development and evaluation of the Universal ACS NSQUIP surgical risk calculator: a decision aide and informed consent tool for patients and surgeons. J Am Coll Surg. 2013;217:833–42, e1–3.
6. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. Educational and Clinical Practice Committee, European Society of Parenteral and Enteral Nutrition (ESPEN) ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22:415–21.
7. Kuppinger D, Hartl WH, Bertok M, Hoffmann JM, Cederbaum J, Küchenhoff H, Jauch KW, Rittler P. Nutritional screening for risk prediction in patients scheduled for abdominal operations. Br J Surg. 2012;99:728–37.
8. Aahlin EK, Tranø G, Johns N, Horn A, Søreide JA, Fearon KC, Revhaug A, Lassen K. Risk factors, complications and survival after upper abdominal surgery: a prospective cohort study. BMC Surg. 2015;15:83. https://doi.org/10.1186/s12893-015-0069-2.
9. Hu WH, Chen HH, Lee KC, Liu L, Eisenstein S, Pamy L, Cosman B, Ramamoorthy S. Assessment of the addition hypoalbuminemia to ACS-NSQIP surgical risk calculator in colorectal cancer. Medicine (Baltimore). 2016;95:e2999.
10. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, Laviano A, Lobo DN, Ljungqvist O, Martindale R, Waitzberg D, Bischoff SC, Singer P. ESPEN guideline clinical nutrition in surgery. Clin Nutr. 2017;36:623–50.
11. Cederholm T, Jensen GL, MITD C, Gonzalez MC, Fukushima R, Higashiguchi T, Baptista G, Barrazzoni R, Blaauw R, Coats A, Crivelli A, Evans DC, Gramlich L, Fuchs-Tarlovsky V, Keller H, Lido L, Malone A, Morgensen KM, Morley JE, Muscaritoli M, Nyulasi I, Prlich M, Pisprasaert V, et al. GLIM criteria for the diagnosis of malnutrition. A consensus report from the global clinical nutrition community. Clin Nutr. 2019;38:1–9.
12. Gomez-Perez SL, Haus JM, Shehan P, Patel B, Mar W, Chaudry V, McKeever L, Braunschweig C. Measuring abdominal circumference and skeletal muscle from a single cross-sectional CT image: a step-by-step guide for clinicians using National Institutes of Health ImageJ. JPEN J Parenter Enteral Nutr. 2016;40:308–18.
13. Gillis C, Buhler K, Bresee L, Carli F, Gramlich l C-RN, Sajobi TT, Fenton TR. Effects of nutritional prehabilitation with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. Gastroenterology. 2018;155:391–410.

14. Steffens D, Young J, Beckenkamp PR, Ratcliffe J, Rubie F, Ansari N, Pillinger N, Koh C, Munoz PA, Solomon M. Feasibility and acceptability of a preoperative exercise program for patients undergoing major cancer surgery: results from a pilot randomized controlled trial. Pilot Feasibility Stud 2021;7:27. https://doi.org/10.1186/s40814-021-00765-8.
15. Dunne DF, Jack S, Jones RP, Jones L, Lythgoe DT, Malik HZ, Poston GJ, Palmer DH, Fenwick SW. Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg. 2016;103:504–12. https://doi.org/10.1002/bjs.10096.
16. Gillis C, Ferton T, Sajobi TT, Minnella EM, Awasthi R, Loiselle SE, Liberman AS, Stein B, Charlebois P, Carli F. Trimodal prehabilitation for colorectal surgery attemuates post-surgical losses in lean body mass: a pooled analysis of randomized controlled trials. Clin Nutr. 2019;38:1053–60.
17. Barberan-Garcia A, Ubre M, Roca J, Lacy AM, Burgos F, Risco R, Mombian D, Balust J, Blanco I, Matinez Pall G. Personalised Prehabilitation in high-risk patients undergoing elective major abdominal surgery: a randomized blinded controlled trial. Ann Surg. 2018;267:50–6.
18. Hughes MJ, Hackney RJ, Lamb PJ, Wigmore S, Christopher Deans DA, Skipworth RJE. Prehabilitation before major abdominal surgery: a systematic review and metaanalysis. World J Surg. 2019;43:1681–68.
19. Lambert J, Hayes L, Keegan T, Subar D, Gaffney C. The Impact of Prehabilitation on Patient Outcomes in Hepatobiliary, Colorectal, and Upper Gastrointestinal Cancer Surgery: A PRISMA-Accordant Meta-Analysis. Ann Surg. 2020 Nov 12. https://doi.org/10.1097/SLA.000000.
20. Smith MD, McCall J, Plank L, Herbison GP, Soop M, Nygren J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. Cochrane Database Syst Rev. 2014;8:CD009161. https://doi.org/10.1002/14651858.CD009161.pub2.
21. Amer MA, Smith MD, Herbison GP, Plank LD, McCall JL. Network meta-analysis of the effect of preoperative carbohydrate loading on recovery after elective surgery. Br J Surg. 2017;104:187–97.
22. Gianotti L, Biffi R, Sandini M, Marrelli D, Vignali A, Caccialanza R, Vigano J, Sabbatini A, Di Mare G, Alesiani M, Antomarchio F, Valsecchi MG, Bernasconi DP. Preoperative oral carbohydrate load versus plcebo in major elective abdominal surgery (PROCY): a randomized placebo-controlled multicenter phase III trial. Ann Surg. 2018;267:623–30.
23. Alazawi W, Pirmadid N, Lahiri R, Bhattacharya S. Inflammatory and immune responses to surgery and their clinical impact. Ann Surg. 2016;64:73–80.
24. Geiger R, Rieckmann JC, Wolf T, Basso C, Feng Y, Fuhrer T, Kogadeeva M, Picotti P, Meissner F, Mann M, Zamboni N, Sallusto F, Lanzavecchia. A Arginine modulates T cell metabolism and enhances survival and anti-tumor activity. Cell. 2016;167:829–42.
25. Probst P, Ohmann S, Klaiber U, Hüttner FJ, Billeter AT, Ulrich A, Büchler MW, Diener MK. Meta-analysis of immunonutrition in major abdominal surgery. Br J Surg. 2017;104:1594–608.
26. Wong CS, Aly EH. The effects of enteral immunonutrition in upper gastrointestinal surgery: a systematic review and meta-analysis. Int J Surg. 2016;29:137–50.
27. Chevrou-Séverac H, Pinget C, Cerantola Y, Demartines N, Wasserfallen JB, Schäfer M. Cost-effictiveness analysis of immunemodulating nutritional support for gastrointestinal cancer patients. Clin Nutr. 2014;33:649–54.
28. Adiamah A, Skorepa P, Weimann A, Lobo DN. The impact of preoperative immune modulating nutrition on outcomes in patients undergoing durgery for gastrointestinal cancer: a systematic review and meta-analysis. Ann Surg. 2019;27:247–56.
29. Moya P, Soriano-Irigaray L, Ramirez JM, Garcea A, Blasco O, Blanco FJ, Brugiotti C, Miranda E, Arroyo A. Perioperative Standard Oral Nutrition Supplements Versus Immunonutrition in Patients Undergoing Colorectal Resection in an Enhanced Recovery (ERAS) Protocol: A Multicenter Randomized Clinical Trial (SONVI Study). Medicine (Baltimore). 2016;95(21):e3704. https://doi.org/10.1097/MD.0000000000003704.
30. Elia M, Normand C, Norman K, Laviano A, Norman K. A systematic review of the cost and cost effectiveness of using standard oral nutritional supplements in the hospital setting. Clin Nutr. 2016;35:370–80.
31. Alverdy JC, Krezalek MA. Collapse of the microbiome, emergence of the pathobiome, and the immunopathology of sepsis. Crit Care Med. 2017;45:337–47.
32. Dahabreh U, Steele DW, Sha N, Trikalinos TA. Oral mechanical bowel preparation for colorectal surgery. Systematic review and meta-analysis. Dis Colon Rectum. 2015;58:698–707.
33. Holubar SD, Hedrick T, Gupta R, Kellum J, Hamilton M, Gan TL, Mythen MG, Shaw AD, Miller TE, Perioperative Quality Initiative (POQUI) I Workgroup. American Society for Enhanced Recovery after Surgery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on prevention of postoperative infection within an enhanced recovery pathway for elective colorectal surgery. Perioper Med (Lond). 2017;6:4. https://doi.org/10.1186/s13741-017-0059-2.
34. Rollins KE, Javanmard-Emamghissi H, Lobo DN. Impact of mechanical bowel preparation in elective colorectal surgery: A meta-analysis. World J Gastroenterol. 2018;24(4):519–36. https://doi.org/10.3748/wjg.v24.i4.519.

32 Safety Considerations for Intraoperative Use of Cytostatic Agents

Gabriel Glockzin

32.1 Regulations, Labelling, and Work Safety

Dependent on the therapeutic regimen in the context of hyperthermic intraperitoneal chemotherapy (HIPEC), different cytostatic agents are applied intraperitoneally and intravenously. The use of these drugs is restricted by national law and regulations including drug preparation, prescription, the patient's informed consent, and patient and staff safety. Moreover, cytostatic agents are drugs with mutagenic potential. Thus, labelling and the responsibilities of employer and employee are also regulated by law. Every cytostatic agent is accompanied by a safety data sheet (in Europe, the 'EC safety data sheet'), which summarizes all relevant user information such as name of drug, danger symbol, special risks, and drug-specific safety recommendations. This information should be available to all involved staff in the operating room (OR) at any time during and after a HIPEC procedure. Moreover, a staff health and safety plan, workplace-specific and individual risk assessment, and standard operation procedures (SOP) should be established. All medical and nursing staff who have direct contact with the patient during and after HIPEC—including, amongst others, staff in the OR, the intensive care unit, the intermediate care unit, the normal ward, perfusionists, cleaning staff, physiotherapists, consultants, and stomal therapists—have to be regularly informed about the general and personal risk, legal regulations, recommendations, and safety measures for the use of cytostatic agents. Due to the genotoxic potential of the drugs, pregnant staff members should be excluded from work with cytostatic agents as well as patients during and at least 72 h after the HIPEC procedure.

32.2 OR Safety

General safety measures in the OR (Table 32.1) include the posting of hazard signs (Fig. 32.1a) and limiting the number of personnel in the OR during the HIPEC procedure. All remaining staff who have to stay in the OR should wear protective clothing consisting of a surgical gown, surgeon's hood, surgical mask, eye protection, and two pairs of gloves (Fig. 32.2). Wearing special filtration masks is not necessary. Frequent change of the outer pair of gloves after patient contact or contact with potentially contaminated material helps to significantly reduce the risk of contamination. Gloves should be changed at least every 30 min. Direct handling of the cytostatic agents is associated with the highest risk of contamination. Thus, the chemotherapy solution should be prepared in the pharmacy and transferred to OR on

G. Glockzin (✉)
Department of Surgery, Muenchen Klinik Bogenhausen, Munich, Germany
e-mail: gabriel.glockzin@muenchen-klinik.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_32

Table 32.1 Safety measures in the OR

General safety measures
Hazard signs/information for all involved personnel
Limit theatre personnel during HIPEC
Wearing protective clothes
Frequent change of gloves
Care and attention to safety recommendations
Active prevention of contamination
Proper disposal of (potentially) contaminated material
Special safety measures
Preparation and transfer of chemotherapy solution on call
Use of infusion bags with preconnected infusion line
Use of chemotherapy infusion sets
Use of single-use scissors and clamps for HIPEC drain disconnection
Use of closed bags without outlet valve
Availability of a chemotherapy spill kit
Availability of safety data sheets
Regular information and teaching of involved staff
Exclusion of pregnant theatre personnel

call. Moreover, infusion bags with preconnected drug-free infusion lines and Luer-Lock connectors should be preferred to perfusor syringes in order to facilitate contamination-free drug application (Fig. 32.1b). For intravenous application of cytostatic agents, a chemotherapy infusion set should be used that also allows for rinsing of the infusion line (Fig. 32.1c). Another critical step during the HIPEC procedure regarding the risk of contamination is the disconnection of the drains at the end of abdominal chemoperfusion. The HIPEC drains should be cut under protection using impermeable and absorbent fabric. Single-use scissors and clamps should be used and discarded after use (Fig. 32.1d). Commercially available preconnected bag sets might help to reduce the risk of contamination. Moreover, closed bags without an outlet valve should be preferred (Fig. 32.1e). For disposal of contami-

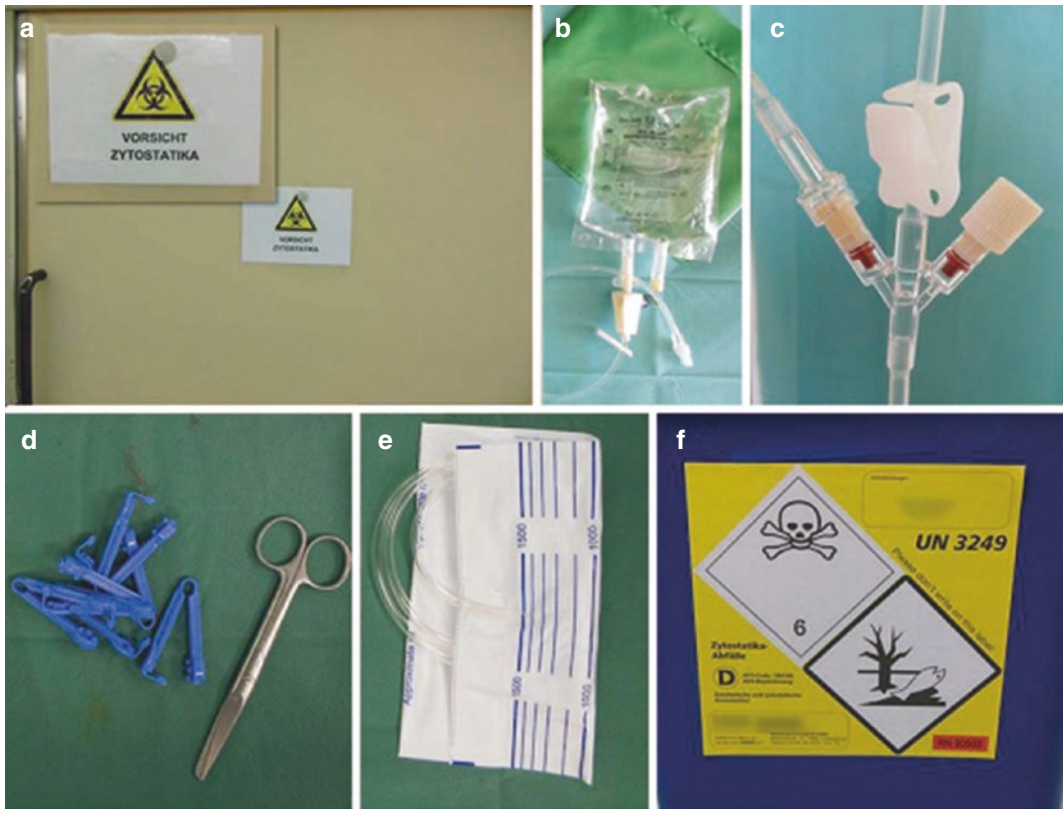


Fig. 32.1 General and specific safety measures in the OR: (**a**) danger signs, (**b**) infusion bags, (**c**) chemotherapy infusion set, (**d**) single-use scissors and clamps, (**e**) closed drain bags without outlet valve, and (**f**) labelled container for cytostatic waste

Fig. 32.2 Protective clothes consisting of surgical gown, surgeon's hood, surgical mask, eye protection, and two pairs of gloves

nated or potentially contaminated material, certified and labelled closable and break-proof single-use containers for cytostatic waste should be used (Fig. 32.1f).

32.3 Action in the Event of Contamination

In the rare event of contamination during a HIPEC procedure, the contaminated area should be kept as small as possible and further dispersion of contaminated fluid should be avoided. Protective clothes should be taken off immediately and disposed of as cytostatic waste. The contaminated area must be labelled and decontaminated by trained personnel. A chemotherapy spill kit should always be available in the OR during a HIPEC procedure. Decontamination starts by soaking up the fluid using soaking pads. Thereafter, the contaminated area is cleaned from the edge to the middle with paper towels and distilled water or other suitable detergents. Schierl et al. [6] have shown that 90% of a cytostatic agent is removed after the first cleaning of contamination with platinum-containing drugs. Thus, three cleaning cycles seem to be sufficient for complete decontamination. Contaminated skin should be rinsed with water immediately. Medical consultation is recommended. Moreover, the responsible person for HIPEC safety should be informed immediately to allow for consistent contamination management and evaluation as well as adjustment of safety regulations and standard operating procedures, if necessary.

32.4 OR Staff Safety

The personnel in the OR may be exposed to cytostatic agents during a HIPEC procedure through direct drug exposure, exposure to perfusate, contaminated material such as instruments or towels, to body fluids and tissues, or inhalation of aerosols. Several studies investigating contamination with mitomycin C, oxaliplatin, or cisplatin in the context of HIPEC have shown that, independent of the HIPEC method, there were no elevated levels of cytostatic agents in the urine or blood of the OR personnel involved [1, 3, 4]. Moreover, no elevated air concentrations of cytostatic agents by formation of aerosols could be detected in the OR using HIPEC regimens with cisplatin [2] or mitomycin C [7, 8]. In conclusion, existing data suggests that under observance of safety measures (Table 32.1), there is no elevated health risk for OR personnel regarding the exposition to cytostatic agents during HIPEC procedure.

32.5 Patient Safety

Beyond staff safety and health protection, patient safety plays a pivotal role using cytostatic agents in the OR. For example, according to the guidelines of the American Oncology Nursing Society for the application of systemic chemotherapy [5], before the application of cytostatic agents in the context of HIPEC, the following parameters must be verified by at least two persons: cytostatic agents, therapeutic regimen, dosage, volume, route of application (intravenous or intraperitoneal), timing, temperature, correct allocation, and integrity of cytostatic agents. Patient identity is routinely verified during preoperative team time-out in the OR. In any case, application of the wrong cytostatic agent and/or the wrong dose should be regarded as a 'Never event'. Increased risks when using bi-directional HIPEC regimens should also be taken into account.

References

1. Gonzalez-Moreno S, Gonzalez-Bayon L, Ortega-Perez G. Hyperthermic intraperitoneal chemotherapy: methodology and safety considerations. Surg Oncol Clin N Am. 2012;21:543–57.
2. Konate A, Poupon J, Villa A, Garnier R, Hasni-Pichard H, et al. Evaluation of environmental contamination by platinum and exposure risks for healthcare workers during a heated intraperitoneal perioperative chemotherapy (HIPEC) procedure. J Surg Oncol. 2011;103:6–9.
3. Kyriazanos I, Kalles V, Stefanopoulos A, Spiliotis J, Mohamed F. Operating personnel safety during the administration of Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Surg Oncol. 2016;25:308–14.
4. Naslund Andreasson S, Anundi H, Thoren SB, Ehrsson H, Mahteme H. Is platinum present in blood and urine from treatment givers during hyperthermic intraperitoneal chemotherapy? J Oncol. 2010;2010:649719.
5. Neuss MN, Polovich M, McNiff K, Esper P, Gilmore TR, et al. 2013 updated American Society of Clinical Oncology/Oncology Nursing Society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. J Oncol Pract. 2013;9:5s–13s.
6. Schierl R, Novotna J, Piso P, Bohlandt A, Nowak D. Low surface contamination by cis/oxaliplatin during hyperthermic intraperitoneal chemotherapy (HIPEC). Eur J Surg Oncol. 2012;38:88–94.
7. Schmid K, Boettcher MI, Pelz JO, Meyer T, Korinth G, et al. Investigations on safety of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) with Mitomycin C. Eur J Surg Oncol. 2006;32:1222–5.
8. Stuart OA, Stephens AD, Welch L, Sugarbaker PH. Safety monitoring of the coliseum technique for heated intraoperative intraperitoneal chemotherapy with mitomycin C. Ann Surg Oncol. 2002;9:186–91.

33 Preventing Complications of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Christoph Raspé and Franz Florian Rückert

33.1 Perioperative Complications

About 40% of all patients suffer at least one perioperative complication after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), with a small number needing ICU intervention for organ support. Despite chemotherapy-induced nephropathy and extensive perioperative volume/fluid shifts, the incidence of acute kidney injury with the need for renal replacement therapy is low (1.3–5.7%) [4], although many patients have a temporary increase in serum creatinine levels. Perioperative kidney injury is an important independent risk factor increasing mortality as much as 6.5 times. As a result a detailed risk assessment with focus on renal function should be performed preoperatively. Risk factors include chronic kidney disease, high BMI, hyperglycemia, preoperative hypoalbuminemia, scheduled OR time over 600 minutes, transfusion of blood products, and an expected blood loss of over 60 ml/kg [4].

In addition, perioperative optimization of fluid balance, cardiac output, and oxygen supply should be achieved through the implementation of goal-directed therapy and the use of hemodynamic monitoring (see Chap. 35). Furthermore, nephrotoxic drugs should be avoided whenever possible, and an adequate renal perfusion should be sought. Perioperative pulmonary complications are also a major cause of morbidity after CRS and HIPEC procedures. Non-invasive ventilation or nasal high-flow systems should be used prophylactically after extubation to avoid atelectasis and reduce recruitment/de-recruitment damage, and thoracic epidural anesthesia should be implemented routinely for preventative therapy [8]. Septic shock is the leading cause of death after CRS and HIPEC. Optimal perioperative thermoregulation, improved fluid management, and multimodal pain therapy should be a focus for every anesthesiologist.

Other complications that should be considered perioperatively are the side effects of chemotherapy such as anaphylactic reactions, hypomagnesaemia following cisplatin application with the risk of amiodarone-refractory ventricular tachycardia, long QT syndrome following cisplatin infusion, arrhythmias or cardiomyopathies after doxorubicin or mitomycin C treatment, hyponatremia, lactate acidosis, or hyperglycemia after HIPEC with oxaliplatin in a dextrose-based carrier solution.

C. Raspé (✉)
Department of Anesthesiology, Operative Intensive Care Medicine and Pain Therapy, Vivantes Auguste-Viktoria- and Wenckebach-Clinic, Berlin, Germany
e-mail: Christoph.Raspe@vivantes.de

F. F. Rückert
Department of Anesthesiology, Ernst von Bergmann Clinic, Potsdam, Germany
e-mail: Florian.Rueckert@klinikumevb.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_33

33.2 Thermoregulation

▶ Maintaining normothermia throughout the procedure is an important goal during perioperative management.

During CRS, hypothermia should be minimized given the large abdominal wound surface. This can be achieved through convective heat or heated infusions. Perioperative hypothermia is a common complication and occurs in up to 70% of all cases. Consequences of hypothermia may include increased blood loss through the attenuated platelet and clotting-factor function, increased incidence of wound infections, weakened immune system, and tachycardia with increased oxygen consumption as well as potential myocardial ischemia and cardiac arrhythmias [5].

Systemic hyperthermia is also a possible risk due to the intra-abdominal temperatures of up to 42 °C during HIPEC. This can lead to an increased metabolic rate and oxygen imbalance with consequent tachycardia, increased end-tidal CO_2 levels, and metabolic acidosis. In addition, the development of myocardial ischemia is a potential complication, especially in patients with pre-existing coronary heart disease [5]. Pulmonary edema, ARDS, and neurocognitive dysfunction are possible. Furthermore, it has been shown that temperatures above 42 °C can lead to neurological and electrophysical changes in peripheral nerves such as the phrenic nerve, the vagus, and the recurrent laryngeal nerve, resulting in dysfunction and dysesthesia [5].

33.3 Coagulation Management

▶ CRS and HIPEC is often associated with significant blood loss [8].

This is due not only to the extent of the surgical procedure but also to an increased bleeding tendency, which is due to coagulation disorders in the context of hypo-/hyperthermia and to chemotherapeutic agents, cancer entity, or hemodilution and fluid shifts.

About one-third to one-half of patients require perioperative red blood cell concentrates. It should be kept in mind that allogeneic blood transfusions are an independent prognostic risk factor for the long-term survival of cancer patients. Blood transfusions are associated with increased morbidity and mortality in oncological surgery. For this reason, in addition to minimally invasive surgical work, the use of a cellsaver and consecutive radiotherapy with 50 Gy to eliminate tumor cells and retransfusion are an option to reduce allogeneic blood transfusions. Irradiated cellsaver blood has a markedly higher rate of morphologically intact red blood cells with higher levels of 2,3-diphosphoglycerate than allogenic RBCs [2, 3, 8]. Further prospective studies are needed to establish the long-term effects of irradiated cellsaver blood in cancer patients. In any case, the transfusion regime should be restrictive. Of course, the transfusion trigger depends on many perioperative factors, including patient morbidity, but the "cross-section guidelines of the German Medical Association on blood component therapy" with a transfusion trigger of 6–8 g/dl (3.7–5.0 mmol/l) should serve as a manifest basis [2].

About one-third of all HIPEC patients develop a clinically relevant bleeding tendency intraoperatively, resulting in a high transfusion rate of fresh frozen plasma (FFP). An international survey showed that >60% of all HIPEC centers perform pre-emptive therapy with FFP before any coagulopathy is evident clinically [1]. Routine application of FFP is currently performed in almost half of all HIPEC centers, whereas only 14% reported regular administration of tranexamic acid. A fall in fibrinogen levels may trigger bleeding during CRS and HIPEC. A regime of tranexamic acid and cryoprecipitate has shown promise in reducing the need for FFP or red blood cell concentrates [10]. In this context, it should be pointed out again that, following European and German transfusion guidelines ("cross-sectional guidelines" [2]), the transfusion of FFP is recommended only in patients with clinically evident bleeding after substitution of single factors such as fibrinogen or PPSB and exclusion of hyperfibrinolysis, since the applica-

tion of FFP is associated with an increased risk of developing multi-organ failure and ARDS. Some HIPEC centers confirm this approach and report a significantly reduced transfusion rate of FFP of only 5% [4].

In more than 90% of all HIPEC centers, coagulation management so far has been controlled by standard coagulation laboratory parameters. Only about a fifth of all hospitals surveyed control coagulation by point-of-care (POC) systems such as thromboelastometry and/or platelet function analyzers [1]. However, it has been shown that, with the aid of these POC systems, the complex pathophysiological changes in coagulation are analyzed much better perioperatively and could be targeted better. Therefore, these devices may have an important role to play in coagulation management of patients undergoing CRS and HIPEC [8]. Last but not least, pre-emptive administration of 1 g tranexamic acid should be considered every 8 hours to prevent hyperfibrinolysis in patients with CRS and HIPEC since this can reduce blood loss and the use of red cell transfusions. A recent study has shown human fibrinogen concentrate may also be useful in managing bleeding during CRS and HIPEC when used with thromboelastometry [9].

33.4 Pain Therapy

▶ It is generally accepted and evident that thoracic epidural anesthesia supplementing general anesthesia in the control of perioperative pain is clearly superior to general anesthesia alone.

Epidural anesthesia (EA) allows early postoperative extubation and mobilization, reduces postoperative pulmonary complications, reduces morbidity after CRS and HIPEC, and significantly improves patient satisfaction [8]. Postoperative ventilation was significantly shortened in patients after HIPEC, and the application of intravenous opioids, which in turn can lead to complications such as gastric atony, was reduced [5, 8]. It is not surprising that some studies have observed a significant reduction in postoperative ileus with epidural anesthesia. Many patients who undergo CRS and HIPEC are dependant on opioids pre-operatively with chronic pain and reduced quality of life, so adequate postoperative pain management can be challenging but is vital.

Supportive EA is now regarded as the gold standard in patients undergoing CRS and HIPEC. With EA it was possible to significantly reduce opioid and non-opioid analgesia as well as numeric rating scale (NRS) levels within the first 60 h after surgery. Residual functional capacity and vital capacity as well as the FEV1 of the lungs were improved and the balance between oxygen consumption and uptake reduced the risk of myocardial ischemia [5]. The fear that EA-induced sympathetic blockade together with the systemic effects of HIPEC leads to hemodynamic instability is unjustified, since these thermodynamic alterations can be avoided with targeted optimization of fluid administration [8].

As thrombocytopenia and coagulation disorders are often seen following CRS and HIPEC, an increased risk of an epidural hematoma has been suggested. Recent studies have shown that, for patients undergoing CRS and HIPEC, epidural anesthesia is a safe treatment option, and the risk of epidural hematoma is not higher than other surgical groups (1:6628) [6]. Considering that the main reasons for an epidural hematoma are the insertion of the catheter and a difficult and traumatic puncture, preoperative detailed coagulation tests as well as an atraumatic puncture and catheter insertion by an experienced anesthetist appear to reduce the risk of bleeding complications.

Finally, retrospective clinical investigations have shown an improvement in the long-term outcome and a reduction in metastatic growth after cancer surgery with supplemental EA [8]. Currently, three quarters of all HIPEC centers perform supportive EA [1, 7, 11].

33.5 Monitoring

Not all patients need to be monitored in the ICU after CRS and HIPEC procedures. Depending on the Eastern Cooperative Oncology Group

(ECOG) performance status, the patient's nutritional status, age, suspected blood loss, and the extent of cytoreduction, the indication for intensive care monitoring should be rigorous and take into consideration the potential complications such as the risk of infections and the costs of ICU stay.

In practice, most of the patients (67–100%) are admitted postoperatively to the ICU, as the fluid loss of up to 10 liters per day within the first 72 h after surgery is very high. It is similar with perioperative coagulation disorders and the ensuing bleeding, which usually occur within the first 24 h after surgery before returning to normal.

33.6 Conclusion

In order to avoid perioperative complications, the anesthesiologist and intensive care physician should focus especially on fluid management, thermoregulation, coagulation therapy, and adequate pain management.

References

1. Bell JC, Rylah BG, Chambers RW, Peet H, Mohamed F, Moran BJ. Perioperative management of patients undergoing cytoreductive surgery combined with heated intraperitoneal chemotherapy for peritoneal surface malignancy: a multi-institutional experience. Ann Surg Oncol. 2012;19:4244–51.
2. Bundesärztekammer. Querschnitts-Leitlinien (BÄK) zur Therapie mit Blutkomponenten und Plasmaderivaten. 2014. www.bundesaerztekammer.de/fileadmin/user_upload/downloads/QLL_Haemotherapie_2014.pdf. Last accessed 31.10.2019.
3. Hansen E, Bechmann V, Altmeppen J. Intraoperative blood salvage with irradiation of blood in cancer surgery: answers to current queries. Anasthesiol Intensivmed Notfallmed Schmerzther. 2002;37:740–4.
4. Kajdi ME, Beck-Schimmer B, Held U, Kofmehl R, Lehmann K, Ganter MT. Anaesthesia in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: retrospective analysis of a single centre three-year experience. World J Surg Oncol. 2014;12:136.
5. Kerscher C, Ried M, Hofmann HS, Graf BM, Zausig YA. Anaesthetic management of cytoreductive surgery followed by hyperthermic intrathoracic chemotherapy perfusion. J Cardiothorac Surg. 2014;9:125.
6. Korakianitis O, Daskalou T, Alevizos L, Stamou K, Mavroudis C, Iatrou C, et al. Lack of significant intraoperative coagulopathy in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) indicates that epidural anaesthesia is a safe option. Int J Hyperth. 2015;31(8):857–62.
7. Osseis M, Weyrech J, Gayat E, Dagois S, Lo Dico R, Pocard M, et al. Epidural analgesia combined with a comprehensive physiotherapy program after cytoreductive surgery and HIPEC is associated with enhanced post-operative recovery and reduces intensive care unit stay: a retrospective study of 124 patients. Eur J Surg Oncol. 2016;42(12):1938–43.
8. Raspé C, Flöther L, Schneider R, Bucher M, Piso P. Best practice for perioperative management of patients with cytoreductive surgery and HIPEC. Eur J Surg Oncol. 2017;43:1013–27.
9. Roy A, Stanford S, Nunn S, Alves S, Sargant N, Rangarajan S, et al. Efficacy of fibrinogen concentrate in major abdominal surgery – a prospective, randomized, controlled study in cytoreductive surgery for pseudomyxoma peritonei. J Thromb Haemost. 2020;18(2):352–63.
10. Sargant N, Roy A, Simpson S, Chandrakumaran K, Alves S, Coakes J, et al. A protocol for management of blood loss in surgical treatment of peritoneal malignancy by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Transfus Med. 2016;26(2):118–22.
11. Teoh DA, Hutton MJH, Else S, Walker A, Lee A, Mack LA. Epidural analgesia? A prospective analysis of perioperative coagulation in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Am J Surg. 2019;217(5):887–92.

34 Nutritional Concepts in Patients with Peritoneal Tumors

Stephan C. Bischoff

34.1 Introduction

Patients suffering from peritoneal tumors, either peritoneal metastases or primary peritoneal tumors such as carcinoma or mesothelioma, frequently suffer from malnutrition. The reasons for malnutrition are manyfold and include anorexia, malassimilation because of motility disorders, adhesions or short bowel syndrome, and tumor cachexia characterized by low-grade inflammation and the release of cachexia-inducing factors from the tumor cells. Therefore, malnutrition is a common complication in patients with peritoneal tumors, and afflicted patients should be carefully examined for malnutrition immediately after diagnosis and in the course of disease. This is of particular relevance since the nutritional status determines to a large extent the quality of life and prognosis.

