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Editorial comments are welcomed. For general inquiries, please contact the Editor directly at Paul.Sugarbaker@outlook.com

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IN THIS ISSUE

Section 1: Progress in Clinical or Laboratory Research

Small Bowel Transplantation for Patients with Pseudomyxoma Peritonei

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Introduction

Pseudomyxoma peritonei (PMP) is a rare clinical disease characterised by mucinous ascites, mucinous tumour implants and omental cake in the peritoneal cavity. In the majority of cases, PMP arises from a perforated mucinous appendix tumour, though PMP can arise from other intra-abdominal organs such as the ovary, urachus, colon, or pancreas. Perforation of the mucinous tumour leads to the shedding of mucin and epithelial mucin-producing cells into the peritoneal cavity, where they spread via the redistribution phenomenon into the right paracolic gutter, the right and left subdiaphragmatic spaces (including the spleen), the omentum and pelvic cul-de-sac (including the ovaries and uterus in females) [Carr NJ et al., Am J Surg Pathol. 2016]. PMP typically progresses slowly, seldom leading to lymphatic or distant metastases.

The standard of care involves a cytoreductive surgery to try and remove all macroscopic tumour through a combination of visceral resections and peritonectomies, followed by intraoperative administration of hyperthermic *intraperitoneal chemotherapy (HIPEC), typically mitomycin C administered intraoperatively, after tumour resection. A typical cytoreduction includes right and left parietal peritonectomy, greater and lesser omentectomy, appendicectomy or right hemicolectomy (in case of high grade appendiceal mucinous neoplasm, goblet cell adenocarcinoma or right colon mucinous adenocarcinoma) and bilateral salpingo-oophorectomy often with hysterectomy in females. Based on disease extent, right and left diaphragmatic peritonectomies, pelvic peritonectomy, splenectomy, gastric and bowel resections and liver capsulectomy can be performed [Sugarbaker PH. Surg Oncol Clin N Am 2003]. Complete cytoreduction can be achieved in up to 80% of patients.

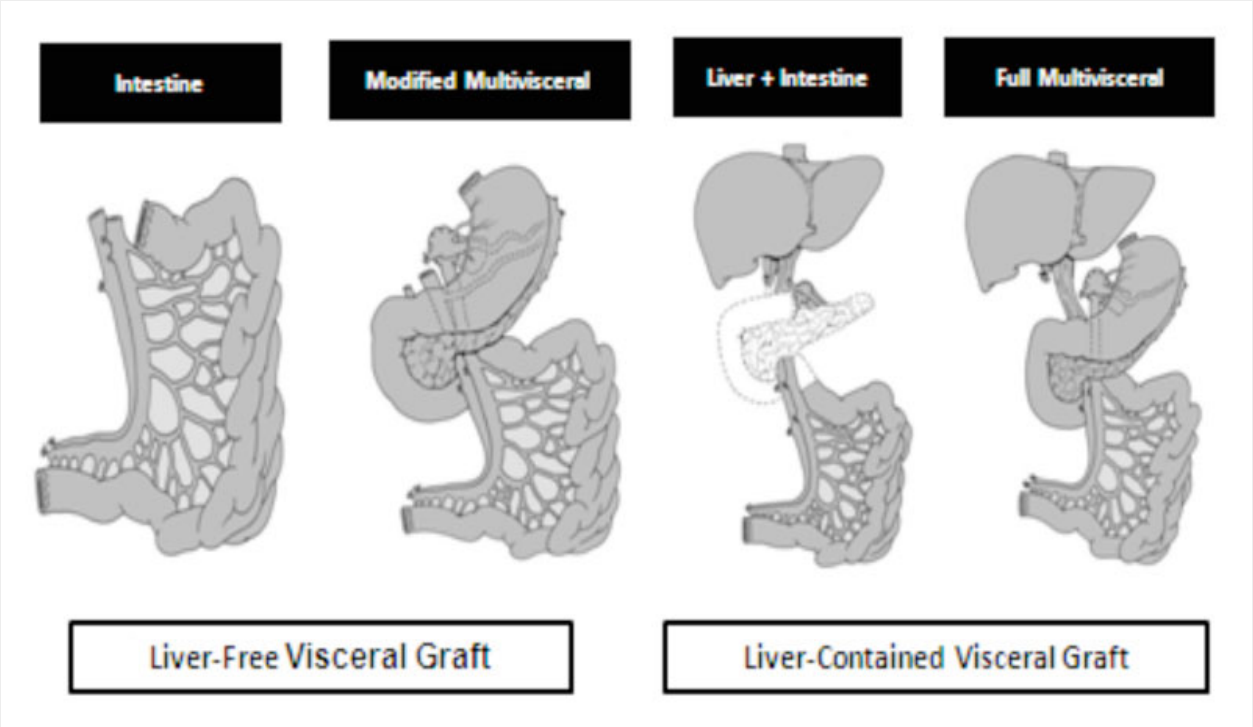
However, despite complete cytoreductive surgery and HIPEC, disease recurrence occurs in 22% to 44% of patients, some of whom may not be suitable for further cytoreductive surgery. In some patients, complete tumour removal is not achievable, almost always due to extensive small bowel involvement, and maximal tumour debulking is the best that can be achieved by conventional means, leading to the inevitable progression of residual disease [Ahmadi N et al., Ann Surg Oncol. 2021].

Patients progressively develop abdominal distention and nutritional failure due to extensive small bowel involvement necessitating parenteral nutrition (PN). Abdominal wall failure and intestinal fistulation commonly occur making effective palliation increasingly difficult or impossible and rendering this phase of the disease particularly distressing. This and the slow progressive pattern of the disease led to the search for surgical solutions, driven and inspired by a patient Steve Prescott [One in a million: My story Vertical Editions ISBN-13 978-1904091844] culminating in consideration of modified multivisceral graft/small bowel transplantation as a possible way to treat and palliate patients to improve their survival and quality of life.

