

First reported clinical implementation of pressurized intraperitoneal aerosol chemotherapy in Japan: Program development and 30-day outcomes in two patients

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Abstract: Described here is the multidisciplinary implementation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) at a Japanese institution and 30-day outcomes of its first two procedures, rather than an interim efficacy analysis of an ongoing five-patient pilot study. Preparation consisted of international training and clinical observation, two porcine experiments, two full-scale operating-room simulations, a four-stage checklist, remote anesthesia management, pharmacy and injector workflows, and high-efficiency particulate air-filtered closed evacuation. Simulations indicated that ventilator-specific parameters were unavailable on the remote vital-sign display, prompting a dedicated ventilator-screen video feed. On August 12, 2026, two men with unresectable peritoneal metastases from appendiceal mucinous adenocarcinoma underwent oxaliplatin-based PIPAC. Three-port access was achieved despite anticipated adhesions; peritoneal cancer index scores were 34 and 28. Oxaliplatin was prepared at 2 mg/mL with a measured circuit dead-space allowance; injector settings were 0.8 mL/s and a pressure limit of 290 pounds per square inch (psi). Both procedures, including aerosolization, a dwell time of 30 min, and closed evacuation, were completed without observed leakage, emergency re-entry, device malfunction, organ injury, or conversion. Patient 1 had exacerbated grade 2 abdominal pain, grade 2 anorexia, and grade 1 vomiting and was discharged on postoperative day 6. Patient 2 had no in-hospital adverse events and was discharged on postoperative day 2. Telephone assessment at 30 days identified no unplanned visit, readmission, re-intervention, or new clinically important adverse event; both patients were considered clinically suitable for next-cycle reassessment. This experience illustrates a structured pathway for clinical PIPAC implementation. Trial registration: jRCTs031260298.

Keywords: PIPAC, multidisciplinary workflow, peritoneal dissemination, occupational safety workflow, remote anesthesia management

1. Introduction

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a laparoscopic drug-delivery technique in which chemotherapy is nebulized into a pressurized pneumoperitoneum. It has been used in patients with unresectable peritoneal metastases and enables repeated assessment of the peritoneal cancer index (PCI), ascites, and biopsy specimens while using lower drug doses than conventional intraperitoneal perfusion (1-3).

Oxaliplatin-based PIPAC has shown technical feasibility and acceptable short-term tolerability in colorectal and appendiceal peritoneal metastases (2,3).

Introducing PIPAC into a new healthcare system requires coordinated preparation beyond acquisition of a nebulizer. Essential elements include regulatory approval; trained multidisciplinary personnel; a closed abdominal and evacuation circuit; ventilation and remote monitoring; cytotoxic-drug preparation and delivery; emergency re-entry planning; and a standardized

checklist (4,5). Early implementation reports from other countries have shown that documenting training, operating-room configuration, and workflow provide practical information distinct from subsequent efficacy analyses (6-8).

We initiated program development in January 2025 and performed our institution's first two clinical PIPAC procedures on August 12, 2026. This Brief Report describes the completed multidisciplinary implementation process and 30-day outcomes of those procedures. It does not present an interim analysis of the ongoing five-patient pilot study's primary endpoint of three-cycle completion or of antitumor efficacy.

2. Materials and Methods

2.1. Study design and ethics

This descriptive implementation report was prepared within a prospective, single-center pilot study of PIPAC for colorectal or appendiceal peritoneal metastases at the National Center for Global Health and Medicine, Japan Institute for Health Security. The Certified Review Board (CRB) of the Japan Institute for Health Security granted initial approval on December 10, 2025 (JIHS-C-005137-00; CRB3250001). Protocol version 1.3 was subsequently approved as an amendment on July 20, 2026, following committee review on July 13, 2026 (JIHS-C-005137-01). Institutional authorization was obtained before clinical use. The study was registered in the Japan Registry of Clinical Trials (jRCT; jRCTs031260298; first posted August 10, 2026) and conducted in accordance with the Declaration of Helsinki. Both patients provided written informed consent for participation and publication of anonymized clinical information and images. Final clinical follow-up was September 11, 2026 (postoperative day 30), and the data cutoff was September 15, 2026.