34.2 The Malnutrition Problem in Patients with Peritoneal Tumors

34.2.1 Epidemiology

The prevalence of malnutrition in patients with peritoneal tumors is not exactly known. Clinical experience implies that the prevalence is very high. With regard to nutritional status and nutritional therapy, there are no fundamental differences between patients with peritoneal metastases such as pseudomyxoma peritonei and patients with primary peritoneal tumors such as carcinoma or mesothelioma. The prevalence of malnutrition in patients with peritoneal metastases can be assumed to be higher than in patients with primary peritoneal tumors because metastatic neoplasms of the peritoneum reflect advanced and uncontrolled disease, which is generally associated with a high probability of malnutrition. In these patients, relevant malnutrition can be expected in at least 50% of patients.

34.2.2 Type of Malnutrition

The typical type of malnutrition in patients with tumors of the peritoneum is "tumor cachexia," which is characterized by a decrease in muscle mass and fat mass as well as subclinical inflammation.

34.2.3 Diagnostics and Malnutrition Assessment

Due to the expected high prevalence of malnutrition in patients with tumors of the peritoneum, every patient who is diagnosed with this problem

S. C. Bischoff (✉)
Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany
e-mail: Bischoff.stephan@uni-hohenheim.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_34

should be screened for malnutrition promptly. Simple, validated screening tools such as the "Nutritional Risk Screening (NRS) 2002" [12] have proven successful.

If such a tool identifies a risk of malnutrition, a more detailed nutritional assessment is indicated. In addition to nutritional parameters—weight, BMI, triceps skinfold, upper arm circumference—and nutritionally relevant laboratory parameters such as albumin, prealbumin (if available), urea, glucose, electrolytes, etc., it is also recommended to measure muscle strength, which is usually reduced in tumor cachexia and which is of prognostic importance [18]. Tumor-associated malnutrition can be further clarified using "bioelectrical impedance analysis" (BIA) and differentiated from malnutrition without cachexia [17].

In addition to the objective tests to determine the nutritional and functional status, the changes in body weight should be carefully monitored and documented. In times when a significant part of the population suffers from obesity, malnutrition due to illness is often overlooked or only recognized late—possibly too late. Both the patient and his relatives as well as the doctor or the nutritionist can overlook such threatening developments in the case of previously obese people.

▶ An unintentional weight loss of more than 5 kg within 3 months or more than 10 kg within 6 months is considered as "significant weight loss" and sufficient for the diagnosis of malnutrition (regardless of BMI). Significant weight loss has been proven to be relevant for the prognosis of the patient.

The criterion "significant weight loss" has become much more important than the criterion "BMI <18.5 kg/m^2" which tumor patients who were previously overweight seldom reach. Significant weight loss must be treated by a suitable specialist in nutritional therapy. The rationale for nutritional screening and assessment in all patients with peritoneal metastases is based not only on the decision for or against nutritional therapy, but also on the fact that the nutritional status is a criterion for the therapy planning itself. The nutritional status—measured here using the PNI ("prognostic nutritional index")—is, for example, an independent predictive factor for the feasibility of cytoreductive surgical therapy in addition to ascites [3].

If the screening has shown no risk of malnutrition, it should be repeated monthly.

34.3 Treatment of Malnutrition in Patients with Tumors of the Peritoneum

34.3.1 Objectives of Nutritional Therapy

Nutritional therapy has several objectives. It is not limited to replacing the failed or restricted oral diet with a medical diet (enteral or parenteral nutrition) in order to maintain and improve the nutritional status. Another important goal is to improve the prognosis and to reduce complications such as infectious diseases. The response to chemotherapy and the feasibility of chemotherapy can also be improved by professional nutritional therapy [1, 21]. The most important goal, however, is to improve the quality of life in patients with advanced disease and a limited prognosis [15].

Objectives of nutritional therapy:

- Maintain or improve nutritional status
- Improve prognosis
- Reduce complications
- Improve feasibility of and response to chemotherapy
- Improve quality of life

34.3.2 Oral Therapy

If screening and assessment have confirmed a risk of malnutrition or manifest malnutrition, nutritional therapy is indicated. This usually begins with nutritional advice from a qualified specialist (certified dietician, nutritionist, or doctor with additional qualifications). The appetite as well as individual intolerance or food aver-

sions should be taken into account. Food intake should be quantified using suitable methods (e.g., plate diagrams, nutritional protocols) and compared with food requirements (e.g., determined using formulas or calorimetry). This makes it possible to create an individualized nutrition plan based on specific needs. The effectiveness of needs-based oral nutrition therapy has been proven [19, 23].

34.3.3 Oral Nutritional Supplements (ONS)/High-Caloric Sip Feeds

If the energy requirement cannot be adequately met by oral nutritional therapy, ONS are indicated. This kind of treatment can be continued for longer time periods, i.e., in the outpatient setting [26]. The effectiveness and acceptance of ONS in tumor patients has been proven [14].

34.3.4 Enteral Nutrition (EN)

The current guideline for "clinical nutrition in surgery" [27] states:

> Medical nutrition is indicated in patients with malnutrition and those without overt malnutrition if it is foreseeable that the patient will be unable to eat orally for more than 7 days postoperatively. The indication also exists for patients who are unable to take more than 60–75% of the recommended amount of energy orally for more than 10 days. For these patients it can be recommended to start medical nutrition (preferably enterally) without delay. (C; strong consensus)

Adequate oral or EN improves not only the nutritional status and quality of life but also the intestinal permeability disorder ("leaky gut"), measured by means of the lactulose/mannitol ratio, which occurs frequently after hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with advanced gastric cancer and peritoneal cancer. The "leaky gut" could almost be prevented by EN; the EN was highly effective compared to placebo and more effective than parenteral nutrition [13].

On the other hand, a few mostly retrospective reports indicated that placement of a tube for EN was not associated with an improved nutritional status [7]. However, these studies do not answer the question whether the indication for an adequate EN should therefore be questioned in general or whether the placement of a tube is not sufficient. The EN must be carried out properly after the tube is placed so that a benefit can be expected (see also Sect. 34.3.5).

Whether EN can be performed in a patient with peritoneal cancer depends on whether there is sufficient intestinal motility. As a rule, EN will be carried out via a nasoduodenal or a nasogastric tube, since percutaneous endoscopic gastrostomy (PEG) is contraindicated in cases of proven peritoneal carcinosis. The EN should be regarded as an interim solution in most cases, especially since it can hardly be practiced as an outpatient action for long periods without PEG. Perhaps a new option is the PTEG ("percutaneous transesophageal gastrostomy tube"), in which the feeding tube is inserted in the neck area and placed in the stomach via the esophagus [22]. This would be an elegant compromise, but experience is limited. If intestinal motility is increasingly restricted, a switch to partial or complete parenteral nutrition must be made. A PEG can then be considered for relief [24]. As a rule, standard formulas are sufficient for EN. A temporary "immunonutrition", for example, before or up to 4 weeks postoperatively, can be considered.

34.3.5 Parenteral Nutrition (PN)

Tumor patients with advanced peritoneal carcinosis are often unable to eat enough orally or enterally, mainly because of increasingly limited intestinal motility. This fulfills the indication for (complete or partial) PN. A retrospective study from Taiwan showed that the prognosis for such patients is variable, but generally short (1–2 months). Ascites was not a relevant prognostic factor, but the nurtritional status, measured here as BMI, was [5].

Another study from the United States examined patients with gynecological tumors and advanced peritoneal cancer who had been treated with gastrostomy stents. These were needed for

an average of 2.2 years after diagnosis. After that, the average life expectancy was limited to 6 weeks. 36% of the patients received PN. Chemotherapy could be carried out significantly more often in these patients than in those without PN, which significantly improved the 10-week prognosis [9].

During PN in particular, it is important to ensure adequate supply of micronutrients. As with other tumor patients, relevant deficiency symptoms may occur otherwise, for example, Wernicke's encephalopathy, which can simply be prevented by administration of thiamine [11].

In the preterminal phase of advanced peritoneal carcinoma, careful assessment of the individual case is essential as far as the indication is concerned, because there are individual, mostly retrospective reports according to which PN did not provide any benefit [6]. However, the studies mostly remain unclear as to whether PN or simultaneous chemotherapy negatively affected the prognosis and whether the type of PN, and not PN per se, caused these effects. In another context, it has been shown that PN, which is supposed to have beneficial effects in these patients, can have negative consequences if, for example, a hypercaloric or too high-fat or too high-sugar PN is carried out. In any case, a "second generation type" of fat (either a mixture of medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) or olive oil instead of LCT only) or a "third generation type" of fat (preparations containing fish oil) should be used. Moreover, serum glucose should be monitored carefully, and, if necessary, individualized insulin therapy in a defined target area should be administered to keep blood glucose levels within the range of 100–160 mg/dl.

The majority of the studies rated PN in patients with peritoneal tumors as safe and successful in terms of survival and quality of life—provided the indication and implementation were correct. For this reason, it is recommended to continue PN after leaving the clinic (see below) [2, 8, 25].

34.3.6 Additional Options in the Palliative Therapeutic Course

Self-expanding stents, such as those used for palliative treatment for stomach stenosis, can also be used in patients with peritoneal cancer [16, 20].

34.3.7 Monitoring During Treatment

Management in the Hospital

It is mandatory to carry out nutritional screening upon admission or when making the diagnosis of peritoneal tumor. The screening should be done by a specialist (e.g., nurse, dietitian, or physician) and repeated monthly. Adequate transfer management is necessary before discharge. For this purpose, the establishment and consultation of an interdisciplinary nutrition team is recommended [4].

Outpatient Management

In many cases, nutritional support must be continued on an outpatient basis, for example, by means of home PN, which can now be carried out safely and effectively with professional care [4].

It is essential to monitor nutritional parameters, functional parameters, and risk parameters in the course of the disease [10], since appropriate adjustments may have to be made, and to regularly review the indication for medical nutrition during treatment.

Conclusion

Parenteral nutrition:

- It is often indicated in patients with peritoneal tumors.
- It can be carried out safely in inpatients and outpatients.
- It improves nutritional status, prognosis, and quality of life.
- It should be checked regularly.

References

1. Alphs HH, Zahurak ML, Bristow RE, Diaz-Montes TP. Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer. Gynecol Oncol. 2006;103:1048–53.
2. Aría Guerra E, Cortés-Salgado A, Mateo-Lobo R, Nattero L, Riveiro J, Vega-Piñero B, Valbuena B, Carabaña F, Carrero C, Grande E, Carrato A, Botella-Carretero JI. Role of parenteral nutrition in oncologic patients with intestinal occlusion and peritoneal carcinomatosis. Nutr Hosp. 2015;32:1222–7.
3. Benizri EI, Bereder JM, Rahili A, Bernard JL, Benchimol D. Ascites and malnutrition are predictive factors for incomplete cytoreductive surgery for peritoneal carcinomatosis from gastric cancer. Am J Surg. 2013;205:668–73.
4. Bischoff SC, Arends J, Dörje F, Engeser P, Hanke G, Köchling K, Leischker AH, Mühlebach S, Schneider A, Seipt C, Volkert D, Zech U, Stanga Z und das DGEM Steering Committee. S3 guideline of the German Society for Nutritional Medicine (DGEM) in cooperation with GESKES and AKE: Medical nutrition in the outpatient area [S3-Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM) in Zusammenarbeit mit der GESKES und der AKE: Künstliche Ernährung im ambulanten Bereich]. Aktuel Ernährungsmed. 2013;38:e101–54.
5. Chen CJ, Shih SC, Wang HY, Sun FJ, Lu SC, Chu CH, Wang TE, Chen MJ. Clinical application of total parenteral nutrition in patients with peritoneal carcinomatosis. Eur J Cancer Care. 2013;22:468–73.
6. Chouhan J, Gupta R, Ensor J, Raghav K, Fogelman D, Wolff RA, Fisch M, Overman MJ. Retrospective analysis of systemic chemotherapy and total parenteral nutrition for the treatment of malignant small bowel obstruction. Cancer Med. 2016;5:239–47.
7. Dineen SP, Robinson KA, Roland CL, Beaty KA, Rafeeq S, Mansfield PF, Royal RE, Fournier KF. Feeding tube placement during cytoreductive surgery and heated intraperitoneal chemotherapy does not improve postoperative nutrition and is associated with longer length of stay and higher readmission rates. J Surg Res. 2016;200:158–63.
8. Disney BR, Karthikeyakurup A, Ratcliffe J, Jones J, Deel-Smith P, Fairhurst A, Maleki K, Cooper SC. Palliative parenteral nutrition use in patients with intestinal failure as a consequence of advanced pseudomyxoma peritonei: a case series. Eur J Clin Nutr. 2015;69:966–8.
9. Diver E, O'Connor O, Garrett L, Boruta D, Goodman A, Del Carmen M, Schorge J, Mueller P, Growdon W. Modest benefit of total parenteral nutrition and chemotherapy after venting gastrostomy tube placement. Gynecol Oncol. 2013;129:332–5.
10. Hartl H, Parhofer KG, Kuppinger D, Rittler P und das DGEM Steering Committee. S3 guideline of the German Society for Nutritional Medicine (DGEM) in cooperation with GESKES and AKE: Special features of monitoring with medical nutrition [S3-Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin (DGEM) in Zusammenarbeit mit der GESKES und der AKE: Besonderheiten der Überwachung bei künstlicher Ernährung]. Aktuel Ernahrungsmed. 2013;38:e90–e100.
11. Kim KH. Wernicke-Korsakoff syndrome in primary peritoneal cancer. Case Rep Oncol. 2013;6:593–7.
12. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22:321–36.
13. Li G, Gu R, Wen X, Wei D, Ming X, Chen H. The effect of early enteral nutrition on hyperthermic intraoperative intraperitoneal chemotherapy-induced mucosal permeability following gastrectomy. JPEN J Parenter Enteral Nutr. 2012;36:213–8.
14. Marienfeld S, Wojzischke J, Lehmann M, Bojunga J. Assessment of the nutritional status and nutritional problems of patients with gastrointestinal tumors: evaluation of the acceptance of high-calorie drinking food [Erfassung des Ernährungsstatus und der Ernährungsprobleme von Patienten mit gastrointestinalen Tumoren: Evaluierung der Akzeptanz hochkalorischer Trinknahrung]. Aktuel Ernährungsmed. 2012;37:P4.
15. McQuellon R, Gavazzi C, Piso P, Swain D, Levine E. Quality of life and nutritional assessment in peritoneal surface malignancy (PSM): recommendations for care. J Surg Oncol. 2008;98:300–5.
16. Mendelsohn RB, Gerdes H, Markowitz AJ, DiMaio CJ, Schattner MA. Carcinomatosis is not a contraindication to enteral stenting in selected patients with malignant gastric outlet obstruction. Gastrointest Endosc. 2011;73:1135–40.
17. Norman K, Smoliner C, Kilbert A, Valentini L, Lochs H, Pirlich M. Disease-related malnutrition but not underweight by BMI is reflected by disturbed electric tissue properties in the bioelectrical impedance vector analysis. Br J Nutr. 2008;100:590–5. https://doi.org/10.1017/S0007114508911545.
18. Norman K, Stobäus N, Smoliner C, Zocher D, Scheufele R, Valentini L, Lochs H, Pirlich M. Determinants of hand grip strength, knee extension strength and functional status in cancer patients. Clin Nutr. 2010;29:586–91. https://doi.org/10.1016/j.clnu.2010.02.007.
19. Poulsen GM, Pedersen LL, Østerlind K, Bæksgaard L, Andersen JR. Randomized trial of the effects of individual nutritional counseling in cancer patients. Clin Nutr. 2014;33:749–53.

20. Rademacher C, Bechtler M, Schneider S, Hartmann B, Striegel J, Jakobs R. Self-expanding metal stents for the palliation of malignant gastric outlet obstruction in patients with peritoneal carcinomatosis. World J Gastroenterol. 2016;22:9554–61.
21. Santarpia L, Alfonsi L, Pasanisi F, De Caprio C, Scalfi L, Contaldo F. Predictive factors of survival in patients with peritoneal carcinomatosis on home parenteral nutrition. Nutrition. 2006;22:355–60.
22. Singal AK, Dekovich AA, Tam AL, Wallace MJ. Percutaneous transesophageal gastrostomy tube placement: an alternative to percutaneous endoscopic gastrostomy in patients with intra-abdominal metastasis. Gastrointest Endosc. 2010;71:402–6.
23. Uster A, Ruefenacht U, Ruehlin M, Pless M, Siano M, Haefner M, Imoberdorf R, Ballmer PE. Influence of a nutritional intervention on dietary intake and quality of life in cancer patients: a randomized controlled trial. Nutrition. 2013;29:1342–9.
24. Vashi PG, Dahlk S, Vashi RP, Gupta D. Percutaneous endoscopic gastrostomy tube occlusion in malignant peritoneal carcinomatosis-induced bowel obstruction. Eur J Gastroenterol Hepatol. 2011;23:1069–73.
25. Vashi PG, Gupta D, Lammersfeld CA, Braun DP, Popiel B, Misra S, Brown KC. The relationship between baseline nutritional status with subsequent parenteral nutrition and clinical outcomes in cancer patients undergoing hyperthermic intraperitoneal chemotherapy. Nutr J. 2013;12:118.
26. Weimann A, Schütz T, Lipp T, Lochs H, Ockenga J, Sieber C, Bischoff SC. Supportive use of drinking food in the outpatient care of adult patients - an algorithm [Supportiver Einsatz von Trinknahrung in der ambulanten Versorgung von erwachsenen Patienten – ein Algorithmus]. Aktuelle Ernährungsmedizin. 2012;37:e1.
27. Weimann A, Breitenstein S, Breuer JP, Gabor SE, Holland-Cunz S, Kemen M, Längle F, Rayes N, Reith B, Rittler P, Schwenk W, Senkal M und das DGEM Steering Committee. Clinical nutrition in surgery, S3 guideline of the German Society for Nutritional Medicine (DGEM) [Klinische Ernährung in der Chirurgie, S3 Leitlinie der Deutschen Gesellschaft für Ernährungsmedizin e.V. (DGEM)]. Chirurg. 2014;85:320–6.

Perioperative Management

35

Wieland Raue, Michael Sander,
and Anja Hawliczek

35.1 Introduction

Extensive cytoreductive surgery in patients with advanced malignant disease frequently results in significant trauma affecting physiologic homeostasis. Preexisting diseases, reduced performance status, and simultaneous intraoperative chemotherapy can increase the risk of morbidity and mortality. In particular, fluid shifts and temperature management can pose challenges. It seems reasonable to use invasive hemodynamic monitoring devices for optimally guided volume and fluid therapy, inotropic support, and vasoconstrictor application.

Postoperative management should adopt well-established programs for enhanced recovery after major gastrointestinal surgery. Close monitoring is required as a result of the increased risk of surgical complication.

A meticulously planned workflow and the use of checklists are recommended because of the complexity of this therapeutic treatment and, particularly, the large number of specialists and units involved.

35.2 Positioning During Anesthesia

Surgeons and anesthetists are both responsible for correct intraoperative patient positioning [3]. A lithotomy position, with the thighs lowered horizontally and with the routine use of a table-mounted retractor system, provides the best possible exposure of the complete abdominal and pelvic cavity. Flexible retractor arms allow continual adjustments and optimal conditions for every step of the resection. The lithotomy position allows ease of access for a transanal stapled anastomosis, for transvaginal manipulation facilitating exposure of the recto-uterine pouch, or for retrograde filling of the urinary bladder. Furthermore, the operating surgeon has the possibility of changing his own position easily, for instance, for better access to the dorsal subphrenic areas.

The insertion of a chest tube should be considered in cases of subdiaphragmatic peritonectomy or intraoperative diaphragmatic injuries.

W. Raue (✉)
Allgemeines Krankenhaus Celle, Klinik für Allgemein-, Viszeral- und Thoraxchirurgie, Celle, Germany
e-mail: wieland.raue@akh-celle.de

M. Sander
Universitätsklinikum Gießen, UKGM GmbH, Justus-Liebig-Universität Gießen, Klinik für Anästhesiologie, Operative Intensivmedizin und Schmerztherapie, Giessen, Germany
e-mail: michael.sander@chiru.med.uni-giessen.de

A. Hawliczek
Zentrum für Akute und Postakute Intensivmedizin, Kreiskliniken Darmstadt-Dieburg, Kreisklinik Jugenheim, Seeheim-Jugenheim, Germany
e-mail: a.hawliczek@kreiskliniken-dadi.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_35

Abducted arm positioning and a broadly fenestrated abdominoperineal drape may also simplify the thoracic access.

Common safety precautions including the padding of vulnerable structures should be applied carefully for prolonged procedure times [18]. Devices for intermittent leg compression can be used to improve venous blood flow in patients while in the lithotomy position.

35.3 Anesthesiological Management

The comprehensive surgical cytoreduction and administration of hyperthermic intraperitoneal chemotherapy (HIPEC) can cause substantial disturbances in fluid homeostasis, altered acid-base balance, and protein losses. Therefore, it is reasonable to apply extended invasive hemodynamic monitoring and to follow the principles of volume-guided early goal-directed therapy. In particular, volume optimization is a basic requirement for the prevention of postoperative complications, particularly for the protection of normal renal functioning. Metabolic changes should be expected, particularly during the hyperthermic perfusion phase. An anticipation of temperature management and normalization of hemostatic function are essential throughout the entire procedure [12, 13, 17].

35.4 Anesthesia

A balance or a combination of general and regional anesthesia is recommended. We prefer total intravenous anesthesia in combination with thoracic epidural application of sufentanil and ropivacaine. Epidural anesthesia offers several advantages: for instance, the possibility of optimal perioperative pain management, which prevents the development of chronic pain, and the reduction in the risk of postoperative pulmonary disorders or myocardial ischemia. Furthermore, the use of thoracic epidural anesthesia can shorten the time of postoperative ileus [7, 13].

The placement of a central venous catheter and measurement of central venous pressure are mandatory. Furthermore, an arterial access line should be inserted. We recommend the use of a device for intensive hemodynamic monitoring, for instance, a transpulmonary thermodilution technique and continuous pulse contour analysis (e.g., PiCCO®), for the estimation of stroke volume and intravascular volume status. This provides exact temperature measurements and allows continuous monitoring of cardiopulmonary function. Repeated calibrations of these monitoring devices should be performed after the induction of anesthesia and regularly in cases of hemodynamic changes. Brain function monitoring (e.g., BIS® or SedLine®) is recommended. Peripheral venous lines for volume replacement, a transnasal feeding tube, and a urinary catheter complete the anesthesiological preparation. Preoperative antibiotic prophylaxis should be administered approximately 30 min before the skin incision. Venous thromboembolic prophylaxis should be discussed with the surgical team.

35.5 Hemodynamic Management and Volume Replacement

Fluid management should focus on the principles of early goal-directed therapy. Preoperative fasting should be kept short. The oral intake of clear liquids can be allowed until 2 h before the induction of anesthesia. But delayed gastric emptying or reduced intestinal motility in patients with peritoneal disease should be kept in mind. The intraoperative volume replacement strategies should be individually adjusted. The following suggestions represent only approximate guidelines. Isotonic colloids should be administered as basic fluid replacement with 3–5 ml/kg body weight per hour. An increased fluid requirement of up to 12 ml/kg/h can be expected during the HIPEC phase due to increasing body temperature, acidosis, and metabolic changes. We use additional colloids of up to 30 ml/kg. The target mean arterial blood pressure (MAP) should

be kept at 60–70 mmHg depending on preexisting conditions and comorbidities. The central venous pressure (CVP) should be <15 mmHg. The stroke volume (SV), stroke volume variation (SVV), and cardiac index (CI) should be assessed after the induction of anesthesia and should be monitored during the complete procedure. The SVV is ideally <12%, and the cardiac index is ideally >2.5 l/min/m^2. A regular reevaluation of hemodynamic parameters for hypovolemia (at least every 30 min, more frequent during the HIPEC phase) should be included in the standardized anesthesiological algorithms. Volume replacement is necessary in cases of decreasing stroke volume, increasing SVV, and a simultaneously declining CI. The first response is a fluid challenge (e.g., 200 ml colloid or crystalloid solution). Successful volume optimization leads to a 10–15% increase in the SV. In that case, a repeated volume challenge can be considered. Crystalloid fluid overload should be prevented, especially overload of the extravascular compartment. Catecholamines should be administered if volume challenges do not lead to aimed cardiac function targets (CI, SVV) or may even cause a further decline. Further indications for differentiated catecholamine therapy may be mixed-venous oxygen saturation (SvO_2) <70% or acidosis despite optimized volume status. The administration of dobutamine to increase the CI should be considered in addition to norepinephrine and/or low dose vasopressin as a vasopressor. Phosphodiesterase-3 inhibitors, such as enoximone or milrinone, could be helpful for patients with pulmonary hypertension or right ventricular impairment. Additional vasopressin can be used as a vasoconstrictor in these patients to avoid the negative effects of norepinephrine on pulmonary blood flow [4, 9, 14, 16].

35.6 Protection of Renal Function

Platinum-based chemotherapy is nephrotoxic even if administered intraperitoneally, and it can increase the preexisting risks of renal failure (e.g., age, chronic renal impairment, cardiac insufficiency, and hepatobiliary diseases). Moreover, there are many more factors of major surgery that are risk factors for renal function. One of the most important goals during anesthesia is to preserve a normovolemic state and to avoid even short-term hypotensive periods (MAP <55–60 mmHg). A standardized meticulous assessment of intraoperative blood loss and replacement according to authorized guidelines is of particular importance [12, 13, 17].

The average amount of diuresis should be at least 1–2 ml/kg/h. Diuresis and other fluid losses should be balanced periodically, e.g., hourly. Closer monitoring is recommended during the HIPEC period. If oliguria persists despite hemodynamic optimization (fluid challenge, differentiated catecholamine therapy), the administration of loop diuretics should be considered. At the same time, the additional nephrotoxicity of chemotherapeutic drugs and diuretics must be taken into account [10, 13].

35.7 Temperature Homeostasis

Maintaining a constant core body temperature is always a goal of perioperative treatment. Postoperative hypothermia is associated with an increased risk of surgical site infections, coagulopathies, and cardiovascular side effects [20]. Hyperthermia during intraperitoneal chemotherapy can induce considerable lactate acidosis, elevated end-expiratory CO_2 levels, and a substantial increase in oxygen consumption that may cause additional cardiovascular stress. It is essential to keep the core temperature <38 °C. Cooled infusions and devices for convective temperature management can be used for active temperature lowering in addition to the possibly necessary adjustment of respirator settings.

The following target values are commonly accepted:

- During cytoreductive surgery: >36 °C intravesical
- HIPEC phase <38 °C intraarterial
- HIPEC phase 42 °C intraabdominal

35.8 Metabolic Changes, Hemostasis, and Antiemetic Treatment

The production of lactate and other metabolic products culminates at the end of the HIPEC phase. The application of chemotherapeutic drugs and their side effects (disturbed electrolyte balance, nephro-, and cardiotoxicity) are uncommon events during anesthesia but are relevant in this setting [13]. Avoiding acidosis is one of the most important goals of anesthesiological management. Periodic tests to assess the current volume state with the consideration of continuous hemodynamic parameters and ongoing catecholamine treatment are essential.

The preservation of intact hemostasis during CRS and HIPEC is another crucial issue. The extensive dimensions of the internal wound surface, the intraoperative loss of blood and clotting factors, a disturbed electrolyte balance, and impaired thermoregulation can contribute to severe hemostatic disorders. The intraoperative aim is to keep the hemoglobin concentration in accordance with national transfusion guidelines (>10 g/dL). An adequate amount of packed red blood cells and clotting factors should be readily available. Close hemostatic monitoring is highly recommended. Techniques for point of care (POC) coagulation testing allow a fast and individualized response to incipient coagulation disorders. This offers the possibilities of reducing the risk of intra- and postoperative bleeding and reducing the number of transfusions [22]. The current coagulation state should be tested before the beginning of the HIPEC phase due to the expectation of rising core temperature and the effects on coagulation and capillary perfusion.

Furthermore, monitoring the intraabdominal pressure can be helpful for evaluating hemodynamic disorders. A substantial increase in intraabdominal pressure should be expected, especially during closed HIPEC. At the same time, this very part of the procedure requires sufficient relaxation of the abdominal wall. Fixed measuring times (e.g., after the following: induction of anesthesia, closing the abdominal wall, prefilling the abdominal cavity, and finishing HIPEC) allow for approximate but comparable trend monitoring.

The complete CRS and HIPEC procedures bear a high risk for long-lasting postoperative nausea and vomiting aggravated by chemotherapeutic drugs. Specific antiemetic medication should be administered prior to chemotherapy. The time of fascial closure is suitable in closed HIPEC techniques. Scheduled antiemetic therapy should last until at least the 3rd postoperative day and should be subsequently continued on demand. Pharmacologic intraoperative antiemetic prophylaxis should consist of a combination of 5-HT3 antagonists and dexamethasone. In cases of highly emetogenic chemotherapy (mostly platinum- or anthracycline-based regimens), the addition of an NK1 antagonist is useful. Postoperative prophylaxis should also follow a fixed schedule and contain drugs such as 5-HT3 antagonists [11].

35.9 Postoperative Phase, ERAS, and Prehabilitation

Prehabilitation and programs for Enhanced Recovery After Surgery (ERAS) are helpful tools for reducing the risk of complications after complex operations [6]. Basically, these concepts aim to systematically accelerate the restoration of patients' autonomy, to improve the quality of life, and, by this means, to prevent complications. Essential elements of ERAS programs include interventions at every step of the treatment process. Preoperative issues such as proper patient selection, extensive information about the treatment and the expected course, and preliminaries for risk reduction are followed by goal-directed anesthesia and surgery that is as atraumatic as possible. The postoperative course [1] should include a schedule for:

- Optimal and opioid-sparing analgesia
- Effective antiemetic treatment
- Early removal of abdominal drains and nasogastric and chest tubes
- Early enteral nutrition
- Accelerated mobilization

There is still a lack of high-quality data from studies with sufficient evidence levels. The pronounced heterogeneity of patients and treatment algorithms hamper data acquisition and evaluation. At the very least, there have been reported advantages of ERAS concepts in CRS/HIPEC treatment described in the few publications available so far [2, 5, 13].

35.10 Ventilation, Analgesic, and Antiemetic Therapy

A planned early weaning program is recommended and should start immediately after admission to the ICU. Clear concepts (e.g., decontamination of the oral cavity, semirecumbent position, spontaneous breathing phases) to prevent ventilator-associated pneumonia should be implemented if a prolonged mechanical ventilation >48 h is necessary. Extensive breathing exercises with regular CPAP episodes and active physiotherapy support are essential after extubation. Attentive surveillance monitoring should also focus on pleural effusions. We prefer to drain even small effusions in the early postoperative period.

Epidural analgesic therapy can be continued until day 4 or 5 and may shorten the time of postoperative ileus. In the absence of an epidural catheter, the establishment of patient-controlled analgesia using highly potent opioids is usually possible depending on the alertness and cognitive states. Additional nonsteroidal anti-inflammatory drugs can be given in scheduled intervals as well during mobilization. Early collaboration with a pain therapy specialist is suggested [7].

35.11 Postoperative Nutrition and Fluid Therapy

Usually, it is possible to start oral nutrition within the first postoperative days with protein drinks, soups, or yogurt. Anastomoses of the GI tract should not delay enteral feeding but often if surgery has been extensive and prolonged such as for advanced pseudomyxoma, it is unlikely that enteral feeding will be tolerated in the early postoperative period [19]. Effective prokinetic therapy (ideally a thoracic epidural catheter with local anesthetics) and active mobilization help stimulate gut motility, appetite, and beginning of enteral nutrition. Intraoperative antiemetic prophylaxis using 5-HT3 antagonists should continue for a few days at regular intervals [11]. The significance of NK1 antagonists after local chemoperfusion has not yet been determined. Further rapid progression of oral nutrition is often hampered by a prolonged loss of appetite. Lack of appetite, nausea, and anorexia may be affected by dronabinol in some cases.

Sufficient fluid therapy is of fundamental importance to avoid renal impairment. Additionally, chemotherapy, preexisting diseases, hemodynamic management, fluid and transfusion replacement strategies, and further nephrotoxic medication avoidance can contribute to renal function. Diuresis should not fall below 1 ml/kg/h [10]. Prolongation of extended continuous hemodynamic monitoring and goal-directed fluid therapy allows maintenance of optimal fluid homeostasis. Therefore, we recommend continuing this monitoring until the 3rd postoperative day or discharge from the intensive care unit (ICU). Volume replacement and transfusion regimens should pursue the same postoperative target values as intraoperative regimens. The current transfusion guidelines generally suggest maintaining hemoglobin concentrations above 8–10 g/dl according to preexisting cardiovascular risk factors.

35.12 Drain Management

Encouraging early mobilization is an essential element of postoperative enhanced recovery protocols. Tubes and drains may be fraught with risks of infection and can hinder mobility and cause pain. Drains should be used judiciously and removed at the earliest opportunity. We recommend leaving only one abdominal silicone drain for the pelvis which we normally remove on the 2nd postoperative day if draining clear, serous fluid. Additional drains can be used especially after splenectomy or (partial) gastrectomy,

although there is no good evidence of their advantages. We always leave a drain in patients with lesions of the pancreatic parenchyma to treat frequently inevitable fistulae.

A chest tube should be inserted in patients with accidental opening of the pleural cavity. This tactic allows us to reroute lost HIPEC perfusate from the thorax and to attack intraoperatively spreading malignant cells at the same time. Therefore, we use a 24 Fr chest tube inserted in the anterior axillary line/intercostal space 5. Extensive peritonectomy of the diaphragmatic cupola frequently results in pleural effusions. Repeated clinical and radiologic examinations are necessary to drain these in a timely fashion. In patients with postoperative effusion, we use flexible Seldinger-guided 16 Fr tubes. This is sufficient for serous collections and causes less pain and discomfort than larger drains.