Small bowel transplantation

Small bowel transplantation is now a well-established therapeutic option for a growing range of conditions; however, it carries a higher complication rate and lower survival compared to other solid organ transplants, such as kidney or liver transplants.

Different options for small bowel transplantations are outlined below and can include a range of organs with the risk and outcomes relating to the complexity of the transplant.



Intestinal Transplant for pseudomyxoma peritonei

A joint collaboration between the Pseudomyxoma Team at the Peritoneal Malignancy Institute in Basingstoke and the Transplantation Team at Oxford University has led to the establishment of a small bowel transplant programme for end stage pseudomyxoma peritonei. The Surgical approach, lessons learned and outcomes from 15 cases of isolated small bowel or modified multivisceral transplants are discussed below.

Criteria for Consideration for Multivisceral/Small Bowel Transplant:

1. Extensive PMP with a peritoneal cancer index of 30 to 39, where no conventional operative solution remains due to small bowel involvement and lack of response to chemotherapy.
2. Low-grade disease as per the PSOGI pathologic classification or high-grade disease with a slow progression rate.
3. Nutritional failure, either requiring or imminently requiring parenteral nutrition.

Exclusion Criteria:

1. Presence of distant metastases.
2. Serious cardiac or other organ insufficiencies that make the patient unable to tolerate transplant surgery.
3. Severe conditions unlikely to improve with transplantation, leading to a short life expectancy.
4. Demonstrated patient nonadherence, posing a risk to the transplanted organ due to failure to follow medical recommendations.
5. Unacceptable potential complications from immunosuppressive medications, as determined by the patient.
6. Acquired immune deficiency syndrome (AIDS) (diagnosed according to the Centers for Disease Control and Prevention (CDC) definition: CD4 count ≤ 200 cells/mm^3), unless the following criteria are met:
    a. CD4 count > 200 cells/mm^3 for more than six months.
    b. HIV-1 RNA undetectable.
    c. On stable antiretroviral therapy for more than three months.
    d. No other complications from AIDS (e.g., opportunistic infections such as aspergillosis, tuberculosis, coccidioidomycosis, resistant fungal infections, Kaposi's sarcoma, or other neoplasms).
    e. Meeting all other criteria for small bowel or multivisceral transplantation.

Donor Operation:

A modified multivisceral (MMV) graft, incorporating the stomach, pancreaticoduodenal complex, small bowel, and right colon, was retrieved from all donors. Additionally, a full-thickness abdominal wall graft based on the inferior epigastric vessels was harvested if needed.

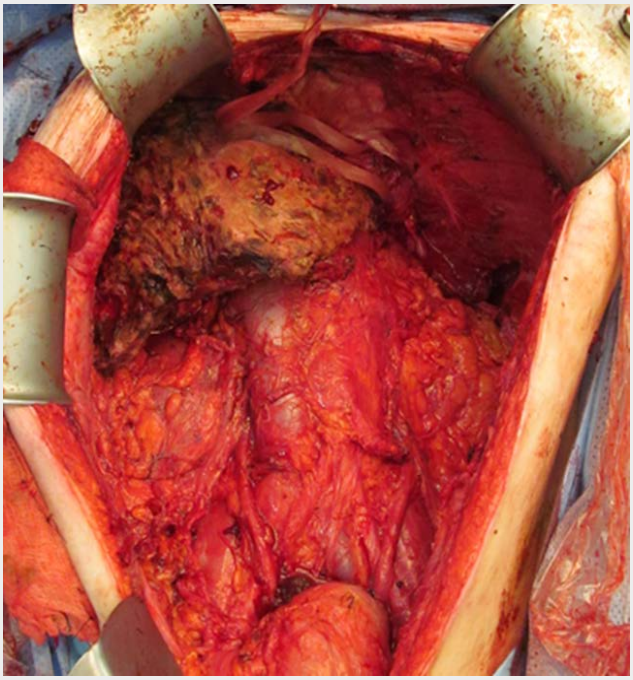
Recipient Operation:

The recipient procedure begins once the donor organs are confirmed as suitable, optimizing the timing for the often-lengthy explantation process. The affected bowel is mobilized and removed. In approximately half of the patients, extensive tumour involvement necessitated the removal of the duodenum, pancreas, stomach, small intestine, and large intestine.

Graft selection is guided by the extent of abdominal organ involvement, with the goal of transplanting the minimal amount of donor tissue required for effective tumour clearance. In some cases, tumour recurrence in the upper abdomen is minimal, allowing for the preservation of the stomach, duodenum, and pancreas. Despite efforts to achieve complete tumour removal, small amounts of residual disease were sometimes left for safety reasons, particularly around the porta hepatis or diaphragm. In certain cases, high-power diathermy liver capsulectomy was performed to excise disease from the liver's surface.

For isolated intestinal grafts, vascular reconstruction involved anastomosing the donor's superior mesenteric vessels to the recipient's native vessels. In multivisceral transplantation, a donor thoracic aorta segment was used as a conduit from the infra-renal aorta, anastomosed to a Carrel patch that included the donor's superior mesenteric and celiac arteries, with venous outflow established through anastomosis to the recipient's portal vein.