Reporting was organized using the Template for Intervention Description and Replication (TIDieR) checklist and relevant CAse REport (CARE) guideline items (9,10); the reporting map is provided in Supplementary Appendix S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>).

We reviewed English- and Japanese-language literature available through September 12, 2026, including PubMed-indexed publications, Ichushi-Web, J-STAGE, and publicly indexed CiNii Research records, using PIPAC and its English and Japanese equivalents. No report of clinical PIPAC performed in Japan before August 12, 2026 was identified. Search details are provided in Supplementary Appendix S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>).

2.2. Patient selection

We enrolled patients aged 20 to <80 years with histologically confirmed colorectal or appendiceal cancer, laparoscopically confirmed peritoneal metastases, no extraperitoneal metastases, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, expected survival of at least 6 months, and adequate organ function (neutrophils $\geq 1,000/\mu\text{L}$, hemoglobin ≥ 8.0 g/dL, platelets $\geq 50,000/\mu\text{L}$, total bilirubin ≤ 1.5 times the upper reference limit, aspartate and alanine aminotransferases ≤ 100 U/L, and Cockcroft-Gault creatinine clearance ≥ 50 mL/min). Patients with PCI < 10 were excluded from PIPAC enrollment because they were considered potential candidates for cytoreductive surgery; no upper PCI limit was set. Other key exclusions were bowel obstruction requiring nasogastric decompression or parenteral nutrition, severe sensory dysfunction, active infection, and prior PIPAC or hyperthermic intraperitoneal chemotherapy. Previous fluoropyrimidine-based systemic therapy with refractoriness or intolerance was required; full criteria followed the approved protocol.

2.3. Program development and safety workflow

Program preparation included formal multidisciplinary training at the third International Society for the Study of Pleura and Peritoneum (ISSPP) PIPAC Workshop in Montpellier, observation of clinical PIPAC at the Institut du Cancer Montpellier, two porcine experiments, and two full-scale simulations in the intended operating room (Figure 1A). The team included surgeons, an anesthesiologist, operating-room nurses, a radiologic technologist, and a pharmacist. During simulations, the team found that the remote vital-sign display did not provide ventilator-specific parameters, including tidal volume and airway pressure. Before clinical use, a dedicated video feed of the ventilator screen was therefore added using an iPad and Microsoft Teams. Simulations were also used to finalize room layout, device and drug pathways, remote medication delivery, emergency re-entry, and closed evacuation. A four-stage checklist defined decision points before the procedure, before aerosolization, before re-entry after a dwell time of 30 min, and upon completion (Figure 1B; Supplementary Table S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>). Each item was read aloud, confirmed by the team, and checked by an operating-room nurse.

2.4. Operating-room and anesthesia safety

Procedures were performed in an International Organization for Standardization (ISO) Class 5 operating room with laminar airflow. During aerosolization and the dwell time, staff remained in the anteroom and remotely monitored vital signs, the patient, the ventilator display, the laparoscopic view, and the injector (Figure

