PSOGI World News

July 2026
Issue #8

A quarterly newsletter with the latest news, views and announcements

IN THIS ISSUE – Definitive Statements from World Opinion Leaders Regarding Controversies in the Management of Tubo-Ovarian Cancer

Section 1:

Operate Upfront Whenever Possible and Safe: Lessons from TRUST and the Future of Primary Cytoreductive Surgery in Advanced Ovarian Cancer.

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Introduction

For the past few decades, gynecologic oncologists have debated the optimal initial treatment strategy for patients with advanced ovarian cancer. Should patients undergo primary cytoreductive surgery followed by chemotherapy, or should treatment begin with neoadjuvant chemotherapy followed by interval debulking surgery?

Randomized trials such as EORTC 55971 and CHORUS (CHemotherapy OR Upfront Surgery) established neoadjuvant chemotherapy as an acceptable alternative to primary surgery and fundamentally changed practice patterns around the world (*Vergote I, Tropé Claes G, Amant F, et al. NEJM. 2010;363(10):943-53; Kehoe S, Hook J, Nankivell M, et al. The Lancet. 2015;386(9990):249-57*). Subsequent studies, including JGOG0602 and SCORPION, further evaluated this treatment paradigm but did not substantially alter clinical practice. Rather, they reinforced the observation that surgical morbidity and mortality can be significant among patients with extensive disease burden who undergo primary debulking surgery (*Onda T, Satoh T, Ogawa G, et al. Eur J Cancer. 2020;130:114-25; Fagotti A, Ferrandina MG, Vizzielli G, et al. Int J Gynecol Cancer. 2020;30(11):1657-64*). These studies also generated considerable controversy. Many surgeons questioned whether the results reflected the true value of primary surgery or whether they reflected differences in surgical quality, patient selection, and rates of complete gross resection.

The recently reported TRUST (Trial of Radical Upfront Surgical Therapy in Advanced Ovarian Cancer) trial provides an important opportunity to revisit this discussion (*Mahner S, Heitz F, Salehi S, et al. J Clin Oncol. 2025;43(17_suppl):LBA5500-LBA*). Unlike previous randomized trials, TRUST was specifically designed to evaluate the timing of surgery in patients who were considered resectable, medically fit for radical surgery, and treated at centers that met predefined surgical quality standards. Participating institutions underwent a rigorous qualification process that included assessment of surgical volume, infrastructure, and complete

resection rates. The goal was simple: compare primary surgery and interval surgery under conditions that reflect modern expert ovarian cancer care.

The results were notable. Complete gross resection was achieved in 70% of patients who underwent primary surgery and 79% who underwent interval surgery. Postoperative morbidity and mortality were low in both treatment arms. Median overall survival exceeded four years regardless of treatment strategy. Most importantly, TRUST became the first randomized trial to demonstrate a statistically significant progression-free survival advantage for primary cytoreductive surgery compared with neoadjuvant chemotherapy and interval surgery.

Although the study did not meet its primary endpoint of demonstrating a statistically significant overall survival benefit, the direction and magnitude of benefit consistently favored primary surgery. Among patients with stage III disease, median progression-free survival was approximately 5 months longer and median overall survival approximately 10 months longer following primary surgery. Similarly, among patients who achieved complete gross resection, primary surgery was associated with approximately 6 months longer progression-free survival and a 12-month numerical improvement in overall survival.

These findings raise an important question: why were the results different from prior randomized trials?

One possible explanation is surgical quality. In EORTC and CHORUS, complete resection rates at primary surgery were approximately 19% and 17%, respectively (*Vergote I, Tropé Claes G, Amant F, et al. NEJM. 2010;363(10):943-53; Kehoe S, Hook J, Nankivell M, et al. The Lancet. 2015;386(9990):249-57*). In contrast, the complete resection rate in the primary surgery arm of TRUST was 68%. When surgery fails to achieve complete tumor clearance, its potential survival benefit is diminished. Conversely, when surgery is performed in experienced centers with high complete resection rates, outcomes improve substantially.

The TRUST trial reinforces the importance of investing in surgical quality assurance programs, surgeon training, and institutional expertise (*Mahner S, Heitz F, Salehi S, et al. J Clin Oncol. 2025;43(17_suppl): LBA5500-LBA*). The question is not simply whether surgery should be performed before or after chemotherapy, but also whether surgery can be performed at a level that maximizes the likelihood of complete gross resection.

Second, complete gross resection alone is not enough. Recent analyses suggest that the best outcomes are not achieved by aggressive surgery alone, but instead when complete gross resection is achieved while

avoiding significant postoperative complications. Data from the international SUROVA (SURgery in OVArian cancer) study demonstrated that patients who underwent primary surgery, achieved complete gross resection, and experienced no postoperative complications had the most favorable survival outcomes (*Chiva L, Ordas P, Mishra J, et al. Int J Gynecol Cancer. 2025;35(12):102688*). Conversely, complications substantially diminished the survival advantage associated with primary surgery. Similar observations have been reported by multiple groups and are consistent with our experience at Memorial Sloan Kettering Cancer Center.

Why complications influence survival remains uncertain. Complications may delay chemotherapy, impair nutritional status, reduce functional recovery, or simply identify patients with more extensive disease and greater physiologic vulnerability. Regardless of the mechanism, the clinical message is clear. The goal should not be maximal surgery at any cost, but instead complete gross resection with minimal morbidity.

This principle has important implications for patient selection. At Memorial Sloan Kettering Cancer Center, our current approach differs from those we used two decades ago. We have not become less aggressive surgically. If anything, our operations have become more complex. What has changed is our ability to identify patients who are most likely to benefit from primary surgery while minimizing the risk of complications.

Advances in imaging, multidisciplinary evaluation, perioperative care, nutritional assessment, and enhanced recovery pathways have improved our ability to select appropriate candidates for primary surgery. Recent work examining preoperative hypoalbuminemia further highlights the importance of physiologic reserve and the relationship between patient fitness, postoperative outcomes, and long-term survival (*Finch L, Dagher C, Harlev C, et al. Gynecol Oncol. 2026;209:138-45*).

The future of ovarian cancer surgery should therefore not be framed as a debate between primary surgery and neoadjuvant chemotherapy. Both strategies remain valuable. The more important challenge is identifying which patients can achieve complete gross resection without unacceptable morbidity.

For carefully selected patients with resectable disease who are treated at experienced centers, the evidence supporting primary cytoreductive surgery has never been stronger. TRUST demonstrated that excellent outcomes can be achieved when surgery is performed within a framework of rigorous quality assurance and appropriate patient selection. The lesson from TRUST is not that every patient should undergo primary surgery. Rather, it is that patients who are likely to achieve complete gross resection with an acceptable risk of morbidity should be offered the opportunity to undergo surgery upfront.

Conclusion

The management of advanced ovarian cancer continues to evolve, but several principles remain unchanged. Complete gross resection remains the cornerstone of successful surgical treatment. Surgical quality matters. Complications matter. Patient selection matters.

The best outcomes are achieved when these factors align.

For appropriately selected patients who are treated at experienced centers, primary cytoreductive surgery should remain the preferred treatment strategy. The challenge moving forward is not deciding between surgery and chemotherapy, but instead identifying patients who are most likely to benefit from each approach.

Section 2:

Secondary Cytoreductive Surgery in Recurrent Epithelial Ovarian Cancer: Platinum Sensitivity and Patient Selection.

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Secondary cytoreductive surgery has long been considered a treatment option for selected patients with platinum-sensitive recurrent ovarian cancer, yet its effect on overall survival has remained one of the most debated questions in gynecologic oncology. Three major phase III randomized trials have addressed this question and reached seemingly divergent conclusions. DESKTOP III demonstrated a significant overall survival benefit, GOG-0213 found no overall survival advantage, and SOC-1 showed no benefit in the intention-to-treat population but a benefit after adjustment for crossover (*Coleman RL, Spirtos NM, Enserro D, et al. N Engl J Med. Nov 14 2019;381(20):1929-1939. doi:10.1056/NEJMoa1902626; Harter P, Sehouli J, Vergote I, et al. N Engl J Med. Dec 2 2021;385(23):2123-2131. doi:10.1056/NEJMoa2103294; Jiang R, Feng Y, Chen Y, et al. Nat Med. Aug 2024;30(8):2181-2188. doi:10.1038/s41591-024-02981-0).* Although all three enrolled patients with platinum-sensitive recurrent disease, their conflicting results have been interpreted in different ways. Here, we review how these discrepancies may be explained and offer our interpretation, drawing on a trial-level meta-analysis of the three trials.

The first and most important difference lies in how each trial selected its surgical candidates. DESKTOP III used the AGO score, an a priori model designed to identify patients in whom complete resection is achievable, and restricted surgery to that group (*Harter P, Sehouli J, Vergote I, et al. N Engl J Med. Dec 2 2021;385(23):2123-2131. doi:10.1056/NEJMoa2103294*). GOG-0213, by contrast, was the only trial that did not apply a validated selection model, relying instead on surgeon-determined eligibility. It also enrolled a high proportion of patients who received bevacizumab, which may have further contributed to its result.[1] SOC-1 used the iMODEL score and, once the substantial crossover from the no-surgery arm was accounted for, a survival benefit emerged (*Jiang R, Feng Y, Chen Y, et al. Nat Med. Aug 2024;30(8):2181-2188. doi:10.1038/s41591-024-02981-0).* Read together, the three trials are not necessarily contradictory; their differences can be at least partly reconciled once selection, bevacizumab use, and crossover are taken into account, suggesting that surgery may help when patients are selected by a validated score and when complete resection is the realistic goal. These remain plausible explanations rather than proven mechanisms.

