PIPAC

Theoretical considerations as well as comprehensive preclinical and clinical data suggest that optimizing physical parameters of intraperitoneal drug delivery might help to circumvent initial or acquired resistance of peritoneal metastasis (PM) to chemotherapy. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) is a novel minimally invasive drug delivery system systematically addressing the current limitations of intraperitoneal chemotherapy. The rationale behind PIPAC is: (1) optimizing homogeneity of drug distribution by applying an aerosol rather than a liquid solution; (2) applying increased intraperitoneal hydrostatic pressure to counteract elevated intratumoral interstitial fluid pressure; (3) limiting blood outflow during drug application; (4) steering environmental parameters (temperature, pH, electrostatic charge etc.) in the peritoneal cavity for best tissue target effect. In addition, PIPAC allows repeated application and objective assessment of tumor response by comparing biopsies between chemotherapy cycles.

1. Introduction

Every 30 seconds worldwide, a new patient is diagnosed with peritoneal metastasis (PM), the spreading of cancer cells into the peritoneal cavity [1]. Upon diagnosis, current therapy guidelines [2][3][4] recommend palliative systemic chemotherapy or best supportive care. In spite of recent progress in the fields of targeted therapy, immunotherapy, cytoreductive surgery (CRS) and intraperitoneal chemotherapy, PM is still perceived as a fatal disease [5].

Patients with PM have shorter survival than those with parenchymatous metastasis, for example patients with liver metastasis in colorectal cancer [6]. This poor prognosis is multifactorial and includes chemoresistance to cytotoxic drugs, poor tolerance of chemotherapy, steeper patient performance decline and intestinal dysfunction associated with tumor bowel invasion [6].

Why are PM relatively resistant to chemotherapeutic drugs administered intravenously? The initial hypothesis was that molecular mechanisms were responsible for resistance so that newly developed targeted drugs would overcome this resistance. However, the effect of new drugs on the prognosis of PM patients was limited. For example, in colorectal cancer, treatment-related resistance of PM did not disappear with the introduction of irinotecan and oxaliplatin [7]. Incremental differences in outcomes between non-peritoneal and peritoneal cohorts even increased after the introduction of targeted agents [8]. Similarly, in advanced gastric cancer, where doublet or triplet systemic chemotherapy is the standard-of-care, their ability in achieving long-term survival in patients with PM is still "modest at best" [8].

Thus, beyond molecular mechanisms, other factors must play a role in the chemoresistance of PM [9]. One hypothesis is anticancer drugs not penetrating tissue efficiently [10]. In order to exert a therapeutic effect, drugs must reach all the cancer cells at an appropriate cytotoxic concentration and period of time. This might not be the case for current therapies of PM.

1.1. The Peritoneum Is Poorly Vascularized

Only 2–5% of the cardiac minute volume reaches the peritoneum, so most chemotherapy (95–98%) administered intravenously is by-passing the peritoneum and causing systemic toxicity. Moreover, the peritoneal microcirculation is characterized by a low capillary density in comparison to other organs [11][12]. In addition, in PM, local vascular distribution varies between vital and necrotic zones, with some areas receiving no blood supply at all [13]. These added factors result in poor tissue uptake of compounds administered into the systemic blood compartment.

1.2. Interstitial Fluid Pressure Is Increased in PM

Fluid pressure is elevated in the interstitial tissue of tumors [14]. For example, interstitial fluid pressure values as high as 33 mmHg have been recorded in some sarcomas [15]. Several studies indicate that high interstitial fluid pressure in the

tumor is correlated with poor prognosis [16]. Most drugs used for systemic treatment of patients with cancer—high-molecular-weight compounds in particular—are transported from the circulatory system through the interstitial space by convection, that is, they are carried by streaming of a flowing fluid [17]. Thus, increased interstitial fluid pressure within the tumor node causes less uptake of drugs into the tumor. Moreover, in PM, interstitial fluid pressure profiles vary between different tumor zones [13], suggesting that exposition of tumor cells to chemotherapeutic drugs might vary within the metastasis.

During tumor progression the extracellular matrix undergoes so-called mesothelial–mesenchymal transition (MMT) [18]. MMT is characterized by the progressive replacement of normal peritoneal mesothelial cells tissue by fibroblasts, a major cellular component of scar tissue [19]. During MMT, peritoneal mesothelial cells lose their epithelial-like characteristics, including cell–cell junctions, tight junctions, adherence junctions and desmosomes, lose their apicobasal polarity and progressively acquire a mesenchymal phenotype, characterized by actin reorganization, stress fiber formation, migration, and invasion [20]. These dramatic changes in tissue architecture, formerly named "desmoplasia", are most pronounced at the tumor invasion front. Due to tissue remodeling and increased interstitial fluid pressure (IFP), drug uptake is less effective into hard, fibrotic tissue than into normal tissue. This results in increased resistance to chemotherapy, which is largely independent of the mode of action of the drug applied.

2. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

PIPAC is a minimally invasive approach relying on physical principles for improving intraperitoneal drug delivery, including: (1) optimizing the homogeneity of drug distribution by applying an aerosol rather than a liquid solution; (2) applying increased intraperitoneal hydrostatic pressure to counteract elevated intratumoral interstitial fluid pressure; (3) limiting blood outflow during drug application; (4) steering environmental parameters (temperature, pH, electrostatic charge etc.) in the peritoneal cavity for best tissue target effect. In addition, PIPAC allows repeated application and objective assessment of tumor response by comparing biopsies between chemotherapy cycles.

Staging laparoscopy has developed to be a standard of care in ovarian cancer [21] and in gastric cancer [22]. During such procedures, carbon dioxide (CO_2) pneumoperitoneum is applied in order to create a working space. This working space allows for the safe placement of access ports through the abdominal wall [23], visualization of organs [21][24] and completion of complex interventions [25][26]. Twenty years ago, we developed a first-generation device suitable for minimally invasive surgery procedures that allowed microdroplets of a therapeutic substance to be distributed into the pneumoperitoneum (CO_2), creating a "therapeutic pneumoperitoneum" [27].

Over the years, in addition to the aerosolization of a drug, we found it useful to add two further components, namely steering the operating environment (pressure, temperature, electrostatic charges, etc.) and objective assessment of tumor response (by comparing biopsies between repeated applications) [28][29]. All three components are now part of PIPAC [30]. Starting with the first preclinical experiments through technology development, first in-human use [31], Phase 1 [32][33][34] and Phase 2 [35][36][37][38][39][40] trials, PIPAC is currently being evaluated in randomized controlled trials [41][42][43][44][45] for palliative therapy of PM [46].

PIPAC (**Figure 1**) is applied through laparoscopic access using two balloon trocars in an operating room equipped with laminar air flow. In a first step, a normothermic capnoperitoneum is established with a pressure of 12 mmHg. A cytotoxic solution (about 10–20% of a normal systemic dose) is nebulized with a micropump into the abdominal cavity and maintained for 30 min. The aerosol is then removed through a closed suction system.
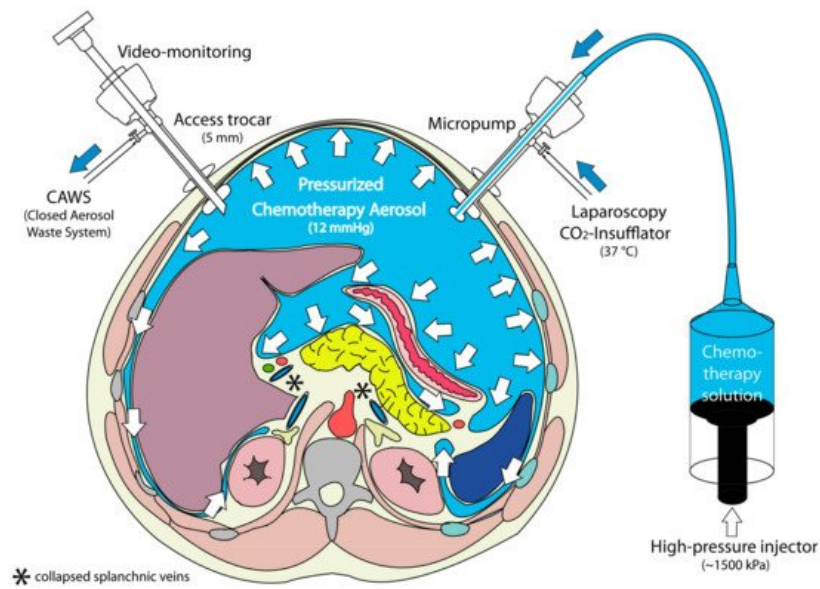
Figure 1. Principle of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). During a staging laparoscopy, an aerosol cytostatic agent is applied in the abdominal space using a nebulizer. The application as an aerosol allows the relatively even distribution of the substance. Increased pressure (12 mmHg) ensures deeper penetration into the tissue. Reproduced with permission from [31].

In contrast to inhalers commonly used in pulmonary medicine, no propellant gas is needed. During PIPAC, a liquid solution is aerosolized into the gaseous (CO_2) environment using a specific nozzle (Capnopen®, Capnomed, Zimmern, Germany). Energy is provided by applying an upstream mechanical force gradient provided by an industry-standard angioinjector (e.g., Accutron HP®, MedTron, Saarbrücken, Germany).

Theoretical considerations suggest that the therapeutic CO_2-pneumoperitoneum ("capnoperitoneum") should be capable of carrying microdroplets of active substances to all exposed peritoneal surfaces. These considerations were confirmed by several preclinical experiments, showing that the active principle is distributed, reaching all exposed [47][48] and even partially hidden surfaces [49].