35.13 Checklists

The use of standardized safety checklists can improve interdisciplinary communication, reduce procedure-dependent morbidity, and prevent intraoperative critical incidents or treatment errors [8, 15, 21]. For this reason, the implementation of a checklist according to the WHO initiative for patient safety should be self-evident. In our department, we extended this query during the preoperative team time-out with some special items on CRS/HIPEC (Fig. 35.1).

Further checklists concerning the optimization of the treatment process and the postoperative treatment are provided in the supplements of this book. A critical adaptation of particular conditions and preexisting treatment standards is recommended.

- The positioning of the patient in the OR should be adjusted for prolonged operation time. The possibility of performing a transanal anastomosis should be taken into account as well as the necessity to explore the complete abdominal cavity with changes in the position and use of retractor devices.

- Rapid changes in fluid homoeostasis, relevant blood loss, potential nephrotoxicity, and the intended hyperthermia are challenging factors for anesthesiological management. Invasive monitoring and early goal-directed therapy are potential measures for treatment optimization.

Preparatory Checklist for OP		
What		**Check**
Signs on all doors	Appropriate?	O
Protective laundry bags	Available?	O
Protective eyewear	Available?	O
Water proof OP gowns	Available?	O
Sterile chemo-resistant gloves	Available?	O
Unsterile chemo-resistant gloves	Available?	O
Respiratory masks FFP 2/FFP 3	Available?	O
Pads/mats for floor	Available?	O
Container for cytostatic waste	Available?	O
Emergency cleanup kit/chemotherapy spill kit	Available?	O
Cytostatics	Ordered? Dosage reviewed?	O O

Fig. 35.1 Preparatory checklist for OP

- We recommend a thoracic epidural catheter for the optimal intra- and postoperative pain management. Well-proven and implemented ERAS concepts for major abdominal surgery should be used after CRS/HIPEC as well as to prevent general complications. Essential components are a sufficient analgesic and antiemetic treatment, early postoperative mobilization, and early enteral feeding. Prehabilitation may be beneficial.

- Checklists should be implemented to improve communication between disciplines and promote patient safety.

References

1. Adamina M, Kehlet H, Tomlinson GA, et al. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011;149:830–40.
2. Arakelian E, Gunningberg L, Larsson J, et al. Factors influencing early postoperative recovery after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol. 2011;37:897–903.
3. BDC. Vereinbarung über die Zusammenarbeit bei der operativen Patientenversorgung. Passion Chirurgie. 2016;6:Art 07_02.
4. Bleiler D, Bleiler S, Sinner B. Perioperatives Management im Rahmen der CRS und HIPEC. Anaesthesist. 2020;69:89–94. https://doi.org/10.1007/s00101-019-00706-4.
5. Cascales Campos PA, Gil Martinez J, Galindo Fernandez PJ, et al. Perioperative fast track program in intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreductive surgery in advanced ovarian cancer. Eur J Surg Oncol. 2011;37:543–8.
6. Cortés-Guiral D, Mohamed F, Glehen O, Passot G. Prehabilitation of patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal malignancy. Eur J Surg Oncol. 2020;S0748-7983(20):30067–6. https://doi.org/10.1016/j.ejso.2020.01.032.
7. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17:131–57.
8. de Vries EN, Prins HA, Crolla RM, et al. Effect of a comprehensive surgical safety system on patient outcomes. N Engl J Med. 2010;363:1928–37.
9. Dupont S, Schiffer ERC, White MJ, Diaper JRA, et al. Changes in hepatic blood flow and liver function during closed abdominal hyperthermic intraperitoneal chemotherapy following cytoreduction surgery. Gastroenterol Res Pract. 2018;2018:8063097. https://doi.org/10.1155/2018/8063097.
10. Goren O, Matot I. Perioperative acute kidney injury. Br J Anaesth. 2015;115(Suppl 2):ii3–ii14.
11. Jordan K, Gralla R, Jahn F, et al. International antiemetic guidelines on chemotherapy induced nausea and vomiting (CINV): content and implementation in daily routine practice. Eur J Pharmacol. 2014;722:197–202.
12. Kajdi ME, Beck-Schimmer B, Held U, et al. Anaesthesia in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: retrospective analysis of a single centre three-year experience. World J Surg Oncol. 2014;12:136.
13. Raspé C, Piso P, Wiesenack C, et al. Anesthetic management in patients undergoing hyperthermic chemotherapy. Curr Opin Anaesthesiol. 2012;25:348–55.
14. Raspé C, Flother L, Schneider R, et al. Best practice for perioperative management of patients with cytoreductive surgery and HIPEC. Eur J Surg Oncol. 2016;43:1013–27.
15. Russ S, Rout S, Sevdalis N, et al. Do safety checklists improve teamwork and communication in the operating room? A systematic review. Ann Surg. 2013;258:856–71.
16. Schluermann CN, Hoeppner J, Benk C, et al. Intra-abdominal pressure, cardiac index and vascular resistance during hyperthermic intraperitoneal chemotherapy: a prospective observational trial. Minerva Anestesiol. 2016;82:160–9.
17. Schmidt C, Moritz S, Rath S, et al. Perioperative management of patients with cytoreductive surgery for peritoneal carcinomatosis. J Surg Oncol. 2009;100:297–301.
18. Schmidt-Bräkling T, Pohl U, Gosheger G, et al. Patientenlagerung im OP. Stuttgart: Thieme; 2016.
19. Swain DR, Yates AL, Mohamed F, et al. Do patients undergoing cytoreductive surgery and HIPEC for peritoneal malignancy need parenteral nutrition? Pleura Peritoneum. 2018;3(4):20180123. https://doi.org/10.1515/pp-2018-0123.
20. Torossian A, Brauer A, Hocker J, et al. Preventing inadvertent perioperative hypothermia. Dtsch Arztebl Int. 2015;112:166–72.
21. Treadwell JR, Lucas S, Tsou AY. Surgical checklists: a systematic review of impacts and implementation. BMJ Qual Saf. 2014;23:299–318.
22. Weber CF, Zacharowski K. Perioperative point of care coagulation testing. Dtsch Arztebl Int. 2012;109:369–75.

Part X

Quality of Life

Quality of Life After CRS and HIPEC

36

Jens Hartmann, Christina Bockelmann, and Pankaj Kumar Garg

36.1 Introduction

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being, and not merely the absence of disease." Furthermore, the WHO describes quality of life (QOL) as "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." It needs to be highlighted that both health and QOL are not defined as the mere absence of disease.

It is generally considered that QOL is a subjective psychological construct that is not easily measurable objectively. Individuals themselves are best able to assess their QOL, which depends upon individual experiences and multiple factors: the individual's needs, goals, expectations, and obligations. Areas such as education, freedom, politics, religion, culture, and wealth play an important role in determining quality of life. Moreover, from a sociological point of view, there are also material and spiritual dimensions to one's QOL.

In medicine, however, what is usually measured is how health affects QOL. This is measured as health-related QOL (HRQOL) [3]. QOL is a larger concept which incorporates all aspects of life while HRQOL measures the effect of illness and the impact the treatment may have on QOL.

In order to measure the quality of life in a scientific study to assess the impact of a treatment modality, precise measurement of its various domains is warranted [2]. The following are the various dimensions that should be taken into consideration while recording quality of life in a study [4]:

- Physical condition
- Psychological well-being
- Social relationships
- Functionality in everyday life

Kuchler described five dimensions to be measured for the evaluation of QOL: somatic, psychological, interpersonal, socioeconomic, and spiritual [11]. These five dimensions have a significant inter-individual difference in rating.

Various researchers have described a number of tools to measure the different dimen-

J. Hartmann (✉)
Department of Surgery, AKH – Celle, Celle, Germany
e-mail: Jens.hartmann@akh-celle.de

C. Bockelmann
Department of Traumatology and Orthopedics, Martin Luther Krankenhaus of Berlin, Berlin, Germany

P. K. Garg
Department of Surgical Oncology, All India Institute of Medical Sciences, Rishikesh, Uttarakhand, India
e-mail: pankaj.sonc@aiimsrishikesh.edu.in

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_36

sions of QOL. In 1948, David Karnofsky and Joseph Burchenal described perhaps the first scale to measure QOL, which they referred to as the performance status. They used this subjective scale in a trial to study the role of nitrogen mustard in lung cancer patients. The scale measured performance status, based on patient activities, on a scale of 11 stages ranging from 100 (perfect health) to 0 (death). Basically, this scale measures the activity index of a patient: how much general and necessary assistance they require to carry out daily life activities due to the extent of the disease. The questionnaire can be filled out by the patient or by the attending physician and is widely used in oncology today. A shortened version to assess performance status was developed by Zubrod et al. for the Eastern Cooperative Oncology Group (ECOG) in the 1950s, and it was endorsed by the World Health Organization (WHO) in 1979 [15].

Over the years, it has been increasingly felt that the subjective feeling of the patient in terms of quality of life differs significantly compared to the objective assessment by the treating physician [10, 18]. This led to a change from the physician-based assessment to self-assessment regarding the state of health and the quality of life of patients. The aim was to standardize tools to measure HRQOL reliably from the patient's perspective during treatment [2, 17].

The real measurement and representation of HRQOL—the so-called "soft" or "subjective" data—is not easy. The collection of objective data such as the 5-year survival rate or the occurrence of postoperative complications is much easier to determine and evaluate [25].

There followed the development of numerous other measuring instruments for the self-assessment of the HRQOL: Functional Living Index—Cancer (FLIC) by Schipper et al. in 1984 and Functional Assessment of Cancer Therapy (FACT) by Cella et al. in 1993 [5, 19]. The EORTC QLQ-C30 questionnaire was developed by the European Organisation for Research and Treatment of Cancer (EORTC) as an integrated, modular approach for evaluating the QOL of patients participating in international clinical trials. In 1993, Aaronson et al. showed that EORTC QLQ-C30 was a reliable and valid measure of the QOL of cancer patients in multicultural clinical research setting based on their experience of using it to evaluate QOL of 305 patients with non-resectable lung cancer from centers in 13 different countries.

The QLQ-C30 (Quality of Life Questionnaire-C30) is the core of the questionnaires of the EORTC for assessing quality of life. The letter "C" in the questionnaire stands for "core" and the number "30" for the number of questions to be answered.

All currently used measuring instruments claim to measure various domains of the HRQOL accurately. In doing so, they must satisfy the psychometric quality criteria: reliability and validity. Reliability refers mainly to stability, internal consistency, and equivalence of a measuring tool, whereas validity refers to the fact that it measures exactly what it is designed to measure. Moreover, the measuring instruments must be user-friendly to allow for good patient compliance.

The concept of QOL gained momentum in the 1970s and 1980s when the focus gradually shifted from treatment to its perceived effect on patients [1]. Since then, there has been consistent conscious awareness of QOL issues in the oncologists' community, and QOL has been a part of treatment outcomes in various trials [17]. Moreover, psychosocial aspects of cancer have also been increasingly acknowledged [14].

The following tools are being utilized to measure QOL in cancer patients worldwide [14]:

- Quality of Life Questionnaire (EORTC QLQ-C30 questionnaire) of the European Organisation for Research and Treatment of Cancer [1]
- Functional Assessment of Cancer Therapy (FACT) Questionnaire [5]
- Functional Living Index—Cancer (FLIC) [19]
- Short Form 36 (SF-36) [22]

These questionnaires are extensively used by the medical oncology community to assess the impact of new therapies based on patient perception. The Eastern Cooperative Oncology

Group (ECOG), Activities of Daily Living (ADL), Brief Pain Inventory (BPI), and Center for Epidemiologic Studies Depression Scale (CES-D) are also used by oncologists and have some utility in patients with peritoneal malignancy [21].

Though the different approaches of questionnaires to assess QOL require standardization, it seems difficult considering the huge heterogeneity in the patient profiles, tumor types, and treatment modalities [21].

When Paul Sugarbaker introduced the concept of cytoreductive surgery (CRS) and HIPEC at the end of the last century, the initial studies focused on the assessment of the effectiveness of the procedure. Subsequently, the studies centered on the morbidity and mortality involved in the procedure. Afterward, surgeons focused on whether CRS/HIPEC was able to make any difference in the QOL of the patients.

In 2001, McQuellon et al. published the first prospective series of 64 patients for analysis of quality of life after CRS/HIPEC. They assessed the functional status and quality of life of patients with disseminated peritoneal cancer (DPC) following CRS/HIPEC using the Functional Assessment of Cancer Therapy—Colon (FACT-C) scale. QOL was measured at baseline, 2 weeks post-surgery, and at 3, 6, and 12 months. Though there was an initial decrease in the QOL parameters in the postoperative period, the authors reported a significant improvement in all domains of QOL in subsequent follow-up visits. Considering the complexity of CRS/HIPEC, an initial decrease in the QOL parameters is to be expected [12].

Another prospective study investigated the course of health-related quality of life over time in 90 patients with peritoneal malignancy (PM) after CRS/HIPEC using the EORTC QOL Questionnaire. The authors noted that most of the QOL indices recover after 6–12 months of surgery. Even emotional function improved to a higher baseline value by 12 months following surgery. An initial reduction in the QOL parameters is expected, and this fact should not be used to deny surgery to the patients (Fig.36.1) [23].

Several international studies have supported the fact that there may be initial deterioration in the QOL parameters following surgery; this may be related to postoperative complications, requirement of systemic chemotherapies, or progressive disease. Moreover, selection of different measurement points and heterogeneous patient populations make the analysis more complex. These factors must be considered while evaluating the results of QOL studies.

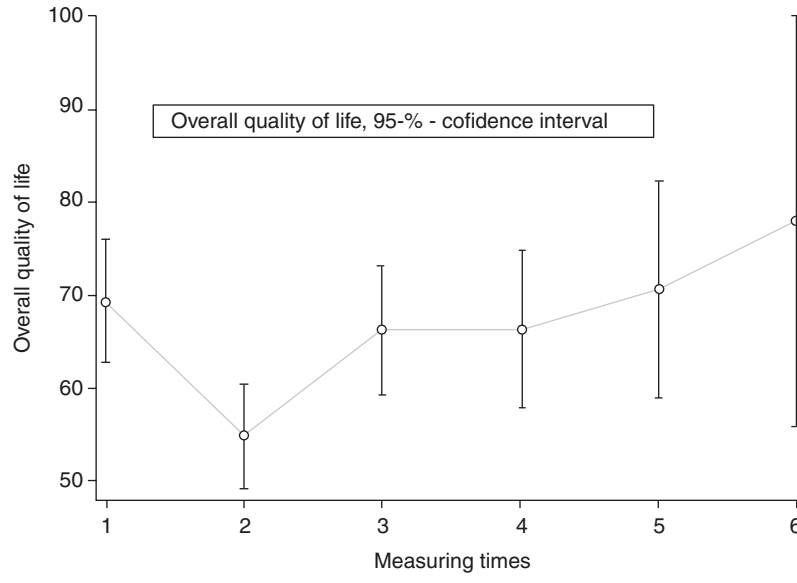


Fig. 36.1 Course of the overall quality of life (GHS) to CRS and HIPEC. (Adapted from Tsilimparis et al. [23])

Table 36.1 offers an overview of the published studies assessing the QOL after HIPEC.

Despite the heterogeneous measuring instruments and times, the majority of the studies show that most of the QOL indices return to baseline or may become better after 6 months to 1 year after surgery.

A systematic review to assess the effect of CRS/HIPEC on HRQOL in patients with peritoneal malignancy highlighted the small- to medium-term benefit of the procedure. The authors included 15 studies (1583 patients) in the review. They also reported that HRQOL declines at the 3–4-month time-point before becoming similar to or better than preoperative levels at 1 year. The pooled effects of combined postoperative functional assessment of cancer therapy and EORTC QOL-questionnaire scores were significantly improved from baseline on overall health status ($p = 0.001$) and emotional health ($p = 0.001$) [21].

The essential goals of the treatment in advanced cancers is not only to bring lasting remission and to extend life but also to either improve or maintain the QOL [7].

36.2 Conclusion

In summary, there are various measuring tools available to assess the QOL of patients undergoing treatment. Though most of the studies confirm that there is initial deterioration in the QOL following CRS/HIPEC, most of the QOL indices either return to normal or improve with time, usually after 6–12 months. The patients who have a long relapse-free period without tumor progres-

Table 36.1 Literature review on quality of life after HIPEC with measuring instruments and conclusions

Studies	Patients (*n*)	QOL measuring tool	Measuring times	Conclusions
Schmidt and Dahlke [20]	67	EORTC QLQ-C30	Median 48 months postoperatively	GHS and emotional and cognitive function value are not changed significantly in comparison to the normal population
McQuellon and Russell [14]	58	FACT-C, FACT- G, TOI, ECOG	Preoperatively; postoperatively 1, 3, 6, 12, 24 months	Emotional functions recover after 6 months. GHS decreases after 3 months and recovers in the course of 1 year
McQuellon et al. [13]	96	FACT-C, FACT-G, TOI, ECOG	Preoperatively; thereafter at 1, 3, 6, 12, 24 months	FACT-G reaches baseline at 3 months; after initial significant reduction, all indices return to normal
Zenasni and Botella [24]	68	EORTC QLQ-C30, EORTC QLQ-CR38	12 months postoperatively	HRQOL returns to normal after 12 months; reduction in sexual functions
Hill and McQuellon [9]	62	FACT-C, FACT-G, TOI, ECOG	Preoperatively; thereafter at 1, 3, 6, 12 months	FACT reduced at 3 months after surgery but returned to normal 1 year after surgery
Duckworth and McQuellon [8]	112	FACT-C, FACT-G, TOI	Median 12 months postoperatively	Normal HRQOL compared with the normal population after 1 year
Tsilimparis et al. [23]	90	EORTC QLQ-C30	Preoperatively; thereafter at 1, 3, 6, 12, 24 months	Reduction of GHS after 3 months, no significant change in functional capabilities postoperatively after 12 months; psychosocial functional values recover slowly
Chia and Tan [6]	63	EORTC QLQ-C30	Median 1.08 years, postoperatively	Better GHS and physical function values compared to the conservatively treated group
Passot and Bakrin [16]	216	GIQLI	Preoperatively; postoperatively, 1, 3, 6, 12 months	HRQOL return to normal after 12 months

FACT-G Functional Assessment of Cancer Therapy—General version, *GHS* Global Health Status, *GIQLI* Gastro Intestinal Quality of Life Index, *HRQOL* health-related quality of life, *TOI* Treatment Outcome Index

sion also usually have a QOL similar to the normal population. However, there can be slow improvement in the emotional and functional indices, highlighting the need for long-term family and social support for the patients.

As in other procedures, good patient selection determines the success of CRS/HIPEC, which has the potential to improve the QOL.

References

1. Aaronson NK, Ahmedzai S, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in International Clinical Trials in Oncology. J Natl Cancer Inst. 1993;85:365–76.
2. Augustin M, Amon U, et al. Empfehlungen zur Erfassung von Lebensqualität in der Dermatologie. Dermatologie Psychosomatik. 2000;1:76–82.
3. Bengel J, Beutel M, et al. Chronische Erkrankungen, psychische Belastungen und Krankheitsbewältigung. Herausforderungen für eine psychosoziale Versorgung in der Medizin. Psychother Psych Med. 2003;53(2):83–93.
4. Bullinger M, Kirchberger I, et al. Der Fragebogen Alltagsleben – Ein Verfahren zur Erfassung der gesundheitsbezogenen Lebensqualität. Z Psychother Med Psychol. 1993;2:121–31.
5. Cella DF, Tulsky DS, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11:570–9.
6. Chia CS, Tan WJ. Quality of life in patients with peritoneal-surface malignancies after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol. 2016;40:909–16.
7. Dizon DS, Kriloy L, et al. Clinical cancer advances 2016: annual report on progress against cancer from the American Society of Clinical Oncology. J Clin Oncol. 2016;34:987–1011.
8. Duckworth KE, McQuellon RP. Patient rated outcomes and survivorship following cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CS + HIPEC). J Surg Oncol. 2012;106:376–80.
9. Hill AR, McQuellon RP. Survival and quality of life following cytoreductive surgery plus intraperitoneal surgery for peritoneal carcinomatosis of colonic origin. Ann Surg Oncol. 2011;18:3673–9.
10. Kramm M. Veränderungen von Indikatoren der «Lebensqualität» nach Hochdosis-Chemotherapie. Dissertation, Faculty of Social Sciences, University of Göttingen; 2003.
11. Kuchler T. Aspekte der Lebensqualität. In: Henne-Bruns D, Dürig M, Kremer B, editors. Duale Reihe – Chirurgie. Stuttgart; 2003. p. 259–65.
12. McQuellon RP, Loggie BW, et al. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. Eur J Surg Oncol. 2001;27:65–73.
13. McQuellon RP, Danhauser SC, et al. Monitoring health outcomes following cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. Ann Surg Oncol. 2007;106:1105–13.
14. McQuellon RP, Russell GB. Survival and health outcomes after cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of appendiceal origin. Ann Surg Oncol. 2008;15:125–33.
15. Oken MM, Creech RH, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. J Clin Oncol. 1982;5:649–55.
16. Passot G, Bakrin N. Quality of life after cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy: a study of prospective 216 patients. Eur J Surg Oncol. 2014;40:529–35.
17. Pöllmann W, Busch C, et al. Lebensqualität bei Multipler Sklerose. Messinstrumente, Bedeutung, Probleme und Perspektiven. Nervenarzt. 2005;76:154–69.
18. Pukrop R. Theoretische Explikation und empirische Validierung des Konstruktes Lebensqualität unter besonderer Berücksichtigung psychopathologischer Subgruppen und facettentheoretischer Methodik. Dissertation, University of Bielefeld; 1997.
19. Schipper H, Clinch J, et al. Measuring the quality of life of cancer patients: the functional living index-cancer: development and validation. J Clin Oncol. 1984;2:472–83.
20. Schmidt U, Dahlke MH. Perioperative morbidity and quality of life in long term survivors following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur J Surg Oncol. 2005;31:53–8.
21. Shan LL, Saxena A, et al. Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis: a systematic review and meta-analysis. Surg Oncol. 2014;23:199–210.
22. Tarlov AR, Ware JE, et al. The Medical Outcomes Study. An application of methods for monitoring the results of medical care. JAMA. 1989;262:925–30.
23. Tsilimparis N, Bockelmann C, et al. Quality of life in patients after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: is it worth the risk? Ann Surg Oncol. 2013;20:226–32.
24. Zenasni F, Botella M. The long-term impact of hyperthermic intraperitoneal chemotherapy on survivors treated for peritoneal carcinomatosis: a cross-sectional study. Support Care Cancer. 2009;17:1255–61.
25. Frost MH, Sloan JA. Quality of life measurements: a soft outcome–or is it? Am J Manag Care. 2002;8(18 Suppl):S574–9.

PIPAC Therapy and Quality of Life

37

Clemens B. Tempfer

37.1 Introduction

Quality of life is defined as the composite of factors constituting the living conditions of a given individual. Typically, quality of life aims to describe the degree of a person's subjective as well as objective well-being. This includes the complex of issues summarized as "standard of living" including material factors such as food, housing, and consumer goods but also social and cultural factors such as education, job issues, social relations, environmental conditions, and health issues [8]. Two basic sociological theories delineate the methods used to measure and describe quality of life. First, the sociopolitical approach assumes that well-being is equivalent to meeting a specific and defined set of basic social needs. Therefore, sociopolitical quality-of-life studies typically look at the level and functionality of public interventions intended to ensure social safety and social security. These interventions are not restricted to but may include public health care, access to education, affordable housing, a healthy environment, labor laws, and pension benefits. From a methodological standpoint, these interventions and their efficacy are best described by objective figures such as public welfare statistics [7]. In contrast, the psychological approach of describing quality-of-life issues uses an individualized definition of quality of life. This approach is typically used in the medical literature, because it focuses on the individual perception of well-being. The scientific rationale of this approach is that only individuals themselves can adequately describe their quality of life. This is based on the belief that definitions of happiness, success, and satisfaction are characterized by significant interindividual and intercultural variations [9]. In other words, the same level of social security and access to education may lead to markedly different degrees of satisfaction and quality of life in two different individuals, both within the same society and within two different societies. Consequently, the psychological approach to describe quality-of-life issues puts a strong emphasis on immaterial values and subjective assessments such as happiness, contentedness, and personal fears. Methodologically, this approach uses interviews and standardized questionnaires [2, 9]. These tools combine both subjective and objective parameters in order to obtain a holistic impression of a person's quality of life [2]. In the medical literature, quality of life in general and the impact of medical therapies on the increase or decrease of quality of life in particular have gained an important role in the last decades.

Among oncological patients, who are typically undergoing therapies with significant side

C. B. Tempfer (✉)
Department of Obstetrics and Gynecology, Marien Hospital Herne, Ruhr-Universität Bochum, Herne, Germany
e-mail: Clemens.tempfer@rub.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_37

effects and subsequent declines in their quality of life, quality-of-life studies are particularly useful. For example, quality-of-life issues have become an established parameter when evaluating the clinical usefulness of palliative therapies. When indicating a palliative treatment, the limited therapeutic efficacy of the palliative treatment must be balanced against the significant reduction in quality of life caused by this intervention. If, for example, a palliative systemic chemotherapy significantly reduces the quality of life while only providing a limited benefit in terms of progression-free survival, therapeutic decisions should be made based on the available evidence regarding the severity of quality-of-life impairment. Therefore, clinical studies assessing quality of life have become an integral part of the oncological literature in recent decades. This is especially true for patients with peritoneal carcinomatosis (PC), because patients with this disease often undergo multiple sequential lines of systemic chemotherapy. Under these circumstances, acute and cumulative toxicities associated with chemotherapy such as alopecia, nausea, diarrhea, neurotoxicity, abdominal pain, and fatigue are common. Facing these problems, patients may be unwilling to undergo further lines of systemic chemotherapy and look for therapy alternatives with less impact on their quality of life. In addition, patients may be too old or too sick to undergo systemic chemotherapy. In all of these cases, locoregional chemotherapy is an alternative therapeutic strategy. The reluctance of many patients with PC to accept multiple systemic chemotherapies was in fact one of the main clinical reasons for developing pressurized intraperitoneal aerosol chemotherapy (PIPAC) [4, 20]. PIPAC is based on the assumption that a local deployment of chemotherapy compounds significantly reduces systemic side effects while preserving or even increasing local therapeutic efficacy. In fact, a phase I dose-escalation trial assessing the pharmacokinetics of PIPAC found no significant systemic uptake of cisplatin and doxorubicin into the blood circulation when applied via PIPAC [24], supporting the rationale of PIPAC to reduce quality-of-life problems associated with systemic chemotherapy.

In the present article, we describe clinical evidence looking at the effects of PIPAC on quality of life, nutrition status, and tumor cachexia in patients with PC.

37.2 Nutrition Status and Tumor Cachexia

PC affects almost the whole digestive tract and is characterized by gastrointestinal symptoms such as ascites, nausea, emesis, diarrhea, and abdominal pain. The cardinal symptom of PC is ascites, which results from an imbalance in the production and reabsorption of abdominal fluid. Ascites impairs nutritional uptake, leads to gastrointestinal compression, and increases subphrenic pressure, with subsequent pleural effusion and dyspnea. Loss of proteins into ascites negatively affects the body's metabolic balance. PC also causes local inflammatory activation in the peritoneum and the small and large intestine, further reducing nutritional uptake. In line with all of these direct and indirect effects of PC and ascites, most patients with this complex disease report a significant decline in their quality of life [3].

Advanced PC leads to a nutritional deficit, and the nutritional status of patients with PC usually declines progressively toward the end of life, resulting in a poor overall survival with a median duration of 10 months [26]. Given the compromised gastrointestinal situation, maintaining the necessary caloric intake is difficult for these patients. In addition, patients spontaneously reduce their caloric intake due to appetite loss and in order to avoid nausea and emesis triggered by oral feeding [11]. In light of an increased metabolic demand due to the malignant process, PC causes a situation of high nutritional demand and low nutritional supply resulting in tumor cachexia. These circumstances, together with the fact that the energy expenditure of the underlying tumor causes an increased resting metabolism, push patients into a downward spiral of lower caloric intake in the presence of an increased caloric demand. This results in the body devouring its reserves, mainly the muscle mass, and ulti-

mately results in anorexia. Low caloric intake, increased malignant energy metabolism, and loss of muscle and fat mass cause the cachexia-anorexia syndrome (CAS), defined as a combination of loss of appetite, weight loss, and skeletal muscle atrophy with or without loss of body fat mass [19]. In a circulus vitiosus, progressive tumor development enhances local and systemic inflammatory processes, which further increase the energy demand and thus also increase the energy deficit [17]. CAS is a complex process and is a characteristic feature of many advanced malignant diseases. In patients with gastrointestinal tumors and other intraabdominal tumors typically associated with PC, tumor cachexia develops faster and earlier than with other malignancies. For example, CAS has been described in up to 80% of patients with PC from gastrointestinal tumors and is predictive of the time to progression and overall survival in this patient population [15].

Appetite loss and low caloric intake in patients with CAS lead to anorexia with a progressive loss of muscle mass and muscular function, i.e., sarcopenia, which is associated with a high morbidity and mortality [10]. Biochemical markers of CAS are anemia, c-reactive protein (CRP), insulin resistance, and reduced levels of anabolic steroids. In patients with PC, CAS has prognostic relevance. For example, Aust et al. demonstrated that loss of muscle mass, measured with routine computed tomographies, is an independent predictor of overall survival in a series of 140 patients with advanced ovarian cancer [1]. In this study, loss of muscle mass directly correlated with markers of inflammation such as interleukin (IL)-10 and eotaxin. Interestingly, the amount of residual tumor mass after upfront cytoreductive surgery was associated with the degree of the loss of muscle mass, suggesting that loss of muscle mass reflects the biological aggressiveness of the tumor.

- Patients with PC often display severe CAS because PC directly affects the whole gastrointestinal tract.

PC leads to mechanical and functional impairment of gastrointestinal resorption and nutritional uptake. This was demonstrated by Nordhausen et al., who retrospectively analyzed metabolic and anthropometric parameters such as body weight, nutritional habits, body mass index (BMI), subcutaneous fat mass, body fat mass, bioelectrical impedance (as a measure of body composition), CRP, total protein, albumin, and transferrin among patients with advanced PC from ovarian cancer and gastrointestinal tumors [13]. These patients were characterized by a nutritional deficit (Subjective Global Assessment Score 22.5 ± 4) and had an increased resting metabolism (1527 ± 248 kcal) and increased CRP levels (2.9 ± 4.1 g/dl), whereas total protein (6.5 ± 0.8 g/dl) and albumin (3.7 ± 0.8 g/dl) levels were reduced. Moreover, CRP and resting metabolism continuously increased (Fig. 37.1), whereas body weight, total protein, and albumin continuously decreased during the course of disease (Fig. 37.2). These data demonstrate that nutritional deficit is a feature of patients with PC and is associated with the progressive course of disease.

Therapeutic interventions aimed at improving nutritional status and energy uptake may improve the quality of life and prognosis of patients with PC. For example, Mantovani et al. treated 125 CAS patients with pharmacological caloric support, medroxyprogesterone acetate, L-carnitine, and thalidomide in a randomized trial [12]. This approach led to a significant improvement in the patients' energy balance and reduced the frequency of fatigue.

