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IN THIS ISSUE – Updates and Clarifications for 2026

Section 1:

Current Treatment Options for HIPEC In Colorectal Peritoneal Metastases. Refinement Necessary Rather Than a Rejection.

By François Quénet

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Two decades after the publication of the Dutch randomized trial (*Verwaal VJ, van Ruth S, de Bree E, et al. J Clin Oncol 2003;21:3737–43*), does the benefit of adding HIPEC to cytoreductive surgery (CRS) still hold? The question is legitimate. The answer, however, remains nuanced. The initial enthusiasm surrounding CRS-HIPEC has undeniably been tempered by the results of the PRODIGE 7 trial (*Quénet F, Elias D, Roca L, et al. Lancet Oncol 2021;22:256–66*) which found no survival benefits when adding high-dose (460 mg/m^2), short-duration (30 minutes) oxaliplatin-based HIPEC to complete CRS. With this HIPEC method severe complications were more frequent in the HIPEC arm. Only patients with an intermediate Peritoneal Cancer Index (11–15) showed a survival benefit, while both groups exhibited unexpectedly high overall survival. The outcome established the importance of high-quality CRS combined with systemic chemotherapy. The results of the PRODIGE 7 trial do not negate the possible value of HIPEC but instead questions the HIPEC regimen used. Data showed that, at the very least, its benefits are modest and limited to specific subgroups of patients.

The impact of this trial was immediate and profound. In some circles, results were interpreted as the definitive end of HIPEC in colorectal peritoneal metastases. Such a conclusion, however, represents an oversimplification and, arguably, a misinterpretation.

HIPEC, as a concept, cannot be reduced to a single drug or a single delivery scheme. The pharmacological behavior of intraperitoneal chemotherapy is highly dependent on the agent used, and the duration of exposure. Its efficacy may rely on its interaction with the systemic chemotherapy treatments administered as neoadjuvant therapy. The pharmacokinetic studies performed to validate the PRODIGE 7 protocol were well conducted and concluded that oxaliplatin metabolites were definitely present in the tissues. It is therefore likely that the ineffectiveness of oxaliplatin is not due to poorly controlled pharmacokinetic issues (although the short duration of exposure remains a valid concern) but rather to the ineffectiveness of the drug itself when administered intraperitoneally in this manner. Aside from this, the extensive use (73% of the patients) of systemic oxaliplatin before HIPEC in the trial may have resulted in increased somatic gene mutations causing oxaliplatin resistance, which would diminish the cytotoxicity of the HIPEC. In PRODIGE 7, complete cytoreduction was achieved in more

than 90% of cases. In patients with colorectal peritoneal carcinomatosis, the therapeutic effect associated with complete cytoreduction is probably so significant that it 'overshadows' the effects of HIPEC.

Further insight can be drawn from trials exploring HIPEC in a prophylactic setting. Of the trials, only the HIPEC T4 trial (*Arjona-Sánchez A, Espinosa-Redondo E, Gutiérrez-Calvo A, et al. JAMA Surg 2023;158(7):683-91*), which used mitomycin C (MMC), demonstrated a benefit in progression-free survival, whereas two other randomised trials using the PRODIGE 7 protocol both failed to show benefit.

On the other hand, MMC, which remains widely used in North America and in the majority of European and Asian centers, exhibits distinct pharmacokinetic properties, with longer exposure times (typically 90 minutes) and a different pattern of tissue penetration. Emerging data from multicenter registries and recent experts Delphi consensus from the PSOGI (*Hübner M, van Der Speeten K, Govaerts K et al, Ann Surg Oncol 2024;31(1):567-576*), suggest that it is currently the only available alternative, whether used on its own in accordance with the Dutch protocol or in combination with cisplatin. Although most studies are based on small sample sizes, the comparison between the efficacy of HIPEC with oxaliplatin and that based on MMC has been extensively studied. The results do not show any clear superiority of one drug over the other, although there appears to be a slight tendency in favour of oxaliplatin; this is confirmed by one of the most recent studies involving the largest number of patients, conducted by Fisher (*Fisher OM, Brown C, Esquivel J, Larsen SG, et al. BJS Open 2024 May 8;8(3)*).

Except for intra-arterial hepatic chemotherapy, HIPEC is currently the only chemotherapeutic treatment administered with a locoregional focus in the management of colorectal cancer metastases. In this context, can we apply the same approach as for liver metastases and consider that complete surgical resection combined with systemic chemotherapy could, on their own, achieve good therapeutic outcomes? Probably not, due to two major differences: Firstly, colorectal peritoneal metastases are not only a manifestation of a systemic disease; they also constitute, at least in part, a locoregional process requiring a locoregional strategy. Secondly, complete microscopic R0 resection does not really exist in the peritoneal setting. This is why we prefer to use the Sugarbaker classification: CC0 or 1. CRS addresses the macroscopic component while HIPEC, when appropriately applied, may contribute to controlling the microscopic residue that defines the risk of peritoneal recurrence. Two recent major studies, although not exempt from limitations, show us that the response to neoadjuvant and perioperative treatments is very different from that seen in other metastatic situations arising from primary colorectal cancer. The CAIRO6 study (*Rovers K, Bakkers C, van den Heuvel TBM, et al. J Clin Oncol 43, 3505(2025) Volume 43, Number 16_suppl*) demonstrates an effect of perioperative systemic chemotherapy on recurrence-free survival, while the retrospective study conducted by Cashin shows an effect in the postoperative setting but not in the neoadjuvant

situation (*Cashin PH, Esquivel J, Larsen SG, et al. EClinicalMedicine 2022;55:101746*). In other words, we cannot rely on a significant response to neoadjuvant therapy and in so doing ignore the locoregional nature of peritoneal carcinomatosis. This significantly reinforces the requirement of local control and, therefore, of HIPEC, particularly in cases where peritoneal metastases are predominant, such as in mucinous histologies.

Ultimately, the central issue is not whether HIPEC should be abandoned, but how it should be refined. The accumulated evidence suggests three key principles. First, complete cytoreductive surgery remains the cornerstone of curative-intent treatment in colorectal peritoneal metastases. Without optimal cytoreduction, HIPEC has no role. Second, oxaliplatin-based HIPEC with short exposure duration, as used in PRODIGE 7, should no longer be considered standard practice. Third, HIPEC still has a very strong rationale in terms of drug concentration in the peritoneal cavity, effect-dose and local action on a microscopic disease that systemic chemotherapy sometimes struggles to target. In this light, abandoning HIPEC altogether would represent an overcorrection, one that risks depriving selected patients of a potentially meaningful therapeutic benefit.

While we eagerly await the results of the Spanish GECOP trial, which compares CRS with HIPEC using mitomycin C against CRS alone, we can offer our patients HIPEC based on mitomycin C, in accordance with expert guidance. The question is no longer whether HIPEC has a role, it is whether we are using it wisely.

Section 2:

Direct Injection of Bromac® For Mucinous Peritoneal Carcinomatosis Shows Promise. Demonstration Of Benefit with CRS Is Next.

By Graham J. Stewart, Ahmed Mekkawy, Steven Davis, Sarah J. Valle, David Morris
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Bromelain (a pineapple stem extract) and Acetylcysteine are both mucolytic agents. A purified combination of these agents (BromAc) has a proven synergistic effect resulting in the dissolution of tumour produced mucin as well as cancer cell growth inhibition, both *in vitro* and *in vivo*.

Mucins have several methods of benefitting cancers and are widely found in GI, gynecological, pancreatic, respiratory and hematological cancers. Mucins can act as a barrier to both intraperitoneal and systemic chemotherapy as well as being involved in several intracellular mechanisms. We developed BromAc® to treat

inoperable symptomatic highly mucinous tumours by direct injection by means of CT-guided pigtail drains. There are now 3 published clinical series of its use in this setting, with a total of 40 patients (*Valle SJ, et al. EJSO 2021; 47:115-122; Rodriguez-Ortiz L, et al. BJS 2024;111(3):znae045; Alpeter S, et al. Ann Surg Oncol 2026;33(4):2993-3003*).

The side effects of BromAc direct injections frequently include some pain, fever and CRP rise. A small number of patients have developed perforation/fistula which we attribute to the direct effect of the drug on full thickness bowel wall disease. We sometimes see bowel wall invasion during surgery. Also, perforation can occur with other anti-tumour agents like bevacizumab. If we suspect this, we cease treatment, start IV antibiotics and leave the pigtail in for drainage. All 3 trials have reported high objective response rates, good QOL and surprisingly positive long-term outcomes in some patients. We have one patient at 5 years following repeated treatments.

