Peritoneal Surface Oncology Group International

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IN THIS ISSUE

Section 1: Progress in Clinical or Laboratory Research

A Classification of Pseudomyxoma Peritonei Based on the Natural History of the Disease

A classification essential for the surgeon to assess prognosis after CRS and HIPEC

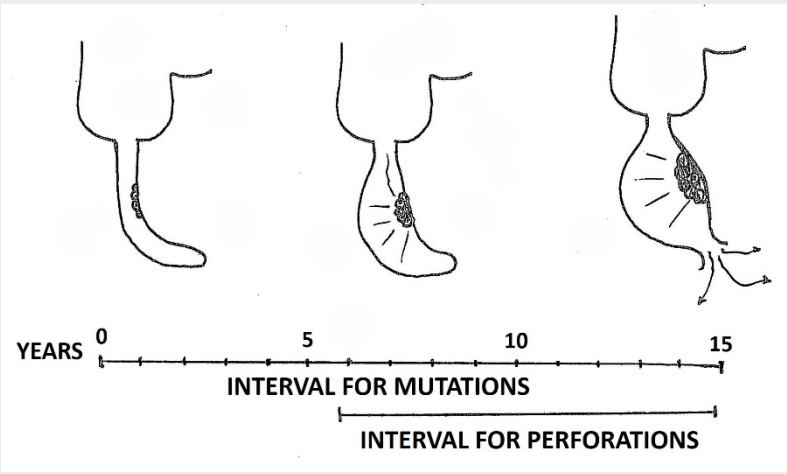
By Paul H. Sugarbaker

For at least 5 decades the histopathology of pseudomyxoma peritonei has remained enigmatic. How could such a small vestigial structure result in such a wide variety of histologies? The differences of histologies between patients with mucinous appendiceal tumors are incredibly large. The histology may show a benign appearing string of cells widely distributed within a sea of mucus with no invasion of the peritoneal surface. In contrast, other patients may show signet ring cells that are markedly atypical and poorly differentiated. These wildly malignant cells and the mucus they produce infiltrate into the structures directly beneath the peritoneum. Metastases to appendiceal and ileocolic lymph nodes are common. In between these two extremes of appendiceal mucinous neoplasms there exists a wide variety of histopathologic subtypes. Normal Carr has described this as a "spectrum of histologies" that describe many different non-aggressive versus aggressive tumor biologies.

There are two absolute requirements for the condition known as pseudomyxoma peritonei to occur. Within the lumen of the appendix a site of transition of normal epithelium to malignant epithelium must occur. This process continues over many years, even decades. The cause of the benign to malignant change is an increasing number of mutations in all likelihood brought about by the presence of a carcinogen. For colon cancer it is estimated that 81 mutations are required for an invasive cancer to develop. The number of mutations required for an invasive appendiceal neoplasm to develop has not been determined, but the requirement for multiple mutations to take place over time should be similar to colon cancer. Although the mutational process is not well understood, the longer the process continues, the greater the number of mutations, and the more aggressive the tumor biology.

The second requirement for pseudomyxoma peritonei to occur is a breach of the wall of the appendix. After this occurs the contents of the appendix may enter the free peritoneal space. The causation of this perforation will be related to several different factors but, as with a benign appendiceal perforation, the timing of this event is not predictable. This malignant process brought about by mutations and a perforation of the wall of the appendix is the basis for the "Mutations and Perforations Hypothesis."

The timing of the perforation controls the histopathology of the mucinous neoplasm that causes pseudomyxoma peritonei in an individual patient. If the blowout of the appendix, as a result of overproduction of mucinous tumor, occurs early in the process of mutation a low-grade appendiceal mucinous neoplasm will occur. If the perforation occurs late in the process of mutation, a high-grade of peritoneal metastases will occur. Perforations that occur between these two extremes will cause the 5 other in-between histologic types of mucinous neoplasms.