These observations are supported by our trial-level meta-analysis of all 1,249 randomized patients from the three trials (*Kim JH, Lim MC, Kim ET, et al. Int J Gynecol Cancer. Jan 2026;36(1):102756. doi: 10.1016/j.ijgc.2025.102756*). Secondary cytoreductive surgery improved progression-free survival (HR 0.67; 95% CI 0.53–0.84) but not overall survival (HR 0.91; 95% CI 0.65–1.27) in the overall population, with the benefit emerging only within selected subgroups. Patients with a favorable validated selection score, defined as a positive AGO score or an iMODEL ≤4.7, had significantly better overall survival with surgery (HR 0.79; 95% CI 0.66–0.96). Most importantly, complete gross resection was the strongest determinant of outcome, with markedly better overall survival (HR 0.53; 95% CI 0.43–0.64) and progression-free survival (HR 0.51; 95% CI 0.42–0.61) than residual disease. Because these subgroup findings derive from post hoc analyses, they should be regarded as hypothesis-generating rather than definitive.

Another important point concerns the platinum-free interval, which showed a pattern that runs against conventional expectation. A longer platinum-free interval is generally regarded as a marker of greater chemosensitivity and more favorable prognosis, yet the overall survival benefit of surgery was confined to patients with a platinum-free interval of 6–12 months (6–16 months in SOC-1; HR 0.70, 95% CI 0.55–0.91), with no benefit in those beyond 12 months (≥16 months in SOC-1; HR 1.04, 95% CI 0.75–1.44). One explanation is that patients with a longer interval already respond well to chemotherapy, leaving little incremental value for surgery, whereas those with a shorter interval retain platinum sensitivity but have more aggressive disease, in which reducing tumour burden may enhance the effect of subsequent treatment. A long platinum-free interval should therefore not by itself be regarded as an indication for surgery.

The discussion so far has concerned platinum-sensitive disease, in which validated selection scores guide the decision to operate. The question becomes harder in platinum-resistant recurrence, where validated surgical selection scores do not apply and systemic options are limited. Here the rationale shifts from cytoreduction alone toward overcoming chemoresistance, which is the basis for adding hyperthermic intraperitoneal chemotherapy (HIPEC). We are addressing this directly in the RECOVER trial (KOV-HIPEC-02R; NCT05316181), a multicenter, open-label, phase III study that randomizes 140 patients with platinum-resistant recurrent ovarian cancer to cytoreductive surgery plus HIPEC (doxorubicin 35 mg/m² and mitomycin 15 mg/m² at 41.5°C) followed by physician-choice chemotherapy, versus physician-choice chemotherapy alone (*Kim JH, Park E, Park SY, Lim MC. Int J Gynecol Cancer. Apr 2025;35(4):101630. doi:10.1016/j.ijgc.2025.101630*). Enrollment was completed in October 2025 and the data are now maturing. RECOVER is intended to answer whether surgery with HIPEC offers a survival advantage in a group that currently has limited options.

Conclusion. The apparent conflict between GOG-0213, DESKTOP III, and SOC-1 can be largely reconciled once selection is taken into account, and our answer to the question of whether to operate is a selective one. In platinum-sensitive recurrence, secondary cytoreductive surgery should be offered to patients identified by a validated selection score (positive AGO or iMODEL ≤4.7) and only when complete resection is achievable, since residual disease removes the benefit. A platinum-free interval longer than 12 months is not in itself an indication for surgery, since these patients did not derive a survival benefit in our analysis. For platinum-resistant disease, the role of cytoreductive surgery with HIPEC remains to be defined, and we await the results of the RECOVER trial.

Table 1. Three randomized trials of secondary cytoreductive surgery in platinum-sensitive recurrent epithelial ovarian cancer

	GOG-0213	DESKTOP III	SOC-1
Patients, CRS+ / CRS− (n)	240 / 245	206 / 201	182 / 175
Selection criteria	Surgeon judgement (broad)	AGO score positive	iMODEL ≤4.7
Primary endpoint	Overall survival	Overall survival	PFS and OS (co-primary)
Subsequent bevacizumab use, CRS+ / CRS−	84% / 84%	22.8% / 23.4%	2% / 1%
Subsequent PARP inhibitor use CRS+ / CRS−	Not reported	3.9% / 6.0%	13% / 11%
Overall survival result	No benefit (HR 1.29)	Benefit (HR 0.75)	No benefit in ITT; benefit after crossover adjustment

CRS, Cytoreductive surgery

Section 3:

Minimally Invasive Resection of Primary and Relapsed Tubo-ovarian Cancer: A Surgical Opinion from the Peritoneal Surface Oncology Perspective.

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The management of advanced tubo-ovarian cancer has changed profoundly during the last decade. However, one principle remains unchanged: the most effective systemic therapy will never compensate for poor-quality cytoreductive surgery. In my opinion, the future of tubo-ovarian cancer treatment is not less surgery, but better surgery: more selective, more standardized, more multidisciplinary, and performed in expert centres able to integrate cytoreductive surgery (CRS), hyperthermic intraperitoneal chemotherapy (HIPEC), systemic therapy, molecular maintenance, and minimally invasive approaches when appropriate.

The first semantic change is important. We should stop speaking about "debulking" as if the operation were a palliative reduction of tumour volume. The PSOGI–ESGO–ISSPP Lyon consensus clearly supports the term cytoreductive surgery for potentially curative surgery in peritoneal malignancy and distinguishes it from debulking (*Bhatt A, et al. Principles of cytoreductive surgery for primary and metastatic peritoneal malignancies–the PSOGI–ESGO–ISSPP Lyon consensus. Lancet Oncology. 2026*). It reflects a surgical philosophy: the goal is complete macroscopic tumour removal, performed according to reproducible peritonectomy principles and documented by objective measures such as PCI, completeness of cytoreduction, and procedure-specific reporting.

In advanced tubo-ovarian cancer, complete cytoreduction is the central prognostic variable. The debate between primary surgery and interval surgery should therefore be reframed. The question is not "upfront or interval?" but "when and where can complete cytoreduction be achieved with acceptable morbidity?" Patients with limited disease, good performance status, and high probability of no residual macroscopic disease should be offered primary CRS in expert hands. Conversely, patients with high tumour burden, poor performance status, diffuse mesenteric disease, or low likelihood of complete resection benefit from neoadjuvant chemotherapy followed by reassessment and interval CRS. This is not a defeat for surgery; it is intelligent sequencing.

HIPEC has become one relevant tool in this strategy. The OVHIPEC-1 trial (*Van Driel WJ, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. Final survival analysis of OVHIPEC-1. Lancet Oncology. 2023*)

and its final survival analysis demonstrated that adding cisplatin-based HIPEC to interval CRS after neoadjuvant chemotherapy improves both progression-free and overall survival without prohibitive toxicity. From a biological perspective, this is logical: after complete macroscopic cytoreduction, the peritoneal cavity is the ideal compartment in which to treat residual microscopic disease. Hyperthermia increases tissue penetration, enhances cytotoxicity, impairs DNA repair, and may have immunomodulatory effects. But the essential point is clinical: HIPEC must not be used to compensate for incomplete surgery. It is a consolidating intraoperative treatment after high-quality CRS, not a substitute for it.

Our position is therefore clear: CRS plus HIPEC should be actively considered in patients with stage III tubo-ovarian carcinoma undergoing interval CRS after response or stability to neoadjuvant chemotherapy, provided complete cytoreduction is achievable in a reference centre. I also believe HIPEC has a role in selected peritoneal recurrences, particularly platinum-sensitive relapse, good performance status, low-volume disease, absence of ascites, and a realistic expectation of CC0 resection (*Canbay Torun B, Glehen O, Kepenekian V, et al. Peritoneal metastasis of advanced epithelial ovarian carcinoma treated with cytoreductive surgery and HIPEC: an international multicentric data analysis. European Journal of Surgical Oncology. 2023*). The recurrent setting is surgically demanding and should not be generalized. It requires surgeons capable of operating across anatomical borders: pelvis, colorectal surgery, upper abdomen, hepatobiliary surgery, diaphragm, vascular exposure, and occasionally pancreatic or gastric procedures. This is the domain of the "stem surgeon": not a lone operator, but a highly trained surgical oncologist embedded in a multidisciplinary peritoneal malignancy programme.

The most recent international data support this philosophy (*Canbay Torun B, Glehen O, Kepenekian V, et al. Peritoneal metastasis of advanced epithelial ovarian carcinoma treated with cytoreductive surgery and HIPEC: an international multicentric data analysis. European Journal of Surgical Oncology. 2023*). In the PSOGI multicentre analysis of 1491 patients with peritoneal metastases from advanced epithelial ovarian carcinoma treated with CRS and HIPEC in specialized units, complete cytoreduction was achieved in more than 80% of cases, with treatment-related mortality below 1%. Median survival reached 58 months for upfront surgery, 60 months for interval surgery and 42 months for recurrent disease. Importantly, incomplete cytoreduction, PCI, major postoperative complications, prior chemotherapy and prior surgical score in recurrence were predictors of poorer outcome.

Minimally invasive CRS + HIPEC represents an additional evolution. It should not be presented as a universal alternative to laparotomy. In unselected advanced ovarian cancer, laparoscopy may be dangerous if it compromises exploration, staging, or completeness of resection. However, in highly selected patients—low

PCI, no bulky masses, no extensive diaphragmatic disease, no multifocal mesenteric involvement, good response to neoadjuvant chemotherapy—the minimally invasive approach can reduce hospital stay, accelerate recovery, and shorten the interval to systemic therapy. Our matched experience in interval laparoscopic CRS + HIPEC for advanced epithelial ovarian cancer refined this concept further: in patients with PCI ≤10 and strict selection criteria, laparoscopic CRS + HIPEC achieved 100% complete cytoreduction, shorter hospital stay, earlier oral intake and mobilization, and faster return to systemic treatment, without compromising early oncological outcomes (*Durán-Martínez M, Gómez-Dueñas G, Rodríguez-Ortiz L, et al. Laparoscopic versus open approach for interval cytoreductive surgery and HIPEC in advanced epithelial ovarian cancer: a matched comparative study. Surgical Endoscopy. 2023*).