HIPEC is our most potent treatment for peritoneal cancer but clearly this often fails locally and the use of BromAc® as an intraoperative adjuvant therapy is being investigated. We see good synergy with mitomycin C (MMC), oxaliplatin, 5FU, doxorubicin and gemcitabine. The potentiating effect in HIPEC was investigated by Wajih et al. (*Wajih N, et al. Ann Surg Oncol 2024;31:5337-5389*) using an organoid (PTO) model with cells derived from 16 PC specimens from 13 patients. First confirming the mucolytic effect of BromAc® (with a reduction of about 50% for 60 minutes exposure). BromAc® was then used in our laboratory with HIPEC. It was found that it potentiated cytotoxicity of several HIPEC regimes. This process is mediated through apoptosis and autophagy.

We have also completed a series of rat HIPEC experiments with MMC and BromAc® (*Mekkawy AH, et al. 2025;15(3):1213-1223*), which showed improved burst strength of colonic anastomoses, especially in the presence of BromAc® compared to MMC alone and no toxicity was observed. A phase 1 HIPEC/MMC/BromAc® is awaiting ethics review with the long-term aims of reducing peritoneal recurrence rates and improving survival.

Our phase 2 US/EU trials of BromAc® for direct injection is waiting for GMP manufacturing which has been developed by and will be distributed by ThermaSolutions. Drug development, especially for rare cancers, is a difficult prolonged and very expensive endeavour – any interest/help would be most greatly received and we thank all those who have contributed to date.

Section 3:

CDK4/6 Inhibition with Palbociclib in Advanced Mucinous Appendiceal Neoplasms (Pseudomyxoma Peritonei): Update and Clinical Considerations

By Shumei Kato, MD[1] and Andrew M. Lowy, MD[2]
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Pseudomyxoma peritonei (PMP) arising from mucinous appendiceal neoplasms continues to represent a rare but clinically challenging problem characterized by progressive accumulation of mucinous tumor within the peritoneal cavity. The standard management for eligible patients remains cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC). However, a subset of patients develops recurrent or unresectable disease, often many years after initial definitive treatment, for which current effective systemic therapies remain limited (*Bevan KE et al. Pseudomyxoma peritonei. World J Gastrointest Oncol. 2010*).

Recent translational and clinical work from our group has suggested that inhibition of cyclin-dependent kinases 4 and 6 (CDK4/6) may represent a promising therapeutic strategy in mucinous appendiceal neoplasms with specific molecular features. Palbociclib, an oral CDK4/6 inhibitor widely used in hormone receptor–positive breast cancer, has been investigated in patients with advanced peritoneal mucinous carcinomatosis (PMC), including pseudomyxoma peritonei of appendiceal origin (*Weitz J et al. Cyclin-Dependent Kinase 4/6 Inhibition as a Novel Therapy for Peritoneal Mucinous Carcinomatosis with GNAS Mutations. Journal of Clinical Oncology. 2024. Childers BG et al. Palbociclib as a novel therapy for low-grade mucinous carcinomatosis peritonei of appendiceal origin. JCO Precision Oncology. 2021*).

Biological Rationale

Mucinous appendiceal tumors frequently harbor activating mutations in the *GNAS* oncogene, often in conjunction with *KRAS* mutations, which drive mucin production and tumor growth (*Foote MB et al. Molecular classification of appendiceal adenocarcinoma. J Clin Oncol. 2023. Alakus H et al. Genome-wide mutational landscape of mucinous carcinomatosis peritonei of appendiceal origin. Genome Medicine. 2014*). These molecular alterations promote activation of signaling pathways that influence cell-cycle regulation, particularly cyclin-dependent kinase activity.

Preclinical work using organotypic culture models of mucinous peritoneal tumors demonstrated that tumors with *GNAS* mutations show increased sensitivity to CDK4/6 inhibition, providing a biological rationale for evaluating palbociclib in this disease. These models suggested that targeting cell-cycle progression in this manner could suppress tumor proliferation in mucinous tumors that otherwise exhibit limited responsiveness to cytotoxic chemotherapy.

Clinical Study and Outcomes

A prospective single-institution study evaluated palbociclib in 16 patients with peritoneal mucinous carcinomatosis, most originating from appendiceal primaries and many previously treated with systemic chemotherapy. Three quarters of the patients (12/16) had previous lines of therapy with continued disease progression prior to enrollment. Patients received palbociclib 125 mg orally once daily for 21 days followed by a 7-day break, the standard schedule used in breast cancer therapy.

The study demonstrated encouraging signals of clinical activity:

- Decrease in carcinoembryonic antigen (CEA) was observed in 13 of 16 patients (81%), with >50% reduction in 6 patients (38%).
- Using clinical and modified peritoneal RECIST criteria, 50% of evaluable patients maintained stable disease at 12 months.
- For most patients who had prior therapy, PFS was significantly longer after receiving palbociclib than on their prior line of therapy
- At a median follow-up of approximately 17.6 months, median overall survival had not yet been reached.
- The estimated 1-year progression-free survival rate was approximately 56%, with 1-year overall survival around 81%.

Importantly, clinical responses correlated with tumors harboring *GNAS* mutations and mucinous histology, supporting the translational findings linking these molecular features to sensitivity to CDK4/6 inhibition. Overall, outcomes appeared more favorable than those historically reported with conventional systemic chemotherapy for this disease.

Patient Selection

Based on current experience, several factors may help identify patients most likely to benefit from palbociclib therapy:

1. ***Molecular profile***
   Patients with *GNAS*-mutant tumors, particularly in combination with mucinous histology, appear most likely to respond. Molecular profiling using tissue or liquid biopsy is therefore recommended when considering this treatment approach.
2. ***Disease biology***
   Patients with low-grade mucinous disease and indolent progression may derive particular benefit from a cytostatic agent such as palbociclib, which tends to stabilize disease rather than induce rapid tumor shrinkage.

3. ***Recurrent or unresectable disease***

   Palbociclib may be considered in patients with recurrent disease following CRS/HIPEC or those with unresectable peritoneal disease not amenable to further cytoreduction.

4. ***Limited chemotherapy options***

   Systemic chemotherapy generally has modest activity in mucinous appendiceal tumors, making targeted approaches attractive in the palliative setting.

Toxicity Profile

The toxicity profile of palbociclib in this population appears consistent with its known safety profile in breast cancer. The most common adverse events include:

- Neutropenia, which is usually manageable with dose adjustments or treatment delays
- Fatigue
- Mild gastrointestinal symptoms
- Anemia or thrombocytopenia (less common)

Importantly, febrile neutropenia is uncommon, and the drug is generally well tolerated in patients with indolent disease requiring long-term therapy. Because palbociclib is an oral therapy with an excellent adverse event profile, it offers a convenient outpatient treatment option compared with intravenous chemotherapy.

Cost and Availability

Palbociclib is an FDA-approved drug with widespread availability in many countries for breast cancer indications. Its use in pseudomyxoma peritonei remains off-label, which may present reimbursement challenges depending on local healthcare systems and insurance coverage.

In the United States, we have found that access is often possible through standard prescribing pathways when molecular rationale and supporting literature are provided to third party payors. Notably, patients in the Veterans Administration healthcare system can more readily access this treatment simply by their oncologist prescribing it. In other healthcare systems, use may require institutional approval, compassionate access programs, or participation in clinical studies.

Given the rarity of appendiceal tumors and PMP, collaboration between specialized centers and the development of registry-based outcomes may help further clarify the clinical utility of CDK4/6 inhibition in this setting.

Practical Considerations

For clinicians considering palbociclib (or other CDK4/6 inhibitors) in patients with advanced mucinous

appendiceal neoplasms, several practical points are worth noting:

- Baseline molecular testing for GNAS mutations is recommended.
- Monitoring should include periodic complete blood counts, especially during early cycles.
- Tumor markers such as CEA or CA19-9 may serve as supporting indicators of response in some patients.
- Radiographic evaluation may be challenging in mucinous peritoneal disease, and clinical assessment of symptoms and tumor markers may complement imaging findings. Remember this is a cytostatic agent and so objective RECIST or mpRECIST responses are not expected.

This given the indolent nature of many PMP cases, durable disease stabilization may represent a meaningful clinical benefit.

Future Directions

While the current data are promising, further investigation is needed to better define the role of CDK4/6 inhibition in mucinous appendiceal neoplasms. Potential areas of interest include:

- Prospective multicenter trials evaluating CDK4/6 inhibitors in PMP
- Identification of predictive biomarkers beyond *GNAS* mutation
- Combination strategies incorporating targeted therapies or immunotherapy
- Integration with surgical approaches in selected patients

Such studies will be essential to confirm the preliminary efficacy signals observed in early clinical experience.

Conclusions

CDK4/6 inhibition with palbociclib represents a new, promising therapeutic strategy for patients with advanced mucinous appendiceal neoplasms and pseudomyxoma peritonei, particularly those harboring *GNAS* mutations. Early clinical data suggest that palbociclib can produce meaningful reductions in tumor markers and durable disease stabilization in a subset of patients with otherwise limited systemic treatment options.