Figure 2 provides a graphical abstract of the differences between non-pressurized, liquid intraperitoneal chemotherapy vs. pressurized, aerosolized intraperitoneal chemotherapy.
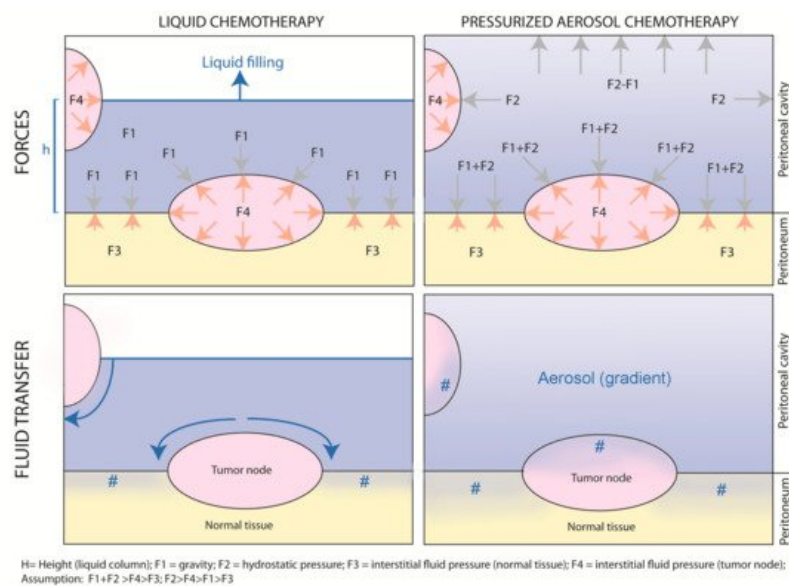

Figure 2. "Intraperitoneal chemotherapy with normobaric liquids vs. pressurized aerosols. Graphical abstract of the physical differences between non-pressurized, liquid intraperitoneal chemotherapy vs. pressurized, aerosolized intraperitoneal chemotherapy." #: drug penetration into the tissue.

As shown in the upper left panel, during liquid intraperitoneal chemotherapy, gravity forces applied to the tumor node depend on the height of the water column (h); the exposition of the tumor node depends on the filling volume. This reflects the situation of open HIPEC. In contrast, during PIPAC (upper right panel), tumor nodes are exposed to unidirectional gravitational and multidirectional hydrostatic forces caused by the pressurized environment. Although an aerosol gradient

exists, all exposed peritoneal surfaces are reached by the drug. The net fluid transfer, as illustrated in the lower panels, results from the balance between gravitational and hydrostatic forces on the one hand and tumor node resistance resulting from increased interstitial fluid pressure on the other hand. As shown in the lower left panel, since resistance in normal tissue is lower than in tumor nodes, liquid chemotherapy will follow the path of least resistance and preferentially enter the normal tissue. In contrast (right lower panel), aerosolized chemotherapy will penetrate both the normal and the tumoral tissue, penetrating the normal deeper than the tumoral tissue.

3. Preclinical Evidence of PIPAC

Several studies have evaluated drug uptake into the target tissue after PIPAC, and some of them have compared PIPAC with other drug delivery techniques such as HIPEC and/or laparoscopic HIPEC. Therapeutic substances investigated include methylene blue [47][50], DNA [51], RNA [52][53], cisplatin [54][55][56][57], doxorubicin [49][58][59][60], oxaliplatin [57][61][62][63] and liposomal doxorubicin [64][65].

3.1. Effect of Hydrostatic Pressure

Increasing intraabdominal hydrostatic pressure during PIPAC significantly enhanced tumor cell toxicity of oxaliplatin in both wild-type and chemotherapy-resistant cells in vitro. A maximum cytotoxicity was observed at 15 mmHg. Pressures >15 mmHg did not show additional cytotoxic effect on cells [63]. Similarly, increasing PIPAC pressure over 15 mmHg did not increase the depth of doxorubicin tissue penetration in an ex vivo model [59].

3.2. Homogeneity of Distribution

Delivery of methylene blue into a large animal model unraveled a more homogeneous and more intensive vital staining of the abdominal cavity after aerosolization than after lavage [47]. Ex vivo experiments on surgical specimens of human peritoneal metastases evidenced a homogeneous distribution of small DNA fragments (Dbait) onto the peritoneum as compared to conventional peritoneal lavage [51]. In a rodent model, bioluminescence analysis showed a superior distribution of RNA complexes after intraperitoneal nebulization as compared to intraperitoneal injection of liquid: bowel exposition to the therapeutic substance was superior after PIPAC (median: 50%) vs. intraperitoneal injection (median: 10%) [52]. In a postmortem swine model, doxorubicin administered as PIPAC reached all areas within the peritoneum, with the highest depth of penetration being measured in the area located in front of the aerosolizer [60]. In two studies, the aerosol reached covered peritoneal areas [49][59]. In a living swine model, homogeneity of drug repartition (as defined by the comparison of the oxaliplatin concentration in the parietal vs. visceral peritoneum) was better after PIPAC (ratio: 11.5) than after HIPEC (ratio: 17.6) [66].