Using the Mutations and Perforations Hypothesis as a guide, the multiple histologic subtypes are predicted. The most minimally aggressive histologic subtype is low-grade appendiceal mucinous neoplasm (LAMN) with copious acellular mucus. This occurred in 78 of our 685 patients (11.4%) and was associated with a survival of 93% at 20 years. Fifty percent of the patients had at least one specimen that contained mucus with tumor cells. Their survival at 20 years was 66%. Approximately 5.4% of patients had the intermediate histologic subtype in which minute foci of high-grade tumor cells were mixed with LAMN. Survival was 60% at 20 years. In 23.2% of patients, all cells within the mucus were high-grade neoplasms. Their survival was 33% at 20 years. The lymph nodes were positive in 5.6% and these patients had a 23% survival at 20 years.

Histopathologic classification of PMP based on the natural history of the disease

TERMINOLOGY	20-Year Survival
LAMNa - acellular	93%
LAMNb – both cells and mucus	66%
HAMN-Int Mucinous appendiceal adenocarcinoma – intermediate type	60%
HAMN 1, 2, 3, S Mucinous appendiceal adenocarcinoma	
HAMN-1 Well differentiated, grade 1	32%
HAMN -2 Moderately differentiated, grade 2	28%
HAMN -3 Poorly differentiated, grade 3	20%
HAMN -S Appendiceal mucinous adenocarcinoma with signet ring morphology	25%
HAMN -LN Appendiceal mucinous adenocarcinoma with positive lymph nodes	23%

A comparison of histologies of mucinous and non-mucinous appendiceal malignancies will verify the importance of mucus production and a blowout of the appendix in the formation of the many different histologic subtypes of the mucinous appendiceal neoplasms. The non-mucinous tumors do perforate the wall of the appendix to cause peritoneal

metastases. However, the perforation occurs after the appendiceal neoplasm has invaded through the wall of the appendix to seed the peritoneal space. In order to acquire this capability for invasion, the number of mutations must have progressed to produce an aggressive tumor biology. Consequently, peritoneal metastases from a non-mucinous appendiceal neoplasm do not show a histologic spectrum as mucinous tumors do. The mechanism of perforation of the appendix with a mucinous as compared to a non-mucinous neoplasm is completely different. A "blowout" of the wall of the appendix occurs from the overproduction of mucus versus invasion of the appendix wall by aggressive cancer progression. For mucinous appendiceal tumors the timing of the perforation in relation to the number of mutations that have occurred is widely variable. Consequently, the tumor biology is widely variable.

In summary, the Mutations and Perforations Hypothesis states that appendiceal neoplasms that produce large amounts of mucus early on in the process of mutation are more likely to cause a blowout after a limited number of mutations. With less mucus the blowout is likely to occur after a larger number of mutations have occurred. High-grade mucinous appendiceal tumors with little mucus will perforate by a direct invasion of the wall of the appendix. There the mechanism for gaining access to the peritoneal space is very similar to that of a non-mucinous tumor. Mucus production along with the thin wall of the appendix and a variable timing of the perforation results in the great variation of histologic tumor types of appendix malignancy.

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

The Basingstoke Story

By Paul H. Sugarbaker and edited by Tom Cecil

The Basingstoke story was initiated three decades ago. It occurred in the operating room on Tuesday, March 22, 1994. The circumstances leading up to this event were definitely unusual. Professor Bill Heald, a world-renowned rectal cancer surgeon, learned of a young man in Scotland who recently had an open-and-close abdominal surgical procedure. A diagnosis of pseudomyxoma peritonei was suggested because biopsies showed a low-grade mucinous adenocarcinoma with tumor cells surrounded by copious mucus. Professor Heald had read or heard about a new controversial surgical treatment strategy that might be appropriate for this patient. Manuscripts suggested that cure of this dreadful disease was an option.

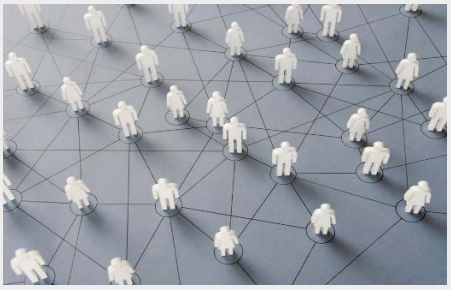
The strategy demanded the use of peritonectomy procedures and visceral resections to remove all visible disease within the abdomen and pelvis. This extensive surgery was followed by a flooding of the abdomen and pelvis with a chemotherapy solution to eradicate microscopic residual disease. Registrar Brendan Moran, Professor Heald and Paul Sugarbaker performed the surgery. It went well and Brian, the patient, was happy to return to Scotland disease-free approximately 2 weeks later. This and other several success stories concerning patients with advanced pseudomyxoma peritonei led to the approval of Basingstoke as the sole National Treatment Centre in the United Kingdom for pseudomyxoma peritonei in April of 2000.

