Peritoneal Surface Oncology PSOGI Group International

# PSOGI World News

January 2026
Issue #6

## A quarterly newsletter with the latest news, views and announcements



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

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# Section 1: Progress in Clinical or Laboratory Research

## *Can NIPS Paclitaxel Plus S1 Succeed with GCPM when All Other Strategies Have Failed? If So, Why?*

By Hironori Ishigami

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**Introduction**

Systemic chemotherapy remains the standard of care for gastric cancer with peritoneal metastasis. Although therapeutic outcomes have improved with the recent development of novel agents, the prognosis remains poor, with a median overall survival of approximately one year or less. The peritoneum has a limited blood supply and restricted drug penetration due to the peritoneal–plasma barrier; consequently, systemically administered agents reach peritoneal lesions only in minimal concentrations, resulting in suboptimal antitumor efficacy. Intraperitoneal administration of anticancer drugs therefore represents a rational strategy to overcome these limitations.

Hyperthermic intraperitoneal chemotherapy (HIPEC) has been developed primarily in Western countries to enhance the cytotoxic efficacy of intraperitoneal chemotherapy by increasing tumor cell sensitivity, improving drug penetration, and inducing direct thermal cytotoxicity. Although promising results have been reported, its superiority over systemic chemotherapy alone has not yet been conclusively demonstrated. More recently, pressurized intraperitoneal aerosol chemotherapy (PIPAC), which aims to improve drug distribution and tissue penetration through aerosolization and intraperitoneal pressurization, has been developed and has attracted considerable interest.

In contrast, in Japan and other East Asian countries, a treatment strategy involving repeated intraperitoneal administration of anticancer agents via an implanted peritoneal access port in combination with systemic chemotherapy has been developed. This approach has traditionally been referred to as neoadjuvant intraperitoneal and systemic chemotherapy (NIPS). However, in recent years, the term neoadjuvant has become increasingly restricted to chemotherapy administered before a preplanned curative resection in patients with resectable disease and without distant metastasis, leading to confusion when applied to metastatic gastric cancer. Because “NIPS” for gastric cancer does not conform to this definition, recent Asian consensus meetings have proposed redefining NIPS as normothermic intraperitoneal and systemic chemotherapy (*Zhu et al., Gastric Cancer 2025;28:731–748*).

**Concept of NIPS**

NIPS represents a treatment concept in which intraperitoneal chemotherapy is administered repeatedly over a prolonged period in parallel with systemic chemotherapy, rather than as a single preoperative intervention. Unlike HIPEC or PIPAC, which are typically administered as single or intermittent procedures, NIPS is intended for long-term disease control. This approach is particularly well suited to the chronic and aggressive nature of peritoneal metastasis from gastric cancer.

Within this framework, intraperitoneal therapy primarily targets peritoneal surface disease, while systemic chemotherapy addresses the primary tumor as well as peritoneal and extra-peritoneal metastases, including occult disease. This complementary division of roles forms the biological and clinical rationale for NIPS.

**Overall Treatment Strategy and Schedule** (Figure 1)

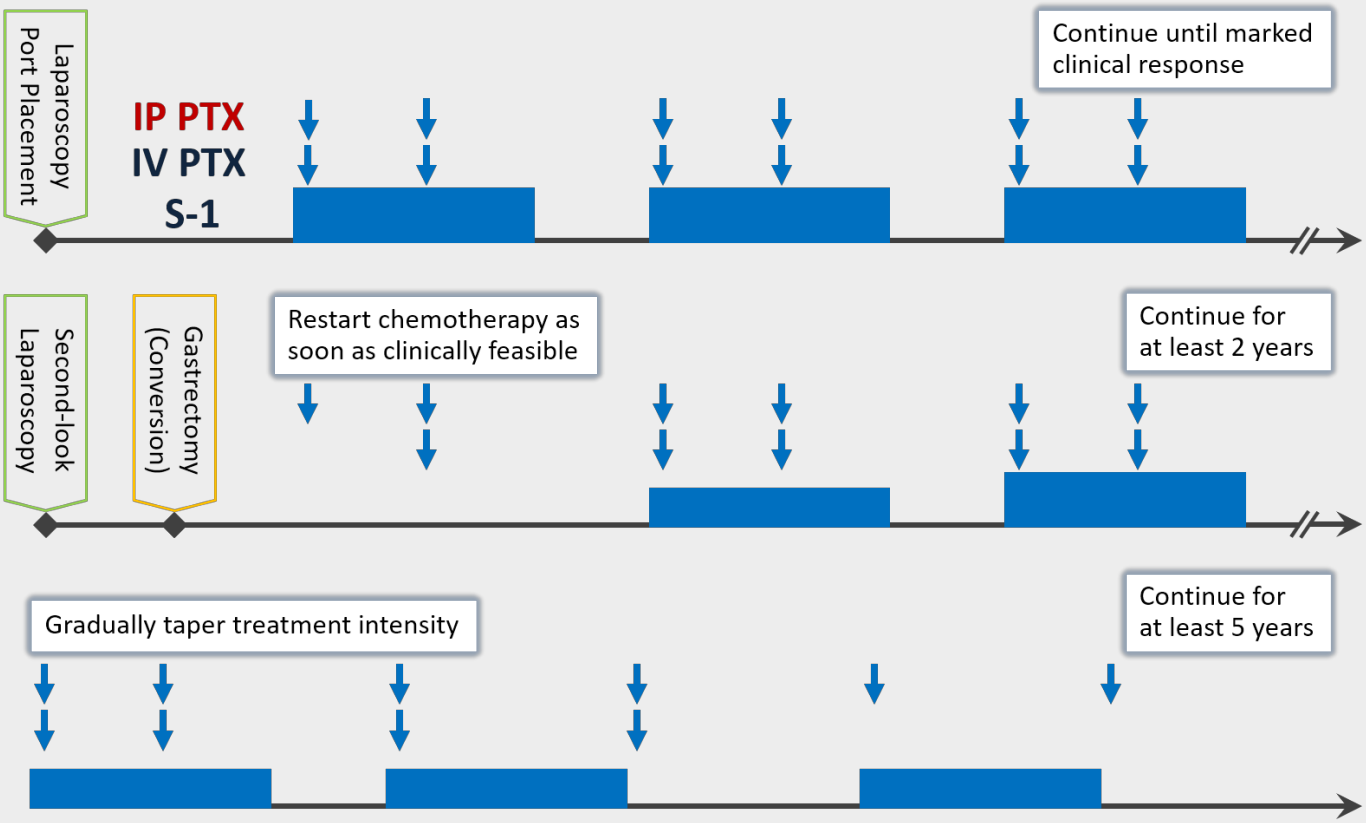


***Figure 1.*** *Treatment Schedule of NIPS Paclitaxel. After diagnostic laparoscopy and intraperitoneal port implantation, combined intraperitoneal and systemic chemotherapy is administered repeatedly until curative-intent resection is considered feasible. Second-look laparoscopy is performed to assess peritoneal disease, followed by gastrectomy when indicated. Postoperative chemotherapy is restarted as soon as clinically feasible and continued long term with gradual tapering. This figure illustrates a representative schedule based on S-1/PTX plus intraperitoneal PTX regimen.*

Following diagnostic laparoscopy and implantation of an intraperitoneal access port (Figure 2), combined intraperitoneal and systemic chemotherapy is administered repeatedly until curative resection is considered potentially achievable based on clinical and radiological assessments. During this induction phase, treatment is continued to maximize control of peritoneal disease while maintaining tolerability.

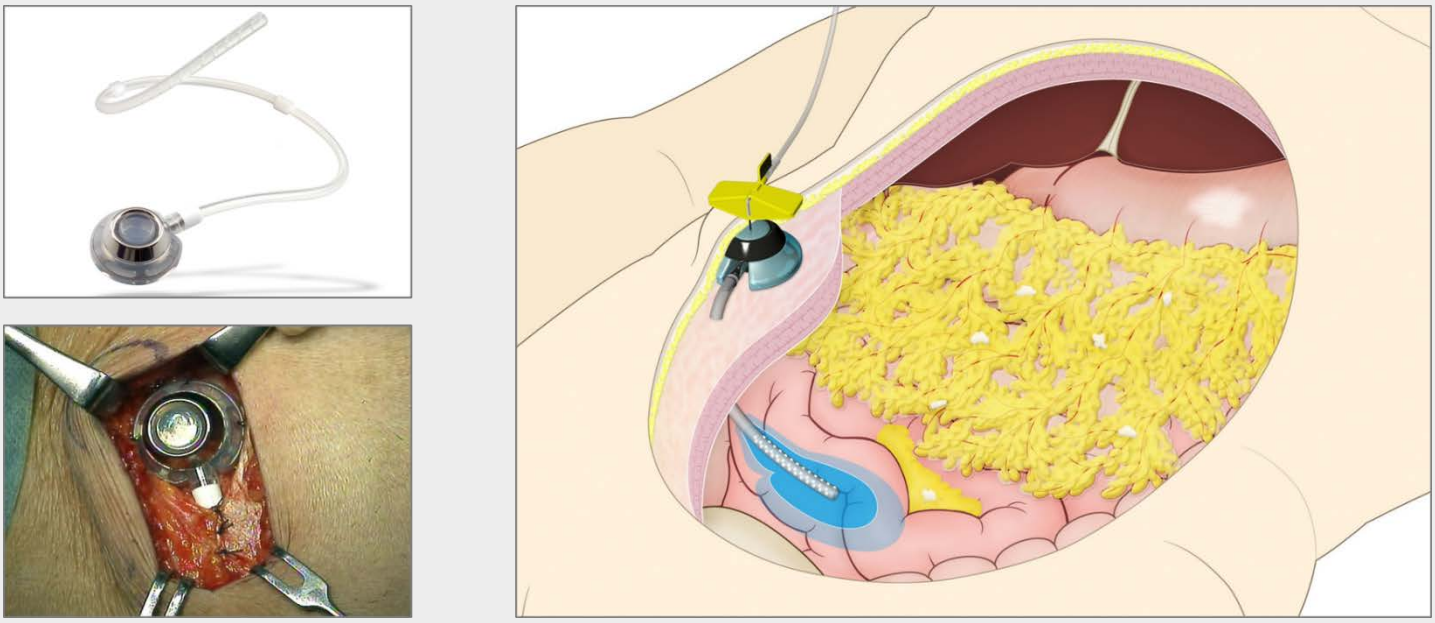

***Figure 2.*** *Intraperitoneal Chemotherapy via an Implanted Port. Intraperitoneal chemotherapy is delivered through an implanted peritoneal access port, allowing repeated administration and combination with systemic chemotherapy.*

Second-look laparoscopy is then performed to directly evaluate the response of peritoneal metastasis. If marked shrinkage or disappearance of peritoneal lesions is confirmed and curative resection is deemed feasible, gastrectomy is performed. In cases in which peritoneal disease remains unresectable, combination chemotherapy is continued.

Postoperatively, combination chemotherapy is restarted as soon as clinically feasible, using a stepwise approach to ensure safety and treatment continuity. Treatment is subsequently continued for a minimum of two years, provided that disease control is maintained and treatment-related toxicities remain manageable. After prolonged disease stabilization, treatment intensity is gradually tapered according to individual patient tolerance and clinical course, with the aim of sustaining long-term disease control.

