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Review

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Intraperitoneal chemotherapy for peritoneal metastases: pharmacokinetic rationale, evidence by tumor site and toxicity

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Abstract

Intraperitoneal chemotherapy exploits the peritoneal–plasma barrier: drugs given into the cavity reach the peritoneal surface at concentrations many times higher than in plasma, but penetrate tumor tissue only to a depth of millimeters, which confines curative-intent hyperthermic intraperitoneal chemotherapy to patients in whom cytoreductive surgery (CRS) leaves no visible or minimal residual disease. This review examines the pharmacokinetic and pharmacodynamic basis of hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC), the randomized evidence by tumor site, and their toxicity for patients and operating-room staff. In ovarian cancer, cisplatin HIPEC at interval cytoreduction (OVHIPEC-1) prolonged overall survival (OS); at surgery for platinum-sensitive first relapse the two randomized trials disagree, CHIPOR improving OS and HORSE not improving progression-free survival; carboplatin HIPEC and a Korean trial in mixed settings were negative, and guidelines are divided. In colorectal cancer, complete cytoreduction in selected patients is the standard, oxaliplatin HIPEC as tested in PRODIGE 7 added late morbidity without survival, and mitomycin C prophylaxis reduced peritoneal recurrence without a survival gain. In gastric cancer, surgery with HIPEC did not improve OS in GASTRIPEC-I or PERISCOPE II, whereas catheter-based intraperitoneal paclitaxel did in DRAGON-01. PIPAC delivers cisplatin and doxorubicin at about one tenth of systemic doses as an aerosol at 12 mmHg, with low systemic exposure, repeatable cycles and histological response assessment, but without a completed phase 3 trial. Toxicity is drug-specific: cisplatin nephrotoxicity reduced by sodium thiosulfate, mitomycin C neutropenia, oxaliplatin-related metabolic derangement and bleeding, and surface platinum contamination controlled by closed circuits and glove discipline. A framework for patient selection, regimens and program safety is proposed.

Keywords: hyperthermic intraperitoneal chemotherapy, pressurized intraperitoneal aerosol chemotherapy, peritoneal metastases, cytoreductive surgery, pharmacokinetics, occupational exposure

Introduction

Peritoneal metastases are a locoregional failure pattern of ovarian, colorectal, gastric and appendiceal cancers and the primary site of peritoneal mesothelioma. Their treatment has moved from palliation to cytoreductive surgery (CRS) with peritonectomy procedures and perioperative in-

traperitoneal chemotherapy, of which hyperthermic intraperitoneal chemotherapy (HIPEC) is the most widely used form [1,2], and pressurized intraperitoneal aerosol chemotherapy (PIPAC) has added a repeatable, laparoscopic, low-dose alternative for unresectable disease [3,4]. Both are pharmacological interventions delivered by surgeons, and drug, dose, carrier, temperature, duration and technique vary between centers as much as the surgery is standardized [5,6]; the mixed results of the randomized trials can only be read with those variables in view.

This review sets out the pharmacokinetic rationale, the contribution and cost of hyperthermia, the drugs and technical variables, the randomized evidence by tumor site, the toxicity in the patient and in the operating room, and a framework for 2026; surgical technique, systemic regimens and the anticoagulant management of cancer-associated venous thromboembolism are not reviewed.

PubMed/MEDLINE was searched through the National Center for Biotechnology Information E-utilities on 6 August 2026 for records from 1978 to August 2026 with the terms hyperthermic intraperitoneal chemotherapy, HIPEC, pressurized intraperitoneal aerosol chemotherapy, PIPAC, intraperitoneal chemotherapy, peritoneal metastases, cytoreductive surgery, sodium thiosulfate, occupational exposure and platinum contamination, combined with the names of the trials discussed; the guideline pages of the European Society for Medical Oncology (ESMO), the European Society of Gynaecological Oncology (ESGO), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), and therapeutics.ro, were consulted for guideline texts. Randomized trials and their updates, prospective phase 1 and 2 trials, registry and propensity analyses, guidelines and consensus statements, pharmacokinetic and occupational-exposure studies published in English were included; conference abstracts were to be used only where no full publication existed, and none was needed. Every record was verified on PubMed or the publisher's page and checked for retractions and errata; ten sources identified during external review were verified the same way and added.

Why the peritoneum: the pharmacokinetic rationale of intraperitoneal delivery

The argument for intraperitoneal delivery was made by Dedrick and colleagues in 1978 from peritoneal dialysis data: the peritoneal permeability of hydrophilic anticancer drugs is much lower than their plasma clearance, so a drug given into the cavity in a large volume maintains a far higher concentration there than in plasma [7]. In the two-compartment model, mass transfer equals the permeability-area product times the concentration difference between cavity and blood; the barrier is not the mesothelium but the subperitoneal capillary wall and interstitium, which is why peritonectomy does not abolish the advantage [8]. The advantage is expressed as the ratio of the areas under the concentration–time curves (AUC) in peritoneal fluid and plasma, and it rises with molecular weight and hydrophilicity and with low peritoneal clearance relative to body clearance: reported AUC ratios are about 7.8 for cisplatin, 10 for carboplatin, 16 for oxaliplatin, 23.5 for mitomycin C, 230 for doxorubicin and 850–1,000 for paclitaxel, with no established value for irinotecan [8]. Measured ratios differ between studies and conditions, as for mitomycin C (about 27 in 145 patients) and oxaliplatin (concentration ratio of 25 at the highest dose), and Table 1 gives them as ranges [9,10].

The advantage has a limit the model does not describe: it predicts exposure at the surface, not penetration into tissue [8]. In the rat, platinum concentrations after intraperitoneal cisplatin exceeded those after intravenous dosing only at the periphery of tumor nodules, while the center was identical, so direct diffusion reaches only the outer layers [41]. Penetration is confined to a few millimeters, and the pressure, density and vascularity of the nodule, rather than the AUC ratio alone, determine the intratumoral concentration; drug levels in dense mucinous carcinomatosis nodules exceeded those in the less dense adenomucinosis subtype at identical pharmacokinetics [8,42]. The clinical consequence is that intraperitoneal chemotherapy treats microscopic and minimal residual disease only. Peritonectomy procedures were designed to reach that state [1], and the two instruments that make trials comparable, the peritoneal cancer index (PCI), which scores lesion size in 13 abdominopelvic regions from 0 to 39, and the completeness of cytoreduction (CC) score, in which CC-0 denotes no visible disease and CC-1 residual nodules of 2.5 mm or less, derive from the same logic [43]. The positive randomized trials of HIPEC in ovarian cancer randomized only patients in whom complete or near-complete cytoreduction had been achieved or was expected [11,13].

Bidirectional chemotherapy adds intravenous fluorouracil during the perfusion so that the drug, cleared in plasma but not in the artificial ascites, reaches the heated subperitoneal tissue from both sides; this was the design of the French oxaliplatin regimens [8,10,20].

Table 1. Drugs used intraperitoneally: exposure, thermal enhancement, regimens tested in the trials cited, and characteristic toxicity