Although further prospective studies are needed, palbociclib may be considered as a rational off-label therapy in carefully selected patients with recurrent or unresectable disease. Continued collaborative research through international networks such as PSOGI will be critical to refine patient selection, optimize treatment strategies, and improve outcomes in this rare malignancy.

Section 4:

Neoadjuvant Systemic Chemotherapy Before Cytoreductive Surgery of Appendiceal and Colorectal Peritoneal Metastases: Not A Simple Decision

By Lana Bijelic, MD, FACS

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A multimodal approach to treatment of patients undergoing cytoreductive surgery for peritoneal metastases of colorectal and high grade appendiceal carcinoma includes both local treatment i.e. cytoreductive surgery, as well as systemic chemotherapy. This is the usual practice in most countries based on numerous published guidelines. This is logical, especially in tumors with a high risk of systemic spread as well as peritoneal spread, such as colon cancer. It has also become frequent practice to administer part or all of the planned chemotherapy in a neoadjuvant fashion, prior to cytoreductive surgery. In fact, in the well-known PRODIGE-7 clinical trial that examined the potential benefits of oxaliplatin-based abbreviated HIPEC added to cytoreductive surgery, approximately 80% of enrolled patients received systemic chemotherapy before cytoreductive surgery. The role of neoadjuvant chemotherapy is well established in other tumors, especially those with a high response rate to systemic chemotherapy, such as Her-2 positive breast cancer or high-grade serous ovarian cancer. In these diseases it may positively impact the extent of surgery and allow organ preservation.

However, for peritoneal surface malignancy surgeons treating colorectal and high-grade appendiceal carcinomatosis the question is: Does neoadjuvant chemotherapy bring clearly recognizable benefits and should it be widely implemented for the majority of patients diagnosed with peritoneal metastases? The potential advantages that neoadjuvant chemotherapy offer are numerous. If these theoretical advantages unequivocally translate into improved outcomes, the response to the above question would be quite easy. First, among the theoretical benefits is earlier treatment of occult systemic disease which should then translate into fewer systemic relapses and better survival. Second, a theoretical reduction of peritoneal tumor burden should facilitate subsequent surgery making it less extensive and therefore less morbid and, at the same time, increase our ability to achieve complete cytoreduction. Finally, the use of neoadjuvant chemotherapy can sometimes serve as a biological test of tumor aggressiveness. This helps us select patients that should proceed to cytoreductive surgery versus those that are likely to show early progression and would, therefore, be less likely to benefit from a major surgical intervention.

For patients who show evidence of strong response to neoadjuvant chemotherapy, the majority of these potential benefits are confirmed. In a cohort of patients with high-grade appendiceal cancers and peritoneal metastases, both mucinous and non-mucinous, we showed that almost 1/3 of patients did have clear histologic evidence of

response, and a small percentage (3/34) even reached complete histologic response. This robust response correlated with reduced tumor burden and better outcomes (*Sugarbaker PH, et al. J Surg Oncol 2010;102:576–581*). However, currently we are unable yet to predict which patients will objectively respond to neoadjuvant chemotherapy. Therefore, we must analyze the results on an intention-to-treat basis, looking for benefit from the entire cohort of patients that received neoadjuvant chemotherapy.

A review of the available studies, both for colon cancer as well as high-grade appendiceal cancer give us a considerable amount of concern regarding actual benefits, or lack of benefits, derived from neoadjuvant chemotherapy. In a large multi-institutional study of 803 patients with high-grade appendiceal cancers that excluded all types of mucinous histologies in whom response to systemic chemotherapy is usually inferior, patients treated with neoadjuvant chemotherapy had worse survival compared to those who underwent upfront surgery. The intraoperative PCI, operative time and percentage of complete cytoreductions were also not improved by neoadjuvant chemotherapy. These results did not change significantly after propensity score matching. The authors concluded that upfront surgery should be preferred to neoadjuvant chemotherapy in all patients with non-mucinous appendiceal carcinomatosis who are thought to have resectable disease and are candidates for cytoreductive surgery (*JC Chen, et al. J Surg Oncol 2020 Sep;122(3):388-398*).

It should not surprise us that similar conclusions were drawn by the team at Mercy Hospital in Baltimore regarding the role of preoperative chemotherapy in high-grade mucinous carcinoma peritonei, with or without signet ring cells. After analyzing outcomes of 140 patients, they concluded that systemic chemotherapy prior to surgery was not associated with less disease burden, better cytoreduction rates, or improved clinical outcomes, regardless of whether signet ring histology was present or not (*Carlos A. Munoz-Zuluaga, et al. Eur J Surg Oncol 2019 Sep;45(9):1598-1606*).

When it comes to colorectal peritoneal metastases, numerous retrospective studies have examined this question but similarly to appendix cancer results, failed to consistently show a benefit. An interesting report from St. George's Hospital in Sydney, Australia describing outcomes in 326 colorectal carcinomatosis patients treated with cytoreductive surgery showed no survival advantage and similar perioperative outcomes between patients treated with neoadjuvant chemotherapy and those who went straight to surgery. Interestingly, among patients with high-volume carcinomatosis, defined as PCI >16 (median 20), survival was significantly worse in patients who received neoadjuvant chemotherapy (*Sarofim et al, World J Surg Oncol (2024) 22:103*). The Netherlands' group took the question a step further and analyzed in a systematic review the evidence related to systemic chemotherapy used in association with cytoreductive surgery for colorectal peritoneal metastases in any form, neoadjuvant, adjuvant or perioperative. They were able to include 12 studies. They concluded that the role of neoadjuvant, adjuvant, and perioperative systemic chemotherapy in patients with resectable colorectal peritoneal metastases remains unclear as the evidence was weak and often contradictory across the included studies. In fact, the standard of care in the

Netherlands, at least until now, did not include any form of systemic chemotherapy for patients undergoing cytoreductive surgery for colorectal peritoneal metastases.

This leads us to the only available prospective, randomized clinical trial that aimed to analyze the role of perioperative systemic chemotherapy in patents undergoing cytoreductive surgery for colorectal cancer. It is important to point out that the study did not only analyze the role of neoadjuvant chemotherapy (versus adjuvant or perioperative for example) but, even more boldly asked whether the addition of any systemic chemotherapy was better than cytoreductive surgery alone. This fascinating Dutch study (CAIRO 6) was recently presented in abstract form and offers important revelations that require careful analysis and interpretations once the full paper is published. The study randomized 358 patients and had overall survival as the primary endpoint. Interestingly, at a median follow-up of 41 months, median and 3-year overall survival were 44 months and 54% in the perioperative systemic therapy group and 39 months and 53% in the surgery alone group, respectively (HR for death 0.85, 95% CI 0.62-1.15, p=0.28). The conclusion therefore was that perioperative systemic therapy did not result in superior overall survival as compared to cytoreductive surgery-HIPEC alone. In a secondary endpoint, median and 3-year progression-free survival were better in the preoperative systemic chemotherapy group: 13.5 months and 20% versus 7.0 months and 5% in the surgery alone group, respectively (HR for progression or death 0.51, 95% CI 0.41-0.65) but the 90-day morbidity was worse in the systemic chemotherapy group (*Rovers et al, J Clin Oncol 43, 3505, 2025*).

What should our overall attitude be in choosing to use or not to use neoadjuvant chemotherapy prior to cytoreduction for high-grade appendiceal and colorectal cancer patients with peritoneal metastases? It is clear that the outcomes of cytoreductive surgery are positive. It should be emphasized and offered to all patients who are reasonable candidates for surgery. It is incumbent on the expert surgical oncologists to advocate for surgery in appropriately selected patients rather than accept that systemic chemotherapy first is always the default approach. On the contrary, the addition (or not) of systemic chemotherapy has to be a more nuanced and individualized decision, based on the fact that the evidence is inconclusive and even points against preoperative chemotherapy use in some groups of patients. Prior to initiating neoadjuvant chemotherapy in patients that have resectable peritoneal disease of appendiceal or colorectal origin we should ask ourselves what specific goals we are hoping to achieve, how likely we are to achieve them and what are the associated risks.

Section 5:

From Postoperative Adjuvant Intraperitoneal Chemotherapy to Preoperative Neoadjuvant Intraperitoneal Chemotherapy in Colorectal Peritoneal Metastases

By Peter H. Cashin
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For colorectal cancer peritoneal metastases (CRC-PM), the Swedish randomized trial remains uniquely important because it demonstrated something that is still underappreciated today: regional therapy can benefit a regional disease compartment, even without systemic chemotherapy in the experimental arm (*Cashin PH, Mahteme H, Spång N, et al. Eur J Cancer. 2016;53:155-162*). In that study, patients with colorectal peritoneal metastases were randomized to either systemic chemotherapy alone or cytoreductive surgery (CRS) combined with adjuvant normothermic postoperative repeat intraperitoneal chemotherapy for 6 months (6 cycles). The surgical arm did not receive systemic chemotherapy as part of treatment, yet outcomes favored the regional treatment strategy. That finding is more than historical – it provides proof of concept that peritoneal disease may, at least in selected patients, be better controlled by a treatment strategy directed primarily at the peritoneal compartment (*Cashin PH, Mahteme H, Spång N, et al. Eur J Cancer. 2016;53:155-162*).