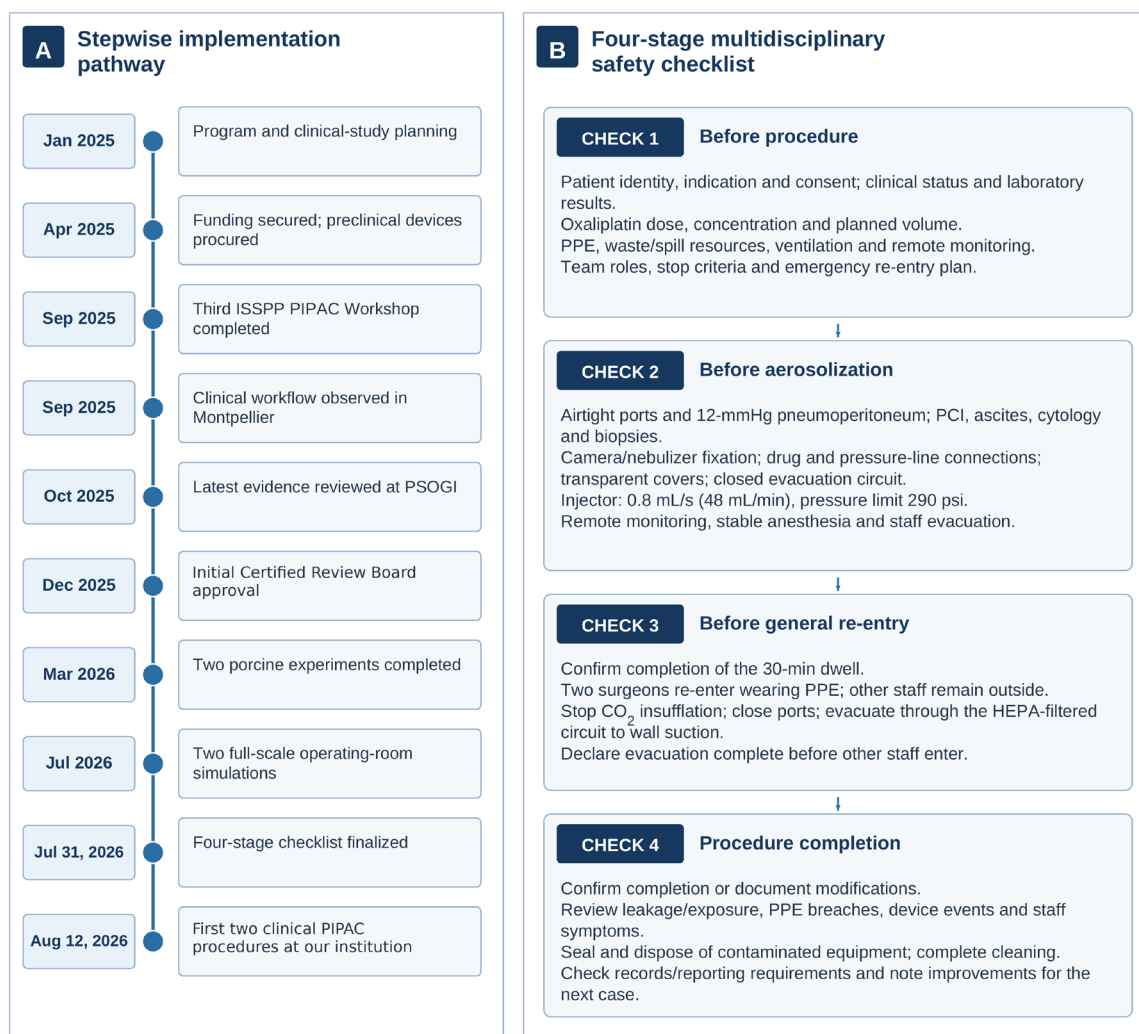


Figure 1. Stepwise development of the institutional PIPAC program in Japan. (A) The 19-month pathway from planning to the first two procedures. The December 2025 entry denotes initial CRB approval on December 10, 2025 (JIHS-C-005137-00). Protocol version 1.3 subsequently received amendment approval on July 20, 2026 (JIHS-C-005137-01), following a review on July 13. **(B)** The four-stage multidisciplinary safety checklist. Each checkpoint was read aloud, confirmed verbally by the team, and checked by an operating-room nurse. This is a summary of the institution-specific workflow; injector settings are the actual settings used. *Abbreviations:* CO₂, carbon dioxide; CRB, Certified Review Board; HEPA, high-efficiency particulate air; ISSPP, International Society for the Study of Pleura and Peritoneum; PCI, peritoneal cancer index; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PPE, personal protective equipment; psi, pounds per square inch; PSOGI, Peritoneal Surface Oncology Group International.