Since this approval there has been a steady progress in the management of pseudomyxoma peritonei. A report of the first 1000 patients to be treated came in 2016. In the 74% of patients who had a complete cytoreduction, the 10-year survival was 70%. In the absence of these treatments most patients died within 10 years. Now, 24 years after the commissioning, the number of patients treated is over 4000. Five senior surgeons are required to manage the large number of patients undergoing cytoreductive surgery for peritoneal surface malignancy as well as a dedicated team of Peritoneal Malignancy Nurse Specialists. The center in Basingstoke is now called the Peritoneal Malignancy Institute (PMI). Currently, patients with appendiceal peritoneal metastases, colorectal peritoneal metastases, and peritoneal mesothelioma are cared for at the PMI but currently this is not the only site for treatment of peritoneal metastases in the United Kingdom. The Christie Cancer Centre in Manchester was appointed as a second designated treatment center in 2002. Also, Good Hope Hospital in Birmingham was commissioned in 2013. Currently, several sites within the UK that treat ovarian cancer are working to manage the peritoneal surface component of ovarian malignancy and deliver HIPEC. PMI have worked with the Royal Marsden team in London where this is now provided for suitable patients with ovarian cancer.

Education of surgeons for the demanding cytoreductive surgery required to successfully treat peritoneal metastases has required a large commitment from the Basingstoke group. They have mentored over 20 surgeons in the European School of Peritoneal Surface Oncology. Also, live surgery for peritoneal metastases from the Pelican Centre is a regular part of their frequent continuing medical education activity. Through the efforts of Mr. Brendan Moran, peritoneal treatment centers have been established in Dublin (Ireland) and Sydney (Australia). The team are now also supporting centers in Cardiff (Wales) and Glasgow (Scotland). They have recently published the PMI Manual: A Practical Guide to Peritoneal Malignancy. This much needed book focuses on understanding and assessing peritoneal surface malignancy, provides an exposition of treatments with cytoreductive surgery and HIPEC and carries with it a special focus on prevention and management of complications. Finally, the manual explores patient care after discharge from the North Hampshire Hospital and attempts to direct the reader towards the development of greater success in the future in the management of peritoneal metastases.

The PMI at Basingstoke treats the largest volume of peritoneal metastases patients with cytoreductive surgery and HIPEC in the world today. With the high level of expertise that they have demonstrated, they have been the stimulus to establish many other PSM treatment centers around the globe. The PMI is continually active in education of peritoneal surface malignancy through an active fellowship program through the European School of Peritoneal Surface Oncology and through the continuing medical education activity at the Pelican Centre. Congratulations from PSOGI World News to the dedicated persons who have maintained the PMI over the last 30 years.

For more information:
https://www.hampshirehospitals.nhs.uk/our-services/az-departments-and-specialties/peritoneal-malignancy



Section 3: Listing of upcoming events

By Aditi Bhatt

Meeting	Date	Venue	Registrations
CONFERENCES			
2nd Middle East PSOGI Conference	8-10th February, 2025	Jeddah, Saudi Arabia	Open https://psogi-me.ksau-hs.edu.sa/home/index
8th INDEPSO-ISPSM Annual Update in Peritoneal Malignancies	5-7th June, 2025 Preceded by a one-day video workshop on the 4th June, 2025	Calicut, India	To open in January 2025
15th International Congress on Peritoneal Surface Malignancies	29-31st October, 2025	Barcelona, Spain	To open in January 2025 https://psogicongress2025.com/
WORKSHOPS			
ESSO Advanced Course on the Management of HIPEC after CRS	6-8th March, 2025 Preceded by a one-day video workshop and live surgery on the 5th March, 2025	Berlin, Germany	Open https://www.essoweb.org/courses/esso-advanced-course-on-the-management-of-hipec-after-crs-2025/
Turkish Society of Colorectal Surgery PSM Video Workshop	11-12th July, 2025	Izmir, Turkey	To open in January 2025
FIRST ANNOUNCEMENT			
5th LATAM Latin American Congress on Peritoneal Surface Malignancies	2026 (dates will be announced in due course)	Colombia, South America	---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Fira Barcelona
The 15th PSOGI International Congress
on Peritoneal Surface Malignancies
October 29th • 31st, 2025
CONGRESS CHAIRS
Dr. Fernando Pereira
Madrid, Spain
Dr. Pedro Bretcha-Boix
Alicante, Spain
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https://psogicongress2025.com