This point matters because colorectal peritoneal metastases are biologically and therapeutically distinct from hematogenous metastatic disease. Small peritoneal tumor deposits, mucinous lesions, and poorly vascularized implants may be relatively protected from systemically delivered drugs. Intraperitoneal chemotherapy addresses this problem directly by exposing the peritoneal surfaces to high locoregional drug concentrations. At the same time, intraperitoneally delivered chemotherapy is not purely regional. In repeat IP administration, drug that is not absorbed into peritoneal implants and periperitoneal tissues is taken up into the portal and systemic circulation, thereby allowing treatment not only of residual peritoneal disease but also of microscopic circulating or occult disease outside the immediate peritoneal surface. The Swedish experience therefore supports a broader therapeutic principle. Regional chemotherapy may have an advantage in peritoneal metastases precisely because it is regionally intensified while also providing systemic exposure through gradual uptake from the peritoneal compartment into the circulation.

The utility of postoperative repeat IP therapy was clear. Instead of limiting regional therapy to a single intraoperative exposure, repeat IP therapy allowed numerous treatments of the compartment at highest risk for recurrence. In addition to long-term oncologic efficacy, quality of life and cost-effectiveness have also supported this approach (*Cashin PH, Mahteme H, Syk I, et al. Eur J Surg Oncol. 2018 Jul;44(7):983-990*).

However, postoperative IP therapy also revealed an important practical limitation: the biology was appealing, but the timing was not ideal. Delivering repeated IP therapy after major cytoreductive surgery is technically and

logistically difficult. Adhesion formation, postoperative recovery, catheter-related problems, and patient tolerance all interfere with the completion of the intended course. In the Swedish experience, only about 40% of patients completed all six planned cycles, and the difficulty of delivering full treatment after surgery became one of the major barriers to broader implementation (*Cashin PH, Mahteme H, Spång N, et al. Eur J Cancer. 2016;53:155-162*). This has also been demonstrated in ovarian cancer as well, where postoperative IP therapy can be difficult to administer successfully, with similarly reduced numbers of completed IP cycles (*Armstrong DK, Bundy B, Wenzel L, et al. N Engl J Med. 2006 Jan 5;354(1):34-43*).

This is exactly why peritoneal surface malignancy treatments should now shift focus from postoperative adjuvant repeat IP therapy to neoadjuvant repeat IP therapy before CRS. The neoadjuvant setting offers several advantages. First, the abdominal cavity is usually more accessible before extensive surgery and before surgically induced adhesions compromise drug distribution. A port can be placed laparoscopically, treatment can begin in a less hostile intraperitoneal environment, and repeated drug delivery is likely to be more feasible than after peritonectomy and visceral resections. Second, preoperative intraperitoneal therapy allows us to treat the disease compartment that most determines future resectability. If tumor burden on the peritoneal surfaces can be reduced before surgery, later CRS may become less extensive, more complete, and potentially safer. Conversion to a lower peritoneal cancer index may itself facilitate a more effective cytoreduction and improve the likelihood of complete macroscopic tumor clearance.

This neoadjuvant logic is strengthened by two ongoing initiatives – the Japanese iPac-1 and iPac-2 trials and the Dutch INTERACT trial. In the Japanese initiative, patients with unresectable colorectal peritoneal metastases receive FOLFOX/CAPOX plus bevacizumab together with IP paclitaxel as first-line treatment. The phase I study has been published, and the phase II study is ongoing (*Murono K, Yokoyama Y, Nozawa H, et al. Int J Colorectal Dis. 2023 Jun 20;38(1):173*). The second initiative comes from the Netherlands, also in unresectable colorectal peritoneal metastatic disease. In this program, patients receive FOLFOX plus bevacizumab with IP irinotecan. In almost synchronized fashion, the INTERACT phase I study has been completed and the phase II study is now ongoing (*van de Vlasakker VCJ, Guchelaar NAD, van den Heuvel TBM, et al. BMJ Open. 2024 Jan 18;14(1):e077667*).

In a similar manner, Sweden is now stepping up to the plate, and a new initiative, the COLOVERT trial, has just received funding. Building on previously published phase I trials of different IP therapies, COLOVERT starts with a randomized phase II "pick-the-winner" design. Both borderline resectable and unresectable patients may be included. In the first experimental arm, patients will receive backbone therapy with systemic capecitabine and bevacizumab combined with IP irinotecan. In the second experimental arm, a novel chemotherapy sensitivity assay will be used to select between eight candidate drugs for IP therapy, combined with the same backbone therapy of capecitabine and bevacizumab. First patient inclusion is currently planned for the third quarter of 2026.

Looking ahead, neoadjuvant repeat combined IP and systemic therapy has the potential to become a promising new modality for improving survival in colorectal cancer patients with peritoneal metastases. By moving repeated regional therapy to a time point when treatment delivery is more feasible, while simultaneously taking advantage of both locoregional intensification and systemic uptake, this strategy may improve downstaging, increase conversion to effective CRS, and ultimately enhance long-term outcomes. If ongoing and upcoming trials confirm these expectations, neoadjuvant repeat intraperitoneal chemotherapy may emerge as an important bridge between systemic therapy and curative-intent surgery in CRC-PM.

Section 6:

Intraperitoneal Paclitaxel: A Promising Treatment for Appendiceal Adenocarcinoma

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Appendiceal tumors have historically been treated with chemotherapy designed for colorectal cancer (CRC) based primarily on the fact that the appendix is anatomically near to the colon and both tissues share a CDX2 promoter lineage. However, recent studies have generated a clear consensus that appendiceal adenocarcinoma (AA) is a clinically and molecularly distinct entity from CRC. Convincingly negative data showing no benefit to 5FU-based chemotherapy, the mainstay treatment for CRC, for patients with low-grade AA from a prospective, randomized phase 2 clinical trial with crossover design (NCT01946854) motivated us to develop AA specific treatments so that we could put an end the practice of blindly using CRC chemotherapy for patients with AA.

Taxane chemotherapy, known to be active in upper GI tumors as well as small bowel adenocarcinoma, but not CRC, was not previously tested in patients with appendix cancer. Observing that AA in many aspects bears more similarity to gastric cancer than CRC, given its propensity for intraperitoneal metastasis and a low incidence of *APC* mutation, we hypothesized that taxanes would be active in AA. To test this hypothesis, we first conducted a retrospective pilot study in 13 patients with high-grade AA. In this heavily pre-treated population (median of 3 prior lines of therapy) there was an encouraging response rate of 30% and disease control rate of 70% to a mix of taxane combinations including line carboplatin + paclitaxel, gemcitabine + nab-paclitaxel, as well as single agent paclitaxel (*Dansby J, et al. Oncologist 28, e1303-e1305 (2023).* https://doi.org/10.1093/oncolo/oyad263). Since the publication of that study, we have treated more than 30 additional patients with AA with taxane regimens at our institution and have seen a similar response rate.

At the same time as our clinical investigation of taxane activity and recognizing that a lack of pre-clinical models was limiting drug development in appendix cancer, we started a systematic program to generate cell line, organoid, patient derived xenograft (PDX) and Genetically Engineered Mouse (GEM) models of AA. This effort, aided by collaborators from the University of Olso, led to the generation of multiple orthotopic PDX models of peritoneal metastasis from AA that captured key elements of the peritoneal microenvironment (*Pattalachinti VK, et al. MCR 22, 329-336 (2024).* https://doi.org/10.1158/1541-7786.mcr-23-0749). Using these orthotopic PDX allowed us to test our hypothesis that intraperitoneal (IP) administration of chemotherapy would be more effective that intravenous (IV) for the treatment of AA. IP administration is attractive given that AA very rarely spreads beyond the peritoneal space, and most complications from AA, such as bowel obstruction, are a result of progressive peritoneal disease. There is also significant concern that systemic therapies are not effective in peritoneal metastases given the relatively avascular nature of these tumors and the abundant presence of mucin in most appendiceal tumors. IP paclitaxel was an obvious first choice to test given its high molecular weight (853.9 g/mol) and its highly lipophilic/hydrophobic nature that prolongs retention in the peritoneal cavity, limiting exposure to tissues such as the bone marrow and liver. Additionally, there is a long history of IP paclitaxel use in the treatment of peritoneal carcinomatosis from ovarian and gastric cancer, including combinations with IV therapies (often called bidirectional treatment). We observed dramatic tumor reduction with single agent paclitaxel in all three orthotopic AA PDX models at doses ranging between 12.5 to 25 mg/kg IP weekly, with a near complete response in model PMP-2 (*Ito I, et al. Cancer Research 83, 3184-3191 (2023).* https://doi.org/10.1158/0008-5472.can-23-0013). Notably in addition to being more efficacious than IV delivery, IP delivery was also less toxic as measured by loss of body weight.