Drug	Molecular weight (Da)	Intraperitoneal-to-plasma exposure (metric, species, source)	Thermal enhancement	Regimens in cited trials (tumor site; dose; carrier; temperature; duration, as reported)	Characteristic toxicity (study, denominator)
Cisplatin	300	AUC ratio about 7.8, human [8]	Strong in vitro and in vivo [8]	Ovarian, interval: 100 mg/m², 40 °C, 90 min, with sodium thiosulfate [11]; 75 mg/m², 42 °C, 60 min [12]; ovarian, relapse: 75 mg/m² in 2 L/m², 41 ± 1 °C, 60 min [13]; 75 mg/m², 41.5 °C, 60 min [14]; ovarian, primary or interval: 75 mg/m², 41.5 °C, 90 min [15]; gastric: with mitomycin C (below)	Acute kidney injury: 19 of 47 (40.4%) with no nephroprotection reported, retrospective [16]; 11 of 35 (31.4%) before and 0 of 38 after sodium thiosulfate, before–after cohorts [17]; 30.7% of 192 without and 6.5% of 46 with thiosulfate, retrospective [18]; renal failure grade ≥3 in 10% of 207 in CHIPOR [13]
Carboplatin	371	AUC ratio about 10, human; tumor-nodule penetration lower than cisplatin in the rat [8]	Not established	Ovarian, secondary cytoreduction: 800 mg/m², 90 min, carrier and temperature not given in the report's abstract (phase 2, no benefit) [19]	Hematologic [8]; no perioperative mortality and no excess postoperative toxicity in the phase 2 [19]
Oxaliplatin	397	AUC ratio about 16, human [8]; peritoneal-to-plasma concentration ratio 25 at 460 mg/m², human, not an AUC ratio [10]	Augmented by heat in a murine model [8]	Colorectal: 460 mg/m² (open) or 360 mg/m² (closed) in 2 L/m² dextrose 5%, 42–44 °C, 30 min, with intravenous fluorouracil–folinic acid [10,20]; adjuvant colon: 460 mg/m², 42 °C, 30 min [21]; gastric (PERISCOPE II): 460 mg/m² at 41 °C, then docetaxel 50 mg/m² at 37 °C [22]; appendiceal: 200 mg/m², 120 min, closed [23]	Hyponatremia, hyperglycemia, hyperlactatemia from the dextrose carrier [24]; hemorrhagic complications 15.7% versus 2.6% with other drugs, registry association [25]; 60-day grade ≥3 events of any kind 26% versus 15% in PRODIGE 7 [20]

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Hyperthermia: what it adds and what it costs

Temperatures of 40–44 °C kill cells directly, sensitize to radiation and enhance the cytotoxicity of several drugs [44]; the thermal enhancement is greatest for platinum compounds and alkylating agents and has been confirmed in randomized trials of regional hyperthermia with chemotherapy [45]. For the drugs used intraperitoneally, cisplatin shows strong thermal augmentation in vitro and in vivo, mitomycin C was enhanced in vitro, oxaliplatin was augmented by heat in a murine model, and the data for taxanes are conflicting [8]. Heat also changes tissue uptake: doxorubicin perfused at 43 °C in the rat reached higher concentrations in spleen, small bowel and omentum than at 37 °C while the peritoneal-to-plasma AUC ratio stayed at about 80–90, so the gain was in tissue, not at the cost of plasma exposure [32].

What hyperthermia adds clinically is not es-

Table 1 (continued). Drugs used intraperitoneally: exposure, thermal enhancement, regimens tested in the trials cited, and characteristic toxicity

Drug	Molecular weight (Da)	Intraperitoneal-to-plasma exposure (metric, species, source)	Thermal enhancement	Regimens in cited trials (tumor site; dose; carrier; temperature; duration, as reported)	Characteristic toxicity (study, denominator)
Mitomycin C	334	AUC ratio 23.5 [8] and 27, human [9]; 62% of the dose retained in the body at 90 min [9]	Enhanced in vitro [8]	Colorectal (Dutch protocol): 35 mg/m² in three fractions, 90 min [26,27]; prophylactic, cT4 colon (HIPECT4): 30 mg/m², 60 min [28]; appendiceal: 40 mg, 120 min, closed [23]; gastric: 30 mg with cisplatin 120 mg in 6 L saline, 43 ± 0.5 °C, 60–90 min [29]; gastric (GASTRIPEC-I): 15 mg/m² with cisplatin 75 mg/m² in 5 L saline, 42 °C, 60 min [30]	Neutropenia <1,000/mm³ after 39% of 120 appendiceal perfusions, dose- and sex-dependent [31]; lower leukocyte counts than after oxaliplatin, randomized [23]
Doxorubicin	580	AUC ratio about 80–90, rat [32]; 230, human [8]	Higher tissue concentrations at 43 °C in the rat [32]	PIPAC: 1.5 mg/m² (original) to 2.1 mg/m² (2022 consensus) with cisplatin 7.5 to 10.5 mg/m², 12 mmHg, 37 °C, 30 min [33,34]	No dose-limiting cardiotoxicity with single intraperitoneal instillation [8]; with cisplatin in PIPAC, plasma concentrations 4.0–6.2 ng/mL and no cumulative renal or hepatic toxicity [33,35]

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tablished by a randomized comparison. In a rat model of colorectal carcinomatosis treated by cytoreduction, mitomycin C perfusion prolonged survival at 37 °C as well as at 41 °C, whereas hyperthermic saline alone did not; the benefit depended on the drug, not the heat [46]. The Peritoneal Surface Oncology Group International (PSOGI) technology consensus of 2022 nevertheless reached its strongest agreement on a target intraperitoneal temperature of at least 42 °C, monitored by at least three probes, and on 90 minutes as the ideal duration [6]; where a program adopts a trial's indication, the trial's own temperature and duration, not the consensus preference, are the tested intervention. What hyperthermia costs is measurable: core temperature rises, metabolic rate and oxygen consumption increase, fluid and protein losses grow, and coagulation and hemodynamics change during a procedure that already lasts many hours, so that advanced hemodynamic monitoring and temperature management are part of the anesthetic plan [47].

Drugs, doses, carriers and technique

Table 1 summarizes the drugs, their exposure ratios, thermal enhancement, the doses, carriers, temperatures and durations used in the trials cited, and their characteristic toxicity. Most groups dose by body surface area in mg/m², which predicts systemic exposure but correlates imperfectly with the peritoneal surface; some dose by concentration in a fixed carrier volume, which gives residual nodules a constant diffusional gradient at the price of unpredictable plasma levels, because transfer to plasma rises with the volume in contact with the membrane [8]. The PSOGI consensus favored mg/m² [6]. Volume and the extent of surgery matter: clearance of mitomycin C from the cavity was little affected by parietal peritonectomy, but resection of large visceral surfaces and a

Table 1 (continued). Drugs used intraperitoneally: exposure, thermal enhancement, regimens tested in the trials cited, and characteristic toxicity

Drug	Molecular weight (Da)	Intraperitoneal-to-plasma exposure (metric, species, source)	Thermal enhancement	Regimens in cited trials (tumor site; dose; carrier; temperature; duration, as reported)	Characteristic toxicity (study, denominator)
Paclitaxel	854	AUC ratio about 850–1,000, human [8]	Conflicting data [8]	HIPEC: one randomized trial in ovarian peritoneal metastases (HIPECOVA, 76 randomized), no significant survival difference [36]; normothermic catheter regimens in ovarian (GOG-172) and gastric (PHOENIX-GC, DRAGON-01) cancer [37-39]; nanoparticle albumin-bound paclitaxel named as a PIPAC alternative [34]	In the GOG-172 regimen with intraperitoneal cisplatin, only 42% completed six cycles and grade 3–4 events were more frequent than with intravenous therapy (regimen, not drug-specific) [37]; grade 3–4 events 38.5% with the DRAGON-01 regimen [39]
Irinotecan	677	Not established [8]	Not established	Combined with oxaliplatin in one permitted regimen of PROPHYLOCHIP (oxaliplatin 300 mg/m² plus irinotecan 200 mg/m²) [40]	Irinotecan-specific toxicity not separately established in the cited trial [40]

AUC, area under the concentration–time curve; Da, dalton; GOG, Gynecologic Oncology Group; HIPEC, hyperthermic intraperitoneal chemotherapy; PIPAC, pressurized intraperitoneal aerosol chemotherapy. Molecular weights as listed by the cited source. Exposure figures are as reported by the cited sources and differ with metric (AUC ratio or concentration ratio), species, dose, volume and temperature; they are not interchangeable.

contracted cavity reduced clearance and lowered plasma concentrations, and 62% of the dose remained in the body at 90 minutes, which argues for standardized volumes and dose adjustment after extensive resection [8,9].