Section 4: Alternatives to traditional HIPEC

Radspherin® - a novel alpha-radiopharmaceutical for intraperitoneal administration to combat residual microscopic disease following CRS with or without HIPEC

By: Stein Gunnar Larsen, Roy Hartvig Larsen, Øyvind Sverre Bruland

Peritoneal metastases (PM) pose considerable therapeutic challenges in several forms of cancer: most abundant in ovarian-, gastric- and colorectal-carcinomas (CRC). There are too many patients with dismal outcomes and unmet clinical needs. Complete cytoreductive surgery of PM (+/- HIPEC) leaves micrometastases and free-floating tumor cells behind in the abdominal cavity. Radspherin® is a microparticle-based radiopharmaceutical that provides non-systemic, receptor-independent, short-range alpha-radiation therapy to the peritoneal linings and liquid volumes of the abdominal cavity following intraperitoneal administration with a strong local retention. Radspherin® is under phase 2 clinical development in ovarian and CRC, but seems applicable in several different cancers, hence representing a "pipeline in a product". In this first issue of PSOGI World News we briefly review the clinical experiences of Radspherin® with CRC at center stage. Furthermore, we discuss some of the tumor biological characteristics of relevance to this novel treatment.

The main characteristics of Radspherin® are a microparticle-suspension suitable for infusion into the peritoneal cavity, with a size and density promoting distribution and local cavity retention, and an alpha-emitting radionuclide attached to the microparticle irradiating the immediate surrounding of the microparticle. As the microparticle is made mainly of calcium carbonate it is slowly degradable into harmless cations and anions. The recommended administered dose of Radspherin® comprises 0.7-1.0 gram of microparticles labelled with 7 MBq of ^{224}Ra in a physiologic buffered saline suspension. This represents several billion microparticles aiming to "cover" the entire serosal surface. This in strong contrast to the colloidal particle therapies based on ^{32}P cromic phosphate microparticles emitting energetic beta-radiation with several millimeters maximum range in tissues. It was used for decades and reported to be as effective as adjuvant cisplatin, but was later abandoned due to a higher late bowel complication rate. The short range of dense and cytotoxic ionizing radiation of less than 0.1 mm (3-10 cell diameters) from the alpha particles indicate that single cells and micrometastases can be irradiated but larger metastases of a few hundred micrometers may not be treated effectively by Radspherin®. Thus, the effect of Radspherin® depends on a complete surgical removal of all visible the tumors in the peritoneum.

A phase 1/2a study (EudraCT 2018-002803-33) has been performed in two dedicated CRS-HIPEC centers in Oslo, Norway and Uppsala, Sweden with the aim to evaluate safety, tolerability and signal of efficacy of Radspherin® injected intraperitoneally two days after CRS-HIPEC. All doses were well tolerated with dose-limiting toxicity (DLT) not reached. No treatment-related deaths occurred and none of the serious adverse events (SAEs) were considered related to Radspherin®. At 18-months, none of the 12 patients receiving 7 MBq experienced peritoneal recurrences, however four had non-peritoneal recurrence. The biodistribution of Radspherin® showed good peritoneal distribution and retention of the radiolabeled microparticles.

