Peritoneal Surface Oncology Group International

PSOGI World News

October 2025
Issue #5

A quarterly newsletter with the latest news, views and announcements

Editorial Staff

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IN THIS ISSUE ***the Editors excerpt selected articles to be presented in person at the PSOGI Biennial Congress in Barcelona, October 28-31, 2025. All contributions concern the methodology of CRS and HIPEC. Plan to come to PSOGI-Barcelona-2025 to get the whole story.***

Standardization of HIPEC Methodology, HIPEC Regimens and Cytoreductive Surgery

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HIPEC methodology

Hyperthermic intraperitoneal chemotherapy (HIPEC) has three important components – the drug regimen, the level of hyperthermia and the duration of perfusion. Other methodological variables like the nature and volume of perfusate and the technique – closed or open, allow differences between institutions in the way HIPEC is performed (*Bhatt et al. Ann Surg Oncol 2021;28:9098-9113*). And indeed, a large number of HIPEC regimens have been used in clinical practice largely dictated by the surgeon's preference and comfort and the local regulatory norms (Figure 1). While few randomized trials have compared different HIPEC methodology, several others are being conducted. While some of these regimens and practices are backed by preclinical studies and phase I/II trials, a large number of regimens have little scientific rationale (*Kusamura et al. Ann Surg Oncol 2023;30:2508-2519*).

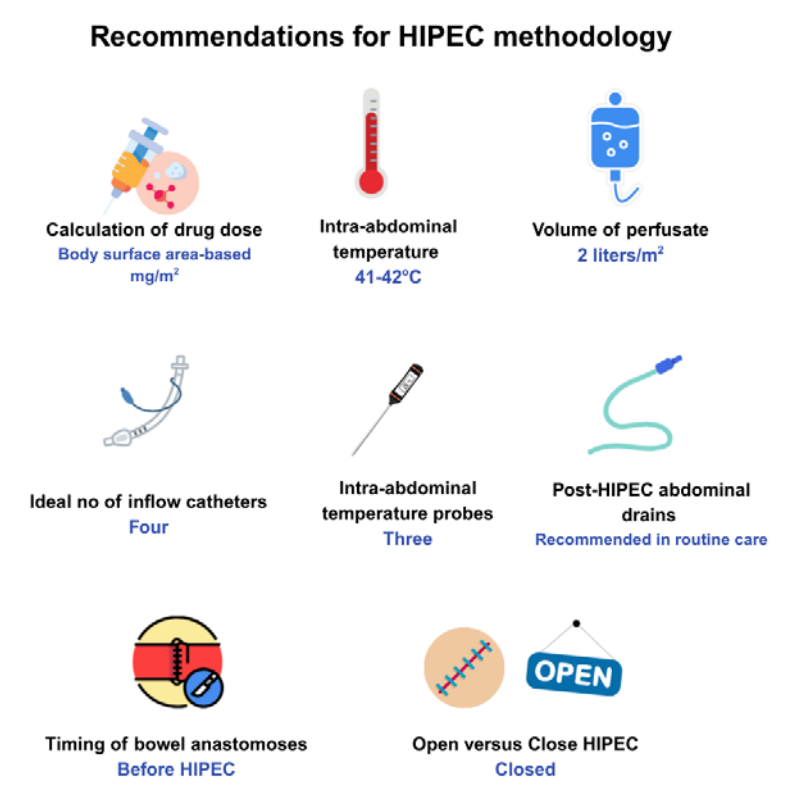

Figure 1. *The 2022 PSOGI HIPEC consensus recommendations for HIPEC methodology.*

HIPEC chemotherapy regimens

A consensus exercise was conducted by PSOGI for performing HIPEC after CRS to identify the preferred chemotherapy regimens for the most common diseases (Figure 2). The main goal of this ongoing effort is to reduce the heterogeneity in day-to-day practice and to enlist the most scientifically sound HIPEC regimens for evaluation in the clinical trials.

Drug	Maximum dose	Split dosing	Target intra-abdominal temperature	Duration of perfusion	Carrier solution	Drug combinations	Prevention of side-effects
Cisplatin	100mg/m^2	Recommended	41-42°C	90 minutes	Normal saline (0.9% NACl)	Mitomycin-C Doxorubicin	Use of sodium thiosulphate
Mitomycin-C	35mg/m^2	Recommended	41-42°C	90 minutes	-	-	-
Oxaliplatin	200mg/m^2	-	41-42°C	90 minutes	Dextrose 5%	5-FU	-
Paclitaxel	175 mg/m^2	-	41-42°C	90 minutes	Normal saline (0.9% NACl)	Cisplatin Mitomycin C	-

Figure 2. *Recommendations regarding the HIPEC chemotherapy regimens for the most common HIPEC drugs.*

The results of this consensus with the exhaustive accompanying literature review have been published (*Bhatt et al. Ann Surg Oncol 2023;30:8115-8137; Van der Speeten et al. Ann Surg Oncol 2024;31:7090-7110; Kepenekian et al. Ann Surg Oncol 2023;30:7803-7813; Hübner et al. Ann Surg Oncol 2024;31:567-576; Kusamura et al. Ann Surg Oncol 2024;31:6262-6273; Kusamura et al. J Surg Oncol 2024;130:1290-1298*).

Cytoreductive surgery

Peritoneal metastases (PM) from gastrointestinal and gynecologic cancer represent a unique diagnostic and therapeutic challenge. PM could present as one nodule or multiple nodules that are confined to one region or distributed over a few or multiple regions thereby affecting the extent of CRS performed for complete cytoreduction. Metastases to most solid organs are hematogenous in origin; in contrast, those to the peritoneum are predominantly due to transcoelomic spread (direct) but may also occur by lymphatic or hematogenous spread.

Imaging is inaccurate in identifying peritoneal disease, particularly in the early stages, as compared with other metastatic sites. Thus, to both identify PM and determine the extent, there is an increased dependence on visual inspection performed by the surgeon during laparoscopy and both visual and palpable means at laparotomy. For a favorable outcome of treatment, the guiding principle for CRS is a complete macroscopic (CC-0) resection. In some low-grade malignancies such as pseudomyxoma peritonei, leaving minimal residual disease (CC-1 resection) may result in a long-term benefit. There is no recommendation on how much surrounding peritoneum to resect for any of the malignancies treated by CRS (*Bhatt A, Glehen O. Ann Surg Oncol 2020;27:1458-1470*). This is in contrast to other cancer resections where local control requires resection of a rim of surrounding normal tissue. It is uncertain whether resections should be performed according to the initial description by Sugarbaker (*Sugarbaker. Ann Surg 1995;221:29-42*). Sugarbaker recommended that the abdomino-pelvic region that contained peritoneal metastases was to be completely stripped of peritoneum. In patients with limited upper abdominal disease, the PM with several cm of normal peritoneum beyond a tumor deposit was to be stripped. In the pelvis which contained PM, a complete parietal peritonectomy was routinely indicated.

Many surgeons have modified their approach to only resect the macroscopically affected peritoneum and not to strictly adhere to the initial anatomical description by Sugarbaker. Furthermore, there is a lack of studies comparing the oncologic outcome of more with less extensive peritoneal resection. A variable histopathological evaluation of the quality of CRS (including intactness of the specimen, margin status, number of nodes dissected) compared to other oncological surgical procedures makes objective assessment of the quality of CRS very challenging.

A review of literature on peritonectomy procedures demonstrates great heterogeneity in the terminology used for describing peritonectomy procedures. When the same term is used, the extent of surgery performed varies from one surgeon to another (*Bhatt et al. Br J Surg 2025. doi: 10.1093/bjs/znaf099*). For example, some surgeons will resect only the peritoneum lining the true pelvis in a pelvic peritonectomy procedure while others will resect the peritoneum lining of both the false and true pelvis. A right upper quadrant peritonectomy procedure for some only includes removal of the diaphragmatic peritoneum while some surgeons routinely include stripping of the Morrison's pouch. Almost all prior manuscripts on the technique of cytoreductive surgery lacked a description of boundaries or had a limited description of the extent of peritoneal resection. The effort to standardize cytoreductive surgery began with a consensus on the nomenclature and boundaries of peritonectomy procedures conducted jointly by the PSOGI, European society of gynecological oncology (ESGO) and the international society for study of the pleura and peritoneum (ISSPP). This is the PSOGI, ESGO, ISSPP consensus on cytoreductive surgery for peritoneal malignancies (Lyon consensus) (*Bhatt et al. Br J Surg 2025. doi: 10.1093/bjs/znaf112*). The first classification of peritonectomy procedures (that includes 6 major peritonectomy procedures) devised by Sugarbaker 30 years ago was successfully revised by a consensus of 112 surgical and gynecological oncologists with expertise in performing cytoreductive surgery (Figure 3). The revised classification incorporates all peritonectomy procedures including small bowel mesenteric peritonectomy, defining the boundaries and subregions of each (*Bhatt et al. Br J Surg 2025. doi: 10.1093/bjs/znaf099*).

Based on the consensus, a format for documenting the extent of peritoneal resection was developed. This reporting format is an important tool for research to document the extent of peritoneal resection that is performed during CRS. It provides a classification of peritonectomy procedures and the subdivisions and boundaries of each peritonectomy procedure. To utilize the standardization of CRS provided by the consensus the peritoneal malignancy community needs to do the following:

1. Use HIPEC methodology and HIPEC regimens recommended by the consensus in day-to-day practice.
2. Follow the recommendations of the consensus while designing clinical trials.
3. Adopt the revised classification of peritonectomy procedures used for CRS.
4. Document the extent of peritoneal resection according to the specified format.

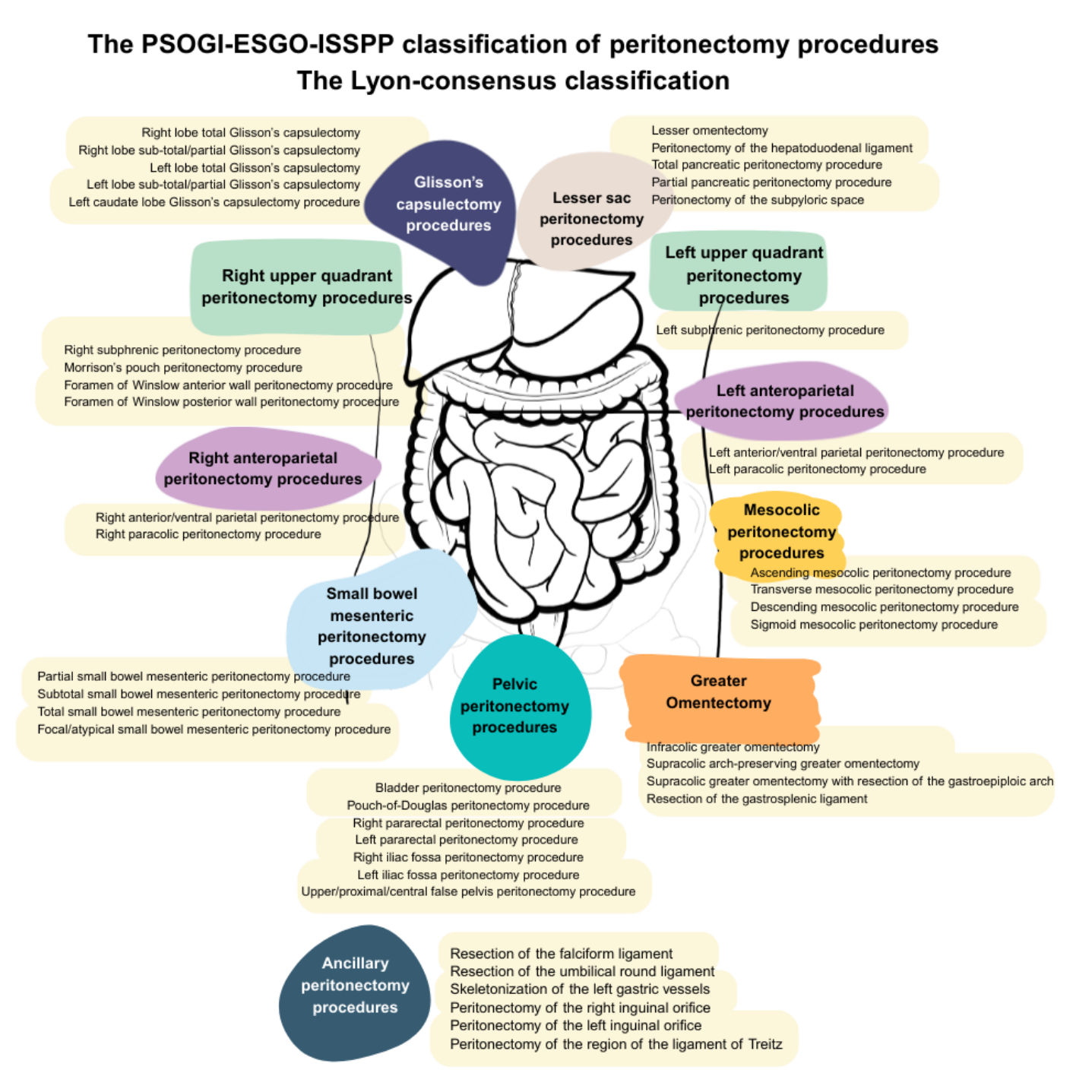

Figure 3. *Consensus classification of peritonectomy procedures.*

To further standardize cytoreductive surgery a standardized operative report form is under preparation to facilitate uniform documentation of cytoreductive surgery.

Potential of Nanosized Therapeutics for Intraperitoneal Delivery

Potential of Nanosized Therapeutics for Intraperitoneal Delivery

By Wim Ceelen, MSc, MD, PhD

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Introduction

One of the main justifications of intraperitoneal drug delivery (IPDD) is the pharmacokinetic advantage: as suggested first by Dedrick and Flessner, the sub-peritoneal matrix slows down systemic resorption from the peritoneal to the systemic compartment. Since systemic clearance occurs faster than peritoneal clearance, intraperitoneal (IP) drug concentration will always be higher than the systemic one. Evidently, transport across the peritoneal-plasma interface occurs from the systemic to the IP compartment as well; that is why peritonitis can be treated with IV antibiotics.