Our own group assessed the nutritional status of 84 women with PC from recurrent ovarian, fallopian, or peritoneal cancer and looked at longitudinal variations of CAS during palliative PIPAC [6]. Nutritional assessments included BMI, bioelectrical impedance analysis (BIA) with body fat, visceral fat, muscle mass, and resting metabolism (RM), caliper body fat, arm/leg circumference, and blood chemistry including albumin, total protein, transferrin, iron, and CRP. The presence or absence of CAS was recorded before and during PIPAC. In this study, RM (1432 ± 172 kcal/day), visceral fat mass (7.5 ± 3.2), skeletal muscle mass (27.2 ± 4.6%), upper arm circumference (27.9 ± 4.6 cm), lower leg circumference (35.1 ± 3.9 cm), and the

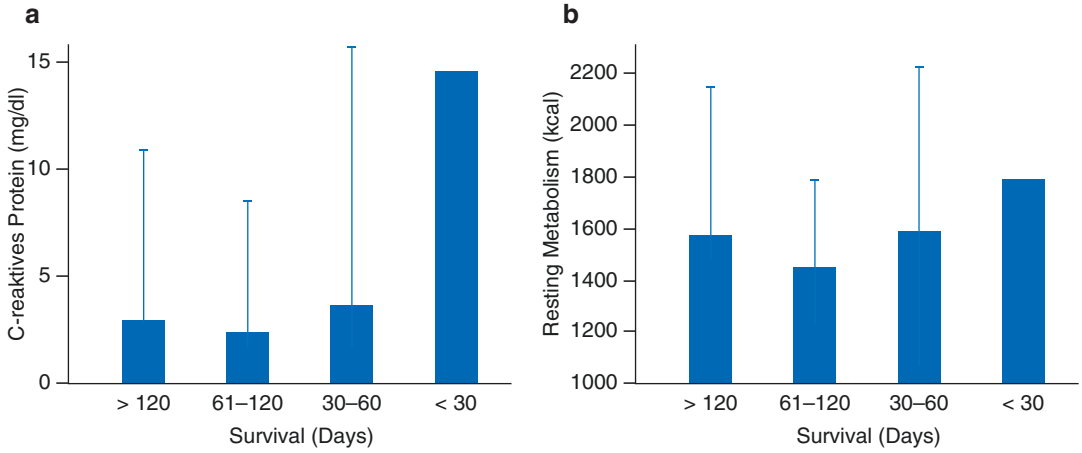


Fig. 37.1 Serum levels of c-reactive protein (CRP) (**a**) and resting metabolism (**b**) among 87 patients with peritoneal carcinomatosis, broken down by survival time. (Adapted from Nordhausen et al. [13])
Datei:
Abb.-Typ: Strich-Abb.
Farbigkeit (IST): 1c
Farbigkeit (SOLL): 1c
Bildrechte: [Urheberrecht beim Autor]
Abdruckrechte: Nicht notwendig
Hinweise Verlag/Setzerei: Bitte Korrekturdatei beachten. Außerdem links a, rechts b anbringen

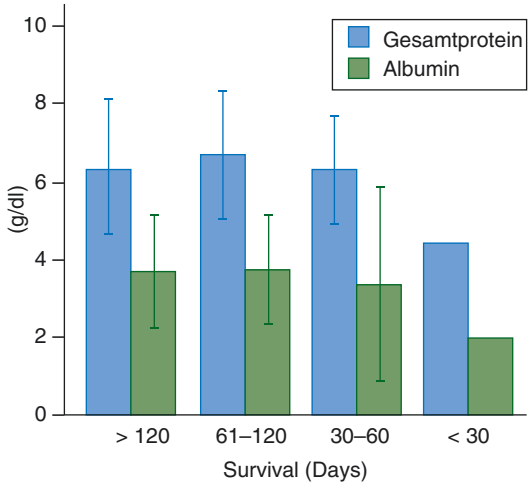


Fig. 37.2 Serum levels of total protein (*blue*) and albumin (*green*) among 87 patients with peritoneal carcinomatosis, broken down by survival time. (Adapted from Nordhausen et al. [13])
Datei:
Abb.-Typ: Strich-Abb.
Farbigkeit (IST): 1c
Farbigkeit (SOLL): 1c
Bildrechte: [Urheberrecht beim Autor]
Abdruckrechte: Nicht notwendig

serum parameters albumin (3.5 ± 0.7 g/dl; reference, 3.5–5.2), total protein (6.3 ± 0.9 g/dl; reference, 6.6–8.6), and transferrin (202 ± 60 mg/dl; reference, 200–360) were below normal limits at baseline, whereas CRP (4.3 ± 6.8 mg/dl; reference, <0.5), caliper body fat (35.7 ± 6.3%), and total body fat mass (35.6 ± 8.5%) were increased above normal limits. Nineteen of the 84 patients (23%) had CAS at baseline. Deterioration or stabilization/improvement of CAS during PIPAC was observed in 9/55 (16.4%) and 46/55 (83.6%) patients with follow-up data, respectively. Interestingly, body fat mass, visceral fat level, skeletal muscle mass, caliper body fat, weight, BMI, ascites, Karnofsky index, RM, and CRP (measured at baseline) were not predictive of CAS deterioration. These data demonstrate that patients with PC typically have a severe nutritional deficit. CAS is frequent among these patients, cannot be predicted at baseline, but can be successfully stabilized by PIPAC.

In summary, it can be stated that tumor cachexia and CAS are common among patients with PC; they correlate with tumor progression and have a strong prognostic impact. Therapies targeting CAS, such as nutrition support or PIPAC, may stabilize locoregional disease and improve CAS-related symptoms as well as quality of life [6, 25].

37.3 PIPAC and Quality of Life

PIPAC is a form of intraabdominal application of chemotherapy with the intent of inducing locoregional tumor regression while avoiding systemic side effects usually associated with systemic chemotherapy [5, 16, 18]. PIPAC may also positively affect quality of life through ascites reduction and local tumor regression. On the other hand, PIPAC may lead to locoregional toxicity. Thus, study evidence looking at the effects of PIPAC on quality of life is important because PIPAC is used with palliative intent. Anecdotal evidence suggests that PIPAC significantly improves quality of life in patients with PC. For example, PIPAC led to a marked improvement in quality of life as assessed by the EORTC (European Organisation for Research and Treatment of Cancer)-QLQ-30 + 3-questionnaire followed by long-term quality-of-life stabilization in a patient with locally advanced ovarian cancer (Fig. 37.3) [4]. In this patient, quality-of-life improvement was paralleled by a clinical, histological, and radiological tumor response. This anecdotal evidence was confirmed in a prospective phase II safety and efficacy trial in 53 patients undergoing three cycles of PIPAC with cisplatin and doxorubicin [21]. Using the EORTC-QLQ-30 questionnaire, gastrointestinal symptoms (nausea, emesis, diarrhea) were reduced and the overall quality of life, role functioning, social functioning, physical fitness, cognitive functioning, as well as social and emotional ability were improved (Fig. 37.4). This positive influence of PIPAC was confirmed in a retrospective cohort study including 99 patients with advanced ovarian cancer and PC undergoing 252 PIPAC applications (Fig. 37.5) [22]. These study observations demonstrate that

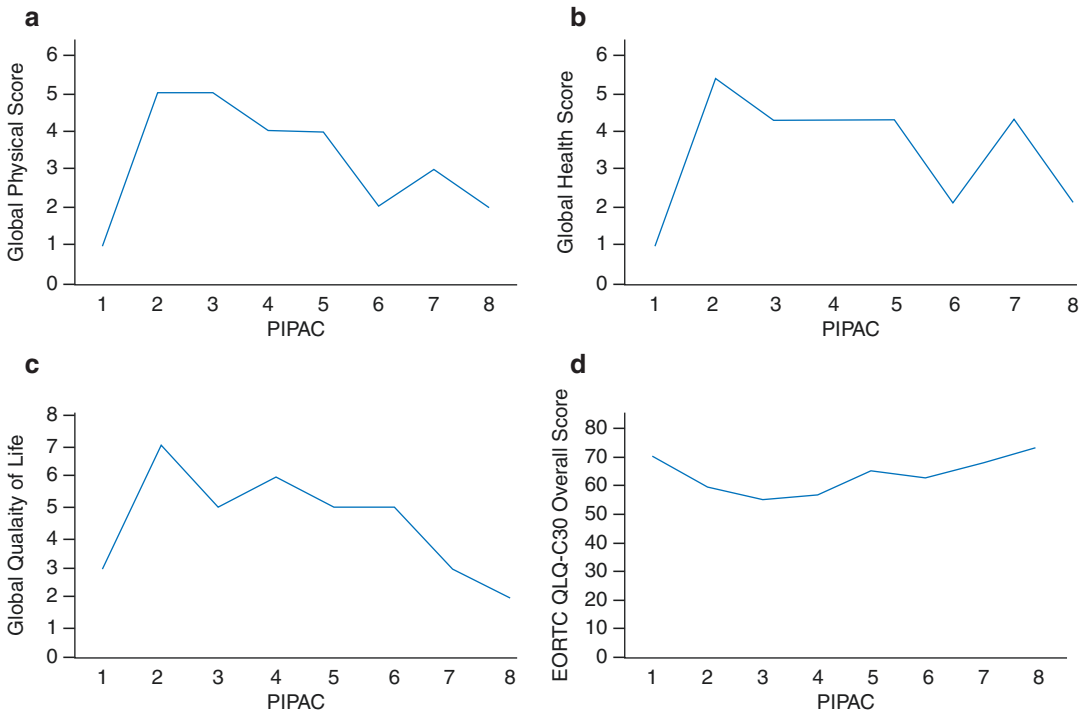


Fig. 37.3 (**a–d**) Measurements of quality of life based on the EORTC-QLQ-C30 questionnaire in a patient with advanced ovarian cancer. (**a**) Global Physical Score, (**b**) Global Health Score, (**c**) Global Quality of Life, and (**d**) EORTC-QLQ-C30 Overall Score. *PIPAC* number of pressurized intraperitoneal aerosol chemotherapies. (Adapted from Giger-Pabst et al. [4])

Datei:
Abb.-Typ: Strich-Abb.
Farbigkeit (IST): 1c
Farbigkeit (SOLL): 1c
Bildrechte: [Urheberrecht beim Autor]
Abdruckrechte: Nicht notwendig
Hinweise Verlag/Setzerei:

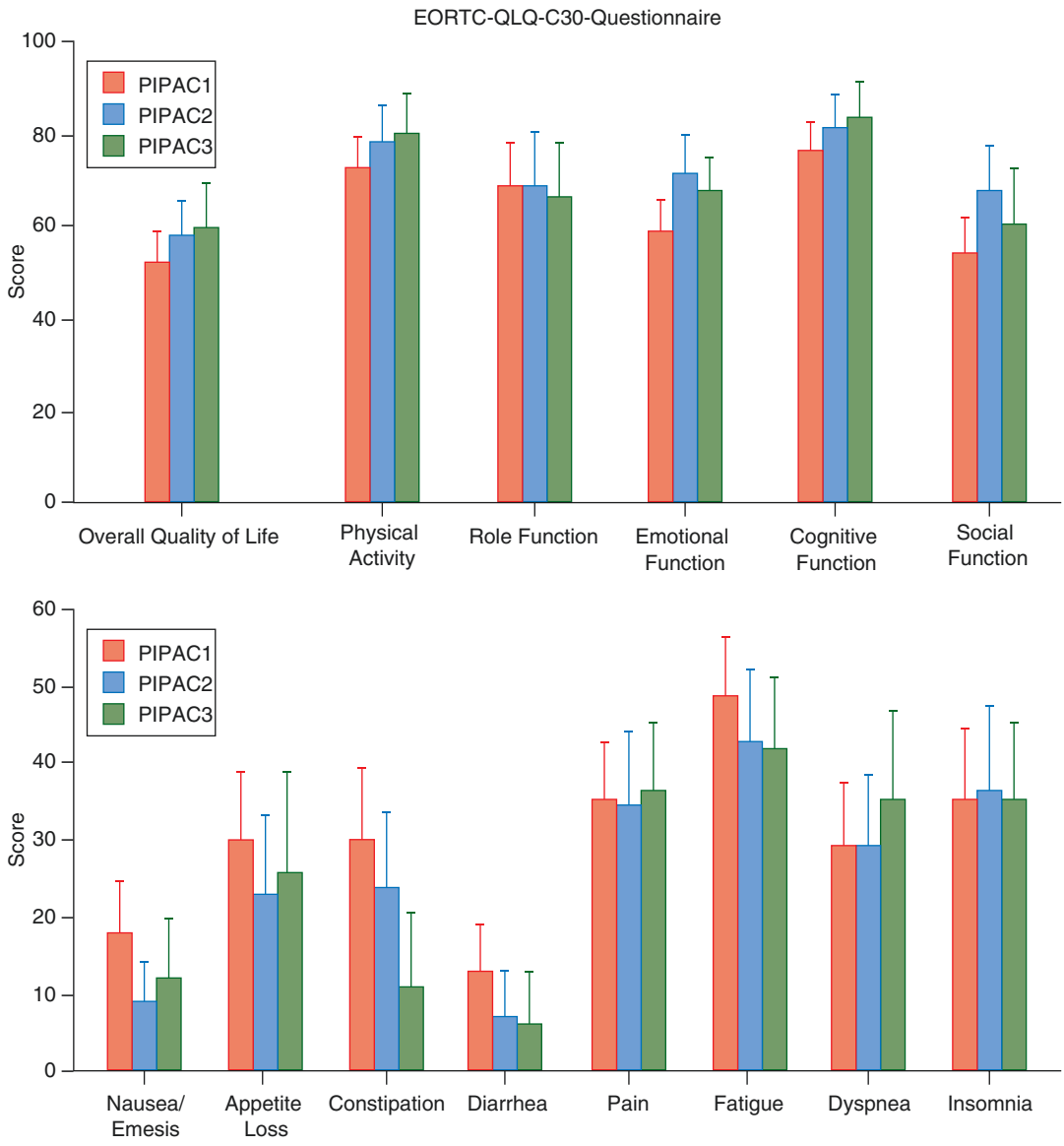


Fig. 37.4 Measurements of quality of life by EORTC-QLQ-C30 questionnaire in a prospective phase II trial among patients with recurrent ovarian cancer and peritoneal carcinomatosis. (Adapted from Tempfer et al. [22])
Datei:
Abb.-Typ: Strich-Abb.
Farbigkeit (IST): 1c
Farbigkeit (SOLL): 1c
Bildrechte: [Urheberrecht beim Autor]
Abdruckrechte: Nicht notwendig
Hinweise Verlag/Setzerei:

repeated PIPAC in patients with ovarian cancer and PC leads to an improvement in their quality of life. It is a matter of discussion as to what extent this effect is caused by the absence of systemic chemotherapy, effective evacuation of ascites, and tumor response. Interestingly, PIPAC did not increase gastrointestinal toxicity, but, on the contrary, improved gastrointestinal items such as nausea and emesis despite the fact that it is a local toxic therapy.

The positive effect of PIPAC in patients with PC was also assessed in patients with PC from

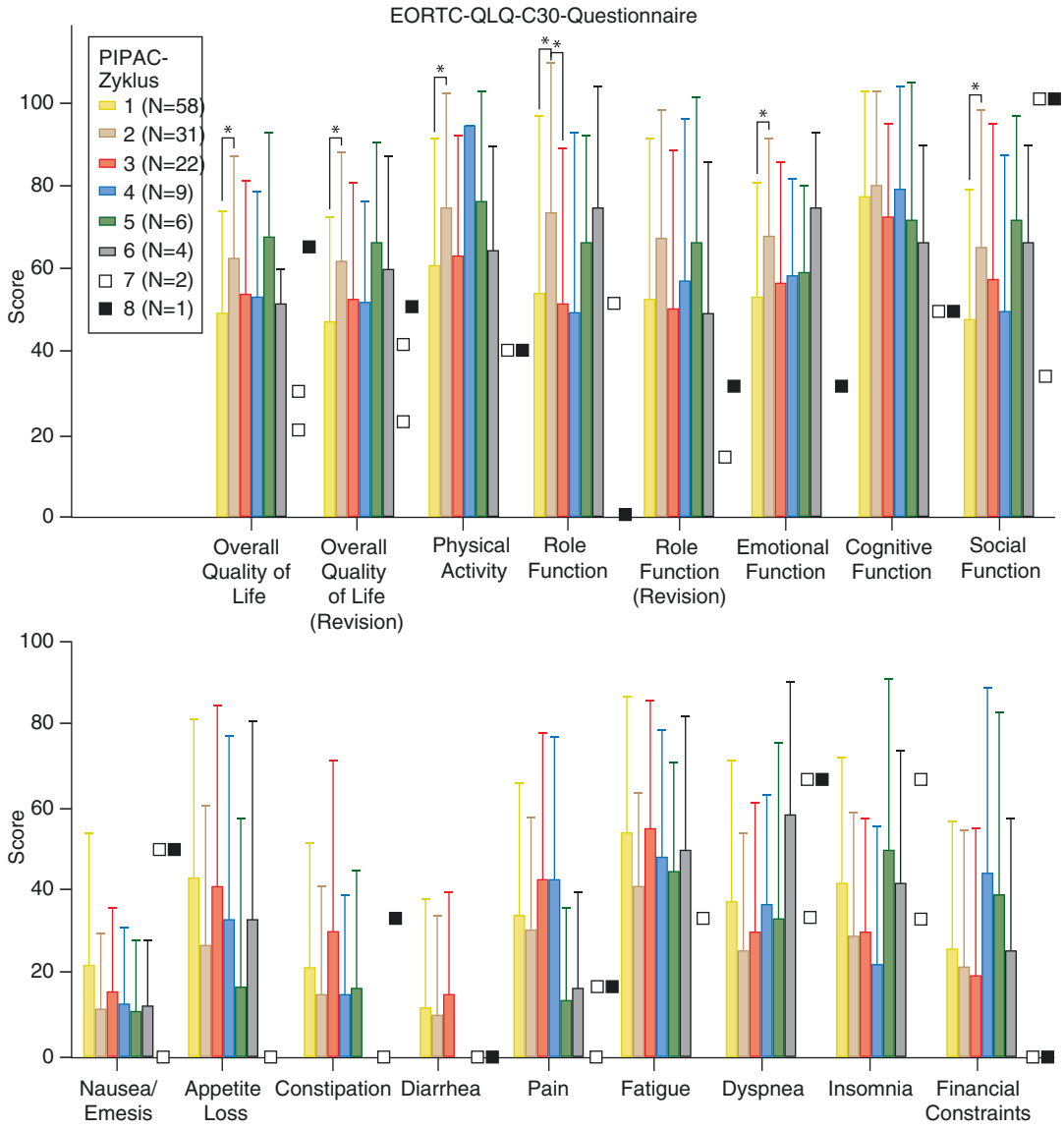


Fig. 37.5 Measurements of quality of life by EORTC-QLQ-C30 questionnaire in a retrospective cohort of patients with ovarian cancer and peritoneal carcinomatosis. (Adapted from Tempfer et al. [21])
Datei:
Abb.-Typ: Strich-Abb.
Farbigkeit (IST): 1c
Farbigkeit (SOLL): 1c
Bildrechte: [Urheberrecht beim Autor]
Abdruckrechte: Nicht notwendig
Hinweise Verlag/Setzerei:

gastrointestinal tumors. In line with the data from ovarian cancer studies, quality of life was stabilized by repeated PIPACs. For example, Odendahl et al. investigated 91 patients with PC from various primary tumors such as gastric cancer, colon cancer, ovarian cancer, mesothelioma, and cancer of unknown origin [14]. In this longitudinal study, patients had low levels of overall quality of life at the beginning of therapy and after the first PIPAC. With increasing numbers of PIPAC applications, overall quality of life continuously improved. Notably, the gastrointestinal morbidity remained stable throughout treatment. In none of these studies did PIPAC lead to a decline in qual-

ity of life. However, selected parameters such as abdominal pain and dyspnea increased under PIPAC [21, 22].

- Clinical studies assessing the long-term effect of PIPAC on quality of life suggest that PIPAC leads to a stabilization and/or improvement of quality of life.

In a case report of a 75-year-old patient with non-resectable ovarian cancer with PC, who was unable to undergo systemic standard chemotherapy with carboplatin and paclitaxel, 13 cycles of PIPAC with cisplatin and doxorubicin were applied [23]. This led to a marked initial improvement of her quality of life followed by a disease stabilization and stable

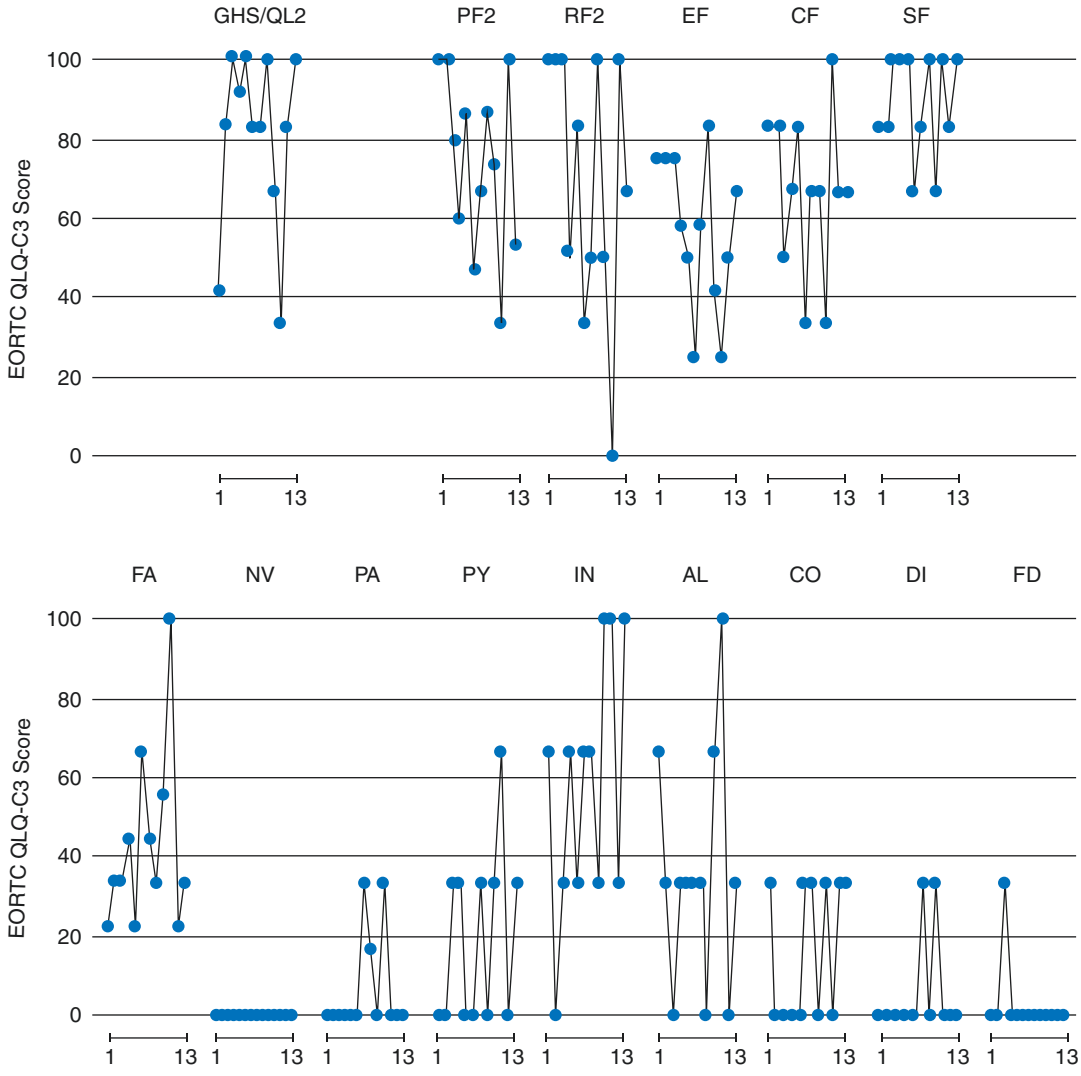


Fig. 37.6 Measurements of quality of life by EORTC-QLQ-C30 questionnaire during 13 cycles of pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in a patient with advanced ovarian cancer (GHS/OL2 global health score, PF2 physical functioning (revised), RF2 role functioning (revised), EF emotional functioning, CF cognitive functioning, SF social functioning, FA fatigue, NV nausea and vomiting, PA pain, DY dyspnea, IN insomnia, AL appetite loss, CO constipation, DI diarrhea, FD financial difficulties). (Adapted from Tempfer et al. [23])

Datei:
Abb.-Typ: Strich-Abb.
Farbigkeit (IST): 1c
Farbigkeit (SOLL): 1c
Bildrechte: [Urheberrecht beim Autor]
Abdruckrechte: Nicht notwendig
Hinweise Verlag/Setzerei:

quality of life over a time period of 2 years (Fig. 37.6).

In summary, the available data suggest that PIPAC does not impair quality of life, but is able to stabilize or improve quality of life in patients with PC in terms of gastrointestinal factors, overall quality of life, and functional parameters such as role and physical functioning.

▶ **Summary and Prospect** PIPAC is a new locoregional treatment for peritoneal carcinomatosis. The safety and efficacy of PIPAC have been documented in case reports, retrospective cohort studies, and prospective clinical phase I and phase II trials in patients with peritoneal carcinomatosis derived from various malignancies such as ovarian, gastric, and colon cancer. PIPAC offers locoregional cytotoxic treatment while preserving and/or improving quality of life. *Important:* A number of clinical studies in various patient populations with PC demonstrated an improvement of gastrointestinal symptoms (nausea, emesis, diarrhea), overall quality of life, role functioning, social functioning, physical fitness, cognitive functioning, as well as social and emotional ability. Therefore, PIPAC offers an alternative for patients with a prolonged disease course characterized by multiple sequential systemic chemotherapies and a subsequent loss of quality of life. In palliative treatment of patients with PC, interventions with a positive effect on quality of life such as PIPAC are rare and therefore of benefit for patients.

References

1. Aust S, Knogler T, Pils D, Obermayr E, Reinthaller A, Zahn L, Radlgruber I, Mayerhofer ME, Grimm C, Polterauer S. Skeletal muscle depletion and markers for cancer cachexia are strong prognostic factors in epithelial ovarian cancer. PLoS One. 2015;10:e0140403.
2. Christoph B. Weiter deutliche Zufriedenheitsdifferenzen zwischen Ost und West trotz Annäherung in manchen Bereichen. Zur Entwicklung des subjektiven Wohlbefindens in der Bundesrepublik 1990–2000. Informationsdienst Soziale Indikatoren, Ausgabe 28, ISI 28, Mannheim, S11–14; 2002.
3. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, Jatoi A, Kalantar-Zadeh K, Lochs H, Mantovani G, Marks D, Mitch WE, Muscaritoli M, Najand A, Ponikowski P, Rossi Fanelli F, Schambelan M, Schols A, Schuster M, Thomas D, Wolfe R, Anker SD. Cachexia: a new definition. Clin Nutr. 2008;27:793–9.
4. Giger-Pabst U, Solass W, Buerkle B, Reymond MA, Tempfer CB. Low-dose pressurized intraperitoneal aerosol chemotherapy (PIPAC) as an alternative therapy for ovarian cancer in an octogenarian patient. Anticancer Res. 2015;35:2309–14.
5. Graversen M, Pfeiffer P, Mortensen MB. Treatment of peritoneal carcinomatosis with pressurized intraperitoneal aerosol chemotherapy. Ugeskr Laeger. 2016;178:pii: V11150928.
6. Hilal Z, Rezniczek GA, Klenke R, Dogan A, Tempfer CB. Nutritional status, cachexia, and anorexia in women with peritoneal metastasis and intraperitoneal chemotherapy: a longitudinal analysis. J Gynecol Oncol. 2017;28(6):e80.
7. Kahle B, editor. Hintergrund: Was ist Lebensqualität? 2016. https://web.archive.org/web/20070928004750/http://www.irs-net.de/anzeigen.php?choice1=monitoring&choice2=monitoring2. Zugriff 10.09.2016.
8. Knecht A. Lebensqualität produzieren. Eine Ressourcentheorie und Machtanalyse. Wiesbaden: VS-Verlag; 2010.
9. Koch T. Lebensqualität und Ethik – am Beispiel der Medizin. In: Seifert G, editor. Lebensqualität in unserer Zeit – Modebegriff oder neues Denken? Göttingen: Vandenhoeck & Ruprecht; 1992. p. 5–15.
10. Laviano A, Gori C, Rianda S. Sarcopenia and nutrition. Adv Food Nutr Res. 2014;71:101–36.
11. Lemoine L, Sugarbaker P, van der Speeten K. Pathophysiology of colorectal peritoneal carcinomatosis: role of the peritoneum. World J Gastroenterol. 2016;22:7692–707.
12. Mantovani G, Maccio A, Madeddu C, Gramignano G, Serpe R, Massa E, Dessì M, Tanca FM, Sanna E, Deiana L, Panzone F, Contu P, Floris C. Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results. Nutrition. 2008;24:305–13.
13. Nordhausen K, Solass W, Demtroeder C, Tempfer CB, Reymond MA. Cachexia-anorexia syndrome in patients with peritoneal metastasis: an observational study. Pleura Peritoneum. 2016;1:57–63.
14. Odendahl K, Solass W, Demtröder C, Giger-Pabst U, Zieren J, Tempfer C, Reymond MA. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Eur J Surg Oncol. 2015;41:1379–85.
15. Ockenga J, Valentini L. Review article: anorexia and cachexia in gastrointestinal cancer. Aliment Pharmacol Ther. 2005;22:583–94.
16. Robella M, Vaira M, De Simone M. Safety and feasibility of pressurized intraperitoneal aerosol

chemotherapy (PIPAC) associated with systemic chemotherapy: an innovative approach to treat peritoneal carcinomatosis. World J Surg Oncol. 2016;14:128.
17. Seelaender M, Laviano A, Busquets S, Püschel GP, Margaria T, Batista ML Jr. Inflammation in Cachexia. Mediat Inflamm. 2015;2015:536954.
18. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, Zieren J, Schwab M, Reymond MA. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21:553–9.
19. Tarricone R, Ricca G, Nyanzi-Wakholi B, Medina-Lara A. Impact of cancer anorexia-cachexia syndrome on health-related quality of life and resource utilisation: a systematic review. Crit Rev Oncol Hematol. 2016;99:49–62.
20. Tempfer CB. Pressurized intraperitoneal aerosol chemotherapy as an innovative approach to treat peritoneal carcinomatosis. Med Hypotheses. 2015;85:480–4.
21. Tempfer CB, Rezniczek GA, Ende P, Solass W, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin in women with peritoneal carcinomatosis: a cohort study. Anticancer Res. 2015;35:6723–9.
22. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, Rezniczek GA, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol. 2015;137:223–8.
23. Tempfer C, Hartmann F, Hilal Z, Rezniczek GA. Intraperitoneal cisplatin and doxorubicin as maintenance chemotherapy for unresectable ovarian cancer: a case report. BMC Cancer. 2017;17(1):26.
24. Tempfer CB, Giger-Pabst U, Seebacher V, Petersen M, Dogan A, Rezniczek GA. A phase I, single-arm, open-label, dose escalation study of intraperitoneal cisplatin and doxorubicin in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Gynecol Oncol. 2018;150(1):23–30.
25. von Haehling S, Anker SD. Treatment of cachexia: an overview of recent developments. Int J Cardiol. 2015;184:736–42.
26. Yonemura Y, Canbay E, Endou Y, Ishibashi H, Mizumoto A, Miura M, et al. Peritoneal cancer treatment. Expert Opin Pharmacother. 2014;15:623–36.

Part XI

Recurrent Disease

38 Follow-Up to Prevent Recurrence of Peritoneal Malignancies

Ruediger Hoerbelt and Winfried Padberg

38.1 Primary Malignancies of the Peritoneum

38.1.1 Mucinous Neoplasia of the Appendix Vermiformis and Pseudomyxoma Peritonei (PMP)

Since 20% of mucinous neoplasia of the appendix ultimately result in PMP [19], even for low-grade appendiceal mucinous neoplasm (LAMN), aggressive therapeutic approaches have been discussed. Mc Donald et al. subdivided LAMN into Type I with intraluminal and Type II with extraluminal deposition of mucin. Whereas patients with Type I LAMN received a follow-up only, cytoreductive surgery and HIPEC was recommended for Type II. Using this strategy, no progression of the disease was observed at 40 months [14].

A retrospective analysis of a group of patients with pseudomyxoma peritonei from the Washington Cancer Center—62% of patients with disseminated peritoneal adenomucinosis (DPAM), 38% with peritoneal mucinous metastases (PMCA)—revealed a 10-year overall survival of 85% and a recurrence rate of 28% (111 of 402 patients). A follow-up including medical history, clinical investigation, serum levels of CEA and CA19-9, and CT scan was performed at 6-month intervals. After a median time of 7 months, 84% of patients received a planned second-look laparotomy (usually for an ostomy closure). In 42 of these cases (50%), a progression of disease was detected. Multivariate analysis identified the extent of the initial surgery (resection of more than 5 regions), PCI >20, and histological differentiation (PMCA-I or PMCA vs. DPAM) as independent risk factors for a reduced recurrence-free survival [24]. Similarly, in a retrospective analysis of 162 patients with mucinous neoplasia of the appendix, recurrent disease was found in 26 cases using CT scan and CEA after a median follow-up of 23 months [17]. The predictive value of CEA and CA19-9 during follow-up was shown in a retrospective analysis of 532 patients with PMP. Normal pretreatment serum levels of CEA and CA19-9 were associated with a better prognosis, whereas elevated levels were detected in 68% of patients with recurrent disease. A normal CEA at the time of recurrence correlated with a good response to second-look surgery [5]. In a retrospective multivariate analysis of 156 patients, Kusamura et al. were able to demonstrate cut-off values for CA125 and CA19-9 (>125 U/ml and >89 U/ml, respectively) to predict recurrence [13, 29]. However, a follow-up of PMP patients should include annual CT of the abdomen and pelvis until 6 years. From year 6 on, reduced frequency of follow-up is proposed, independent of the histology [27, 29].

R. Hoerbelt (✉) · W. Padberg
University of Giessen, Giessen, Germany
e-mail: Ruediger.Hoerbelt@chiru.med.uni-giessen.de; winfried.padberg@chiru.med.uni.giessen.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_38

Recently a consensus statement was initiated by the members of the Peritoneal Surface Oncology Group International (PSOGI). Recommendations are provided based on three Delphi voting rounds with GRADE-based questions among a panel of 80 worldwide PMP experts.

Within this recommendation, tumor markers (CEA and Ca19-9) are mandatory preoperatively and in the follow-up. Preoperative CT evaluation of patients with appendiceal PMP should be the preferred diagnostic imaging modality.

38.2 Peritoneal Mesothelioma

The establishment of CRC and HIPEC as the standard treatment for resectable peritoneal mesothelioma resulted in a median overall survival of 53 months and 5-year survival of 47% in the largest retrospective multicenter study. The multivariate analysis identified the epithelioid subtype, the completeness of cytoreduction, and the absence of lymphatic disease as relevant factors for a good prognosis [25]. The value of a complete cytoreduction was further supported by more recent data from Baratti et al., who, in a matched-pair analysis, compared selective peritonectomy with complete parietal peritonectomy. A significantly better median overall survival (>50 months vs. 29.6 months) and progression-free survival (>50 months vs. 14.4 months) were detected in the group of complete peritonectomy [1].

The effectiveness of repeated cytoreductive surgery and HIPEC for recurrent peritoneal mesothelioma has been investigated by Wong et al. in a retrospective study. Out of 26 patients, 8 received repeat CRS with HIPEC. As compared to patients with single surgery, morbidity and mortality were not different in the group undergoing repeated surgery. Furthermore, second cytoreductive surgery and HIPEC led to improved median overall survival (>80 months vs. 27.6 months after single surgery) [23].