Based on the excellent response seen with IP paclitaxel in PDX models of AA we designed a prospective Phase 1/2 study of IP paclitaxel that is currently open and enrolling at MD Anderson (NCT06207305). The first patient was treated in April of 2024 and thus far 14 patients have been enrolled. The Phase 1 (dose finding) portion of the trial has been completed with a dose of 75 mg/m^2 given biweekly determined as the recommended Phase 2 dose; notably this was the minus 1 dose level. At the initial dose level of 100 mg/m^2 biweekly, which was well tolerated in a Phase 2 study of gastric cancer patients (NCT04220827), we observed one bowel perforation as well as one admission due to post infusion abdominal pain. Initial response looks promising with 6 of 8 patients with elevated serum tumor markers showing a significant decrease in those values and direct visualization of tumors during laparoscopy showing signs of treatment response. This is especially encouraging given the amount of chemotherapy given to these patients prior to IP paclitaxel treatment (median 2.6 prior lines of therapy, average of 18.7 months after start of systemic treatment). Interestingly we have also observed signs

and symptoms of inflammatory response after IP paclitaxel infusion including post-infusion pain (largely relieved with NSAIDS such as Toradol and ibuprofen) and elevated inflammatory markers. Performing scRNAseq analysis of cells from peritoneal washing pre- and post-IP paclitaxel treatment we found that the Mononuclear phagocytes population (MNPs, monocytes, macrophages and dendritic cells) changed with upregulation of MERTK, CD226, ABCA1, ABCG1 and downregulation of SPP1 consistent with improved phagocytic activities consistent with a tumor microenvironment (TME) that may be more responsive to immune activating therapies.

The potential for synergy between paclitaxel with immune therapy is particularly promising given the recent positive Phase II study of Atezolizumab (anti-PDL1 antibody) and bevacizumab (anti-VEGF antibody) in patients with metastatic mucinous AA (NCT03074513). Atezo+Bev significantly improved PFS relative to SOC control (18.3 vs. 4.6 months, HR = 1.9, p = 0.041) in a cohort of patients with mostly well or moderately differentiated tumors (*Hornstein NJ, et al. Cancer Res Commun 4, 1363-1368 (2024).* *https://doi.org/10.1158/2767-9764.CRC-24-0019*). Given the favorable toxicity profile, with no grade 4/5 events and no patients requiring treatment discontinuation due to side-effects, Atezo-Bev has now become a standard of care treatment option particularly for patients with low-grade tumors. Performing a RWE analysis using time-on-treatment (TOT) as a surrogate for PFS we found that patients with high-grade tumors (grade 2 and higher) had much faster progression relative to low-grade (24.8 vs. 4.1 months, HR=2.3, p=0.036). The lack of response to Atezo+Bev alone in high-grade tumors combined with the efficacy and immune stimulation seen with IP paclitaxel in these tumors was the rationale for a soon to open study of IP paclitaxel in combination with Ivonescimab (Summit Therapeutics). Ivonescimab is a novel first-in-class humanized, tetravalent bi-specific antibody targeting PD-1 and VEGF. We expect this study will open to enrollment in the summer of 2026.

KRAS inhibition is another promising future combination with IP paclitaxel and/or immune therapy. We have recently demonstrated that single agent KRAS inhibition is active in organoid and PDX models of AA causing apoptosis in tumor cells and also influencing TME interactions (*Shen JP, et al. Cancer Research 86, B024-B024 (2026).* *https://doi.org/10.1158/1538-7445.rasoncother26-b024*). These data as well as clinical data from other lineages including pancreas and CRC suggest that combining KRAS inhibition could have a synergistic effect with both cytotoxic chemotherapy and ICB for patients with AA.

Section 7:

Precision Oncology in an Era of Emerging Cancer Tissue Engineering: Patient-Derived Organoids and the Redefinition of Oncologic Drug Sensitivity Testing

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For as long as oncology has existed as a discipline, its most consequential failure has not been the absence of effective drugs – it has been the inability to know, before treatment begins, which drug will work for *this* patient's tumor. Cancer has been treated as a population problem: define a histology, conduct a trial, establish a regimen, apply it broadly. This approach has produced meaningful advances – and consigned generations of patients to treatments that were statistically justified but often individually wrong, with toxicity borne by tumors resistant from the first cycle. The aspiration of precision oncology has long exceeded our technical capacity to fulfill it. That gap is closing – through molecular sequencing, multi-omic tumor profiling, and the molecular characterization of individual cancer biology. Yet molecular knowledge alone cannot tell us how a living tumor will behave when confronted with a specific drug. The platform that bridges genomic understanding and functional drug response – translating the molecular portrait of a patient's tumor into an actionable, real-time pharmacotypic readout – is the patient-derived organoid.

From Monolayers to Organoids: A Revolution in Preclinical Modeling

The history of in vitro cancer modeling is a history of progressive approximation – each generation of platforms moves closer to biological truth, yet each is constrained by what it could not replicate. Two-dimensional cell line culture reduced tumor complexity to monolayers of clonally selected cells drifting from their tissue of origin with every passage (**Figure 1**). Tumor spheroids – three-dimensional aggregates grown in suspension – advanced the field by restoring spatial architecture, but lacks patient-specific stromal components, excludes the immune microenvironment that governs therapeutic response, and models a tumor type rather than a patient's tumor. Patient-derived organoids (PDOs) are categorically different. Biofabricated directly from a patient's own surgically resected or biopsy-derived tumor tissue – without cell sorting, without xenogeneic growth factors, without genetic drift – PDOs preserve architectural heterogeneity, stromal composition, and cellular diversity in three-dimensional extracellular matrix constructs available within days. When autologous immune cells from matched lymph node or peripheral blood are incorporated, the resulting immune-enhanced construct – the iPTO – reconstitutes the tumor-immune microenvironment at the individual patient level, enabling simultaneous interrogation of chemo- and immunosensitivity in a single, patient-specific platform.

Figure 1.
Evolution of Preclinical Drug Sensitivity Testing Platforms in Oncology: From Monolayer Culture to Immune-Enhanced Patient-Derived Organoids