2A and Figure 3). Seven extension tubes connected in series permitted intravenous medication from outside the room; a three-way stopcock and 50-mL saline syringe were placed at the external end. Emergency re-entry criteria included ventilation failure, unexplained shock, intravenous-line failure, inadequate anesthesia or patient movement, life-threatening arrhythmia, and cardiac arrest (11).

2.5. PIPAC procedure and drug preparation

Because preoperative computed tomography suggested periumbilical and upper-abdominal adhesions, a 12-mm balloon port was inserted infraumbilically using an open technique, followed by two 5-mm ports. Pneumoperitoneum was maintained at 12 mmHg. PCI,

adhesions, and ascites were documented; ascites was collected and four pre-exposure biopsies were mapped to PCI regions. The laparoscope was placed through a 5-mm port and the nebulizer through the 12-mm port. The ports, instruments, operative field, and pressure-resistant tubing were covered with transparent sterile drapes or waterproof sleeves (Figure 2).

The CapnoPharm nebulizer (CapnoPharm GmbH, Tübingen, Germany) was connected by pressure-resistant tubing to an Illumena high-pressure injector (Gadelius Medical K.K., Tokyo, Japan). Oxaliplatin was prepared in 5% dextrose at 2 mg/mL using the 92-mg/m² regimen reported for colorectal PIPAC and included in the approved protocol (2,5). Before clinical use, the internal volume of the intended circuit was measured by filling it with 5% dextrose and was 4 mL. An allowance of 8 mg

A Operating-room layout for PIPAC

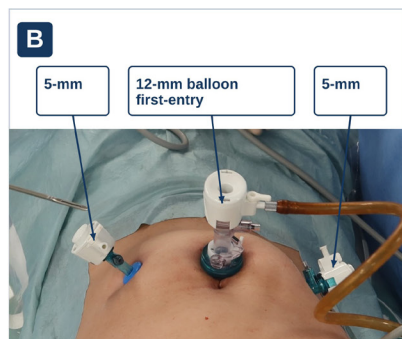
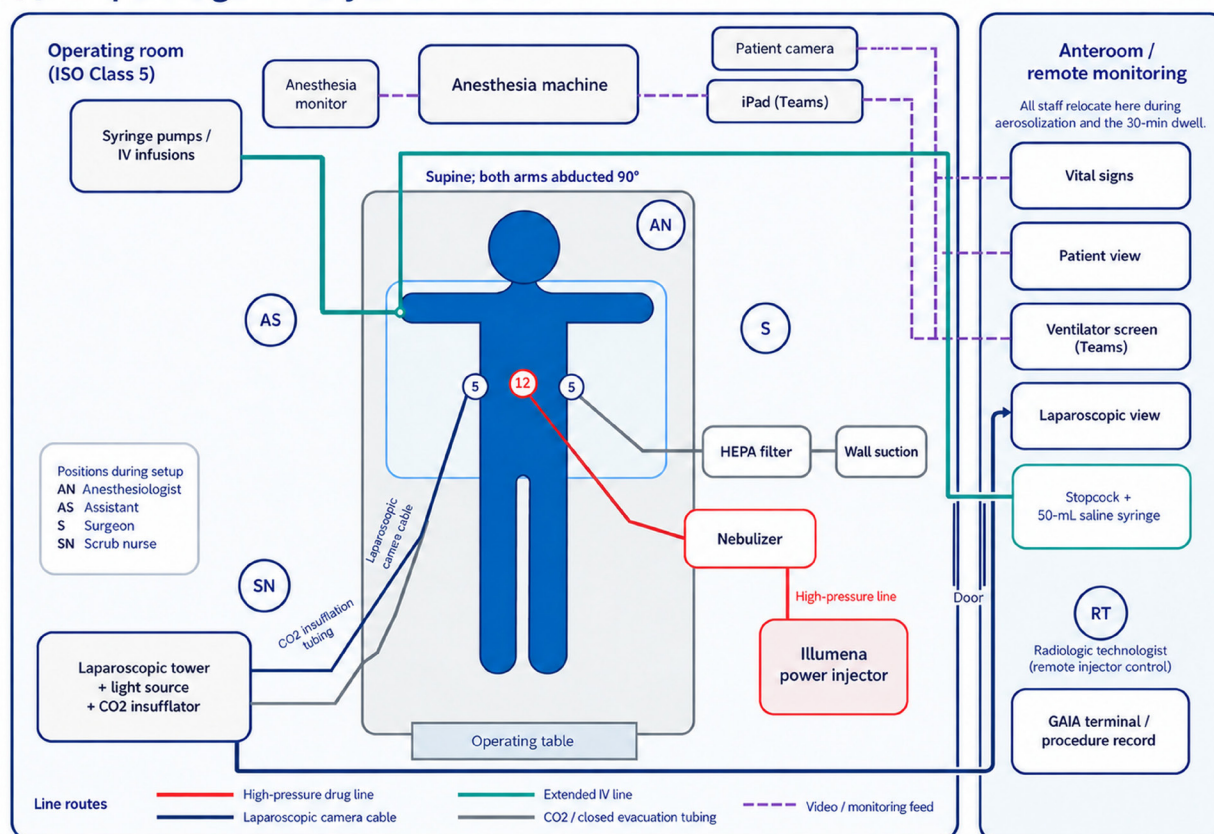