3.3. Tissue Concentration

All pharmacological data published so far show a superior therapeutic ratio (tissue concentration/dose applied) of PIPAC vs. systemic administration [52], of PIPAC vs. intraperitoneal liquid chemotherapy [52], of PIPAC vs. HIPEC [61] and of PIPAC vs. laparoscopic HIPEC [66]. In the swine model, tissue delivery of oxaliplatin was compared between laparoscopic HIPEC (with 12–15 mmHg pressure), PIPAC (20% of HIPEC dose applied) and electrostatic precipitation PIPAC (ePIPAC, same dose as PIPAC): overall concentrations in the peritoneum were not different among the three groups, documenting an improvement of the therapeutic index (target tissue dose/dose applied) of PIPAC vs. HIPEC by a factor of five. In the visceral peritoneum, the improvement of the therapeutic index reached a factor of 7.4 in favor of PIPAC (p = 0.02).

3.4. Depth of Tissue Penetration

Most studies on depth of tissue penetration have been performed with doxorubicin, a large auto-fluorescent molecule with a molecular weight of 543 g/mol [67]. Doxorubicin only penetrates a few cell layers after HIPEC [68], corresponding to a depth of 10–30 µm. After PIPAC, depths of doxorubicin tissue penetration reached up to 469 µm in the ex vivo model [59], more than 300 µm in the small intestine of swine post-mortem [60] and up to 500 µm in human patients [31].

3.5. Local Effect vs. Systemic Uptake

Since the dose applied is reduced by an order of magnitude (as compared to a usual systemic dose) [69] and due to the properties of the peritoneum–plasma barrier, the plasma concentration of the chemotherapeutic agent remains low [30] and, accordingly, the organ toxicity [43]. In addition, pressure enhances the pharmacokinetic advantage of regional delivery by reducing blood outflow from the abdomen over the liver and the abdominal wall during the uptake phase. Thus, during the time of PIPAC exposition (currently around 30 min) at a pressure of 12–15 mmHg, the abdominal vascular compartment is expected to be partially isolated from the systemic compartment, contributing to better local uptake and less systemic toxicity.

This hemodynamic effect of pressure during laparoscopy has been documented in the preclinical model and in the human patient. Specifically, in a swine model of laparoscopic nephrectomy at a pressure of 12 mmHg, hepatic perfusion (both arterial and portal) was reduced by half: a decrease of portal flow from 974 mL/min to 547 mL/min and a decrease of hepatic artery flow from 278 mL/min to 133 mL/min was seen [70]. When splanchnic blood flow was measured at an increasing intraabdominal pressure from 0 mmHg to 15 mmHg in 18 patients undergoing routine laparoscopy, portal venous flow was decreased by 39% and microcapillary flow in the parietal peritoneum by 60% [71]. In the swine model, systemic oxaliplatin concentrations were significantly lower during PIPAC application time (in the presence of an intraabdominal pressure of 12–15 mmHg) than in the laparoscopic HIPEC group ($p < 0.05$) [66]. In vitro, the rate of apoptotic and proliferative cells as well as the level of oxaliplatin penetration in tumor nodes was higher in PIPAC groups with less systemic passage through the peritoneum [61]. In vivo, in a mouse model of colorectal PM, systemic passage was lower in the PIPAC group [61].

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424.

2. Van Cutsem, E.; Cervantes, A.; Adam, R.; Sobrero, A.; Van Krieken, J.H.; Aderka, D.; Aranda Aguilar, E.; Bardelli, A.; Benson, A.; Bodoky, G.; et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann. Oncol. 2016, 27, 1386–1422.

3. Benson, A.B.; Venook, A.P.; Cederquist, L.; Chan, E.; Chen, Y.J.; Cooper, H.S.; Deming, D.; Engstrom, P.F.; Enzinger, P.C.; Fichera, A.; et al. Colon Cancer, Version 1.2017, NCCN Clinical Practice Guidelines in Oncology. J. Natl. Compr. Cancer Netw. 2017, 15, 370–398.

4. Yoshino, T.; Arnold, D.; Taniguchi, H.; Pentheroudakis, G.; Yamazaki, K.; Xu, R.H.; Kim, T.W.; Ismail, F.; Tan, I.B.; Yeh, K.H.; et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: A JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann. Oncol. 2018, 29, 44–70.

5. Lambert, L.A. Looking up: Recent advances in understanding and treating peritoneal carcinomatosis. CA Cancer J. Clin. 2015, 65, 284–298.

6. Franko, J.; Shi, Q.; Meyers, J.P.; Maughan, T.S.; Adams, R.A.; Seymour, M.T.; Saltz, L.; Punt, C.J.A.; Koopman, M.; Tournigand, C.; 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, 1709–1719.

7. Kerscher, A.G.; Chua, T.C.; Gasser, M.; Maeder, U.; Kunzmann, V.; Isbert, C.; Germer, C.T.; Pelz, J.O. Impact of peritoneal carcinomatosis in the disease history of colorectal cancer management: A longitudinal experience of 2406 patients over two decades. Br. J. Cancer 2013, 108, 1432–1439.

8. Dahdaleh, F.S.; Turaga, K.K. Evolving Treatment Strategies and Outcomes in Advanced Gastric Cancer with Peritoneal Metastasis. Surg. Oncol. Clin. N. Am. 2018, 27, 519–537.