This is, in our view, the "minimal approach": radicality without unnecessary aggression. Minimally invasive surgery is not a smaller operation; it is the same oncological operation performed through a less invasive access in the rare patient in whom that access does not reduce surgical quality. The laparoscopic decision must be made after systematic exploration of the entire abdominal cavity, objective PCI calculation, and honest conversion or exclusion when complete cytoreduction cannot be guaranteed. The completeness of cytoreduction score, not the cosmetic incision, is the relevant endpoint.

Innovation also requires humility. Laparoscopic CRS + HIPEC is technically complex and has a learning curve. In our learning-curve analysis, consolidation was achieved after approximately 14 procedures, with a significant reduction in operative time and no increase in morbidity. This means that L-CRS + HIPEC should not be adopted casually. It belongs in high-volume peritoneal surface malignancy units, with surgeons already experienced in open CRS + HIPEC, advanced laparoscopy, peritonectomy procedures and multidisciplinary rescue of complications. The international PSOGI laparoscopic HIPEC (*Arjona-Sanchez A, Aziz O, Passot G, et al. Laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: long-term oncologic outcomes from the international PSOGI registry. European Journal of Surgical Oncology. 2023*) registry confirms the same message: in selected patients treated in specialized centres, minimally invasive CRS + HIPEC offers low major morbidity, short length of stay and satisfactory oncologic outcomes, but it remains a programme-level innovation rather than a routine procedure for all hospitals.

The choice of HIPEC drug is another area of practical innovation. Cisplatin remains the best-supported

regimen in randomized trials, but paclitaxel has attractive pharmacokinetics for intraperitoneal use and may be useful in frail patients, renal impairment, or platinum intolerance. The Spanish REGECOP multicentre analysis comparing cisplatin- and paclitaxel-based HIPEC during interval CRS found comparable disease-free and overall survival after matching, with no increase in morbidity for paclitaxel (*González Sánchez et al., JAMA Network Open 2025*). These data do not replace randomized evidence, but they support a pragmatic approach: HIPEC should be protocolized, audited, and adapted to patient biology and comorbidity.

The arrival of PARP inhibitors, bevacizumab, antibody-drug conjugates, and immunotherapy has not diminished the value of surgery; it has increased the need for precise integration. PARP maintenance has changed outcomes, especially in BRCA-mutated and homologous recombination deficient tumours, and modern treatment algorithms increasingly require biomarker-driven decisions. Anti-PD-L1 strategies, by contrast, have not yet produced a consistent practice-changing benefit in unselected ovarian cancer, although combinations with antiangiogenic therapy and PARP inhibition remain scientifically attractive. The surgical community should not view these treatments as competitors. They are partners. The real question is how to combine maximal local-regional control with optimal systemic maintenance.

Future clinical research should move away from simplistic comparisons of surgery versus drugs. The next generation of trials must stratify patients by tumour biology, surgical quality, PCI, completeness of cytoreduction, HIPEC protocol, BRCA/HRD status, and maintenance therapy. Surgical quality is not a confounder; it is the treatment.

Our definitive statement is this: selected patients with primary and relapsed tubo-ovarian peritoneal disease should be managed in reference centres where complete cytoreduction is the central objective, HIPEC is integrated when evidence and patient selection support it, and minimally invasive CRS is used only when it preserves oncologic radicality. The future is not “open versus laparoscopic”, “surgery versus systemic therapy”, or “HIPEC versus no HIPEC”. The future is precision surgery combined with precision oncology. For our patients, that future must be centralized, audited, and delivered by teams whose results can be measured.

Section 4:

Laparoscopy Provides Crucial Information and an Advanced Technology That Allows Knowledgeable Management of Tubo-Ovarian Cancer

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Introduction

The use of laparoscopy in the management of ovarian cancer is receiving growing attention as increasing scientific evidence support the feasibility and safety of this approach. Recent data suggest that this minimally invasive surgery may provide significant benefits such as, reduced morbidity, faster postoperative recovery and a chance for an improved quality of life for those patients with advanced tubo-ovarian cancer.

Laparoscopy for diagnosis of tubo-ovarian cancer

Adequate staging is crucial in determining histological diagnosis and subsequent treatment. The laparoscopic surgical approach differs in women of childbearing age that present with a mass suspicious for malignancy ovarian neoplasm. In these patients, a fertility-sparing initial surgical management is preferred. In fertility-sparing operations, laparoscopic surgery is feasible and safely performed. Fertility-sparing surgery may be performed with laparoscopic unilateral salpingo-oophorectomy, without uterus removal but with a complete surgical staging. Surgical staging in early stage tubo-ovarian cancer is of great importance, as patients with apparent early-stage disease may have microscopic metastases in the retroperitoneum or in hidden locations in the upper abdomen, with a subsequent "upstaging" of the disease.

The National Comprehensive Cancer Network (NCCN) with a category 2B level of evidence, have included staging laparoscopy in their guidelines, as a tool to assess whether patients with advanced stage ovarian cancer should be treated by upfront surgery or receive neoadjuvant chemotherapy (NACT) prior to surgery (*NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 4.2026 – April 10, 2026 https://www.nccn.org*). Also, given the increased complexity in the management of recurrent ovarian cancer, it is crucial to identify the location and distribution of the recurrence in order to estimate resectability and surgical planning.

So far, the most popular laparoscopic prediction models for assessing the spread of ovarian cancer are the Fagotti Score and the Sugarbaker-described peritoneal cancer index (PCI) (*Eman Amin El Gindy, et al. IJCBS, 24(10) (2023):771-775*).

Laparoscopy for treatment of tubo-ovarian cancer

Despite the absence of robust scientific support, perioperative data supports the laparoscopic approach to definitive surgical management. Advantages of laparoscopic surgery include shorter operation time, less postoperative complications, less blood loss and shorter hospital stay. The European Society of Gynecologic Oncology (ESGO), the International Society of Gynecologic Endoscopy (ISGE) and the American Society of Clinical Oncology (ASCO) recommend for early stage tubo-ovarian cancer patients, laparoscopic surgical treatment, performed by well-trained laparoscopic gynecologic oncologists (*Chul Kwon Lim, et al. Gland Surg 2021;10(3):1252-1259*). Laparoscopic sentinel lymph node mapping in early-stage ovarian cancer with the injection of indocyanine green in the ovarian vessels (SELLY study) was evaluated in a prospective multicenter study, but results did not reach the expected sensitivity in identifying metastatic lymph node disease.

Avoiding unforeseen negative outcomes

The size of the adnexal tumor is an important factor, creating controversy, since the laparoscopic surgical approach was not initially considered safe for large suspicious for malignancy masses. Concerns such as, the intra-operative rupture of the tumor with subsequent dissemination of the cancerous cells in the peritoneal cavity and the upstaging of the malignancy, are gradually resolving, as these patients are referred to specialized laparoscopic oncologic centers.

Despite the many advantages in the use of laparoscopic surgery in early-stage ovarian cancer, certain concerns identified in the literature should be kept in mind. A) Avoidance of port-site metastases by using endobags and by reducing the manipulations of surgical specimens. B) Avoidance of tumor spillage by carefully avoiding tumor capsule rupture. C) Avoidance of the laparoscopic extraction of ovarian masses by morcellation (increased risk for tumor cell dissemination and alteration of the pathologic evaluation). Risk factors for the use of laparoscopic surgery have been described and include patients with severe obesity, history of previous abdominal surgery, pelvic inflammatory disease and diaphragmatic hernia.

Laparoscopy as a treatment option with some unique benefits

The treatment options in advanced stage epithelial ovarian cancer include, surgery and perioperative chemotherapy. Cytoreductive surgery as described by Sugarbaker is the cornerstone of treatment by laparotomy but also by laparoscopy. In cases where primary cytoreduction is not feasible (extensive tumor spread, large tumor burden, poor performance status), NACT followed by interval debulking surgery (IDS) is indicated (*Roni Nitecki, et al. Int J Gynecol Cancer 2020;30:1450–1454*). After NACT, laparoscopy carries minimal risk of major problems, usually connected to the initial abdominal access, with potential bowel or vascular injury.

Laparoscopy is characterized by specific advantages, such as, an optical magnification of the abdominal vessels, decreased postoperative adhesion formation and a shorter recovery time. Compared to cytoreduction by laparotomy, a majority of patients are able to receive adjuvant chemotherapy at an earlier time. Laparoscopy may also allow, in a select group of patients, administration of hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) at the end of cytoreduction.

Laparotomy versus laparoscopy for resection of primary and recurrent tubo-ovarian cancer

Data available from the gynecologic oncology literature for the use of laparoscopic surgery in advanced ovarian cancer has controversial results. Current evidence, however, suggest that survival after laparoscopic surgery in selected patients is not inferior to those patients operated on by laparotomy (*V. Ghirardi, et al. Facts Views Vis Obgyn, 2023, 15 (1): 25-28*). The ongoing LANCE trial is an international, randomized multicenter phase III trial comparing minimally invasive surgery versus laparotomy in women with advanced stage ovarian cancer with a complete or partial response to NACT and normalization of CA125. Results are pending.

Only retrospective, small number studies have reported on the use of laparoscopy in recurrent ovarian cancer, with secondary cytoreductive surgery. However, laparoscopy does not seem to be inferior to laparotomy in terms of oncological outcomes.

Conclusions

Laparoscopy is considered by many expert centers to be essential for knowledgeable diagnosis and staging of tubo-ovarian cancer. Accepting the fact that CC-0/1 cytoreduction is required for resection of tubo-ovarian

cancer, laparoscopy is considered by these authors as non-inferior to laparotomy for upfront resection, interval resection and resection of recurrent disease. Proper patient selection is crucial. The continuous development of laparoscopic surgical technologies in both early and advanced stage disease promises to provide further interesting research results and improvements in patient management. In the future, a larger number of patients will benefit from the integration of laparoscopy into the treatment strategies.