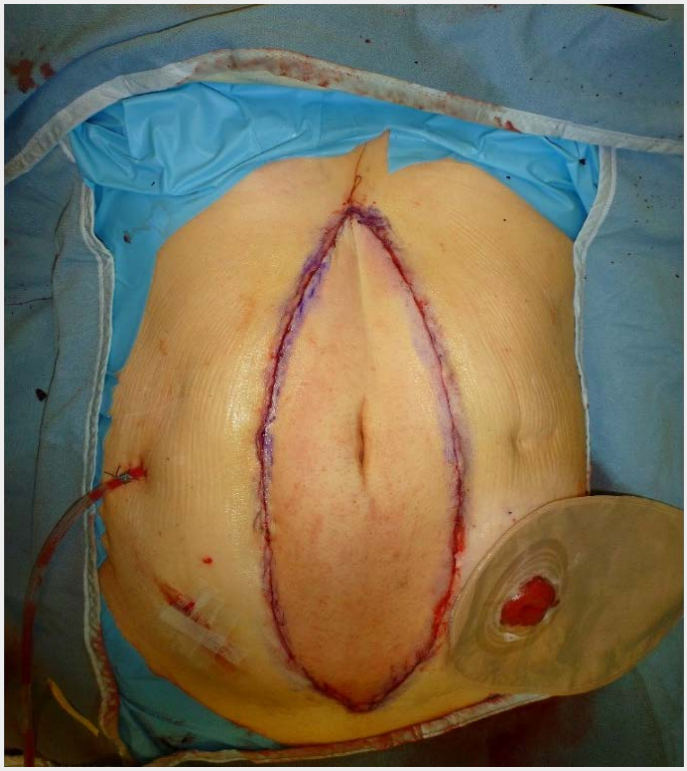
Explant of pseudomyxoma



Complete cytoreduction achieved after explant

Abdominal wall transplant

In patients with extensive abdominal wall failure where resection results in domain loss, the donor abdominal wall was transplanted as a free flap with microvascular anastomosis onto the inferior epigastrics by the plastic surgeons. Alternatively, if enough skin can be preserved, the donor abdominal fascia can be used [Reddy et al., Ann Surg 2023].



Abdominal wall transplant

Immunosuppression Protocol:

- Patients received 500 mg of intravenous methylprednisolone before reperfusion.
- Intravenous alemtuzumab (30 mg) was administered intraoperatively post-reperfusion, with a second dose given 24 hours later.
- Tacrolimus was used as maintenance therapy, targeting trough levels of 10–12 ng/mL for the first six months, then 8–10 ng/mL thereafter.
- Since 2018, additional immunosuppressive therapy has included:
    - Azathioprine (50–75 mg daily).
    - Mycophenolate mofetil (250–500 mg twice daily).
    - Prednisolone (5–10 mg daily).

Rejection Diagnosis and Treatment

Rejection of the small intestine was diagnosed through endoscopy and biopsy, graded according to the criteria established by the VIII International Small Bowel Transplant Symposium. For patients with abdominal wall grafts, skin biopsies were performed if a rash was present and assessed using the 2007 Banff criteria.

Treatment for rejection included three daily intravenous doses of methylprednisolone and adjustments to immunosuppressive therapy. Cases of persistent or severe rejection were managed with additional antithymocyte globulin.

Intestinal Graft Failure

Intestinal graft failure was defined by the occurrence of any of the following events after transplantation:

1. **Graft enterectomy for any cause, including** anastomotic leak**,** bleeding**,** ischemia**,** rejection**,** infection**,** malignancy and graft-versus-host disease (GVHD).
2. **Relisting for an intestinal graft transplant.**
3. **Dependence on total parenteral nutrition (TPN):**
    - Resumption of TPN after transplant.
    - Inability to discontinue TPN within three months post-transplant.

Results

At a median follow-up of 4.5 years, six patients had died following transplantation. One death occurred within a month, while two others (13%) took place between one and six months. The remaining three deaths (20%) happened beyond six months. Causes of mortality varied, including anastomotic leak at 24 days, upper gastrointestinal bleeding at 69 days, and graft-versus-host disease at 181 days. Other fatalities resulted from multifactorial complications leading to palliative care at 1,001 days, disease progression at 1,204 days, and post-transplant lymphoproliferative disorder at 1,300 days.

Despite these challenges, nutritional independence was achieved by most survivors. Of the 14 patients who lived beyond the first month, 12 successfully weaned off total parenteral nutrition (TPN), although two developed enterocutaneous fistulas and remained on parenteral nutrition. By the one-year mark, 72% (8 out of 11) were free from home parenteral nutrition (HPN), though two later required supplemental HPN due to post-transplant complications, including lymphoproliferative disorder and recurrent pelvic disease. Meanwhile, tumour progression or recurrence remained a significant concern, affecting 91% of patients with at least six months of follow-up. The median time to recurrence was just under a year, at 363 days, with cases ranging from 110 to 727 days [Reddy et al., Ann Surg 2023].

This study highlighted the feasibility of modified multivisceral (MMV) and small bowel transplantation for end-stage pseudomyxoma peritonei (PMP) in carefully selected patients with no remaining surgical options. Early outcomes from the first treated patients show a 78% survival rate at one year and 55% at five years, with most experiencing significant improvements in quality of life. Key factors influencing success include strict patient selection, prioritizing younger, fitter individuals with low-grade disease, and ensuring near-complete cytoreduction, even in high-tumour-volume cases, particularly after prior unsuccessful laparotomy.

Abdominal wall involvement posed a challenge for all patients, with nearly half (7 out of 15) experiencing severe loss of abdominal domain due to tumour infiltration and tissue destruction. In these cases, primary closure was not possible, as excessive tension on transplanted organs increases surgical risks. Despite these obstacles, survival outcomes remain promising. The 1-year survival rate of 79% aligns with global standards for intestinal transplantation, while the 5-year survival rate of 55% is slightly below the 60%–70% reported for non-PMP intestinal transplants. However, these figures far surpass the grim prognosis of non-resectable PMP patients on parenteral nutrition alone, who typically survive only 6 to 12 months. Notably, MMV transplantation also outperforms the 5-year survival rates of major cancer surgeries such as pancreatic cancer resection, highlighting its potential as a viable option for this challenging condition [Reddy et al., Ann Surg 2023].

While high recurrence rates remain a challenge in transplantation for pseudomyxoma peritonei (PMP), careful patient selection and increasing surgical expertise offer hope for improved outcomes. Transplantation has shown potential benefits for select adenocarcinoma patients, and despite disease recurrence under immunosuppression, most cases progress slowly. Notably, only one of the 15 patient deaths in this study was directly attributed to recurrent disease.