The absorption rate of IP delivered drug depends on the properties of the sub-peritoneal matrix (vascular density, hydraulic permeability, surface area) and on those of the drug (size, shape, charge, water/fat solubility). Most anticancer drugs such as the platinum compounds have a relatively small molecular weight (around 300 g/mol), and are cleared rapidly from the peritoneal cavity: the typical half-life of IP cisplatin and oxaliplatin is 15-30 minutes (*PMID 22983312, 30255585*). The use of larger molecules such as antibodies significantly prolongs peritoneal residence time, and may enhance efficacy against peritoneal metastases (*PMID 20565453*). Nanoparticles (NPs) offer significant potential for IPDD including (i) prolonged retention and limited systemic toxicity due to their size, (ii) the possibility for targeted delivery by incorporating ligands (antibodies, peptides, aptamers) that bind specific receptors on cancer cells, (iii) to possibility to shield labile cargo such as nucleic acids; and (iv) the potential for stimulus - responsive release (pH, enzyme activity, oxygen content, temperature, external electromagnetic fields). In addition, as discussed below, the use of NPs allows lymphatic targeting, which may be of interest when cancer draining lymph nodes, rather than peritoneal metastases, are the therapeutic target (*PMID 39427777*).

Nanoparticles: definition and current clinical use

Although the definition of nanoparticles (NPs) is variable (e.g. ISO/TS 80004-2:2015: up to 100 nm; FDA: up to 1000 nm), in the context of drug delivery nanoparticles usually refer to engineered carriers in the 10–200 nm range that can encapsulate, adsorb, or conjugate therapeutic molecules. Nanoparticles with a dazzling variety of chemical and physical properties have been synthesized, but the most commonly used categories pursued NPs in clinical trials are lipid-based, polymeric, and inorganic (including metals such as Au). Following the success of COVID-19 vaccines, lipid NP mRNA cancer vaccines have gathered significant momentum.

Despite their obvious potential and thousands of preclinical candidates, only a handful of nano-sized anticancer drugs have been approved for clinical use (e.g. nanoparticle albumin bound paclitaxel, nanoliposomal irinotecan, pegylated liposomal doxorubicin). Reasons cited for this difficult clinical translation include unclear toxicities and nano-bio interactions, lack of reproducibility in the synthesis of nanoparticles, and complexity and cost of nanoparticle manufacturing under good manufacturing practice (GMP) requirements (*PMID 35941223*).

Fate of nanoparticles after IP delivery

After IP delivery, IP drugs that are not bound to their target, metabolized, or degraded are cleared from the peritoneal cavity either by systemic absorption, or by lymphatic drainage. Preclinical studies have shown that large molecules, NPs, cells, and particulate matter are primarily cleared through the lymphatic system (*PMID 3155917*). The anatomy, role, and function of the peritoneal lymphatic system are incompletely understood. Key components include diaphragmatic stomata and lacunae, mesenteric and retroperitoneal lymphatic structures, and the lymph vessels of the abdominal viscera and mesenteries (Figure 1). Lymphatic drainage of the peritoneal cavity occurs mostly through the (right) diaphragmatic peritoneum, and absorption from the mesenteries, omentum, and parietal peritoneum seems to play a minor role (*PMID 3309431*).

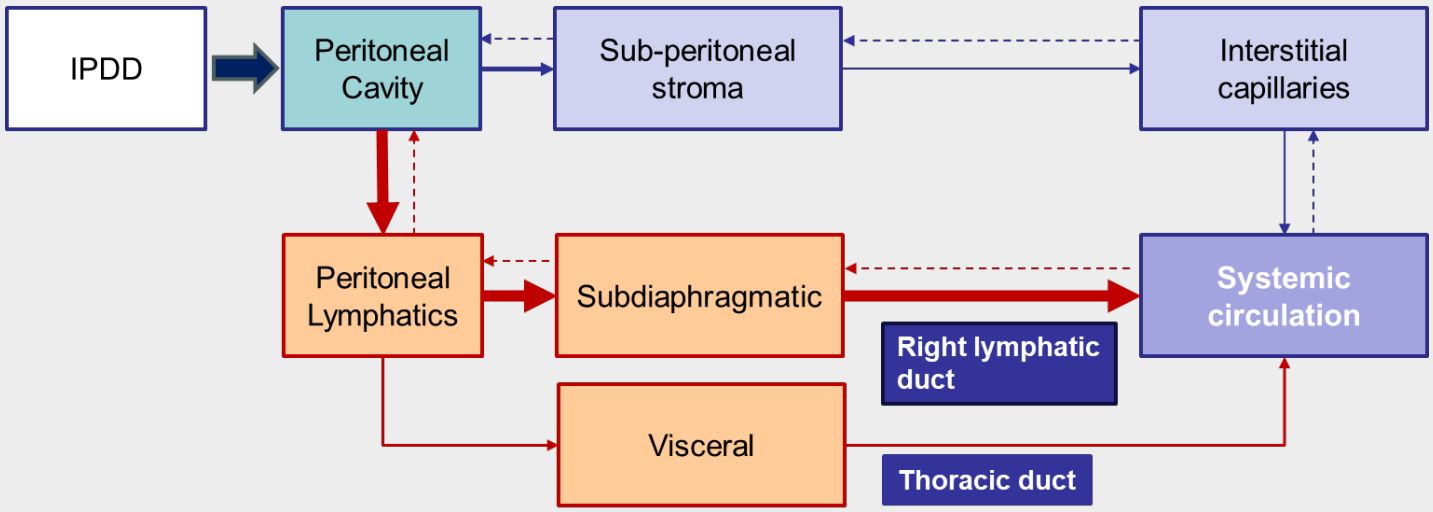

Figure 1. *Transport routes after intraperitoneal delivery of nanoparticles. Absorption occurs mainly through the lymphatics, with the right subdiaphragmatic lymphatics accounting for approximately 70% of mass transport. Of note, retrograde transport into the peritoneal cavity is possible, via the systemic vascular and lymphatic pathways.*

Physicochemical properties affecting nanoparticle transport

Size

The endothelial lining of healthy microvessels is impermeable for particles larger than >1 nm. In the 20-50 nm range, NPs are rapidly cleared from the peritoneal cavity, mainly through lymphatic absorption. Of note, this size range seems to result in maximal penetration into tumor tissue (*PMID 26348965*). Particles larger than >100 nm tend to be increasingly taken up by components of the mononuclear phagocyte system (MPS) and to accumulate in the liver and spleen; this effect seems to be maximal with NPs having a size of 400-600 nm (*PMID 19729056*). Particles with a size in the micrometer range are retained in the peritoneal cavity much longer, but they were found to cause chronic inflammation and adhesions due to foreign body reactions (*PMID 27422808*).

Surface charge

Interestingly, not only does the surface charge affect the main transport route, but there is also a clear charge – size interaction: for a NP given size, its charge will determine the extent and route of absorption. Of note, mesothelial cells are covered with a glycocalyx, composed of glycoproteins and proteoglycans, and which

carries anionic (negative) charges. Unsurprisingly, therefore, experiments have shown that positively charged NPs are retained in the peritoneal cavity much longer compared to negatively charged NPs. Macrophages will also preferentially engulf negatively charged particles. Lee et al. Showed that NP charge affects lymphatic drainage pathways: positively charged liposomes preferentially drained to visceral lymphatics, resulting in enhanced retention in mesenteric compared to the mediastinal lymph nodes, while negatively charged and neutral liposomes tended to drain via the diaphragmatic lymphatics to the mediastinal LNs and the thoracic duct (*PMID 31625752*).

Chemical properties

The degree of PEGylation, the incorporation of targeting ligands (e.g. against folic acid, HERS-2, hyaluronic acid,...), and the composition of the carrier are all known to affect transport routes and tumor penetration after IP delivery of NPs.

Tumor penetration after IP delivery of nanoparticles

The traditional tenet of systemic delivery of NPs is the enhanced permeability and retention (EPR) effect, which describes the relative selectivity of NPs for tumor tissue characterized by structurally abnormal microvessels which, in contrast with normal endothelium, are permeable for NP transport. However, the prominence of this mechanism has been challenged recently, and other mechanisms such as active endothelial transcytosis seem to be much more important (*PMID 31932672*). When NPs are delivered intraperitoneally, the extremely low hydraulic conductivity of tumor tissue represents an additional formidable obstacle to drug transport (*PMID 36084861*). In preclinical experiments, several methods have succeeded in enhancing tumor tissue penetration of NPs after IP delivery. Examples include the use of aerosolized deliver (Figure 2), paclitaxel loaded tumor priming microparticles, pH responsive NPs, and the use of receptor based, tumor targeting NPs (*PMID 18780831, 27343465, 21926976*).

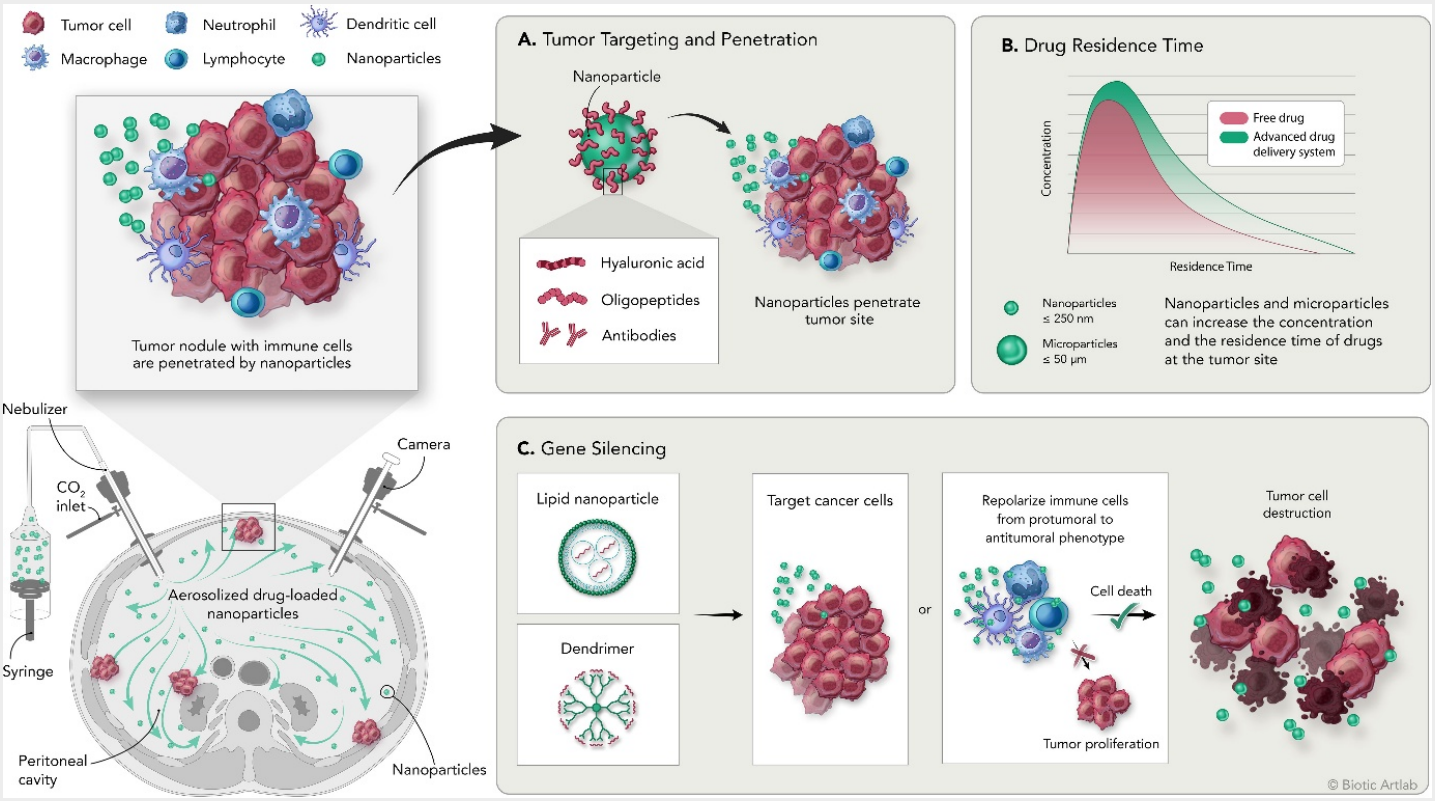

Figure 2. Overview of the PIPAC procedure and the application of nanomedicine for the treatment of peritoneal carcinomatosis. Bottom left: schematic representation of intraperitoneal aerosolization of nanoparticles by PIPAC; top left: schematic representation of tumor nodules with tumor infiltrating immune cell populations and delivered nanoparticles. (A) Nanoparticles can be modified by adding surface moieties of different origins to increase their targeting and penetration capabilities into the tumor. (B) Delivery systems are designed to increase the concentration and residence time of the drug at the tumor site compared with free drug. (C) Delivery systems designed to carry genetic material are used to induce silencing of specific genes on tumor or immune cells to promote direct or immune-mediated destruction of tumor cells. Reprinted under Creative Commons Attribution License (CC BY) from Breusa et al. (PMID 37287910)

A promising method is the use of physical mechanisms such as electric currents, magnetic fields, temperature, pressure, or photons to enhance tumor tissue penetration. We recently showed that a DC current dramatically improves penetration of positively charged NPs in a rodent model of colorectal carcinomatosis (Figure 3).