Section 5:

HIPEC Is Necessary but Not Sufficient to Eradicate Sites of Treatment Failure in Patients Having Cytoreductive Surgery for Tubo-Ovarian Cancer

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Failure analysis of patients having hysterectomy for stage 3 ovarian cancer

Study of the natural history of stage 3 tubo-ovarian cancer shows that the most prominent site for disease progression following surgery to resect the primary disease occurs local-regionally within the abdomen and pelvis. However, systemic recurrence may also occur after resection plus systemic chemotherapy. Systemic disease is a prominent feature in latter stages of disease progression. Both lymphatic and hematogenous routes for systemic disease progression are seen. Cormio et al. (*Int J Gynecol Cancer, 2003*) reported progressive tubo-ovarian cancer within the abdomen and pelvis in 75% of patients and systemic disease in 25%.

The anatomic location of the progressive abdomino-pelvic disease may provide clues regarding the cause of treatment failure. To document sites of recurrent disease following hysterectomy and systemic chemotherapy, Sugarbaker and Chang recorded the disease progression at 23 anatomic sites. Data was prospectively recorded at the time of reoperative surgery (*Sugarbaker PH. Chinese J Clin Oncol, 2022*) with all sites of recurrence confirmed histologically. Prominent sites of disease progression were the right subphrenic space (70% of patients), unresected portions of the greater omentum (65%), rectosigmoid colon (65%) and lesser omentum (45%). Anatomic sites that were free of disease following hysterectomy were also prominent sites of treatment failure. These sites were the abdominal incision (55%), visceral surface of the bladder (50%), distal left ureter (50%) and vaginal cuff (50%). These sites of disease recurrence that were documented on surfaces left as free of disease after hysterectomy confirm that tumor cell entrapment of intraperitoneal free cancer

cells (IFCCs) are a prominent cause of treatment failure. A major question arises from these data. Can hyperthermic intraperitoneal chemotherapy (HIPEC) eradicate IFCCs and thereby bring about a major change in the high incidence of local-regional treatment failure in the surgical management of tubo-ovarian cancer.

Clinical trials showing benefit from HIPEC suggest reduced tumor cell entrapment of IFCCs

In 2018 in the New England Journal of Medicine, van Driel and coworkers published their results of a randomized controlled trial to test HIPEC in patients treated for tubo-ovarian cancer (*van Driel, New England J Med, 2018*). All patients were treated with systemic carboplatin and paclitaxel prior to a surgery that resulted in an optimal cytoreduction with residual disease 10 mm or less in diameter. Half of the 245 patients were treated by HIPEC cisplatin and half by surgery alone. At a median of 4.7 years following cytoreduction, 62% of the surgery plus HIPEC group were alive and 50% of the surgery alone group were alive. The improved survival with HIPEC cisplatin was significant (p=0.02).

Lei and coworkers compared the results of a triple HIPEC cisplatin on days 1, 3 and 5 postoperatively in 584 patients. The survival of a primary cytoreductive surgery in 425 patients at 3 years was 60%. Survival was 47% in 179 patients who had surgery alone. The improved survival was significant (p=0.003).

Causation of improved survival of the van Driel et al. trial and the Lei et al. trial has not been determined. These authors are convinced that the most likely explanation is reduced IFCCs and less tumor cell entrapment in HIPEC-treated patients.

A study to quantitate the impact of HIPEC on IFCCs in patients treated or untreated by HIPEC was performed by Ji et al. (*Ji ZH, Sun JH, Wu HT. Transl Oncol, 2016*). The peritoneal lavage fluid (or ascites) from 50 peritoneal metastasis patients was collected before and after intraoperative HIPEC. Cells from the lavage were tested by conventional cytology and molecular tumor biology. It was found that the positive cytology pre-HIPEC *vs.* post-HIPEC was 100.0% (50/50) *vs.* 22.0% (11/50) (p=0.000). This result indicated that single-dose HIPEC could achieve approximately 78% success in eliminating IFCCs. There are still 22% viable IFCCs after single-dose HIPEC (Figure 1).

In the molecular studies performed by Ji et al., the positive rates of CEA mRNA and CK20 mRNA pre-HIPEC *vs.* post-HIPEC were 100.0% versus 86.0% (P = 0.012) and 100.0% versus 96.0% (p=0.495), respectively. Therefore, in terms of molecular tumor biology, single-dose HIPEC could only eliminate 14% CEA mRNA and

4% CK20 mRNA. The clinical significance of this result indicates that single-dose HIPEC could not achieve molecular eradication of peritoneal metastases (Figure 2).

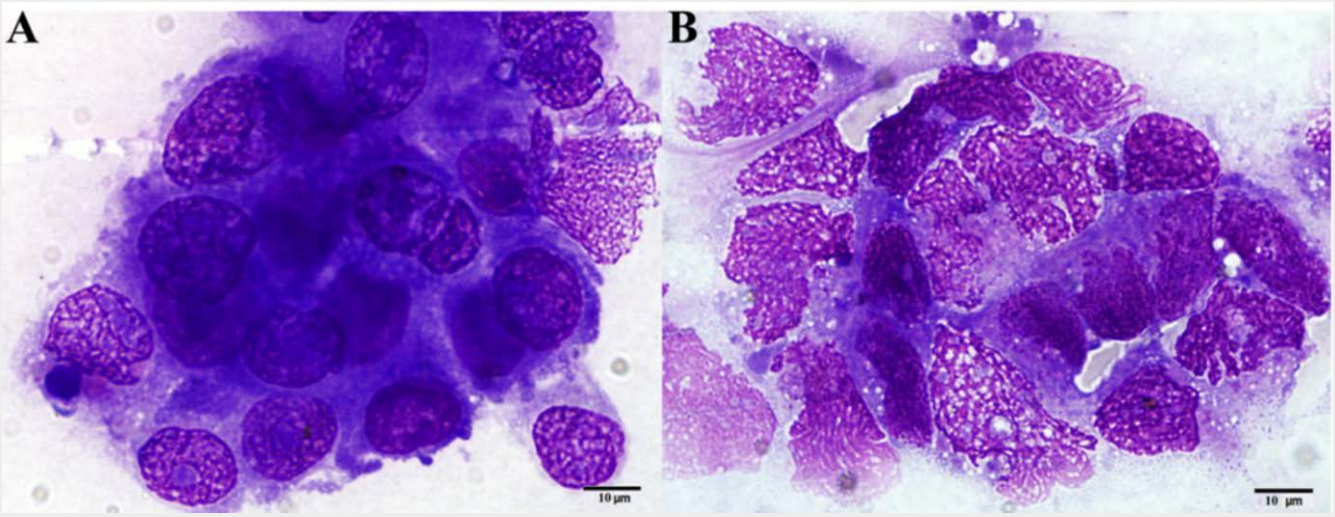

Figure 1. Conventional cytology results: positive IFCCs (A) and cytolysis after HIPEC (B) (Wright's stain, 1000×, scale bar = 10 μm). Single-dose HIPEC could eliminate 78% IFCCs. There are still 22% viable IFCCs. (*Ji ZH et al., Transl Oncol. 2016; 9(1): 18-24. doi: 10.1016/j.tranon.2015.11.015*)

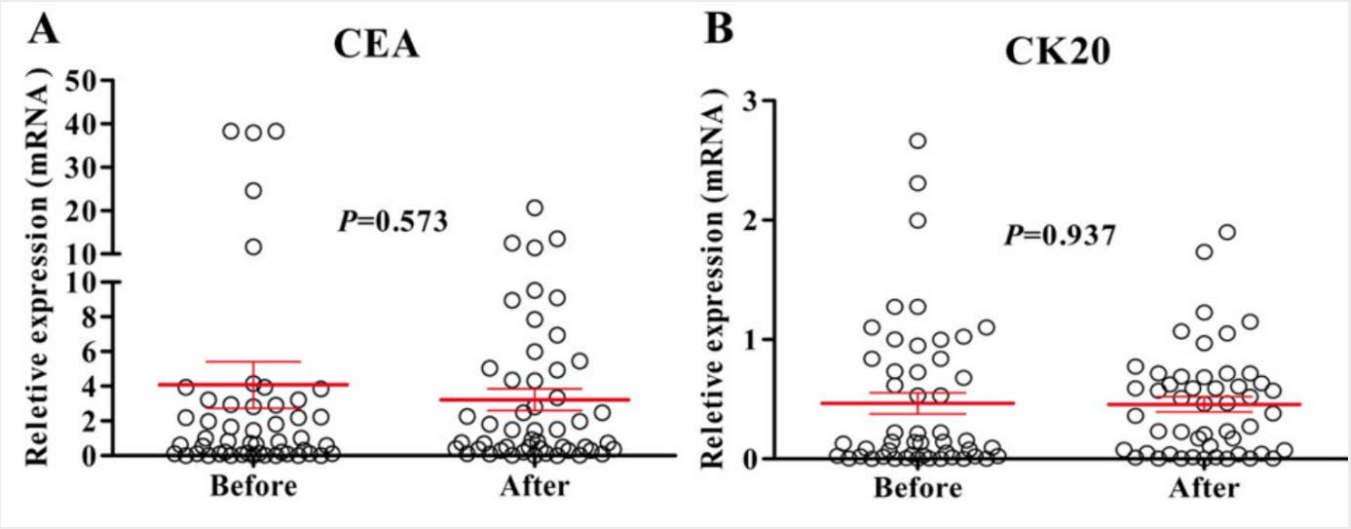

Figure 2. Relative expressions of CEA mRNA (A) and CK20 mRNA (B) before HIPEC and after HIPEC acquired by real-time quantitative RT-PCR. Horizontal lines represent mean ± standard error. (*Ji ZH et al., Transl Oncol. 2016; 9(1): 18-24. doi: 10.1016/j.tranon.2015.11.015*).

These experimental studies may be interpreted in a similar manner as the clinical studies. HIPEC has an effect. It is necessary to initiate the elimination of IFCCs from the abdomen and pelvis following cytoreductive surgery. HIPEC can be regarded as a weak tool by which to control small volume residual disease. It may, when a very small extent of IFCCs remain after a complete cytoreduction, prolong survival. However, in a

majority of ovarian cancer patients it is not sufficient to result in the total eradication of IFCCs, prevent tumor cell entrapment, and thereby result in prolonged survival.