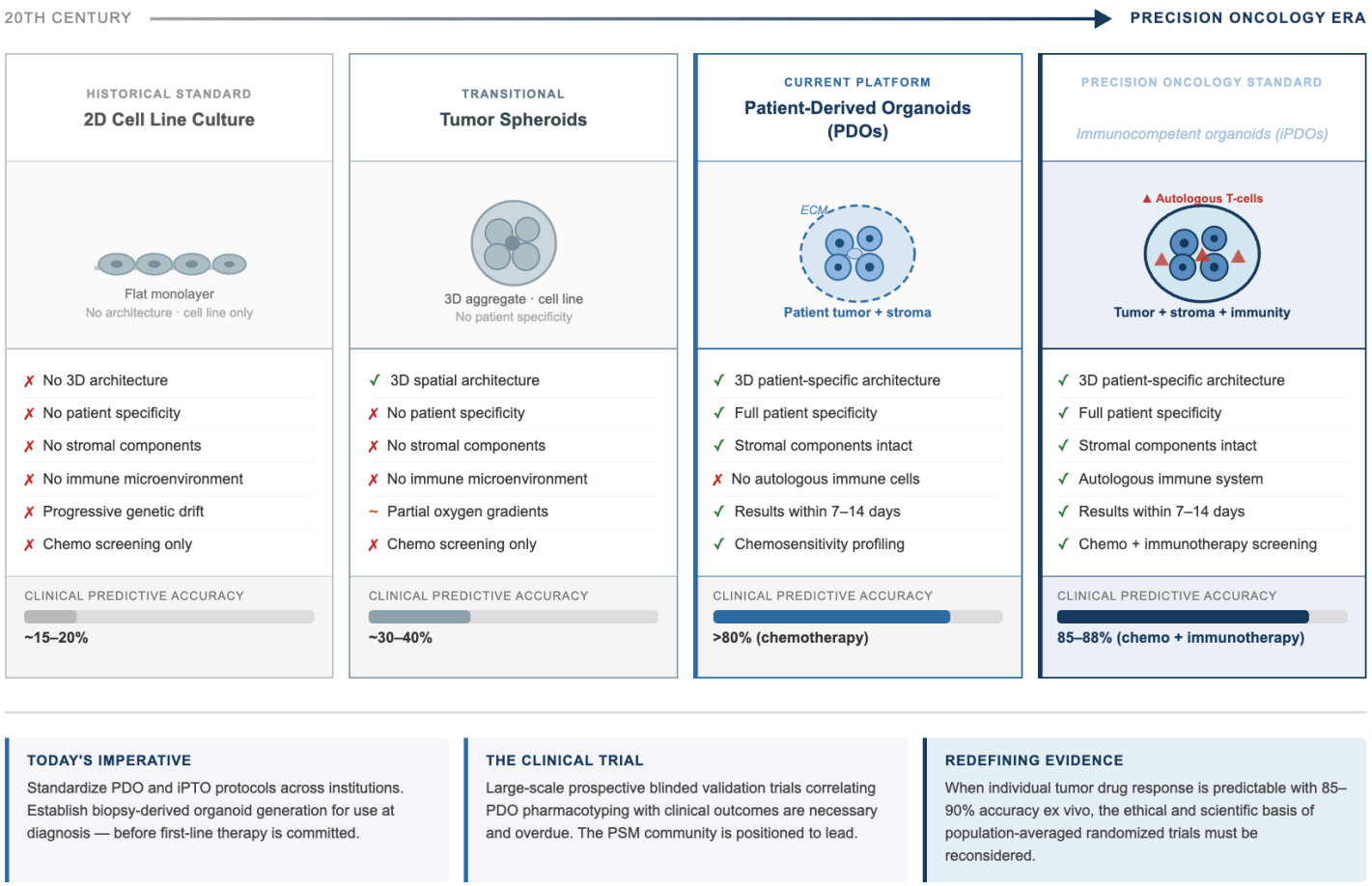

Figure 1. Evolution of preclinical drug sensitivity testing platforms from two-dimensional (2D) cell line culture to immune-enhanced patient-derived organoids (iPTOs). Two-dimensional monolayer cultures and tumor spheroids, while historically foundational, lack patient specificity and the immune microenvironment critical for predicting therapeutic response. Patient-derived organoids (PDOs) — biofabricated from individual patient tumor specimens without cell sorting or xenogeneic growth factors — preserve tumor heterogeneity and stromal composition, achieving chemotherapy predictive accuracy exceeding 80%. Immune-enhanced PDOs (iPTOs) incorporate autologous lymphocytes and peripheral blood mononuclear cells, reconstituting the tumor-immune microenvironment and enabling simultaneous chemosensitivity and immunosensitivity profiling with 85–88% clinical accuracy. Red triangles (iPTO panel) denote infiltrating autologous T-cells. **Abbreviations:** ECM, extracellular matrix; iPTO, immune-enhanced patient tumor organoid; PDO, patient-derived organoid; PSM, peritoneal surface malignancy.

The Reckoning with Animal Models

The parallel reckoning is with animal models – and it is now institutional. For six decades, the mouse served as oncology's primary surrogate for human tumor biology. The translational record is unambiguous: greater than 95% of oncologic agents demonstrating efficacy in murine models fail in human clinical trials. The biological distance between rodent and human tumor microenvironments – in immune composition, stromal architecture, and drug metabolism – is too great to bridge reliably. The National Institutes of Health has recognized this and is actively redirecting research investment away from animal models toward human-relevant platforms including organoids and organ-on-chip systems. This is not a policy adjustment. It is an institutional acknowledgment that the preclinical modeling paradigm of the 20th century is scientifically incompatible with the precision oncology demands of the 21st century.

Proof of Concept: From the Operating Room to the Bench

The proof-of-concept work has advanced rapidly across multiple fronts. In peritoneal surface malignancies — where CRS/HIPEC provides routine access to tumor specimens of exceptional quality — the organoid platform found an early and natural home. Prior work has demonstrated that appendiceal cancer PDOs generated directly from CRS/HIPEC specimens faithfully recapitulated individual patient chemosensitivity profiles, identifying differential drug efficacy across patients sharing the same histologic diagnosis and regimen (*Votanopoulos KI, Mazzocchi A, Sivakumar H, et al. Ann Surg Oncol. 2019;26:139–147*). Additional work subsequently demonstrated that immune-enhanced iPTOs predicted immunotherapy response with 85% clinical accuracy in melanoma — and, in appendiceal cancer where immunotherapy trial data are essentially nonexistent, showed measurable checkpoint inhibitor efficacy at the individual patient level, with pembrolizumab reducing organoid viability below 15% in responding high-grade tumors (*Votanopoulos KI, Forsythe S, Sivakumar H, et al. Ann Surg Oncol. 2020;27:1956–1967; Forsythe SD, Sasikumar S, Erali RA, et al. Ann Surg Oncol. 2021*). Beyond PSM, Ooft and colleagues demonstrated prospectively that PDOs from metastatic colorectal cancer biopsies predicted irinotecan response in over 80% of patients (*Ooft SN, Weeber F, Dijkstra KK, et al. Sci Transl Med. 2019;11:eaay2574*), while Tiriac and colleagues established multi-institutional organoid pharmacotyping as a predictor of chemotherapy response in pancreatic cancer (*Tiriac H, Belleau P, Engle DD, et al. Cancer Discov. 2018;8:1112–1129*). These findings collectively establish PDO pharmacotyping as a validated, histology-agnostic platform ready for its next phase.

Standardization: The Bridge to Standard of Care

Proof of concept is not standard of care. PDO technology currently exists in institutional heterogeneity: variability in extracellular matrix platforms, culture conditions, drug protocols, and viability benchmarks limits cross-institutional comparisons. Just as flow cytometry and next-generation sequencing required standardization before broad clinical adoption, PDO pharmacotyping requires a universal framework built on four principles — feasibility, fidelity, functionality, and frugality — ensuring high establishment success rates, preservation of the tumor microenvironment, actionable turnaround times, and cost structures enabling universal access. The critical frontier is the biopsy-derived organoid. Surgical specimens are available only at operative intervention, limiting the current platform to patients undergoing resection. The decade ahead must be defined by establishing PDO generation from core needle biopsies at clinically acceptable success rates and within decision-compatible timeframes — transforming PDO pharmacotyping from a perioperative tool into a universal diagnostic tool available at the moment of diagnosis. For PSM patients, the implications are immediate: HIPEC agent selection, systemic regimen design, and immunotherapy or immunomodulation eligibility could be driven by individual tumor biology tested ex-vivo before any treatment begins.

The Clinical Trial Imperative – and a New Architecture of Evidence

Large-scale prospective clinical validation of PDO-guided therapy is both necessary and overdue. The field requires its definitive trial – prospective, blinded, multi-institutional – correlating pharmacotyping predictions with clinical outcomes at a scale sufficient for regulatory and payer recognition. This is not optional; it is the scientific obligation of the organoid community. The PSM community, with its tradition of multi-institutional collaboration and access to large surgical cohorts, is ideally positioned to lead this effort. Yet we must be simultaneously honest about what success in that trial would mean for the broader architecture of oncologic evidence. The classical randomized controlled trial is built on the assumption that we cannot predict individual drug response – and must therefore randomize populations and measure averages. PDO pharmacotyping directly challenges that assumption. If a platform can predict with 85–90% accuracy whether this patient's tumor will respond to this agent, the ethical and scientific justification for randomizing that patient to a potentially ineffective arm – with attendant toxicity, cost, and lost time – becomes increasingly indefensible. This is not an argument against rigor. It is an argument for a new architecture of evidence: PDO-stratified adaptive trial designs, pharmacotypically enriched cohort studies, and regulatory frameworks recognizing organoid-based predictive validity as an independently actionable endpoint.

Conclusions

We stand at a genuine inflection point. Patient-derived organoids have emerged as the most biologically faithful and clinically versatile preclinical platform for drug sensitivity testing across virtually every solid tumor histology – superseding spheroids in fidelity, outperforming animal models in translational accuracy, and extending through the iPTO architecture into the immunotherapy and immunomodulation era. The agenda ahead is clear: standardize the technology, establish biopsy-derived organoid generation as a peridiagnostic tool, conduct the prospective validation trials the field requires, and build the regulatory framework for an evidence paradigm designed for individual patients rather than average populations. The peritoneal surface malignancy community – with its surgical access to tumor specimens, its culture of translational innovation, and its history of driving the most meaningful advances in regional cancer therapy – has a unique obligation to lead this transformation. The patients we operate on today deserve more than statistical probability. They deserve a treatment plan derived from the biology of their own tumor. The tools to provide that are, for the first time, within reach.

Section 8:

Is HIPEC Indicated for Index Cytoreduction and for Reoperative Surgery in Pseudomyxoma Peritonei Patients?

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Biological constraints to chemotherapy

The role of hyperthermic intraperitoneal chemotherapy (HIPEC) in pseudomyxoma peritonei (PMP) has long been debated, largely due to the unique biological characteristics of this disease. PMP is widely recognized as a tumor with intrinsic resistance to systemic chemotherapy, raising concerns about the effectiveness of any chemotherapeutic strategy, including intraperitoneal delivery.

Several biological features underpin this resistance. PMP—particularly in its low-grade form—is characterized by very low cellular proliferative activity, with Ki-67 indices typically below 5% (Yan F, Shi F, et al. J Int Med Res. 2021 Jun;49(6):03000605211022297). Because cytotoxic agents primarily target actively dividing cells, this low proliferative activity inherently limits chemotherapy efficacy. This paradigm is well established across oncology, where low proliferative tumors tend to be less responsive to treatment (Chatzkel J, Lewis JS, Ley JC, et al. Head and Neck Pathol. 2017 Sep;11(3):338–45; Narendra RN, Vijayakumar C, Haritha G, et al. Cureus. 2025 Apr 29).