A groundbreaking technique performed by Dr. Anil Vaidya in the United States in 2021 introduced an innovative approach to multivisceral transplantation. In that case, both the liver and intestines were transplanted, with a temporary transplant of the donor's spleen to enhance immune protection and improve pancreatic blood flow. Additionally, the donor's right colon was included to help protect the new intestine from infection and aid in nutrient absorption. Both the spleen and colon were later removed after successfully serving their temporary roles in safeguarding the newly transplanted organs.

Despite these advancements, the study's small sample size and highly selective patient group limit its broader applicability. Several key questions remain unanswered, including the optimal timing of transplantation, its potential role in treating higher-grade disease, and whether integrating hyperthermic intraperitoneal chemotherapy (HIPEC) at the time of tumor resection could improve disease control. Future research will be essential to refine patient selection criteria and explore ways to enhance long-term survival in this complex and evolving field of transplantation.

In conclusion, intestinal transplantation is a **feasible option** for **selected patients** with end-stage PMP, achieving **long-term survival and improved QOL**. Further research is needed to refine patient selection criteria and explore adjunctive therapies to enhance outcomes.

Section 2: Exposition of progress and productivity of a PSOGI/PSM established Center of Excellence

The Contribution of Istituto Tumori in Milan for Peritoneal Surface Oncology: Past, Present and Future

By Marcello Deraco and Shigeki Kusamura

Past

In the mid-1990s, the Peritoneal Surface Malignancies (PSM) Program at Fondazione IRCCS Istituto Nazionale dei Tumori in Milan emerged as one of the pioneering centers in Europe. Following surgical training with Dr. Paul Sugarbaker in Washington, D.C., Marcello Deraco assembled a dedicated team to treat peritoneal malignancies—then considered universally incurable. Systemic chemotherapy offered limited benefit, and surgery was regarded as purely palliative.

Building on the foundational work of international leaders such as Paul Sugarbaker, Brendan Moran, David Morris, François Noël Gilly, Dominique Elias, and Frans Zoetmulder, the Milan team played a pivotal role in validating and implementing cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in Southern Europe. Their main contribution lay in incorporating this combined approach into structured clinical pathways, making it reproducible, safe, and applicable to broader clinical practice.

During the late 1990s and early 2000s, the group refined peritonectomy techniques and perioperative protocols, gradually specializing in rare conditions such as pseudomyxoma peritonei (PMP) and peritoneal mesothelioma. They also helped advance the scientific understanding of these diseases by publishing influential single-center series and initiating translational research to clarify their pathophysiology. The team's multidisciplinary approach—integrating surgical, medical, biological, and pathological expertise—provided insights into tumor biology and progression, identifying novel prognostic markers and consequently, improving patient selection for the combined procedure.

In 2006, the unit hosted a landmark international PSOGI congress, promoting consensus in the rapidly evolving field of peritoneal surface oncology. By the end of the decade, Milan had become one of international leaders—not by working in isolation, but by translating innovative concepts into standardized, adoptable models of care. Their efforts contributed to the transformation of CRS and HIPEC from experimental interventions to essential therapies in the management of peritoneal surface malignancies.

Present

Today, the Milan center is internationally recognized, having treated over 1,500 patients with CRS and HIPEC. Its multidisciplinary team manages complex cases across all peritoneal surface malignancy (PSM) subtypes, with particular expertise in pseudomyxoma peritonei (PMP) and peritoneal mesothelioma. Care is highly personalized, combining surgical, systemic, and intraperitoneal treatments with comprehensive supportive strategies tailored to each patient's needs.

From a surgical perspective, the Milan team has been a pioneer in the continuous evolution of cytoreductive techniques. They have refined and systematized complex procedures such as total parietal peritonectomy, and mesenteric peritonectomy, enabling complete cytoreduction even in anatomically challenging scenarios. Their innovations have addressed previously unmet technical challenges, such as safe dissection in areas traditionally considered high-risk due to vascular proximity. The team has also participated in the recent Consensus on Cytoreductive Surgery promoted by PSOGI, ISSPP and ESGO to the standardization of peritonectomy procedures and nomenclature.

The unit remains a leader in innovation and research, supported by competitive grants from national bodies such as the Italian Association for Cancer Research (AIRC) and the Ministry of Health (Ricerca Finalizzata). It has conducted multiple clinical trials and translational studies to improve the efficacy of HIPEC, explore novel drug combinations, and optimize perfusion protocols. A strong focus has been placed on understanding tumor biology to tailor therapeutic strategies.

In peritoneal mesothelioma, research has investigated pathways involving tyrosine kinase receptors, telomerase deregulation, apoptosis, epithelial–mesenchymal transition (EMT) and its reversal (MET), and tumor cell proliferation. The identification of Ki-67 as a prognostic biomarker has significantly informed therapeutic decision-making.

The Milan team has also developed patient-derived organoids—an innovative platform for drug sensitivity testing, discovery of predictive markers, and identification of actionable targets. Furthermore, the center coordinates the ACCELERATOR project, a European network dedicated to translational research in PMP.

Clinicians from Milan have contributed significantly to national and international guidelines. In collaboration with RENAPE, they coordinated the development of PSOGI recommendations for PMP and mesothelioma, played a central role in the standardization of HIPEC, and led the recent Multisociety Consensus Statements on CRS and HIPEC—presented at the PSOGI International Congress organized by the Milan team in Venice in 2023.

The unit continues to publish extensively and train professionals worldwide through ESPSO (European School of Peritoneal Surface Oncology), disseminating knowledge in peritoneal surface oncology across the globe. In 2011, it launched the biannual ESSO theoretical course on PSM, whose first edition was held in Bergamo (Italy) and the most

recent in Basingstoke (UK) in 2024. Its leadership has improved global standards and inspired the establishment of new expert centers internationally.