9. Jain, R.K. Barriers to drug delivery in solid tumors. Sci. Am. 1994, 271, 58–65.

10. Minchinton, A.I.; Tannock, I.F. Drug penetration in solid tumours. Nat. Rev. Cancer 2006, 6, 583–592.

11. Solass, W.; Horvath, P.; Struller, F.; Königsrainer, I.; Beckert, S.; Königsrainer, A.; Weinreich, F.J.; Schenk, M. Functional vascular anatomy of the peritoneum in health and disease. Pleura Peritoneum 2016, 1, 145–158.

12. Hamizi, S.; Freyer, G.; Bakrin, N.; Henin, E.; Mohtaram, A.; Le Saux, O.; Falandry, C. Subcutaneous trastuzumab: Development of a new formulation for treatment of HER2-positive early breast cancer. Onco. Targets Ther. 2013, 6, 89–94.

13. Steuperaert, M.; Debbaut, C.; Carlier, C.; De Wever, O.; Descamps, B.; Vanhove, C.; Ceelen, W.; Segers, P. A 3D CFD model of the interstitial fluid pressure and drug distribution in heterogeneous tumor nodules during intraperitoneal chemotherapy. Drug Deliv. 2019, 26, 404–415.

14. Heldin, C.H.; Rubin, K.; Pietras, K.; Ostman, A. High interstitial fluid pressure—An obstacle in cancer therapy. Nat. Rev. Cancer 2004, 4, 806–813.

15. Nathan, S.S.; Huvos, A.G.; Casas-Ganem, J.E.; Yang, R.; Linkov, I.; Sowers, R.; DiResta, G.R.; Gorlick, R.; Healey, J.H. Tumor interstitial fluid pressure may regulate angiogenic factors in osteosarcoma. J. Orthop. Res. 2008, 26, 1520–1525.

16. Milosevic, M.; Fyles, A.; Hedley, D.; Pintilie, M.; Levin, W.; Manchul, L.; Hill, R. Interstitial Fluid Pressure Predicts Survival in Patients with Cervix Cancer Independent of Clinical Prognostic Factors and Tumor Oxygen Measurements.

Cancer Res. 2001, 61, 6400–6405.

17. Rippe, B.; Haraldsson, B. Transport of macromolecules across microvascular walls: The two-pore theory. Physiol. Rev. 1994, 74, 163–219.

18. Li, L.; Li, W. Epithelial-mesenchymal transition in human cancer: Comprehensive reprogramming of metabolism, epigenetics, and differentiation. Pharmacol. Ther. 2015, 150, 33–46.

19. Wilson, R.B. Hypoxia, cytokines and stromal recruitment: Parallels between pathophysiology of encapsulating peritoneal sclerosis, endometriosis and peritoneal metastasis. Pleura Peritoneum 2018, 3, 20180103.

20. Lopez-Cabrera, M. Mesenchymal Conversion of Mesothelial Cells Is a Key Event in the Pathophysiology of the Peritoneum during Peritoneal Dialysis. Adv. Med. 2014, 2014, 473134.

21. Zeff, N. Role of laparoscopy in initial tumour staging in advanced epithelial ovarian cancer: A systematic review. Pleura Peritoneum 2018, 3, 20180106.

22. Garg, P.K.; Jara, M.; Alberto, M.; Rau, B. The role of Pressurized IntraPeritoneal Aerosol Chemotherapy in the management of gastric cancer: A systematic review. Pleura Peritoneum 2019, 4, 20180127.

23. Glatz, T.; Horvath, P.; Lang, S.A.; Archid, R.; Nadiradze, G. Staging laparoscopy and Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for peritoneal metastasis: Safe access to the abdomen. Pleura Peritoneum 2019, 4, 20190004.

24. Ramos, R.F.; Scalon, F.M.; Scalon, M.M.; Dias, D.I. Staging laparoscopy in gastric cancer to detect peritoneal metastases: A systematic review and meta-analysis. Eur. J. Surg. Oncol. 2016, 42, 1315–1321.

25. Park, Y.S.; Son, S.Y.; Oo, A.M.; Jung do, H.; Shin, D.J.; Ahn, S.H.; Park do, J.; Kim, H.H. Eleven-year experience with 3000 cases of laparoscopic gastric cancer surgery in a single institution: Analysis of postoperative morbidities and long-term oncologic outcomes. Surg. Endosc. 2016, 30, 3965–3975.

26. Pedziwiatr, M.; Małczak, P.; Pisarska, M.; Major, P.; Wysocki, M.; Stefura, T.; Budzyński, A. Minimally invasive versus open pancreatoduodenectomy-systematic review and meta-analysis. Langenbecks Arch. Surg. 2017, 402, 841–851.

27. Reymond, M.A.; Hu, B.; Garcia, A.; Reck, T.; Köckerling, F.; Hess, J.; Morel, P. Feasibility of therapeutic pneumoperitoneum in a large animal model using a microvaporisator. Surg. Endosc. 2000, 14, 51–55.