These good results for repeat surgery underline the high value of sufficient follow-up after treatment of peritoneal mesothelioma. Accordingly, recommendations for follow-up include clinical examination, CA125 [1], and CT scan at 4-month intervals within the first 2 years and every 6 months thereafter [8, 28].

Another consensus statement by the PSOGI Group was done for peritoneal mesothelioma [28]. Cross-sectional imaging with CT for preoperative evaluation for mesothelioma should be the preferred diagnostic imaging modality. The determination of baseline serum CA125 and mesothelin level could be included in the preoperative workup of the patients.

38.3 Secondary Peritoneal Malignancies

38.3.1 Peritoneal Metastasis from Colorectal Cancer

During follow-up for colorectal carcinoma, several situations can occur with regard to peritoneal metastases.

38.3.1.1 Colorectal Carcinoma Without Risk Factors

The primary cancer was treated by surgery and (neo-)adjuvant (radio-)chemotherapy, and no synchronous peritoneal metastases was detected.

According to the German S3 guideline for colorectal carcinoma, medical history, physical examination, CEA, endoscopy, and CT scan at 6-month intervals for the first 2 years and in yearly intervals thereafter are recommended.

Epidemiological data by Quere et al. show that the cumulative risk of developing peritoneal metastases is about 6% following resection of a colorectal carcinoma without risk factors (i.e., Stage >II, mucinous type, or perforation), and there is no need to intensify surveillance.

38.3.1.2 Colorectal Carcinoma with High Risk

Following sufficient therapy of a colorectal primary, there are risk factors for the development of metachronous peritoneal metastases.

One of the most important prognostic factors in the therapy for peritoneal metastases is the extent of disease [12]. This is a strong argument in favor of attempting to detect and treat peritoneal

metastases at an early stage. Several risk factors promoting metachronous peritoneal metastases have been identified, such as resected synchronous peritoneal metastases (64–91% recurrence rate), resected isolated ovarian metastases (27–56% recurrence rate) [10], mucinous adenocarcinoma (MCA; synchronous PC 22.2% in MCA vs. 6% in non-MCA) [15], spontaneous or inadvertent tumor perforation (14–58% peritoneal recurrence rate) [4, 9, 18, 22], and locally advanced stage (pT4) [26]. Based on encouraging results of a retrospective analysis on the value of an intensified follow-up including second-look surgery [9], Goéré et al. recently performed a prospective randomized phase III trial. After resection of the primary colorectal carcinoma and 6 months of adjuvant chemotherapy, patients at high risk of developing colorectal peritoneal metastases were randomized into conventional follow-up or systematic second-look surgery plus HIPEC (intraperitoneal oxaliplatin). The authors were able to confirm the role of a peritoneal-centered surveillance showing a 52% rate of peritoneal metastases during the second-look laparotomy (median peritoneal cancer index of 4 (0–26)). However, overall survival was not affected by the proactive follow-up protocol including HIPEC with oxaliplatin (published at ASCO 2018 Abstract no. 3531; ProphyloCHIP Trial NCT01226394).

Given the high rate of peritoneal relapse, and regardless of the discouraging result of preemptive HIPEC in the ProphyloCHIP Trial, patients with a high risk for metachronous peritoneal metastases should undergo second-look surgery, depending on the results of the preoperative CT scan.

38.3.1.3 Colorectal Carcinoma Following Cytoreductive Surgery and HIPEC for Peritoneal Metastases

Synchronous and metachronous peritoneal metastases were adequately treated by cytoreduction and HIPEC.

The rate of recurrence following cytoreductive surgery and HIPEC has been shown to be between 62% and 73% [3, 11, 21], and peritoneal relapse usually occurs between 10 and 13.7 months after initial treatment [3]. The sensitivity of the CT scan to detect peritoneal metastases ranges between 60% and 70%. By adding a FDG-PET scan, sensitivity could be improved to 82.6% [2]. Others have found rates of false-negative results of imaging studies higher than 50% [10].

Due to the high probability of recurrence following resection of colorectal peritoneal metastases, and in order to detect the disease at an early stage, follow-up should be complemented with second-look laparoscopy at 12 months after initial surgery, depending on the result of the CT scan.

38.3.2 Peritoneal Metastases from Gastric Cancer

There is no good evidence that prognosis of gastric cancer can be improved by a follow-up with early detection of recurrence. Accordingly, the German S3 guideline for gastric cancer recommends only a symptom-based surveillance. Furthermore, it is unclear whether treatment of peritoneal recurrence or progression can improve survival. Data from a recent French register study showed long-term survival only for synchronous peritoneal metastases and for a peritoneal cancer index below seven [6]. Compared to other entities, detection of peritoneal disease at an early stage seems even more important in gastric cancer. Therefore, strategies aiming for the selection of gastric cancer patients at high risk for the development for peritoneal metastases are desirable. Roviello et al. identified diffuse subtype, locally advanced tumor, serosal infiltration, and lymphonodular involvement as risk factors for recurrence—the latter comprised of peritoneal, lymphonodular, and hematogenic relapse, which occurs within the first year in 80% and within the first 6 months after multimodal treatment in 50% of cases [16]. Coccolini et al. performed a retrospective case control study investigating the effect of prophylactic HIPEC in advanced gastric cancer (T3/T4) without manifestation of peritoneal metastases. Compared to patients who were treated with neoadjuvant chemotherapy and gastric surgery alone, the addition of HIPEC (paclitaxel and cisplatin) to the otherwise identical

protocol led to increased overall survival (34.8 months vs. 27.1 (T4) and 28.2 (T3)). Although these data did not reach significance due to the low number of patients (n = 44) included [7], the strategy of prophylactic HIPEC seems convincing and is currently being investigated in more detail in the prospective randomized phase III GASTRICHIP Trial (NCT01882933). A meta-analysis by Sun et al. revealed a significant advantage in overall survival for prophylactic HIPEC compared to gastrectomy alone [20].

Since there is a high risk of peritoneal recurrence in advanced gastric cancer, surveillance should be intensified individually in selected patients. Clinical examination, CEA, CA19-9 and CA72-4, and CT scan or PET/CT scan should be performed at 4-month intervals within the first 2 years and every 6 months thereafter [16]. In order to detect peritoneal recurrence early with higher sensitivity, staging laparoscopy should be considered starting at 6 months after initial treatment.

References

1. Baratti D, Kusamura S, Cabras AD, Deraco M. Cytoreductive surgery with selective versus complete parietal peritonectomy followed by hyperthermic intraperitoneal chemotherapy in patients with diffuse malignant peritoneal mesothelioma: a controlled study. Ann Surg Oncol. 2012;19:1416–24.
2. Berthelot C, Morel O, Girault S, Verrièle V, Poirier A-L, Moroch J, Lorimier G. Use of FDG-PET/CT for peritoneal carcinomatosis before hyperthermic intraperitoneal chemotherapy. Nucl Med Commun. 2011;32(1):23–9.
3. Bijelic L, Yan TD, Sugarbaker PH. Treatment failure following complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from colorectal or appendiceal mucinous neoplasms. J Surg Oncol. 2008;98(4):295–9.
4. Brodsky JT, Cohen AM. Peritoneal seeding following potentially curative resection of colonic carcinoma: implications for adjuvant therapy. Dis Colon Rectum. 1991;34(8):723–7.
5. Carmignani CP, Hampton R, Sugarbaker CE, Chang D, Sugarbaker PH. Utility of CEA and CA 19-9 tumor markers in diagnosis and prognostic assessment of mucinous epithelial cancers of the appendix. J Surg Oncol. 2004;87(4):162–6.
6. Chia CS, You B, Decullier E, Vaudoyer D, Lorimier G, Abboud K, et al. Patients with peritoneal carcinomatosis from gastric cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: is cure a possibility? Ann Surg Oncol. 2016;23:1971–9.
7. Coccolini F, Celotti A, Ceresoli M, Montori G, Marini M, Catena F, Ansaloni L. Hyperthermic intraperitoneal chemotherapy (HIPEC) and neoadjuvant chemotherapy as prophylaxis of peritoneal carcinosis from advanced gastric cancer—effects on overall and disease free survival. J Gastrointest Oncol. 2016;7(4):523–9.
8. Deraco M, Bartlett D, Kusamura S, Baratti D. Consensus statement on peritoneal mesothelioma. J Surg Oncol. 2008;98(4):268–72.
9. Elias D, Goéré D, Di Pietrantonio D, Boige V, Malka D, Kohneh-Shahri N, et al. Results of systematic second-look surgery in patients at high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2008;247(3):445–50.
10. Elias D, Honore C, Dumont F, Ducreux M, Boige V, Malka D, Goere D. Results of systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2011;254(2):289–93.
11. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, Gilly FN. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol. 2004;22(16):3284–92.
12. Goéré D, Souadka A, Faron M, Cloutier AS, Viana B, Honoré C, Elias D. Extent of colorectal peritoneal carcinomatosis: attempt to define a threshold above which HIPEC does not offer survival benefit: a comparative study. Ann Surg Oncol. 2015;22(9):2958–64.
13. Kusamura S, Hutanu I, Baratti D, Deraco M. Circulating tumor markers: predictors of incomplete cytoreduction and powerful determinants of outcome in pseudomyxoma peritonei. J Surg Oncol. 2013;108(1):1–8.
14. McDonald JR, O'Dwyer ST, Rout S, Chakrabarty B, Sikand K, Fulford PE, Renehan AG. Classification of and cytoreductive surgery for low-grade appendiceal mucinous neoplasms. Br J Surg. 2012;99(7):987–92.
15. Nozoe T, Anai H, Nasu S, Sugimachi K. Clinicopathological characteristics of mucinous carcinoma of the colon and rectum. J Surg Oncol. 2000;75(2):103–7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11064389.
16. Roviello F, Marrelli D, De Manzoni G, Morgagni P, Di Leo A, Saragoni L, De Stefano A. Prospective study of peritoneal recurrence after curative surgery for gastric cancer. Br J Surg. 2003;90(9):1113–9.
17. Sardi A, Jimenez WA, Nieroda C, Sittig M, Macdonald R, Gushchin V. Repeated cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in peritoneal carcinomatosis from appendiceal cancer:

analysis of survival outcomes. Eur J Surg Oncol. 2013;39(11):1207–13.
18. Slanetz CA. The effect of inadvertent intraoperative perforation on survival and recurrence in colorectal cancer. Dis Colon Rectum. 1984;27(12):792–7.
19. Smeenk RM, van Velthuysen MLF, Verwaal VJ, Zoetmulder FAN. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. Eur J Surg Oncol. 2008;34(2):196–201.
20. Sun J, Song Y, Wang Z, Gao P, Chen X, Xu Y, Xu H. Benefits of hyperthermic intraperitoneal chemotherapy for patients with serosal invasion in gastric cancer: a meta-analysis of the randomized controlled trials. BMC Cancer. 2012;12(1):526.
21. Verwaal VJ, van Ruth S, de Bree E, van Slooten GW, van Tinteren H, Boot H, Zoetmulder FAN. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21(20):3737–43.
22. Willett C, Tepper JE, Cohen A, Orlow E, Welch C. Obstructive and perforative colonic carcinoma: patterns of failure. J Clin Oncol. 1985;3(3):379–84.
23. Wong J, Koch AL, Deneve JL, Fulp W, Tanvetyanon T, Dessureault S. Repeat cytoreductive surgery and heated intraperitoneal chemotherapy may offer survival benefit for intraperitoneal mesothelioma: a single institution experience. Ann Surg Oncol. 2014;21(5):1480–6.
24. Yan TD, Bijelic L, Sugarbaker PH. Critical analysis of treatment failure after complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from appendiceal mucinous neoplasms. Ann Surg Oncol. 2007;14(8):2289–99.
25. Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Sugarbaker PH, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma : multi-institutional experience. J Clin Oncol. 2009;27(36):6237–42.
26. Yang S-H, Lin J-K, Lai C-R, Chen C-C, Li AF-Y, Liang W-Y, Jiang J-K. Risk factors for peritoneal dissemination of colorectal cancer. J Surg Oncol. 2004;87(4):167–73.
27. Govaerts K, Chandrakumaran K, Carr NJ, Cecil TD, Dayal S, Mohamed F, Thrower A, Moran BJ. Single centre guidelines for radiological follow-up based on 775 patients treated by cytoreductive surgery and HIPEC for appendiceal pseudomyxoma peritonei. Eur J Surg Oncol. 2018;44(9):1371–7.
28. Kusamura S, Kepenekian V, Villeneuve L, Lurvink RJ, Govaerts K, De Hingh I, Moran BJ, Van der Speeten K, Deraco M, Glehen O. Peritoneal mesothelioma: PSOGI/EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol. 2021;47(1):36–59. https://doi.org/10.1016/j.ejso.2020.02.011.
29. Taflampas P, Dayal S, Chandrakumaran K, Mohamed F, Cecil TD, Moran BJ. Pre-operative tumour marker status predicts recurrence and survival after complete cytoreduction and hyperthermic intraperitoneal chemotherapy for appendiceal Pseudomyxoma Peritonei: analysis of 519 patients. Eur J Surg Oncol. 2014;40(5):515–20.

39 Localization of Peritoneal Tumor Recurrence

Ines Gockel, Boris Jansen-Winkeln, and Alexey Surov

39.1 Introduction

Summary

Recurrences of peritoneal tumors are frequent. Their localization is of utmost importance, because mainly this aspect builds the basis for repeated therapy and potential cure. The combination of modern imaging and re-exploration by diagnostic laparoscopy, probably laparotomy, plays an important role in the context of exact localization diagnostics and consecutive therapy measures.

Multidetector (MD)-CT is the diagnostic tool of choice for tumor recurrences of the peritoneum. These can be presented by specific imaging-morphologic patterns. During diagnostic re-exploration (laparoscopic or open), the rate of "non-access" abdomen is high and specified by about 20%. Ultimately, histological verification and correlation of findings with imaging is crucial.

I. Gockel (✉) · B. Jansen-Winkeln
Department of Visceral, Transplant, Thoracic and Vascular Surgery, Department of Operative Medicine (DOPM), University Hospital of Leipzig, Leipzig, Germany
e-mail: ines.gockel@medizin.uni-leipzig.de; boris.jansen-winkeln@medizin.uni-leipzig.de

A. Surov
Department of Radiology, Otto-von-Guericke-University, Medical Faculty, University Hospital of Magdeburg, Magdeburg, Germany
e-mail: alexey.surov@med.ovgu.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_39

Multimodal therapy concept of peritoneal tumor recurrences, also following extensive cytoreduction with hyperthermic intraperitoneal chemotherapy (HIPEC), is orientated on diverse tumor- and patient-specific factors, which have to be weighed up against each other carefully with regard to indication to reoperation with repeated cytoreduction and HIPEC in the interdisciplinary tumor conference.

Early detection of peritoneal tumor recurrence represents the only chance of potentially curative treatment, although the prognosis for recurrent tumor manifestation—independent of the present entity and the distribution—remains poor. Recurrences after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are reported to develop in approximately 80% of patients [12]. Recurrences can present either intraabdominally or occur as distant metastases. In the present chapter, special focus is placed on manifestations of intraperitoneal tumor recurrence. After an initial suspected diagnosis has been established—based on the medical history, results of the clinical examination, sonographic findings, and an analysis of the tumor markers—the combination of modern imaging techniques and re-exploration via diagnostic laparoscopy is of crucial importance for accurate localization diagnostics and subsequent therapeutic measures. Since peritoneal recurrence can, on principle, occur at any time following initial remission after systemic

therapy or cytoreductive surgery—with or without intraperitoneal chemotherapy—specific recommendations on structured aftercare are currently not available. It remains, however, indisputable that the temporal interval to disease recurrence is associated with poorer survival after treatment of the respective local recurrence [12]. In addition to patient-specific immunological factors, the risk for local recurrence is determined according to Sugarbaker's Peritoneal Cancer Index (PCI) and the CCR-Stage (Completeness of Cytoreduction Score), as well as by following the identification of histopathologic characteristics of the original tumor or its metastases (degree of differentiation), the original presence of a primary or secondary malignant peritoneal tumor, and the response to systemic treatment. However, clinically established risk-factor scores for the purpose of stratification of the frequency and intensity of aftercare measures are not available at this time. Clinical practice is therefore characterized by a more symptom-oriented application of imaging and diagnostic laparoscopy in patients with suspected recurrence of peritoneal cancer. In these cases, the cardinal symptoms—in parallel with general tumor signs, such as appetite and weight loss, fatigue, or paraneoplastic manifestations—include newly emerged ascites and gastrointestinal dysfunction in the sense of an ileus or subileus. Pathognomonic, in these instances, is the presence of ascites, which enables a rapid although localization-unspecific diagnosis on the basis of paracentesis and cytology.

The distribution pattern of primary malignant tumors as, for example, pseudomyxoma peritonei, is not coincidental but determined by gravity, since it follows the flow pattern of the peritoneal fluid, whereby the mucus-producing epithelial cells tend to collect deep within the pelvis, as well as paracolically, in the omentum, in the diaphragm, and in the right subhepatic space [13]. In contrast, information on the predilection sites for recurrent primary or secondary peritoneal malignancies remains limited. However, contrary to local recurrence, disseminated distribution patterns may be an indication of the lack of adhesion properties of the tumor cells, independent of the presence of a primary or a recurrence situation [9].

39.2 The Role of Diagnostic Imaging

Multidetector computed tomography (MD-CT) is the diagnostic method of choice for recurrent peritoneal tumors. These may be visualized with the use of different imaging modalities [6]:

- Solitary or multiple, nodular peritoneal densities (Figs. 39.1 and 39.2) – highly variable in size, number, and pattern of contrast enhancement
- Diffuse, plaque-like densifications covering the viscera (Fig. 39.3a, b)
- Striated or striated-finely nodular densifications of the mesentery and the serosa (Figs. 39.4 and 39.5)

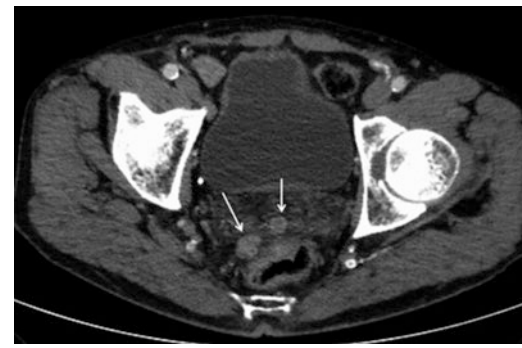


Fig. 39.1 Various homogenous nodules in the lesser pelvis pararectal, depicting the peritoneal recurrence of a primary peritoneal metastatic gastric carcinoma

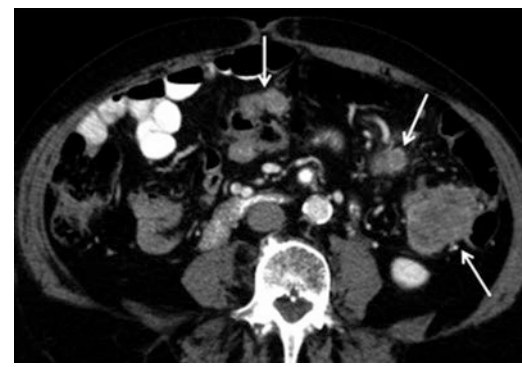


Fig. 39.2 Large inhomogeneous, diffusely distributed intraperitoneal nodes adhering to the intestinal loops are representative of recurrent peritoneal metastases of an ovarian carcinoma after initial cytoreductive surgery with peritonectomy

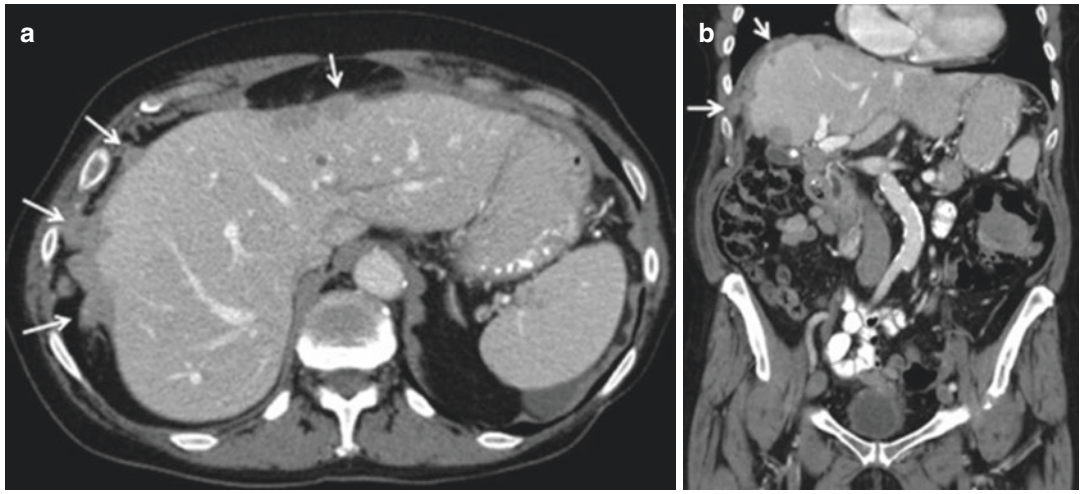


Fig. 39.3 (**a**, **b**) Pronounced nodular, plaque-like parahepatic densifications as recurrent peritoneal metastases of an ovarian carcinoma

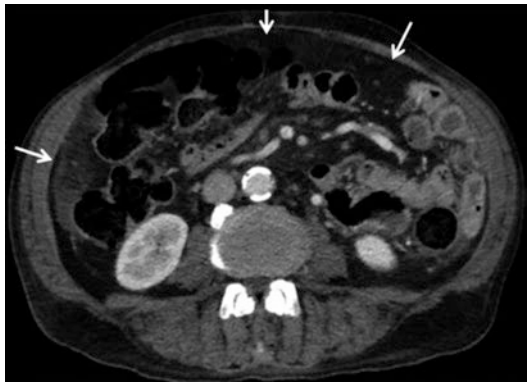


Fig. 39.4 Delicate, striped densifications of mesenteric tissue representative of peritoneal cholangiocellular carcinoma recurrence

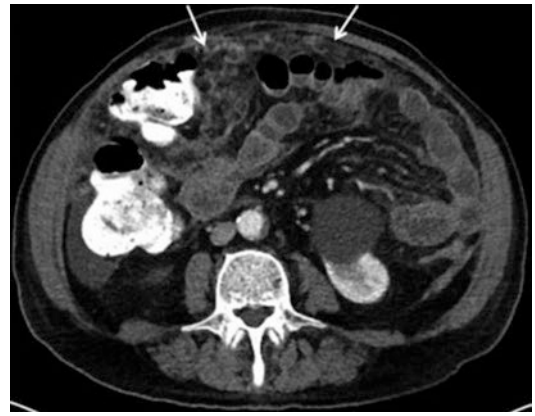


Fig. 39.5 Marked stripy-nodular changes in peritoneal recurrence of gastric cancer

- Nodular or plate-like thickening of the omentum, the so-called omental cake (Fig. 39.6a, b)
- Mucinous, imposing lesions (similar to ascites) with scalloping of the liver and the spleen (Fig. 39.7)

Also possible is a mixed clinical manifestation form representing a combination of the different patterns described above. In the majority of cases, the peritoneal alterations are associated with variable quantities of ascites (frequently high in protein with increased density) (Fig. 39.8).

Peritoneal recurrences tend to infiltrate the abdominal wall with frequently large space-occupying lesions (Fig. 39.9), which may already be palpable on clinical examination. In principle, the surgical entryways associated with the previous operations as well as trocar- or drainage-insertion sites are possible locations of predilection for peritoneal recurrence—here in the sense of previous intraoperative (iatrogenic) tumor cell spread.

The radiographic examination generally does not enable a differentiation between the shape, density, spread, or infiltration pattern of recurrences and peritoneal primary tumors. However, no data regarding correlation with histopathological findings are currently available so that, in

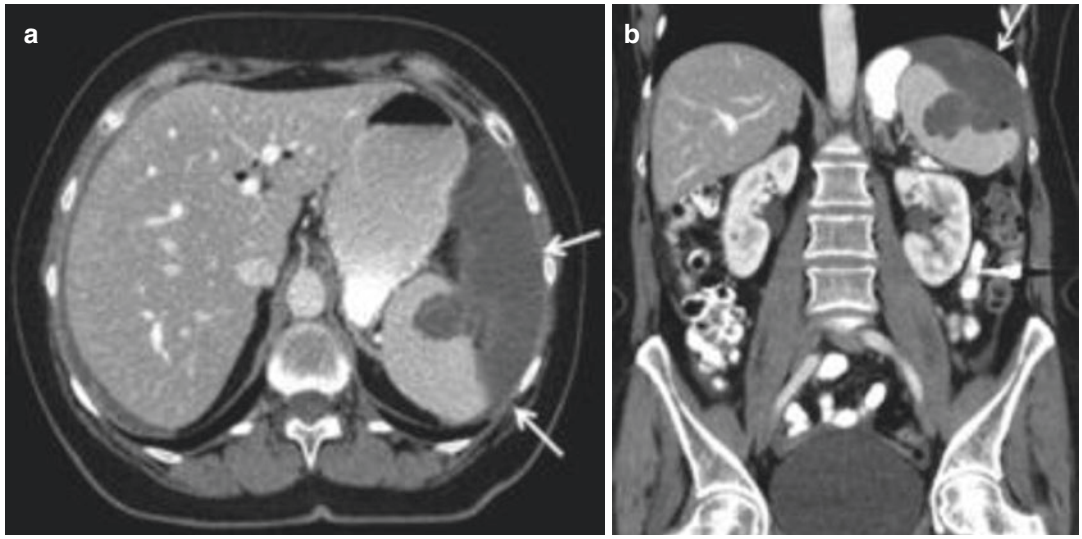


Fig. 39.6 (**a**, **b**) Marked nodular changes in the greater omentum in peritoneal recurrence of gastric cancer

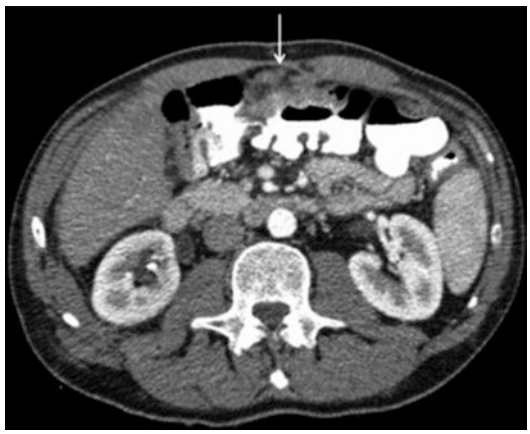


Fig. 39.7 Axial section. Peritoneal recurrence with ascites-like encapsulated and septated solid masses indenting the spleen in histologically proven peritoneal recurrence of low-grade type pseudomyxoma peritonei

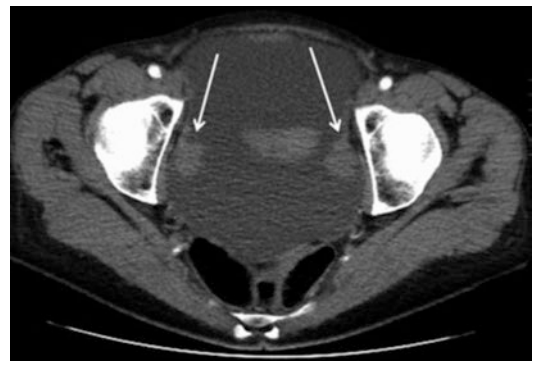


Fig. 39.8 Clear evidence of ascites and ovarian tumor (Krukenberg tumor) presenting as peritoneal recurrence of gastric cancer

individual cases, the possibility of postoperative scar and adhesion formation cannot be excluded after extended cytoreduction and peritonectomy, and the performance of a differential diagnosis needs to be considered [6]. Localizations of recurrences may occur both locoregionally and being disseminated intraabdominally and in the small pelvis. Recurrences may further present as a solitary tumor at a considerable distance from the primary localization, as shown in Fig. 39.10, thus similar to the peritoneal recurrence of a pararectally draining metastasis from a peritoneal metastatic gastric carcinoma. Radiologic predictors of the type and localization of the peritoneal recurrence for use in primary diagnostics do not exist.

Analogous to MD-CT, there is a lack of information in the literature on individual imaging characteristics of MRI, PET-CT, and PET-MRI with a view to specific localization diagnostics of recurrent peritoneal tumors, requiring these masses to be evaluated like primary peritoneal lesions.

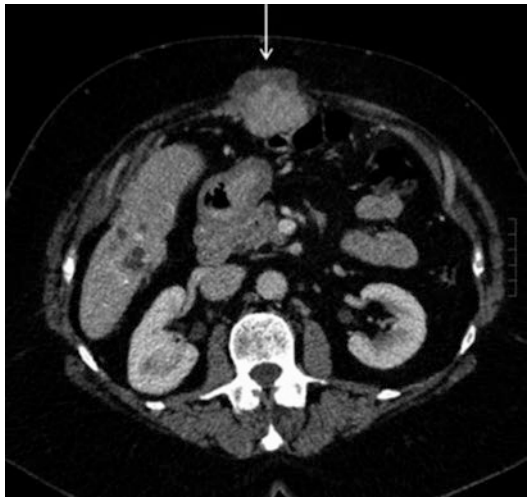


Fig. 39.9 Large ventral peritoneal node with infiltration of the ventral abdominal wall presenting as recurrence of gastric carcinoma. In principle, the iatrogenic implantation of peritoneal tumors or metastases in the course of a previous operation may potentially be responsible for metastatic invasion in the areas of surgical access routes or trocar and drainage insertion points

39.3 The Role of Diagnostic Laparoscopy in Localization Diagnostics

The challenge for diagnostic laparoscopy in localization diagnostics of recurrent peritoneal tumors arises from the fact that a significant number of patients have previously undergone surgical exploration (possibly with cytoreductive surgery and HIPEC or EPIC—early postoperative intraperitoneal chemotherapy), and re-exploration with precise determination of the PCI by Sugarbaker may be hampered by the presence of adhesions.

The rate of "non-access" abdomen is very high and ranges at approximately 20% in our patient population, which is in accordance with rates reported in the literature [10]. Even if successful access to the abdominal cavity is achieved, the assessment may nevertheless be significantly limited. Furthermore, both a detailed laparo-

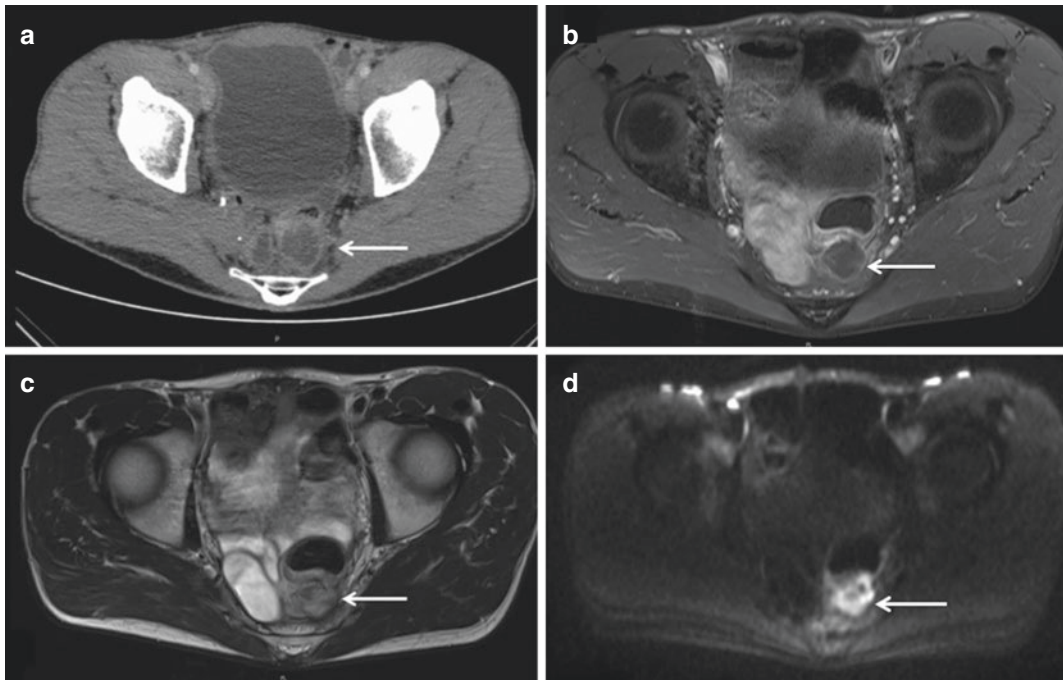


Fig. 39.10 (**a**–**d**) Second recurrence of a peritoneal metastasized gastric carcinoma with draining metastases in the small pelvis (pararectal). (**a**) The CT image shows a pararectal liquid formation (arrow) that was initially interpreted as a bulging of the bowel. (**b**) MRI of the pelvis (T1w) after intravenous administration of contrast medium demonstrates enhancement of the rim and demarcation from the rectum. (**c**) The MRI (T2w) image documents a textural signal intensity which is also different from that of the rectum. (**d**) DWI image (b800). Marked reduction of diffusion within the finding, thus rendering it highly suspect for the presence of recurrence of the peritoneal/pararectal metastasized gastric carcinoma

scopic inspection of all quadrants and an adequate biopsy may not be possible. Ultimately, the decisive factor is the histological verification and correlation of the findings with imaging results [2]. However, the meaningfulness of an extended adhesiolysis is questionable, taking into account the risks involved in the surgical procedure.