Future

Looking ahead, the Milan team is committed to advancing precision oncology. Ongoing studies are exploring the tumor microenvironment, particularly its interaction with cancer-associated fibroblasts (CAFs)—known promoters of tumor growth—and their role in suppressing anti-tumor immunity. A major challenge will be to identify strategies to reverse this immune suppression and to evaluate CAFs as therapeutic targets. In parallel, the potential role of immunotherapies in peritoneal surface malignancies is under active investigation.

Technological innovations in imaging (such as radiomics) and intraoperative navigation will enhance surgical precision. Additionally, the center is planning to foster the use of artificial intelligence into clinical practice and research, with platforms for decision support, outcomes predictive modeling, and interpretation of multiomic data.

Minimally invasive approaches—including laparoscopic and robotic CRS—are currently under investigation through a prospective validation study. Likewise, other locoregional approaches such as PIPAC and normothermic intraperitoneal chemotherapy will be explored for the definition of their clinical roles.

Efforts to improve perioperative care—especially through structured prehabilitation programs—aim not only to improve survival but also to reduce morbidity and mortality associated with CRS and HIPEC, enhancing patients' quality of life. Education and mentorship remain central pillars, as the team continues to train the next generation of specialists and support the global expansion of expert centers.

Needless to say, the achievements of the Milan team would not have been possible without the collaboration of international referral centers in Washington, Basingstoke, Lyon, Manchester, Paris, Montpellier, Eindhoven, Genk, Ghent, Madrid, Barcelona, Córdoba, Lausanne, Athens, Thessaloniki, Regensburg, Berlin, Uppsala, Odense, Oslo, Sydney, Beijing, Singapore, Kishiwada, Tokyo, Maryland, Connecticut, Lewes, San Diego, Salt Lake City, Winston-Salem, New York, Houston, Salvador, Sao Paulo, Rio de Janeiro, Rome, Padova, Torino, Bangalore, Ahmedabad, Tel Aviv, Najran, and many others that compose the global peritoneal surface oncology community.

From challenging the concept of incurability in the 1990s to defining global standards today, Milan's unit will continue to strengthen the PSOGI network and push the boundaries of current knowledge in PSM—to offer hope where once there was none.

Section 3: Listing of upcoming events

Meeting	Date	Venue	Registrations
CONFERENCES			
9th INDEPSO-ISPSM Annual Update in Peritoneal Malignancies	5-7th June, 2025 Preceded by a one-day video workshop on 4 June, 2025 Pathology workshop on 7 June, 2025	Calicut, India	Open https://www.onlinesbi.sbi/sbicollect/icollecthome.htm?corpID=639211
15th International Congress on Peritoneal Surface Malignancies	29-31st October, 2025	Barcelona, Spain	https://psogicongress2025.com/
WORKSHOPS			
Turkish Society of Colorectal Surgery PSM Video Workshop	11-12th July, 2025	Izmir, Turkey	To be announced
FIRST ANNOUNCEMENT			
5th LATAM Latin American Congress on Peritoneal Surface Malignancies	2026 (dates will be announced in due course)	Colombia, South America	---

9th INDEPSO-ISPSM Annual Update in Peritoneal Malignancies

4th-7th June, Kozhikode, India
https://annualperitonealupdate2025.mvrcancerhospital.com/

By Aditi Bhatt

The 9th INDEPSO-ISPSM annual update in peritoneal malignancies is round the corner. A decade has passed since the first peritoneal malignancy conference in India (Bangalore, 2015). This year the meeting will be held in the historical town of Kozhikode (Calicut) situated on the Malabar coast in the Southern Indian state of Kerala, home to the backwaters of the Arabian sea.

The theme of the conference this year is 'Towards multidisciplinary care and collaborative research'. Through didactic lectures, debates and case discussions, the speakers will provide a comprehensive update on the latest developments in management of peritoneal malignancies in India and around the world, focusing on multidisciplinary care.

Speakers from India, Europe, USA, China, Malaysia, Nepal, Bangladesh and Sri Lanka that include some leading clinicians and researchers in the field will participate in the conference.

Video workshop on cytoreductive surgery (4th June, 2025)

The conference will be preceded by a video workshop of cytoreductive surgery that will be conducted by Paul Sugarbaker. The 8-hour comprehensive program will include a series of lectures and video demonstration of the techniques of cytoreductive surgery. This course goes beyond what is written in books and published in scientific journals on the techniques of cytoreductive surgery. Beginning with how to explore the abdominal cavity and calculate the PCI to performing some of the most complex peritonectomy procedures, the program offers the participants a unique opportunity to discuss the nuances of cytoreductive surgery with the Paul Sugarbaker. He will be ably supported by a panel of international experts. The numerous topics of practical help to the surgeon include the use of energy devices, major and minor visceral resections and reconstructions, tips for avoiding ostomies and placement of intraperitoneal ports.

Pathology workshop (7th June, 2025)

This workshop will be conducted by Frederic Bibeau, the head of RENEPATH in France. This workshop is for pathologists and surgeons both covering the basics of pathology for peritoneal malignancies like the diagnosis and classification of rare peritoneal tumors, assessment of pathological response to systemic treatments and its clinical significance and processing and reporting of cytoreductive surgery specimens. The program includes lectures, cases discussions and presentation of slides representing diagnostic dilemmas.

Perioperative management workshop (6th June, 2025)

One of the important aspects of multidisciplinary management of peritoneal malignancies is the perioperative management of patients undergoing cytoreductive surgery and HIPEC. The workshop is for surgeons, anesthesiologists and critical care specialists who wish to start a peritoneal malignancy program and those with a limited experience in the field. Current standards of perioperative management, enhanced recovery after cytoreductive surgery and HIPEC, prevention and management of complications from the anesthesia and surgical viewpoints will be the main focus of this workshop. This workshop will be led by the critical care team from MVR cancer center, Kozhikode and other experts from the country. The delegates will learn what is practical, feasible, evidence-based and effective in the Indian context.

Who should attend the meeting and why?