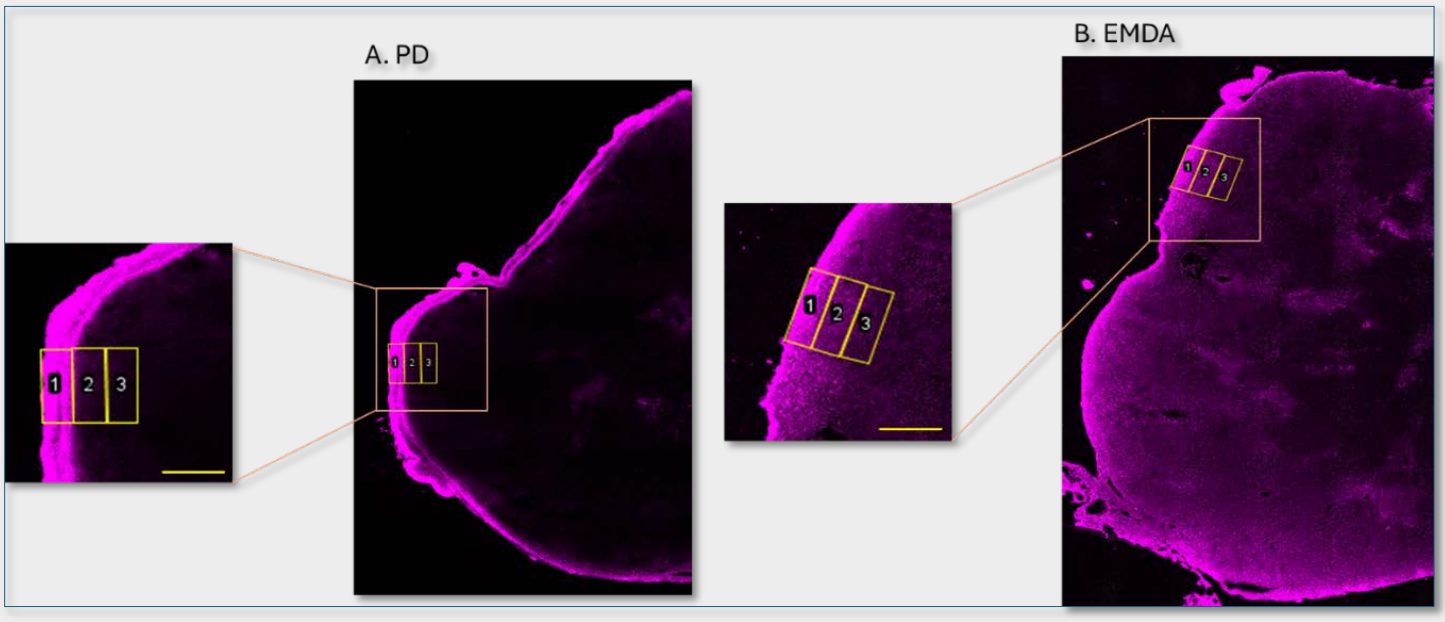

Figure 3. Representative confocal microscopy images of a rodent colorectal peritoneal metastasis after intraperitoneal delivery of positively charged nanoparticles (Cy5-siRNA-RNAiMAX, diameter 100 nm) using either (A) passive diffusion (PD) or (B) electromotive drug administration (EMDA). The scale bar represents 500 µm. Data generated by Nidda Saeed, PhD student, unpublished results.

Clinical studies using IP nanoparticles to treat peritoneal metastases

A large number of preclinical studies has reported intraperitoneal delivery of NPs. However, clinical translation has been slow, and the results of published and ongoing clinical studies are summarized in Table 1.

Taken together, these studies show that IP delivery of NPs as 'off label' treatment is well tolerated, confers a pharmacokinetic advantage, and causes promising anticancer activity. Obviously, the true merit of this strategy remains to be tested in randomized comparative trials.

Author (year) – (PMID)	NCT	Drug	Setting	Main findings
Indwelling catheter-based IP chemotherapy				
Armstrong (2006) (16626792)	00005046	Polymer microsphere formulation of paclitaxel	Phase I study in persistent ovarian cancer	MTD not reached; release > 8 weeks
Chen (2022)	05159050	Paclitaxel-loaded tumor penetrating microparticles	Phase I study in peritoneal carcinomatosis	Suspended due to drug supply issues
Williamson (2015) (25898813)	00666991	Submicron particles of paclitaxel (SPP)	Phase I study in peritoneal carcinomatosis	MTD not reached; persistent IP exposure
Cristea (2019) (30623229)	00825201	Nab-paclitaxel	Phase I study in peritoneal carcinomatosis	MTD 140 mg/m^2; promising activity
Mullany (2020) (32953961)	03029585	Submicron particles of paclitaxel (SPP)	Phase II study in EOC (post CRS)	PFS at 6 and 12 months 66%
HIPEC and EPIC				
Harrison (2008) (18157576)	-	Nanoparticle pegylated liposomal doxorubicin	Phase I study of HIPEC in peritoneal carcinomatosis	MTD not reached
Sugarbaker (2021) (30954354)	-	Nanoparticle pegylated liposomal doxorubicin	IP instillation for HIPEC or EPIC – prospective PK study	Slow and partial tissue uptake; not suitable for HIPEC
Choi (2023) (36344711)	04088786	Nal-IRI	Phase I study of HIPEC in peritoneal carcinomatosis	MTD not reached; favorable PK profile
Zhou (2024) (38367177)	-	Nab-paclitaxel	Intraoperative and postoperative HIPEC – retrospective study	Well tolerated
Aerosolized IP drug delivery (PIPAC)				
Ceelen (2022) (35843174)	03304210	Nab-paclitaxel	PIPAC in patients with unresectable peritoneal metastases	MTD 140 mg/m^2; accumulation of drug in tumor tissue with repeated treatments

Conclusions and future perspectives

There is a compelling theoretical rationale for the use of nanoparticles for intraperitoneal drug delivery. Numerous promising candidates have been tested in preclinical models, but due to the lack of industrial interest clinical translation has been limited to off label use of NPs approved for systemic administration. These studies confirm the potential advantages of NPs in terms of pharmacokinetics and safety. The results of ongoing and planned comparative trials are awaited to provide evidence of anticancer efficacy in patients with peritoneal metastases.

Multidose Hyperthermic Intraperitoneal Chemotherapy: Its Application in Cholangiocarcinoma Patients with Peritoneal Metastases

By Feiling Feng, Qingxiang Gao, Yingjun Wu, Xiaoqing Jiang*

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Due to its concealed anatomical location and atypical early symptoms, most patients with cholangiocarcinoma (CCA) are diagnosed at an advanced stage. Peritoneal Metastases (PM) is one of its main metastatic routes, which can lead to severe complications such as malignant ascites and intestinal obstruction, significantly affecting the quality of life and survival time of patients. Systemic chemotherapy (such as the gemcitabine combined with cisplatin regimen) is the standard treatment, but the intraperitoneal drug concentration is low after passing through the plasma-peritoneal barrier, resulting in poor efficacy against peritoneal metastases. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) technology combines chemotherapy, hyperthermia, and peritoneal lavage, allowing for a one-time, high-dose, high-concentration chemotherapeutic wash of the abdominal cavity during surgery. However, for established macroscopic or microscopic lesions, the penetration depth of a single HIPEC is limited, and tumor cells may exhibit heterogeneity, with some cells being insensitive to treatment. Therefore, exploring repeated, multidose HIPEC treatment, aiming to maximally control abdominal disease progression through periodic and sustained attacks, is becoming a new research hotspot in this field (*Feng et al. Eur J Surg Oncol 2021;47:2363-2368*).

Theoretical Basis and Advantages of Multidose HIPEC

Utilizing the Peritoneal-Plasma Barrier

The existence of the peritoneal-plasma barrier limits the penetration of intravenous chemotherapy drugs into the peritoneal cavity. Multidose HIPEC can periodically and directly achieve and maintain drug concentrations in the peritoneal cavity that are far higher than plasma levels, creating a significant concentration gradient that forces drugs to penetrate into tumor tissue, thereby efficiently killing cancer cells.

Synergistic and Sensitizing Effects of Hyperthermia

Hyperthermia (usually 41-43℃) can directly induce apoptosis and necrosis of tumor cells. More importantly, the thermal effect can increase the permeability of tumor cell membranes and inhibit DNA repair enzyme activity, thereby significantly enhancing the cytotoxic effects of chemotherapy drugs (such as platinum agents, mitomycin C). Repeated application of hyperthermia can provide repeated "strikes" against tumor cells, inhibiting their repair and proliferation capabilities.

Eliminating Circulating Shed Tumor Cells

PM of CCA is a dynamic process, and tumor cells will continuously shed from the primary tumor or metastatic lesions into the abdominal fluid. Although a single HIPEC can eliminate free cells present during surgery, it cannot prevent new shedding postoperatively. Multidose HIPEC (e.g., postoperative adjuvant multidose HIPEC) can, like an "intraperitoneal chemotherapy bath", regularly clear newly shed tumor cells, theoretically effectively preventing or delaying peritoneal recurrence (*Mao et al. Mol Clin Oncol 2024;20:31*).

Targeting Tumor Heterogeneity and Cell Cycle

Tumor cells are in different cell cycles and have varying sensitivities to chemotherapy. Single chemotherapy mainly kills cells in the active proliferation phase, while quiescent (G0 phase) cells may survive and become the source of recurrence. Fractionated and multidose HIPEC treatment may capture and kill tumor cells when they enter the proliferation cycle, improving the overall efficacy.

Reducing the Toxic and Side Effects of Chemotherapy

Multidose HIPEC can distribute the drug dose across each treatment session. Although the dose given per session is lower than that of a single dose HIPEC, the total cumulative dose can be higher, yet the toxic side effects of chemotherapy are significantly reduced (*Lei et al. Acta Obstet Gynecol Scand 2025;104:988-997*).

Clinical Practice and Efficacy Exploration

Currently, data on multidose HIPEC for PM in CCA mainly come from retrospective studies and a small number of prospective clinical trials, lacking evidence from large-scale randomized controlled clinical trials.

Treatment Method for Multidose HIPEC

During surgery, before performing HIPEC, tumor burden should be maximally reduced. After cytoreductive surgery (CRS), the abdominal cavity and anastomoses are checked. Perfusion catheters are placed into the abdominal cavity: the two outlet tubes are placed four finger breadths below the costal arch, at the intersection with the midclavicular line; the two outlet tubes are each placed into the pelvis; the two inlet tubes are placed at the lateral one-third point of the line connecting the umbilicus and the anterior superior iliac spine; the two inlet tubes are placed in front of the liver diaphragm and the spleen, respectively. The internal cross-catheter method ensures the heated perfusion fluid fills the entire abdominal cavity without leaving blind spots. Circulatory perfusion is performed with 4 L of perfusion fluid at a flow rate of 400-600 mL/min, adding chemotherapy drugs (5-FU and DDP), and heating the perfusion fluid to 43°C, for 60-90 minutes. Under sterile conditions, connect the dedicated circulation pathway to each pre-placed catheter to

form a closed loop, allowing the heated perfusion fluid to flow into the abdominal cavity and circulate continuously. Simultaneously, administer pethidine hydrochloride plus promethazine hydrochloride for analgesia. The perfusion speed is 400-600 ml/min, repeated every other day, with 3 sessions constituting one course. During the entire perfusion process, the patient's vital signs are closely monitored. If the patient experiences abdominal discomfort, the perfusion rate can be appropriately slowed down. All patients receive antiemetics after chemotherapy to prevent nausea, vomiting, and other gastrointestinal adverse reactions, along with supportive treatments such as liver protection, hydration, alkalization, and diuresis.

Other applications of Multidose HIPEC

Adjuvant multidose HIPEC has also been used. After successful completion of CRS+HIPEC, pre-placed abdominal drainage tubes, are available to consolidate efficacy and prevent recurrence. This is commonly used in HIPEC for CCA. For patients with extensive PM who cannot undergo immediate CRS, use neoadjuvant multiple HIPEC sessions first to reduce the abdominal tumor burden, creating an opportunity for secondary surgical resection. This approach is more common in HIPEC for gastrointestinal cancers but less common in CCA, possibly due to the higher malignancy of biliary tumors and insufficient experience with neoadjuvant therapy in CCA. For end-stage patients with refractory malignant ascites, performing palliative multiple HIPEC sessions can effectively control ascites, alleviate symptoms, and improve quality of life. This modality is also commonly used in HIPEC for CCA.

Clinical Efficacy

A retrospective analysis based on a tumor database of patients with PM from biliary tract cancer found that 34 patients received combined CRS and single HIPEC treatment, while 21 patients received systemic palliative chemotherapy. The results confirmed that the HIPEC combination group had a longer overall survival (OS) (*Amblard et al. Eur J Surg Oncol 2018;44:1378-1383*).

However, there is currently limited research on multidose HIPEC treatment in CCA. A retrospective cohort study by Feng et al. on 51 patients receiving CRS combined with triple HIPEC (postoperative days 2, 4 and 6) and 61 patients receiving CRS alone showed that the OS of CCA patients was significantly prolonged. The median OS was longer in the CRS+HIPEC group than in the CRS group (25.53 vs. 11.17 months, $P<0.001$). The occurrence of overall complications was similar in the two groups (37.2% vs. 34.4%, $P=0.756$). Therefore, CRS combined with HIPEC can be a treatment option for patients with advanced CCA (Figure 1).

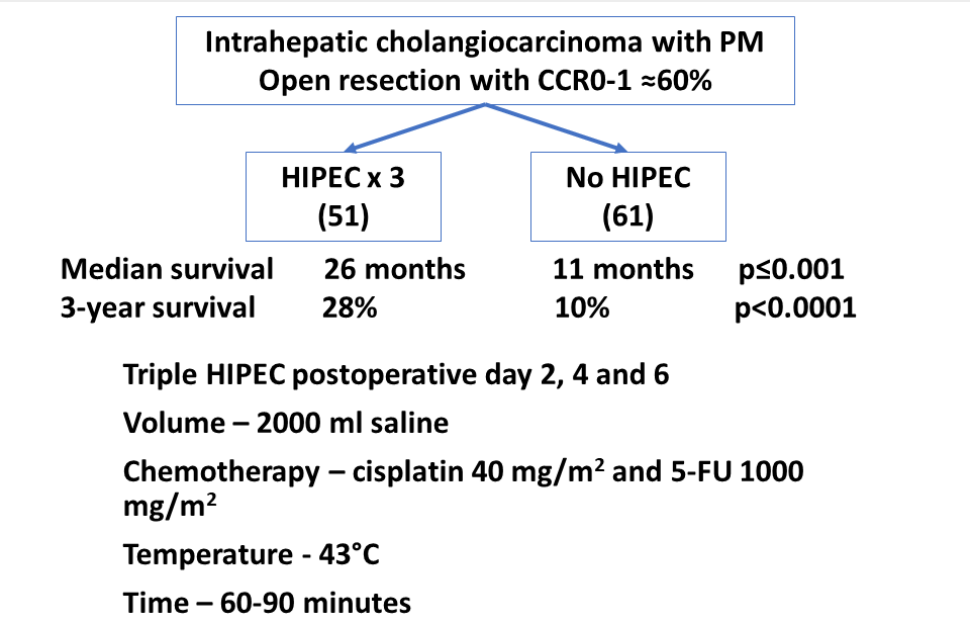

Figure 1. *Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy vs. cytoreductive surgery alone for intrahepatic cholangiocarcinoma with peritoneal metastases: A retrospective cohort study. (Feng et al. Eur J Surg Oncol 2021;47:2363-2368).*

Another retrospective study on gallbladder cancer with PM found that patients (n=31) who received CRS combined with postoperative multidose HIPEC (once every other day, 1-5 sessions total) and systemic chemotherapy had a significantly better median overall survival than the control group (n=53) who received only CRS plus systemic chemotherapy (21.72 months vs. 14.93 months, P=0.044). Multivariate analysis showed that HIPEC, completeness of cytoreduction (CCR score), tumor differentiation degree, and stage were independent prognostic factors. This study suggests that for PM of gallbladder cancer, the combined modality of CRS+multidose HIPEC+systemic chemotherapy is a promising treatment strategy (*Gao et al. Chinese J Clin Oncol 2020;47:140-144*).