From a theoretical perspective, HIPEC after complete cytoreduction for tubo-ovarian cancer should show a large benefit

The rationale of HIPEC to eradicate minimal residual disease after a complete cytoreduction is strong. Success with HIPEC in tubo-ovarian cancer should be greater than in any of the other diseases currently treated for peritoneal metastases. Superior results are expected when compared to colorectal cancer, gastric cancer, and peritoneal mesothelioma. Prediction of a large improvement in long-term survival comes about from clinical and pharmacologic considerations: 1) The natural history of the surgical treatment of tubo-ovarian cancer shows that 75% of recurrences are within the abdomen and pelvis. Systemic disease in the liver, lungs or retroperitoneal lymph nodes occurs in only 25% of patients. 2) The chemotherapy agents used for ovarian cancer show remarkable short-term success with 70% of patients showing a response. 3) The chemotherapy agent used for HIPEC is synergized by hyperthermia more than any other HIPEC drug. Hyperthermic cisplatin has been referred to as an "intraperitoneal superdrug." 4) Tests used to knowledgeably select patients for cytoreductive surgery plus HIPEC are available. The serum tumor marker CA125 used to monitor over time the extent of disease is very accurate. Patients who respond to neoadjuvant chemotherapy can be identified. Radiologic assessment of the peritoneal cancer index (PCI) has been extensively studied and compared well to the PCI at laparotomy. Laparoscopy is routinely used so patients who will have a poor outcome from cytoreductive surgery are not taken to the operating theater. 5) The surgical expertise to achieve an optimal cytoreduction with no visible residual disease remaining at the completion of the intervention has progressed. The great majority of patients who have cytoreductive surgery are now ideal candidates for a successful HIPEC. There is a greatly improved surgical outcome. Despite these five features predicting extraordinary success, the survival advantage at 5 years is limited to 10-15%!

What's wrong with the current HIPEC for tubo-ovarian cancer?

Are there defects in the HIPEC methodology that interfere with a large decrease in local-regional treatment failure? The limitations of HIPEC cisplatin are as follows: 1) Although many IFCCs are controlled, a sufficient proportion survive and develop over time as recurrent disease. Stem cells, cancer cells with natural resistance and cancer cells with acquired resistance, remain even though a large proportion have been killed. 2) Current HIPEC methodology utilizes a single 90-minute exposure of cancer cells to chemotherapy and heat. Success with a single chemotherapy treatment in oncology is very unusual. 3) Contact of the chemotherapy is on

parietal peritoneal surfaces with visceral peritoneal surface contact minimal, sometimes absent. 4) Penetration of chemotherapy solution by simple diffusion may not be deep enough to eradicate all foci of cancer cells. The peritoneal-plasma barrier that contains the peritoneal metastases has two sides and only the peritoneal side is treated by HIPEC.

A way forward toward better outcomes combines hyperthermic intraperitoneal and systemic (HIPS) chemotherapy and normothermic intraperitoneal and systemic (NIPS) chemotherapy for tubo-ovarian cancer

The limitations of current HIPEC methodology, particularly regarding a single dose of drug, short drug dwell time and a lack of cytotoxicity for residual disease, have prompted clinical exploration of repeated or long-term intraperitoneal chemotherapy in the neoadjuvant and adjuvant setting. The repeated normothermic intraperitoneal and systemic chemotherapy (NIPS), in addition to CRS+HIPS, constitute a comprehensive package solution to eradicate peritoneal metastases (*Yonemura Y, Elnemr A, Endou Y, et al. World J Gastrointestinal Oncol. 2010; 2(2): 85-97*) (Figure 3). Note that HIPEC, which uses single agent intraperitoneal chemotherapy is replaced by hyperthermic intraperitoneal and systemic (HIPS) chemotherapy. Both sides of the peritoneal-plasma barrier must be treated.

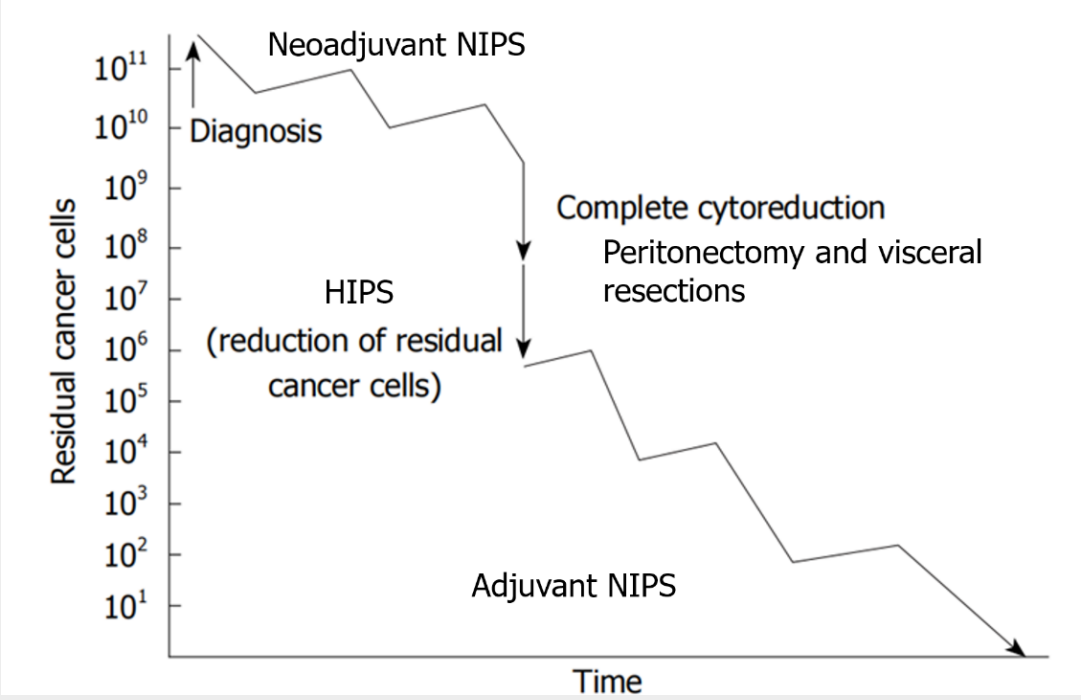

Figure 3. Treatment strategy for peritoneal metastases from tubo-ovarian cancer. NIPS: Normothermic intraperitoneal and systemic chemotherapy; HIPS: Hyperthermic intraperitoneal and systemic chemotherapy; Integration of CRS+HIPS and NIPS chemotherapy, will achieve sustainable control of peritoneal disease. (Modified from: *World J Gastrointestinal Oncol. 2010; 2(2): 85-97. doi: 10.4251/wjgo.v2.i2.85*)

Modifications of current management strategies by using normothermic intraperitoneal and systemic (NIPS) chemotherapy to replace systemic chemotherapy

Since tubo-ovarian cancer is largely a local-regional disease process, the chemotherapy administration should be both systemic and local-regional. The intraperitoneal chemotherapy is paclitaxel. Its pharmacokinetics strongly recommend an intraperitoneal route for administration (Mohamed F and Sugarbaker PH. Surgical Oncol Clin N Am, 2003). The systemic component of NIPS is reduced dose intravenous cisplatin. The two drugs are given as a combined treatment package (intraperitoneal paclitaxel first, then intravenous cisplatin). NIPS is used in both the neoadjuvant and adjuvant setting.

Modifications of current management strategies by using hyperthermic intraperitoneal and systemic (HIPS) chemotherapy to replace HIPEC

The abdominal-pelvic surfaces that are the site of entrapped tumor cells after a complete cytoreductive surgery has two sides. There is a peritoneal side that can be in direct contact with an intraperitoneal chemotherapy solution. Intraperitoneal chemotherapy will result in cytotoxicity as drugs move by diffusion from peritoneal cavity into the plasma. There is another side of the peritoneal-plasma barrier in direct contact with the body compartment. Intravenous chemotherapy will result in cytotoxicity as a drug moves by diffusion from the body compartment to the peritoneal surface. The extent of uniform contact of chemotherapy with the peritoneal-plasma barrier by the systemic route of administration is much more uniform than contact from an intraperitoneal route of administration. The bidirectional HIPS has been safely used in hundreds of tubo-ovarian cancer patients. The intraperitoneal heated drug is cisplatin. The systemic drug heat targeted to the peritoneal surface is ifosfamide.

An example of success with HIPEC plus NIPS

Li et al. analyzed 209 patients with peritoneal metastases treated with CRS + HIPEC combined with systemic or NIPS chemotherapy (Li B, et al. Normothermic intraperitoneal chemotherapy as an essential part of PM treatment. Manuscript in preparation, 2026). The cohort included malignant peritoneal mesothelioma (28.2%), pseudomyxoma peritonei (22.5%), ovarian carcinoma with peritoneal metastases (15.3%), colorectal carcinoma with peritoneal metastases (13.4%), and others. The CC-0 or CC-1 rate reached 69.4%, and 79.9% of patients who received postoperative NIPS. Patients who completed ≥ 4 cycles of NIPS achieved a median OS of 54 months, which was significantly superior to those who discontinued or did not receive NIPS (32–36 months). Multivariate analysis revealed that CC score (HR=2.08, $p<0.001$) and NIPS completion (HR=1.58,

p=0.004) were independent prognostic factors. With regard to NIPS chemotherapy regimens, taxane-based protocols (docetaxel combined with platinum agents) demonstrated clear superiority, and the pemetrexed plus cisplatin regimen was particularly effective for malignant peritoneal mesothelioma.

Conclusion

HIPS and NIPS have a strong clinical and pharmacologic rationale. They are promising strategies for treatment of peritoneal metastases from ovarian cancer. They can also be applied to several other causes of peritoneal surface malignancy.

Section 6:

The Beginnings of CRS and HIPEC in Latin America: The Legacy of Eduardo L. Huertas, MD

By Fernando Sánchez Loria[1] and Pablo Carmignani[2]
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The development of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in Latin America can be traced back to the pioneering efforts of Dr. Eduardo L. Huertas in Argentina during the 1980s.