Figure 2. Operating-room and operative-field configuration. (A) Simplified operating-room layout and closed-system connections; the patient was positioned in the supine with both arms abducted to 90°. The physical drug pathway was the Illumena injector, pressure-resistant tubing, a nebulizer, and a 12-mm balloon port; the evacuation pathway consisted of a 5-mm port, closed tubing, a HEPA filter, and wall suction. (B) The three actual ports, from left to right in the photograph: 5 mm, 12-mm balloon first-entry port below the umbilicus, and 5 mm. Arrowheads identify the white port housings. (C) Mechanical securing of the laparoscope and nebulizer. (D) Transparent sterile draping of the ports, laparoscope, nebulizer, operative field, and pressure-resistant tubing. Abbreviations: AN, anesthesiologist; AS, assistant; CO₂, carbon dioxide; HEPA, high-efficiency particulate air; ISO, International Organization for Standardization; IV, intravenous; PIPAC, pressurized intraperitoneal aerosol chemotherapy; RT, radiologic technologist; S, surgeon; SN, scrub nurse. GAIA and Teams are system/product names.

(4 mL) was added to the body-surface-area-calculated amount before rounding and was included in the total quantity prepared for injection. The calculated doses were 183.08 and 172.96 mg, and the final preparations were 190 mg/95 mL and 180 mg/90 mL for Patients 1 and 2, respectively. The clinical pressure line was not separately primed before aerosolization; the allowance accounted for drug solution remaining in the circuit

at completion, rather than a separate priming dose. Prepared quantities were not independently measured intraperitoneal doses. The injector was set to 0.8 mL/s with a pressure limit of 290 pounds per square inch (psi; approximately 20 bar). This pressure ceiling is consistent with published PIPAC technical descriptions (12), and 0.8 mL/s has been evaluated experimentally with the CapnoPen nebulizer using saline (13).