The current published data is from a limited number of patients. Accordingly, the results must be evaluated carefully. A further expansion cohort of 24 additional patients with colorectal origin given 7 MBq of Radspherin® have also been completed and closed for recruitment at the end of 2023, and patients are currently in long-term follow-up. The readout confirmed the previously published results on safety with only 15% peritoneal recurrences after 18 months follow-up. With current standard therapy, the expected peritoneal recurrence rate is approximately 50% after 18 months. 36 patients in total with colorectal cancer have received the selected dose, with results from the final 16 patients still pending full follow-up. This adds further confidence in the ongoing randomized controlled Phase 2 clinical trial for Radspherin® in patients with ovarian cancer. A similar randomized controlled multicentre studies for CRC are planned, but not yet started (IND no 168540/ EU CT no 2023-508496-37-00).

Even extensive parietal peritonectomy does not solve the possibility of tumor spread from visceral peritoneum. The visceral peritoneum is a surface penetrated by milky spots and lymphatic stomata that may allow malignant cells to proliferate also in sub peritoneal lymphatic channels, assumed to be a sanctuary site of tumor cells giving rise to failure of traditional HIPEC treatment. This challenging tumor biology may be a limitation also of Radspherin® that generates a very short-range alpha-particle radiation field to the surfaces and liquid volumes of the peritoneum and abdominal cavity, thereby delivering lethal doses to remaining micrometastases in the peritoneal linings and free-floating tumor cells after surgical resection. Aa mentioned above, alpha-emitting particles have limited penetration to 0.1 mm, and therefore single cells and micrometastases can be irradiated with low risk for damage to healthy surrounding tissues.

The low number of AEs and SAEs deemed related to Radspherin® supports that the treatment is well tolerated. The low amount of radioactivity detected in blood and urine indicate a low systemic exposure and no precautions related to external exposure from the associated gammas and X-rays seems to be required. The level of radiation exposure from the patients to workers at the hospital and family members is very low. Radspherin® has a mode of action and a benign safety profile that renders it suitable to be studied in combination with other treatments.

In conclusion, Radspherin® is a novel alpha-emitting radiopharmaceutical for postoperative administration into the peritoneal cavity, with minimal risk of damage to healthy tissue. Two early phase studies with Radspherin® in patients with peritoneal metastases have completed recruitment at the end of 2023 with 68 patients treated. One study in patients with peritoneal metastases from platinum-sensitive recurrent epithelial ovarian, Fallopian tube or primary peritoneal carcinoma (RAD-18-001, n=21, phase 1) scheduled for secondary cytoreduction, and one in patients with peritoneal metastases from colorectal cancer (RAD-18-002, n=47, phase 1/2a) scheduled for cytoreduction and HIPEC. The results are encouraging and warrant further clinical development in randomized studies. One in ovarian cancer is running and one in colorectal are planned, but not yet started.

Section 5: Pioneers of progress in peritoneal surface malignancy

Who was John Stricklin Spratt, Jr., MD?

By Paul H. Sugarbaker

John Stricklin Spratt, Jr., MD (3 January 1929 – 13 February 2005) holds an unforgettable position in the battle to eradicate peritoneal metastases from the natural history of gastrointestinal cancer. Dr. Spratt invented HIPEC.

John S. Spratt, Jr. was born in Texas and graduated from the University of Texas Southwestern Medical School in Dallas, Texas. After completion of his military service in Korea as a battalion surgeon in the Marines, he went to St. Louis, Missouri to complete a surgical residency at Washington University Barne's Hospital. After completing a research fellowship at the Mallinckrodt Institute, Dr. Spratt succeeded Everett D. Sugarbaker as the Surgeon-in-Chief and Medical Director of the Ellis Fischel State Cancer Hospital in Columbia, Missouri. This Cancer Hospital was built as part of the 1937 National Cancer Act. Dr. Spratt was the esteemed Director of the first National Cancer Institute-affiliated Cancer Center west of the Mississippi River. He served at the Ellis Fischel from 1961-1976.