28. Solass, W.; e Sempoux, C.; Detlefsen, S.; Carr, N.J.; 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.

29. Solass, W.; Sempoux, C.; Carr, N.J.; Bibeau, F.; Neureiter, D.; Jäger, T.; Di Caterino, T.; Brunel, C.; Klieser, E.; Fristrup, C.W.; et al. Reproducibility of the peritoneal regression grading score for assessment of response to therapy in peritoneal metastasis. Histopathology 2019, 74, 1014–1024.

30. Blanco, A.; Giger-Pabst, U.; Solass, W.; Zieren, J.; Reymond, M.A. Renal and hepatic toxicities after pressurized intraperitoneal aerosol chemotherapy (PIPAC). Ann. Surg. Oncol. 2013, 20, 2311–2316.

31. Solass, W.; Kerb, R.; Mürdter, T.; Giger-Pabst, U.; Strumberg, D.; Tempfer, C.; Zieren, J.; Schwab, M.; Reymond, M.A. 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.

32. Kim, G.; Tan, H.L.; Chen, E.; Teo, S.C.; Jang, C.J.M.; Ho, J.; Ang, Y.; Ngoi, N.Y.L.; Chee, C.E.; Lieske, B.; et al. Study protocol: Phase 1 dose escalating study of Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) with oxaliplatin in peritoneal metastasis. Pleura Peritoneum 2018, 3, 20180118.

33. Dumont, F.; Senellart, H.; Pein, F.; Campion, L.; Glehen, O.; Goere, D.; Pocard, M.; Thibaudeau, E. Phase I/II study of oxaliplatin dose escalation via a laparoscopic approach using pressurized aerosol intraperitoneal chemotherapy (PIPOX trial) for nonresectable peritoneal metastases of digestive cancers (stomach, small bowel and colorectal): Rationale and design. Pleura Peritoneum 2018, 3, 20180120.

34. Van De Sande, L.; Graversen, M.; Hubner, M.; Pocard, M.; Reymond, M.; Vaira, M.; Cosyns, S.; Willaert, W.; Ceelen, W. Intraperitoneal aerosolization of albumin-stabilized paclitaxel nanoparticles (Abraxane) for peritoneal carcinomatosis—A phase I first-in-human study. Pleura Peritoneum 2018, 3, 20180112.

35. Tempfer, C.B.; Winnekendonk, G.; Solass, W.; Horvat, R.; Giger-Pabst, U.; Zieren, J.; Rezniczek, G.A.; Reymond, M.A. Pressurized intraperitoneal aerosol chemotherapy in women with recurrent ovarian cancer: A phase 2 study. Gynecol. Oncol. 2015, 137, 223–228.

36. Khomyakov, V.; Ryabov, A.; Ivanov, A.; Bolotina, L.; Utkina, A.; Volchenko, N.; Kaprin, A. 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, 159–166.

37. Graversen, M.; Detlefsen, S.; Fristrup, C.; Pfeiffer, P.; Mortensen, M.B. Adjuvant Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) in resected high-risk colon cancer patients—Study protocol for the PIPAC-OPC3 Trial. A prospective, controlled phase 2 Study. Pleura Peritoneum 2018, 3, 20180107.

38. Struller, F.; Horvath, P.; Solass, W.; Weinreich, F.J.; Strumberg, D.; Kokkalis, M.K.; Fischer, I.; Meisner, C.; Königsrainer, A.; Reymond, M.A. 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.

39. Graversen, M.; Detlefsen, S.; Asmussen, J.; Mahdi, B.; Fristrup, C.; Pfeiffer, P.; Mortensen, M.B. Treatment of peritoneal carcinomatosis with Pressurized IntraPeritoneal Aerosol Chemotherapy—PIPAC-OPC2. Pleura Peritoneum 2018, 3, 20180108.

40. Rovers, K.P.; Lurvink, R.J.; Wassenaar, E.C.; Kootstra, T.J.; Scholten, H.J.; Tajzai, R.; Deenen, M.J.; Nederend, J.; Lahaye, M.J.; Huysentruyt, C.J.; et al. Repetitive electrostatic pressurised intraperitoneal aerosol chemotherapy (ePIPAC) with oxaliplatin as a palliative monotherapy for isolated unresectable colorectal peritoneal metastases: Protocol of a Dutch, multicentre, open-label, single-arm, phase II study (CRC-PIPAC). BMJ Open 2019, 9, e030408.

41. Bakrin, N.; Tempfer, C.; Scambia, G.; De Simone, M.; Gabriel, B.; Grischke, E.M.; Rau, B. PIPAC-OV3: A multicenter, open-label, randomized, two-arm phase III trial of the effect on progression-free survival of cisplatin and doxorubicin as Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) vs. chemotherapy alone in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer. Pleura Peritoneum 2018, 3, 20180114.

42. Oliver Goetze, T.; Al-Batran, S.E.; Pabst, U.; Reymond, M.; Tempfer, C.; Bechstein, W.O.; Bankstahl, U.; Gockel, I.; Königsrainer, A.; Kraus, T.; et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in combination with standard of care chemotherapy in primarily untreated chemo naive upper gi-adenocarcinomas with peritoneal seeding —A phase II/III trial of the AIO/CAOGI/ACO. Pleura Peritoneum 2018, 3, 20180113.