Cisplatin is dosed at 75–100 mg/m² over 60–90 minutes in the ovarian trials and with mitomycin C in gastric regimens [11,13,15,29,30]. Mitomycin C is given at 35 mg/m² in three fractions over 90 minutes in the Dutch protocol, chosen in a dose-finding study for the highest AUC ratio with acceptable toxicity, or as a fixed 40 mg dose over 120 minutes in the American appendiceal trial [8,23,27]. Oxaliplatin degrades in chloride-containing solutions, so the high-dose French protocols used dextrose 5%: the original regimen of 460 mg/m² in 2 L/m² at 42–44 °C for 30 minutes, after intravenous fluorouracil and folinic acid, absorbed half the dose within 30 minutes, and PRODIGE 7 used 360 mg/m² closed and 460 mg/m² open [8,10,20]; an in vitro study at 42 °C found less than 10% degradation in chloride-containing carriers after 30 minutes and less than 20% after 120 minutes, so the restriction is a matter of formulation and protocol rather than an absolute one [48]. Carboplatin at 800 mg/m² for 90 minutes was tested at secondary cytoreduction [19]; paclitaxel HIPEC has one small randomized trial, HIPECOVA, in which 76 patients were randomized after cytoreduction for ovarian peritoneal metastases and recurrence-free (23 versus 19 months) and overall survival (48 versus 46 months) did not differ significantly [36]; doxorubicin has no randomized HIPEC evidence and is used in PIPAC [8]. The open (coliseum) technique allows manual distribution of the perfusate under a plastic sheet; the closed technique perfuses a sutured abdomen with less staff exposure and less certainty about distribution; both were allowed in PRODIGE 7 [6,20,49]. Perfusion lasted 30 minutes in the French oxaliplatin protocols, 60 minutes in HIPECT4, and 60–120 minutes for cisplatin, mitomycin C and the American appendiceal oxaliplatin regimen in the trials in Table 2 [23,28,50].

Table 2. Randomized trials of hyperthermic intraperitoneal chemotherapy by tumor site (HIPEC versus none unless stated)

Tumor site, trial (key)	n	Design	Regimen	Primary end point	Result	Key limitation
Ovarian, OVHIPEC-1 [11,51]	245	Interval CRS ± HIPEC after 3 cycles of neoadjuvant carboplatin–paclitaxel, stage III	Cisplatin 100 mg/m², 40 °C, 90 min, sodium thiosulfate	Recurrence-free survival	HR 0.66 (0.50–0.87); OS HR 0.67 (0.48–0.94), at 10 years 0.70 (0.53–0.92); grade 3–4 events 27% vs 25%	Interval setting only; open-label
Ovarian, Cascales Campos et al. [12]	71	Interval CRS ± HIPEC after neoadjuvant chemotherapy, single center	Cisplatin 75 mg/m², 42 °C, 60 min	Disease-free survival	Median 18 (HIPEC) vs 12 months; adjusted HR for recurrence 0.12 (0.02–0.89); mortality 2.9% vs 2.8%	Small, single center
Ovarian, Lim et al. [15]	184	Primary or interval CRS ± HIPEC, residual <1 cm, stage III–IV	Cisplatin 75 mg/m², 41.5 °C, 90 min	Progression-free survival	No overall difference (HIPEC 19.8 vs control 18.8 months; OS 69.5 vs 61.3 months); interval subgroup PFS HR 0.60 (0.37–0.99), OS HR 0.53 (0.29–0.96)	Two settings mixed; subgroup finding
Ovarian, CHIPOR [13]	415	Complete CRS ± HIPEC at first relapse ≥6 months after platinum, after 6 cycles	Cisplatin 75 mg/m² in 2 L/m², 41 ± 1 °C, 60 min	Overall survival	HR 0.73 (0.56–0.96); median 54.3 vs 45.8 months; grade ≥3 events 49% vs 27%; renal failure 10% vs 1%	Toxicity; open-label

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Pressurized intraperitoneal aerosol chemotherapy

PIPAC was designed to overcome the two weaknesses of liquid instillation, uneven distribution and shallow penetration, by exploiting the pressure of the capnoperitoneum. The device is a nozzle introduced through a trocar and driven by a high-pressure injector; in the porcine model, a dye sprayed for 30 minutes at 12 mmHg stained a larger surface, including hidden recesses, and penetrated the peritoneal membrane immediately, whereas lavage did not [3]. The first human applications used doxorubicin 1.5 mg/m² followed by cisplatin 7.5 mg/m², about one tenth of the usual systemic doses of these two drugs, at 12 mmHg and 37 °C for 30 minutes; nuclear doxorubicin was documented throughout the peritoneum while plasma concentrations were 4.0–6.2 ng/mL, and the procedure created no significant adhesions and could be repeated [33]. The claim of homogeneous distribution should be read against the physics of the aerosol: the median droplet diameter is about 25 µm, more than 97.5% of the volume settles by gravity and impaction mainly beneath the nozzle, and homogeneity would require droplets below 1.2 µm; distribution is better than lavage but not uniform [60]. In 32 women, cisplatin and doxorubicin concentrations in ascites and peritoneal tissue rose after PIPAC, and doxorubicin accumulated in tumor tissue with

Table 2 (continued). Randomized trials of hyperthermic intraperitoneal chemotherapy by tumor site (HIPEC versus none unless stated)

Tumor site, trial (key)	n	Design	Regimen	Primary end point	Result	Key limitation
Ovarian, HORSE (MITO-18) [14]	167	Secondary CRS ± HIPEC at platinum-sensitive relapse, no preceding chemotherapy, residual ≤2.5 mm	Cisplatin 75 mg/m², 41.5 °C, 60 min	Progression-free survival	Median 25 (HIPEC) vs 23 months, not significant; 5-year post-recurrence survival 75.9% vs 61.6% (secondary); adverse events similar	Different sequence from CHIPOR; secondary end point favors HIPEC
Ovarian, HIPECOVA [36]	76	CRS ± HIPEC for ovarian peritoneal metastases, single center	Paclitaxel	Recurrence-free and overall survival	Median RFS 23 (HIPEC) vs 19 months, OS 48 vs 46 months, not significant; morbidity similar	Small; exclusions after randomization
Ovarian, Spiliotis et al. [52,53]	120	CRS ± HIPEC in recurrent disease	Not detailed in abstract	Survival	Mean 26.7 vs 13.4 months	Design and reporting criticized; did not change guidelines
Ovarian, Zivanovic et al. [19]	98	Secondary CRS ± HIPEC, platinum-sensitive relapse, phase 2	Carboplatin 800 mg/m², 90 min	Progression-free at 24 months	16.3% vs 24.5%; PFS HR 1.54 (1.00–2.37)	Phase 2 pick-the-winner design
Colorectal, Verwaal [26,54]	105	CRS + HIPEC + systemic fluorouracil vs systemic therapy ± palliative surgery	Mitomycin C	Survival	Median 22.3 vs 12.6 months; treatment-related mortality 8%	Control arm without CRS
Colorectal, PRODIGE 7 [20]	265	CRS ± HIPEC, PCI ≤25, residual <1 mm	Oxaliplatin 460 (open) or 360 (closed) mg/m², 30 min, with intravenous fluorouracil–folinic acid	Overall survival	Median 41.7 vs 41.2 months; HR 1.00 (95.37% CI 0.63–1.58); 60-day grade ≥3 events 26% vs 15%	Only one regimen tested

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repeated cycles [61]; after repeated procedures, gamma-glutamyltransferase rose transiently, creatinine did not change and no cumulative toxicity was seen [35].

Oxaliplatin PIPAC has real systemic exposure. A French phase 1 set the maximum tolerated dose at 90 mg/m² after two dose-limiting toxicities at 140 mg/m², found tissue concentrations three- to four-fold higher in aerosol-exposed tissue, and documented substantial absorption at the higher dose (plasma maximum concentration 1,035 µg/L) [62]; a Singapore phase 1 escalated to 120 mg/m², observed pancreatitis at 45 and 90 mg/m², showed a linear dose–exposure relation and recommended 120 mg/m² for phase 2 [63]. The 2022 consensus settled the doses: doxorubicin 2.1 mg/m² with cisplatin 10.5 mg/m², and oxaliplatin 120 mg/m², reduced to 90 mg/m² in frail patients, preferably with systemic fluorouracil; mitomycin C and nanoparticle albumin-bound paclitaxel were named as alternatives [34]. The technical consensus agreed on an advanced

Table 2 (continued). Randomized trials of hyperthermic intraperitoneal chemotherapy by tumor site (HIPEC versus none unless stated)