**Pharmacologic Rationale for Intraperitoneal Paclitaxel (PTX)**

Paclitaxel (PTX) is predominantly used in NIPS because of its favorable pharmacokinetic properties. PTX is a lipophilic agent with a high molecular weight, resulting in slow absorption from the peritoneal cavity after intraperitoneal administration and sustained high intraperitoneal drug concentrations. PTX is administered

intraperitoneally in a total of one liter of normal saline through an implanted port or catheter, concurrently with intravenous administration of PTX or other drugs. A pharmacokinetic study of the PHOENIX-GC regimen, combining intravenous PTX at 50 mg/m² with intraperitoneal PTX at 20 mg/m², demonstrated that intraperitoneal PTX concentrations remained above the effective therapeutic level for more than 72 hours. The area under the concentration–time curve (AUC) in the peritoneal cavity was approximately 60-fold higher than that in the systemic circulation (*Ishigami et al., Oncology 2009;76:311–314*). Because of slow absorption through the peritoneum, systemic exposure is limited, resulting in minimal systemic adverse events and allowing safe combination with systemic chemotherapy.

**Local Safety of Intraperitoneal PTX**

When administering anticancer agents intraperitoneally, careful attention must be paid to potential local adverse events within the peritoneal cavity, including damage to intraperitoneal organs and the peritoneum. In an early dose-escalation study of intraperitoneal PTX, grade 2 abdominal pain, nausea, and vomiting were reported at a dose of 75 mg/m², suggesting transient peritoneal irritation. However, these adverse events have not been observed at the currently adopted dose range of 20–60 mg/m², and no cases of intraperitoneal organ injury have been reported.

Second-look laparoscopy after several courses of intraperitoneal PTX occasionally reveals mild, map-like white opacities and thickening of the small intestinal serosa, which are clinically asymptomatic and do not cause functional impairment. In addition, because PTX inhibits cellular proliferation, intraperitoneal administration rarely induces intra-abdominal adhesions, enabling long-term continuation of treatment. These favorable pharmacokinetic and safety profiles provide an important foundation for repeated and prolonged intraperitoneal administration.

**Rationale for NIPS PTX**

Intraperitoneal PTX is effective against tumors located on the peritoneal surface owing to sustained high drug concentrations within the peritoneal cavity; however, the depth of drug penetration from the tumor surface is limited and has been reported to be less than 1 mm in preclinical studies. Consequently, PTX fails to reach deeper tumor compartments when peritoneal metastases form bulky nodules or infiltrate subperitoneal tissues.

Furthermore, in patients with a history of abdominal surgery, postoperative adhesions may create intraperitoneal compartments that are inaccessible to intraperitoneally administered agents, further compromising drug distribution. In addition, intraperitoneal chemotherapy has no therapeutic effect on extra-peritoneal metastases, including occult disease, or on the primary tumor.

Taken together, these limitations provide a strong rationale for NIPS, in which intraperitoneal PTX is administered repeatedly in combination with systemic chemotherapy to achieve sustained control of peritoneal disease while simultaneously targeting the primary tumor and extra-peritoneal metastases (Figure 3).

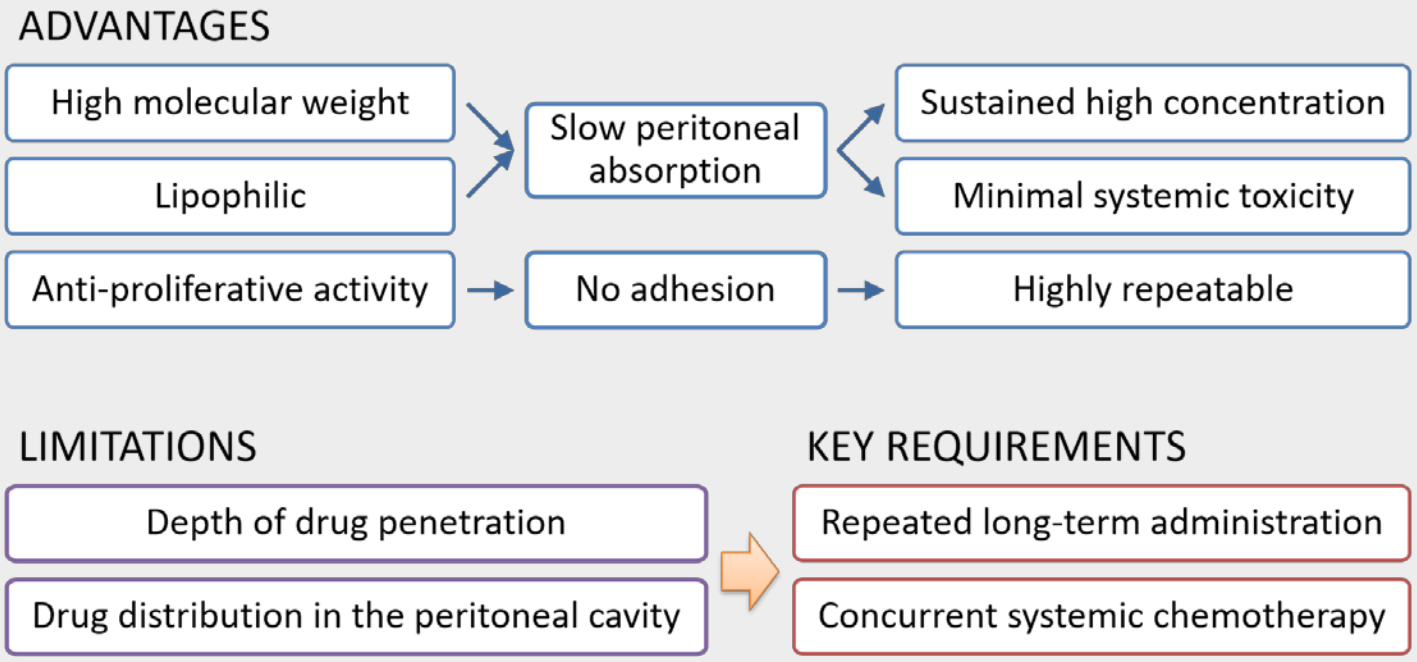


***Figure 3.*** *Rationale for NIPS Paclitaxel. Intraperitoneal paclitaxel achieves sustained high peritoneal drug concentrations but is limited by restricted tissue penetration, necessitating frequent administration and combination with systemic chemotherapy, which together constitute the rationale for NIPS.*

**Selection of Systemic Chemotherapy to Augment in NIPS PTX**

Ideally, systemic chemotherapy combined with intraperitoneal therapy would consist of agents highly effective against peritoneal metastasis. However, no evidence currently identifies an optimal systemic regimen for peritoneal disease, and such comparisons are unlikely to be addressed in future trials. Given that peritoneal metastasis can be effectively controlled by intraperitoneal PTX, it is more rational to select systemic agents with broad antitumor activity against systemic tumor components.

Accordingly, systemic chemotherapy should follow national or regional treatment guidelines. In Japan, fluoropyrimidine–platinum combinations with the addition of trastuzumab, nivolumab, or zolbetuximab based on biomarker status are recommended, whereas FLOT-based regimens are commonly used in Western countries.

To date, clinical trials have evaluated combinations of intraperitoneal PTX with cytotoxic regimens such as S-1/PTX, S-1/oxaliplatin, capecitabine/oxaliplatin, and FOLFOX. Trials incorporating immune checkpoint inhibitors, including nivolumab, are currently ongoing. Preliminary information from personal communications suggests no unexpected toxicities and notable clinical responses in selected cases. Based on its pharmacokinetic profile, intraperitoneal PTX is expected to be compatible with a wide range of systemic agents, making NIPS a flexible platform for combination strategies.

**Importance of Safety and Treatment Continuity**

When combining systemic chemotherapy with intraperitoneal PTX, safety and treatment continuity are as important as antitumor efficacy. In NIPS, intraperitoneal PTX constitutes the backbone of treatment; therefore, maintaining the planned weekly or biweekly schedule is critical. Delays or omissions due to systemic chemotherapy–related toxicities may compromise overall efficacy.

Current systemic regimens are often administered at relatively high doses, which may limit their tolerability in real-world practice. When patients suffer from adverse events, reducing the dose or the number of agents should be considered. Once peritoneal metastasis is adequately controlled by intraperitoneal PTX, there is no compelling rationale to intensify systemic chemotherapy to near-maximal doses.

**Clinical Evidence Supporting NIPS PTX**

Clinical trial results evaluating NIPS PTX have been reported from multiple countries, including Japan, China, Korea, and Singapore. In phase I studies, the recommended dose of intraperitoneal PTX was established at 20–80 mg/m² based on systemic dose-limiting toxicities (Table 1), and phase II studies subsequently reported comparable survival outcomes across this dose range (Table 2). These findings suggest that intraperitoneal drug concentrations may already be sufficiently high even at 20 mg/m², and that drug penetration depth, rather than dose escalation, may represent the primary limiting factor for therapeutic efficacy. Notably, gastrectomy following a marked response to combination chemotherapy was performed in approximately 18–63% of patients, and several studies have reported improved survival outcomes among those who underwent conversion surgery (*Ishigami et al., Gastric Cancer 2017;20:128–134*).

**Table 1. Phase I studies of IP PTX combined with systemic chemotherapy**

| Author Year | Regimen | IP PTX dose schedule | n | RD | MTD | DLT (adverse event, n/cohort, dose) | Preliminary efficacy results |
|---|---|---|---|---|---|---|---|
| Ishigami 2009 | S-1/PTX +IP PTX | 20–40 mg/m$^2$ day1, 8, q21 | 9 | 20 mg/m$^2$ | 30 mg/m$^2$ | leukopenia in 1/6 at 20 mg/m$^2$, FN, diarrhea in 2/3 at 30 mg/m$^2$ | CY1 -> CY0 86% |
| Ishigami 2012 | SOX +IP PTX | 20–40 mg/m$^2$ day1, 8, q21 | 12 | 40 mg/m$^2$ | Not reached | no | CY1 -> CY0 100% |
| Kobayashi 2020 | S-1/CDDP +IP PTX | 15–20 mg/m$^2$ day1, 8, 22, q35 | 9 | 20 mg/m$^2$ | Not reached | no | CY1 -> CY0 57% |
| Vatandoust 2021 | Cape/CDDP +IP PTX | 10–30 mg/m$^2$ day1, 8, q21 | 15 | 30 mg/m$^2$ | Not reached | bowel obstruction in 1/6 at 10 mg/m$^2$, FN in 1/3 in 30 mg/m$^2$ | 1-yr OS 46.7% |
| Kim 2021 | SOX +IP PTX | 20–80 mg/m$^2$ day1, 8, q21 | 9 | 80 mg/m$^2$ | Not reached | no | PCI decreased 44% |
| Kang 2022 | FOLFOX +IP PTX | 40–100 mg/m$^2$ day1, q14 | 13 | Bi-weekly 60 mg/m$^2$ | 80 mg/m$^2$ | FN in 2/6 at 80 mg/m$^2$ | mOS 16.6 months |
| Badgwell 2024 | IP PTX | 40–100 mg/m$^2$ d1, 8, 15, q28 | 25 | Bi-weekly 100 mg/m$^2$ | 100 mg/m$^2$ | neutropenia, leukopenia in 4, FN, fatigue, abd. pain in 1 at 100 mg/m2 | mOS 17.9 months |

*Abbreviations: RD, recommended dose; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; PTX, paclitaxel; IP, intraperitoneal; SOX, S-1/oxaliplatin; Cape, capecitabine; CDDP, cisplatin; mOS, median overall survival.*