At that time, access to international medical literature in Argentina was limited, with only a small number of institutions receiving major surgical and oncologic journals. Among the publications that profoundly influenced Dr. Huertas was a report by Fujimoto and colleagues describing the treatment of gastric cancer-associated peritoneal carcinomatosis using surgery combined with intraperitoneal chemotherapy and hyperthermia. This landmark work sparked his interest in regional cancer therapies and initiated a lifelong commitment to the study of peritoneal surface malignancies.

During the same period, the pioneering investigations of Armstrong, Markman, and others on intraperitoneal chemotherapy for ovarian cancer further reinforced the potential of locoregional treatment strategies. In 1989, the publication of Regional Cancer Therapy: State of the Art and Innovative Approaches, edited by Kemeny and Markman, provided an additional source of inspiration. The volume included contributions from

Paul Sugarbaker, whose work would later become fundamental to the development of CRS and HIPEC worldwide.

Driven by scientific curiosity and surgical innovation, Dr. Huertas began adapting perfusion systems and conducting experimental studies in animal models while deepening his understanding of tumor biology, pharmacokinetics, hyperthermia, and intraperitoneal drug delivery. Recognizing the importance of multidisciplinary care, he assembled a collaborative team of medical oncologists, internists, and surgeons to evaluate the potential role of cytoreduction and intraperitoneal chemotherapy in Argentina.

Over the following years, through the treatment of a growing number of patients with diverse peritoneal malignancies, the group progressively refined its technical expertise. The remarkable responses observed in advanced ovarian cancer, together with mounting evidence supporting maximal cytoreduction as a determinant of oncologic outcomes, contributed substantially to the expansion of the program.

By 2009, Dr. Huertas had performed cytoreductive procedures in 203 patients with advanced ovarian cancer, including 128 who received intraperitoneal chemotherapy, 94 of whom underwent HIPEC. These experiences paralleled the growing international body of evidence supporting CRS and HIPEC and helped establish the foundations of modern peritoneal surface oncology in Argentina.

A Continuing Legacy

Over subsequent decades, patient selection criteria, surgical techniques, and perioperative management strategies became increasingly standardized, reflecting the evolution of international clinical trials and evidence-based practice.

Today, Dr. Huertas continues to contribute to the field, bringing decades of accumulated experience in CRS, HIPEC, and multidisciplinary cancer care. Throughout his career, he has maintained a strong belief in the value of innovation, collaboration, and continuous professional development.

He also emphasizes that the future of oncology will be shaped by advances in molecular profiling, genomics, precision medicine, and artificial intelligence, which are expected to transform patient selection, treatment planning, and outcome prediction in the years ahead.

The Current Program at Instituto Alexander Fleming

At the Instituto Alexander Fleming in Buenos Aires, Argentina, HIPEC has been integrated into the multidisciplinary management of selected patients with advanced ovarian cancer. The procedure is routinely performed during interval cytoreductive surgery following neoadjuvant chemotherapy, according to the protocol established by the landmark OvHIPEC-1 trial (van Driel et al., New England Journal of Medicine, 2018). To mitigate cisplatin-associated nephrotoxicity, sodium thiosulfate is systematically administered as part of the institutional protocol.

The institution has also developed extensive expertise in CRS-HIPEC for a broad spectrum of peritoneal surface malignancies, including malignant peritoneal mesothelioma and pseudomyxoma peritonei, conditions in which CRS-HIPEC remains a cornerstone of treatment in appropriately selected patients. In addition, selected patients with peritoneal metastases from colorectal and gastric cancers are evaluated within a dedicated multidisciplinary framework and may undergo CRS-HIPEC when clinically appropriate.

Through its dedicated Peritoneal Surface Malignancy Program, Instituto Alexander Fleming continues to advance the field of locoregional cancer therapy by integrating evidence-based surgical oncology, perioperative optimization, and multidisciplinary decision-making to improve patient outcomes.

Conclusion

Dr. Eduardo L. Huertas played a seminal role in introducing and developing CRS and HIPEC in Argentina and was among the earliest surgeons in Latin America to embrace these emerging therapeutic strategies. His contributions helped establish the foundations of peritoneal surface oncology in the region and fostered the dissemination of knowledge regarding the management of peritoneal malignancies.

Beyond his technical achievements, his enduring commitment to education, innovation, and multidisciplinary collaboration has influenced generations of surgeons and oncologists. His career stands as a testament to the transformative impact that visionary leadership can have on the development of a surgical subspecialty and on the care of patients with peritoneal surface malignancies.

The story of Dr. Eduardo L. Huertas reflects the emergence of peritoneal surface oncology in Latin America and illustrates how scientific curiosity, multidisciplinary collaboration, and perseverance can facilitate the adoption of innovative therapies, even in environments with limited access to information and technology.

His career serves as an enduring example of how vision, commitment, and academic leadership can transform clinical practice and expand therapeutic opportunities for patients with peritoneal malignancies throughout an entire region.

Section 7:

Artificial Intelligence for Longitudinal Monitoring of Peritoneal Metastases in Tubo-Ovarian Cancer: From Subjective Assessment to Digital Biomarkers

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The management of advanced tubo-ovarian cancer (OC) has undergone profound changes over the last decade. The introduction of neoadjuvant chemotherapy, maintenance therapies, targeted agents, immunotherapy, and regional treatment strategies has significantly altered the clinical course of peritoneal metastases (PM). As a result, the assessment of tumor burden and treatment response has become increasingly important and complex. The challenge in evaluating OC is no longer limited to mapping the distribution or resectability of PM. Instead, a more fundamental question has emerged: how can we objectively measure the response of peritoneal disease to the various treatment modalities currently available within the peritoneal cavity?

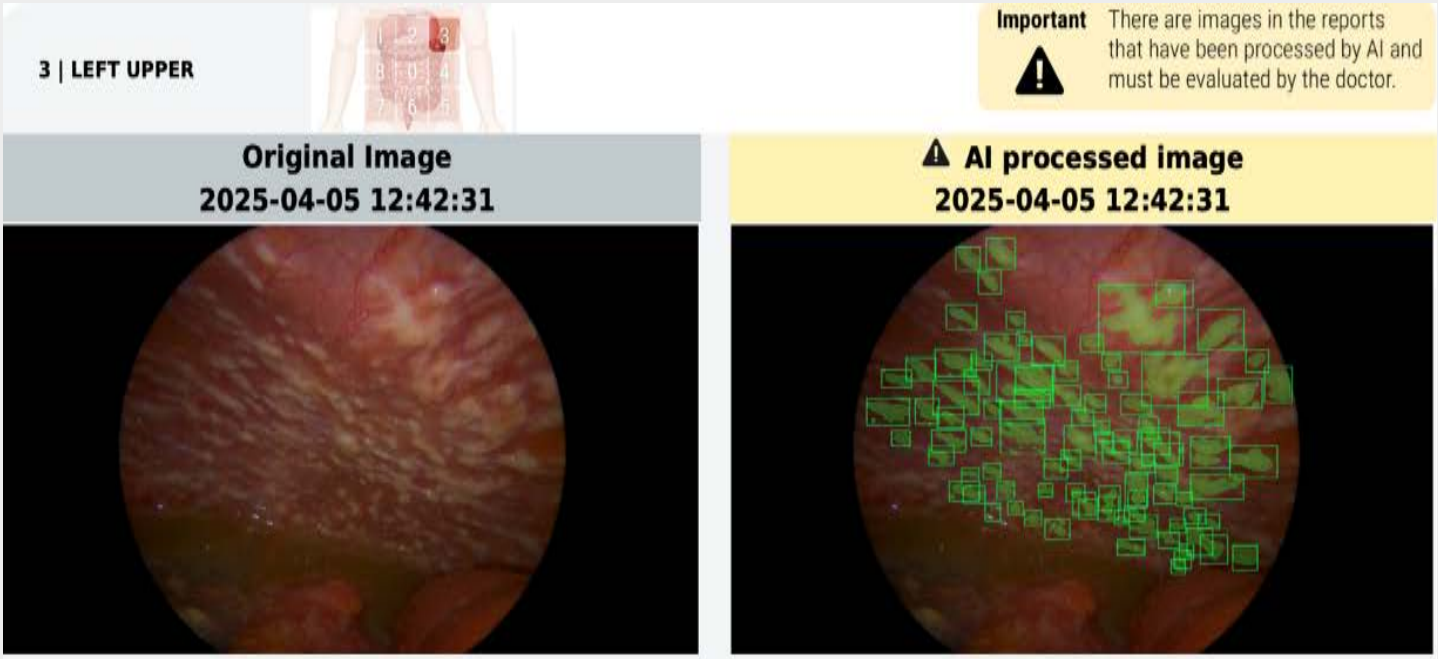
For more than three decades, the Peritoneal Cancer Index (PCI) has remained the primary tool for assessing PM and has has *provided the foundation* for much of the research *on* the treatment of peritoneal carcinomatosis. Solass et al. introduced the peritoneal regression grading score (PRGS) as the first instrument specifically designed to measure tumor response in PM, and its prognostic value transformed histological response into a clinically meaningful *tool* capable of supporting patient selection and guiding therapeutic strategy. Although PRGS established histological response as an important prognostic biomarker (*Baake J, Nadiradze G, Archid R, et al. Pleura and Peritoneum 2023;8:55–63.* https://doi.org/10.1515/pp-2023-0014). The visual assessment of PM—which continues to underpin many intraoperative decisions—remains highly subjective and dependent on individual observer interpretation. The recent MORPHEUS initiative illustrates this problem: 80 images of peritoneal metastases were assessed by 41 international experts *(Bhatt A, Sharma V, Pawar A, et al. Ann Surg Oncol 2026.* https://doi.org/10.1245/s10434-026-19344-3*)*, Consensus was achieved in only 22.5% of the images, with a Krippendorff's alpha coefficient of approximately 0.17. These findings suggest that even highly experienced specialists frequently disagree when classifying the same

peritoneal lesion. Small differences in visual interpretation may influence decisions regarding cytoreductive surgery, continuation of systemic therapy, enrollment in clinical trials, or transition to palliative care. Artificial intelligence (AI) has emerged as a potential solution to this challenge. Advances in computer vision have demonstrated that AI systems can identify visual patterns that are difficult for humans to recognize consistently. One of the first studies specifically evaluating AI for the intraoperative identification of PM was conducted by Schnelldorfer and colleagues (*Schnelldorfer T, Castro J, Goldar-Najafi A, Liu L. Ann Surg 2024;280:1006–13.* https://doi.org/10.1097/SLA.0000000000006294). Using more than 4,000 peritoneal lesions obtained during staging laparoscopies, they trained the Computer-Assisted Staging Laparoscopy (CASL) system, which outperformed experienced surgical oncologists in the United States. The AI model achieved an area under the ROC curve (AUC) of 0.78 versus 0.69 for surgeons alone. More importantly, the integration of AI support increased the accuracy of biopsy-related decisions from 52% to 66% while reducing unnecessary biopsies by 28% (*Schnelldorfer T, Castro J, Goldar-Najafi A, Liu L. Ann Surg 2024;280:1006–13.* https://doi.org/10.1097/SLA.0000000000006294). These findings provided the first evidence that AI may not only reproduce human interpretation but also enhance clinical decision-making during surgical staging.