Tumor site, trial (key)	n	Design	Regimen	Primary end point	Result	Key limitation
Colorectal, PROPHYLOCHIP [40]	150	Second-look surgery + HIPEC vs surveillance, high risk	Oxaliplatin 460 mg/m² or oxaliplatin 300 plus irinotecan 200 mg/m²; mitomycin C 35 mg/m² if neuropathy	3-year disease-free survival	44% vs 53%; HR 0.97 (0.61–1.56)	Systematic surgery in the experimental arm
Colon, COLOPEC [21,55]	204	Adjuvant HIPEC + chemotherapy vs chemotherapy, T4 or perforated	Oxaliplatin 460 mg/m², 42 °C, 30 min	18-month peritoneal-metastasis-free survival	80.9% vs 76.2%; 5-year OS 69.6% vs 70.9%	Delayed HIPEC in 91%
Colon, HIPECT4 [28,56]	184	Resection + HIPEC vs resection, cT4, both with adjuvant chemotherapy	Mitomycin C 30 mg/m², 60 min	3-year locoregional control	97.6% vs 87.6%, HR 0.21 (0.05–0.95); final analysis HR 0.19 (0.04–0.86); no DFS or OS difference	Prophylactic setting; no survival gain
Colorectal, CAIRO6 [57,58] (treatment-sequence trial, HIPEC in both arms)	358 randomized, 351 analyzed	Perioperative systemic therapy + CRS-HIPEC vs upfront CRS-HIPEC	Mitomycin C- or oxaliplatin-based in both arms	Overall survival	Median 44 vs 39 months; HR 0.85 (0.62–1.15); major 90-day morbidity 36% vs 26% among 292 with complete or near-complete CRS	Does not test HIPEC itself
Appendiceal, Levine et al. [23,59]	121	CRS + HIPEC, mitomycin C vs oxaliplatin	Mitomycin C 40 mg vs oxaliplatin 200 mg/m², 120 min, closed	Hematologic toxicity	Lower leukocytes days 5–10 with mitomycin C; 10-year OS 56.2% vs 47.5%	Regimen comparison only
Gastric, Yang et al. [29]	68	CRS ± HIPEC, carcinomatosis	Cisplatin 120 mg + mitomycin C 30 mg in 6 L saline, 43 °C, 60–90 min	Overall survival	Median 11.0 vs 6.5 months	CC-0/1 in 59%; single center

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operating-room ventilation system, remote administration, a safety checklist and the Peritoneal Regression Grading Score (PRGS) for response assessment [64]; the PRGS grades quadrant biopsies from 1, complete response, to 4, no response, the histological end point that radiology cannot provide for low-volume disease [65]. Electrostatic precipitation (ePIPAC) charges the aerosol so that it settles within seconds; a field of 7,500–9,500 V was feasible in the first patients, and 135 procedures in 48 patients caused no grade 4–5 morbidity [66,67].

The clinical evidence (Table 3) consists mostly of uncontrolled phase 1–2 studies and retrospective series, with one single-center randomized phase 2 trial. In recurrent ovarian cancer, three cycles of cisplatin–doxorubicin PIPAC gave disease control (partial response or stable disease) in 33 of 53 evaluable women (62%) and histological regression in 26 of the 34 who completed three cy-

Table 2 (continued). Randomized trials of hyperthermic intraperitoneal chemotherapy by tumor site (HIPEC versus none unless stated)

Tumor site, trial (key)	n	Design	Regimen	Primary end point	Result	Key limitation
Gastric, GASTRIPEC-I [30]	105	Perioperative chemotherapy + CRS ± HIPEC	Mitomycin C 15 mg/m² + cisplatin 75 mg/m² in 5 L saline, 42 °C, 60 min	Overall survival	Median 14.9 vs 14.9 months; PFS 7.1 vs 3.5 months	Stopped early; 55 patients never reached surgery
Gastric, PERISCOPE II [22]	102	Gastrectomy + CRS + HIPEC vs systemic therapy, PCI <7 or positive cytology	Oxaliplatin 460 mg/m² at 41 °C, then docetaxel 50 mg/m² at 37 °C	Overall survival	Surgery 15.7 vs systemic 16.6 months; HR 1.10 (0.69–1.74) for surgery; grade ≥3 events 42% vs 20%; 3 treatment-related deaths within 100 days, all with surgery	Closed for futility

CC, completeness of cytoreduction; CI, confidence interval; CRS, cytoreductive surgery; DFS, disease-free survival; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio (95% confidence interval in parentheses unless stated); OS, overall survival; PCI, peritoneal cancer index; PFS, progression-free survival; RFS, recurrence-free survival. Results are given as HIPEC (or the experimental strategy) versus control unless labeled otherwise.

cles (76%), without grade 4 toxicity [68]; in gastric peritoneal metastasis, 24 patients had a histological response in 50% and a median survival of 15.4 months [69]; in unresectable colorectal disease, oxaliplatin 92 mg/m² monotherapy caused major treatment-related adverse events in 15% of 20 patients, with a median overall survival of 8.0 months [70]; in refractory gastrointestinal disease, oxaliplatin 90 mg/m² with fluorouracil produced grade 3–4 events in 32% and a median progression-free survival of 6.1 months [71]. The prospective PIPAC-OPC2 study of 110 patients found a complete or major histological response (PRGS 1–2) in 38 patients (61%) among those who received three cycles, an exploratory association with survival rather than a validated surrogate, and a median overall survival of 10 months [72]. A systematic review of 45 studies and 838 patients found repeated PIPAC feasible in 64%, adverse events above grade 2 after 12–15% of procedures, and objective responses of 62–88% in ovarian, 50–91% in gastric and 71–86% in colorectal cancer, all uncontrolled [4]. The International Society for the Study of Pleura and Peritoneum (ISSPP) registry, launched in June 2020, recorded 459 procedures in 181 patients in its first six months [73].

No randomized phase 3 result has been published as of this search. PIPAC-OV3 compares cisplatin–doxorubicin PIPAC with physician's-choice systemic therapy in 244 patients with platinum-resistant recurrent ovarian cancer [74]; in gastric peritoneal metastasis, PIPAC EstoK 01 is a randomized phase 2 trial alternating PIPAC with systemic chemotherapy [77], and PIPAC VEROne is a multicenter phase 3 trial of PIPAC plus systemic chemotherapy versus systemic chemotherapy in oligometastatic disease (PCI of 6 or less or positive cytology) with secondary resectability as primary end point, published as a protocol without results [78]. A single-center randomized phase 2 trial published in 2026 reported that three adjuvant cisplatin–doxorubicin PIPAC procedures added to carboplatin–paclitaxel in 182 women with newly diagnosed ovarian cancer and residual disease above 1 cm after primary surgery, none of whom had received neoadjuvant chemotherapy, improved progression-free survival (hazard ratio [HR] 0.31; 95% confidence interval [CI] 0.23–0.42) and overall survival (HR 0.48; 95% CI 0.32–0.72); the population, the single center and the size of the effect call for confirmation before it changes practice [75]. PIPAC can also serve as a bridge: of 146 consecutive patients with unresectable disease, 26 (17.8%) became candidates for CRS and HIPEC, and complete cytoreduction was achieved in 21 (14.4%) [79].