**Table 2. Phase II studies of IP PTX combined with systemic chemotherapy**

| Author Year | Regimen | IP PTX dose schedule | n | Course (median) | Primary endpoint | Results | Other efficacy results | Conversion surgery N (%), mOS |
|---|---|---|---|---|---|---|---|---|
| Yamaguchi 2013 | S-1/PTX +IP PTX | 20 mg/m$^2$ day1, 8, q21 | 35 | 11 | 1-yr OS | 77.1% (95% CI, 60.5–88.1) | mOS 17.6 months (95% CI, 13.4–NR) | 21 (60%) N/A |
| Fujiwara 2016 | SOX +IP PTX | 40 mg/m$^2$ day1, 8, q21 | 60 | 10 | 1-yr OS | 71% (95% CI, 58–81) | N/A | 22 (37%) NR |
| Kobayashi 2020 | S-1/CDDP +IP PTX | 20 mg/m$^2$ day1, 8, 22, q35 | 53 | 7 | 1-yr OS | 74% (95% CI, 60–83) | mOS 19.4 months (95% CI, 16.7–NR) | 14 (26%) N/A |
| Saito 2021 | SOX +IP PTX | 40 mg/m$^2$ day1, 8, q21 | 44 | 16 | 1-yr OS | 79.5% (95% CI, 64.4–88.8) | mOS 25.8 months (95% CI, 16.3–NR) | 20 (45%) NR |
| Shi 2021 | SOX +IP PTX | 40 mg/m$^2$ day1, 8, q21 | 30 | 6 | mPFS | 6.6 months (95% CI, 4.7–8.5) | mOS 15.1 months (95% CI, 12.4–17.8) | 11 (37%) 24.6 months |
| Yang 2022 | S-1/PTX +IP PTX | 20 mg/m$^2$ day1, 8, q21 | 67 | N/A | 1-yr OS | 67.2% (95% CI, 56.8–79.4) | mOS 19.3 months (95% CI, 16.4–22.2) | 42 (63%) 22.3 months |
| Tu 2022 | SOX +IP PTX | 80 mg/m$^2$ day1, q21 | 49 | 3 | 1-yr OS | 81.6% (95% CI, 68.6–90.0) | mOS 16.9 months (95% CI, 13.6–20.2) | 9 (18%) 33.4 months |
| Chia 2022 | CapeOX +IP PTX | 40 mg/m$^2$ day1, 8, q21 | 44 | 8 | mOS | 14.6 months (95% CI, 12.6–16.6) | 1-yr OS 67.8% | 13 (30%) 24.2 months |

*Abbreviations: PTX, paclitaxel; IP, intraperitoneal; SOX, S-1/oxaliplatin; CDDP, cisplatin; CapeOX, capecitabine/oxaliplatin; mOS, median overall survival.*

The phase III PHOENIX-GC trial did not reach statistical superiority of NIPS PTX over S-1 plus cisplatin (median overall survival [OS], 17.7 vs. 15.2 months; $p$ = 0.080; hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.49–

1.04); however, exploratory analyses suggested a clinically meaningful survival benefit (Ishigami et al., *J Clin Oncol* 2018;36:1922–1929). More recently, the DRAGON-01 trial demonstrated a significant survival advantage of NIPS PTX compared with S-1 plus PTX (median OS, 19.4 vs. 13.9 months; $p = 0.005$; HR, 0.66; 95% CI, 0.49–0.88) (*Yan et al., J Clin Oncol 2025;43:suppl 4; abstr 327*). Although the control regimen does not fully reflect current standard-of-care practice and has therefore been subject to debate, this study nonetheless provides robust evidence supporting the therapeutic efficacy of NIPS PTX. Comparisons between the PHOENIX-GC and DRAGON-01 trials are summarized in Table 3.

**Table 3. Comparisons between the PHOENIX-GC and DRAGON-01 trials**

| | **PHOENIX-GC trial** | | **DRAGON-01 trial** | |
|---|---|---|---|---|
| | **NIPS** | **Control** | **NIPS** | **Control** |
| Regimen | S-1/PTX + IP PTX | S-1/cisplatin | S-1/PTX + IP PTX | S-1/PTX |
| Patients in the full analysis set | 114 | 50 | 148 | 74 |
| Prior chemotherapy (<2 months) | 26 (23%) | 12 (24%) | 0 | 0 |
| Limited peritoneal metastasis* | $P_1$: 3 (3%) | $P_1$: 3 (6%) | P1a: 32 (22%) | P1a: 19 (26%) |
| Ascites volume at baseline | Unbalanced | | Balanced | |
| No / small / moderate | 42 / 34 / 38 | 29 / 14 / 7 | | |
| ≤ 300 mL / > 300 mL | | | 98 / 50 | 48 / 26 |
| Median overall survival | 17.7 months | 15.2 months | 19.4 months | 13.9 months |
| Log-rank test, Cox regression | $p = 0.080$; HR 0.72 (95% CI, 0.49–1.04) | | $p = 0.0072$; HR 0.67 (95% CI, 0.50–0.90) | |
| Crossover to NIPS | – | 6 (12%) | – | 0 |
| Median OS excluding crossover | – | 14.3 months | – | 13.9 months |
| Median follow-up period | 16.6 months | | 72.2 months | |
| Trial period | 4 years (2011–2015) | | 7 years (2017–2024) | |

** Peritoneal metastasis classified as $P_1$ (until 1999) or P1a (since 2017) according to the Japanese classification system.*

*$P_1$: Disseminated metastasis in the peritoneum adjacent to the gastric carcinoma (above the transverse colon, including the greater omentum) without involvement of the distant peritoneum. P1a: Disseminated metastasis involving the stomach, spleen, omentum, lesser omentum, anterior mesentery of the transverse colon, and pancreatic capsule.*

Based largely on these trial results, an Asian expert consensus meeting concluded that "NIPS is recommended for patients with confirmed peritoneal metastasis" (*Zhu et al., Gastric Cancer 2025;28:731–748*). In addition, the Peritoneal Metastasis Working Group of the International Gastric Cancer Association issued a consensus statement that "catheter-administered PTX may be recommended in clinical practice in Eastern Asian populations." Randomized controlled trials are currently ongoing in Korea, Europe, and the United States, and their results are eagerly awaited.

**Conceptual Comparison with Other Intraperitoneal Modalities (**Figure 4**)**

| | HIPEC | PIPAC | NIPS |
|---|---|---|---|
| Intrinsic antitumor activity of commonly used agents | ★★ | ★ | ★★★ |
| Intraperitoneal drug concentration | ★★ | ★★ | ★★ |
| Duration of effective tumor drug exposure | ★ | ★★ | ★★★ |
| Depth of drug penetration into tumor tissue | ★★★ | ★★★ | ★★ |
| Feasibility of frequent and long-term treatment | ★ | ★★ | ★★★ |

***Figure 4.*** *Conceptual comparison of intraperitoneal chemotherapy modalities. HIPEC, PIPAC, and NIPS are qualitatively compared across key pharmacologic and treatment-related dimensions, including antitumor activity, intraperitoneal drug concentration, duration of tumor exposure, tissue penetration, and feasibility of frequent and long-term treatment. Star ratings indicate relative, conceptual assessments based on typical pharmacologic characteristics and clinical implementation, reflecting the authors' expert opinion rather than direct comparative clinical evidence.*

The efficacy of intraperitoneal therapy is influenced by multiple factors, including intrinsic antitumor activity, intraperitoneal drug concentration, duration of tumor exposure, penetration depth, and treatment frequency and duration. While HIPEC and PIPAC enhance penetration depth through hyperthermia or pressure, NIPS PTX offers advantages in other critical aspects.

PTX is one of the most active monotherapy agents against gastric cancer, allows sustained intraperitoneal exposure, and can be administered repeatedly over prolonged periods. Given the aggressive biology of peritoneal metastases from gastric cancer and their rapid regrowth after response, treatment frequency and duration appear to be particularly important determinants of durable disease control. Although direct superiority among the three modalities cannot be determined, the optimal intraperitoneal approach should be individualized according to disease extent and biology, taking into account the distinct advantages and limitations of each treatment strategy. We anticipate that the accumulation of further clinical experience and clinical studies will help to clarify these considerations and refine treatment selection in the future.

**Conclusions and Future Perspectives**

NIPS PTX is a biologically rational and clinically feasible strategy for gastric cancer with peritoneal metastasis. Its pharmacokinetic profile enables sustained intraperitoneal exposure with minimal systemic toxicity, allowing long-term repetitive treatment.

Within the NIPS framework, intraperitoneal PTX functions as the therapeutic backbone for peritoneal disease control, while systemic chemotherapy complements this approach by targeting primary and extra-peritoneal disease. Treatment continuity and prolonged exposure, rather than maximal dose intensity, appear central to its clinical effectiveness.

Looking forward, NIPS PTX should be regarded as a treatment platform that can be augmented by immune checkpoint inhibitors and biomarker-driven targeted agents. As evidence from ongoing trials accumulates, NIPS PTX may play an increasing role in sustained disease control and selected conversion strategies for gastric cancer with peritoneal metastasis.

# Section 2: Exposition of progress and productivity of an established PSM Center of Excellence

## *Rationale for PIPAC in Gastric Cancer. Is GCPM the Perfect Disease for Aerosolized Chemotherapy Administration?*

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**Introduction**

Peritoneal metastases (PM) represent a frequent pattern of dissemination in gastric cancer and are associated with a dismal prognosis. Conventional systemic chemotherapy (SC) has consistently demonstrated limited efficacy in this setting. Although recent advances - including HER2 and claudin-18.2 targeted therapies, and immune checkpoint inhibitors - have improved outcomes in selected patients, a substantial proportion remain ineligible for these treatments. Moreover, despite rapid therapeutic innovation in metastatic gastric cancer, clinical trials predominantly focus on patients with hepatic, lymph nodes or pulmonary metastases, largely due to the intrinsic challenges of assessing treatment response in PM. This paradigm neglects the distinct biological behavior of PM, which differs from hematogenous dissemination.

Intraperitoneal chemotherapy has been explored for several decades in gastric PM, with encouraging and reproducible signals of efficacy. However, its integration into clinical practice varies considerably across regions, reflecting differences in oncological culture and in the degree of collaboration between medical oncologists and peritoneal surface malignancy surgeons. This heterogeneity - both a cause and a consequence - has directly influenced the role attributed to intraperitoneal therapies in gastric PM, as well as the level of engagement of medical oncologists in clinical research dedicated to this specific condition.

**What is PIPAC?**

Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) is an innovative drug-delivery technic designed to administer intraperitoneal chemotherapy as an aerosol. Beyond exploiting the pharmacokinetic advantages of the plasma-peritoneal barrier shared by all intraperitoneal approaches, PIPAC leverages the physicochemical properties of aerosolization (*Reymond MA, Hu B, Garcia A, et al. Surg Endosc. 2000;14:51–55. https://doi.org/10.1007/s004649900010*). Using a high-technicity nebulizer, treatment agents (chemotherapy, targeted therapies, oncolytic viruses, nanoparticles…) are transformed into micronized droplets which, under a standardized 12-mmHg capnoperitoneum, achieve enhanced tissue penetration, particularly within PM characterized by elevated interstitial pressure. The liquid-to-gas phase transition results in more homogeneous intraperitoneal distribution and deeper tissue diffusion, translating into a markedly increased tissue drug uptake - reported to be more than twice (x2.2) that achieved with HIPEC - while allowing a ten-fold reduction in drug dosage. Consequently, systemic exposure is minimal, leading to a favorable toxicity profile and excellent tolerability (*Davigo A, Passot G, Vassal O, et al. Int J Hyperthermia. 2020;37(1):144-150. https://doi.org/10.1080/02656736.2019.1704891*). PIPAC is performed under general anesthesia and includes a staging laparoscopy with systematic peritoneal cytology and biopsies, allowing to follow-up disease evolution.