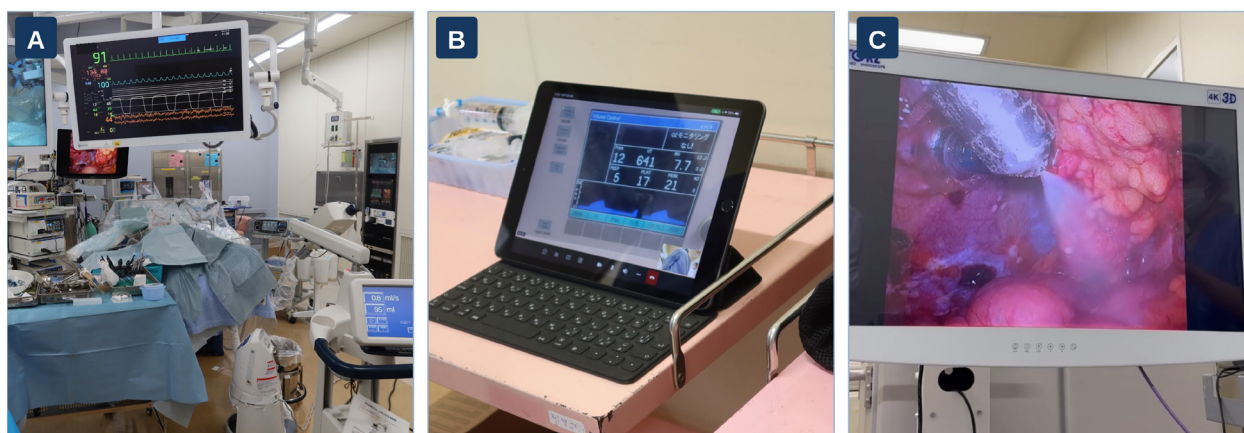


Figure 3. Remote monitoring during aerosolization and the dwell time. (A) Simultaneous display of the patient, vital signs, laparoscopic view, and high-pressure injector settings. **(B)** External display of the ventilator screen using Microsoft Teams. **(C)** Laparoscopic monitoring of aerosolization from outside the operating room. Patient-identifying text on the vital-sign monitor was obscured. *Abbreviation:* PIPAC, pressurized intraperitoneal aerosol chemotherapy.

After aerosolization, the pneumoperitoneum remained closed for a dwell time of 30 min. Two surgeons wearing personal protective equipment (PPE) then re-entered, stopped carbon dioxide insufflation, and evacuated the aerosol through a closed circuit with a high-efficiency particulate air (HEPA) filter connected to wall suction. Other staff re-entered only after evacuation was declared complete (Figure 2 and Figure 3).

2.6. Outcomes

We recorded technical completion, access, PCI, ascites, mapped biopsy sites, histology, cytology, procedural time logs, intraoperative events, CHECK 4 findings, laboratory results, in-hospital adverse events, and 30-day outcomes. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (14). The abdominal-pain grade was assigned retrospectively by the treating clinician using the clinical severity assessment and functional information, rather than the numerical rating scale (NRS) alone. Periods of aerosolization were transcribed from nursing and anesthesia event records. Day-30 status was assessed by telephone on September 11, 2026. Clinical suitability to proceed to next-cycle reassessment was judged based on the reported recovery and absence of new clinical problems; actual repeat administration remained conditional on confirmation of protocol-defined treatment criteria before the next procedure. Implementation of the occupational safety workflow was assessed using incident and leakage checks and staff symptom review; air, surface, and biological platinum concentrations were not measured. No hypothesis testing was conducted.

3. Results and Discussion

Two men ages 48 and 52 years with appendiceal

mucinous adenocarcinoma, extensive peritoneal metastases, and an ECOG performance status of 0 underwent consecutive PIPAC procedures (Table 1). Both had received oxaliplatin-based systemic therapy and were not candidates for complete cytoreduction. Infraumbilical access was achieved despite extensive omental and transverse-colon adhesions in Patient 1 and two small-bowel adhesions in Patient 2; no enterotomy or conversion occurred. PCI scores were 34 and 28, and pelvic ascites volumes were 30 and 40 mL, respectively. Representative laparoscopic findings are provided in Supplementary Figure S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>).