Ovarian cancer

Normothermic catheter-based chemotherapy set the scene. In the Gynecologic Oncology Group (GOG) trial GOG-172, intraperitoneal cisplatin 100 mg/m² and paclitaxel after optimal primary surgery prolonged median overall sur-

Table 3. Pressurized intraperitoneal aerosol chemotherapy: regimens and evidence status by tumor site

Tumor site	Regimen (standard conditions 12 mmHg, 37 °C, 30 min unless the study states otherwise)	Best available evidence (key)	Main results	Status
Ovarian, platinum-resistant or recurrent	Cisplatin 7.5 mg/m² + doxorubicin 1.5 mg/m² (phase 2); cisplatin 10.5 + doxorubicin 2.1 mg/m² (2022 consensus)	Single-arm phase 2, 64 enrolled, 53 evaluable [68]; consensus [34]	Disease control (partial response or stable disease) 33 of 53 (62%); histological regression 26 of 34 who completed 3 cycles (76%); no grade 4 toxicity; non-access 11 of 64 (17%)	Phase 3 PIPAC-OV3 (244 patients) against systemic therapy, protocol [74]
Ovarian, newly diagnosed, residual >1 cm after primary surgery	Cisplatin–doxorubicin (three adjuvant procedures) with carboplatin–paclitaxel	Single-center randomized phase 2, 186 randomized, 182 analyzed [75]	PFS HR 0.31 (0.23–0.42), OS HR 0.48 (0.32–0.72); no increase in grade 3–4 toxicity	Awaiting confirmation; population without neoadjuvant chemotherapy or maximal cytoreduction
Gastric	Cisplatin–doxorubicin as above	Retrospective series of 24 patients [69]; meta-analysis [76]	Histological response 12 of 24 (50%); median survival 15.4 months; pooled median 9.0 months across studies	Randomized phase 2 PIPAC EstoK 01 [77] and phase 3 PIPAC VEROne (secondary resectability) [78], both protocols without published results
Colorectal	Oxaliplatin 92 mg/m² (phase 2); 120 mg/m², 90 in frail patients, with systemic fluorouracil (2022 consensus)	Single-arm phase 2, 20 patients [70]; phase 1 studies [62,63]; consensus [34]	Major treatment-related events 15% of patients; pain after 88% of procedures; median OS 8.0 months	No randomized trial
Gastrointestinal, mixed	Oxaliplatin 90 mg/m² with systemic fluorouracil	Phase 1/2, 34 patients [71]	Grade 3–4 events 32%; median PFS 6.1 and OS 13 months	No randomized trial

Continued on the next page.

vival from 49.7 to 65.6 months, but only 42% of patients completed six cycles [37]; GOG-252 then found no progression-free survival advantage for either intraperitoneal regimen over intravenous carboplatin with bevacizumab (24.9, 27.4 and 26.2 months in 1,560 patients) [80]. Catheter-based therapy lost its place, and HIPEC, a single intraoperative administration, became the question.

OVHIPEC-1 randomized 245 patients with stage III epithelial ovarian cancer and at least stable disease after three cycles of neoadjuvant carboplatin–paclitaxel, at interval cytoreduction when residual disease of 10 mm or less was feasible, to surgery with or without HIPEC with cisplatin 100 mg/m² over 90 minutes at 40 °C with sodium thiosulfate nephroprotection. Recurrence-free survival improved (HR 0.66; 95% CI 0.50–0.87), median overall survival was 45.7 versus 33.9 months (HR 0.67; 95% CI 0.48–0.94) and grade 3–4 adverse events were 27% versus 25% [11]; at 10 years the effect held, with progression-free survival HR 0.63 (95% CI 0.48–0.83) and overall survival HR 0.70 (95% CI 0.53–0.92), medians 44.9 versus 33.3 months [51]. The Korean trial of Lim and colleagues randomized 184 women with stage III–IV disease and residual tumor below 1 cm after primary or interval surgery to cisplatin 75 mg/m² at 41.5 °C for 90 minutes or no HIPEC and found no overall difference with HIPEC versus control in progression-free (19.8 versus 18.8 months) or overall survival (69.5 versus 61.3 months); in the interval subgroup HIPEC improved both (progression-free

Table 3 (continued). Pressurized intraperitoneal aerosol chemotherapy: regimens and evidence status by tumor site

Tumor site	Regimen (standard conditions 12 mmHg, 37 °C, 30 min unless the study states otherwise)	Best available evidence (key)	Main results	Status
Mixed primaries	Oxaliplatin (colorectal, appendiceal) or cisplatin–doxorubicin (others)	Prospective phase 2, 110 patients, 336 procedures [72]	PRGS 1–2 in 38 patients (61%) of those who had 3 cycles, an exploratory prognostic association; median OS 10 months	Registry follow-up through the ISSPP database [73]
Bridge to cytoreduction	Any of the above with systemic chemotherapy between cycles	Consecutive series, 146 patients [79]	17.8% scheduled for CRS-HIPEC; complete CRS-HIPEC in 14.4%	Selection-dependent
Electrostatic PIPAC	Cisplatin–doxorubicin with 7,500–9,500 V	First-in-human, 3 patients [66]; 48 patients, 135 procedures [67]	Feasible; no grade 4–5 morbidity; response or stable disease in about half after 3 procedures with chemotherapy	No randomized trial

CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio (95% confidence interval in parentheses); ISSPP, International Society for the Study of Pleura and Peritoneum; OS, overall survival; PFS, progression-free survival; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PRGS, Peritoneal Regression Grading Score.

survival HR 0.60, 95% CI 0.37–0.99; overall survival HR 0.53, 95% CI 0.29–0.96), while after primary surgery the point estimates favored the control group [15]. The two trials point the same way in the interval setting, with the caveat that the Korean estimate is a subgroup of a negative trial; OVHIPEC-1 tested one setting with a higher dose, the Korean trial mixed two and was powered for neither. OVHIPEC-2, randomizing 538 patients after complete or near-complete (2.5 mm or less) primary cytoreduction with overall survival as the primary end point, is expected to report in 2026 [81].

In recurrent disease the evidence is discordant. The trial of Spiliotis and colleagues, 120 women randomized to CRS with or without HIPEC, reported a mean survival of 26.7 versus 13.4 months [52], but its design and reporting were criticized in detail [53]. The carboplatin phase 2 of Zivanovic and colleagues randomized 98 women with platinum-sensitive recurrence to carboplatin 800 mg/m² over 90 minutes at secondary cytoreduction or no HIPEC; the HIPEC arm missed its success criterion and progression-free survival was 12.3 versus 15.7 months (HR 1.54; 95% CI 1.00–2.37) [19]. CHIPOR, published in full in 2024, randomized 415 patients with first relapse at least six months after platinum, after six cycles of platinum-based chemotherapy and at complete cytoreduction, to HIPEC with cisplatin 75 mg/m² in 2 L/m² at 41 ± 1 °C for 60 minutes or no HIPEC: overall survival improved (HR 0.73; 95% CI 0.56–0.96; median 54.3 versus 45.8 months), at the cost of grade 3 or worse events within 60 days in 49% versus 27%, including renal failure in 10% versus 1%; the three deaths within 60 days were all in the no-HIPEC group [13]. HORSE (MITO-18) randomized 167 patients with platinum-sensitive recurrence, at secondary cytoreduction without preceding chemotherapy and with residual tumor of 2.5 mm or less, to cisplatin 75 mg/m² for 60 minutes at 41.5 °C or no HIPEC: median progression-free survival was 25 versus 23 months, the primary end point was not met, postoperative adverse events did not differ, and five-year post-recurrence survival, a secondary end point, was 75.9% versus 61.6% [14]. The two trials differ in sequence, end point and size, and the carboplatin phase 2 in drug and design.

Guidelines are divided. The ESGO–ESMO–European Society of Pathology (ESP) consensus conference of 2024 reached no consensus on HIPEC at interval cytoreduction and did not recommend HIPEC at surgery for relapse [II, D], a position taken before CHIPOR was published in full [82]. The ASCO guideline update of 2025 states that HIPEC may be offered during interval cytoreduction to patients with stage III disease, good performance status and adequate renal function after neoadjuvant chemotherapy [83], and the NCCN patient guideline based on Version 3.2025 presents HIPEC as an option at interval debulk-

ing surgery [84]. A 2025 multisocietal consensus coordinated by PSOGI, using GRADE methodology, strongly recommended HIPEC with interval cytoreduction in stage III high-grade serous disease on the basis of OVHIPEC-1 and made only a conditional recommendation for secondary cytoreduction with systemic therapy or systemic therapy alone at first platinum-sensitive recurrence [85]. A small single-center phase 3 trial from Spain adds to the interval setting: 71 patients randomized after neoadjuvant chemotherapy to cisplatin 75 mg/m² for 60 minutes at 42 °C or no HIPEC had a median disease-free survival of 18 versus 12 months [12]. The evidence supports cisplatin HIPEC with nephroprotection at interval cytoreduction after neoadjuvant chemotherapy; at platinum-sensitive first relapse it is CHIPOR's sequence, chemotherapy first and HIPEC at complete cytoreduction, that improved survival, and HORSE did not show an improvement in its primary end point, progression-free survival, with HIPEC at upfront secondary cytoreduction; carboplatin HIPEC and HIPEC at primary surgery are not supported.