In addition, PMP is defined by abundant extracellular mucin production, which profoundly alters the tumor microenvironment. Mucin acts as a physical barrier, limiting drug penetration and reducing effective drug concentrations at the cellular level. Tumor cells are sparsely distributed within mucin pools, further diminishing drug–cell interaction. Combined with poor vascularization, this results in a microenvironment characterized by low cellularity, hypoxia, and impaired drug delivery, all of which contribute to treatment resistance (Chen C, Patel A, Demirkhanyan L, Gondi CS. CIMB. 2025 May 29;47(6):406; Kusamura S, Busico A, Conca E, et al. Biomedicines. 2023 Jul 20;11(7):2049).

Finally, PMP exhibits a high prevalence of KRAS mutations, reported in up to 89% of cases. These alterations lead to constitutive activation of survival pathways and may reduce the pro-apoptotic effects of chemotherapy, further contributing to chemoresistance (Kusamura S, Busico A, Conca E, et al. Biomedicines. 2023 Jul 20;11(7):2049; Torgunrud A, Lund-Andersen C, Davidson B, et al. Pleura and Peritoneum. 2026 Mar 19;11(1):11–8; Pietrantonio F, Perrone F, Mennitto A, et al. Ann Oncol. 2016 Nov;27(11):2097–103).

Together, these features explain why systemic chemotherapy achieves limited response rates in PMP, typically less than 25%, and provide a strong rationale for exploring regional therapeutic strategies (Govaerts K, Lurvink RJ, De Hingh IHJT, et al. Eur J Surg Oncol. 2021 Jan;47(1):11–35).

HIPEC in index cytoreductive surgery

Despite these biological constraints, clinical evidence supports the use of HIPEC in the index management of PMP. A large international multicenter analysis including 1924 patients demonstrated a significant survival benefit associated with the addition of HIPEC to cytoreductive surgery (CRS) (Kusamura S, Barretta F, Yonemura Y, et al. JAMA Surg. 2021 Mar 1;156(3):e206363). After adjustment for confounding variables, the weighted 5-year overall survival was 57.8% in the CRS-HIPEC group compared with 46.2% in patients undergoing CRS alone (hazard ratio 0.65).

This benefit was consistent across multiple clinically relevant subgroups, including both low- and high-grade disease, as well as across different levels of surgical completeness. Patients achieving complete cytoreduction (CC-0/1) and even those with residual disease (CC-2/3) appeared to benefit, suggesting that HIPEC may exert a therapeutic effect beyond that achieved by surgery alone.

From a safety perspective, HIPEC did not significantly increase postoperative mortality or major morbidity overall, although outcomes varied according to the chemotherapeutic regimen used. Mitomycin-based protocols were associated with higher complication rates, whereas other regimens demonstrated more favorable safety profiles.

Not all HIPEC regimens were equally effective. Combinations such as oxaliplatin with fluorouracil–leucovorin and cisplatin with mitomycin were associated with the greatest survival benefit, highlighting the importance of optimizing pharmacologic strategies.

The apparent contradiction between the intrinsic chemoresistance of PMP and the observed benefit of HIPEC may be explained by the unique pharmacokinetic advantages of intraperitoneal chemotherapy under hyperthermic conditions, including higher local drug concentrations, improved tissue penetration, and heat-enhanced cytotoxicity.

Overall, current evidence supports HIPEC as a valuable adjunct to index CRS, associated with meaningful survival benefit and acceptable morbidity when performed in experienced centers, although prospective randomized data remain lacking.

HIPEC in reoperative surgery

In contrast to the index setting, the role of HIPEC in reoperative surgery for recurrent PMP is far less clearly defined. Recurrence after initial CRS-HIPEC occurs in a substantial proportion of patients, and its management remains complex.

Across major series, including those from Baratti et al., Ahmadi et al., and Sugarbaker et al., a consistent conclusion emerges: outcomes following reoperative CRS are primarily determined by tumor biology, disease distribution, and the ability to achieve complete cytoreduction, rather than by the addition of HIPEC (Baratti D, Kusamura S, Guaglio M, et al. Ann Surg Oncol. 2023 Jan;30(1):404–14; Sugarbaker PH, Chang D. Ann Surgery Open. 2023 Sep;4(3):e335; Ahmadi N, Kostadinov D, Sakata S, et al. Ann Surg Oncol. 2021;28(12):7809–20).

Patients most likely to benefit from reoperation are those with low-grade histology, limited (focal) recurrence, longer disease-free intervals, and resectable disease amenable to complete cytoreduction (CC-0/1). In these selected patients, long-term survival can approach that observed after primary surgery. In the Basingstoke series, repeat CRS was associated with a significant survival benefit (hazard ratio approximately 0.41), with 5- and 10-year survival rates comparable to those achieved after initial CRS when complete resection was obtained.

Similarly, Baratti and colleagues demonstrated that selected patients undergoing curative-intent reoperation achieved outcomes comparable to non-recurrent patients, reinforcing the concept that PMP behaves as a locoregional disease amenable to iterative surgical control.

However, none of these studies provide compelling evidence supporting a routine role for HIPEC at reoperation. Favorable outcomes have been reported even in the absence of systematic HIPEC use, suggesting that its incremental contribution in this setting may be limited. The heterogeneity of treatment strategies and the lack of comparative data further prevent definitive conclusions.

An additional insight arises from Sugarbaker's experience with iterative cytoreduction. In this series, the use of early postoperative intraperitoneal chemotherapy (EPIC) with 5-fluorouracil at the time of index CRS emerged as an independent favorable prognostic factor for patients undergoing subsequent reoperative surgery. This finding suggests that early regional control of microscopic disease may influence long-term outcomes and highlights the potential importance of perioperative intraperitoneal chemotherapy strategies beyond HIPEC alone.

Taken together, these observations indicate that in the reoperative setting, surgical completeness and patient selection remain the dominant determinants of outcome, while the role of HIPEC appears secondary and not clearly established.

Conclusion

The management of pseudomyxoma peritonei reflects a complex interplay between tumor biology and therapeutic intervention. While PMP exhibits clear features of chemoresistance, regional chemotherapy—particularly when combined with hyperthermia—can still provide clinical benefit.

At the time of index cytoreductive surgery, HIPEC is supported by a large observational data demonstrating a consistent survival advantage and acceptable safety profile. In this setting, it can reasonably be considered a standard adjunct to CRS in experienced centers.

In contrast, in the reoperative setting, outcomes are primarily driven by tumor biology, disease extent, and the ability to achieve complete cytoreduction, while the routine use of HIPEC remains unsupported by strong evidence. Its application should therefore be individualized.

In summary, HIPEC appears justified at index CRS, whereas its role in redo surgery remains uncertain and non-essential, with surgery itself continuing to represent the cornerstone of treatment in recurrent PMP.

Section 9:

HIPEC After Upfront CRS for Advanced Tubo-Ovarian Cancer – What Do the Ongoing Randomized Trials Tell Us?

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Rationale for intraperitoneal treatment in advanced tubo-ovarian cancer

Tubo-ovarian carcinoma (TOC) is unique among all malignancies giving rise to peritoneal malignancy because peritoneal spread represents locoregional disease and not distant metastases. Pelvic peritoneal spread is classified as stage II according to the current FIGO staging system. Cytoreductive surgery (CRS) is the cornerstone of first-line treatment of advanced TOC (Stages III-C and above). The goal of CRS is complete

resection of all macroscopic disease (CC-0 resection). The concept of CC-0 is not the same as R0 resection performed for other solid malignancies where a R0 resection implies that microscopic disease around the tumour is resected along with the primary tumour. In contrast, it is well known that free-intraperitoneal cancer cells are shed during CRS with a propensity to get implanted in the surgical resection sites leading to disease recurrence/progression. It has been demonstrated that systemically administered mitomycin C achieves lower concentrations in peritoneal tumour nodules compared to intraperitoneal administration likely due to poor vascularity of peritoneal tumours nodules. Intraperitoneal treatments were developed to achieve high concentrations of chemotherapy drugs in peritoneal tumour nodules, to destroy the free intraperitoneal cancer cells and eradicate all microscopic residual disease.

TOC has a high response rate to systemic chemotherapy (SC) in the first line setting with overall response rates of up to 80%. The standard first line treatment of advanced TOC is primary (performed upfront) or interval (performed after few cycles of SC) CRS combined with SC resulting in a median overall survival of 40-60 months. More than 80% of the patients with advanced TOC recur after first line treatment and the most common site of recurrence is the peritoneum. This pattern of treatment failure of advanced TOC is an ideal target for intraperitoneal treatments.