43. Tempfer, C.B.; Giger-Pabst, U.; Seebacher, V.; Petersen, M.; Dogan, A.; Rezniczek, G.A. 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, 23–30.

44. Eveno, C.; Jouvin, I.; Pocard, M. PIPAC EstoK 01: Pressurized IntraPeritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC C/D) in gastric peritoneal metastasis: A randomized and multicenter phase II study. Pleura Peritoneum 2018, 3, 20180116.

45. Sgarbura, O.; Gourgou, S.; Tosi, D.; Bakrin, N.; Bouazza, N.; Delaine, S.; De Forges, H.; Pocard, M.; Quénet, F. MESOTIP: Phase II multicenter randomized trial evaluating the association of PIPAC and systemic chemotherapy vs. systemic chemotherapy alone as 1st-line treatment of malignant peritoneal mesothelioma. Pleura Peritoneum 2019, 4, 20190010.

46. Hubner, M. In search of evidence—PIPAC on the fast lane. Pleura Peritoneum 2018, 3, 20180119.

47. Solass, W.; Hetzel, A.; Nadiradze, G.; Sagynaliev, E.; Reymond, M.A. Description of a novel approach for intraperitoneal drug delivery and the related device. Surg. Endosc. 2012, 26, 1849–1855.

48. Seitenfus, R.; Kalil, A.N.; de Barros, E.D.; Galeano Zettler, C.; Dos Santos, G.O.; Glehen, O.; Cereser Junior, C.H.; Ferreira, P.R.W. Assessment of the aerosol distribution pattern of a single-port device for intraperitoneal administration of therapeutic substances. Surg. Endosc. 2019, 33, 3503–3510.

49. Khosrawipour, V.; Khosrawipour, T.; Diaz-Carballo, D.; Förster, E.; Zieren, J.; Giger-Pabst, U. Exploring the Spatial Drug Distribution Pattern of Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC). Ann. Surg. Oncol. 2016, 23, 1220–1224.

50. Kakchekeeva, T.; Demtröder, C.; Herath, N.I.; Griffiths, D.; Torkington, J.; Solaß, W.; Dutreix, M.; Reymond, M.A. In Vivo Feasibility of Electrostatic Precipitation as an Adjunct to Pressurized Intraperitoneal Aerosol Chemotherapy (ePIPAC). Ann. Surg. Oncol. 2016, 23, 592–598.

51. Solass, W.; Herbette, A.; Schwarz, T.; Hetzel, A.; Sun, J.S.; Dutreix, M.; Reymond, M.A. Therapeutic approach of human peritoneal carcinomatosis with Dbait in combination with capnoperitoneum: Proof of concept. Surg. Endosc. 2012, 26, 847–852.

52. Shariati, M.; Zhang, H.; Van de Sande, L.; Descamps, B.; Vanhove, C.; Willaert, W.; Ceelen, W.; De Smedt, S.C.; Remaut, K. High Pressure Nebulization (PIPAC) Versus Injection for the Intraperitoneal Administration of mRNA Complexes. Pharm. Res. 2019, 36, 126.

53. Shariati, M.; Willaert, W.; Ceelen, W.; De Smedt, S.C.; Remaut, K. Aerosolization of Nanotherapeutics as a Newly Emerging Treatment Regimen for Peritoneal Carcinomatosis. Cancers 2019, 11, 906.

54. Jung do, H.; Son, S.Y.; Oo, A.M.; Park, Y.S.; Shin, D.J.; Ahn, S.H.; Park do, J.; Kim, H.H. Feasibility of hyperthermic pressurized intraperitoneal aerosol chemotherapy in a porcine model. Surg. Endosc. 2016, 30, 4258–4264.

55. Sautkin, I.; Solass, W.; Weinreich, F.J.; Königsrainer, A.; Schenk, M.; Thiel, K.; Reymond, M.A. A real-time ex vivo model (eIBUB) for optimizing intraperitoneal drug delivery as an alternative to living animal models. Pleura Peritoneum 2019, 4, 20190017.

56. Tavernier, C.; Passot, G.; Vassal, O.; Allaouchiche, B.; Decullier, E.; Bakrin, N.; Alyami, M.; Davigo, A.; Bonnet, J.M.; Louzier, V.; et al. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) might increase the risk of anastomotic leakage compared to HIPEC: An experimental study. Surg. Endosc. 2019, 1–8, in press.

57. Weinreich, J.; Struller, F.; Sautkin, I.; Giuashvili, S.; Reymond, M.; Königsrainer, A.; Schott, T.C. Chemosensitivity of various peritoneal cancer cell lines to HIPEC and PIPAC: Comparison of an experimental duplex drug to standard drug regimens in vitro. Invest. New Drugs 2019, 37, 415–423.