Colorectal cancer

The Verwaal trial of 2003 randomized 105 patients to systemic fluorouracil–leucovorin with or without palliative surgery, or to cytoreduction with mitomycin C HIPEC followed by the same chemotherapy: median survival was 22.3 versus 12.6 months, treatment-related mortality in the HIPEC arm 8%, most complications were related to bowel leakage, and the benefit was confined to patients with five or fewer of seven regions involved and to complete cytoreduction [26]. The eight-year update confirmed the difference and a five-year survival of 45% after complete cytoreduction [54], but because the control arm had no cytoreduction, the trial could not separate surgery from HIPEC.

PRODIGE 7 did. It randomized 265 patients with a PCI of 25 or less, once resection to less than 1 mm of residual tumor had been achieved, to oxaliplatin HIPEC (360 mg/m² closed or 460 mg/m² open, 30 minutes, with intravenous fluorouracil and folinic acid) or no HIPEC, with systemic chemotherapy in all: median overall survival was 41.7 versus 41.2 months (HR 1.00; 95.37% CI 0.63–1.58), 30-day treatment-related mortality 2% in each arm, and grade 3 or worse events at 60 days 26% versus 15% (p = 0.035), which led the investigators to conclude that cytoreductive surgery alone should be the cornerstone of curative-intent treatment [20]. Oxaliplatin-based prophylaxis failed twice more. PROPHYLOCHIP-PRODIGE 15 randomized 150 patients at high risk of peritoneal recurrence after adjuvant chemotherapy to surveillance or second-look surgery with HIPEC and found three-year disease-free survival of 53% versus 44% (HR 0.97; 95% CI 0.61–1.56), with grade 3–4 complications in 41% of operated patients [40]. COLOPEC randomized 204 patients with T4 or perforated colon cancer to adjuvant oxaliplatin HIPEC (460 mg/m², 30 minutes, 42 °C) with chemotherapy or chemotherapy alone: 18-month peritoneal-metastasis-free survival was 80.9% versus 76.2% [21] and five-year overall survival 69.6% versus 70.9% [55]. Mitomycin C prophylaxis has a different result: HIPECT4 randomized 184 patients with cT4 colon cancer in 17 Spanish centers to resection with mitomycin C HIPEC (30 mg/m² over 60 minutes) or resection alone, both with adjuvant chemotherapy, and found three-year locoregional control of 97.6% versus 87.6% (HR 0.21; 95% CI 0.05–0.95) without a difference in disease-free (81.2% versus 78.0%) or overall survival (91.7% versus 92.9%) [28]; the final analysis at 36 months confirmed better locoregional control (HR 0.19; 95% CI 0.04–0.86) and no survival difference [56].

Whether a different drug, dose or duration would perform differently is open. Mitomycin C at 35 mg/m² over 90 minutes is the regimen of the Verwaal trial and of the Dutch program, and the 2022 PSOGI consensus on colorectal regimens reached a strong negative consensus on short high-dose oxaliplatin and a weak positive vote for mitomycin C, conditionally recommending HIPEC after cytoreduction while naming its role as the most important research question [27]. The randomized comparison of mitomycin C with oxaliplatin in appendiceal neoplasms speaks to hematologic toxicity, not to this question [23,59]. After PRODIGE 7, experts of 19 countries reported a shift to mitomycin C and longer perfusion, fewer referrals and the removal of HIPEC from some national guidelines, while more than 3,800 patients a year were still treated in about 430 centers [50,86]. CAIRO6 asked a different question, perioperative systemic therapy versus upfront surgery in resectable disease, with mitomycin C- or oxaliplatin-based HIPEC in both arms: the phase 2 showed feasibility and a major pathological response in 38% [57], and the phase 3, published in July 2026, randomized 358 patients and analyzed 351: median overall survival was 44 versus 39 months (HR 0.85; 95% CI 0.62–1.15), and among the 292 patients who underwent complete or near-complete cytoreduction, major 90-day morbidity was more frequent after perioperative therapy (49 of 138, 36%, versus 40 of 154, 26%) [58].

Guidelines follow the trials. The ESMO guideline of 2023 states that complete cytoreductive surgery should be performed for peritoneal-only metastases [II, A] and that HIPEC is an experimental procedure whose use cannot be recommended outside trials [II, D] [87]; the ASCO guideline of

2023 states that cytoreductive surgery plus systemic chemotherapy may be recommended for selected patients and that the addition of HIPEC is not recommended [88]. For selected patients with resectable peritoneal-only disease, complete cytoreduction is the treatment; oxaliplatin HIPEC as tested added morbidity without survival; mitomycin C HIPEC reduces peritoneal recurrence in the prophylactic setting without a survival gain and remains, after cytoreduction of established metastases, a reasonable subject of a trial and an unproven addition outside one.

Gastric cancer

The Yang trial randomized 68 patients with gastric carcinomatosis to cytoreduction alone or with HIPEC (cisplatin 120 mg and mitomycin C 30 mg in 6 L of saline at 43 ± 0.5 °C for 60–90 minutes); median survival was 11.0 versus 6.5 months, but CC-0/1 cytoreduction was achieved in only 59% of each arm [29]. GASTRIPEC-I, a German phase 3 trial of perioperative chemotherapy and cytoreduction with or without HIPEC (mitomycin C 15 mg/m² and cisplatin 75 mg/m² in 5 L of saline at 42 °C for 60 minutes), stopped early at 105 patients, 55 of whom never reached surgery: median overall survival was 14.9 months in both arms, progression-free survival 7.1 versus 3.5 months, and grade 3 or worse events 43.6% versus 38.1% [30]. PERISCOPE II, published in August 2026, randomized 102 patients with resectable cT3–4a tumors and limited peritoneal disease (PCI below 7) or positive cytology, without progression after at least three cycles of systemic therapy, to continued systemic therapy or gastrectomy with cytoreduction and HIPEC (oxaliplatin 460 mg/m² at 41 °C, then docetaxel 50 mg/m² at 37 °C); it was closed for futility, with median overall survival of 16.6 versus 15.7 months (HR 1.10; 95% CI 0.69–1.74), grade 3 or worse events in 20% versus 42%, and three treatment-related deaths, all in the surgical arm [22]. The CYTO-CHIP propensity analysis of 277 French patients treated by complete cytoreduction had suggested the opposite, an adjusted overall survival HR of 0.60 (95% CI 0.42–0.86) in favor of HIPEC [89]; registry patients compared with each other and a randomized population compared with systemic therapy answer different questions.

Prophylactic HIPEC after curative gastrectomy rests on a meta-analysis of 11 randomized and 21 non-randomized studies that found a survival advantage in patients without carcinomatosis (risk ratio 0.82) at the price of roughly doubled complication rates from systemic drug toxicity [90]; GASTRICHIP, the French phase 3 trial of D2 gastrectomy with or without oxaliplatin HIPEC, has a published protocol and no published result at the time of this search [91]. Catheter-based intraperitoneal paclitaxel is a different route with a different result. PHOENIX-GC randomized 183 patients to intraperitoneal and intravenous paclitaxel with S-1 (tegafur–gimeracil–oteracil) or to cisplatin with S-1 and did not reach superiority (median 17.7 versus 15.2 months; HR 0.72; 95% CI 0.49–1.04), although the analysis adjusted for baseline ascites favored the intraperitoneal arm (HR 0.59; 95% CI 0.39–0.87) [38]. DRAGON-01, a Chinese phase 3 trial published in 2026, randomized 238 untreated patients with laparoscopically confirmed peritoneal metastasis 2:1 to intraperitoneal paclitaxel 20 mg/m² plus intravenous paclitaxel 50 mg/m² with S-1 or to intravenous paclitaxel 70 mg/m² with S-1; among the 222 treated patients, median overall survival was 19.4 versus 13.9 months (HR 0.67; 95% CI 0.50–0.90), progression-free survival 11.2 versus 7.2 months, grade 3–4 adverse events 38.5% versus 41.9%, with no treatment-related deaths [39]. A meta-analysis pooled a median survival of 18.4 months for intraperitoneal paclitaxel against 9.0 months for cisplatin–doxorubicin PIPAC, with the confounding such comparisons carry [76].