If the performance of repeated CRS and (repeated) HIPEC is advisable from an oncological point of view, and if laparoscopy permits only a limited assessment of the abdomen due to the presence of adhesions, a laparotomy should be carried out in the next stage. A complete abdominal exploration and the decision on the performance of extended surgery for tumor recurrence are not possible before this occurs.

Laparoscopic exploration may not always prove satisfactory, especially in the regions of the diaphragmatic cupola and the small pelvis (Fig. 39.11). However, even if this can be compensated with preoperative imaging, the finely knobbed, flat recurrence with foci from one to a few millimeters in size can nevertheless be assessed only with the use of laparoscopy. However, even if, after the described preliminary examination, a conclusive laparoscopic assessment of the small intestinal mesentery and the mesenteric root is not yet possible, the final decision can only be taken after open surgical exploration. Under conditions of peritoneal recurrence, laparoscopic visualization with histological confirmation is nevertheless achieved in the majority of patients, and vital information for therapy planning is thus obtained.

In the majority of cases, the combination of preoperative modern imaging techniques and laparoscopy paves the way for further treatment.

- The combination of modern imaging techniques and diagnostic laparoscopy is

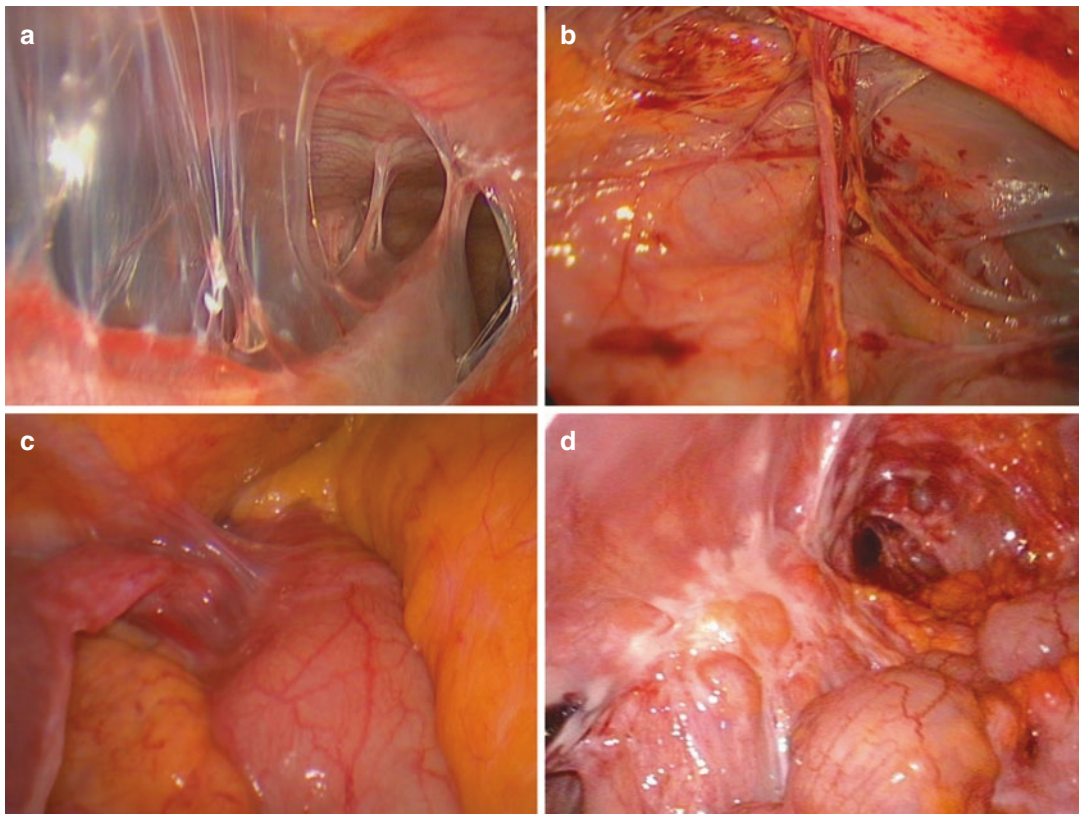


Fig. 39.11 (**a**–**d**) Diagnostic laparoscopy for peritoneal recurrence of metastasized gastric cancer. Laparoscopy generally does not yield satisfactory results, in particular in the region of the diaphragmatic cupola and the small pelvis

crucial for localization diagnostics of recurrent peritoneal tumors.

To date, no valid data have been reported in the literature on the sensitivity, specificity, diagnostic accuracy, and the negative and positive predictive value of modern imaging techniques and diagnostic laparoscopy or their combined use in localization diagnostics. All of the described factors are of particular importance in determining a suitable therapy for peritoneal tumor recurrences, which therefore need to be considered in analogy to available literature references on the initial diagnosis of peritoneal tumors.

39.4 Therapeutic Options

The multimodal therapy concept for recurrent peritoneal tumors, as well as for tumor recurrence after prior extended cytoreductive surgery with hyperthermic intraperitoneal chemotherapy, is based on a number of different tumor- and patient-specific factors, which have to be carefully weighed against each other in order to determine the indication for reoperation with repeat cytoreductive surgery and HIPEC. The ultimate decision reached after an interdisciplinary discussion always constitutes an individual recommendation, which has to take the benefits and risks of a possible multivisceral resection procedure into consideration. Due to the lack of basic data reported by prospective randomized studies on (a) repeat cytoreduction + HIPEC (embedded in an overall concept of systemic therapy) vs. (b) systemic therapy alone vs. (c) a system-oriented "watch-and-wait" strategy, it is currently impossible to make any clear statements pertaining to individual histological entities. The significance of (additive/complementary) PIPAC (pressurized intraperitoneal aerosol chemotherapy) and its long-term effect on situations, where it is (a) contraindicated and only the above options (b) and (c) are available for selection, remain to be seen [8]. Based on currently available data, under conditions of an overall palliative therapeutic approach, at least a symptom-oriented optimization potential in the sense of a reduction of ascetic fluid, as well as of an improvement of the quality of life in cases of disseminated recurrence of peritoneal tumors, may be assumed [5].

Close clinical and imaging follow-ups nevertheless remain essential after previous primary tumor resection (+ chemoperfusion) in order to enable the earliest possible detection of tumor recurrence and to initiate further treatment at the earliest possible time. Only under these conditions can a highly selected patient population receive a prognostic benefit with acceptable morbidity and mortality from the repeated surgical procedure [3, 4, 11].

Table 39.1 shows the spectrum of possible therapeutic options under conditions of existing recurrence localizations or tumor- and patient-specific characteristics.

In determining an oncologically adequate patient- or symptom-oriented therapy for the peritoneal recurrence, multiple factors that may interact with each other or become additively effective need to be considered. For example, a localized pattern of recurrence, the absence of organ-specific metastases, good differentiation, an achieved CCR-0 situation, and a long interval from primary surgery at a renewed opportunity for achieving complete cytoreduction, a good performance status of the patient, low comorbidity, good compatibility and a complication-reduced course of prior therapies constitute the "ideal" situation for repeated CRS + HIPEC. A poor response to systemic therapy as an alternative option to CRS with HIPEC in cases of a disseminated pattern of involvement must further be taken into account, so that treatment with radiotherapy alone is to be ruled out in patients with recurrent peritoneal mesothelioma or pseudomyxoma, thus rendering surgery for recurrent disease—on condition of a potentially curative achievement of CCR-0—the therapy of choice in this patient population [1, 7]. In view of the minimal invasiveness of PIPAC with only very few systemic side effects, the therapy may be applied in almost all situations that can no longer be treated with potentially curative therapy and where the focus has shifted toward symptom and ascites control. Future studies are expected to identify the histological entities

Table 39.1 Therapeutic options under conditions of existing recurrence localizations and tumor- and patient-specific characteristics

Characteristics	Repeated CRS and HIPEC	Systemic therapy and PIPAC	PIPAC alone	Watch and wait
Recurrence localization				
Localized (close[a])	+++	++	+	+(?)
Localized (distant[b])	+++	++	+	+(?)
Oligolocular	++	+++	++	–
Multilocular/disseminated	(+)	+++	+++	–
Tumor specific				
Distant metastases	–	+++	–	–
Tumor entity:				
PM	+++	(+)	++	–
PMP	+++	(+)	++	–
GC	++	++(+)	++	–
CRC	++	++(+)	++	–
OVC	++	++(+)	++	–
Poorly differentiated	+(+)	++	++	–
Well-differentiated	+++	++	++	–
Long interval[b]	+++	++	++	+(?)
Short interval[b]	+(+)	++	++	+(?)
CCR-0 at first operation	+++	++	++	–
≥CCR-1 at first operation	+	++	++	-(?)
CCR-0 possible	+++	+	+	–
CCR-0 not possible	–	+++	+++	–
Patient specific				
ECOG 0–1	+++	++	+++	–
ECOG >2	–	(+)	++	++(+)
Comorbidity	–	(+)	++	++(+)
Systemic therapy (intolerance/toxic side effects)	++(+)	–	++	++(+)
Complications at first operation (Clavien-Dindo > II–III)	(+)	(+)	+(+)	+(+)

PM peritoneal mesothelioma, *PMP* pseudomyxoma peritonei, *GC* gastric cancer, *CRC* colorectal cancer, *OVC* ovarian cancer

+++ strong recommendation, ++ mixed recommendation, + cautious recommendation, – no recommendation

[a]Recurrent tumor located in close proximity to or at a distance from the primary tumor

[b]Long or short interval from first operation

responsive to PIPAC-directed therapy as well as to indicate a possible prognostic benefit from PIPAC treatment.

Attention should further be drawn to the possibility of conditioning recurrent tumors—in the context of an overall multimodal concept—with repeated PIPAC applications to enable subsequent cytoreduction + HIPEC, whose therapeutic benefit remains, however, purely speculative based on available data. In special cases where a suspected localized recurrence has developed shortly after the first operation and becomes clearly apparent despite the absence of histological proof, a "watch-and-wait" approach may be taken on condition of close control examinations. However, in patients with a good general condition, re-explorations should be carried out in a timely manner so as not to miss the optimal time for potentially curative treatment.

39.5 Conclusions

In summary, both the localizing diagnostics and the multimodal therapy of recurrent peritoneal tumors are complex and require close interdisci-

plinary consultation at qualified centers with in-depth expertise in the therapy of peritoneal tumors. The prerequisite for achieving an optimal long-term quality of life and oncological outcome is the selection of a patient collective suitable for repeated CRS/HIPEC based on the combination of modern imaging techniques and laparoscopy as well as on a tumor- and patient-centered benefit-risk assessment and continuous weighing up of alternative therapies.

References

1. Alexander HR Jr, Burke AP. Diagnosis and management of patients with malignant peritoneal mesothelioma. J Gastrointest Oncol. 2016;7:79–86.
2. Chung AD, Schieda N, Flood TA, Cagiannos I, Mai KT, Malone S, Morash C, Hakim SW, Breau RH. Plasmacytoid urothelial carcinoma (PUC): imaging features with histopathological correlation. Can Urol Assoc J. 2017;11:E50–7.
3. Huang Y, Alzahrani NA, Liauw W, Morris DL. Repeat cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent diffuse malignant peritoneal mesothelioma. Eur J Surg Oncol. 2015;41:1373–8.
4. Ihemelandu C, Bijelic L, Sugarbaker PH. Iterative cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent or progressive diffuse malignant peritoneal mesothelioma: clinicopathologic characteristics and survival outcome. Ann Surg Oncol. 2015;22:1680–5.
5. Odendahl K, Solass W, Demtröder C, Giger-Pabst U, Zieren J, Tempfer C, Reymond MA. Quality of life of patients with end-stage peritoneal metastasis treated with Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC). Eur Surg Oncol. 2015;41:1379–85.
6. Pfannenberg C, Schwenzer NF, Bruecher BL. State-of-the-art imaging of peritoneal carcinomatosis. Rofo. 2012;184:205–13.
7. Pietrantonio F, Maggi C, Fanetti G, Iacovelli R, Di Bartolomeo M, Ricchini F, Deraco M, Perrone F, Baratti D, Kusamura S, Tamborini E, Castano A, Consonni PV, Bossi I, Gavazzi C, Milione M, Pelosi G, de Braud F. FOLFOX-4 chemotherapy for patients with unresectable or relapsed peritoneal pseudomyxoma. Oncologist. 2014;19:845–50.
8. Solass W, Kerb R, Mürdter T, Giger-Pabst U, Strumberg D, Tempfer C, Zieren J, Schwab M, Reymond MA. Intraperitoneal chemotherapy of peritoneal carcinomatosis using pressurized aerosol as an alternative to liquid solution: first evidence for efficacy. Ann Surg Oncol. 2014;21:553–9.
9. Sugarbaker PH. Observations concerning cancer spread within the peritoneal cavity and concepts supporting an ordered pathophysiology. In: Sugarbaker PH, editor. Peritoneal carcinomatosis: principles of management. Norwell: Kluwer; 1996. p. 79–99.
10. Tempfer CB, Winnekendonk G, Solass W, Horvat R, Giger-Pabst U, Zieren J, Rezniczek GA, Reymond MA. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: a phase 2 study. Gynecol Oncol. 2015;137:223–8.
11. Vassos N, Förtsch T, Aladashvili A, Hohenberger W, Croner RS. Repeated cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with recurrent peritoneal carcinomatosis. World J Surg Oncol. 2016;14:92.
12. Verwaal VJ, Boot H, Aleman BMP, van Tinteren H, Zoetmulder FAN. Recurrences after peritoneal carcinomatosis of colorectal origin treated by cytoreduction and hyperthermic intraperitoneal chemotherapy: location, treatment, and outcome. Ann Surg Oncol. 2004;11:375–9.
13. Zoetmulder FAN, Sugarbaker PH. Patterns of failure following treatment of pseudomyxoma peritonei of appendiceal origin. Eur J Cancer. 1996;32:1727–33.

Treatment Options for Peritoneal Tumor Recurrence

40

Hubert Leebmann and Pompiliu Piso

Multimodal therapy of peritoneal carcinomatosis, including maximal cytoreduction, hyperthermic intraperitoneal chemotherapy, and systemic therapy, leads to a significant increase of disease-free survival and overall survival in strictly selected patients. This treatment is offered in curative intent. However, in reality, for the majority of patients, peritoneal carcinomatosis is a recurrent and persistent problem.

- Most tumor recurrences are intraabdominal. Even after initial complete cytoreduction and intraperitoneal chemotherapy, in most cases tumors recur solely in the peritoneal cavity.

In approximately 80% of patients with peritoneal carcinomatosis of colorectal carcinoma, for 24–44% of patients with pseudomyxoma peritonei, and 40% of patients with mesothelioma, tumor recurrence is confined to the peritoneum after previous cytoreductive surgery and intraperitoneal chemotherapy [10].

- Depending on the patient population, 4–16% of all previously multimodally treated patients are considered to be candidates for a successful iterative cytoreduction [4].

For strictly selected patients, there is a chance of long-term tumor control and improved overall survival.

- Through this aggressive approach 1-, 3-, and 5-year survival rates of 92%, 60%, and 34% were possible for different tumor entities in a mixed patient sample.

So far, no selection criteria for repeated cytoreductive surgery with intraperitoneal chemotherapy have been defined. Therefore, patient selection is extrapolated from the established selection criteria for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) (Table 40.1). Early diagnosis of the recurrence is crucial for improved survival. Isolated peritoneal recurrence after CRS and HIPEC usually occurs in the mid-term postoperative course. Patients who are deemed eligible for iterative cytoreduction should receive a follow-up at intervals of 3–6 months within the initial 5 years [10]. Tumor recurrence usually affects the visceral peritoneum. Therefore, tumor distribution primarily determines resectability. A structured postoperative follow-up ensures the recognition of patients with localized recurrence

H. Leebmann (✉) · P. Piso
Clinic for General and Visceral Surgery, Barmherzige Brüder Hospital, Regensburg, Germany
e-mail: hubert.leebmann@barmherzige-regensburg.de; Pompiliu.Piso@barmherzige-regensburg.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_40

Table 40.1 Selection criteria

Pro	Contra
ECOG performance status 0–1	Extraabdominal metastases
CC0 resection in previous CRS	Small bowel PCI >2
Favorable tumor biology	Small bowel syndrome
Long disease-free interval	Malnutrition
Chance of a CC0 cytoreduction	Serious comorbidity
Localized tumor	Retroperitoneal tumor
	Diffuse/multilocular peritoneal metastases

and low tumor burden. Early re-intervention in locally limited tumor manifestations minimizes the extent of subsequent visceral peritonectomy procedures. Thus the extent of iterative cytoreduction is usually less extensive than previous resections.

Despite the very complex surgery, the rate of grade III/IV complications remains within an acceptable range. The incidence of postoperative complications correlates with the peritoneal carcinomatosis index and ranges between 2.3% and 40% [6, 7, 9].

In several studies, HIPEC was a positive prognostic parameter [4, 7]. Especially with recurrences in the short-term follow-up, a change of intraperitoneally applied chemotherapeutic drugs seems advisable. However, clear recommendations cannot be made as long as data is insufficient.

5-year survival rates of 53% and 75% were achieved for pseudomyxoma peritonei [3–5, 11]. Due to its biology, pseudomyxoma peritonei is suitable for iterative cytoreductive surgery. In pseudomyxoma peritonei, extra-abdominal metastases are rare. Thus a local procedure seems particularly promising. Especially low-grade tumors show predominantly expansive and only minimally invasive growth. The recurrent tumor distributes at anatomic predilection sites, such as sites for peritoneal fluid resorption, and mostly spares the small intestine. Therefore, repeated surgery is often possible while avoiding a short bowel syndrome. Prognostically favorable parameters after repeated CRS and HIPEC are complete cytoreduction (CCR-0 resection) and a significantly lower peritoneal carcinomatosis index (<50%) compared to initial surgery. In addition, the abdominal regions treated during initial cytoreduction must remain free of disease or show only minimal tumor progression [5].

For colorectal carcinoma, study results vary. In an older retrospective study, with a median survival of 23 months, 1- and 3-year survival rates were 90% and 0% [4]. In another case series, 1- and 2-year survival rates were 74% and 50% [8]. During a median follow-up period of only 10 months, 78% of patients were diagnosed with a—usually intraabdominal—tumor recurrence after a second cytoreduction and intraperitoneal chemotherapy. The median disease-free time was only 4.5 months. In contrast to these disappointing results, the evaluation of current data for 189 patients with isolated peritoneal recurrence and iterative CRS and HIPEC yielded a median survival of 46.2 months and 1-, 3-, and 5-year survival rates of 96.5%, 66.3% and 41.6% [1]. All studies published are retrospective case series with a correspondingly low level of evidence. However, recent results from the largest published case study suggest that long-term tumor control can be achieved in peritoneal metastasized colorectal cancer by repeated CRS and HIPEC. The indication for a second cytoreduction and repeated intraperitoneal chemotherapy should be based on a strict patient selection and consideration of possible alternative treatments. Decisions regarding surgical treatment must be primarily based on the characteristic of intraabdominal recurrence. The completeness of cytoreduction (CC score) is the major determinant of survival. Patients with incomplete cytoreduction do not benefit from the multimodal treatment. As complete cytoreduction is only possible in localized disease, patients with diffuse peritoneal metastases do not benefit from repeated CRS and HIPEC [2].

Peritoneal mesothelioma is a very rare tumor. Therefore, data on repeated CRS and HIPEC in peritoneal recurrence is poor. So far there are only retrospective studies with a very small number of cases. In the largest case study available, 44 patients with peritoneal tumor recurrence

achieved a median survival of 54 months with CRS and HIPEC [7]. The 3- and 5-year survival rates were 61% and 46%. The survival rates for patients with optimal cytoreduction tumor recurrence were nearly identical to the survival rates for patients with a CCR-0 resection following the initial procedure (3-year survival 60%, 5-year survival 52%). Similar survival rates were reported in a study by Chua et al. (median survival 57 months, 3- and 5-year survival rates 80% and 27%) [4]. Positive prognostic criteria were young patient age, an interval between first and second CRS and HIPEC of more than 18 months, minor tumor growth on the small intestine, and the performance of hyperthermic intraperitoneal chemotherapy.

40.1 Conclusion

For patients with isolated peritoneal recurrence after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, there is currently no standardized approach. The decision for a second or further CRS and HIPEC must be made on an individual basis, taking into account the tumor biology and the expected postoperative quality of life. Due to the complexity of the procedure, both patient selection and surgery should be performed at a high-volume center. The most important prognostic criterion is the ability to achieve complete cytoreduction. Therefore a CCR-0 situation after the first peritonectomy is usually considered mandatory for a successful second intervention. However, a CCR-1 or CCR-2 situation after the initial procedure is not an absolute contraindication for further cytoreduction if there is a chance of achieving complete cytoreduction in the subsequent, more extensive procedure. The extent of resection must be determined while taking into consideration the expected postoperative quality of life. Despite the methodological weaknesses of retrospective studies, the good survival rates in selected patients and the as-yet unsatisfactory systemic treatment options justify a second or repeated CRS and HIPEC for pseudomyxoma peritonei, peritoneal mesothelioma, and colorectal carcinoma. In conclusion, an iterative CRS and HIPEC is another treatment option in addition to palliative systemic therapy for strictly selected patients.

References

1. Alzahrani N. Repeat cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in colorectal cancer in 189 patients (PSOGI collaboration). J Peritoneum (and other serosal surfaces). 2016;1:5–6.
2. Bijelic L, et al. Failure analysis of recurrent disease following complete cytoreduction and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer. Ann Surg Oncol. 2007;14(8):2281–8.
3. Bijelic L, et al. Treatment failure following complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from colorectal or appendiceal mucinous neoplasms. J Surg Oncol. 2008;98(4):295–9.
4. Chua TC, et al. Iterative cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent peritoneal metastases. J Surg Oncol. 2013;108(2):81–8.
5. Esquivel J, et al. Second-look surgery in patients with peritoneal dissemination from appendiceal malignancy: analysis of prognostic factors in 98 patients. Ann Surg. 2001;234(2):198–205.
6. Golse N, et al. Iterative procedures combining cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal recurrence: postoperative and long-term results. J Surg Oncol. 2012;106(2):197–203.
7. Ihemelandu C, et al. Iterative cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent or progressive diffuse malignant peritoneal mesothelioma: clinicopathologic characteristics and survival outcome. Ann Surg Oncol. 2015;22(5):1680–5.
8. Klaver YL, et al. Secondary cytoreductive surgery and peri-operative intraperitoneal chemotherapy for peritoneal recurrence of colorectal and appendiceal peritoneal carcinomatosis following prior primary cytoreduction. J Surg Oncol. 2013;107(6):585–90.
9. Saxena A, et al. A critical evaluation of risk factors for complications after cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis. World J Surg. 2010;34(1):70–8.
10. Vassos N, et al. Repeated cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with recurrent peritoneal carcinomatosis. World J Surg Oncol. 2016;14(1):42.
11. Yan TD, et al. Critical analysis of treatment failure after complete cytoreductive surgery and perioperative intraperitoneal chemotherapy for peritoneal dissemination from appendiceal mucinous neoplasms. Ann Surg Oncol. 2007;14(8):2289–99.

Part XII

Environmental Aspects

Importance of Psycho-oncology for Tumors of the Peritoneum

41

Ute Goerling and Amy Rohrmoser

Facing a life-threatening disease can lead to considerable psychosocial distress, regardless of tumor type or prognosis. Thus, modern tumor therapy views the continuous offer of psycho-oncological support as an indispensable part of comprehensive treatment. An increase of somatic and psychosocial impairments may otherwise lead to a manifestation of reactive mental disorders. In order to prevent these, highly distressed patients need to be identified early on and, preferably, a psycho-oncologist should be involved.

41.1 Mental Distress in Tumor Patients

The German Guideline defines psycho-oncology as "a separate discipline in the oncological context that addresses cancer patients' experience and behavior as well as social resources related to their cancer disease, its treatment, and associated problems" [1, p. 24]. Problems surrounding a cancer disease can stem from various areas (Table 41.1).

Table 41.1 Distress in the context of cancer

Area of distress	Sources
Disease and treatment	Invasive treatments, pain, fatigue, invalidity, psycho-somatic symptoms, disabilities
Medical care	Incongruous physician-patient communication, lack of information, depersonalized treatment, lack of time, lack of intimacy
Family strain	Changes in social roles and tasks, changes in the relationship with the partner, children, and friends
Occupational, financial, and social strain	Loss of important social and occupational functions, new dependencies, isolation
Existential and spiritual strain	Facing one's own mortality, searching for meaning, spiritual and religious explanations

41.2 Psychological Reactions to a Tumor Disease

Stress reactions to a tumor diagnosis can vary widely and are influenced by a range of factors. For example, prior experience with cancer in family members, friends, or others may affect a patient's perception and expectations of their own diagnosis. Media reports about the patient's type of cancer or the death of a public person from that cancer may be burdening. In addition, one's personality impacts how one copes with the disease. Based on the given factors, patients may

U. Goerling (✉) · A. Rohrmoser
Charité – Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Charité Comprehensive Cancer Center, Berlin, Germany
e-mail: ute.goerling@charite.de; amy.rohrmoser@charite.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_41

either be able to adapt to having cancer, leading to an inner balance. Alternatively, if an adaptation to the given situation is unsuccessful, an acute crisis may result. In the case of continuous overload, patients may develop mental disorders.

Reactions range from a common reaction in the form of fears, worries, and sadness to severe reactions such as depression, adjustment disorders, and post-traumatic stress disorders. Distress levels below the diagnostic criteria's threshold for mental disorders are reported in 59% of patients [2]. Studies estimate the prevalence of psychological comorbidities to be a third of all cancer patients [3, 4]. Disease- and treatment-induced risk factors for mental distress are an advanced cancer stage, unfavorable prognosis, pain, and low level of physical functioning. Young age, female gender, severe impairment of body image and self-image, as well as lacking individual and social resources are also associated with increased distress [5]. If comorbidities exist, these can affect the compliance with necessary diagnostics and therapy as well as the duration of hospitalization.

41.3 Detecting the Need for Psycho-oncological Support

A study in visceral surgery showed that 31% of patients already wanted professional psycho-oncological support at the beginning of their inpatient treatment [6]. However, the surgical team identified the psycho-oncological need only in 38–60% of patients actually in need. Brandl et al. could show that a large number (70%) of patients show high distress before CRS and HIPEC [7].

Therefore, comprehensive diagnostics of a patient's psychological and social situation should take place at initial diagnosis. There is evidence suggesting that patients who feel stigmatized by having cancer do not necessarily take the initiative to discuss their mental state. Here, various screening tools for psychosocial distress are available to provide valuable insight. Table 41.2 displays a selection.

Psycho-oncological screenings should take place throughout the course of treatment. In addition to delivering a standardized assessment of a patient's psychosocial well-being, screenings may influence the communication between patients and their physician in positive ways. Still, empathetic communication is crucial.

The following list of indications for psycho-oncological support may help physicians to notice support needs in all phases of the patient's illness:

- Requesting professional psycho-oncological support
- Reaching the cut-off value on a screening tool
- Ongoing emotional distress (e.g., fears, anger, grief, lack of drive)
- Treatment-related difficulties (e.g., handling side effects)

Table 41.2 Screening tools for the assessment of psychosocial distress

Tool	Authors	Type	Scales	Number of items
Psycho-Oncological Basic Documentation (PO-Bado)	Herschbach et al. [12]	External assessment	Somatic stress, psychological stress, additional stressors	15
Questionnaire on Stress in Cancer Patients revised version (QSC-R23)	Herschbach et al. [13]	Self-assessment	Psychosomatic complaints, fears, information deficits, everyday life restrictions, social strains	23
Hospital Anxiety and Depression Scale (HADS)	Zigmond and Snaith [14]	Self-assessment	Anxiety, depressiveness	14
Distress Thermometer	National Comprehensive Cancer Network [15]	Self-assessment	Visual analog scale, problem list: practical, family, emotional, and physical problems; spiritual/religious concerns	40

- Considerable familial distress (e.g., conflicts with caregivers, social isolation)
- Communicative problems with healthcare professionals (e.g., difficulties in treatment decisions)

41.4 Psychological Effects of Diagnostics and Oncological Treatment

Patients with tumors of the peritoneum may face diverse types of distress. Some receive the diagnosis entirely by surprise while seemingly completely healthy. Others already have a long history of primary therapies with multimodal treatment concepts. Patients may be particularly distressed if they are diagnosed with peritoneal metastases while the primary cancer is still unknown; here, the perceived loss of control may be amplified.

The phase of extensive diagnostics and waiting for their results is usually challenging for patients and caregivers. Whereas caregivers reported higher depressive symptom burden before surgery, patients reported more depressive symptoms at the postoperative visit [8]. A diagnostic laparoscopy may destroy the hope for a surgery. Chemotherapies are associated with manifold side effects and their anticipation alone may already impact patients' condition. Mental distress and depression may increase over the course of systemic chemotherapy. In this context, anxiety may increase pain, nausea, and vomiting, in turn potentiating anxiety [9]. Familiar coping strategies may fail to help sufficiently in this situation. Even after conclusion of radiotherapy, many patients keep reporting states of exhaustion such as fatigue for weeks and months. Surgery and anesthesia increase the experienced lack of control accompanied by the fear of pain and the loss of stabilizing factors. Postoperative delirium and the impairment of cognitive abilities often unsettle caregivers, and patients recall them to be very disabling.

Overall, increased mental distress before surgery may lead to higher pain and more use of morphine afterward [10]. Adequate preparation regarding the impact of surgery—for example, concerning functional impairments—is of particular importance. Specific procedures such as hyperthermic intraperitoneal chemotherapy (HIPEC) are only offered in specialized institutions. Unless one of these centers is close to the patient's place of residence, they accept long travels and temporary separation from their family in order to undergo treatment while strongly hoping for therapeutic success. This in turn often leads to a lack of social support during the inpatient stay that professionals cannot necessarily compensate.

41.5 Psycho-oncological Concepts and Interventions

The discipline of psycho-oncology aims to reduce distress that may arise due to an oncological disease and its treatment. This support should be offered to patients facing the illness and resulting consequences. With early intervention, prolonged psychological dysfunction may be prevented. In palliative care, continuous stabilizing support for patients and their family is indicated at all times. In addition, children of a parent with cancer need to receive attention and information appropriate for their age, ideally accompanied by support specifically designed for the whole family. In outpatient settings, counseling centers and licensed psychotherapists may offer psycho-oncological services, including individual or group therapy. In inpatient settings, many institutions now provide psycho-oncological support via psychologists who are an important part of the multi-disciplinary team.

> A psycho-oncological intervention is defined as a non-pharmacological intervention in which psychological and social-work methods such as psychosocial counselling, psycho-education, stress-management training, psychotherapy, relaxation techniques, by themselves or in combination, are conducted by a professional therapist in personal interaction with cancer patients in order to reduce their mental and social distress and increase their quality of life [1, p. 56].

The effectiveness of various psychological interventions in oncology has been shown repeat-

edly [11]. This applies in particular to symptom reduction of, for example, depression, fear, pain, and fatigue. Psycho-oncological interventions also improve the patients' ability to cope with the disease and their quality of life. Throughout, the personal resources and individual preferences of patients need to be taken into consideration.

41.6 Conclusion

Patients with tumors of the peritoneum may exhibit serious mental distress. Its spectrum ranges from distress below classified disorders to psychological comorbidities. Psycho-oncological care as an interdisciplinary approach should be offered to both patients and their caregivers. The effectiveness of various interventions has been shown repeatedly. Overall, interventions are supportive and resource-oriented and should be suited to patients' individual needs and demands. The overarching goal is to support patients and their caregivers in coping with the disease and improving their quality of life.

References

1. Krebsgesellschaft D, Krebshilfe D, AWMF. Leitlinienprogramm Onkologie. Psychoonkologische Diagnostik, Beratung und Behandlung von erwachsenen Krebspatienten, Langversion 1.1 2014. Available from: https://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/.
2. Gao W, Bennett MI, Stark D, Murray S, Higginson IJ. Psychological distress in cancer from survivorship to end of life care: prevalence, associated factors and clinical implications. Eur J Cancer. 2010;46(11):2036–44.
3. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011;12(2):160–74.
4. Kuhnt S, Brähler E, Faller H, Härter M, Keller M, Schulz H, et al. Twelve-month and lifetime prevalence of mental disorders in cancer patients. Psychother Psychosom. 2016;85(5):289–96.
5. Singer S. Psychosocial impact of cancer. In: Goerling U, Mehnert A, editors. Recent results cancer research**.** 210: Springer International Publishing; Switzerland. 2018. p. 1–11.
6. Krauß O, Hauss J, Jonas S, Leinung S, Halm U, Albani C, et al. Psychische Begleiterkrankungen bei Krebspatienten in der Viszeralchirurgie. Chirurg. 2011;82(3):263–70.
7. Brandl A, Katou S, Pallauf A, Pratschke J, Rau B, Goerling U. Psycho-oncological distress in patients with peritoneal surface malignancies treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Eur Surg. 2019;51(6):315–24.
8. Duckworth KE, McQuellon RP, Russell GB, Perry KC, Nightingale C, Shen P, et al. Caregiver quality of life before and after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Am Coll Surg. 2020;230(4):679–87.
9. Schwarz R, Singer S. Einführung Psychosoziale Onkologie. München: Ernst Reinhardt, GmbH & Ko KG, Verlag; 2008.
10. Cohen L, Fouladi RT, Katz J. Preoperative coping strategies and distress predict postoperative pain and morphine consumption in women undergoing abdominal gynecologic surgery. J Psychosom Res. 2005;58(2):201–9.
11. Faller H, Schuler M, Richard M, Heckl U, Weis J, Küffner R. Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. J Clin Oncol. 2013;31(6):782–93.
12. Herschbach P, Book K, Brandl T, Keller M, Marten-Mittag B. The basic documentation for psycho-oncology (PO-Bado) – an expert rating scale for the psychosocial experience of cancer patients. Oncol Res Treat. 2008;31(11):591–6.
13. Herschbach P, Marten-Mittag B, Henrich G. Revision und psychometrische Prüfung des Fragebogen zur Belastung von Krebskranken (FBK-R23). Z Med Psychol. 2003;12(2):69–76.
14. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361–70.
15. National Comprehensive Cancer Network. Distress management. Clinical practice guidelines. J Natl Compr Cancer Netw: JNCCN. 2003;1(3):344–74.