In another study, 103 patients admitted from August 2014 to June 2016 were reviewed. 46 patients were given single dose HIPEC as the study group, and 57 patients were given conventional chemotherapy as the control group. The survival time of the study group was 12.00 ± 2.47 months, significantly higher than the 6.00 ± 0.80 months in the control group (P<0.01). The incidence of leukopenia, thrombocytopenia, and liver function impairment in the study group was significantly lower than in the control group (P<0.05), while there was no statistical difference in hemoglobin reduction, gastrointestinal reactions, and renal function impairment (P>0.05) (*Yu et al. Academic Journal of Second Military Medical University 2017;38:570-575*).

In addition, a study retrospectively analyzed the data of 80 patients treated in Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine from January 2018 to January 2020. The control group included 44 patients who received only CRS. The study group consisted of 36 patients who received CRS combined with single dose HIPEC. Six days after the operation, the levels of alanine aminotransferase, aspartate aminotransferase, total

bilirubin and direct bilirubin in both groups were significantly lower than those before the operation ($P < 0.05$), but there was no significant difference in the above indicators between the two groups 6 days after the operation ($P > 0.05$). The incidence of postoperative adverse reactions in the study group was lower than in the control group ($P = 0.027$). Finally, multivariate Cox analysis showed that tumor stage, distant metastasis, and treatment regimen were independent factors affecting prognosis ($P<0.05$). The three-year survival rate of the study group was higher than that of the control group ($P = 0.002$) (*Wu et al. World Gastrointest Surg 2023;15:2413-2422*).

Multidose HIPEC has also been used after radical surgery for gallbladder cancer with good efficacy by Liu and coworkers. A retrospective analysis of seventy-eight patients with stage III gallbladder cancer who received radical surgery at Hunan Provincial People's Hospital between December 2015 and April 2019 was reported. The median survival time of the multiHIPEC group (treated on postoperative days 2 and 4) was 19.2 months, which was longer than the 15.3 months in the control group. The 1-year survival rates of the two groups were 91.43% vs. 76.71%, and the 2-year survival rates were 26.29% vs. 17.53%, respectively ($P < 0.05$). The average hospitalization time of the HIPEC group was 23.0 ± 6.9 days, which was longer than the 20.0 ± 5.8 days of the control group ($P < 0.05$) (*Liu et al. Can J Gastroenterol Hepatol 2021;2021:4006786*).

Final remarks

Cytoreductive surgery combined with multidose HIPEC can improve the survival rate of CCA patients with PM without increasing postoperative complication rates. However, significant challenges remain, and its clinical application in CCA is still limited, requiring broader use to obtain more supporting data. Multidose HIPEC, as an innovative treatment strategy based on a solid theoretical foundation, has shown potential in preliminary clinical exploration to prolong survival and improve quality of life. It breaks through the limitation of the "once and for all" of single HIPEC, aligns better with the biological behavior of PM, and offers new hope for patients.

Nevertheless, the current level of evidence remains low. Future rigorously designed prospective, multicenter randomized controlled trials are needed to clarify the optimal indications for multidose HIPEC, such as the peritoneal cancer index (PCI) threshold, standardized chemotherapy regimens, treatment cycles, etc. Simultaneously, combining technologies like genomics and liquid biopsy (detecting ctDNA in peritoneal lavage fluid) to screen the patient population most likely to benefit from HIPEC and achieve true precision individualized treatment is an important research direction in the future. Although the road ahead is long, multidose HIPEC undoubtedly opens a promising path to tackling the challenge of PM in CCA.

Rationale for Combined Intraperitoneal and Systemic Treatment in Gastric Cancer Peritoneal Metastases

By Zhong-He Ji and Yan Li

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Introduction

Gastric cancer peritoneal metastasis (GCPM) is the major cause of treatment failure in the era of standard D2 gastrectomy plus systemic chemotherapy, characterized by the rapid development of refractory ascites, intestinal obstruction and abdominal pain. The development of GCPM has historically signified a terminal condition, with a median survival measured in months and systemic chemotherapy offering limited benefit.

Poor prognosis of GCPM treated with systemic chemotherapy

The EVOCAPE 1 study, published in 2000, serves as a baseline for subsequent research, showing that the median overall survival for GCPM patients treated with systemic chemotherapy was just 3.1 months (Cancer, 2000, 88(2): 358-363). A Dutch population study conducted in 2021 examined data from 1999 to 2017, involving 3,773 patients with synchronous peritoneal metastases of gastric cancer. The study found that the incidence of synchronous peritoneal metastasis increased from 18% in 2008 to 27% in 2017. The rate of systemic treatment usage rose significantly, from 15% between 1999 and 2002 to 43% between 2013 and 2017 ($p < 0.001$). Consequently, the median survival of patients receiving systemic treatment improved from 7.4 months to 9.4 months ($p = 0.005$), while those not receiving treatment experienced a decline in median survival from 3.3 months to 2.1 months ($p < 0.001$). Despite the increasing number of patients receiving systemic treatment and the modest improvement in survival duration, there has been no significant enhancement in overall survival over time, suggesting that the effectiveness of systemic treatment remains uncertain (*Gastric Cancer, 2021, 24(4): 800-809*).

Theoretical limitations of systemic chemotherapy alone for peritoneal metastases

While the peritoneum is lined by a mesothelial layer and has a rich blood and lymphatic supply, a functional "peritoneal-plasma barrier" exists. This is not an anatomical barrier but a physiological one, where high-molecular-weight substances and large molecules administered intravenously achieve significantly lower concentrations in the peritoneal cavity compared to plasma. For many cytotoxic drugs, the ratio of

intraperitoneal (IP) area under the curve (AUC) to plasma AUC after intravenous administration is less than one, meaning that the peritoneal tumor deposits are exposed to sub-therapeutic drug levels. This situation creates a pharmacologic sanctuary where tumor cells can proliferate despite seemingly adequate systemic therapy.

The fundamental tumor biology in GCPM

Although new theories of peritoneal metastasis have been proposed, such as the lymphatic metastasis theory and the retrograde metastasis theory of the fallopian tubes, the seed-soil theory remains the currently recognized theory of peritoneal metastasis. The development of GCPM is a multi-factorial and multi-step process; the fundamental tumor biology is relatively simple, i.e., the selected seeding of intraperitoneal free cancer cells (IFCCs), and the trapped proliferation of cancer cells on the damaged peritoneum due to breakdown of the peritoneal barrier (Figure 1). The former is mainly due to natural progress of gastric cancer, while the latter is mainly due to iatrogenic causes.

In the natural process of GCPM development, IFCCs are produced by the spontaneous exfoliation of cancer cells from the original site when gastric cancer progresses beyond the T4 stage. Once into the peritoneal cavity, such IFCCs set off a cascade of peritoneum invasion and colonization through transmesothelial and translymphatic pathways. The first specific site of colonization is the milky spots in the peritoneum, which is a lymphoid structure composed of lymphocytes, macrophages, endothelial cells, fibroblasts, and mesothelial cells. Once having colonized the milky spots, IFCCs create an immunotolerant microenvironment characterized by turning macrophages from the M1 phenotype, which is immunosuppressive, to the M2 phenotype, which is immunopermissive. It is this immunotolerant microenvironment that sets off accelerated IFCCs proliferation, mesothelium-mesenchymal transition, and adipocyte-mesenchymal transition. Under the continuous interactions between the proliferating IFCCs and mesenchymal cells, the transformed mesenchymal cells become cancer-associated fibroblasts (CAFs). In turn, CAFs set off the peritoneal fibrosis process, which intermingles with proliferating IFCCs and tumor angiogenesis, leading to the final formation of visible peritoneal tumor nodules. Therefore, in the natural process of GCPM, the major components of the peritoneal tumor are proliferating cancer cells, activated fibroblasts with progressive sclerosis, and prominent angiogenesis. The most striking clinical features of such natural process of GCPM are the prominent mesentery contraction and the prominent ascites production.

In the theory of trapped proliferation of cancer cells, IFCCs and detached cancer cell clusters are mainly due to iatrogenic causes. Many inappropriate surgical procedures (such as laparoscopic surgery for T4+ gastric

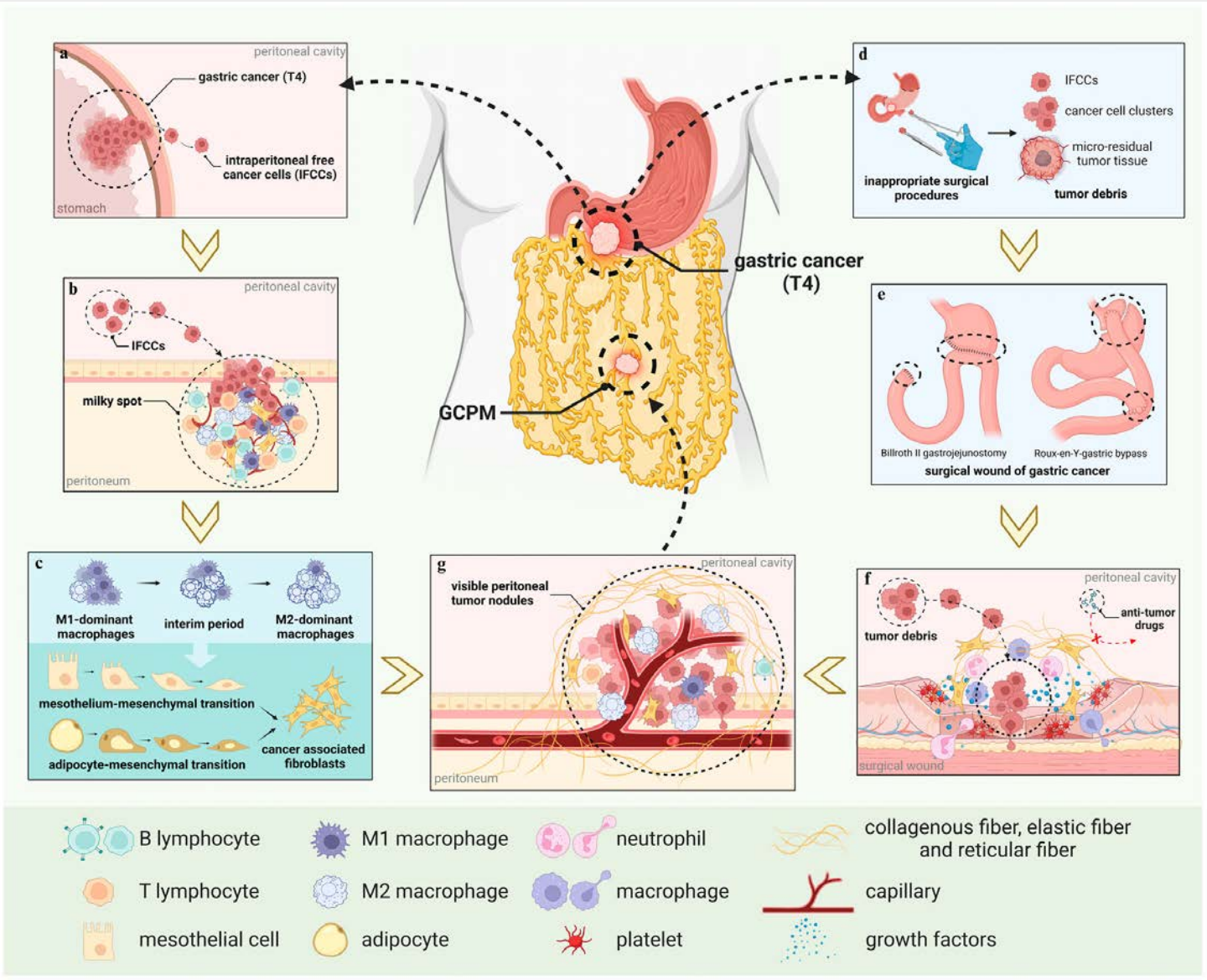

Figure 1. *The fundamental tumor biology underlying the GCPM development. GCPM develops via two different pathways, termed as selective colonization of intraperitoneal free cancer cells (IFCCs) (a-c), and the trapped proliferation of cancer cells on the damaged peritoneum (d-f). When gastric cancer progress to T4 stage, it would break through the serosa and release the IFCCs into peritoneal cavity (a). IFCCs would first invade the peritoneum through the milky spot, a lymphoid structure composed of lymphocytes, macrophages, endothelial cells, fibroblasts, and mesothelial cells (b). During the peritoneal colonization of IFCCs, the phenotypes of macrophages in the tumor microenvironment would transit from M1-dominant to M2-dominant, which results in an immunopermissive microenvironment (c). Consequently, the proliferation of IFCCs would be promoted (c). Moreover, mesenchymal cells, including mesothelial cells and adipocytes, would also experience the transition oriented to CAFs (c). The peritoneal fibrosis triggered by CAFs would combine growing tumor cells with newborn capillaries to form visible nodules, and the key symptoms of this pathway are severe mesentery contraction and large amounts of ascites (g). In addition, the inappropriate surgical procedures would produce free tumor debris into the peritoneal cavity, including IFCCs, cancer cell clusters, and even micro-residual tumor tissue (d). By this time, the surgical wounds are more susceptible to tumor invasion (e), due to the loss of natural barrier, exposed collagens, and high local concentration of growth factors (f). CAFs would also differentiate and proliferate, producing fibers which could isolate the trapped tumor nodules from the anti-tumor drugs (f). Eventually, the visible peritoneal tumor nodules are formed, and the relevant symptoms of this pathway are prominent abdominal adhesions and intestinal obstruction (g). (J Surg Oncol, 2024, 130(6): 1190-1195.)*

cancer) could result in accelerated detachment and dissemination of IFCCs, cancer cell clusters and even micro-residual tumor tissue, all of which could be generally termed as tumor debris. These detached tumor tissue debris will preferentially lodge in the surgical field because the freshly created surgical wounds have lost the natural barrier to ward off the tumor. The exposed collagen due to tissue damage not only facilitates tumor debris colonization but also promotes cancer cell growth. Trapped in fibrin and inflammatory cells, the detached tumor debris will first colonize into the peritoneal wound area. This will create two important conditions favoring peritoneal tumor development. On the one hand, the growth-factor-enriched microenvironment during wound-healing process promotes tumor cell proliferation. On the other hand, the fibrosis surrounding the tumor could isolate the trapped tumor nodules from the anti-tumor drugs. Because of these two unique features, there is an accelerated production and wider distribution of CAFs due to mesothelium-mesenchymal transition and adipocyte-mesenchymal transition. This will lead to the final formation of visible peritoneal tumor nodules, composed of tumor cells, angiogenesis, and fibroblasts. Therefore, in the iatrogenic GCPM, the pathological process is usually faster due to enriched growth factors stimulation from wound-healing, wider in distribution proportional to the scope of the surgical procedure, and clinically more serious due to the most striking symptoms of prominent abdominal adhesions and intestinal obstruction.