Operating-room times were 205 and 171 min, and operative times were 133 and 108 min for Patients 1 and 2, respectively. The charted periods of aerosolization were 11:28–11:30 for Patient 1 and 15:18–15:20 for Patient 2. These clock-time intervals were transcribed from nursing and anesthesia event records and were not independently validated as continuous injector-on durations. Both procedures included the planned dwell time of 30 min and high-efficiency particulate air-filtered closed evacuation. No drug leakage, suspected aerosol exposure, personal protective equipment breach, device malfunction, unplanned emergency re-entry, organ injury, transfusion, or conversion was reported. No immediate staff symptoms were reported at CHECK 4.

Baseline biopsies showed treated peritoneal dissemination of appendiceal adenocarcinoma in Patient 1 and mucinous adenocarcinoma dissemination or high-grade mucinous carcinoma peritonei after systemic chemotherapy in Patient 2. Ascites cytology was Class V (malignant) in both patients. These specimens reflected prior systemic treatment and were not interpreted as a response to the first PIPAC procedure.

Patient 1 had pre-existing cancer pain treated with extended-release hydromorphone (6 mg/day); the

Table 1. Patient characteristics, procedural details, pathology, and 30-day outcomes

Characteristic	Patient 1	Patient 2
Age/sex	48 years/male	52 years/male
Primary disease	Appendiceal mucinous adenocarcinoma	Appendiceal mucinous adenocarcinoma
Prior systemic therapy	FOLFOXIRI plus bevacizumab; then FOLFIRI plus bevacizumab	FOLFOX plus bevacizumab; then 5-FU/LV plus bevacizumab
ECOG performance status	0	0
PCI/pelvic ascites	34/30 mL	28/40 mL
Main adhesions	Omentum and transverse colon adhesions, from the umbilicus to the upper abdomen	Two small-bowel adhesions around the umbilicus and upper abdomen
Mapped biopsy regions	#8 × 2, #7, #6	#0 × 2, #7, #6
Prepared oxaliplatin quantity/volume†	190 mg/95 mL (calculated dose 183.08 mg)	180 mg/90 mL (calculated dose 172.96 mg)
Injector settings	0.8 mL/s (48 mL/min); pressure limit 290 psi	0.8 mL/s (48 mL/min); pressure limit 290 psi
OR/operative/anesthesia time	205/133/197 min	171/108/161 min
Charted aerosolization period*	11:28–11:30	15:18–15:20
In-hospital adverse events	Grade 2 abdominal pain exacerbation; grade 2 anorexia; grade 1 vomiting	None
Discharge	POD 6	POD 2
Peritoneal biopsy	Appendiceal adenocarcinoma dissemination after systemic chemotherapy	Mucinous adenocarcinoma dissemination/high-grade mucinous carcinoma peritonei after systemic chemotherapy
Ascites cytology	Class V (malignant)	Class V (malignant)
30-day outcome	No unplanned visit, readmission, re-intervention, or new clinically important adverse event reported by telephone; clinically suitable for next-cycle reassessment	No unplanned visit, readmission, re-intervention, or new clinically important adverse event reported by telephone; clinically suitable for next-cycle reassessment

*Clock-time intervals transcribed from nursing/anesthesia event records; they were not validated as continuous injector-on durations. †Circuit volume was measured beforehand with 5% dextrose (4 mL). An 8-mg (4-mL) allowance was added to the calculated amount before rounding and included in the total preparation for injection. The line was not separately primed before aerosolization; the allowance accounted for solution remaining in the circuit at completion. Prepared quantities are not independently measured intraperitoneal doses. Biopsies were collected before aerosolization during the first PIPAC procedure. Treatment-related histological changes refer to prior systemic chemotherapy. *Abbreviations:* CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; OR, operating room; PCI, peritoneal cancer index; PIPAC, pressurized intraperitoneal aerosol chemotherapy; POD, postoperative day; psi, pounds per square inch; 5-FU/LV, fluorouracil/leucovorin.