Pseudomyxoma peritonei, appendiceal neoplasms and peritoneal mesothelioma

Here registries take the place of trials. Among 2,298 patients with pseudomyxoma peritonei treated at 16 PSOGI units, treatment-related mortality was 2%, major complications 24%, median survival 196 months and 10- and 15-year survival 63% and 59%; not using HIPEC independently predicted poorer progression-free survival, alongside prior chemotherapy, high-grade histology, high PCI, incomplete cytoreduction and major complications [92]. A propensity-weighted analysis of 1,924 registry patients found HIPEC after cytoreduction associated with better overall survival (weighted HR 0.65; 95% CI 0.50–0.83; five-year survival 57.8% versus 46.2%), the advantage being seen with oxaliplatin–fluorouracil–leucovorin and cisplatin–mitomycin C schedules, and with no worse surgical outcomes except higher morbidity with mitomycin C alone [93]. The only randomized trial in appendiceal neoplasms compared regimens: mitomycin C 40 mg and oxaliplatin 200 mg/m² for 120 minutes gave similar 10-year survival (56.2% versus 47.5%) and differed only in leukocyte counts [23,59]. In diffuse malignant peritoneal mesothelioma, a multi-institutional registry of 405 patients, 92% treated with HIPEC after cytoreduction, reported a median overall

survival of 53 months, five-year survival of 47%, grade 3–4 complications in 31% and perioperative mortality of 2%, with epithelial subtype, absence of nodal metastasis and completeness of cytoreduction as prognostic factors [94]. Complete cytoreduction comes first; the perfusion, cisplatin-based in mesothelioma and mitomycin C- or oxaliplatin-based in appendiceal disease, is part of the standard on registry and propensity-weighted evidence, and its independent contribution has not been tested against cytoreduction alone in a randomized trial [23,93,94].

Toxicity in the patient

The toxicity of HIPEC is that of a drug given at high concentration to a large absorbing surface after a long operation, and it is drug-specific (Table 4). Cisplatin is nephrotoxic: in 47 women treated at 40 °C for 60 minutes with no nephroprotection reported, acute kidney injury occurred in 40.4%, grade 3–4 injury in 8.5% and long-term dialysis in 4.3%, with baseline renal function, albumin, prior carboplatin, the interval since chemotherapy and transfusion as risk factors [16]. Sodium thiosulfate before and after the perfusion, as in OVHIPEC-1, reduces the risk: in a French program, renal impairment fell from 11 of 35 patients (31.4%), two needing permanent hemodialysis, to none of 38 [11,17], and in a German series of 238 patients acute kidney injury occurred in 6.5% with thiosulfate and 30.7% without, with hypertension and a raised preoperative urea as independent predictors, so a residual risk remains [18]. CHIPOR recorded renal failure in 10% and electrolyte disturbance in 14% of HIPEC patients [13]. Mitomycin C is myelotoxic: neutropenia below 1,000/mm^3 followed 39% of 120 perfusions, with female sex (odds ratio 3.58; 95% CI 1.52–8.43) and dose per square meter (odds ratio 3.37 per 5 mg/m^2) as independent risk factors, without excess mortality or infection [31]; the randomized comparison confirmed lower leukocyte counts than after oxaliplatin [23]. Oxaliplatin carries two costs of its own. Its dextrose 5% carrier and the sodium lost into the perfusate, about 257 mmol, produce severe hyponatremia (mean 126.5 mmol/L), hyperglycemia (mean 22.4 mmol/L) and hyperlactatemia, a picture not seen with cisplatin or mitomycin C and preventable by glucose control and sodium replacement [24]. Oxaliplatin was also associated with bleeding: in the French registry, hemorrhagic complications followed 15.7% of oxaliplatin perfusions and 2.6% of those with other drugs, and in the multivariable model a PCI above 12 was the only independent predictor [25]. Anastomotic leak and intra-abdominal sepsis are surgical complications that HIPEC may aggravate; the signals are indirect, an excess of grade 3 or worse events of any kind at 60 days in PRODIGE 7 (26% versus 15%) and bowel leakage as the main complication in the Verwaal trial [20,26]. Postoperative mortality was 2% at 30 days in PRODIGE 7 and in the pseudomyxoma and mesothelioma registries, 8% in the first randomized trial, and three treatment-related deaths within 100 days of randomization among the 50 patients in the safety population of the surgical arm of PERISCOPE II [20,22,26,92,94]; hyperthermia contributes through temperature rise, metabolic demand, fluid shifts and coagulopathy [47]. A PubMed search restricted to Romanian affiliations found no national outcome series with cytoreduction and HIPEC and no PIPAC series; the published experience consists of case reports from one private center in Brașov, including a Takotsubo cardiomyopathy with cardiac arrest 18 hours after CRS and HIPEC for recurrent colon cancer [95].

PIPAC toxicity is that of a laparoscopy with a low drug dose: surgical complications in about 3% of prospective procedures and adverse events above grade 2 after 12–15%, most often bowel obstruction, bleeding and abdominal pain [4]; pain after 88% of oxaliplatin procedures and one possibly treatment-related death from sepsis in the colorectal phase 2 [70]; trocar hernia, bowel obstruction and bleeding in the ovarian phase 2, with non-access in 17% [68]; and pancreatitis with oxaliplatin [63].

Toxicity in the operating room: occupational exposure

The evidence is reassuring for air and urine and cautionary for surfaces. During ten open mitomycin C perfusions, none was detected in air above the skin edge or in the urine of the surgeon and perfusionist, but glove permeability varied tenfold between types [49]. During oxaliplatin HIPEC, urinary platinum in 11 staff members stayed below the detection limit and air filters were negative, but the surgeon's gloves were heavily contaminated and surfaces carried 2–183 ng of platinum [99]; in two hospitals, open perfusions contaminated the table, the floor at the surgeon's feet and overshoes, hands were contaminated with double but not triple gloving, and urinary platinum stayed undetectable [100]. Biomonitoring across HIPEC and PIPAC found contamination of floor, gloves, shoes and devices, while urinary platinum was below 10 ng/L in more than half of staff samples and did not differ from controls [101]. For PIPAC, remote-controlled administration with a closed abdomen, laminar airflow and a closed aerosol-waste system kept cisplatin below the detection limit of 0.000009 mg/m^3 in air at the surgeon's and anes-

Table 4. Toxicities of intraperitoneal chemotherapy and their mitigation

Toxicity	Drug or cause	Frequency in cited sources	Mitigation (key)
Acute kidney injury, dialysis	Cisplatin	Any-grade injury 19 of 47 (40.4%), long-term dialysis 2 of 47 (4.3%), no nephroprotection reported, retrospective [16]; renal impairment 11 of 35 (31.4%) before vs 0 of 38 after sodium thiosulfate, before–after cohorts [17]; acute kidney injury by Acute Kidney Injury Network criteria in 30.7% of 192 without vs 6.5% of 46 with thiosulfate, retrospective [18]; renal failure grade ≥3 within 60 days 10% of 207 in CHIPOR [13]	Sodium thiosulfate before and after perfusion reduces but does not abolish the risk [11,17,18]; adequate baseline renal function [83]; hypertension and raised urea as predictors [18]
Neutropenia	Mitomycin C	Neutropenia <1,000/mm³ after 39% of 120 perfusions; female sex and dose per m2 as risk factors [31]; lower leukocytes than with oxaliplatin, randomized [23]	Dose by body surface area as in the tested protocol; female sex and extensive visceral resection are risk factors, not a validated dose-adjustment rule [9,31]; daily blood counts [23]
Hyponatremia, hyperglycemia, hyperlactatemia	Oxaliplatin in dextrose 5%	Mean sodium 126.5 mmol/L, glucose 22.4 mmol/L during perfusion [24]	Glucose monitoring with insulin, intravenous sodium replacement [24,96]
Hemorrhagic complications	Oxaliplatin	15.7% of oxaliplatin vs 2.6% of other perfusions, registry association; PCI >12 the independent predictor in that model [25]	Regimen choice; caution at high PCI [25]
Anastomotic leak, late intra-abdominal morbidity	HIPEC after extensive surgery	Leak-specific rates not reported in the randomized trials; overall 60-day grade ≥3 events 26% vs 15% in PRODIGE 7 [20]; bowel leakage the main complication in the Verwaal trial [26]	Patient selection and complete cytoreduction within the trial criteria; ERAS pathway [96,97]

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thesiologist's positions [104]; with International Organization for Standardization (ISO) class 5 ventilation, no platinum was found in operating-room air or in the blood of two surgeons after 50 procedures [102]. The cautionary study measured air platinum below 3.1 pg/m³ during 14 procedures but surface contamination from 0.01 to 1,733 pg/cm², highest on injector parts and trocars and often higher before than after the procedure, pointing to cleaning and cross-contamination rather than the aerosol [103]. The measures follow: closed circuits or remote administration, ventilation and waste systems meeting the PIPAC technical consensus, triple gloving for open perfusion, defined cleaning of devices and floors, and periodic surface and urinary platinum monitoring [64,100,103].