Conclusions regarding the rationale for combined intraperitoneal and systemic treatment in GCPM

Once the fundamental tumor biology underlying GCPM is understood, it becomes self-evident that intraperitoneal treatment is an option of locoregional management for GCPM. According to this theory, free cancer cells in the abdominal cavity are the pathological basis of peritoneal metastasis. Before and in the early stage of colonization under the mesothelial cells of free cancer cells in the abdominal cavity, theoretically, local chemotherapy in the abdominal cavity can kill free cancer cells in the abdominal cavity and reverse or control the process of peritoneal metastasis. In the later stage of peritoneal metastasis formation and progression, local treatment in the abdominal cavity combined with systemic treatment can also achieve beneficial therapeutic significance, such as effectively controlling tumor progression and reducing ascites formation. In the latest meta-analysis, intraperitoneal chemotherapy (including transcatheter intraperitoneal chemotherapy, pressurized intraperitoneal aerosol chemotherapy) combined with systemic chemotherapy, and intraperitoneal hyperthermic perfusion chemotherapy, whether used as conversion therapy or adjuvant therapy, significantly improved survival, with a median overall survival of 16.4 months, far exceeding the efficacy of systemic chemotherapy alone. (*Eur J Surg Oncol, 2025, 51(2): 109499*).

Both theoretical insights and clinical outcomes suggest that the combination of intraperitoneal chemotherapy with systemic chemotherapy produces favorable results in treating peritoneal metastasis from gastric cancer. However, it is important to note that most current clinical research findings have a low level of evidence. Therefore, there is a compelling need for high-quality, evidence-based medical research to further substantiate these findings.

Hydrogel-Based Systems for Intraperitoneal Drug Delivery in Peritoneal Metastases

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Introduction

Hydrogel-based intraperitoneal drug delivery systems exploit the pharmacokinetic advantage provided by the peritoneal–plasma barrier. Drugs administered directly into the peritoneal cavity achieve higher local concentrations with limited systemic exposure. While HIPEC, PIPAC and normothermic intraperitoneal chemotherapy long-term (NIPEC-LT) represent established clinical approaches, both remain constrained by short exposure times, heterogeneous distribution, and procedure-related toxicity. There is therefore a strong need for innovative delivery systems that provide sustained, homogeneous, and safe intraperitoneal chemotherapy.

Hydrogels are three-dimensional polymeric networks with high water content, biocompatibility, and controllable degradation properties. They can serve as local depots for anticancer drugs, allowing gradual release over days to weeks. This unique profile offers the potential to overcome the major limitations of current intraperitoneal therapies.

Hydrogel families and mechanisms

Hydrogels can be classified as:

- **Natural polymers** (alginate, chitosan, hyaluronic acid), biocompatible and sometimes bioactive.
- **Synthetic polymers** (polyethylene glycol (PEG), polyvinyl alcohol (PVA), peptide-based), with reproducible and controllable physicochemical properties.
    - **Supramolecular hydrogels** (ureido-pyrimidine poly(ethylene) glycol (UPy-PEG), offering reversible crosslinks and injectability.

- **Stimuli-responsive gels** (thermo, pH, enzymatic, reactive oxygen species (ROS)-sensitive, allowing smart drug release triggered by local conditions.

These systems can be engineered to control porosity, gelation, adhesiveness, and degradation, making them adaptable to surgical needs after cytoreductive surgery (CRS).

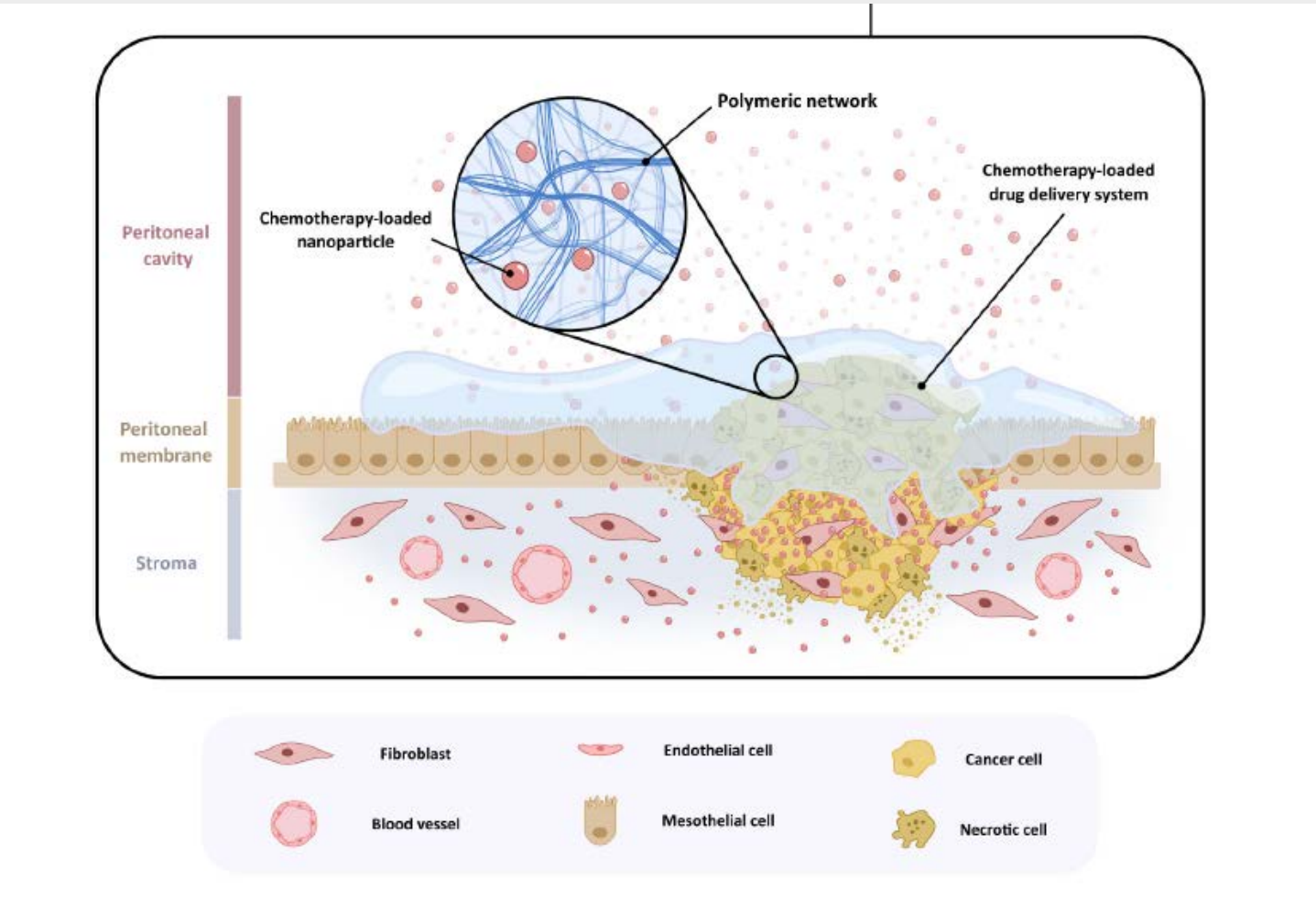

Figure 1. *Schematic representation of a hydrogel-based intraperitoneal drug delivery system. The polymeric network entraps chemotherapy-loaded nanoparticles, enabling sustained release within the peritoneal cavity and direct interaction with tumor nodules, while minimizing systemic exposure. (Perelló-Trias et al., J Control Release 2024;373:70-92)*

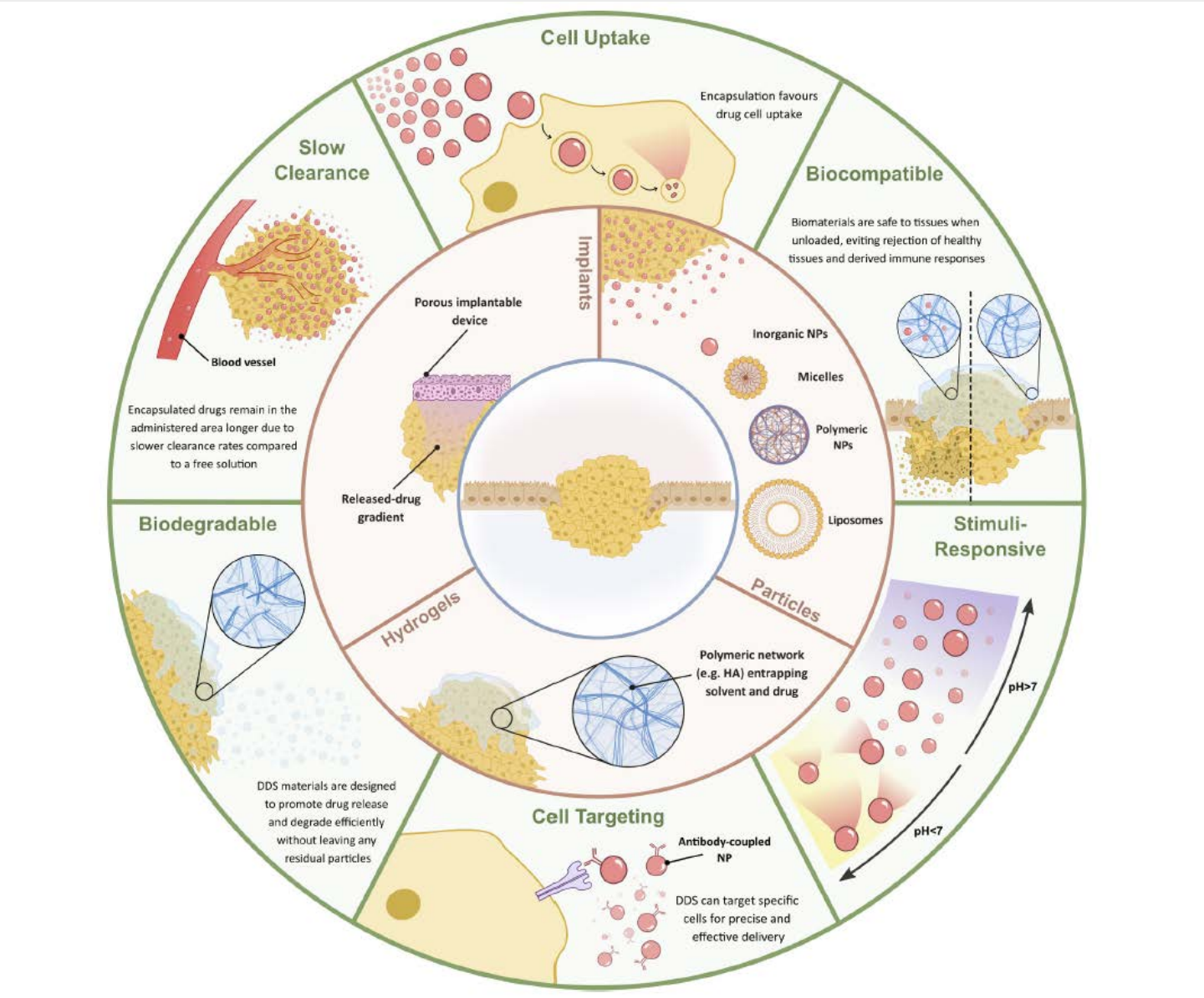

Figure 2. *Key features of hydrogel and nanoparticle drug delivery systems for peritoneal carcinomatosis. Advantages include biocompatibility, biodegradability, stimuli-responsive release, improved clearance profile, enhanced cellular uptake, and targeted delivery. (Perelló-Trias et al., J Control Release 2024;373:70-92)*

Preclinical evidence

Over 50 preclinical studies have evaluated hydrogel-based IP chemotherapy. Representative preclinical hydrogel studies illustrate efficacy across ovarian, colorectal, gastric, and mesothelioma models (Table 1).