As one would expect, the most challenging cancer patients from all over the State of Missouri were referred to the National Cancer Institute facility in Columbia. One of these patients who referred himself in the early 1970s had pseudomyxoma peritonei. The patient was a 35-year-old man who had a two-year history of early satiety and gradually increasing abdominal distention. Exploratory surgery evacuated a large volume of mucinous tumor. An omental biopsy showed a low-grade mucinous tumor compatible with pseudomyxoma peritonei. Dr. Spratt prepared his team to perform the first HIPEC in history. He was well aware of the two essential components of HIPEC. Heat and intraperitoneal chemotherapy were circulated throughout the abdomen and pelvis. The fluid that returned to the heat pump was filtered to remove cancer cells. The apparatus was called the Therapeutic Infusion Filtrations System (TIFS). The design and construction of the TIFS apparatus was presented by J. R. Palta, as a Master's thesis at the University of Missouri at Columbia, Missouri.

In 1976, Dr. Spratt moved from Columbia, Missouri to Louisville, Kentucky where he joined the University of Louisville faculty as the American Cancer Society Professor of Clinical Oncology in Surgery. The patient with pseudomyxoma peritonei was becoming more symptomatic. On February 24, 1979, Dr. Spratt performed a second surgical procedure. He found the appendix to be normal except for mucinous tumor on its surface. The greatest bulk of the peritoneal tumor was in the left abdomen. The ascending and transverse colon, greater omentum, spleen and distal pancreas were resected. Although this extensive resection removed a large extent to the tumor, the peritoneal surfaces were still studded extensively. The case report describes that tubes and drains were placed and then the abdomen was closed, making this a closed HIPEC procedure. The chemotherapy agent for HIPEC was thiotepa administered for 90 minutes. In the first 5 postoperative days, early postoperative intraperitoneal chemotherapy with methotrexate was administered. The final diagnosis was cystadenocarcinoma of the distal pancreas.

The patient's postoperative course was uneventful. He was well for the next eight months with a slow increase in the CEA. No further follow-up was available. Apparently, only a single patient was treated. In 1986, Dr. Spratt and coworkers published the monograph "Peritoneal Carcinomatosis: Anatomy, Physiology, Diagnosis and Management" in Current Problems in Cancer. It summarized his years of study of cancer dissemination into the peritoneal spaces. John S. Spratt, Jr. contributed throughout his surgical career to our fund of knowledge regarding gastrointestinal cancer and led the way towards the current global use of HIPEC.

Section 6: Focus of an important PSM protocol

Peritoneal metastasis in gastric cancer treated with bidirectional approach comprising PIPAC and systemic chemotherapy

By Shigeki Kusamura

Peritoneal metastasis (PM) in advanced gastric cancer represents a critical clinical challenge, often leading to terminal outcomes. Current systemic chemotherapy options provide a median survival of no more than six months. Established treatments, such as cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), are applicable only to a subset of patients with a very limited Peritoneal Cancer Index (PCI). This limitation highlights the need for novel therapies. One promising innovation is Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC), which can be used to expand eligibility through a neoadjuvant convergent approach.

PIPAC introduces a novel method of delivering chemotherapy directly into the peritoneal cavity as an aerosol. This technique ensures even drug distribution and generates a pressure gradient to overcome tumor interstitial fluid pressures—a common barrier in cancer therapy. Like other intraperitoneal approaches, compared to conventional intravenous chemotherapy, PIPAC achieves higher local drug concentrations with minimal systemic absorption, reducing toxicity. Experimental studies validate its benefits, including superior drug penetration and fewer side effects. Furthermore, PIPAC is designed for repeated applications every 4–6 weeks, enabling concurrent intravenous chemotherapy.

The EstoK 01 Trial

The EstoK 01 trial was developed to assess the efficacy of PIPAC combined with intravenous chemotherapy (Arm A) compared to intravenous chemotherapy alone (Arm B) in gastric cancer patients with PM. This multicenter, randomized Phase II study includes patients with PCI >8, randomized 1:1 during laparoscopic assessment. The primary endpoint is progression-free survival (PFS) over two years, defined as the time from randomization to clinical or radiological progression or death. Secondary endpoints include 24-month overall survival, safety, quality of life (QoL) measured using EORTC QLQ-C30 and QLQ-STO22, feasibility of completing three PIPAC cycles, and secondary resectability.