A distinctive feature of PIPAC is the highly controlled dissemination of the technique. Since its development by Professor Marc Reymond and the first-in-human application in Bielefeld (Deutschland) in November 2011, implementation has been strictly regulated through mandatory accreditation and adherence to standardized procedural protocols. In parallel, an international prospective registry has been established to monitor both safety and efficacy outcomes, ensuring continuous quality control and real-world data collection (*Jørgensen MS, et al. Pleura Peritoneum. 2025;10(4):163–170. https://doi.org/10.1515/pp-2025-0014*).

PIPAC is most commonly delivered within a sequential bidirectional treatment strategy, consisting of two cycles of SC followed by one PIPAC procedure, repeated for three cycles. This approach offers two major advantages: first, a reduction in SC exposure by sparing one cycle out of three; second, the opportunity for serial laparoscopic reassessment at six-week intervals, enabling repeated peritoneal biopsies.

Given the well-recognized limitations of cross-sectional imaging in detecting and monitoring gastric PM, repeated laparoscopies allow a comprehensive evaluation of disease evolution. This includes assessment of disease distribution using the Peritoneal Cancer Index (PCI), macroscopic morphological changes documented by standardized photography, and histopathological response quantified using the Peritoneal Regression Grading Score (PRGS) (*Solass W, et al. Pleura Peritoneum. 2022;7(4):179–185.* https://doi.org/10.1515/pp-2022-0118).

PIPAC should be viewed not merely as a technique, but as a therapeutic concept integrating technological, pharmacological, and strategic innovations. The field is currently characterized by strong international momentum, driven by competition among nebulizer manufacturers and the development of novel drug formulations (*Taibi A, et al. Ann Surg Oncol. 2025 Aug 5.* https://doi.org/10.1245/s10434-025-18002-4). This dynamic environment is expected to translate into progressive improvements in oncological outcomes.

**Clinical evidence in gastric peritoneal metastases patients**

PIPAC is primarily proposed for patients with unresectable gastric PM, with two main objectives: to enhance locoregional disease control and to assess the feasibility of secondary resectability, potentially enabling subsequent complete cytoreductive surgery (CRS) and HIPEC. In selected contexts, PIPAC has also been investigated as a prophylactic strategy following total gastrectomy for locally advanced disease.

To date, the only prospective comparative oncological data derive from the French multicenter randomized phase II PIPAC-EstoK-01 trial (*Eveno C, et al. Pleura Peritoneum. 2018;3(2):20180116.* https://doi.org/10.1515/pp-2018-0116). This study compared progression-free survival (PFS) between patients treated with SC plus cisplatin-doxorubicin PIPAC and those receiving SC alone. Conducted during the first COVID-19 outbreak, the trial faced major data-collection challenges and was prematurely stopped for safety concerns related to suspected increased death with bowel obstruction linked to PIPAC. Ultimately, obstruction rates were similar between arms. Among 64 randomized patients (out of 94 planned), no significant differences were observed in oncologic outcomes, with

median overall survival (OS) - from randomization - of 10.5 months in the control arm versus 8.1 months in the experimental arm (p=0.29). Notably, 72% of patients experienced grade ≥3 CTCAE adverse events, while 5% underwent secondary CRS-HIPEC. Interpretation of these results must consider that 19% of patients had received two or more prior lines of therapy and that the mean PCI was 19.5 (13-27), reflecting a population with very advanced peritoneal disease, potentially beyond the reach of meaningful prognostic improvement.

Beyond randomized data, several retrospective analyses of prospectively maintained databases have reported outcomes of PIPAC in gastric PM. Analysis of the international ISSPP registry presented at ASCO GI 2022 demonstrated a median overall survival of 15.4 months, increasing to approximately 20 months in patients completing at least three PIPAC procedures. In 2024, our group reported outcomes in 146 patients with gastric PM - 81% harboring signet-ring cell histology and a mean baseline PCI of 19.3 (8.6) - with a median OS of 16 months from PM diagnosis. Importantly, 12% of patients achieved secondary complete CRS-HIPEC (*Orgad R, et al. Ann Surg. 2024 Jul 23.* *https://doi.org/10.1097/sla.0000000000006447*).

The apparent discrepancy between prospective trials and real-world data underscores the need for continued clinical research, with particular emphasis on patient selection. In this regard, the ongoing Italian phase III VEROne trial is evaluating cisplatin-doxorubicin PIPAC in patients with gastric PM and a PCI <7, with secondary resectability as the primary endpoint (*Casella F, et al. Pleura Peritoneum. 2022;7(3):135–141.* *https://doi.org/10.1515/pp-2022-0111*).

Most reported outcomes have been achieved using low-dose cisplatin-doxorubicin (10.5 mg/m² and 2.1 mg/m², respectively). Recently, a phase I trial evaluating nanoparticle albumin-bound paclitaxel - NAB-PTX-PIPAC - was conducted in 23 patients, 13 with gastric PM. Of note, 35% of patients had NAB-PTX-PIPAC without SC and 20 patients had at least 2 consecutive PIPAC. It demonstrated promising safety, as limited surgical complications (one trocar site dehiscence) and few severe hematologic toxicities occurred (8 grade 3 toxicities observed in 5 patients at the highest dose level). This trial exhibited the advantages of PIPAC: first the nanoparticles was usable as PIPAC agent without loss of their physicochemical properties and cytotoxic efficacy, second the possibility given by PIPAC to iteratively biopsy PM along treatment suggested a dose-response relationship when focusing on PRGS and a NAB-PTX accumulation in PM with the repetition of PIPAC (*Ceelen W, et al. eBioMedicine. 2022;82:104151.* *https://doi.org/10.1016/j.ebiom.2022.104151*).

That possibility to use modern molecules with PIPAC is to be added to the option of increasing doses while preserving tolerance. Confidential dose-escalation data from the ongoing PIPACOVA trial in ovarian PM support the tolerability of higher doses of the most used PIPAC regimen: the dose level of cisplatin 18.9 mg/m² and doxorubicin 4.6 mg/m² was safe and well tolerated in that condition (unpublished data).

Another level of innovations allowed by PIPAC is therapeutic strategies innovation, as showed by the phase I PIANO trial led by the Singapore team (*Sundar R, et al. ESMO Open. 2024;9(9):103681. https://doi.org/10.1016/j.esmoop.2024.103681*). Overall, 18 gastric PM patients were treated with oxaliplatin-PIPAC at 90 mg/m² every 6 weeks and intravenous nivolumab every 2 weeks. The hypothesis was that the combination would be catalyzed by the immunogenic cell death of peritoneal tumor cells initiated by the intraperitoneally delivered oxaliplatin. The median PCI was 20 (12-30), 39% of patients had 2 or more previous line and 11% had limited extraperitoneal disease. As for PIPAC-Estok, questions were raised about the relation between severe adverse outcomes and PIPAC. An independent data monitoring committee confirmed that a majority of grade 3-5 events were unrelated to oxaliplatin-PIPAC or nivolumab, especially considering the advanced illness of a majority of the patients. Regarding the efficacy, PCI decreased by 5 and 7 points, and PRGS grade 1-2 (good response) was seen on pathological assessment in 67% and 100% at the second and third PIPAC, respectively (50% of patients had 2 and 28% 3 PIPAC). The median OS was 6.0 months (95%CI, 2.4-18.4 months). There was no significant deterioration in quality-of-life scores during treatment. Of note, dynamic changes in tumor microenvironment, immune cells composition and gene expression, attributed to the experimental treatment, were observed in PM and normal peritoneum.

**Future directions**

PIPAC is supported by a strong rationale and offers broad spaces for continued innovation aimed at overcoming chemoresistance in gastric PM. While current clinical evidence remains limited and heterogeneous, experience with other intraperitoneal strategies - such as normothermic intraperitoneal and systemic chemotherapy (NIPS) - has demonstrated substantial survival benefits. Intensified international translational and clinical research efforts are now required to refine indications, optimize combinations, and ultimately improve long-term outcomes in this particularly aggressive form of peritoneal disease.

# Section 3: Alternatives to traditional HIPEC

## *Conversion Surgery in Patients with Gastric Cancer and Peritoneal Metastases: Is this the Key to Unlock Improved Outcomes?*

By Yu Chuan Tan, MRCS[1], Daryl KA Chia, FRCS[1], Jimmy BY So, FRCS[1,2,3]

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### Introduction

Gastric cancer with peritoneal metastases (GCPM) is associated with significant symptom burden and a dismal prognosis (*Tan, 2017; Chu, 1989*). Although systemic therapy remains the current standard of care, its effectiveness is limited by the plasma–peritoneal barrier, which restricts drug penetration into the peritoneal cavity (Manzanedo, 2023). In recent years, the integration of systemic chemotherapy with peritoneal-directed treatment strategies has challenged the traditional palliative paradigm for GCPM. Bidirectional chemotherapy—combining systemic and intraperitoneal drug delivery—has demonstrated encouraging cytological response rates and disease control in selected patients (*Ishigami, 2017; Arigami, 2020; Chia, 2020; Chia, 2022; Gwee, 2022*). Intraperitoneal chemotherapy can be administered via several routes, such as normothermic intraperitoneal chemotherapy through an indwelling catheter, laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC), and pressurized intraperitoneal aerosol chemotherapy (PIPAC). In parallel, immunotherapy and targeted therapy have emerged as promising adjuncts, further expanding the therapeutic opportunities (*Bang, 2010; Janjigian 2020; Shitara, 2023; RHA, 2023; Shah, 2023; Ogawa, 2024*).

In patients demonstrating favourable response following bidirectional therapy, conversion surgery – defined as curative-intent surgery after good response and downstaging – has emerged as a potential treatment strategy. Several institutional series have reported median overall survival ranging from 24.2 to 34.6 months in patients undergoing conversion surgery, superior to historical outcomes with systemic therapy alone (*Ishigami, 2017; Arigami, 2020; Chia, 2020; Chia, 2022*). These findings suggests that surgical cytoreduction with gastrectomy may meaningfully reduce tumour burden, prevent disease-related complications and improve overall survival for patients demonstrating favourable response with preoperative therapy. With continued advancements of bidirectional therapy, conversion surgery may even represent a potential curative strategy for a selected subset of GCPM patients.