Year	Author	Drug(s)	Hydrogel system	Model / Outcome	Key result
2012	**Bajaj et al.**	Paclitaxel	HA hydrogel	Ovarian xenograft – tumor weight	↓ Tumor weight vs IP free
2012	**Zahedi et al.**	Docetaxel	Hydrogel depot	Ovarian xenograft – tumor volume	↓ Tumor volume
2015	**Cho et al.**	Cisplatin	In situ crosslinkable HA gel	Ovarian xenograft – survival, tumor	Effective, safe
2016	**Sun et al.**	Paclitaxel	HA hydrogel + nanocrystals	Ovarian xenograft – survival	↑ Survival, sustained release
2016	**Xu et al.**	Paclitaxel	Thermosensitive hydrogel	Ovarian xenograft – tumor & animal weight	↓ Tumor, no ↑ toxicity
2020	**Luo et al.**	Multi-chemo	HA hydrogel (colorectal PM)	Colorectal PM model	↓ Tumor growth
2021	**Yamaguchi et al.**	Cisplatin	Hybrid nanogel-in-hydrogel	Ovarian xenograft – tumor volume	Effective, safe
2023–2025	**Wintjens et al.**	Mitomycin C	UPy-PEG supramolecular hydrogel	Colorectal PM – survival, PK studies	Sustained release, first PK in humans
2025	**Perelló-Trias et al.**	Cisplatin	HA hydrogel ± patch	OVCAR-3, SEM, release assays	Controlled release ≥96 h, cytotoxicity maintained, slower release with patch integration

Table 1. *Representative selection of preclinical hydrogel studies, illustrating the main drug delivery strategies and outcomes reported. More than fifty such studies have been published overall. (Simonsen et al., Front Oncol 2025;15:1487376)*

A recent systematic review and meta-analysis (*Simonsen et al., Front Oncol 2025;15:1487376*) confirmed that intraperitoneal drug delivery systems – including hydrogels – significantly reduce tumor weight and volume without increasing systemic toxicity. Forest plots consistently demonstrated efficacy across different agents and delivery platforms.

The translational gap

Despite robust preclinical data, translation into the clinic is still limited. Key hurdles include:

- Tumor heterogeneity and variable peritoneal fluid dynamics.
- Concerns regarding adhesions and anastomotic healing.
- Rapid clearance of small molecules if not retained in depot systems.
- Regulatory and Good Manufacturing Practice (GMP) standards causing production barriers.

Large-animal models have begun to address surgical safety; for example, supramolecular UPy-PEG gels did not impair anastomotic healing in rats (*Heuvelings et al., Life (Basel) 2023;13:2076*). Pharmacokinetic studies in rodents confirm sustained intraperitoneal exposure without systemic accumulation. Integration of hydrogels into surgical patches or hemostatic matrices represents an additional translational step.

Clinical outlook

At present, no hydrogel-based chemotherapy system has reached late-phase clinical testing. Among the different hydrogel systems under development, supramolecular UPy-PEG loaded with mitomycin C appears to be one of the most translationally advanced, supported by pharmacokinetic and surgical safety data in rodents. Future efforts will require:

- Scaling production under GMP standards.
- Designing early-phase clinical trials with endpoints beyond feasibility, including pharmacodynamics and quality-of-life.
- Exploring combination strategies (hydrogels + immunotherapy, PARP inhibitors, or nanoparticle hybrids).

Conclusions and perspectives

Hydrogel-based intraperitoneal chemotherapy offers a compelling strategy to overcome the current limitations of HIPEC, PIPAC, and NIPEC-LT. Preclinical evidence demonstrates consistent efficacy, safety, and versatility across multiple drugs and models. Translational studies, including safety in anastomotic models and hydrogel–patch integration, pave the way for clinical readiness.

The challenge now is to bridge the gap from bench to bedside through good manufacturing practice, carefully designed early-phase trials, and multidisciplinary collaboration between surgeons, pharmacologists, and material scientists. If successful, hydrogels will result in a paradigm shift in the management of peritoneal metastases.

Organoids Provide Individualized Therapies for Peritoneal Surface Malignancies: From Bench to Bedside

By Shigeki Kusamura, Luca Varinelli, and Manuela Gariboldi

Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Istituto Nazionale Tumori dei Tumori di Milano, Milan, Italy

Organoids are three-dimensional cellular structures derived from patient tissues that faithfully reproduce many of the biological and genetic characteristics of the tumor of origin. Unlike traditional two-dimensional cell cultures, they preserve cell–cell and cell–matrix interactions, maintain intratumoral heterogeneity, and can be expanded over long periods without losing genomic integrity. These features make them a powerful model for understanding cancer biology and developing personalized therapeutic strategies.

Tumor-derived organoids can be generated from patient biopsies or surgical specimens. The tissue is mechanically and/or enzymatically dissociated, and the resulting cells are embedded in a scaffold such as Matrigel. These cells are then cultured in a medium enriched with growth factors and signaling pathway inhibitors, tailored to the tissue of origin. This environment mimics the *in-vivo* niche, allowing the cells to self-organize into three-dimensional structures that mirror the histological and molecular features of the original tumor. Once established, organoids can be maintained, expanded, and biobanked for future research and drug testing.

The utility of organoids in gastrointestinal cancers has been extensively reviewed by Onno Kranenburg and colleagues (*Lau et al. Nat Rev Gastroenterol Hepatol 2020;17:203-222*). They highlighted how these models more accurately replicate tumor initiation, metastatic progression, and therapeutic response than conventional cell lines or xenografts. Organoid biobanks derived from colorectal, gastric, pancreatic, and liver cancers now represent a powerful resource for high-throughput drug screening, biomarker discovery, and translational research.

In colorectal cancer peritoneal metastases, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) remains the most effective therapeutic strategy, yet the optimal choice of intraperitoneal drugs has been debated for years. To address this challenge, Varinelli and collaborators developed an *in-vitro* platform in which patient-derived organoids from peritoneal metastatic tissue were exposed to clinically relevant HIPEC regimens (*Varinelli et al. J Exp Clin Cancer Res 2024;43:132*). Their results showed substantial variability in drug response among patients, but consistently identified mitomycin-C,

either alone or combined with cisplatin, as the most effective treatment options. In contrast, oxaliplatin in short high-dose perfusion schemes, showed limited efficacy.

This work has led to a prospective clinical trial at the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, where drug sensitivity testing on organoids derived from laparoscopy biopsies is used to guide individualized HIPEC treatment (OrganoHIPEC protocol NCT06057298). Similarly, a Dutch group demonstrated that organoids can predict clinical response to systemic chemotherapy (*Ubink et al. Br J Surg 2019;106(10):1404-1414*). By optimizing culture conditions and drug screening methodologies, they showed that organoid sensitivity to drugs such as oxaliplatin or irinotecan correlated with patient progression-free survival, supporting the use of organoids as biomarkers for treatment efficacy in clinical practice.

Researchers in Milan has also advanced the field by integrating organoids with key elements of the metastatic microenvironment, specifically the extracellular matrix derived from the peritoneum, decellularized to remove its cellular component, and cancer-associated fibroblasts regimens (*Varinelli et al. J Exp Clin Cancer Res 2024;43:132*). In one model, organoids preferentially grew on scaffolds obtained from neoplastic peritoneum, which displayed increased stiffness compared to healthy tissue. Under these conditions, organoids showed a reduced response to HIPEC regimens, suggesting that the matrix can impair drug efficacy. This model revealed how the extracellular matrix influences tumor cell growth and modulates sensitivity to chemotherapy. In a complementary model, organoids were co-cultured with cancer associated fibroblasts isolated from the same neoplastic tissue. These fibroblasts are known to promote colorectal cancer progression, metastatic spread, and development of chemotherapy-resistance. Presence of cancer associated fibroblast was found to negatively affect treatment response. Together, these findings highlight the critical role of the metastatic niche and suggest new avenues for therapeutic intervention that target not only tumor cells but also their surrounding microenvironment.

Recently, Varinelli and collaborators successfully extended the organoid approach to rare conditions like pseudomyxoma peritonei, a particularly challenging tumor type due to its extremely low cellularity and slow growth kinetics (*Varinelli et al. J Surg Oncol 2024;130:1213-1224*). Despite these challenges, they successfully established organoid models from this tumor type, providing an unprecedented opportunity to investigate key signaling pathways such as IL-6/STAT3 and KRAS/GNAS, and to identify novel therapeutic targets. This work represents a turning point for pseudomyxoma peritonei, a condition that has long lacked preclinical models.

Organoids have already become an integral component of precision oncology. Their use to personalize HIPEC regimens in colorectal peritoneal metastases represents a first step towards clinical integration. Further

implementation of the models developed in Milan will include incorporation into organoid cultures of other components of the metastatic microenvironment, such as immune cells, endothelial cells, and inflammatory components, to study immunotherapy responses and tumor–stroma crosstalk in a more physiologically relevant context. Combining organoids with microfluidic systems and engineered extracellular matrices will generate dynamic "organoid-on-chip" platforms, capable of reproducing drug perfusion, gradients, and mechanical stress in a physiologically relevant manner. Moreover, the establishment of multicenter organoid biobanks, particularly for rare diseases like PMP, will foster collaboration and accelerate the development of new treatments.

In summary, organoids have progressed from a technical curiosity into a powerful tool in translational oncology. The efforts of researchers in Milan have placed peritoneal surface malignancies at the forefront of this scientific revolution, with organoid models now driving the search for more effective and individualized therapies. Their work demonstrates how close collaboration between surgeons, oncologists, pathologists, and basic scientists can transform clinical practice, offering new hope to patients facing some of the most challenging malignancies in our field.

Lessons Learned from Continuous Ambulatory Peritoneal Dialysis regarding the Peritoneal-Plasma Barrier

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Peritoneal dialysis

Continuous ambulatory peritoneal dialysis (CAPD) has been widely available as a kidney replacement therapy technique since the 1970s (*Misra M, Phadke GM. Contrib Nephrol 2019;197:1-8*). Before that, it had been used for the in-hospital treatment of acute kidney injury since 1946. CAPD was made possible by the availability of chronic peritoneal access through peritoneal catheters and sterile peritoneal dialysis (PD) fluids. PD fluids are infused into the peritoneal cavity, where they dwell for 1 hour (automated PD with cycler) to 8-10 h (CAPD) (Figure 1). At the end of the dwell, PD fluid is removed and replaced by fresh PD fluid for a total of 1 to 8 exchanges per day. Throughout the dwell, the concentration of solutes inside the peritoneal cavity changes, veering from the original composition of the PD fluid towards equilibration with solute concentrations in the peritoneal wall interstitial fluid which, in turn, is in equilibrium with plasma. Overall, the peritoneal cavity is usually filled with PD fluid for 24h/7 days/365 days, frequently for years. Each year, around 1000 to 2000 L of PD fluid enter and leave the peritoneum in a PD patient.

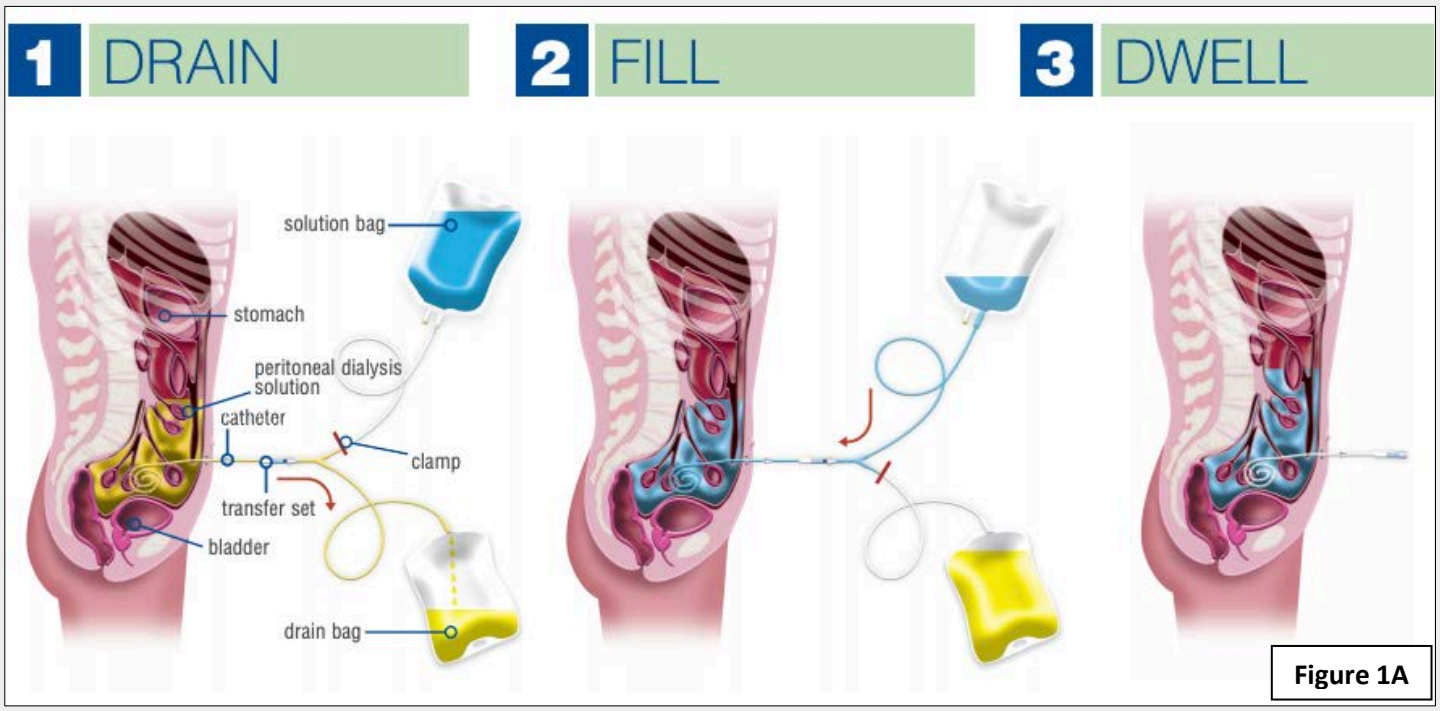

Figure 1. *The basis of peritoneal dialysis (PD):* ***A)*** *Drain-fill-dwell cycle. In CAPD there is always PD fluid in the peritoneum.* ***B)*** *Twin-bag for PD. Consists of PD fluid bag, waste product bag and continuous ambulatory PD (CAPD) connecting tube (transfer set) that is connected to the PD catheter in the patient abdomen.*