However, reproducing human lesion score classifications may not be the ultimate goal of AI algorithms. A fundamental challenge exists: if expert interpretation itself exhibits substantial variability, training algorithms exclusively on human labels may directly transfer this subjectivity to the model. This phenomenon, known as label noise, represents one of the major limitations of supervised AI systems in medicine. Our pilot study, presented at the 5th International Scientific Congress of the ISSPP in São Paulo earlier this year, explored this issue directly. The study utilized laparoscopic images obtained from patients with OC as well as other PM histologies. Rather than focusing exclusively on lesion classification, the project investigated the extraction of quantitative information from laparoscopic images. A total of 49 laparoscopic images were independently classified by 21 physicians and compared with the performance of three diferentes AI models. The first two models (named-AI2025 and AI2026) employed conventional supervised learning approaches designed to reproduce human lesion score classifications. The third model introduced the concept of the **Oncologic Risk Pixel (PRO - *Pixel de Risco Oncológico in portuguese*):** image regions identified by the algorithm as having a high probability of corresponding to neoplastic tissue (*Seitenfus R, Dipp de Barros E, et al. J Surg Res 2025;8:484–7.* https://doi.org/10.26502/jsr.10020474).

This tool incorporates quantitative metadata extracted directly from the images, thereby reducing exclusive dependence on human-generated labels. The initial analyses demonstrated that image processing could provide quantitative information extending beyond the simple identification of peritoneal metastases or suspicious regions. Parameters such as total affected area, number of nodules, mean nodule size, largest

lesion size, and total number of oncologic risk pixels were automatically extracted from laparoscopic images, creating a novel digital biomarker of tumor burden (Figure 1). The AI2025 model achieved an accuracy of 53.1% and a kappa coefficient of 0.353 when compared with the human reference standard. Following dataset expansion and training rebalancing, the AI2026 model demonstrated similar accuracy (48.9%) and a kappa coefficient of 0.361, although with a more balanced distribution of classifications across the Lesion Score (LS) categories. The best overall performance was achieved by the PRO-based model, which reached an accuracy of 73.4% and a kappa coefficient of 0.642 (Table 1). This model also demonstrated a more balanced performance across all Lesion Score categories, with sensitivities of 90.9% for LS0, 50% for LS1, 75% for LS2, and 70% for LS3, suggesting greater robustness and improved generalizability. These findings suggest that incorporating quantitative biomarkers derived from image metadata may reduce the influence of human subjectivity and label noise, producing more stable and reproducible classifications than conventional supervised learning models.



Parameter	PCI	Largest nodules pixels	Smallest nodules pixels	Average nodules pixels	Standard deviation	Total pixels	Nodules count
Calculated value	3	18911	142	2162.13	2516.88	198916	92

Figure 1. Representative automated report generated by the PRO-based system for a single peritoneal region, showing the original laparoscopic image, the AI-annotated image (oncologic risk pixels PROs outlined in green), and the quantitative parameters extracted as a digital biomarker of tumor burden.

Model	Correct Classifications	Accuracy	Cohen's Kappa / Weighted Kappa
AI2025 V1	26	53.1%	0.353 / 0.600
AI2026 V1	24	48.9%	0.361 / 0.415
PRO	36	73.4%	0.642 / ---

Table 1. Comparative performance of the three successive AI models in lesion-score (LS) classification against the human reference standard, showing the progression from supervised models trained on human labels (AI2025, AI2026) to the metadata-driven PRO model

However, another challenge remains unresolved: longitudinal comparison. In tubo-ovarian cancer, treatment response is frequently assessed through repeated laparoscopic procedures. Unlike radiologic imaging, where anatomical structures remain relatively stable over time, the peritoneal cavity undergoes continuous transformation. Tumor regression, fibrosis, adhesions, inflammation, and prior surgical manipulation can substantially alter anatomical landmarks between procedures. As a result, determining whether two images obtained months apart truly represent the exact same anatomical location becomes extremely challenging. The potential of the PRO digital biomarker to address this limitation appears promising, as it may provide a quantitative and reproducible framework for longitudinal assessment of peritoneal disease. However, whether this approach can reliably overcome the challenge of anatomical variability within the peritoneal cavity remains to be determined by future studies.

Therefore, the future role of AI in PM may extend far beyond the simple detection of lesions or suspicious areas. AI systems may evolve into quantitative longitudinal monitoring tools capable of comparing serial laparoscopic examinations, measuring the biological response to treatment, and generating digital biomarkers that complement traditional pathological and radiological assessments. Ultimately, the goal should not be to replace the surgeon, but rather to enhance clinical decision-making capabilities. As demonstrated by the current evidence regarding the application of AI in medicine, the combination of human expertise and AI frequently produces better results than either approach alone. This concept of augmented intelligence may become particularly valuable in peritoneal surface malignancies, where subjective interpretation remains one of the major limitations of current clinical practice.

Section 8:

Laparoscopy Provides Crucial Information That Allows Knowledgeable Management of Tubo-Ovarian Cancer

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Introduction

In tubo-ovarian cancer, laparoscopy has diagnostic, staging, strategic, and selective therapeutic roles. It provides direct visualization of peritoneal surfaces, permits safe tissue acquisition, and may support minimally invasive treatment in selected patients with early-stage disease, at interval cytoreduction, or platinum-sensitive recurrence, when complete gross resection and oncologic principles are not compromised. In advanced ovarian cancer, however, its most important contribution is strategic: diagnostic laparoscopy (d-LPS) helps deciding whether the first step should be primary debulking/cytoreductive surgery (PDS/PCS) or neoadjuvant chemotherapy (NACT) potentially followed by interval surgery (IDS/ICS). The question is therefore not surgery versus chemotherapy, but the safest and most effective sequence to achieve complete gross resection (CGR) while avoiding futile laparotomy, excessive morbidity, and treatment delay.

Upfront triage starts before the operating room. Clinical assessment should define patient's physiologic reserve through age, frailty, comorbidities, ASA score, ECOG performance status, nutritional status and albumin. Imaging with thoraco-abdomino-pelvic CT, expert ultrasound, and MRI when indicated remains essential to identify extra-abdominal disease, parenchymal metastases, retroperitoneal disease, and radiologic signs of unresectability. Serum tumor markers may help to identify primary site of disease. These data also define whether the surgical effort is compatible with patient and center's capability. If the patient is clearly unfit for major surgery, or if imaging shows unequivocally unresectable disease, exploratory laparotomy should be avoided; histologic confirmation by image-guided or laparoscopy-guided biopsy must precede NACT.

For patients who are not clearly excluded by the initial assessment, d-LPS represents the pivotal step in the evaluation pathway. Its value extends beyond the superior detection of disease compared with

imaging alone; it enables an experienced surgeon to translate the observed disease distribution into its operative implications, including the likelihood of achieving CGR, the anticipated need for upper abdominal procedures, bowel resection, or stoma formation, and the expected postoperative morbidity. This is particularly important in the assessment of diffuse peritoneal disease and involvement of the small-bowel serosa, mesentery, diaphragm, liver surface, and anatomically challenging regions such as the stomach, spleen, lesser omentum, and sometimes porta hepatis.

The Fagotti laparoscopic Predictive Index Value (PIV) transformed this judgment into a reproducible language (*Fagotti A, Ferrandina G, Fanfani F, et al. Ann Surg Oncol. 2006;13(8):1156-1161. doi:10.1245/ASO.2006.08.021*). The score assigned two points to each major laparoscopic site of disease and identified patients at high risk of suboptimal cytoreduction (*Fagotti A, Ferrandina G, Fanfani F, et al. Am J Obstet Gynecol. 2008;199(6):642.e1-642.e6. doi:10.1016/j.ajog.2008.06.052*). In the current operational Fagotti approach, two findings should be treated as absolute markers of non-cytoreducibility: fixed mesenteric retraction and miliary small-bowel carcinomatosis. The quantitative score then evaluates six stations, each scored 0 or 2 points, for a total from 0 to 12: bowel, diaphragm, stomach/spleen/lesser omentum, parietal peritoneum, greater omentum, and liver surface. Pelvic involvement, including pelvic peritoneum, uterus, and rectum, is deliberately not counted because it is usually within the standard surgical technique and should not by itself drive the patient away from primary surgery. The threshold for high risk of incomplete cytoreduction is PIV ≥10 (*Petrillo M, Vizzielli G, Fanfani F, et al. Gynecol Oncol. 2015;139(1):5-9. doi:10.1016/j.ygyno.2015.07.095*). However, the SCORPION randomized controlled trial demonstrated that women with a score ≥8 had no difference in survival outcomes whether they underwent primary debulking surgery or neoadjuvant chemotherapy (NACT), but patients treated with NACT experienced lower perioperative morbidity (*Fagotti A, Ferrandina MG, Vizzielli G, et al. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2020;30(11):1657-1664. doi:10.1136/ijgc-2020-001640*).