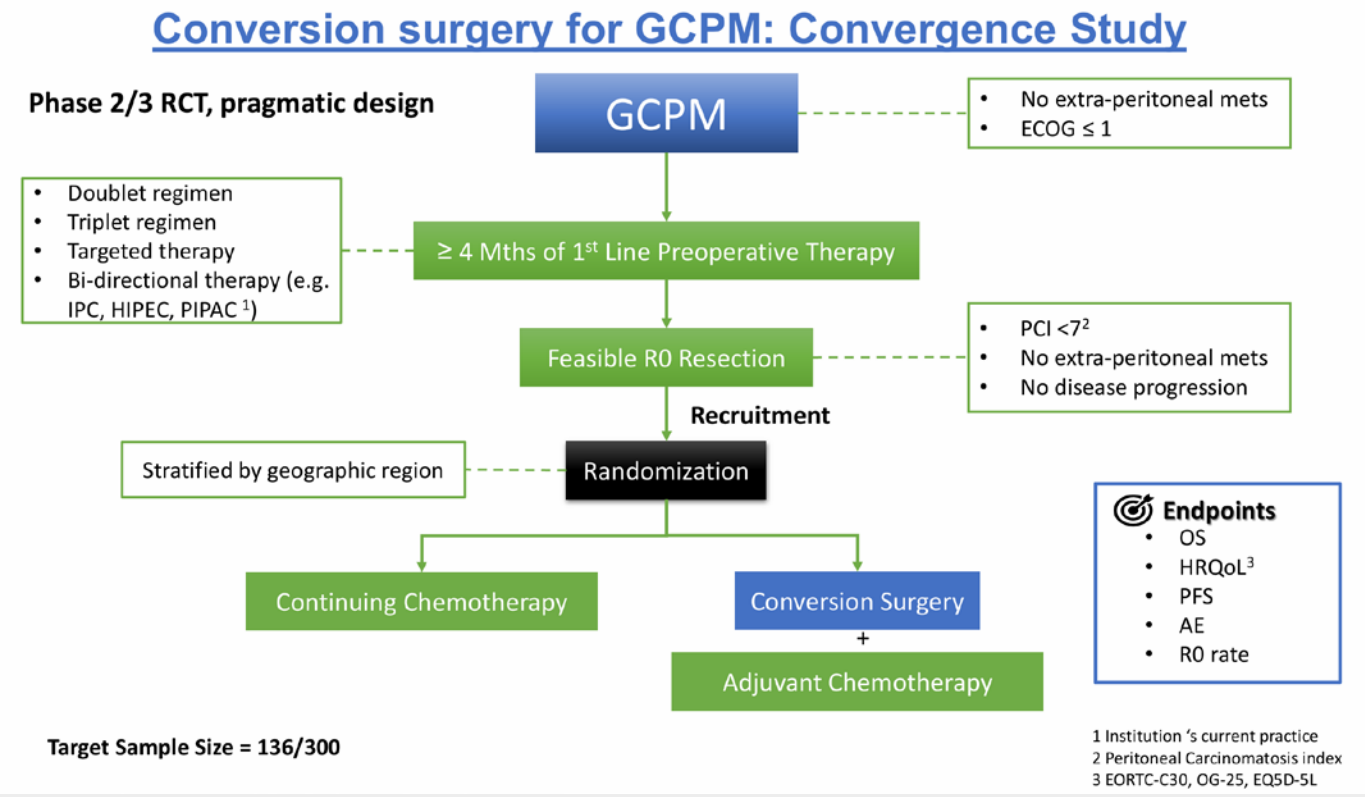
**Rationale for Conversion Surgery**

The rationale for conversion surgery in GCPM is underpinned by the recognition that peritoneal metastases represent a biologically heterogeneous disease spectrum rather than a uniformly terminal condition (*Yoshida, 2016; Smyth, 2020*). Tumours that demonstrate sensitivity to systemic and intraperitoneal chemotherapy are likely to exhibit less aggressive behaviour and lower intrinsic chemoresistance (*Yak, 2017*). Induction therapy can reduce macroscopic peritoneal tumour burden, eradicate free intraperitoneal cancer cells, and convert positive peritoneal cytology to negative status. Furthermore, in the absence of haematogenous dissemination, peritoneal metastases often remain confined to the peritoneal cavity for a prolonged period. In such patients, complete macroscopic clearance of disease through gastrectomy with or without limited cytoreduction may interrupt further peritoneal seeding and delay disease progression thereby potentially conferring survival benefit.

Advances in surgical technique, perioperative care, and patient selection have significantly reduced morbidity and mortality associated with radical gastrectomy when performed in high-volume centres (*Ishigami H, 2017*). When combined with bidirectional chemotherapy, conversion surgery may further enhance locoregional disease control by targeting both primary tumour and microscopic residual disease that is not detectable intraoperatively (*Chia, 2020; Arigami, 2020*).

**Selection Criteria for Conversion Surgery**

Given the potential benefits and morbidity of conversion surgery, meticulous patient selection is critical. A newly registered international multi-centre phase II/III clinical trial (the CONVERGENCE trial, NCT07241715) has been designed to evaluate the oncological efficacy and safety of conversion surgery in patients demonstrating good response to preoperative therapy. Eligibility criteria reflect a combination of oncological, biological, and pragmatic considerations (Figure 1).



Given the differing treatment strategies for GCPM, various combinations involving systemic +/- peritoneal-directed treatments are allowed. Patients must first have GCPM re-evaluated after preoperative therapy. Candidates for conversion surgery should demonstrate favourable tumour biology and be medically fit to tolerate major surgery. Response to preoperative systemic or bidirectional therapy serves as a key surrogate marker of tumour biology and is assessed using both clinical and radiological parameters.

Low-volume peritoneal disease is a prerequisite for conversion surgery, as tumour burden is closely correlated with the likelihood of achieving complete macroscopic resection and long-term survival (*Yonemura, 2017; Chia, 2022*). Diagnostic laparoscopy following at least four months of preoperative therapy is essential to directly assess residual peritoneal disease and to evaluate technical resectability. Patients demonstrating partial or complete response with feasible resection of both the primary tumour and peritoneal metastases may be considered for conversion surgery.

Peritoneal cancer index (PCI) score of less than 7 is required for eligibility to conversion surgery. This threshold is supported by the CYTO-CHIP study, which demonstrated a strong association between low PCI scores and the ability to achieve complete cytoreductive surgery, with a mean PCI of 7.2 among patients successfully undergoing CRS-HIPEC (*Bonnot et al, 2019*). Higher PCI scores have consistently been associated with incomplete cytoreduction and inferior survival outcomes (*Yonemura, 2017*).

**Absence of Extra-peritoneal Disease and Radiological Response**

Radiological staging must confirm the absence of extra-peritoneal metastases (liver, lung, adrenal, bone, and non-regional lymph node involvement). Disease response following bidirectional therapy is assessed using cross-sectional imaging based on Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, or iRECIST for patients receiving immunotherapy. The development of new peritoneal nodules, increasing ascites, or new distant metastases suggests radiological disease progression and precludes consideration for conversion surgery.

**Feasibility of Complete Macroscopic Resection**

The feasibility of achieving R0 or R1 resection is central to the concept of conversion surgery. Extensive small bowel serosal involvement, disease at the mesenteric root, or diffuse retroperitoneal spread generally preclude curative-intent resection. Surgical decision-making should be undertaken within a multidisciplinary team involving experienced gastric surgeons to balance oncological benefit against operative risk.

**Extent of Resection and Patient Fitness**

The extent of resection during conversion surgery should be judiciously limited to minimize postoperative morbidity and mortality, as excessive resection has been associated with increased complications without clear survival benefit (*Yonemura Y, 2017; Smyth, 2020*). Beyond radical gastrectomy with D2 lymphadenectomy, only limited additional cytoreduction should be undertaken. Pancreaticoduodenectomy and trans-thoracic esophagectomy should be avoided. Patients should undergo no more than two bowel resections in order to preserve adequate small bowel length (>200 cm) and reduce the risk of short bowel syndrome, which is associated with significant long-term morbidity and impaired quality of life (*Iyer, 2022*). Candidates should have good performance status (ECOG ≤ 1). Preoperative optimization and structured prehabilitation are therefore integral components of patient selection and preparation.

**Conclusion**

Conversion surgery represents an evolving paradigm in the management of gastric cancer with peritoneal metastases. Rigorous patient selection, systematic restaging, and performance of surgery in specialized centres are essential to maximize benefit and minimize harm. If survival benefit in conversion gastrectomy is demonstrated by the CONVERGENCE trial, this could potentially be a new standard of care for patients with peritoneal metastases from gastric or gastroesophageal junction cancer. Conversely, negative findings would provide evidence to avoid unnecessary surgical procedures and morbidity in these patients.

# Section 4: Listing of upcoming events

By Aditi Bhatt

*Shalby Cancer and Research Institute, Ahmedabad, India*

## ESSO Video Workshop on Cytoreductive Surgery is now open for registration

24 March 2026, Berlin, Germany
8:30 – 17:00 (CET)

📣 **New update - online participation is now available.**

The ESSO Video Workshop on Cytoreductive Surgery, led by Professor Paul Sugarbaker, can now be attended online, allowing you to join from anywhere. An intimate 7 hours with 4 videos, 106 slides and 5 world experts. Your path to excellence in peritoneal metastases surgery.

Register at: https://www.essoweb.org/courses-and-webinars/video-workshop-on-cytoreductive-surgery/
For more information, email Ana Galan at: ana.galan@essoweb.org

| MEETING | CITY/ COUNTRY | DATES | ORGANIZER/ CHAIR | REGISTRATION LINK/WEBSITE |
|---|---|---|---|---|
| **Society of Surgical Oncology Advanced Cancer Therapies** | Fort Lauderdale, Florida, USA | 14-15 February 2026 | Michael Lidsky | https://act2026.eventscribe.net/index.asp |
| **2026 SingHealth Peritoneal Surface Oncology Conference** | Singapore | 9-10 March 2026 | Claramae Chia | https://www.spsoconference.org/ |
| **Hands on HIPEC and PIPAC Workshop** | Singapore | 11-13 March 2026 | Claramae Chia | https://www.spsoconference.org/ |
| **ESSO Video Workshop on Cytoreductive Surgery** | Berlin, Germany | 24 March 2026 | Paul Sugarbaker Beate Rau | https://www.essoweb.org/courses-and-webinars/video-workshop-on-cytoreductive-surgery/ |
| **ESSO/PSOGI Berlin Course on HIPEC following CRS** | Berlin, Germany | 25-27 March 2026 | Beate Rau Aditi Bhatt | https://www.essoweb.org/courses-and-webinars/esso-advanced-course-on-the-management-of-hipec-after-crs/ |
| **The 5th International Scientific Congress of the ISSPP – "New Frontiers in Peritoneal Cancer: From Diagnosis to Cure"** | Sao Paolo, Brazil | 7-9 May 2026 | Rafael Seitenfius | https://issppcongress2026.com/ |
| **HIPEC & PIPAC Workshop - Ege University Faculty of Medicine** | Izmir, Turkey | 11–13 June 2026 | Volkan Sayur Taylan O. Sezer | https://www.hipekpipak2026.com/ |
| **Latin American Congress on Peritoneal Surface Malignancies Biennial Meeting** | Bogota/Cartagena, Colombia | 16-20 August 2026 | Maikel Pacheco Silvia Guerrero Macias | TBD |
| **Workshop on Peritoneal Surface Malignancies and Gynecological Malignancies** | Pune, India | 17-19 September 2026 | Snita Sinukumar | TBD |
| **ESSO Advanced Course on Treatment of Peritoneal Surface Malignancy** | Barcelona, Spain | 15-16 October 2026 | Lana Bijelic | TBD |

# Section 5: Focus on a PSM Protocol

## Gastrectomy, Peritonectomy and HIPEC for GCPM: What Does Periscope II Trial Tell Us?

By [1]*Shigeki Kusamura*, [2]*Kurt Van der Speeten*, [2]*Beate Rau*

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The PERISCOPE II trial was a phase III, multicenter, randomized study designed to determine whether gastrectomy combined with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) improves overall survival compared with continued systemic therapy in patients with gastric or gastroesophageal junction adenocarcinoma and limited peritoneal disease (*Koemans WJ, et al. BMC Cancer. 2019 May 6;19(1):420. doi: 10.1186/s12885-019-5640-2.*). Eligible patients had either macroscopic peritoneal metastases with a peritoneal cancer index (PCI) below 7 or tumour-positive peritoneal cytology without visible implants. All participants were required to have non-progressive disease following first-line systemic chemotherapy. They were then randomized 1:1 to continue systemic therapy alone or to undergo gastrectomy with CRS followed by HIPEC using oxaliplatin (460 mg/m² for 30 minutes at 41°C) and normothermic docetaxel (50 mg/m² for 90 minutes). The primary endpoint was overall survival.