Source: https://www.bioteq.com.tw/en/products/twin-bag-for-peritoneal-dialysis; https://sainephrology.com/peritoneal-dialysis/

Requirements for successful peritoneal dialysis

Patients with kidney failure have a decreased ability to clear uremic toxins as well as dietary fluid, sodium and potassium. Eventually they will become anuric. The composition of PD fluids is designed to fulfill the needs of patients with kidney failure: removal of water, sodium, potassium and other uremic retention solutes, without causing a negative calcium balance while contributing to correct the metabolic acidosis (low serum bicarbonate levels) associated to kidney failure. To achieve those goals, PD fluids are hypertonic, to promote fluid removal (ultrafiltration) from the body rather than contributing to the fluid overload of anuric patients. This is achieved by an osmotic agent, usually glucose at very high concentrations (1360 to 4250 mg/dl, osmolarity 345-511 mOsm/L). Aminoacids (1.1% weight/volume) or polyglucose (icodextrin, 7.5%) are alternative osmotic agents that may be used only once per day. Given its large size (molecular weight 1640

to 45000 Da), as compared to glucose (180 Da) and amino acids (≈75-200 Da), polyglucose is absorbed more slowly from the peritoneum and provides more stable fluid removal over longer time dwells. The volume of each fluid exchange infusion is usually 2.0 L but may range from 1.5 to 3.0 L in adults, depending on body size. A buffer to correct acidosis consists of lactate (which is metabolized by the body to bicarbonate), bicarbonate or lactate/bicarbonate. Sodium concentration is low (132 to 134 mmol/L) to promote sodium removal without causing hyponatremia. Additional components include calcium (1.25-1.75 mM), magnesium (0.25-0.75 mM) and chloride (96-103 mM). There is no potassium, as patients with kidney failure tend to have hyperkalemia. The pH is 5.5 for older glucose-based solutions, 5.8 for polyglucose, 6.5 for amino acids and 7.0 to 7.4 for newer, more biocompatible glucose-based PD fluids. Biocompatibility is a concern for PD fluids expected to be used for years by patients. Removing acetate, increasing pH towards physiological levels and improved heat sterilization techniques have contributed to improved biocompatibility. The latter includes bicameral (double chamber) bags, that allow sterilization of the glucose-containing compartment at low pH, so as to decrease the generation of potentially toxic glucose degradation products (GDPs). Both chambers are mixed to generate the final PD fluid just before use. PD fluids are warmed to 37°C prior to infusion to decrease patient discomfort. Warming for longer time periods may increase glucose degradation products (GDPs) concentrations.

Intraperitoneal administration of antibiotics

In patients on PD, the peritoneum is used as route for parenteral drug administration, usually in the context of antimicrobial agents for PD peritonitis, a common complication, usually mild if treated early. Regularly updated international guidelines provide guidance on antibiotic dosing and timing (*Li et al. Perit Dial Int 2022;42(2):110-153*) that includes the possibility for intermittent dosing, i.e., a once daily or less frequent antimicrobial dose in a PD fluid bag with a dwell time of at least 6 h. Vancomycin may be administered at a dose of 15–30 mg/kg every 5–7 days in CAPD, i.e., every 5 to 7 days, vancomycin is absorbed from the peritoneal cavity and over that period, it slowly diffuses back from the circulation into the peritoneum, where it reaches antimicrobial concentrations.

Conceptual and physical structure of the peritoneal-plasma barrier

The peritoneal wall barrier is formed by the mesothelium, the interstitial space and, mainly, the submesothelial capillary wall, of which the endothelium is the key component. From a conceptual physical point of view, peritoneal permeability is best summarized by the three-pore model of peritoneal transport (*Devuyst O, Rippe B. Kidney Int 2014;85(4):750-758*) (Figure 2). This model treats the capillary endothelium as a primary barrier

determining the amount of solute that transports to the interstitium and the peritoneal cavity. The principal peritoneal exchange route for water and water-soluble molecules are small, protein-restrictive pores (radius 40–55 A), accounting for approximately 99% of the total exchange (pore) area. Protein passage is confined to uncommon (0.01% of the total pore population) large pores (≈250 Å). A water-only pathway, thought to consist of endothelial aquaporin-1, is permeable to water but impermeable to solutes. The relative contribution of each pore type to ultrafiltration depends on the type of osmotic agent in the peritoneal cavity. The three-pore model predicts the transport of water, small solutes (radius 2.3–15 Å), intermediate size solutes (15–36 Å) and albumin (36 Å) and larger molecules across the peritoneal membrane.

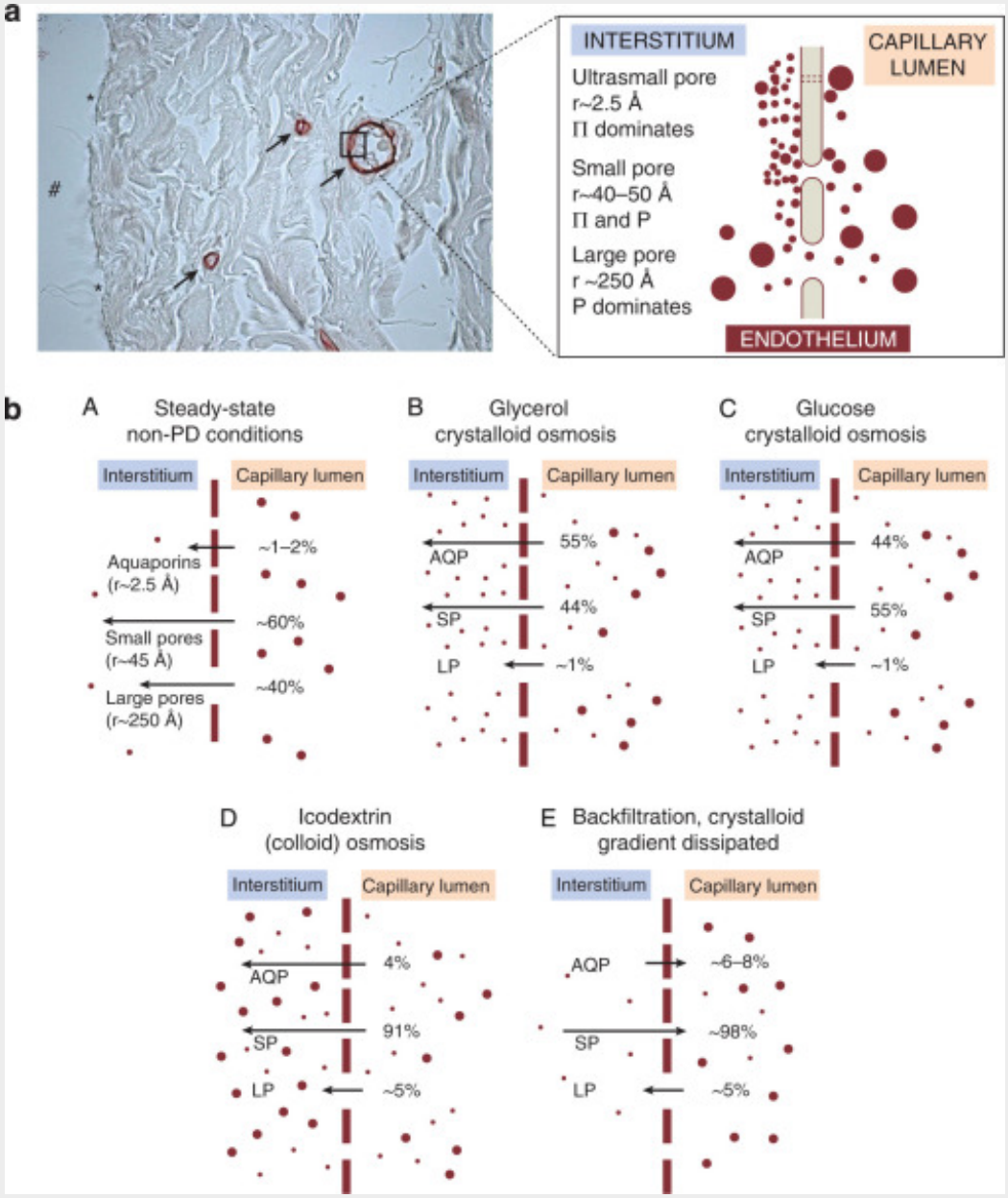

Figure 2. *Three-pore model of peritoneal transport and ultrafiltration (fluid volume) kinetics according to intraperitoneal contents. Source: Devuyst O, Rippe B. Water transport across the peritoneal membrane. Kidney Int. 2014;85(4):750-758.*

Assessment of peritoneal function in clinical practice

From the start of CAPD programs, it became apparent that there were interindividual differences in the behavior of the peritoneal wall barrier with regards to the speed of transport of small molecules. This was most notable for glucose. In people with rapid peritoneal transport, glucose would be rapidly absorbed, the intraperitoneal hyperosmolarity would disappear earlier, precluding the possibility to make a negative fluid balance, so necessary for people with anuria (Figure 3). Moreover, peritoneal transport characteristics were found to evolve over time. PD may be needed for up to over 10 years in countries with low kidney transplantation rates. Older PD fluids were less biocompatible than current ones, due to the presence of acetate as a buffer and of glucose degradation products (GDPs) generated during the heat sterilization step. Thus, over time the peritoneal barrier would be damaged. Peritoneal damage is characterized by demesothelization and peritoneal fibrosis. Functionally, peritoneal permeability and transport rates may increase over time, limiting the ability to generate a negative fluid balance.

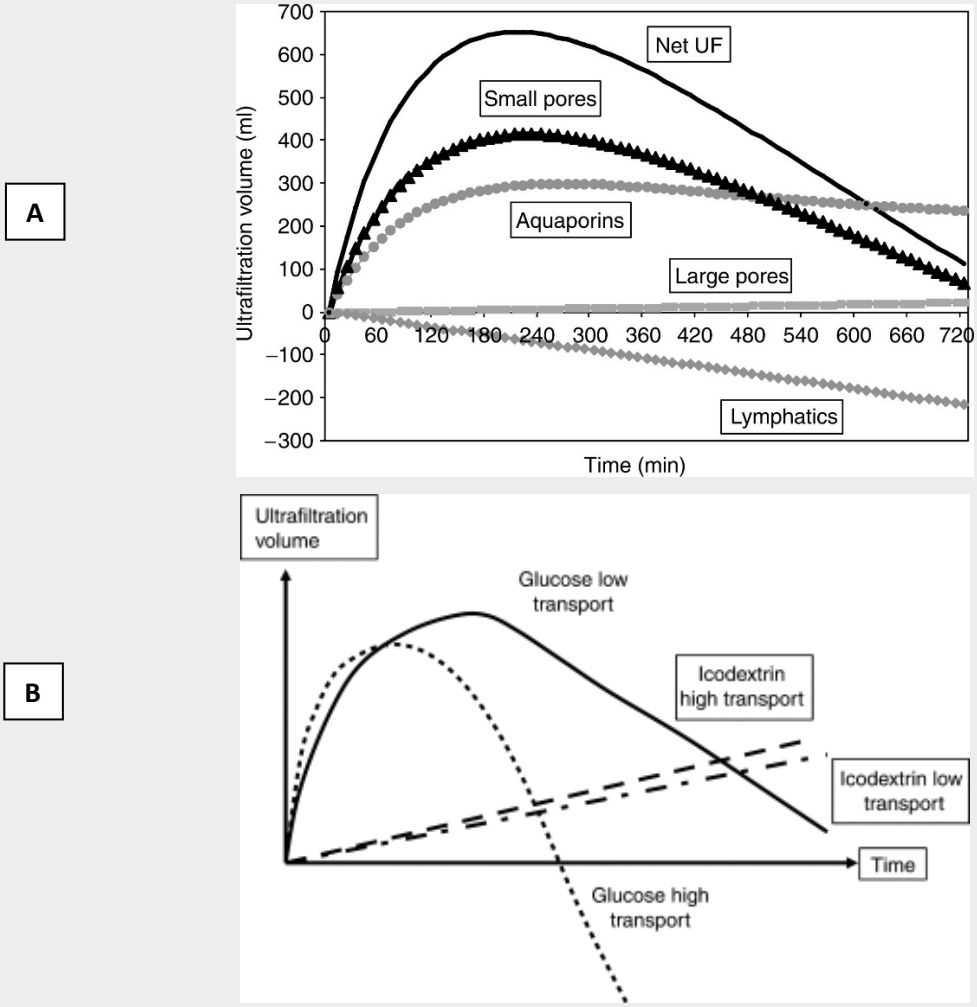

Figure 3. *Ultrafiltration (fluid volume) kinetics in PD over time.* ***A)*** *Ultrafiltration over time and contribution of different types of pores.* ***B)*** *Ultrafiltration volume according to peritoneal transport characteristics evaluated by PET. Source: Davies SJ. Mitigating peritoneal membrane characteristics in modern peritoneal dialysis therapy. Kidney Int Suppl. 2006;(103):S76-S83*

The peritoneal equilibration test (PET) is used to assess peritoneal transport characteristics to help guide PD prescription and monitor peritoneal injury (*Gu et al. Perit Dial Int 2023;43(5):361-373; Morelle et al. Perit Dial Int 2021;41(4):352-372*) (Figure 4). It is typically performed as a 4-h PD fluid exchange using 2.27% glucose with serial measurements of blood and dialysate creatinine, urea, and glucose concentrations. The percentage absorption of glucose and the dialysate/plasma creatinine ratio are used to determine peritoneal solute transfer rates, identifying high, low and intermediate transporters. In high transporters, the intraperitoneal glucose concentration falls rapidly, and shorter dwells are required to obtain a negative fluid balance. Conversely, the concentration of small uremic retention solutes, represented by creatinine, rapidly increases inside the peritoneum of rapid transporters. While this may appear to be an ideal situation, rapid transporters frequently have worse outcomes. Inability to maintain a healthy fluid balance is a key issue, as clearance of larger uremic retention solutes (which are transferred more slowly than smaller ones) still needs to use the 24 h in a day for PD. Some people are rapid transporters from the start, while in others a progressive increase in peritoneal transport rates reflects ongoing peritoneal wall damage.