Nursing Aspects of Peritoneal Surface Malignancy

42

Ilona Baumann and Jesse Smith

42.1 Introduction

Working and communicating with patients with peritoneal malignancies is challenging for many staff nurses during treatment. It is hard to find the right and most appropriate words in sensitive situations during the hectic clinical daily routine. The patients concerned are sometimes relatively young and severely ill – a huge psychological burden for all concerned. In this phase of confronting themselves with the diagnosis, the possibility of a treatment with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) plays an important role. In the foreground is the patient's search for a successful treatment, fueled by motives like "try everything," "seize every opportunity," and "improve the situation" [1].

The following chapter will focus on the particular nursing care of patients with tumors of the peritoneum and, in particular, on their treatment with the HIPEC therapy procedure.

I. Baumann (✉)
Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany
e-mail: baumann.ilona@email.de

J. Smith
University Hospital, Charité Campus Virchow-Klinikum, Berlin, Germany
e-mail: beate.rau@charite.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_42

42.2 Preoperative Preparation of the Patient

During the daily routine on the general ward, the focus lies not only on the handling of hazardous agents, such as cytotoxic drugs, but also on the psychological stress upon the nursing staff which results when taking care of severely ill patients. It is very important for staff to know the potential risk of contamination with cytotoxic drugs during the treatment with HIPEC. It takes a lot of time to prepare those undergoing CRS and HIPEC for this complicated and mentally very stressful procedure. Depending on the resection areas and the symptoms of the patient, the staff nurse initiates bowel preparation on the afternoon of the day before the operation. With laxatives, such as Laxativum or a combination of Laxativum with a macrogol-based laxative, bowel cleansing is performed. From this point in time onward, it is recommended that the patient only consumes clear broth and a lot of clear liquids to help clear the colon. The phase of food and water abstention starts after midnight the day before the operation takes place.

To achieve complete cytoreduction, anterior resection is sometimes required, and the creation of a protective stoma may be necessary to protect the anastomoses. In the setting of a preoperative talk with a professional stoma-care nurse, the patient is informed about the best possible position of the stoma as well as the stoma care after

the operation. The building of trust by marking the future stoma position together with the patient is the main goal during this talk immediately before the operation. The patient and the relatives are screened for their ability to facilitate stoma self-care, and they will be introduced to the hard-to-accept topic of a possible permanent stoma potential sensorineural challenges such as blindness as well as mobility limitation scan also be addressed.

On the day of surgery, the patient is given an antiemetic in a short infusion as prophylaxis. The vital signs are checked and premedication is given. Significant preoperative preparation means that nursing staff spend a lot of time with patients undergoing surgery [2, p. 10ff].

42.3 Anesthesiological Preparation of the Patient

Detailed anesthesiological preparation is of great importance for an operation of this complexity. This complex and, for the patient, physically as well as mentally stressful operation also presents the anesthesiological team with specific challenges. Already on the day before the operation, the department for anesthesiology and the OR staff team are notified about the planned HIPEC procedure. The coordinators of both departments designate the specially trained staff members who will take part in the surgery. On the day of the operation, the induction room is prepared for standard intubation anesthesia. A central venous catheter, a thoracic epidural catheter for intra- and postoperative pain management, a nasogastric tube, and a device for the invasive measurement of the arterial blood pressure are organized before the patient enters the operating room. Special training for the safe handling of cytotoxic drugs is also required for the anesthesiological staff.

When the patient arrives, the personal data is double-checked to confirm identity of the patient. The patient is asked for the information they gave the day before during the premedication interview. The placement of the thoracic epidural catheter can take some time. The nurse supports the patient in assuming and holding the right position for the application. While the nurse does so, the patient and the nurse come close in a physical way. Words of encouragement and comfort toward the patient, as well as the answering of open questions from the patient, can become mentally challenging for the staff. Further measures, such as inserting the central venous catheter and the arterial blood pressure measurement systems, take place after the patient has been securely intubated. During anesthesia the anesthetist and anesthetic nurse follow standard operating protocols developed by the department of anesthesiology for CRS and HIPEC. Core temperature monitoring is of importance during the HIPEC phase of the procedure with the use of cooling techniques if core temperature rises too high with the use of HIPEC at 42°C [2, p. 12ff].

42.4 Nursing Interventions in the OR During Treatment of the Patient

The surgical interventions are carried out depending on the tumor type and extent. The treatment goal is a complete removal of all macroscopically visible tumor masses combined with hyperthermic intraperitoneal chemotherapy to destroy any microscopic circulating tumor cells [5]. Cytostatic drugs can be carcinogenic in their own right, so it is essential to protect all persons involved in the treatment process against cytostatic contamination by implementing various protective measures [4].

The cytostatic bag, which is connected to the tubes and drains, is connected directly to the reservoir so that the solution can be transferred to the patient without contamination. Even after complete emptying, the cytostatic bag remains attached to the system.

Before the cytostatic preparation is added to the circulation, the entire surgical and anesthesia team puts on protective clothing. In addition to the surgical clothing (surgical pants and surgical gowns), this consists of a liquid-impermeable disposable sheath, protective goggles, a surgical mask, and two pairs of protective gloves. The first

glove pair are sterile surgical gloves, the second pair are nitrile gloves, which are non-sterile.

The HIPEC procedure is performed only by trained personnel. The specially selected nurses from the Department of Visceral Surgery are educated and trained at least once a year, or when the procedure changes, about the latest safety regulations and health protection.

The operating room is marked with signs warning "Caution cytostatics."

At the end of the HIPEC therapy, the entire perfusate is pumped out into the reservoir. This reservoir and all other consumables that might have been in contact with cytostatics, such as the tube system, temperature probes, disposable items (gloves, gowns, and goggles), and disposable mops, are placed in designated waste containers for hospital-specific cytostatic waste. The drains on the patient remain in the abdomen and are provided with drainage bags. These bags collect the remaining rinsing fluid in which small amounts of the cytostatic solution are still present. 24 hours later, the drainage bags are also disposed of by the ICU nursing staff in the special disposal containers.

42.5 Postoperative Care of the Patient

At the end of surgery patients are transferred to the surgical intensive care unit (ICU). Patients are accommodated in single rooms to prevent contamination of other patients. On the outside of the room, a sign reading "Caution – HIPEC" is placed. Both protective clothing and a special drop-off for cytostatic waste are located in the patient's room in the intensive care unit. Wearing the protective clothing is mandatory from the time the patient is picked up from the OR until at least 48 hours postoperatively, or as long as there are still drains in the abdomen from which the staff could come into contact with the remaining quantities of cytostatics. By adhering to this time interval, the occupational health and safety component is certainly fulfilled. It is important in advance to educate patients about the reason for the protective clothing, because most patients are otherwise surprised that protective clothing is worn in their rooms. In addition, during the first 48 hours postoperatively, any material that has come into contact with the HIPEC patients must be disposed of in special disposal containers intended for cytostatic waste.

In the abdomen of the operated patient, there are five drains, attached to drainage bags. The special collection bags are changed daily by the nursing staff and care must be taken to avoid contamination with chemotherapy solution. When the drainage bag is removed from the drainage tube, contaminated material can be released into the environment by spraying when separating these two systems. Here, the nursing staff of the intensive care unit sees the greatest need for action with regard to occupational safety. Currently, new improved drainage systems are being tested.

Fluid balance including drain and nasogastric tube volumes are recorded and documented daily by the nursing staff.

In addition to the special nursing activities that are particularly relevant to patients following CRS and HIPEC, regular controls of vital signs, excretion, fluid substitution, and laboratory controls are required, as is routine for the nursing team in ICU. After an average stay of 48 hours, patients leave the ICU in a stable state of health and, after consultation with the treating physicians, are transferred to the general-care unit. If the prescribed 48 hours has not yet expired, the protective measures for the personnel already described above also apply to the general-care unit. Only at the end of this period or after all drains have been removed may the protective measures, such as protective gowns, gloves, and isolation of the patient, be dismissed. Renal function, skin changes, urinary volumes, and vital signs are also of importance for nurses and doctors on the general ward. Platinum-containing cytostatics can impair renal function causing extensive tubular necrosis and electrolyte imbalance. Other general postoperative monitoring measures, such as wound treatment and wound drainage monitoring, are performed jointly by physicians and nurses. Abdominal drains if not already removed can be removed after 48 hours

and disposed of in the special receptacle systems for cytostatic waste.

One of the most common postoperative side effects is bowel ileus. As a rule, a nasogastric tube is placed intraoperatively and used depending on the patient's state of health in order with parenteral nutrition to allow return of intestinal motility before starting enteral feeding. After consultation with the doctors, it is possible to start gradually with oral nutrition after the recovery of bowel function and the removal of the nasogastric tube. Epidural analgesia helps pain management in the immediate postoperative setting.

Based on the guidelines of the scientific medical society, the patient receives an adapted anticoagulative therapy as thrombosis prophylaxis for 5 weeks postoperatively. Due to the average stay of 3 weeks in the hospital, the patients or their relatives are consulted and instructed by the nursing staff to administer independently the subcutaneous injection [2, p. 19ff].

42.6 Challenge of Stoma Care

If a stoma is required during CRS and HIPEC, the stoma nurses and ward nurses provide support with stoma care. This particular phase of the patient's life requires specific skills and knowledge from the nursing staff and special care experts of oncological patients. Professional expertise and care is required so that the patient can learn self-sufficiency and independence. In addition to the postoperative inspection of the stoma and monitoring stoma output, support is provided in changing and emptying the stoma bag. The specialized stoma-care nursing team, who also educate the patient and carers, may be family members primarily provide this. A precisely coordinated pattern of care and adequate handling of the appropriate supplies prevent any possible complications; the nursing experts for stoma, continence, and wound care as well as palliative care and nutrition consultants play a large role in the perioperative care of patients undergoing CRS and HIPEC. A goal-oriented mind-set for all persons involved is important, because only with effective multi-disciplinary care can this complex task be accomplished. The aim of the attending physicians and care-givers is to provide optimal quality assurance in patient-oriented care while accompanying the relatives through this situation, which is difficult for all involved [2, p. 44ff].

42.7 Legal Aspects of Workplace Safety and Guidelines for Management of Cytotoxic Drugs in the OR

As the use of CRS and HIPEC in cancer treatment becomes more widespread, the Association for Health Service and Welfare Work has raised questions about the risk posed by HIPEC to healthcare workers. Cytostatic contamination could happen through inadvertent swallowing or puncture injury, as well as through absorption via the lungs and skin. In 2010, in a project funded by the Association of Health Service and Welfare Work, experts debated whether more extensive measures are required at centers performing CRS and HIPEC due to the possible cytostatic hazards employees might face. The result of the investigation determined that there are several areas of risk in the HIPEC process. Definitive health and safety recommendations were issued after many investigations, samplings, and analyses. These include:

- The use of infusion bags instead of perfusion syringes for chemotherapy (these must not be disconnected)
- Careful cleaning and disinfection of HIPEC equipment after completion of the process
- The wearing of two pairs of gloves on top of each other during activities with direct cytostatic contact

In this pilot study, it has been demonstrated that surface exposure to cytostatic agents may be possible in operating theaters where CRS and HIPEC is performed. However, further observations also show that hygiene standards are high in German hospitals and can be effectively verified by swab samples. The recommendations for occupational safety in this study correspond to the evidence cat-

egory IIb. These evidence categories are based on the recommendations of the Association for Healthcare Research and Quality [3].

In order to protect the employees, working instructions regarding the handling of cytostatics in connection with the HIPEC procedure should be made available to the operating staff for the documentation of HIPEC therapy in hospitals [2].

42.8 Guidelines for Workplace Safety

Target Group

- Nursing staff of operating room, healthcare professionals, medical service

Objectives

- Minimizing the risk of contamination from cytostatics
- Safety in dealing with emergencies regarding contamination by chemotherapeutic agents
- Avoiding mistakes regarding work safety
- Concrete action in an emergency

Measures

- Training twice a year
- Specific description of action for possible incidents
- Development of initial measures in case of incidents
- Biomonitoring only on specific occasions and consultation with company medical department
- Special registration form for medical-care incidents in HIPEC therapy
- Medical consultation when contaminations occur

Materials

- Mandatory protective clothing for HIPEC therapy
- Special waste bin for cytostatic waste labeled "cytostatics" (white box)
- Berner "Spill Kit XP" (emergency kit for leaked chemotherapeutic agents)
- Berner protective gloves (Manu protective gloves for the perfusionist)

Content Berner "Spill Kit":

- Safety goggles
- Protective coat
- Overshoes
- Hood
- P 2 = respirator
- Cytostatic protective gloves
- Absorber pads
- Isopropanol

Implementation – Regulations for HIPEC Incidents

1. Leakage of chemotherapeutics (floor, machine, etc.):
   - Wearing prescribed protective clothing (double gloves, protective goggles, protective coat)
   - Using Berner "Spill Kit Box"
   - Wearing Berner protective gloves (Manu protective gloves)
   - Thoroughly cleaning the contaminated area three times (using disposable wipes and solution buckets, diluting by repeated use)
   - Then changing gloves (protective clothing only after contact with the chemical fluid)
   - Urgently avoiding cross-contamination (= additional contamination due to non-compliance with the protective measures)
   - Disposing of one-use wipes with cytostatics in special disposal container (white box)

2. Defective machine, hose system, or reservoir:
   - Analysis of the problem, calling the emergency number of the company Kardialgut.
   - If necessary, replace the machine.
   - Close the hose system and reservoir completely.
   - If necessary, replace the hose system.
   - Leaks are usually detected on the tube system before (with pre-filling of the abdomen with 0.9% NaCl or 5% glucose).

- Swap reservoir if necessary.
- Initiate cleaning process in case of contamination (see above).

3. Exit of chemotherapeutic agents in case of leakage of fascia or drain incision:
   - Waterproofing with gauze and additional gauze bandages
   - Flow reduction or stopping the pump on the HIPEC machine
   - Checking the attached secretion bags on the side of the patient (take care when disposing of the cover: use abdominal towels to absorb the leaked HIPEC fluid)
   - Disposal of contaminated materials in the white special disposal container

4. Postoperative bleeding during HIPEC therapy:
   - Continue to wear protective clothing (gloves tested for chemical impermeability).
   - Wear special respirator mask (FFP3).
   - Allow the perfusate to drain into the machine (reservoir) completely.
   - Rinse abdomen thoroughly when opening (2–3 passes with at least 2 l rinsing liquid)!
   - Dispose of the one-use suction bag with HIPEC fluid in the white special disposal container.
   - Initiate cleaning measures (see point 1) and change shoes.
   - Urgently avoid cross-contamination!

5. Disconnection of drain bag – skin contact:
   - Immediately take off and dispose of contaminated clothing (white special waste container).
   - In case of contamination of the skin, rinse immediately with water and then with soap and water.
   - In case of puncture wounds, ingestion, splashes in the eye, or inhalation, consult the company medical department (official report to the emergency center).
   - All items where possible are disposed of in the special waste container (white box) for cytostatics.
   - Items that cannot be disposed of are cleaned with the help of the Berner "Spill Kit Box."

6. Chemofluid is absorbed by the patient:
   - Stop HIPEC therapy.
   - Perform ultrasound and have breathing pressure checked by the anesthesia department (if necessary, check the thorax for fluid).
   - Do not connect an extractor to the HIPEC machine! Bowel may be damaged!

7. HIPEC fluid enters the thorax from the abdomen:
   - Inform the anesthesiologist that HIPEC fluid has entered the thorax (monitor ventilation!).
   - Stop the HIPEC machine and switch to drain mode; drain HIPEC liquid into the reservoir.
   - When the thorax is full of HIPEC fluid, there is great pressure in the thoracic space!
   - When creating the chest drain: take protective measures! Violent spraying when piercing the thorax is possible!
   - If thoracic drainage is present, connect the HIPEC device to the chest drain and drain into the reservoir.
   - Await the decision of the doctors.

Safety Instructions

- Regular training on the safety, application, and effects of the HIPEC procedure to gain additional acceptance for the therapy.
- Guidance and training for the adequate and safe use of the HIPEC device (perfusionists).
- Have cytostatics – as directed by the surgeon – delivered to the pharmacy as soon as possible and stored in a dark container in the designated box until use; delivery always in a bag.
- Identification of the OR doors: "*Attention cytostatics*!"
- As soon as cytostatics are added to the solution, the HIPEC device should only be operated by trained personnel, who will exclusively take care of the machine during the HIPEC therapy and will not take on additional tasks. Any distraction can lead to errors and emergency situations. During the entire duration of the perfusion, a responsible doctor in the operating theater must be available!

- No pregnant women or nursing mothers during HIPEC therapy in the operating room!
- Only necessary personnel should be in the operating room!
- Appropriate protective clothing for all persons in the operating room.
- Regular renewal of gloves (contact with components).
- Otherwise, change the outer gloves every 30 minutes.
- Change gloves after contact with highly concentrated chemotherapy.
- Avoid unnecessary contact with contaminated material.
- Protective clothing should be worn by employees for at least 48 hours or as long as there are drains in the abdomen.
- Laundry and excrements of the HIPEC patient are contaminated.
- During perfusion, temperatures are controlled and recorded manually.
- All materials required for HIPEC therapy (tube systems, reservoir, waste bags, gloves, coats, etc.) are disposed of in the chemobox (white box). This is firmly closed and marked accordingly.
- Thoroughly clean perfusion device and floor after stopping HIPEC therapy.
- Monitoring by doctors and nursing staff (cytostatics, type, amount, application site).

42.9 Conclusion

A positive aspect in this context is the fact that the exposure of the HIPEC personnel to cytostatic agents is low. Nevertheless, it makes sense to monitor HIPEC staff for health issues. With a high degree of probability, a regular check-up containing wipe samples or occupational health checks could be monitored and controlled by structured quality management. In light of the latest medical research on the HIPEC process, occupational safety measures need to be readapted to the process and taught. Here it is necessary to create the optimal conditions for the employees so that both quality and safety can be maintained.

References

1. Aulbert E, Nauck F, Radbruch L. Lehrbuch der Palliativmedizin. 3rd ed. Stuttgart: Schattauer; 2012. p. 694.
2. Baumann I. Pflegemanagement; Psychische und physische Auswirkungen der Behandlung und Betreuung von “HIPEC-Patienten” auf das Pflegepersonal – Risikominimierung einer Kontamination – Prozessoptierung im Qualitätsmanagement. Bachelorarbeit, Krankenhaus Barmherzige Brüder, Regensburg. 2014.
3. Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege, editor. Arbeitssicherheit & Gesundheitsschutz. Grundlagen und Forschung. Gefährdung durch Zytostatika bei der HIPEC-Technik. Hamburg: Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege BWG; 2011.
4. Novotná J. Exposition von OP-Personal gegenüber Cis/Oxaliplatin bei Operationen nach HIPEC-Verfahren. Dissertation zum Erwerb des Doktorgrades der Medizin an der Fakultät der Ludwig-Maximilians-Universität, Institut für Arbeits- Sozial- und Umweltmedizin, München. 2012. p. 14.
5. Siewert JR, Rothmund M, Schumpelick V. Praxis der Viszeralchirurgie. Onkologische Chirurgie. 3rd ed. Heidelberg: Springer; 2010. p. 905.

Part XIII

Guidelines and Centers

43 Guideline Preparation and Center Development for the Treatment of Peritoneal Tumors in Germany

Sebastian Blaj and Pompiliu Piso

The therapy of peritoneal carcinomatosis must be based on the guideline recommendations for the primary site of each cancer. There is to date no general guideline regarding the therapy of peritoneal carcinomatosis in Germany. The most frequent situation is that of peritoneal carcinomatosis originating from a colorectal cancer. The diagnosis and treatment of colorectal carcinomas in Germany is based on the recommendations of the S3-guideline for colorectal carcinomas (S3-Leitlinie Kolorektales Karzinom). This guideline is issued under the auspices of the Association of the Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF), German Cancer Society (Deutsche Krebsgesellschaft e.V.), and German Cancer Support-Group (Deutsche Krebshilfe e.V.).

The first issue of this guideline was published in 2014. There were 53 authors involved, representing various scientific societies and patient groups. The surgical specialties were represented by DGAV (German Society for General and Visceral Surgery), AG CACP (Surgical Workgroup for Colo-proctology), CAMIC (Surgical Working Group for Minimally Invasive Surgery), CAO-V (Surgical Working Group for Oncology), and DGCH (German Society of Surgery).

This guideline included for the first time recommendations for the treatment of peritoneal carcinomatosis. The strength of recommendation was 0, though the level of evidence has been 2a. The recommendation of the DGAV was:

> *Recommendation of the S3-Guideline Colorectal Carcinoma (DGAV 2014)*
> *Cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC) can be performed in patients with an isolated and limited peritoneal carcinomatosis if the following criteria are met:*
>
> - *PCI (Peritoneal Cancer Index) <20;*
> - *No extraabdominal metastases;*
> - *Possible complete macroscopical cytoreduction or destruction of all tumor lesions;*
> - *The therapy should take place in a specialized center.*
> - *Clinical studies should be favored for the therapy.*

The NHS issued in 2013 a similar recommendation based on a NICE (National Institute for Health and Care Excellence) survey. Therefore, there are now two strong guidelines in the German-speaking and English-speaking countries, respectively, which are expected to show a high influence in this area.

At least in Germany the tumor boards are intensively discussing the possibility of the

S. Blaj (✉) · P. Piso
Klinik für Allgemein- und Viszerachirurgie, Krankenhaus Barmherzige Brüder Regensburg, Regensburg, Germany
e-mail: sebastian.blaj@barmherzige-regensburg.de; pompiliu.piso@barmherzige-regensburg.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_43

multimodal therapy in patients with peritoneal carcinomatosis. The number of centers that are offering this kind of therapy is steadily growing.

S3-guidelines do exist in Germany for other tumor entities as well. Cytoreductive surgery and HIPEC for gastric cancer are only recommended inside clinical studies. The positive publications have been nevertheless mentioned and commented in the additional free text of the guideline. On the other hand, the ovarian cancer guideline has advised against HIPEC. The expert committees did not recognize any justification of the intraperitoneal chemotherapy for the clinical practice.

Many skeptical critics carefully follow the fact that in Germany cytoreductive surgery and HIPEC are gaining recognition. In order to maintain transparence, the DGAV decided to collect the data of the patients treated with HIPEC in a nationwide register. This register was started on April 6, 2011, and is being coordinated by CAO-V together with the DGAV. Meanwhile there are approximately 3500 patients included in this register. Although some data is still missing, the analysis of mortality and morbidity showed similar values as reported in the literature, thus making cytoreductive surgery and HIPEC in the German setting a safe therapy for patients with peritoneal carcinomatosis. The general mortality lies under 3%. The first analysis of the data of the HIPEC register has been presented by the 10th world congress on peritoneal carcinomatosis in Washington and subsequently published in Annals of Surgical Oncology in 2019.

The DGAV and the collaborating societies have introduced a certification system that intends to standardize the clinical pathways, thus ensuring a high quality of the therapy as well as transparent presentation of its results.

The main purpose of this system was to grant transparency and continuous improvement of the therapy. The patient should be confident that the clinic which bears a certificate for his/her disease fulfills all the under-mentioned criteria.

Certification system of the DGAV: Surgical therapy of peritoneal surface malignancies (DGAV 2016):

§101: Definition and grading

1. The organ work group "Peritoneum" of the CAO-V has defined its own criteria for establishing the competence and the reference centers for the treatment of peritoneal surface malignancies.

§102: Qualification of the accredited center surgeons

1. The accredited surgeons in a center for treatment of peritoneal surface malignancies must provide evidence for at least 2 years' experience in the diagnosis and treatment of such patients.
2. The accredited surgeons must be members of the DGAV, CAO-V, and the organ work group "Peritoneum" and actively take part in the activities of the aforementioned groups.

§103: Internal organization of the center

1. The center should provide outpatient consultation on a regular basis for patients with peritoneal surface malignancies.
2. All the cases should be discussed pre- and post-operatively in tumor boards. At least a surgeon, a gastroenterologist, a medical oncologist, and a radiologist should take part in the tumor board.
3. A dedicated pain unit should be part of the center.

§104: Technical and diagnostic facilities

1. The center should provide 24/7 the complete spectrum of diagnostic and therapeutic facilities, including CT and MRI, as well as the possibility of placing CT-guided drains.
2. A special pump system for hyperthermic intraperitoneal chemotherapy should be provided in every center.

§105: Cooperation

1. The center should provide an interdisciplinary cooperation between consultants (oncological surgeons, gynecologists, and medical oncologists).
2. The clinic should provide an intensive care unit with the possibility of hemodialysis.
3. The center should include a department of pathology and intraoperative frozen sections should be available.

§106: Minimum number of procedures

1. The competence centers should perform yearly at least 15 parietal and visceral peritonectomies with HIPEC.
2. The reference centers should perform yearly at least 30 parietal and visceral peritonectomies with HIPEC.
3. The minimum number of cases that need to be discussed in a tumor board for a competence center is at least 50, that for a referral center is at least 75 patients. These patients with peritoneal carcinomatosis need to be discussed at a multidisciplinary conference and the final decision needs to be documented.
4. A certified surgeon needs to be present at all of these operations, not needing to perform the surgery himself.

§107: Quality management

1. The data of all the patients who have been operated due to a peritoneal carcinomatosis are to be introduced into the register of the DGAV.
2. The quality management indicators are the so-called TV30 factor (number of patients who died within 30 days after the operation, number of patients who stayed in the clinic after the operation reported to the total number of operated patients) and the rate of re-operations.
3. The reference value for the TV30 factor is <15% and that for revisional surgery also <15%.
4. The follow-up must include at least 80% of the patients.

§108: Continuous medical education

1. Each of the accredited surgeons must take part each year at the courses and congresses that are recommended by the DGAV.
2. Each of the certified surgeons must acquire at least 16 CME points each year.

To this day, there are in Germany three referral centers for peritoneal surface malignancies: in the Charité (Berlin), in the Hospital Saint John of God (Barmherzige Brüder, Regensburg), and in the University Medical Center Tübingen (Baden-Württemberg, southwest Germany).

It is difficult to assess how many certified centers are necessary in Germany; probably 20–25 centers would be enough to satisfy the demand. With about 50 (better though 100) patients treated yearly in one clinic, one can achieve better processes, therefore leading in this manner to lower mortality and morbidity rates, which furthermore could help achieve better long-term oncological results in this group of patients.

Suggested Reading

1. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF (Hrsg). Leitlinienprogramm Onkologie: S3-Leitlinie Kolorektales Karzinom, Langversion 1.1. 2014. http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html. Zugriff 20 Sept 2017.
2. Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (Hrsg). www.dgav.de/arbeitsgemeinschaften/cao-v/hipec-register.html. Zugriff 20 Sept 2017.
3. Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie (Hrsg). ORDNUNG. Das Zertifizierungssystem der DGAV (ZertO 5.1). 2016. www.dgav.de/fileadmin/media/texte_pdf/zertifizierung/Zertifizierungsordnug_DGAV_5_1.pdf. Zugriff 20 Sept 2017.

44 Establishment of Guidelines and Centers for CRS and HIPEC – AUSTRIA

Thomas Bachleitner-Hofmann

44.1 Historical Development of CRS and HIPEC in Austria

In Austria, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) date back to the year 1992, when the pioneer Friedrich Kober first established a treatment center for CRS and HIPEC at the Kaiserin Elisabeth Spital in Vienna [6]. In 2009, the second treatment center at the Medical University of Innsbruck was opened, followed in 2011 by two further treatment centers at the University Hospital for Surgery in Vienna and at the Department of Surgery of Paracelsus Medical Private University in Salzburg. As of October 2019, there are a total of nine active centers for CRS and HIPEC in Austria (for a list of the current treatment centers in Austria, see [2]). Given a population of 8.7 million inhabitants in Austria (Source: Eurostat, as of 1/1/2016), the density of treatment centers for CRS and HIPEC in Austria is 1.05 centers per million inhabitants.

44.2 Peritoneal Surface Malignancy Working Group of the Austrian Society of Surgical Oncology (ACO-ASSO)

The treatment centers for CRS and HIPEC in Austria are organized within the framework of the ACO-ASSO PCNetwork of the Austrian Society of Surgical Oncology (ACO-ASSO). The aim of the ACO-ASSO PCNetwork is to offer all patients with peritoneal surface malignancies a standardized, high quality treatment. In addition, the ACO-ASSO has instituted a Peritoneal Surface Oncology Working Group, which regularly organizes continuing medical education (CME) events on a national level.

44.3 Establishment of a National Treatment Guideline for CRS and HIPEC in Austria

In order to offer a standardized treatment to all patients with peritoneal surface malignancies in Austria, the Peritoneal Surface Oncology Working Group decided, in 2012, to issue a National Treatment Guideline. The guideline was designed according to existing treatment guidelines from Germany (S3 Guideline Colorectal Carcinoma, Certification requirements for CRS and HIPEC centers issued by the German Society of General

T. Bachleitner-Hofmann (✉)
Department of Surgery, Medical University of Vienna, Vienna, Austria
e-mail: thomas.bachleitner-hofmann@muv.ac.at

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_44

and Visceral Surgery [DGAV] [4]) and the United Kingdom (Interventional Procedures Guidance 56 and 331 of the National Institute for Health and Care Excellence [NICE] [7, 8]). The ACO-ASSO guideline was established using a consensus process, which involved a total of 8 representatives from all active treatment centers for CRS and HIPEC in Austria at that time (n = 5; 3 academic centers and 2 centers within a community hospital setting). In a first step, the representatives were asked for a review of literature relating to one of the following topics: "Effectiveness of CRS and HIPEC in the treatment of peritoneal neoplasms," "Morbidity and mortality after CRS and HIPEC," "Indications for CRS and HIPEC," "Exclusion criteria for CRS and HIPEC," "Patient selection for CRS and HIPEC," "Pre- and postoperative systemic chemotherapy in patients with peritoneal neoplasms," and "Requirements for treatment centers offering CRS and HIPEC." The literature reviews of the individual representatives were presented at a consensus conference on December 6, 2012, in Linz, Austria. Following an open discussion, a first version of the guideline was drafted and sent out to all representatives. Following their written feedback, the guideline text was adapted until the guideline text was finally agreed upon. The guideline was finally presented at the 30th Annual Meeting of the Austrian Society of Surgical Oncology in St. Wolfgang, Austria, and subsequently published on the ACO-ASSO webpage (www.aco-asso.at, Working Group Peritoneal Malignancies of the Austrian Society of Surgical Oncology 2013 [1]).

44.4 Inclusion Criteria

The inclusion criteria for CRS and HIPEC, according to the ACO-ASSO guideline, are as follows:

Indications for CRS and HIPEC according to the ACO-ASSO guideline:

- *Pseudomyxoma peritonei* in patients with tumors of the vermiform appendix without evidence of extra-abdominal metastasis if a complete removal of all abdominal tumor deposits ("complete surgical cytoreduction") can be achieved.
- *Diffuse malignant peritoneal mesothelioma* without evidence of extra-abdominal metastasis, if a complete surgical cytoreduction can be achieved.
- *Colorectal cancer with peritoneal metastasis* without evidence of extra-abdominal metastasis, if the Peritoneal Cancer Index (PCI) is 20 or less, and if a complete surgical cytoreduction is possible. According to the guideline, the presence of liver metastases is not an exclusion criterion for CRS and HIPEC. However, the number of liver metastases should not exceed three lesions and the metastases should be easily resectable using a minor resection. Patients with a Peritoneal Surface Disease Severity Score (PSDSS) of IV [9] should not undergo CRS and HIPEC.
- *Gastric cancer with peritoneal metastasis* without evidence of extra-abdominal metastasis, if the PCI is 12 or less, and if a complete surgical cytoreduction is possible. Patients with signet ring cell cancers are a prognostically unfavorable group and should only be considered for CRS and HIPEC under highly selected circumstances.

The upper limit of the PCI of 12 or less in patients with peritoneal metastasis from gastric cancer was defined due to the significantly more aggressive tumor biology of gastric cancer as compared with colorectal cancer. The upper limit of the PCI of 20 or less in patients with peritoneal metastasis from colorectal cancer was chosen according to the German S3 guideline Colorectal Carcinoma. The ACO-ASSO guideline also indicates that not only the PCI per se, but also the technical resectability of the peritoneal lesions should be taken into account: That is, miliary tumor deposits along the small intestinal serosa should be considered a criterion for inoperability, regardless of the PCI. By definition, complete surgical cytoreduction cannot be achieved in these patients. Likewise, patients with tumor progression during prior systemic chemotherapy should not undergo CRS and HIPEC.