Figure 1 summarizes this algorithm, which consists of three sequential steps: an initial non-surgical phase, a laparoscopic assessment, and a final laparotomic confirmation before committing to maximal cytoreduction.

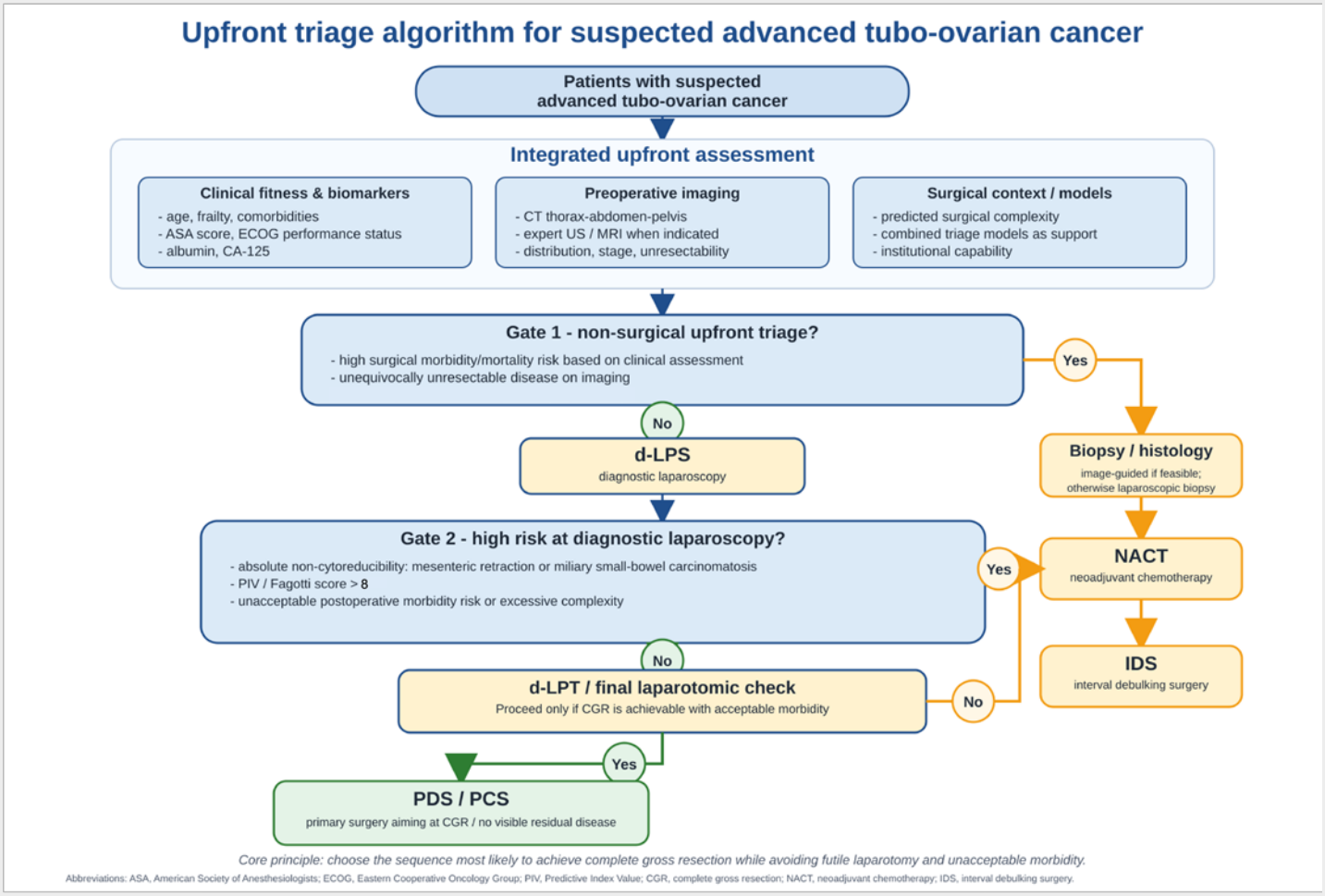

Figure 1. General upfront triage algorithm for suspected advanced tubo-ovarian cancer. Initial assessment integrates clinical fitness, biomarkers, imaging, combined models, and institutional surgical capability. d-LPS evaluates absolute non-cytoreducibility criteria and the PIV/Fagotti score; d-LPT is a final laparotomic confirmation before PDS/PCS. Patients with PIV >8, absolute non-cytoreducibility, unresectable disease, or unacceptable perioperative risk are triaged to NACT followed by IDS.

Abbreviations: ASA, American Society of Anesthesiologists; ECOG, Eastern Cooperative Oncology Group; PIV, Predictive Index Value; CGR, complete gross resection; PDS/PCS, primary debulking/cytoreductive surgery; NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery.

During d-LPS, the surgeon should address three questions: (1) are there absolute criteria for non-cytoreducibility; (2) is the PIV ≥8; and (3) would the anticipated procedure entail unacceptable morbidity or excessive complexity for the individual patient and the treating center? If the answer to any of these questions is affirmative, NACT should be considered the preferred initial treatment strategy. Conversely, if all answers are negative, the patient may proceed to the primary surgery pathway.

The laparotomic phase represents the final confirmatory assessment. If complete gross resection (CGR) is feasible with acceptable morbidity, PDS/PCS should be performed. However, when intraoperative findings at laparotomy contradict the laparoscopic prediction and suggest that CGR is not achievable, cytoreductive surgery should be abandoned and the patient redirected to NACT.

This approach has changed practice because it makes selection explicit. It reduces non-therapeutic laparotomies, shortens recovery when upfront cytoreduction is inappropriate, facilitates timely chemotherapy, and provides tissue for histology, molecular testing, and trial eligibility. It also prevents some presumed tubo-ovarian cancers that are metastases from other primary sites from proceeding to inappropriate treatment. Just as importantly, it has changed clinical research: eligibility for trials, comparison of surgical outcomes, and audit of quality of care are more meaningful when tumor distribution and predicted surgical effort are described in a standardized way before treatment. The Olympia-MITO 13 multicenter experience showed that, after focused training, laparoscopic assessment of peritoneal spread can be taught and reproduced across centers (*Fagotti A, Vizzielli G, De Iaco P, et al. Am J Obstet Gynecol. 2013;209(5):462.e1-462.e11. doi:10.1016/j.ajog.2013.07.016*).

The limitations must also be stated. d-LPS is not informative for parenchymal liver or splenic metastases, and retroperitoneal nodal disease; these domains remain primarily radiologic. It also requires anesthesia, surgical expertise, standardized exploration, and structured reporting. These limits do not weaken the method but simply highlight its correct use. Laparoscopy adds the greatest value when uncertainty concerns intraperitoneal disease and its surgical meaning.

The next step is to move from subjective vision to structured visual biomarkers. Standardized video capture, structured reports, multi-surgeon review, and artificial intelligence may improve reproducibility and dissemination, especially outside high-volume referral centers. Recent data suggest that laparoscopic tumor load is not only a feasibility marker but also an independent prognostic factor for progression-free and overall survival (*Fagotti A, Vizzielli G, De Iaco P, et al. Am J Obstet Gynecol. 2013;209(5):462.e1-462.e11. doi:10.1016/j.ajog.2013.07.016*). Future research should test whether macroscopic laparoscopic patterns can be linked with histotype, molecular alterations, treatment response, and prognosis, so that the same procedure that guides the first treatment sequence may also inform risk stratification and therapeutic innovation.

In conclusion, laparoscopy provides crucial information for knowledgeable management of advanced tubo-ovarian cancer. Its transformative role is not simply diagnostic or therapeutic, but strategic. Integrated with clinical risk assessment, imaging, biomarkers, molecular testing, and institutional expertise, d-LPS helps choose the most effective sequence to achieve CGR while avoiding futile laparotomy and unacceptable morbidity.

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.

Dear Colleagues,

On behalf of the **Indian Society of Peritoneal Surface Malignancies (ISPSM)** and the **Indian Network for Development of Peritoneal Surface Oncology (INDEPSO)**, the two Indian societies focused on research and education in peritoneal oncology, we are pleased to welcome you to **PSOGI 2027**, the 16th PSOGI International Congress on Peritoneal Surface Malignancies.

This is the first time this biennial meeting will be held outside Europe and North America, a matter of great honour and pride for us.

Keeping up with the previous PSOGI meetings that have gradually transformed from being purely surgical meetings to ones involving the whole spectrum of specialties involved in the treatment of peritoneal malignancies–including patients, caregivers, and patient support groups–this congress will focus on bringing the latest advances in the field from around the world. The involvement of leading global experts, both clinicians and basic scientists, will make this the go-to event on peritoneal oncology in the year 2027.

The theme for the congress is, "***Peritoneal Malignancy Moonshot: NO PATIENT should be LEFT behind***"—a simple yet powerful line that covers the whole spectrum of challenges, laying down a motto for the future. The underserved are the ones that lead us—patients with disease that has limited therapeutic options, those lacking physical fitness for various reasons, or those who have no access to specialized care or resources.

The congress will be preceded by workshops addressing the needs of trainees, early career surgeons, and experienced clinicians who wish to learn more about specialties different from their own.

Ahmedabad is India's first city to be designated a UNESCO World Heritage Site. The city is well known for its architectural and cultural heritage, vibrant festival celebrations throughout the year, and its traditional local cuisine.

Participants can be assured of a cutting-edge scientific program, opportunities to connect and collaborate with researchers from all over the world, and a chance to experience Indian culture and hospitality.

We invite all those involved in the management of peritoneal malignancies to participate in this meeting in large numbers and make it a huge success.

With best regards,

Aditi Bhatt
Congress Chair (Ahmedabad, India)

Somashekhar SP
Congress Chair (Bangalore, India)