All clinicians involved in the management of peritoneal malignancies should attend this meeting:

1. To learn about
    a. The basics of peritoneal malignancy
    b. The latest developments in the field
    c. The current standards of care
    d. Forthcoming research and trials
    e. Latest developments in India
2. Opportunity to interact with national and international experts
3. Networking, collaboration and participation in research activities
4. To get inspired and pursue peritoneal surface oncology as a specialty

The peritoneal oncology community awaits the presentation of the results of two important trials at the 2025 ASCO annual meeting- the CAIRO-6 trial (colorectal peritoneal metastases) and the TRUST trial (advanced ovarian cancer). Following close on the heels of the ASCO annual meeting, the stage is set for some surprise presentations and engaging discussions.

Section 4: Alternatives to traditional HIPEC

Triple and Quadruple HIPECs

By Paul H. Sugarbaker

Hyperthermic intraperitoneal chemotherapy (HIPEC) has been used essentially unchanged for 30 years. Its goal is to PREVENT peritoneal metastases in gastric cancer or colorectal cancer patients at high-risk for a progression of disease. More frequently, HIPEC is used after a complete cytoreductive surgery in patients with ovarian, gastric, colorectal, and appendiceal peritoneal metastases to help MAINTAIN A DISEASE-FREE STATUS within the abdomen and pelvis. From a theoretical perspective and also from a failure analysis of HIPEC, the treatment is deficient in several ways. First, and perhaps the most severe criticism of HIPEC is its lack of "RESIDENCE TIME" within the abdominopelvic space. The instillation of chemotherapy solution maintained at 41-43°C by a hyperthermia pump continues for only 90 minutes. To make the limited exposure of residual microscopic disease even worse, the high concentration of chemotherapy within the peritoneal space continues for only 30-60 minutes for most chemotherapy agents. The drugs like paclitaxel with a high molecular weight diffuse more slowly from the peritoneal space. Low molecular weight drugs like cisplatin no longer have high concentration in the peritoneal space after only 20 minutes. It is my conclusion that an increased residence time within the peritoneal space is a first requirement for greater benefit from HIPEC.

In the last 5 years a HIPEC modification that would markedly increase residence time has been published. This involves the utilization of MULTIPLE HIPECS employed after cytoreductive surgery. Somewhat surprising to me, the multiple HIPEC data shows efficacy even after an incomplete cytoreduction. I would doubt that an improved survival if gross disease remains behind after surgery so that major portions of the abdominal space are closed off to direct contact to the chemotherapy solution. However, if fibrous adhesions and gross disease are eliminated and heated chemotherapy reaches a majority of the abdominal and pelvic spaces, a significant improvement in the proportion of patients with peritoneal metastases that experience significant improvement in survival is expected occur.

The Chinese clinical research and innovation has given us valuable information regarding the use of multiple HIPECs. Yan and colleagues from Nanchang, China in 2019 quadrupled the residence time for HIPEC after a gastric resection. Primary gastric cancer patients with peritoneal metastases underwent gastrectomy but were not subjected to extensive cytoreductive surgery. Palliative laparoscopic resection was performed in all patients. In the quadruple HIPEC group, a single inflow catheter was positioned on the upper and lower abdominal wall. Outflow catheters were on the diaphragmatic surface of the liver, splenic fossa and pelvis. The carrier solution was 2000 ml of normal saline, the chemotherapy was 150 mg of oxaliplatin plus 1000 mg of 5-fluorouracil, the temperature within the abdomen and pelvis was gradually increased to 43°C, and time for the HIPEC was 60 minutes. The HIPEC treatment occurred on the first postoperative day and was repeated on postoperative days 3, 5 and 7 (Yan K et al. JBUON, 2019).

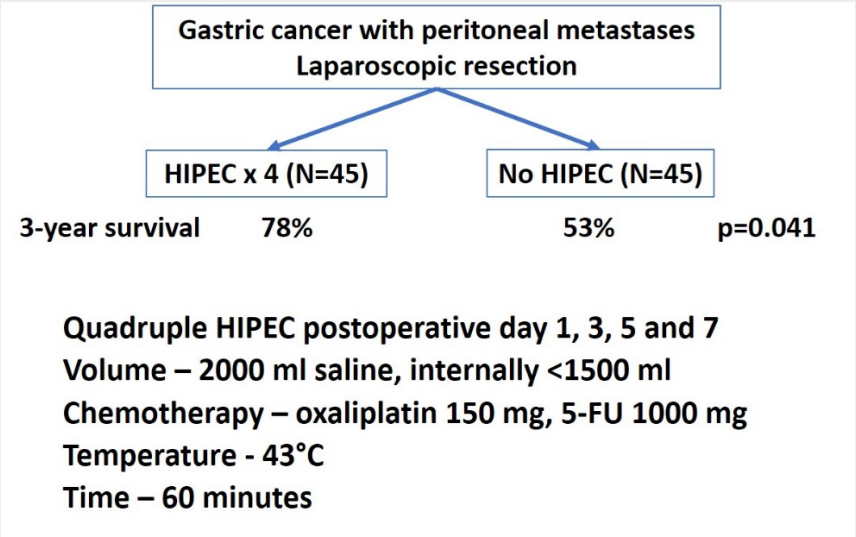


Figure 1. Evaluation of laparoscopic resection of gastric cancer with peritoneal metastases with or without quadruple hyperthermic intraperitoneal chemotherapy with oxaliplatin + 5-fluorouracil.

Following quadruple HIPEC, Yan reported that no major alteration in postoperative pain management was required and performance status after surgery and at 3 months were not significantly different. The percent survival with a 34.3 month median follow-up was 78% in the 45 patients in the quadruple HIPEC group and 53% in the control (p=0.041). Long-term follow-up is not available. The means whereby patients were placed in the laparoscopic gastrectomy alone group versus laparoscopic gastrectomy plus quadruple HIPEC group is not specifically stated in the manuscript.