44.5 Exclusion Criteria

The exclusion criteria for CRS and HIPEC according to the ACO-ASSO guideline are as follows:

Exclusion criteria for CRS and HIPEC according to ACO-ASSO guideline:

- Evidence of extra-abdominal metastasis
- Extensive para-aortic/paracaval lymph node metastasis
- Severe cardiac, pulmonary, or renal comorbidities
- Bowel obstruction/ileus
- PSDSS IV in patients with colorectal carcinoma
- Age >70 years (relative exclusion criterion)
- Incomplete surgical cytoreduction or remaining tumor areas with a diameter >2.5 mm

According to the guideline, HIPEC should be avoided in patients with incomplete surgical cytoreduction. However, the administration of HIPEC after incomplete surgical cytoreduction may be justified in selected cases (e.g., palliative ascites therapy). An extensive multivisceral resection should, if a complete surgical cytoreduction is not possible, be avoided and the surgery limited to the necessary minimum.

44.6 Preoperative Systemic Therapy

Patients with secondary peritoneal neoplasms and advanced disease (e.g., PSDSS III in colorectal carcinoma) should receive preoperative systemic chemotherapy prior to a planned CRS and HIPEC. Likewise, postoperative systemic chemotherapy should be considered in these patients after CRS and HIPEC have been performed.

44.7 Patient Selection

All patients with peritoneal surface malignancies should be discussed in a multidisciplinary tumor board. As a minimum requirement, the tumor board should consist of representatives of the following medical specialties:

- A visceral surgeon with a special interest in surgical oncology and previous experience in the treatment of patients with peritoneal neoplasms using CRS and HIPEC
- A medical oncologist with experience in the multidisciplinary management of patients with peritoneal neoplasms
- A radiologist

44.8 Definition of Treatment Centers for CRS and HIPEC

Centers offering CRS and HIPEC should meet the following requirements:

- Presence of at least two experienced visceral surgeons, one of them with previous experience in the delivery of CRS and HIPEC.
- Presence of at least one medical oncologist with experience in treatment of patients with peritoneal neoplasms.
- Presence of at least one anesthetist with experience in the intraoperative and perioperative management of patients undergoing CRS and HIPEC.
- Presence of an interdisciplinary tumor board with regular meetings.
- Presence of an intensive care department.
- Surgical staff that is familiar with the handling of intraoperative chemotherapy and its possible risks for patient and staff.
- Presence of a CE-certified HIPEC device.
- Constant availability (24/7) of a visceral surgeon/surgical oncologist.
- Availability of an interventional radiology department.
- Existence of a special outpatient clinic for patients with peritoneal neoplasms.
- A minimum of 10 CRS and HIPEC procedures should be carried out per year.
- Surgical and oncological outcomes should be reviewed annually (morbidity, mortality, oncological outcome) and comply with internationally accepted standards (mortality <5%, relaparotomy rate <15%).

- The center should be a member of the ACO-ASSO Peritoneal Surface Oncology Working Group.
- The center should participate in a HIPEC registry and/or clinical trials.
- The staff of the center should regularly attend CME courses and conferences.

44.9 Register/Studies

Patients undergoing CRS and HIPEC should be included into a national HIPEC registry. If possible, patients should be included in clinical trials.

44.10 Quality Indicators and Minimum Case Numbers

As the two main quality indicators, the guideline indicates a mortality of <5% as well as a relaparotomy rate of <15% after CRS and HIPEC. In addition, a regular update on postoperative morbidity and oncological outcome should be provided. The minimum number of procedures is 10 CRS and HIPEC interventions per year.

44.11 Number/Density of Treatment Centers

A numerical restriction of the number of treatment centers in Austria is not recommended by the ACO-ASSO guideline since there is no available health economic data on the relation between density of treatment centers for CRS and HIPEC and patient outcome. Even though Chua et al. [3] conclude that the medical outcome in tertiary reference centers for CRS and HIPEC is better than in treatment centers with lower patient frequency, the optimal center size remains yet to be defined. Internationally, the availability of treatment centers for CRS and HIPEC is extremely heterogeneous: For example, in the United Kingdom (UK) with a population of 65.3 million (Source: Eurostat, as of 1/1/2016) there are currently only 2 CRS and HIPEC centers (Basingstoke and North Hampshire Hospital, Basingstoke, and The Christie Hospital, Manchester), whereas in France, with a nearly identical population of 66.7 million, a total of 34 treatment centers is available [5]. For comparison, the density of treatment centers for CRS and HIPEC in Austria is in the upper range, currently amounting to 1.05 per million inhabitants. Whether this high density of treatment centers for CRS and HIPEC will be maintained is a question that remains to be answered.

References

1. Arbeitsgruppe Peritoneale Malignome der Österreichischen Gesellschaft für Chirurgische Onkologie. Leitlinie zur Behandlung von Patienten mit peritonealen Neoplasmen mittels zytoreduktiver Chirurgie und hyperthermer intraperitonealer Chemotherapie in Österreich. 2013. www.aco-asso.at/arbeitsgruppen/ag-peritoneale-malignome/leitlinie-zurbehandlung-von-patienten-mit-peritonealen-neoplasmen-mittels-zytoreduktiver-chirurgie-und-hyperthermerintraperitonealer-chemotherapie-in-oesterreich/. Accessed 20 Sept 2017.
2. Arbeitsgruppe Peritoneale Malignome der Österreichischen Gesellschaft für Chirurgische Onkologie. Die Peritonealkarzinosezentren ("HIPEC-Zentren") der AG "Peritoneale Neoplasmen" der ACO-ASSO und des ACOASSOPCNetworks. 2015. www.aco-asso.at/arbeitsgruppen/ag-peritoneale-malignome/die-peritonealkarzinosezentren-hipeczentren-der-ag-peritoneale-neoplasmen-der-aco-asso-und-des-aco-assopcnetworks/. Accessed 20 Sept 2017.
3. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann Surg. 2009;249:900–7.
4. Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie e.V. Das Zertifizierungssystem der DGAV (ZertO 5.1). 2016. www.dgav.de/savc/zertifizierungen/zertifizierungsordnung.html. Accessed 4 Jan 2017.
5. Ferron G, Simon L, Guyon F, Glehen O, Goere D, Elias D, Pocard M, Gladieff L, Bereder JM, Brigand C, Classe JM, Guilloit JM, Quenet F, Abboud K, Arvieux C, Bibeau F, De Chaisemartin C, Delroeux D, Durand-Fontanier S, Goasguen N, Gouthi L, Heyd B, Kianmanesh R, Leblanc E, Loi V, Lorimier G, Marchal F, Mariani P, Mariette C, Meeus P, Msika S, Ortega-Deballon P, Paineau J, Pezet D, Piessen G, Pirro N, Pomel C, Porcheron J, Pourcher G, Rat P,

Regimbeau JM, Sabbagh C, Thibaudeau E, Torrent JJ, Tougeron D, Tuech JJ, Zinzindohoue F, Lundberg P, Herin F, Villeneuve L, BIG-RENAPE Working Group. Professional risks when carrying out cytoreductive surgery for peritoneal malignancy with hyperthermic intraperitoneal chemotherapy (HIPEC): a French multicentric survey. Eur J Surg Oncol. 2015;41:1361–7.

6. Kober F, Heiss A, Roka R. Diffuse and gross peritoneal carcinomatosis treated by intraperitoneal hyperthermic chemoperfusion. Cancer Treat Res. 1996;82:211–9.
7. National Institute for Health and Clinical Excellence. Complete cytoreduction for pseudomyxoma peritonei (Sugarbaker technique). 2004. www.nice.org.uk/guidance/ipg56. Accessed 4 Jan 2017.
8. National Institute for Health and Clinical Excellence. Interventional procedure guidance on cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. 2010. www.nice.org.uk/guidance/ipg331. Accessed 4 Jan 2017.
9. Pelz JO, Stojadinovic A, Nissan A, Hohenberger W, Esquivel J. Evaluation of a peritoneal surface disease severity score in patients with colon cancer with peritoneal carcinomatosis. J Surg Oncol. 2009;99:9–15.

45 Guideline Preparation and Centre Development for the Treatment of Peritoneal Tumours in Switzerland

Thomas Steffen

45.1 Preparation of Guidelines in Switzerland

The preparation of medical guidelines in Switzerland has so far been limited to published expert recommendations. In Switzerland, the Swiss Academy of Medical Sciences (SAMS) is primarily responsible for establishing medical guidelines. It was founded in 1943 by the five Faculties of Medicine and the two Faculties of Veterinary Medicine, as well as the Association of Swiss Physicians FMH in Switzerland. The SAMS regularly publishes the currently valid guidelines in four languages. The Central Ethics Commission of the SAMS anticipates and discusses medical ethics-related issues. It formulates these guidelines and recommendations to support medical practice or biomedical research. They are usually included in the FMH Code of Professional Conduct and are thus binding for FMH members (www.samw.ch) [1]. The guidelines are reviewed and revised at regular intervals. A review of the currently published guidelines indicates that they primarily correspond to scientific contributions to medical ethics-related issues. They hardly contain any concrete technical guidelines. However, a survey indicated that the existing SAMS Guidelines are well-known and widely used in practice [2].

45.2 Coordination and Concentration of Highly Specialised Medicine

The Swiss Conference of Cantonal Health Directors (GDK) unites the cantonal government members responsible for health care within a political coordination body. The purpose of the GDK is to promote cooperation between the 26 cantons, as well as between them, the Confederation and other important health-care organisations (www.gdk-cds.ch). In addition to numerous other subjects, the GDK also deals with so-called highly specialised medicine (HSM). The cantons have been commissioned with the performance of joint planning for the HSM area. To implement this mandate, the cantons signed the Inter-Cantonal Agreement on Highly Specialised Medicine (IVHSM) on 1 January 2009. The cantons are thus obliged to jointly plan and allocate highly specialised services. Thus, instead of 26 cantonal plans, there is only a single one for the HSM. The IVHSM forms the legal basis for the allocation of benefits. Additionally, the IVHSM determines the decision-making processes of the IVHSM organs and defines the criteria to be fulfilled by a range of services to be regarded as an HSM in the sense of the IVHSM.

T. Steffen (✉)
Surgical Clinics, Cantonal Hospital St. Gallen, St. Gallen, Switzerland
e-mail: Thomas.Steffen@kssg.ch; http://www.surgery.ch/; http://www.spcg.ch/

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*, https://doi.org/10.1007/978-3-030-62640-2_45

The joint planning of the HSM takes place with a view to requirements-based, high-quality and economically efficient medical care. An intercantonal decision-making body (HSM decision-making body) is responsible for the planning of HSM. It is elected by the GDK members and advised by an expert committee (HSM Specialist Body). Both committees are supported administratively by the HSM project secretariat. The HSM decision-making body is composed of health directors from various cantons. The Federal Office of Public Health, the Swiss University Conference and the leading industry organisation of Swiss health insurers (santésuisse) are represented on the committee in an advisory capacity. The HSM decision-making body deals with the medical-scientific processing of the HSM areas. It is made up of a 15-member expert committee of physicians from various specialised medical departments in Switzerland and abroad. The HSM expert body develops proposals for the increased coordination and concentration of the investigated service areas. It establishes the conditions for the provision of services and adopts recommendations for the allocation of services, which serve as a basis for decision-making for the resolution committee. The IVHSM service allocations have so far been performed for the various subareas, including the subarea of highly specialised visceral surgery (Table 45.1). This as well as additional information can be found on the GDK homepage (www.gdk-cds.ch).

Table 45.1 Existing IVHSM benefit allocations (published in the Federal Gazette of 10 September 2013) (www.gdk-cds.ch) [3]

Highly specialised visceral surgery subarea
Oesophageal resection
Liver resection
Pancreatic resection
Deep rectal resection
Complex bariatric surgery

Table 45.2 Requirements for institutions performing HIPEC treatments

Structural quality	Existing specialist disciplines at the institution Structures implemented at the institution Technical, device-related prerequisites Composition and qualification of the tumour boards Further education at the institution Research at the institution
Process quality	Availability of specialists The compliant preparation or production of cytostatic solutions The holding of tumour board meetings The implementation of treatment plans (SOP)
Outcome quality	Registration of data

45.3 HIPEC as Complex Highly Specialised Visceral Surgery

To achieve a standardisation of the HIPEC therapy, the following requirements, for example, would have to be fulfilled in Switzerland, as formulated by the HSM professional body:

- Definition of the requirements for a tumour centre with a special focus on tumour boards
- Operationalisation of the proposed quality criteria
- Definition of a binding cooperation within the framework of a supra-regional network, with due consideration of patient pathways

In the case of selected indications, which are to be defined, prerequisites must be established for structural quality, process quality and outcome quality. Possible requirements are listed in Table 45.2.

In 2015, a working group of the Swiss Group for Clinical Cancer Research (SAKK) prepared a report on the "HIPEC" subject for the SAKK General Assembly. It was to be referred to the HSM expert body.

45.4 Tasks of the Swiss Peritoneal Cancer Group (SPCG)

In 2013, a technical working group on peritoneal malignant tumours and HIPEC was established in Switzerland. This working group was established by surgeons who perform HIPEC for the purpose of promoting cooperation and jointly developing the subject in Switzerland. In 2015, this working group was incorporated as an offi-

cial associate working group of the Swiss Society of Visceral Surgery (SGVC) and given the name Swiss Peritoneal Cancer Group (SPCG). The SPCG has set itself the following objectives:

- Organisation of specialist congresses
- Maintaining contacts with international groups pursuing the same goals
- Assuming an active role in the development of HSM for HIPEC
- Definition of quality requirements
- Establishment of a national register
- Support for scientific development in Switzerland

The provision of recommendations for the surgical treatment of patients with peritoneal malignant tumours will represent a challenging task for the SPCG. It therefore strives for a multidisciplinary, university and non-university composition. Furthermore, the specialist topic should be further publicised. One of the ways in which this is achieved is by facilitating membership in the working group for all physicians from Switzerland and abroad involved in the treatment of peritoneal malignant tumours. The implementation of a Swiss data register is the second challenge for the near future. Due to the comparatively low prevalence, a link to an existing foreign register will also have to be examined, provided that the requirements regarding data protection and data sovereignty are ensured. In this context, the possibility of a European database should also be taken into consideration. For example, this has been achieved in the field of endocrine surgery (www.eurocrine.eu).

In summary, it should be noted that there are currently no institutionalised bodies in Switzerland dealing with the preparation of technical guidelines. A working group of the medical associations could assume such tasks along the same lines as the German model. The extent to which the SAMS should establish itself in this sense remains open. There may therefore be a certain limited availability of systematically developed Swiss guidelines for doctors in the context of specific treatments. However, this lack is unlikely to be of great significance in practical terms, as the range of guidelines offered by the Association of the Scientific Medical Societies (AWMF) is already much more advanced and can be applied to Switzerland in most cases.

References

1. Rüetschi D. The medical ethical guidelines of the SAMS from a legal perspective Switzerland. Med J. 2010;85(23):1222–5.
2. Pfister E, Biller-Andorno N. The reception and implementation of ethical guidelines of the Swiss Academy of Medical Sciences in medical and nursing practice. Swiss Med Wkly. 2010;140(11–12):160–7.
3. Conference of Swiss cantonal health directors. www.gdk-cds.ch.

Part XIV

Service

46 Checklists for the Treatment of Tumors of the Peritoneum: Framework SOP

Wieland Raue, Maik Kilian, Andreas Brandl, and Beate Rau

46.1 Introduction

Definition of the area and time of application for this standard.	
(Professions, departments, period)	
Signature (Head of surgical department)	**Signature** (Head of anesthesiological department)

46.2 Flowchart Treatment Algorithm

Adapt to the particular department.

W. Raue
Department of Surgery, AKH Group, Hospital of Celle, Celle, Germany

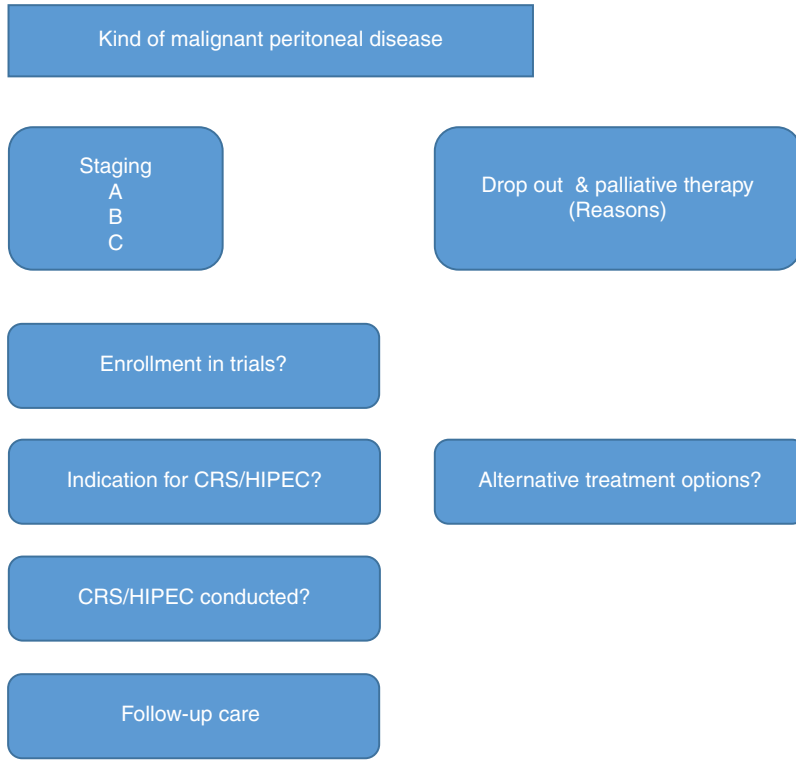
M. Kilian
Department of Surgery, Evangelische Elisabeth Klinik, Berlin, Germany

Evangelic Elisabeth Hosipital, Berlin, Germany
e-mail: maik.kilian@pgdiakonie.de

A. Brandl
Digestive Unit, Champalimaud Foundation, Lisbon, Portugal
e-mail: andreas.brandl@fundacaochampalimaud.pt

B. Rau (✉)
Department of Surgery, Charité – Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität of Berlin, Berlin, Germany
e-mail: beate.rau@charite.de

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2_46



46.3 Recent Clinical Trials

TitleRegistration number
Sponsor

46.4 Manual for Pre- and Postoperative Treatment

46.4.1 Tasks Prior to Admission

Diagnostics

- Meticulous anamnesis
- Screening for multiresistant bacteria, COVID-19
- Contrast-enhanced CT scan thorax/abdomen/pelvis (PET/CT)

Discussion in a GI tumor board
Patient information

- Detailed information about the disease, options, prognosis, and risks of treatment
- Minimization of risk factors possible? Malnourishment? Cardiological/pulmonary/renal optimization possible?

Schedules

- Malnourishment: enteral or parenteral supplementation for 7–10 days
- Specific perioperative treatment
- Order the perfusion equipment
- Order the chemotherapeutics

Anesthesiological consultation

46.4.2 Day Before Surgery

Order the chemotherapeutics

- Exact definition – Who? What? When? How?
- Safety data sheets accessible?

General

- Check for completeness
- Tumor board recommendations?
- Involve hospital social services
- Offer psycho-oncological support

Diagnostics

- Optional if required

Laboratory values

- That is, CBC, electrolytes, AST/ALT, LDH, liver and renal function tests
- Tumor markers
- Blood group, transfusion request

Patient information

- Obtain informed consent for the planned operation and HIPEC.
- Obtain informed consent for enrolment in clinical trials, if applicable.
- Discuss the postoperative course and possible complications, ERAS.

Nutrition

- Liquid diet
- Routine bowel preparation
- In the case of motility disorders/ileus, parenteral nutrition: product, amount, infusion rate

DVT prophylaxis

- What? When? Dose?

Anesthesia

- Obtain informed consent for the planned operation and HIPEC.
- Obtain informed consent for enrolment in clinical trials, if applicable.
- Discuss the postoperative course and possible complications, ERAS.

46.4.3 Day of Surgery

- Check for completeness of required information and the plan of operative strategy
- Follow the regular standards and SOPs of the department
- Thoracic epidural: What? When? Dose?

Antibiotic prophylaxis

- What? When? Dose?

Antiemetic therapy

- What? When? Dose?

Intraoperative measures

- SOP OR-nurse?
- SOP anesthetist and anesthesia nurse?
- SOP surgery?
- Recommendations for occupational health and safety available?

46.4.4 Day of Surgery ICU

Monitoring

- What? When? Interval?
- Vigilance CVP, results
- Ventilation, oxygenation
- Circulation
- Laboratory values
- Renal function/diuresis, core temperature, drained fluid balances

Circulation support

- What? When? Dose?

Diuresis

- Aim at ~1 ml/kgKG/h

Infusions

- What? When? Dose?

Transfusions

- Aim at Hb 8 (−10) mg/dl

Analgesia

- Thoracic epidural: What? When? Dose?
- Without PDA: What? When? Dose?

Ventilation

- Strive for early extubation
- Spontaneous: O_2 4 l/min via nasal probe, CPAP/NIV/HFNC

Nutrition

- What? When? Dose?

Antiemetic Therapy

- What? When? Dose?
- Intraoperative administration?

Mobilization

- Early mobilization according to ERAS recommendations
- Physiotherapeutic support

DVT prophylaxis

- What? When? Dose?

General

- Motivate the patient for active participation

Expect side effects

- Nausea, vomiting, diarrhea, fever
- SIRS
- Impaired vigilance
- Cardiac impairment, cardiac rhythm disorders
- Renal insufficiency
- Paralytic ileus
- Micturition disorders
- Reduction of immunologic competence
- Surgical complications (bleeding, anastomotic insufficiency)
- Pleural effusions

46.4.5 POD 1

Center-specific postoperative monitoring and treatment

For example……
Strive for discharge from ICU

- Stabile circulation without inotropic support
- Sufficient spontaneous breathing, max 3lO_2 via nasal probe
- Stabile renal function
- Efficient pain relief

Monitoring

- What? When? Interval?

Circulation support

- What? When? Dose?

Diuresis

- Aim at ~1 ml/kgKG/h

Infusions

- What? When? Dose?
- No basal infusion rate if possible

Transfusions

- Aim at Hb 8 (−10) mg/dl

Analgesia

- Thoracic epidural: What? When? Dose?
- Daily check for infection of the catheter insertion
- Without PDA: What? When? Dose?

Ventilation

- Strive for early extubation
- Spontaneous: O_2 4 l/min via nasal probe, CPAP/NIV/HFNC

Nutrition

- What? When? Dose?

Antiemetic Therapy

- What? When? Dose?
- Intraoperative administration?

Mobilization

- Early mobilization according to ERAS recommendations
- Physiotherapeutic support

DVT prophylaxis

- What? When? Dose?

General

- Motivate the patient for active participation

46.4.6 POD 2

Strive for discharge from ICU
Monitoring

- What? When? Interval?

Circulation support

- What? When? Dose?

Diuresis

- Aim at ~1 ml/kgKG/h
- If stable: remove bladder catheter

Infusions

- What? When? Dose?
- No basal infusion rate if possible

Transfusions

- Aim at Hb 8 (−10) mg/dl

Analgesia

- Thoracic epidural: What? When? Dose?
- Daily check for infection of the catheter insertion
- Without PDA: What? When? Dose?

Ventilation

- Strive for early extubation
- Spontaneous: O_2 4 l/min via nasal probe, CPAP/NIV/HFNC

Nutrition

- What? When? Dose?

Antiemetic Therapy

- What? When? Dose?
- Intraoperative administration?

Mobilization

- Early mobilization according to ERAS recommendations
- Physiotherapeutic support

DVT prophylaxis

- What? When? Dose?

General

- Motivate the patient for active participation

Dressings

- Removal of abdominal drains (consult surgeon).
- Change wound and stoma dressings.

46.4.7 POD 3

Strive for discharge from ICU
If a treatment on a normal peripheral ward is not achievable the further treatment on ICU should follow the regular ICU-SOPs with the aim of an early complete enteral nutrition and complete mobilization.

Monitoring

- What? When? Interval?

Diuresis

- Aim at ~1 ml/kgKG/h
- If stable: remove bladder catheter

Infusions

- What? When? Dose?
- No basal infusion rate if possible

Transfusions

- Aim at Hb 8 (−10) mg/dl

Analgesia

- Thoracic epidural: What? When? Dose?
- Daily check for infection of the catheter insertion
- Without PDA: What? When? Dose?

Ventilation

- O_2 max. 4 l/min via nasal probe, intermittent CPAP or intensive breathing exercises

Nutrition

- What? When? Dose?

Antiemetic Therapy

- What? When? Dose?

Mobilization

- Early mobilization according to ERAS recommendations
- Physiotherapeutic support, walk on ward, 6–8 h out of bed

DVT prophylaxis

- What? When? Dose?

General

- Motivate the patient for active participation.
- Psycho-oncological support.
- Nutritional counseling.

Dressings

- Removal of abdominal drains (consult surgeon).
- Change wound and stoma dressings.

46.4.8 POD 4–7 or Normal Surgical Ward

Planning the discharge from hospital

Planning the discharge from hospital

- Hospital Social Service counseling
- Organization of ambulant wound and ostomy care
- Organization of ambulant psycho-oncological support
- Organization of palliative care or hospice if needed
- Criteria for discharge:
  - Stabile vital functions
  - Normal inflammation parameters
  - Efficient pain relief
  - Ensured ambulant treatment without interruption
  - Widely independent participation in activities of daily living
  - Intention of the patient

Monitoring

- What? When? Interval?

Infusions

- What? When? Dose?

Transfusions

- Aim at Hb 8 (−10) mg/dl

Analgesia

- What? When? Dose?

Ventilation

- Intensive breathing exercises

Nutrition

- What? When? Dose?

Antiemetic Therapy

- What? When? Dose?

Mobilization

- Physiotherapeutic support, walk on ward, 6–8 h out of bed

DVT prophylaxis

- What? When? Dose?
- Pause for removal of the epidural catheter if necessary

General

- Motivate the patient for active participation.

Dressings

- Removal of abdominal drains (consult surgeon).
- Change wound and stoma dressings.

46.5 Tasks After Discharge

- Check for histopathological report
- Tumor board counseling
- Removal of sutures/staples after 12 days, discussion of the definitive pathologic report
- Discussion and organization of the recommended tumor-specific therapy
- In case of splenectomy: vaccination according to national recommendations (pneumococcus, hemophilus, meningococcus, and seasonal influenza)
- Psycho-oncological counseling
- Definition of the follow-up

46.6 SOP Anesthesia Nursing

Duration of surgery: ~3–8 h

Special features

- Extensive measures for occupational safety reasons: safety glasses, special gloves, and scrubs

Patient positioning

- Lithotomy position
- Active temperature control

Preparation

- Venous access lines
- Arterial access line
- Thoracic epidural catheter
- Endotracheal intubation

Drugs

- What? When? Dose?

Monitoring

- ECG, blood pressure, SaO_2
- CVP
- Intensive hemodynamic measurement (stroke volume, cardiac index)

46.7 SOP Anesthesia

Transfusion requirements

- Blood type, pRBC/FFP

Anesthesia

- TIVA with additional thoracic epidural analgesia

Drugs

- What? When? Dose?

Monitoring

- Internal standards/SOP

Induction

- Internal standards/SOP

Hemodynamic targets

- Mean arterial blood pressure MAP 60–70 mmHg
- Stroke volume variation SVV < 12%
- Cardiac index CI > 2.5
- Hb > 10 g/dl
- DO_2 > 450 ml/min/m^2

Intraoperative fluid administration:

- Crystalloids approx. 500 ml/h
- pRBC according to blood loss and targeted Hb
- FFP in case of massive bleeding or coagulopathy
- (Colloids according to internal standards)

Criteria for hypovolemia/vasopressors

- Internal standards/SOP

Criteria for inotropic support with dobutamine or enoximone

- Internal standards/SOP

Active temperature control

- During CRS: core/bladder >36 °C
- During HIPEC: arterial <38 °C
- During HIPEC: abdominal: 42 °C (cave >42.5 °C)

Renal function

- Awareness for nephrotoxic chemotherapeutics, abdominal hypertensive, impaired renal blood flow, and possible extensive fluid shifts during HIPEC
- Diuresis at least 1 ml/kg/h
- Avoid hypovolemia
- In case of oliguria or hypervolemia high-ceiling diuretics

Antiemetic therapy

- Internal standards/SOP

Postoperative management

- Planned extubation at the ICU

46.8 SOP Surgery

Detailed standard operating procedures and internal guidelines should be developed for at least the following issues:

- Preoperative aspects (patient selection, preparation for surgery, anesthesiological management)
- Typical surgical techniques and techniques for CRS
- General surgical principles for frequently applied resection steps (i.e., oncologically adequate colonic resection, techniques of anastomotic formation, chest tube insertion, techniques of fascia closure, etc.)

46.9 Histopathologic Workup

The pathologic report should describe the basic oncologic findings (assessment, staging). Additional examinations should be possible and follow the (molecular) tumor board counseling.

Additional aspects in cases of colorectal carcinoma
That is, MSI, all-RAS, BRAF

Additional aspects in cases of gastric carcinoma
That is, HER2/neu expression

Additional aspects in cases of mucinous appendix neoplasm
Proliferation index

46.10 Preparation for CRS/HIPEC

HIPEC techique (open/closed)
Diagnosis
Indication
Operating table
Patient positioning
Auxiliary positioning devices
Electrical instruments
Trays
Retractor systems
Trays in standby
Drapes
Scrubs
Sutures
Drains
Additional
Notes
Safety features

46.11 Occupational Health and Safety

- Annual education and training on safety aspects during HIPEC.
- The OR should be indicated using warning signs.
- Only absolutely essential staff should enter the OR during HIPEC.
- Personal safety equipment should be used.
- Excretions are potentially contaminated for up to 24 h depending on the chemotherapeutic drug.

Measures in case of surrounding contamination
Internal standards/SOP

Measures in case of contamination of the personnel
Internal standards/SOP

46.12 Checklist for the Use of Chemotherapeutics for HIPEC

What	Note	Check
Warning signs Caution! Chemotherapy/ biohazard Contact staff before entering the OR	On site? Attached to all entries of the OR?	☐ ☐
Impermeable laundry bags	On site?	☐
Safety glasses with lateral protection	On site?	☐
Impermeable scrubs	On site?	☐
Chemoresistant sterile gloves	On site?	☐
Chemoresistant unsterile gloves	On site?	☐
Chemotherapeutic drugs	On site?	☐
Chemotherapy waste containers	On site?	☐
Spill kit	On site?	☐

Date: Signature:

46.13 Chemotherapeutic Regimen for HIPEC

Origin	Chemotherapeutics center specific
Colorectal	i.p.: mitomycin C 30 mg/m² 90 min (Cisplatin 100 mg/m²)
Appendiceal	i.p.: mitomycin C 30 mg/m² 90 min (Cisplatin 100 mg/m²)
Pseudomyxoma	i.p.: mitomycin C 30 mg/m² 90 min (Cisplatin 100 mg/m²)
Ovarian	i.p.: cisplatin 75 mg/m² + doxorubicin 15 mg/m² 90 min
Gastric	i.p.: cisplatin 75 mg/m² + doxorubicin 15 mg/m² 90 min
Mesothelioma	i.p.: cisplatin 75 mg/m² + doxorubicin 15 mg/m² 90 min

Carrier solution: NaCl 0.9%
Mitomycin C should be given in three doses for 30 min each, due to its short half-life.

46.14 PCI Assessment

0	Central	7	Right lower
1	Right upper	8	Right flank
2	Epigastrium	9	Upper jejunum
3	Left upper	10	Lower jejunum
4	Left flank	11	Upper ileum
5	Left lower	12	Lower ileum
6	Pelvis		

Lesion size
0 – no tumor visible
1 – tumor up to 0.5 cm
2 – tumor up to 5.0 cm
3 – tumor >5.0 cm or confluence

46.15 Information Material for the Anesthetist

Preparation and intraoperative management

- Internal standards/SOP

Severe fluid shifts and coagulation disorders are to be expected due to extensive wound surfaces and the duration of the complete procedure.

Frequent postoperative complications or side effects

- Nausea, vomiting, diarrhea, fever
- SIRS
- Impaired vigilance
- Cardiac impairment, cardiac rhythm disorders
- Renal insufficiency
- Paralytic ileus
- Micturition disorders
- Reduction of immunologic competence
- Surgical complications (bleeding, anastomotic insufficiency)

46.16 Checklist for Outpatient Department

	Ordered	Executed
Documentation of bodyweight and height	☐	☐
Tumor board counseling	☐	☐
Information material for surgery delivered	☐	☐
Information material for chemo/HIPEC delivered	☐	☐
Consent for transfusions delivered	☐	☐
Check for participation in trials	☐	☐
Fix a date for anesthesiological counseling	☐	☐
Fix a date for further diagnostics	☐	☐
Fix a date for CRS/HIPEC	☐	☐

46.17 Checklist Surgical Ward

	Ordered	Executed
Detailed anamnesis and examination	☐	☐
Preparation for surgery		
Blood type + pRBCs	☐	☐
Bowel preparation	☐	☐
…	☐	☐
Intraoperative antibiotics		
Drug 1	☐	☐
Drug 2	☐	☐
Others…	☐	☐
Intraoperative antiemetics		
Drug 1	☐	☐
Drug 2	☐	☐
Drug 3	☐	☐
DVT prophylaxis		
Drug 1	☐	☐
Compression devices	☐	☐
Others…	☐	☐
Final check		
Documents complete?		☐
Tumor board counseling		☐
Counseling the hospital social service team		☐
Psycho-oncological counseling		☐

Index

B. Rau et al. (eds.), *Peritoneal Tumors and Metastases*,
https://doi.org/10.1007/978-3-030-62640-2