At the ESMO Congress in October 2025, it was reported that the trial had been stopped early for futility in September 2024 after enrolling 102 patients, of whom 101 formed the intention-to-treat (ITT) population (*https://oncodaily.com/oncolibrary/periscope-ii-trial-gastric-cancer-esmo25*). Fifty-one patients were assigned to systemic therapy alone and fifty to CRS-HIPEC. Median overall survival was 16.6 months in the control arm versus 15.7 months in the CRS-HIPEC arm (HR 1.10; p=0.70). There was no advantage in progression-free survival or quality of life. By contrast, treatment-related morbidity was substantially higher with CRS-HIPEC, with 45 serious adverse events compared with only 4 in the control arm, and three treatment-related deaths (6%). These findings have generally been interpreted as definitively negative for CRS-HIPEC in gastric peritoneal metastases. Nevertheless, a structured methodological review suggests that such a conclusion may be premature.

Trial validity was examined using the Risk of Bias 2 (RoB 2) framework recommended by the Cochrane Collaboration and incorporated within the GRADE methodology. This tool evaluates potential bias at the level of each outcome, which is particularly relevant in surgical oncology (*Nejadghaderi SA, et al. Health Sci. Rep. 2024;7:e2165. doi: 10.1002/hsr2.2165*).

In the first domain—bias arising from the randomization process—the PERISCOPE II design appears methodologically sound. Randomization was prospective and baseline characteristics were broadly comparable.

However, early termination resulted in only 101 ITT patients instead of the recalculated target of 226. With such a small sample size, the capacity of randomization to balance measured and unmeasured prognostic factors is inevitably reduced. This limitation is compounded by missing biomarker data: Combined Positive Score (CPS) status for PD-L1 expression was unknown in 61% of control-arm patients and 62% of CRS-HIPEC patients, while Microsatellite Instability (MSI) status was unavailable in about half of all participants. These gaps raise the possibility of residual biological imbalance. In addition, the precise criteria applied by the Data Safety Monitoring Board in invoking the futility rule have not yet been fully detailed, making it difficult to assess whether prespecified stopping boundaries were strictly followed.

The second RoB 2 domain—deviations from intended interventions—represents an even more important limitation. Of the 50 patients randomized to CRS-HIPEC, only 37 ultimately underwent the allocated procedure. Ten patients (20%) were found intraoperatively to have PCI ≥7 and were therefore excluded from CRS-HIPEC; two declined surgery after randomization; and one died before surgery. Thus, 26% of patients assigned to CRS-HIPEC never actually received the intervention. Meanwhile, 7 of 51 control-arm patients (14%) underwent CRS-HIPEC outside the trial.

This created a critical methodological problem. Patients discovered at surgery to have PCI ≥7 were excluded from the experimental treatment but not from the systemic-therapy arm, where they continued to contribute outcome data. Consequently, higher-risk patients were disproportionately retained in the control group, while comparable patients randomized to surgery were removed from intervention and remained within the ITT denominator. This introduced post-randomization biological imbalance and diluted the contrast between study arms. Such distortion might have been minimized had all patients undergone standardized laparoscopic confirmation of PCI immediately prior to randomization, following chemotherapy, thereby stabilizing eligibility criteria and ensuring symmetrical verification of disease burden.

A per-protocol analysis restricted to the 81 adherent patients reported median overall survival of 17.3 months in the CRS-HIPEC arm versus 15.2 months in the control arm (HR 0.65; p=0.12). Although numerically favourable, these findings are highly vulnerable to selection bias, as only fitter patients with low-volume disease who survived to surgery were included.

Bias from missing outcome data was minimal, since survival ascertainment was complete. However, early termination reduced the number of events and shortened follow-up, widening confidence intervals and limiting power to detect late survival separation. Outcome measurement bias was negligible, as survival is objective, although PCI inaccuracy may have indirectly influenced attribution of treatment effect. Selective reporting bias cannot yet be fully assessed until complete publication.

An additional clinical issue is that advances in systemic therapy—including the use of targeted agents—may have been implemented asymmetrically across study arms. The control group appears to have benefited more consistently from individualized systemic strategies, whereas the CRS-HIPEC arm largely followed a uniform perioperative approach.

A further concern relates to the HIPEC regimen itself. High-quality evidence supporting an oxaliplatin-based HIPEC strategy in gastric peritoneal metastasis remains limited, and substantial preclinical data suggest that this regimen may be suboptimal (*Ceelen W. Eur J Surg Oncol. 2019 Mar;45(3):400-402. doi: 10.1016/j.ejso.2018.10.542; Sugarbaker PH, Van der Speeten K. J Gastrointest Oncol. 2021 Apr;12(Suppl 1):S129-S130. doi: 10.21037/jgo-2020-15*). Although Yan Kangpeng and colleagues reported benefit with perioperative oxaliplatin–5FU-based intraperitoneal therapy delivered repetitively, those retrospective observations are vulnerable to significant confounding (*Yan K, et al. J BUON. 2019 Jul-Aug;24(4):1587-1594, PMID: 31646813*). Reflecting this uncertainty, the 2022 PSOGI HIPEC consensus identified cisplatin 75 mg/m² combined with mitomycin-C 12.5 mg/m² as the regimen with the strongest supporting evidence and therefore the most advisable in clinical practice (*Kusamura S, et al. J Surg Oncol. 2024 Nov;130(6):1290-1298. doi: 10.1002/jso.27885*).

With respect to toxicity, two considerations are important. The true mortality rate associated with CRS-HIPEC was 4%, as one reported death occurred prior to surgery. Although the overall severe complication rate was high and the median postoperative stay prolonged at 25 days, these figures should be interpreted in light of the participating centres' expertise in Peritoneal Surface Malignancies. They reinforce the requirement for strict patient selection and concentration of CRS-HIPEC in high-volume specialist units.

Beyond these methodological and clinical considerations, several key questions remain unresolved and will require clarification in the final peer-reviewed publication. These include: (1) the precise criteria used to assess tumour response prior to randomization; (2) whether subgroup analyses demonstrate a consistent absence of benefit across prognostic strata, including signet-ring histology and biologically defined categories such as Claudin-18.2– or PD-L1–expressing tumours; (3) whether survival among optimally cytoreduced CC-0 patients was truly equivalent to that observed in the control arm; and (4) the case volume and expertise of the participating centres. Addressing these issues will be essential to fully interpret the trial's findings and understand their applicability to contemporary clinical practice.

The PERISCOPE II trial results are particularly relevant when viewed alongside the Multisocietal Consensus on CRS-HIPEC in gastric cancer with peritoneal metastases, published prior to the trial. Using a GRADE-based framework, after an extensive systematic review and meta-analysis of the literature, the expert panel concluded that CRS-HIPEC may benefit highly selected patients—specifically those with synchronous disease, PCI ≤6, ECOG 0–1, and response to systemic therapy—when delivered in specialist centres. The recommendation was explicitly conditional (*Jain AJ,*

*et al. Multisocietal Consensus on the Use of Cytoreductive Surgery and HIPEC for the Treatment of Gastric Cancer with Peritoneal Metastasis: A GRADE Approach for Evidence Evaluation and Recommendation. Journal of Surgical Oncology 2025 accepted*).

The crucial question, therefore, is whether PERISCOPE II overturns that conclusion. Based on the currently available data, the most reasonable answer is probably not—at least not on methodological grounds alone. Early closure, treatment non-adherence, crossover, asymmetric exclusion of high-PCI cases in the surgical arm, regimen selection, and small sample size collectively weakens the trial's ability to evaluate CRS-HIPEC in precisely the subgroup identified by the consensus panel.

The appropriate next step is to integrate the PERISCOPE II data transparently and update the meta-analytic evidence that supported the Multisocietal Consensus. A thorough synthesis of PERISCOPE II with the existing body of evidence (*Granieri S, et al. Eur J Surg Oncol. 2021 Nov;47(11):2757-2767. doi: 10.1016/j.ejso.2021.05.016*) is warranted before abandoning the current conditional recommendation.

In summary, the most defensible position is cautious continuity rather than abandonment. CRS-HIPEC should remain restricted to expert centres, applied only in rigorously selected patients, and ideally offered within structured research programmes and registries. PERISCOPE II is not the end of CRS-HIPEC in gastric cancer with peritoneal metastasis; rather, it highlights the urgent need for better-designed, biologically informed trials in this challenging disease setting.

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# Section 6: Pioneers of progress in peritoneal surface malignancy

## *Yutaka Yonemura, A Pioneer in the Progress with Peritoneal Surface Malignancy, Responds to Our Request for a Summary of His Many Contributions*

By Aditi Bhatt and Paul Sugarbaker

***Background information***

I was born in 1949, at Kanazawa, a city, located in the center of the Japanese archipelago and graduated from Kanazawa University in 1973. After completing my postgraduate training, I obtained the position of head of gastric cancer treatment at the 2nd Department of Surgery of Kanazawa University. The main focus of my work was to investigate the development of peritoneal metastasis (PM) from gastric cancer (GC), and develop novel treatments for this condition.

In 1980, John Spratt reported the use of hyperthermic intraperitoneal chemoperfusion (HIPEC) in a male patient with pseudomyxoma peritonei (PMP). In Japan, Shigemasa Koga was the first to begin treatment of GC with PM (GCPM) using HIPEC. Koga referred to his version of HIPEC as Continuous Hyperthermic Peritoneal Perfusion (CHPP) (10.1002/1097-0142(19880115)61:2<232::aid-cncr2820610205>3.0.co;2-u).

According to Sapareto SA and Dewey W (10.1016/0360-3016(84)90379-1), HIPEC alone can kill up 99.9% of HeLa cells, cultured on dish when exposed to a temperature of 43.5°C for 40 minutes. However, in-vivo, heat penetrates 2-3 mm from the surface of the peritoneum. Accordingly, tumors with a diameter greater than 3 mm cannot treated by heat alone. Additionally, tumors with a good blood supply cannot be heated sufficiently due to the cooling effects of blood.

***Our earliest work with GCPM***

We started the use of HIPEC to treat GCPM in 1983. In 1986, we treated a 56-year-old GC-patient with a peritoneal cancer index (PCI) of 39 by D2-distal gastrectomy (CCR-3) and HIPEC using mitomycin C (MMC). Two months after the procedure, complete resolution of PM was confirmed at second-look laparotomy (10.1002/1097-0142(19900101)65:1<65::aid-cncr2820650115>3.0.co;2-l). The patient subsequently died of a brain metastasis 5 years and 8 months after the surgery.

The first peritonectomy procedures with a total gastrectomy and HIPEC for GC in Japan were performed in a 34-year-old male on January 17, 1994, but the patient died of peritoneal recurrence 12 months after CRS+HIPEC.

Despite the complete cytoreduction, the disease recurred because of the limited capacity of HIPEC to eliminate residual micrometastases (MM) remaining after CRS.