58. Khosrawipour, V.; Giger-Pabst, U.; Khosrawipour, T.; Pour, Y.H.; Diaz-Carballo, D.; Förster, E.; Böse-Ribeiro, H.; Adamietz, I.A.; Zieren, J.; Fakhrian, K.; et al. Effect of Irradiation on Tissue Penetration Depth of Doxorubicin after Pressurized Intra-Peritoneal Aerosol Chemotherapy (PIPAC) in a Novel Ex-Vivo Model. J. Cancer 2016, 7, 910–914.

59. Khosrawipour, V.; Khosrawipour, T.; Falkenstein, T.A.; Diaz-Carballo, D.; Förster, E.; Osma, A.; Adamietz, I.A.; Zieren, J.; Fakhrian, K. Evaluating the Effect of Micropump(c) Position, Internal Pressure and Doxorubicin Dosage on Efficacy of Pressurized Intra-peritoneal Aerosol Chemotherapy (PIPAC) in an Ex Vivo Model. Anticancer Res. 2016, 36, 4595–4600.

60. Khosrawipour, V.; Khosrawipour, T.; Kern, A.J.; Osma, A.; Kabakci, B.; Diaz-Carballo, D.; Förster, E.; Zieren, J.; Fakhrian, K. Distribution pattern and penetration depth of doxorubicin after pressurized intraperitoneal aerosol chemotherapy (PIPAC) in a postmortem swine model. J. Cancer Res. Clin. Oncol. 2016, 142, 2275–2280.

61. 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, 103–109.

62. Khosrawipour, V.; Diaz-Carballo, D.; Acikelli, A.H.; Khosrawipour, T.; Falkenstein, T.A.; Wu, D.; Zieren, J.; Giger-Pabst, U. Cytotoxic effect of different treatment parameters in pressurized intraperitoneal aerosol chemotherapy (PIPAC) on the in vitro proliferation of human colonic cancer cells. World J. Surg. Oncol. 2017, 15, 43.

63. Schubert, J.; Khosrawipour, V.; Chaudhry, H.; Arafkas, M.; Knoefel, W.T.; Pigazzi, A.; Khosrawipour, T. Comparing the cytotoxicity of taurolidine, mitomycin C, and oxaliplatin on the proliferation of in vitro colon carcinoma cells following pressurized intra-peritoneal aerosol chemotherapy (PIPAC). World J. Surg. Oncol. 2019, 17, 93.

64. Mikolajczyk, A.; Khosrawipour, V.; Kulas, J.; Kocielek, K.; Migdal, P.; Arafkas, M.; Khosrawipour, T. Release of doxorubicin from its liposomal coating via high intensity ultrasound. Mol. Clin. Oncol. 2019, 11, 483–487.

65. Robella, M.; Vaira, M.; Argenziano, M.; Spagnolo, R.; Cavalli, R.; Borsano, A.; Gentilli, S.; De Simone, M. Exploring the Use of Pegylated Liposomal Doxorubicin (Caelyx((R))) as Pressurized Intraperitoneal Aerosol Chemotherapy. Front. Pharmacol. 2019, 10, 669.

66. Giger-Pabst, U.; Bucur, P.; Roger, S.; Falkenstein, T.A.; Tabchouri, N.; Le Pape, A.; Lerondel, S.; Demtröder, C.; Salamé, E.; Ouaissi, M. Comparison of Tissue and Blood Concentrations of Oxaliplatin Administrated by Different Modalities of Intraperitoneal Chemotherapy. Ann. Surg. Oncol. 2019, 26, 4445–4451.

67. Available online: https://pubchem.ncbi.nlm.nih.gov/compound/Doxorubicin (accessed on 19 December 2019).

68. Sugarbaker, P.H.; Van der Speeten, K.; Stuart, O.A.; Chang, D. Impact of surgical and clinical factors on the pharmacology of intraperitoneal doxorubicin in 145 patients with peritoneal carcinomatosis. Eur. J. Surg. Oncol. 2011, 37, 719–726.

69. Nowacki, M.; Alyami, M.; Villeneuve, L.; Mercier, F.; Hubner, M.; Willaert, W.; Ceelen, W.; Reymond, M.; Pezet, D.; Arvieux, C.; et al. Multicenter comprehensive methodological and technical analysis of 832 pressurized intraperitoneal aerosol chemotherapy (PIPAC) interventions performed in 349 patients for peritoneal carcinomatosis treatment: An international survey study. Eur. J. Surg. Oncol. 2018, 44, 991–996.

70. Saenz Medina, J.; Asuero de Lis, M.S.; Galindo Alvarez, J.; Villafruela Sanz, J.; Correa Gorospe, C.; Cuevas Sánchez, B.; Linares Quevedo, A.I.; Páez Borda, A.; Pascual Santos, J.; Marcén Letosa, R.; et al. Modification of the hemodynamic parameters and peripheral vascular flow in a porcine experimental of model of laparoscopic nephrectomy. Arch. Esp. Urol. 2007, 60, 501–518.

71. Schilling, M.K.; Redaelli, C.; Krähenbühl, L.; Signer, C.; Büchler, M.W. Splanchnic microcirculatory changes during CO2 laparoscopy. J. Am. Coll. Surg. 1997, 184, 378–382.