Lei and coworkers presented data for the Chinese Peritoneal Oncology Study Group. They evaluated a triple HIPEC in patients with stage III primary ovarian cancer. They used a volume of 2000 ml of saline instilled on postoperative days 1, 3 and 5. The chemotherapy solution contained 50 mg/m^2 of cisplatin. The temperature was 43°C and the time for the lavage was 60 minutes. This was a propensity matched study with triple HIPEC being used in 423 patients and no HIPEC in 159 patients. The median survival was 50 months in the triple HIPEC-treated patients and 34 months with no HIPEC (p<0.001). Also, the 3-year survival was 60% with triple HIPEC and 50% without HIPEC (p<0.001). The data was analyzed using propensity matching of treated patients versus historical control patients (Lei et al. JAMA Open, 2020).

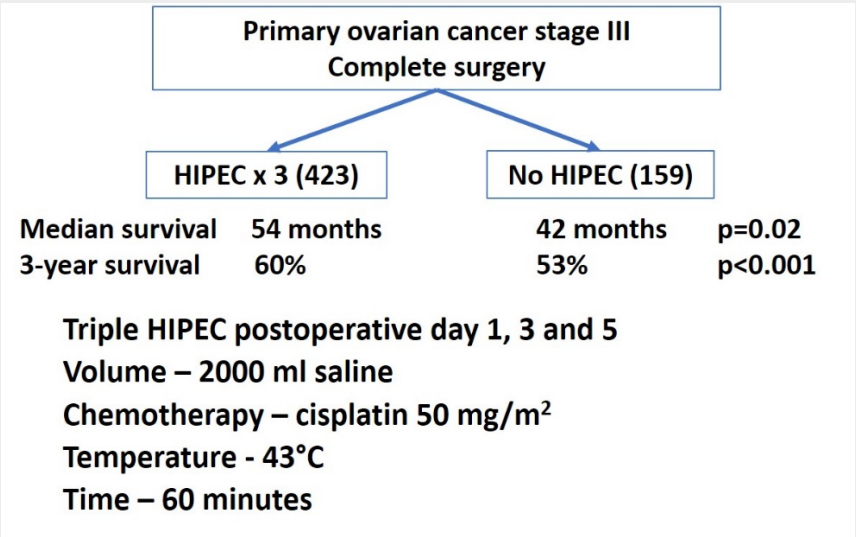


Figure 2. Evaluation of cytoreductive surgery with or without triple hyperthermic intraperitoneal cisplatin chemotherapy for stage III epithelial ovarian cancer.

In patients with cholangiocarcinoma, the intrahepatic bile ducts are often heavily contaminated by cancer cells. Resection of the cholangiocarcinoma is frequently accompanied by peritoneal metastases. In a retrospective cohort study, Feng and colleagues from Shanghai, China published the results of a triple HIPEC in patients with peritoneal metastases from cholangiocarcinoma (Feng et al. Eur J Surg Oncol, 2021). These patients underwent an open resection of the cholangiocarcinoma. Fifty-one patients were treated with a triple HIPEC and were compared to 61 patients treated by surgery alone. The triple HIPEC was given on postoperative days 2, 4 and 6. The intraperitoneal volume of chemotherapy solution was 2 L/m^2. There was 40 mg/m^2 of cisplatin and 1000 mg/m^2 of 5-fluorouracil in each of the 3 instillations. The temperature was maintained at 43°C and the time for lavage was 60-90 minutes. Meperidine hydrochloride and promethazine hydrochloride were given for pain relief during HIPEC.

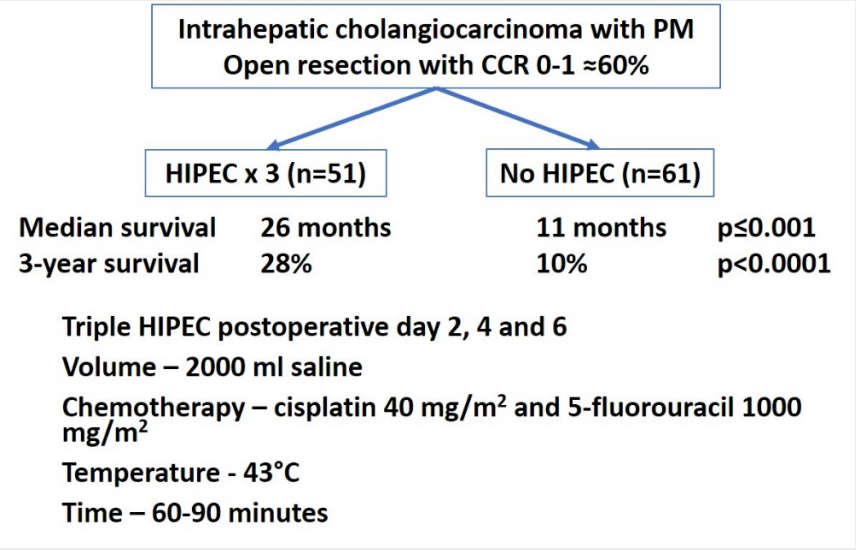


Figure 3. Evaluation of cytoreductive surgery with or without triple hyperthermic intraperitoneal chemotherapy in patients with peritoneal metastases from cholangiocarcinoma.

Data provided in these 3 reports on the use of multiple HIPECs after an abdominal or pelvic cancer resection establish the following conclusions. First, a randomized controlled trial is necessary in these cancers with peritoneal metastases to confirm the benefits of multiple HIPECs. Secondly, and perhaps most important, the feasibility of multiple HIPECs outside of the operating room has been established. Patients accept the instillation of 2 liters of intraperitoneal chemotherapy solution, 43°C is tolerable and repeated treatments are possible with well-motivated patients. Third, reasonable doses of chemotherapy are possible. A 1/3 to 1/2 dose reduction from a traditional single HIPEC was utilized. Finally, 3 to 4 times the residence time for HIPEC is possible and these data suggest greater benefit than expected with traditional HIPEC.