***NIPS opened up the clinical practice and research with GCPM***

To treat MM before CRS, I developed NIPS (Neoadjuvant intraperitoneal and systemic chemotherapy) in 2002 (10.1016/j.canlet.2004.03.018). The term 'NIPS' was coined by Paul Sugarbaker at the PSOGI meeting in Milan. NIPS can generate a greater dose-intensity of anti-cancer drugs in the peritoneal cavity compared to systemic chemotherapy. NIPS significantly reduces PCI levels and improves the intraperitoneal cytologic status from class V to class I.

Additionally, in our experience, NIPS markedly improves the complete cytoreduction rate (56%, 325/589 in GC-patients with PM) compared with neoadjuvant systemic chemotherapy alone (44%, 35/84). The effects of NIPS

were validated by Coccolini F and colleagues (10.1016/j/ijsu.2018.01.008). Conversion surgery after response to NIPS was a reality!

***Collaborative efforts within PSOGI in Japan and globally***

From 1994-2008, I performed peritonectomy procedures (cytoreductive surgery) in 3283 patients (Table 1). Our unit developed neoadjuvant laparoscopic HIPEC too, to address MM (10.1245/s10434-016-5487-6).

In 2008, I funded the establishment of the Peritoneal Surface Malignancy Treatment (PSMT) Center in Kishiwada, Osaka, and the Asian School of PSMT.

At the Asian School of PSMT, I trained 49 surgeons who subsequently established PSMT centres in their regions (Japan-22, Taiwan-6, India-5, China-4, Brazil-4 and 1 each from Germany, Spain, Italy, Czech Republic, Philippines, Saudi Arabia, Mexico, and Korea).

The Peritoneal Surface Oncology Group International (PSOGI) is a non-profit organization that was established in 2014. The PSOGI is currently composed of 19 executive members. I was a co-founder of the PSOGI with Paul Sugarbaker and have been a board member since its inception. One of the main goals of the PSOGI has been to train and educate surgeons around the world in the definitive treatment of PM comprising of complete cytoreductive surgery and HIPEC. Another objective has been to generate new evidence by conducting international multi-institutional studies and providing recommendations for day-to-day practice. These studies have helped to define the comprehensive treatment for peritoneal metastases from colorectal cancer (10.1200/JCO.2004.10.012), biliary cancer (10.1016/j.ejso.2018.04.023) gastric cancer (10.1016/j.ejso.2013.10.019 and 10.1016/j.ejso.2020.10.006), peritoneal sarcomatosis (10.1016/j.ejso.2017.08.011) and peritoneal mesothelioma (10.1016/j.ejso.2020.02.011). Through several international Delphi consensuses, the PSOGI has established a new classification of pseudomyxoma peritonei (10.1097/PAS.0000000000000535), provided guidelines for the management of PMP (10.1016/j.ejso.2020.02.012) and peritoneal mesothelioma (10.1016/j.ejso.2020.02.011), provided recommendations for performing HIPEC (10.1002/jso.27885) and revised the classification of peritonectomy procedures (10.1093/bjs/znaf112).

Regarding my activities in Japan, I have conducted a seminar on HIPEC at the annual Japanese Hyperthermic Oncology Congress (JHOC) for the last 10 years. The JHOC endorsed the use of HIPEC in the treatment of PM in 2022 for gastric and ovarian PM, PMP and peritoneal mesothelioma.

Since 2015, we have used NIPS to treat PMP leading to a reduction in the PCI preoperatively thereby reducing the operative time, blood loss and organ resections (10.3390/cancers12082212). We are now surveying the prognostic significance of NIPS for patients with pseudomyxoma peritonei.

In 2024, we published the results of a randomized trial demonstrating the benefit of HIPEC in GC patients with PM to confirm the effects of intraoperative HIPEC on patients treated with NIPS (10.37871/jbres1946). The survival after CRS + HIPEC was significantly better than those after CRS alone, (5 year-survival rate in HIPEC group 22%; non-HIPEC group 14.4%).

To improve the detection of MM, we started using 5-aminolevulinic acid (ALA) (10.3390/cancers9030023). We could detect small MM of mesothelioma or serous carcinoma with a diameter of approximately 1 mm. However, the method was unable to detect small MM from gastric or colorectal cancer.

***Past failures are now a success using NIPS***

Two of the most important factors that determine the probability of cure in patients with gastric PM are a complete cytoreduction and extensive disease indicated by a high PCI. Our conversion rate of CC-0 resections is 63.8% (2095/3283, Table 1) mainly because we treated patients with a high PCI in our initial experience. In GCPM, we have exceeded what is possible with CRS+HIPEC by using NIPS: 21 (6%) of 354 GCPM patients were cured by NIPS+CRS+HIPEC (Table 1). The definition of cure is surviving for 5 years without recurrence following CRS.

In colorectal cancer with PM, 27 patients (7.6%, 27/357) were cured.

I am still performing cytoreductive surgery and HIPEC. My goal is to continue to popularize this treatment, established by the PSOGI, in Japan.

**Table 1.** Results of definitive management of peritoneal metastases at our centre using CRS, HIPEC, NIPS and laparoscopic HIPEC.

| Cancers | Number of Patients | Number of Operations | Complete Resections | Reoperations for Recurrence | Cured Patients |
|---|---|---|---|---|---|
| PMP | 2128 | 1528 | 1000 | 318 | 321 |
| Gastric cancer | 1314 | 639 | 354 | 18 | 21 |
| Colorectal cancer | 997 | 508 | 381 | 107 | 31 |
| Mesothelioma | 111 | 105 | 42 | 11 | 9 |
| Ovarian cancer | 354 | 165 | 108 | 22 | 14 |
| Pancreas cancer | 150 | 44 | 24 | 2 | 1 |
| Biliary cancer | 83 | 23 | 17 | 2 | 1 |
| Small bowel cancer | 28 | 16 | 10 | 1 | 2 |
| Uterine cancer | 125 | 53 | 34 | 8 | 4 |
| Carcinoid tumor | 45 | 37 | 25 | 5 | 2 |
| Others | 305 | 165 | 100 | 5 | 8 |
| **TOTAL** | **5640** | **3283** | **2095** | **499** | **406** |

# Section 7: Focus on PSM protocols

## *A Short History of the Management of Gastric Cancer Peritoneal Metastases (GCPM): Time for a Paradigm Shift?*

By Paul Sugarbaker

There is no doubt that John Spratt from Louisville, Kentucky was the originator of hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of peritoneal metastases. He treated a single patient twice with HIPEC, first with intraperitoneal thiotepa and then 5 days later with intraperitoneal methotrexate (*Spratt JS, et al. Cancer Res, 1980, PMID: 6766084*). Surgery was performed because the patient was progressing. A mucinous adenocarcinoma of the tail of the pancreas was resected. It was the cause of the pseudomyxoma peritonei.

***Prevention of gastric cancer peritoneal metastases with HIPEC***

No one in the Western part of the world seemed to take notice of Spratt's innovation. However, Shigemasha Koga at Tottori University in Yonago, Japan saw the potential usefulness of HIPEC for the prevention of peritoneal

metastases in patients with serosal-positive gastric cancer. His laboratory work with a new drug especially suited for HIPEC, mitomycin C, was impressive (*Koga S, et al. Cancer Res, 1984, PMID: 6424932*). Also, his randomized trial, although seriously underpowered, strongly suggested that HIPEC mitomycin C was of value as an adjuvant treatment for gastric cancer patients at high risk for surgical treatment failure as a result of peritoneal metastases (*Koga S, et al. Cancer, 1988, PMID: 3121165*). Yonemura in Kanazawa City, Japan performed a similar prevention trial with HIPEC mitomycin C and cisplatin (*Yonemura Y, et al. Hepatogastroenterology, 2001, PMID: 11813623*). Hirose from Fukui also found HIPEC effective for prophylaxis of peritoneal metastases (*Hirose K, et al, Oncology, 1999, PMID: 10461056*). Five systematic reviews support the use of HIPEC for prevention of peritoneal metastases as a prominent cause of treatment failure for resectable gastric cancer.

***Treatment of gastric cancer peritoneal metastases with HIPEC***

Not only were there studies to prevent peritoneal metastases. Clinical research to treat a limited extent of peritoneal dissemination was a prominent part of the Japanese effort to control GCPM. Fujimoto et al. from Chiba, Japan performed a prospective study using mitomycin C HIPEC in 30 patients versus no HIPEC in 29 patients. His results in these patients with advanced gastric cancer were positive with a p-value of 0.001 (*Fujimoto S, et al. Ann Surg, 1990, doi: https://doi.org/10.1097/00000658-199011000-00005*). Yonemura and coworkers in Kanazawa, Japan reported a correlation of the survival of patients with response of a patient's gastric cancer cells to the HIPEC drugs and with the completeness of cytoreduction (p=0.005 and p=0.034, respectively). A multidose HIPEC with repeated drug instillation every 10 minutes was used. One-year survival of responders was 88% and five patients survived long-term (*Yonemura Y, et al. Surgery, 1996, doi: https://doi.org/10.1016/s0039-6060(96)80145-0*). Another randomized study suggesting the efficacy of HIPEC to treat GCPM was published by Yang et al. from Wuhan University, Wuhan, China (*Yang XJ, et al. Ann Surg Oncol, 2011, PMID: 21431408*). There were 68 GCPM patients, 30 of whom were treated with HIPEC with cisplatin and mitomycin C. The HIPEC group survived longer with a p-value of 0.046.

In Europe, the first group to pursue CRS and HIPEC for gastric cancer with peritoneal metastases was from Lyon, France headed by Francois Gilly (*Glehen O, et al. Arch Surg, 2004, doi: https://doi.org/10.1001/archsurg.139.1.20*). In a non-randomized study of 49 patients treated with HIPEC mitomycin C after extensive cytoreduction, they saw a median survival of 10.3 months. They concluded that in highly selected patients with a good general status, resectable primary tumor, and resectable peritoneal metastases, CRS plus HIPEC may result in long-term survival. Bonnot and colleagues published results of the CYTO-CHIP study (*Bonnot PE, et al. J Clin Oncol, 2019, doi: https://doi.org/10.1200/jco.18.01688*). They compared the results of CRS alone versus CRS plus HIPEC in 277 patients. The median overall survival was 18.8 versus 12.1 months for CRS plus HIPEC versus CRS only patients. This showed a p-value of 0.05. As a result of this propensity-matched study and other data, the NCCN Guidelines

suggested that gastrectomy combined with cytoreductive surgery and with HIPEC could be considered as a treatment option for GCPM.

Add to these data regarding GCPM innumerable manuscripts from individual institutions suggesting a utility of CRS plus HIPEC for GCPM and 6 systematic reviews that cautiously support CRS plus HIPEC for small volume peritoneal metastases.

Currently, we are forced to reexamine these 3 decades of limited success to develop a viable treatment option for low volume peritoneal metastases using gastrectomy, cytoreductive surgery, and HIPEC. In the PERISCOPE II randomized study, Quik et al. from the Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital in Amsterdam compared systemic therapy, gastrectomy, and CRS/HIPEC versus systemic therapy alone for GCPM. There was no survival benefit with CRS/HIPEC. Also, the CRS/HIPEC resulted in an alarming increase in adverse events - 44% in the experimental arm of the trial vs. 8% in those receiving systemic chemotherapy. There were 3 treatment-related deaths in the experimental arm of the trial. This was presented by Quik at the 2025 ESMO Congress. As a result of these recent data, for many gastric cancer surgeons and almost all medical oncologists, an aggressive surgical approach to GCPM is no longer an option.