preoperative screening record documented an NRS score of 2/10. This screening result was not a separately documented measurement immediately before anesthesia. Pain increased to NRS 8/10 approximately 3 h after PIPAC, decreased to 6/10 on postoperative day (POD) 1, and returned to the preprocedural baseline by POD 4. On retrospective treating-clinician assessment, the exacerbation of pain was moderate and daily activities remained possible; it was classified as CTCAE v5.0 grade 2 abdominal pain on the basis of the moderate-pain criterion, and not the peak NRS score alone. Additional analgesia included intravenous acetaminophen 1,000 mg as needed, up to three times daily, and intravenous

flurbiprofen axetil 50 mg once daily. Grade 2 anorexia and grade 1 vomiting also occurred. Oral intake improved, and the patient was discharged on POD 6. Patient 2 had no in-hospital adverse events and was discharged on POD 2. Postoperative tests showed transient leukocytosis and increased C-reactive protein without clinically important hepatic or renal deterioration (Supplementary Table S2, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>), consistent with previously reported inflammatory changes after PIPAC (15). Upon telephone follow-up on September 11, 2026, neither patient reported an unplanned visit, emergency assessment,

readmission, reoperation, interventional radiology procedure, or new clinically important adverse event. Both were considered clinically suitable to proceed to next-cycle reassessment, subject to the protocol-required checks before repeat administration.

The principal contribution of this report is the implementation process. Over 19 months, international training and clinical observation were translated through preclinical experiments and full-scale simulations into a locally executable multidisciplinary workflow. Simulations allowed the team to rehearse room setup, remote anesthesia, extended intravenous access, drug preparation and injector operation, sterile containment, emergency re-entry, and high-efficiency particulate air-filtered evacuation before treating patients. The four-stage checklist established shared decision gates and explicit responsibilities across surgery, anesthesiology, nursing, radiology, and pharmacy. Comparable implementation reports also emphasize regulatory and logistical preparations before clinical treatment (6,8).

Remote anesthesia management was feasible in these two procedures without invasive monitoring or postoperative intensive care. Published experience emphasizes advanced preparation because direct access to the patient is restricted during aerosolization (11). Our setup combined external displays, remote intravenous access, defined emergency criteria, and readiness for protected re-entry. The occupational safety workflow was informed by exposure studies conducted under containment, ventilation, and remote-operation conditions (12,16-18) and combined engineering controls, personal protective equipment, incident and leakage checks, and staff symptom review. No exposure incident was noted; however, no air, surface, or biological platinum measurements were performed, so this report demonstrates implementation of the workflow rather than quantitative occupational safety.

Both patients had prior oxaliplatin exposure, so sensory symptoms and function should be compared to the baseline before repeat cycles (19); the protocol provides for treatment cessation or further dose reduction for grade ≥ 3 cumulative neurotoxicity. We used three ports for independent, stable positioning of the laparoscope, nebulizer, and evacuation circuit. In a published series, additional ports were required in 12% of procedures (20). Mapping each biopsy to a PCI region established a baseline for subsequent procedures.

This report is limited to the first treatment of two patients, a short follow-up, and clinical rather than quantitative occupational surveillance. It documents program development, workflow implementation, and technical completion but does not establish repeated-treatment feasibility, antitumor efficacy, or generalizability to other primary cancers.

In conclusion, international training, preclinical testing, full-scale simulation, remote anesthesia management, coordinated drug and device workflows,

closed evacuation, and a four-stage multidisciplinary checklist substantiated clinical implementation of PIPAC in Japan. Both procedures were completed as planned, and both patients were considered clinically suitable for next-cycle reassessment at telephone follow-up on day 30.

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Conflict of Interest: CapnoPharm's support has been disclosed. CapnoPharm had no role in the study design, patient selection, data collection, analysis, interpretation, manuscript preparation, or decision to submit or publish. The authors declare no additional conflicts of interest.

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