Evidence supporting the use of HIPEC as a part of primary CRS

Currently, adding HIPEC to primary CRS is not the standard of care and should be performed only in a clinical trial. The KOV-HIPEC-1 trial randomized patients with newly diagnosed advanced TOC to HIPEC versus no-HIPEC in addition to primary or interval CRS. There was no difference in progression-free survival (PFS) and overall survival (OS) between the HIPEC and no-HIPEC groups. One large retrospective study from China evaluated the role of triple HIPEC (HIPEC performed three times after CRS in the first postoperative week) in addition to primary CRS (*Lei Z, et al. JAMA Netw Open 2020;3(8):e2013940*). Within the cohort of 584 patients, 425 underwent primary CRS plus HIPEC while 159 underwent primary CRS alone. The HIPEC regimen was 50 mg/m^2 cisplatin administered on days 1, 3, and 5. At median follow-up of 42.2 months, addition of HIPEC led to nearly a 16-month increase in OS for the primary CRS-HIPEC group (median, 49.8 months) compared with the primary CRS group (median, 34.0 months). The triple HIPEC was associated with a 36% reduction in the risk of death without a significant increase in severe surgical complications or clinically relevant systemic toxicities. Given the retrospective nature of the study, the methodological variations and the use of an unconventional HIPEC protocol, the grade of evidence allotted to this study by a recent consensus was 'low'. Moreover, more patients with a low surgical complexity score were included in the HIPEC group.

Two randomized trials – OVHIPEC 2 (NCT03772028) and CHIPPI (NCT03842982) are evaluating the role of HIPEC in addition to primary CRS. The OVHIPEC 2 (multi-country/multi-continent) has completed recruitment with 538 patients randomized to HIPEC versus no-HIPEC after complete primary CRS (CC-0/1 resection). The primary endpoint is OS with an anticipated 33% reduction in the risk of death at 5 years. The CHIPPI trial is similar to the KOV-HIPEC 1 trial with the aim of recruiting 432 patients at 16 centres in France and 2 in Belgium. A 35% reduction in the risk of relapse is anticipated with the addition to HIPEC to primary CRS.

What should we expect from ongoing randomized trials and why?

Advanced TOC is the only disease in which there is evidence from randomized trials supporting the use of HIPEC. The OVHIPEC-1 trial reported a 12-month gain in OS with the addition of HIPEC to interval CRS (*Kim SI, et al. Gynecol Oncol 2022;167(3):547-556*). A similar 14-month OS gain was observed in the interval CRS subgroup of the KOV-HIPEC 1 trial and the retrospective SUROVA study (*Kim SI, et al. Gynecol Oncol 2022;167(3):547-556; Chiva L, et al. Int J Gynecol Cancer 2025;35(12):102688*). Advanced TOC is a disease in which evidence from randomized trials supported the use of long-term normothermic intraperitoneal chemotherapy (administered through a port) and systemic chemotherapy (NIPS). However, with the GOG-252 showing no benefit of NIPS and the challenges and complications associated with intraperitoneal catheters, NIPS has fallen out of use (*Walker JL, et al. J Clin Oncol 2019;37(16):1380-1390*). The GOG-252 was not the ideal trial to evaluate the role of NIPS as it included inherently unsuitable patients for intraperitoneal therapy (stage IV disease and large residual tumors), populations that were specifically excluded from previous landmark IP trials like GOG 104, 114, and 172.

With the successful long-term use of NIPS in gastric peritoneal metastases, does this strategy need revisiting in the modern era especially with the availability of more patient-friendly percutaneously implantable catheters?

HIPEC is a one-shot treatment and it may not be enough to prevent recurrence but it affects long-term outcomes favourably. When HIPEC and maintenance treatments are not used, the PFS is limited to 12-15 months in advanced TOC. Thus, recurrence occurs over a period of time as a result of a poorly understood tumour biology. The goal of CRS is to reduce the tumour cell burden to a critically low level which can then be effectively addressed with SC. The lesser the burden of residual disease, the more effective is the SC. However, residual disease after neoadjuvant systemic chemotherapy is known to contain chemotherapy-resistant stem cells. Consequently, a CC-1 resection after interval CRS cannot be equated to a CC-1 after primary CRS since the former contains disease that has not be eradicated by SC. Cisplatin is a super drug

when used simultaneously with hyperthermia. As the temperature increases, the cytotoxicity of the drug increases and it is known to overcome platinum resistance. This could explain the benefit of HIPEC observed in all the studies on interval CRS. The minimal gain in PFS compared to the larger gain in OS is difficult to explain. Perhaps HIPEC, by preventing tumour cell entrapment following CRS reduces the incidence of bowel obstruction and preserves the quality of life for longer, making patients more eligible for systemic treatments.

So, can we expect similar results from the trials on primary CRS? Theoretically, a single shot HIPEC is less likely to prove effective in this setting for the aforementioned reasons. Another challenge is the time to adjuvant chemotherapy. It is crucial to start adjuvant treatment within 4-6 weeks after surgery and primary CRS being more extensive, HIPEC which adds 90 minutes to the operative time with known physiological consequences could delay the time to adjuvant treatment and thereby affect survival. In the KOV-HIPEC-1 trial, the median time to adjuvant chemotherapy was 21 days which is likely to have contributed favourably to the survival outcomes. In **Table 1**, the HIPEC-KOV-03R trial shows a long-term benefit of HIPEC in patients undergoing consolidation surgery (*Yoo JG, et al. J Gynecol Oncol 2023;34(6):e72*). In the scenario of consolidation surgery, HIPEC could be added (*Bhatt A, et al. Ann Surg Oncol 2023;30(6):3300-3301*).

From a summary of available data of the current scenario, primary CRS plus SC is the standard of care for newly diagnosed advanced TOC amenable to complete primary CRS. Pending the results of randomized trials, the addition of HIPEC to primary CRS defies both evidence and logic.

Table 1 – Korean trials on CRS and HIPEC

Trial name and identifier	**KOV-HIPEC 1 trial** (NCT01091636)	**KOV-2R** (RECOVER) (**RE**sistant **C**ancer of **OV**ari**E**s) (NCT05316181)	**HIPEC-KOV-03R**	**KOV-04 (FOCUS)** Stage Three & Four Ovarian Cancer After Interval Cytoreductive Surgery (NCT05827523)
Patient population	Primary FIGO stage III-IV epithelial ovarian, peritoneal or fallopian tube cancer undergoing primary or interval CRS	Patient with platinum resistant ovarian cancer not suitable for platinum therapy	Patient with partial or complete response to primary cytoreductive surgery and adjuvant chemotherapy (FIGO I C-III C)	Primary FIGO stage III-IV epithelial ovarian, peritoneal or fallopian tube cancer after neoadjuvant chemotherapy
Design	RCT; 1:1 randomization	RCT; 1:1 randomization	Retrospective cohort study	RCT; 1:1 randomization
Control arm	Primary or interval CRS + adjuvant chemotherapy	Physician's choice of systemic chemotherapy	Second-look surgery	Interval CRS + adjuvant chemotherapy+/- maintenance therapy
Experimental arm	Primary or interval CRS + HIPEC + adjuvant chemotherapy	Cytoreductive surgery + HIPEC	Second-look surgery + HIPEC	Interval CRS + HIPEC adjuvant chemotherapy +/- maintenance therapy
HIPEC drug	Cisplatin	Mitomycin C + Adriamycin	350 mg/m^2 carboplatin or 175 mg/m^2 paclitaxel	Cisplatin
Duration	90 minutes	90 minutes	90 minutes	90 minutes
Temperature	41.5°C	41.5°C	43-44°C	41.5°C
Primary endpoint	PFS	PFS	-	OS
Secondary endpoints	OS Adverse events Quality of life	OS Safety Quality of life (QLQ-C30, QLQ-OV28, EQ-5D-5L) KELIM CA125 model	-	PFS Cancer specific survival TFST Adverse events Quality of life (QLQ-C30, QLQ-OV28, EQ-5D-5L) Cost effectiveness
Stratification factors	Use of neoadjuvant chemotherapy	Institution Histology: HGSOC vs. others Number of prior lines of chemotherapy	-	Institution Stage BRCA status Size of residual disease
Sample size	184	140	87 (44 no HIPEC; 43 HIPEC)	520
Status	Complete results published	Recruitment complete	10y PFS and OS results published	88% recruitment complete
Results if available	Primary endpoint not met with no benefit of HIPEC in the overall population but significant benefit in PFS and OS in the subgroup undergoing interval CRS+ HIPEC	-	10y PFS and OS were significantly longer in the HIPEC group; HIPEC was an independent predictor of a longer PFS and not OS	-

Abbreviations: CRS - cytoreductive surgery; HIPEC - hyperthermic intraperitoneal chemotherapy; OS - overall survival; PFS - progression-free survival; TFST - Time to first subsequent therapy

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.