PIPAC procedures involve establishing a pneumoperitoneum (12 mmHg, 37°C) via laparoscopy and delivering aerosolized chemotherapy (cisplatin 10.5 mg/m², doxorubicin 2.1 mg/m²). Treatments are repeated every 6–8 weeks, with patients typically undergoing 2.5 cycles. Sample size calculations used a two-sided log-rank test, with type I error set at 5% and power at 85%. Assuming a median PFS of six months in the control arm and 12 months in the experimental arm, 78 events were required, resulting in a total sample size of 94 patients. Recruitment was completed earlier this year, and results are eagerly awaited.

Challenges in Trial Design and Execution

Despite its strong design, the EstoK 01 trial faces key challenges, particularly in assessing PFS as the primary endpoint. PFS evaluation in PM is limited by the Response Evaluation Criteria in Solid Tumors (RECIST), which depend on measuring solid tumor dimensions. These criteria are often ineffective for PM, characterized by diffuse, nodular, or non-mass-forming lesions. Standard imaging modalities, such as CT and MRI, struggle to detect small implants and assess disease extent accurately, further complicated by the absence of standardized imaging protocols. Recommendations from ESGAR, in collaboration with ESUR, PSOGI, and EANM, propose improvements but are not yet widely implemented in practice.

Another challenge is the baseline median PFS of six months assumed for the control arm in the sample size calculation. While this figure reflects real-world data, outcomes in clinical trials often improve due to optimized care provided to all participants. Enhanced monitoring, strict protocols, and better supportive treatments can lead to improved baseline outcomes, reducing the observed delta between arms and affecting statistical power. For example, in the PRODIGE 7 trial for colorectal peritoneal metastases, both the experimental (HIPEC) and control (CRS alone) groups achieved a median OS of approximately 40 months, significantly better than real-world outcomes. This demonstrates how trial conditions can elevate outcomes across arms. Similarly, the EstoK 01 trial may face reduced PFS differences due to improved baseline performance, highlighting the importance of cautious statistical assumptions to accurately assess PIPAC's benefits.

Addressing Feasibility and Optimism in Design

Feasibility concerns, particularly about completing the trial within a reasonable timeframe, led to inflating the delta to six months, assuming a 12-month PFS in the experimental arm (a 50% risk reduction). This strategy reduces the required sample size by increasing the assumed difference between experimental and control arms. However, this optimistic assumption lacks strong evidence. Most PIPAC studies in gastric cancer PM report overall survival, not PFS, and the assumed benefit appears extrapolated from limited pathological response data. While inflating the delta improves feasibility, it risks overestimating the effect and missing smaller but meaningful benefits.

Population variability adds complexity to the trial by increasing the variability in treatment outcomes, which can dilute the observed effect size of PIPAC. Broad eligibility criteria, including diverse subgroups such as gastroesophageal and distal tumors, diffuse and intestinal histologies, and both synchronous and metachronous metastases, contribute to this variability. The allowance of multiple systemic chemotherapy regimens further amplifies this effect. Additionally, the inherent heterogeneity of gastric cancer, with distinct molecular phenotypes linked to varying biological behaviours and therapeutic responses, increases outcome variability. This broader variability makes it more challenging to detect the assumed six-month improvement in PFS and heightens the risk of a Type II error, where the trial fails to detect a true effect due to the masking influence of heterogeneity.

In summary, inflating the delta increases the risk of false negatives. A smaller actual effect could lead to trial failure, potentially dismissing a beneficial treatment of PIPAC. While smaller sample sizes improve feasibility of completing the accrual of patients, overly optimistic assumptions risk wasting resources and hindering therapy development. A more realistic delta, such as a 33% risk reduction (median PFS improvement from 6 to 9 months), combined with adjustments like lowering power to 70% and increasing alpha to 10%, would be more practical. These modifications align with the exploratory nature of Phase II trials, which aim to identify signals for Phase III testing rather than provide definitive evidence.

Conclusion

The EstoK 01 trial marks a significant step forward in evaluating PIPAC for gastric cancer PM. However, balancing feasibility with realistic assumptions is essential for meaningful results. Refining endpoints, acknowledging population heterogeneity, and adopting practical statistical adjustments could have maximized the trial's potential to detect true experimental treatment effects while minimizing the risk of overlooking them due to overoptimistic expectations. These strategies are crucial for advancing novel treatment options for challenging condition like GCPM.

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.