Perioperative pharmacology and care

The Enhanced Recovery After Surgery (ERAS) Society issued two-part recommendations for cytoreductive surgery with or without HIPEC in 2020, with consensus on 71 of 72 care items [96,97]. Intraoperatively this means goal-directed fluid management against large fluid and protein losses, advanced hemodynamic monitoring, control of core temperature and thoracic epidural analgesia, with preconditioning before surgery [47,97]. The postoperative recommendations include pharmacological thromboprophylaxis started 12 hours before surgery and extended to four weeks, mechanical prophylaxis until mobilization, thoracic epidural analgesia for at least 72 hours (the timing of anticoagulant doses around catheter insertion and removal follows the agent-specific neurax-

Table 4 (continued). Toxicities of intraperitoneal chemotherapy and their mitigation

Toxicity	Drug or cause	Frequency in cited sources	Mitigation (key)
Postoperative mortality	Procedure	30-day treatment-related mortality 2% per arm in PRODIGE 7 [20]; 2% in the pseudomyxoma and mesothelioma registries [92,94]; 8% treatment-related in the first randomized trial [26]; 3 treatment-related deaths within 100 days of randomization in the surgical arm (n = 50) of PERISCOPE II [22]	Center volume, selection by performance status and response to systemic therapy [22,83]
Systemic hyperthermia, fluid and coagulation derangement	Heat	Physiological consequences described [47]	Advanced hemodynamic monitoring, temperature management, goal-directed fluids [47,97]
Cardiac stress event	Procedure	Single case report [95]	Cardiac risk assessment; intensive-care monitoring [47]
PIPAC: bowel obstruction, bleeding, pain, pancreatitis	Aerosol chemotherapy, laparoscopy	Events >grade 2 after 12–15% of procedures [4]; pain after 88% of oxaliplatin procedures [70]; pancreatitis with oxaliplatin [63]	Consensus doses [34]; safety checklist [64]
Venous thromboembolism	Surgery and cancer	Addressed by ERAS recommendations [96]	Pharmacological prophylaxis from 12 h before surgery, extended to 4 weeks, timed around neuraxial catheters by agent-specific rules [96]; anticoagulant choice for established events [98]
Occupational platinum exposure	Open perfusion, aerosol	Airborne platinum undetectable or below the analytical limit in all studies; urinary platinum undetectable in three studies and below the quantification limit in most samples, not different from controls, in the fourth; blood negative in two surgeons; gloves, floor, table and devices contaminated [49,99-103]	Closed circuit or remote administration, ventilation and closed waste [64,102,104]; triple gloving [100]; cleaning of injector and trocars [103]; periodic surface and urinary monitoring [101]

ERAS, Enhanced Recovery After Surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal cancer index; PIPAC, pressurized intraperitoneal aerosol chemotherapy.

ial rules), no routine nasogastric drainage, and glucose control at 140–180 mg/dL in critically ill patients [96]; the choice of anticoagulant for cancer-associated venous thromboembolism after cytoreduction is reviewed elsewhere in this journal [98]. Two drug-specific items belong in every protocol: sodium thiosulfate before and after cisplatin perfusion [11,17], and, for oxaliplatin in dextrose, glucose monitoring with insulin and sodium replacement [24]. Adequate renal function is a condition for offering cisplatin HIPEC [83], and extensive visceral resection should prompt attention to the plasma exposure of mitomycin C [9].

A framework for 2026

Patient selection begins with the histology and the trial that supports the indication. In ovarian cancer, cisplatin HIPEC belongs at interval cytoreduction after at least stable disease on neoadjuvant chemotherapy, when residual disease of 10 mm or less is anticipated, in patients of

World Health Organization performance status 0–2 with adequate renal function as in OVHIPEC-1, and, in centers able to manage its renal toxicity, at complete cytoreduction after chemotherapy for first relapse at least six months after platinum in patients of performance status 0–1 as in CHIPOR [11,13,83]. In colorectal cancer, the candidate has resectable peritoneal-only disease, a PCI of 20 or less as in CAIRO6 (25 or less in PRODIGE 7), and a realistic prospect of CC-0 cytoreduction; the intraperitoneal component is a matter for a trial and, if given, mitomycin C rather than short high-dose oxaliplatin [20,27,58]. In gastric cancer, the randomized evidence does not support cytoreduction and HIPEC over systemic therapy even for a PCI below 7, and prophylactic HIPEC belongs in trials [22,30,90]. In pseudomyxoma peritonei and mesothelioma, high PCI values are compatible with long survival if cytoreduction is complete, and HIPEC is part of the standard [92,94]. Performance status and renal function are gatekeepers in every histology; response to preceding systemic therapy is a gatekeeper where the trials made it one, in ovarian and gastric cancer [11,22,83].

The regimens with randomized or registry evidence are those of Table 1. Our proposal is that a program adopt one tested regimen per disease and setting rather than a local variant, dose in mg/m², measure temperature at three or more sites, and record PCI, CC score, drug, dose, volume, temperature and duration for every procedure, which is what the technology consensus and the registries ask for [6,73], with nephroprotection, metabolic monitoring, thromboprophylaxis, the occupational controls of the PIPAC technical consensus, and an anesthetic and intensive-care team trained for hyperthermia [47,64,96,97]. PIPAC remains investigational: a palliative or bridging option for unresectable disease in specialist or trial settings, given at the 2022 consensus doses with PRGS response assessment, with the number of cycles governed by access, tolerance and disease evolution, and not a substitute for cytoreduction where cytoreduction is possible [34,65,79].

The open questions are precise: whether mitomycin C HIPEC adds survival to complete cytoreduction in colorectal cancer, which PRODIGE 7 did not test; whether prophylactic HIPEC after D2 gastrectomy, tested in GASTRICHIP, changes recurrence and survival in a Western population; whether OVHIPEC-2 extends the ovarian indication to primary cytoreduction; whether PIPAC-OV3, PIPAC VEROne and the gastric phase 2 trials turn histological responses into survival; whether the catheter-based paclitaxel result of DRAGON-01 holds outside China; and which biomarkers, from nodule density and vascularity to histological regression, identify the patients whose residual disease lies within the millimeters the drug can reach [8,27,39,74,78,81,91].

Conclusion

Intraperitoneal chemotherapy is a pharmacological intervention bounded by physics: high surface exposure, shallow penetration, and drug-specific gains from heat. The randomized trials of the last decade confirm cisplatin HIPEC at interval cytoreduction in ovarian cancer and, in one of two trials, at first relapse; they show that short high-dose oxaliplatin HIPEC adds nothing to cytoreduction in colorectal cancer, that surgery with HIPEC did not improve survival over systemic therapy in the gastric populations tested, and that catheter-based intraperitoneal paclitaxel did; mitomycin C after cytoreduction, gastric prophylaxis and PIPAC remain questions for trials under way. The toxicities are drug-specific and can be reduced but not removed, in the patient by sodium thiosulfate, metabolic monitoring, regimen choice and patient selection, and in the operating room by closed circuits, ventilation and glove discipline. A program that selects by histology, cytoreduction and renal function, uses tested regimens, audits its morbidity and records what it does can offer these treatments with known and declared risks while the open questions are answered.

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Conflict of interest

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Author contributions

S.C.V.: conceptualization, methodology, investigation (literature search and source verification), writing – original draft, writing – review and editing, project administration. The author approved the final version and agrees to be accountable for the work.

Ethics statement

No ethical approval was required; no human or animal data were collected.

Data availability

No new data were generated.

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