Some varieties of PET have been developed. It is worth mentioning the 3.86/4.25% glucose PET that includes assessment of the intraperitoneal sodium concentration dip at 60 minutes and is helpful to assess patients with low ultrafiltration and difficulty to maintain fluid balance.

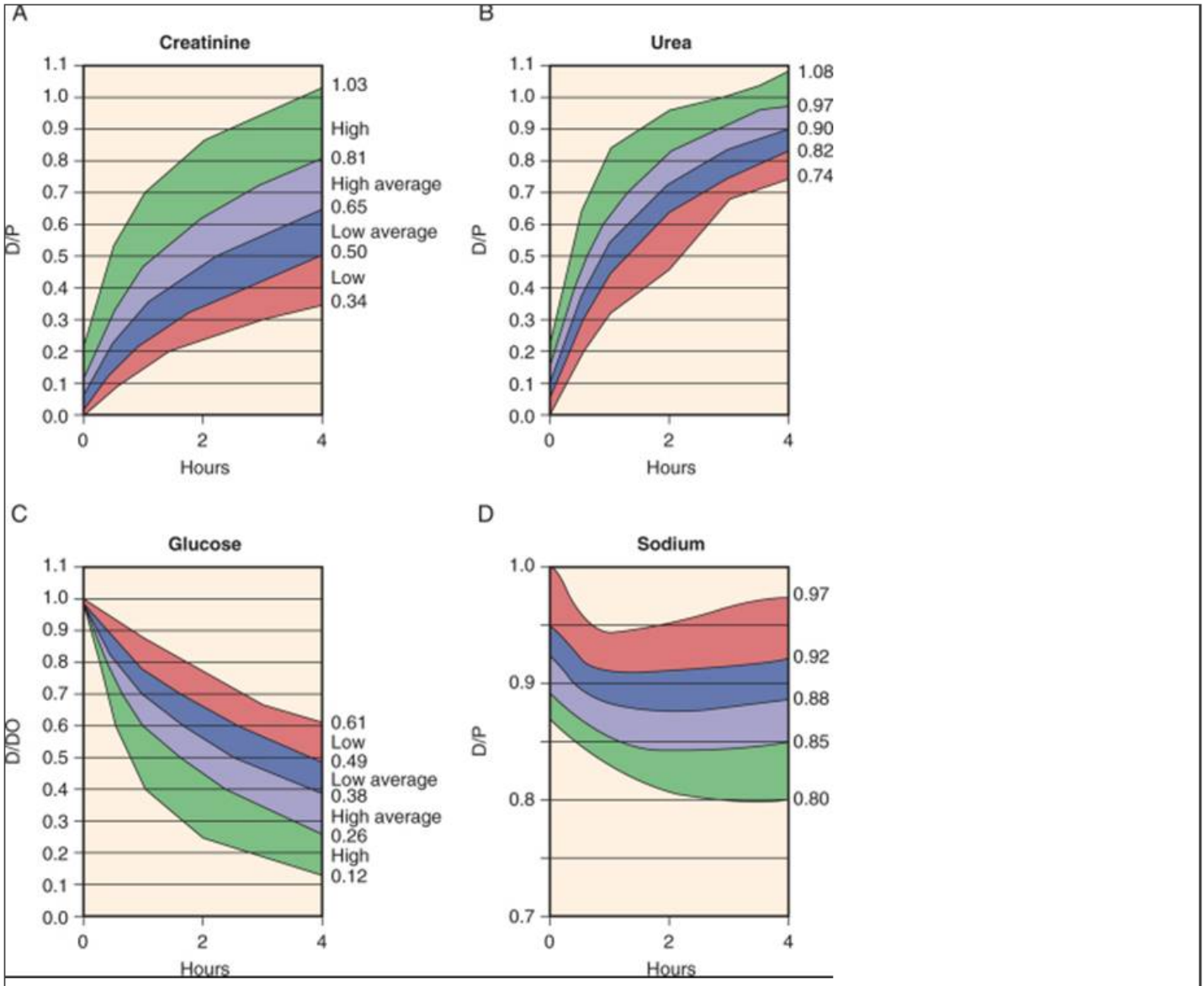

FIGURE 59-3 A-D, Peritoneal equilibration curves for creatinine, urea, glucose, and sodium. *(Adapted from Twardowski ZJ, Nolph KD, Khanna R, et al: Peritoneal Equilibration Test. Perit Dial Bull 7:138–144, 1987.)*

Figure 4. *Peritoneal equilibration curves: Results and interpretation of peritoneal equilibration tests (PET).* ***A)*** *Dialysate/plasma (DP) creatinine ratio over time.* ***B)*** *Dialysate/plasma (DP) urea ratio over time.* ***C)*** *Dialysate time x/dialysate time zero glucose concentration ratio over time.* ***D)*** *Dialysate/plasma (DP) sodium ratio over time.*

Source: https://doctorlib.org/nephrology/kidney/60.html: Brenner and Rector's The Kidney, 8th ed.
CHAPTER 59. Peritoneal Dialysis. Ajay Sharma Peter G. Blake

Pharmacokinetic and Pharmacodynamic Aspects of Drugs Used in HIPEC

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Introduction

Intraperitoneal (IP) drug delivery of cancer chemotherapy drugs in patients with peritoneal surface malignancy (PSM) has a sound pharmacologic rationale: dose intensification as defined by Dedrick et al in 1978 (*Dedrick et al. Cancer Treat Rep 1978;62(1):1-11*). This provides a pharmacokinetic (what the body does to the drug) optimization of the cancer chemotherapy drug delivery to the residual peritoneal cancer tumor cells after Cytoreductive Surgery (CRS). As such, it aims to increase the efficacy of the IP drug while decreasing systemic toxicity (*Van der Speeten et al. Gastroenterol Res Pract 2012;2012:378064*). This approach has resulted in encouraging clinical results in PSM patients. Unfortunately, the majority of patients with PSM will eventually relapse in the abdominal cavity. The pharmacodynamics (what the drug does to the body) of IP chemotherapy were poorly understood until recently.

Evolution in Pharmacologic Endpoint of IP Chemotherapy

For a very long time, the area under the curve (AUC) ratio of IP over IV in a pharmacokinetic concentration times time graph was considered the optimal pharmacological endpoint of IP chemotherapy (*Ceelen WP, Flessner MF. Nat Rev Clin Oncol 2010;7(2):108-115*). The IP concentration was hypothesized to be responsible for the efficacy and the IV concentration for the toxicity of the HIPEC drug. This is an oversimplification. High IP (or intratumoral) cancer chemotherapy concentrations are a necessary but insufficient condition for tumor cell death. The 30-minute high-dose oxaliplatin regimen used in the PRODIGE randomized control trial did not result in any significant tumor cell apoptosis when replicated in a rodent model (*Lemoine et al. Oncotarget 2019;10(14): 1407-1424*). The negative PRODIGE 7 trial invigorated a renewed interest into pharmacokinetic and pharmacodynamic IP research (*Quenet et al. Lancet Oncol 2021;22(2):256-266; Sugarbaker PH, Van der Speeten K. J Gastrointest Oncol 2021;12(Suppl 1):S129-S30*).

The Ideal IP Chemotherapy

Lessons can be learned from 50 years of progress in systemic chemotherapy. Presently, all successful chemotherapy regimens meet 4 criteria: multidrug, multicycle, cell-cycle specific and personalized. Unfortunately, no current IP regimen replicates these criteria

A Research Network for Improving IP Chemotherapy

There is a pressing need for a better understanding of the tumor biology of PSM. This will require a multi-modality research pathway (Figure 1) (Reproduced from *Kranenburg et al. Front Oncol 2021;11:650098*).

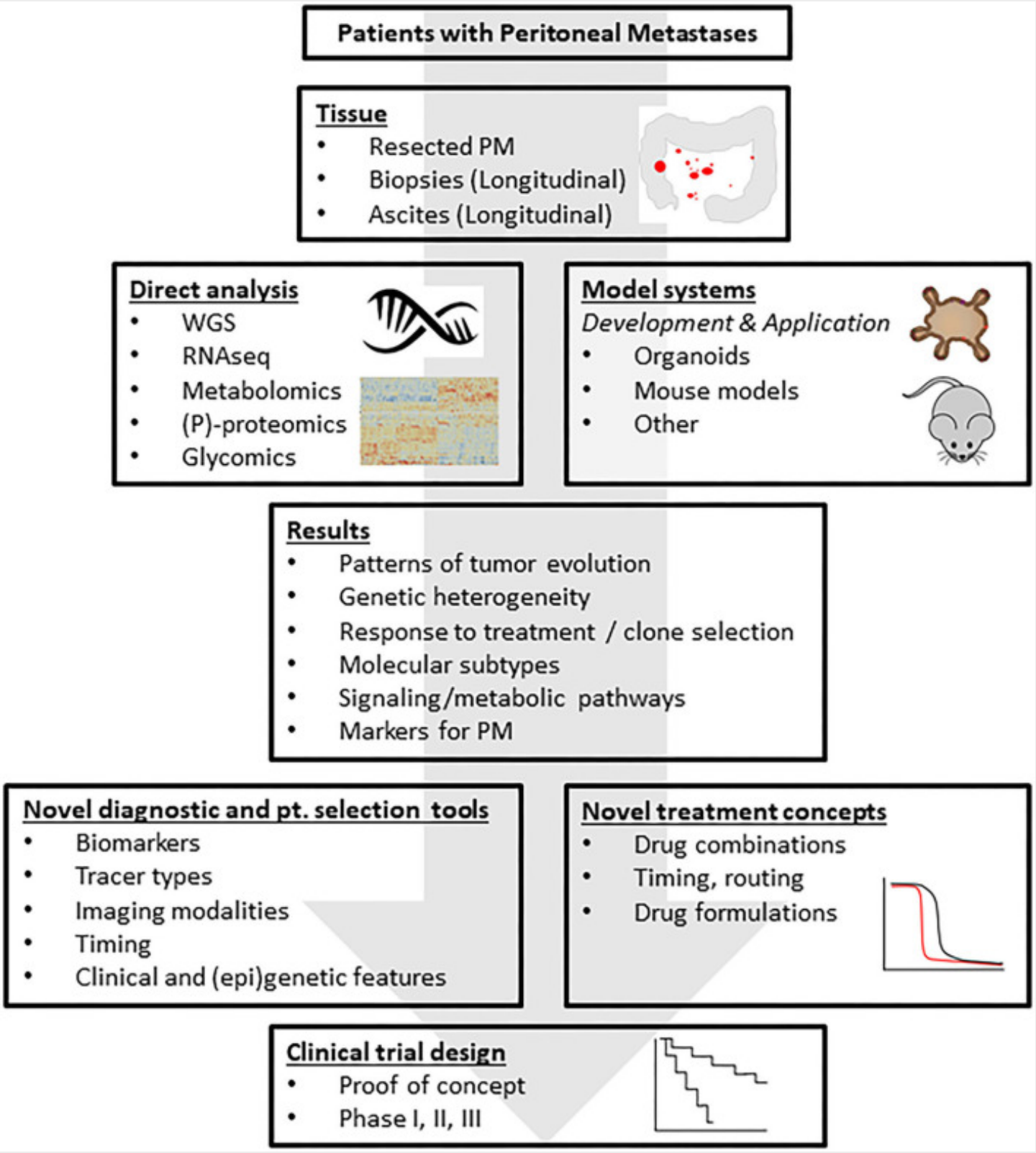

Figure 1. *Understanding the tumor biology of peritoneal surface malignancy.*

Novel Pharmacologic Strategies to Improve IP Chemotherapy

A better understanding of PSM tumor biology should subsequently lead to improved IP chemotherapy regimens. In line with developments in systemic chemotherapy, novel drug delivery systems are equally important to new drug discovery. Potential pharmacologic strategies include:

Hydrogels, Micelles

IP chemotherapy exposure time (next to concentration) is the most important pharmacokinetic variable in IP chemotherapy (*Helderman et al. Front Oncol 2023; 13:1122755*). There are however physiological limitations to the duration of a HIPEC procedure. These can be overcome by clever drug delivery systems such as hydrogels that leverage the exposure time beyond the duration of the HIPEC.

Nanoparticles

Nanoparticles (bio-engineered drug carriers (20-1000 nm)) that contain cytotoxic drugs can increase the retention time of an IP chemotherapy drug due to decreased clearance from the peritoneal space, meanwhile offering opportunities for selective targeting and selective activation (pH, temperature) (*Pan et al. J Control Release 2024;376:266-285*).

Multi-Cycle IP chemotherapy

A one-time IP chemotherapy application like HIPEC has only limited potential for eradicating all residual microscopic peritoneal tumor cells after CRS. New IP application strategies such as Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS), Sequential Long-term Intraperitoneal Chemotherapy, Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC) and Early Postoperative Intraperitoneal Chemotherapy have the potential for supercharging the dose-intensification of IP route of delivery, while at the same time open the IP route to the use of cell-cycle specific drugs (5-fluorouracil, taxanes).

IP immunomodulation

Systemic Immunotherapy is generally known to be less effective in PSM due to the characteristics of immunologic change, such as an immunosuppressive environment created by the tumor, which hinders the activation of immune cells against cancer cells (*Lim et al. Oncotarget 2016;7(7):8055-8066*). However, recent studies have demonstrated promising results by using IP immunotherapeutic strategies to activate the immune cells infiltrating the peritoneal area. Such strategies include IP CAR-T cells, IP monoclonal antibodies and immune checkpoint inhibitors (*Ornella et al. Cancers (Basel) 2023; 15(8):2383*).

Conclusions

After almost 50 years, IP chemotherapy is finally coming of age. The sound pharmacologic rationale of IP delivery of cancer chemotherapy drugs is currently consolidated in elaborate multicycle, multidrug, personalized IP chemotherapy regimens that are based on structured preclinical research. IP chemotherapy has evolved from a single-shot intraoperative effort into a mature drug delivery system encompassing the neoadjuvant, intraoperative and adjuvant phases of treatment in PSM patients.

Peritoneal metastases when optimally treated can be cured; in selected patients peritoneal metastases can be prevented. The ultimate goal is to eliminate local-regional recurrence and peritoneal metastases from the natural history of gastrointestinal and gynecologic malignancy.