What has changed over the last 40 years to discourage the use of gastrectomy, peritonectomy and HIPEC for GCPM? Gastric cancer surgery has steadily improved with the routine use of D2 gastrectomy to resect lymph nodes and peritonectomy to resect visible peritoneal dissemination. Also, HIPEC has changed very little, if at all, in its local-regional effects. The dramatic change is in the efficacy of systemic chemotherapy and molecular therapies for GCPM.

Before leaving the discussion of gastrectomy, peritonectomy and HIPEC for treatment of limited GCPM, an important fact needs to be established. The failure of aggressive local-regional treatments (surgery plus HIPEC) to show benefit in 2026 does not indicate that they were never effective. In the past, data show that they did prolong survival. What has changed is the effectiveness of systemic chemotherapy. The benefits of aggressive local-regional treatments may disappear as the efficacy of systemic chemotherapy alone increases. Systemic chemotherapy is now able to eradicate the disease that, in the past, was required to be controlled by local-regional treatments. A competition exists between local-regional treatments and systemic treatments for cancer.

Perhaps the most impressive demonstration of this local-regional/systemic therapy competition occurred in patients with stage 3 ovarian cancer. In a SWOG randomized controlled trial, Alberts and coworkers showed conclusively that intraperitoneal cisplatin improved survival and decreased toxic side effects when compared to systemic cisplatin (*Alberts DS, et al. New Engl J Med, 1996, PMID: 8960474*). In a GOG randomized controlled trial, Armstrong showed that the survival improved when combined intraperitoneal and systemic cisplatin and paclitaxel

were compared to intravenously administered drugs (*Armstrong DK, et al, New Engl J Med, 2006, doi: 10.1056/NEJMoa052985*). In an attempt to confirm the superiority of combined intraperitoneal and systemic chemotherapy for stage 3 ovarian cancer, Walker et al. performed a 3-armed GOG randomized trial. A new and effective systemic targeted treatment, bevacizumab, was administered to all patients entered into the trial (*Walker JL, Gynecol Oncol, 2016, PMID: 27328898, doi: https://doi.org/10.1016/j.ygyno.2016.06.011*). With the new and effective systemic treatment, bevacizumab, the improvement in survival documented in prior randomized trials for intraperitoneal cisplatin and intraperitoneal paclitaxel was lost. With an addition of bevacizumab, adjuvant intraperitoneal chemotherapy for stage 3 ovarian cancer was no longer a treatment option.

In my experience with neoadjuvant chemotherapy added to CRS and HIPEC, I identified 4 groups of patients:

1. The complete response occurred in about 10% of patients. These patients had a repeat laparotomy plus HIPEC that was, in reality, an open and close procedure with extensive biopsy. They did extremely well long-term. I doubt that the exploratory laparotomy plus HIPEC was of any help in their long-term survival.
2. A second group of patients had a robust response to the NAC. However, with exploration and extensive biopsy there were isolated sites of persistent disease. The most common site was within the gastrointestinal primary cancer. With complete CRS these patients showed long-term survival equivalent to that of the complete responders. I doubt that HIPEC was of any benefit to these patients.
3. The third group of patients had a moderate response. When they were explored, it was clear that the chemotherapy had caused regression but there was still a moderate amount of disease. Complete CRS plus HIPEC in these patients did seem to improve their outcome. This is the group of patients with PCI of 11-15 in the PRODIGE 7 Trial (*Quenet et al. Lancet Oncol, 2021, doi: https://doi.org/10.1016/s1470-2045(20)30599-4*). Also, Rau identified a group of GCPM patients with a complete cytoreduction and PCI ≥7 who received benefit from HIPEC in addition to CRS (*Rau et al. J Clin Oncol, 2024, doi: https://doi.org/10.1200/jco.22.02867*). It is important that the chemotherapy agents used in NAC and HIPEC have a different mechanism of action.
4. The fourth group failed to respond to NAC. If a complete CRS is possible, resection is indicated and HIPEC should be used. Again, it is important that the NAC and HIPEC are from different classes of chemotherapy agents. The extent of disease in group 4 is such that CRS and HIPEC are usually not effective. Consequently, only a small number of patients in group 4 may experience a benefit from CRS and HIPEC.

Although HIPEC after gastrectomy and peritonectomy may have lost favor, other intraperitoneal treatment options for GCPM have persisted. Normothermic intraperitoneal and systemic chemotherapy (NIPS) delivered through an intraperitoneal port long-term is a treatment option for GCPM. Sugarbaker et al. used multiple cycles of intraperitoneal 5-fluorouracil with systemic mitomycin C after gastrectomy, cytoreduction and HIPEC. Two long-term survivors were reported (*Sugarbaker PH. Int J Surg Case Reports, 2019, doi: 10.1016/j.ijscr.2019.09.009*).

Markman and colleagues studied paclitaxel pharmacologically after its intraperitoneal administration (*Markman M, et al. J Clin Oncol, 1992, doi: https://doi.org/10.1200/JCO.1992.10.9.1485*). Retention of the drug within the peritoneal space for 24 hours suggested that it was capable of exposing the peritoneal surfaces to cancer chemotherapy over many hours rather than only over a few minutes as with HIPEC. Also, the drug was determined safe for multiple intraperitoneal instillations without the development of peritoneal sclerosis. Mohamed and Sugarbaker studied the pharmacokinetics of intraperitoneal paclitaxel after extensive cytoreductive surgery (*Mohamed F, et al. Cancer Chemother Pharmacol, 2003, doi: https://doi.org/10.1007/s00280-003-0680-2*). They determined that this was an ideal drug for neoadjuvant and adjuvant intraperitoneal chemotherapy.

A new strategy for management of GCPM was invented by Yonemura at Shizuoka Cancer Center in Shizuoka, Japan. Yonemura used multiple cycles of normothermic intraperitoneal and systemic (NIPS) chemotherapy to eradicate the peritoneal metastases in GCPM patients. The patients who showed a response could then go on to a gastrectomy with complete cytoreduction (*Yonemura Y, et al. Eur J Surg Oncol, 2006, doi: https://doi.org/10.1016/j.ejso.2006.03.007*). Combined intraperitoneal docetaxel and carboplatin combined with systemic methotrexate and 5-fluorouracil were used for 4 to 6 cycles prior to the conversion gastrectomy. Prolonged survival of 20.4 months was reported in 14 of 61 patients who were able to have a complete resection.

Kitayama and colleagues from the University of Tokyo in 2012 reported on 100 patients with GCPM (*Kitayama J, et al. Gastrointest Cancer Res, 2012, PMID: 22876333*). The strategy was intraperitoneal and systemic paclitaxel via a subcutaneously implanted peritoneal port. S1 was also administered at 80 mg/m$^2$ for 14 consecutive days. The median survival of this group of patients was 23.6 months with a 1-year survival of 80%.

A critical evaluation of the NIPS approach was reported by Ishigami and colleagues from the University of Tokyo. They performed the PHOENIX-GC randomized trial in 164 patients. Half of the patients received multiple cycles of intraperitoneal plus systemic paclitaxel plus S1 and half received intravenous paclitaxel plus S1. The 3-year overall survival was 21.9% in the intraperitoneal paclitaxel arm and 6% in the systemic paclitaxel arm. Currently, these protocol patients are monitored laparoscopically for response to treatments and are considered for conversion surgery if peritoneal metastases were controlled by NIPS (*Ishigami H, et al. J Clin Oncol, 2018, doi: https://doi.org/10.1200/jco.2018.77.8613*).

This work was continued by Chia et al. The NIPS was intraperitoneal paclitaxel plus oral capecitabine plus intravenous oxaliplatin. If there was a good response, the protocol called for a conversion surgery. In the intraperitoneal paclitaxel group, 36% of patients received conversion surgery with an overall median survival of 24.2 months (*Chia DKA, et al. Ann Surg Oncol, 2023, PMID: 36564654*).

The DRAGON-01 trial provided good news regarding NIPS with intraperitoneal and intravenous paclitaxel plus S1 versus systemic paclitaxel plus S1. A superior outcome of NIPS was confirmed in a randomized trial of 238 patients (*Yan C, et al. J Clin Oncol, 2025, doi: https://doi.org/10.1200/JCO.2025.43.4_suppl.327*). The median survival was 19.4 months in the NIPS group and 13.9 months in the systemic chemotherapy group with p-value of 0.005. The 2-year overall survival was 37.2% in the NIPS group as compared to 20.3% in the systemic paclitaxel group. There were no treatment-related deaths in either arm of the trial. These authors conclude that in this randomized trial, intraperitoneal and intravenous paclitaxel plus S1 significantly improved the overall survival of GCPM patients as compared to systemic paclitaxel alone. Conversion surgery was not performed as part of the DRAGON-01 trial.

As a result of the continued efforts with normothermic intraperitoneal chemotherapy long-term, the concept of NIPS as a preparation for conversion surgery in gastric cancer with peritoneal metastases has become a reality. Median survival in those patients fortunate enough to have complete resection following a response to NIPS is approximately 2.5 years. Occasional long-term survivors (cured patients) are reported.

Are there implications of these favorable results of NIPS in GCPM for other gynecologic and gastrointestinal cancers with peritoneal dissemination? Is NIPS likely to be of greater benefit than CRS plus HIPEC for colon or rectal cancer with peritoneal metastases? Completely possible. What about malignant peritoneal mesothelioma? Yes, a paradigm shift from CRS and HIPEC alone toward a postoperative NIPS is strongly suggested for malignant peritoneal mesothelioma (*Sugarbaker PH, et al. Eur J Surg Oncol, 2017, doi: https://doi.org/10.1016/j.ejso.2017.01.009*). Is the same radical change away from CRS and HIPEC alone indicated for ovarian cancer? NIPS, an intraperitoneal port, laparoscopic and cytologic monitoring, and conversion surgery may show success for control of peritoneal metastases in the face of prior failure. Let's make progress happen!

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## Section 8: Links to suggested videos

### *Videos that Illustrate the Placement of an Intraperitoneal Port:*

**Hironori Ishigami: Intraperitoneal port placement technique for NIPS --**
https://www.dropbox.com/scl/fi/znklv3wqpbgvsjk1oivyw/IP-port-placement-ISHIGAMI-20260209.mp4?rlkey=56rd1ggc9knu8lgroodjr2vk6&st=d7ogwyye&dl=0

**Paul H. Sugarbaker: Cytoreductive surgery plus HIPEC to treat aggressive peritoneal mesothelioma in a young man --** https://www.dropbox.com/scl/fi/eklfcocig5xqy5nskf13h/Ch12-SB-Peritoneal-Mesothelioma-in-a-Young-Man-case1080_1_1.mp4?rlkey=4f1jf9l8q5fuciqizd0emw6eu&st=coaqd77n&dl=0

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# Section 9: Questions you can answer after reading this Edition of PSOGI World News

1. In current practice, does HIPEC following gastrectomy and peritonectomy persist as an alternative for treatment of peritoneal metastases with a PCI ≤6?

2. Is NIPS (normothermic intraperitoneal and systemic chemotherapy) with repeated doses of IV and IP paclitaxel delivered through an intraperitoneal port the most likely option for maximal efficacy and safety?

3. Is conversion surgery after NIPS the most sought-after goal in the treatment of gastric cancer with peritoneal metastases?

4. Is PIPAC a treatment option? If so, what drugs are indicated for intraperitoneal administration and alternating systemic treatments?

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.