Section 5: Focus on active PSM protocols

Update on Nordic Research in Cytoreductive Surgery and HIPEC

By Peter Cashin

Introduction

Colorectal cancer with peritoneal metastases remains a significant therapeutic challenge. While cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has been a mainstay of treatment, questions about the optimal HIPEC regimen persist. The PRODIGE 7 trial questioned the efficacy of oxaliplatin-based HIPEC, leading to an increased focus on novel combination therapies. The ongoing EFFIPEC trial aims to refine HIPEC protocols by evaluating intensified chemotherapy regimens. This article provides an update on the trial's interim morbidity analysis and highlights the international collaboration, particularly with the Indian Network for Development of Peritoneal Surface Malignancy (INDEPSO) HIPEC network. Also, I present potential new research initiatives in the Nordic countries concerning pseudomyxoma peritonei (PMP).

The Efficacy of Hyperthermic Intraperitoneal Chemotherapy in Colorectal Cancer – The EFFIPEC Trial

The EFFIPEC trial, a combined Phase I/III study, investigates the efficacy of 5-fluorouracil (5-FU) and irinotecan-based HIPEC in patients with colorectal peritoneal metastases. As of September 2024, an unplanned interim morbidity analysis has been conducted due to neutropenia concerns and two mortalities after 52 patients were included. This was an assessment of postoperative complications in patients receiving different dosing regimens. At the surgeon's discretion, the HIPEC dosages were allowed to be reduced to 75% of the total dose for any reason.

Key findings include:

- A comparison of standard single-oxaliplatin HIPEC (n=26) versus experimental oxaliplatin + irinotecan HIPEC with 1 day 5-FU EPIC (n=26) - divided between 75% (n=9) and 100% (n=17) dosages.
- The Clavien-Dindo grade 3+ was 23% in the control group (no deaths), 22% in the 75% experimental group (no deaths), and 30% in the 100% experimental group (including two deaths).
- The neutropenia was 4% in the control group, 11% in the 75% experimental group, and 53% in the 100% experimental group.

- The reoperation rate was 12% in the control group, 11% in the 75% experimental group, 24% in the 100% experimental group.

Based on these findings, the trial's Data Monitoring Committee has recommended discontinuing the full-dose regimen due to an unexpected rate of neutropenia despite receiving prophylactic G-CSF. The neutropenia potentially contributing to at least one of the postoperative mortalities. Moving forward, only the 75% dose-level will be administered to ensure patient safety while maintaining therapeutic efficacy.

Expansion of International Collaboration: INDEPSO Joins the Effort

A significant milestone for the EFFIPEC trial is the participation of INDEPSO. Their inclusion enhances the trial's reach and diversity, allowing a broader evaluation of treatment responses across different patient populations. With INDEPSO's involvement, patient recruitment is expected to accelerate, increasing the likelihood of obtaining robust, generalizable results.

Progress on an Appendix HIPEC Research – the APPIPEC Trial

In addition to the ongoing EFFIPEC study, Nordic centers are exploring the feasibility of a randomized trial for pseudomyxoma peritonei (PMP). Previous studies have questioned the benefit of HIPEC in PMP, particularly in single-agent mitomycin C regimens. The proposed APPIPEC trial aims to evaluate whether a combination of mitomycin C and cisplatin offers superior outcomes compared to mitomycin alone or hyperthermic perfusion alone without chemotherapy. This initiative aligns with ongoing international efforts to optimize intraperitoneal chemotherapy regimens for various peritoneal surface malignancies. This trial effort will necessarily require centers outside the Nordic countries to be successful. Discussions have taken place at the Trial Taskforce meeting in Lausanne last year. There is hope that an agreement on a protocol will be forthcoming.

Investigating Conversion Therapy for Non-Resectable Peritoneal Metastases – the COLOVERT Trial

Another promising trial in the Nordic research landscape is the COLOVERT trial, which is currently seeking funding. COLOVERT is a phase II randomized controlled study designed to evaluate conversion therapy in colorectal cancer patients with peritoneal metastases who are not initially eligible for CRS+HIPEC. The trial employs a "pick-the-winner" design, comparing two experimental arms: Arm A receives oral capecitabine with intravenous bevacizumab and intraperitoneal oxaliplatin, while Arm B includes the same backbone

therapy but with an intraperitoneal chemotherapy agent selected based on chemotherapy-resistance testing. The study's primary objective is to assess response rates and determine whether personalized intraperitoneal chemotherapy can improve conversion rates for CRS+HIPEC eligibility. Secondary endpoints include overall survival, quality of life, and progression-free survival. The trial will be conducted at major Swedish HIPEC centers, and its outcome could significantly influence treatment strategies for patients with extensive peritoneal disease.

Conclusion

The EFFIPEC trial continues to make progress and will soon reach 60 randomized patients out of 196. The interim morbidity analysis underscores the importance of dose adjustments to balance efficacy and safety. The inclusion of INDEPSO marks a significant step toward global collaboration in peritoneal surface oncology research. Moreover, the potential Nordic trial on PMP and the planned COLOVERT study highlight the region's commitment to advancing HIPEC research across different disease subtypes. Completing these studies is essential to establishing evidence-based standards that will improve patient outcomes worldwide. Continued collaboration and dedication from the international HIPEC community will be pivotal in shaping the future of peritoneal malignancy treatment.

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.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Key topics

- Controversies in appendiceal neoplasms
- Advanced Surgical Techniques in PSM
- Neoadjuvant therapy in PSM
- Minimally invasive surgery in PSM
- Patient Advocacy session
- Most expected Clinical Trials in PSM
- Young Surgeons in PSM
- Prehabilitation
- Peritoneum-plasma barrier and Pharmacokinetics of HIPEC
- Historical PSOGI consensus
- Radiomics in PSM
- Tumor Board sessions
- Pro/Con Debate sessions
- ISSPP sessions
- Joint sessions with other societies:
  1. European Society of Coloproctology (ESCP)
  2. European Society of Gynaecological Oncology (ESGO)