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Survival Benefit of Combining HIPEC with Laparoscopic Pancreaticoduodenectomy in Resectable Pancreatic Head Cancer

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ABSTRACT

Surgical removal of pancreatic cancer carries a substantial risk of locoregional return of disease and peritoneal spread, contributing to a discouraging outlook. This research sought to examine the safety profile and therapeutic benefit of laparoscopic pancreaticoduodenectomy (LPD) when paired with an adapted perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) schedule for malignancies of the pancreatic head amenable to resection. This investigation employed a dual-center, retrospective cohort design, enrolling individuals with resectable pancreatic head cancer who underwent LPD between May 2018 and July 2024. Participants were divided into two groups: one receiving LPD only (n = 54) and one receiving LPD with HIPEC (LPD+HIPEC; n = 55). The HIPEC procedure included hyperthermic saline lavage during the operation, intraperitoneal gemcitabine on day 2 after surgery, and an additional saline lavage on day 4. Overall survival (OS) served as the primary endpoint. Secondary endpoints captured postoperative adverse events and the distribution of disease recurrence. Independent survival determinants were sought using a multivariate Cox proportional hazards framework. The analysis covered 109 subjects. Baseline demographic, clinical, and core oncologic parameters did not differ meaningfully between cohorts. The frequency of severe postoperative adverse events (Clavien-Dindo grade ≥ III) was comparable for the LPD+HIPEC and LPD cohorts (5.5% vs. 5.6%, P = 1.000). Median OS was notably longer in the LPD+HIPEC cohort (27 months; 95% CI: 24.1–29.9) than in the LPD cohort (23 months; 95% CI: 20.5–25.5; P = 0.045). OS rates at the 1-, 2-, and 3-year marks reached 84.9%, 58.2%, and 26.3% for the LPD+HIPEC cohort, whereas the LPD cohort achieved 74.6%, 40.0%, and 15.0%, respectively. The occurrence of locoregional disease recurrence was significantly curtailed in the LPD+HIPEC cohort (14.6% vs. 31.5%, P = 0.035). Multivariate assessment confirmed that receipt of LPD+HIPEC independently predicted better OS (Hazard Ratio: 0.58; 95% CI: 0.35–0.97; P = 0.038). Within the confines of this retrospective review, the integration of LPD with an adapted perioperative HIPEC approach was associated with improved overall survival and reduced locoregional disease recurrence in resectable pancreatic head cancer, without a meaningful increase in severe postoperative complications. These data suggest a potential therapeutic niche for this combined modality, warranting confirmation through a prospective randomized trial.

Keywords: Laparoscopic pancreaticoduodenectomy, Hyperthermic intraperitoneal chemotherapy, Pancreatic cancer, Overall survival, Locoregional recurrence

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Introduction

Pancreatic cancer stands as a markedly aggressive digestive malignancy and represents the seventh most frequent contributor to cancer-related deaths on a global scale [1]. In resectable pancreatic ductal adenocarcinoma (PDAC), curative-intent management hinges upon radical surgical extirpation, achieving microscopically clear margins (R0 resection) [2, 3]. Yet, prolonged survival after technically successful surgery remains elusive; 5-year survival approximates 14% for stage I-II disease and drops below 5% for more advanced presentations [4, 5]. A principal determinant of these disappointing figures is the high likelihood of postoperative cancer recurrence, which manifests in the majority of individuals within two years. Predominant relapse patterns encompass distant organ

involvement, especially hepatic metastases, alongside locoregional re-emergence, including peritoneal carcinomatosis [6].

Peritoneal metastatic involvement constitutes a particularly formidable recurrence scenario, frequently giving rise to intractable ascites, gastrointestinal obstruction, and marked erosion of life quality. The gland's retroperitoneal anatomical position and unavoidable operative manipulation can facilitate the exfoliation and dispersal of malignant cells directly into the coelomic cavity during surgery. Peritoneal washing cytology has revealed tumor cells in up to 33% of specimens procured post-resection, contrasting sharply with a mere 8% positivity rate before tumor removal [7]. Having gained access to the peritoneal compartment, these unattached tumor clusters rely on a poor vascular supply, thereby limiting the penetration and efficacy of systemically administered agents [8].

Hyperthermic intraperitoneal chemotherapy (HIPEC) represents a locoregional treatment paradigm engineered to seek out and annihilate residual microscopic peritoneal tumor deposits. By instilling a warm, drug-laden perfusate throughout the abdominal cavity, HIPEC achieves high local antineoplastic drug concentrations while minimizing systemic absorption, with thermal energy further potentiating the chemotherapeutic cytotoxicity [9]. Although its utility is firmly established for several peritoneal surface malignancy subtypes, the adjuvant deployment of HIPEC alongside surgical extirpation for primary pancreatic adenocarcinoma remains exploratory. Early-phase clinical observations, including a prior publication from our institution, have suggested that intraperitoneal thermal chemoperfusion may confer a survival advantage without introducing prohibitive toxicity [10]. Nevertheless, the most advantageous timing, pharmaceutical agent, and technical execution of HIPEC tailored to this disease entity lack standardization, and rigorous data investigating its concurrent application with minimally invasive laparoscopic pancreaticoduodenectomy (LPD) are scarce.

The current study was conceived to bridge this evidentiary void by scrutinizing the safety and therapeutic value of LPD combined with a modified, multi-staged perioperative HIPEC regimen at two high-volume clinical centers. Our working postulate was that this integrative treatment schema would produce a meaningful reduction in locoregional recurrence and improvements in survival endpoints compared with LPD as a standalone procedure, while avoiding a discernible increase in severe postoperative morbidity.

Materials and Methods

Study design and patient population

This two-center, retrospective cohort analysis was executed in alignment with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [11]. Records were examined for consecutive individuals diagnosed with resectable pancreatic head cancer who received LPD at the First and Second Hospitals of Hebei Medical University between May 2018 and July 2024. The study received ethical approval from the Ethics Committee of the First Hospital of Hebei Medical University, and written informed consent was obtained from each subject.

Entry conditions were: (1) aged 18 years or above; (2) histological confirmation of pancreatic ductal adenocarcinoma situated in the head; (3) tumor staging fulfilling National Comprehensive Cancer Network (NCCN) resectability definitions [12]; (4) treatment with LPD undertaken with curative intent; and (5) capacity to tolerate the standard postoperative adjuvant chemotherapy combination (gemcitabine plus capecitabine). Grounds for exclusion were: (1) administration of neoadjuvant chemotherapy or radiotherapy beforehand; (2) identification of distant metastases during the operative procedure; (3) need for resection of vascular or other extra-pancreatic structures; (4) concurrent existence of other synchronous primary malignancies; (5) contraindications precluding HIPEC or general anesthesia; and (6) postoperative failure or declination to finish adjuvant chemotherapy.

Commencing in 2018, our centers began providing the adapted HIPEC protocol as an alternative treatment modality. All eligible individuals meeting the study's inclusion criteria were briefed on both management options (LPD alone or LPD with HIPEC) during preoperative consultations. These exchanges addressed the proven foundation of LPD, the exploratory status of supplementary HIPEC, its conceptual benefits in curbing local failure, and the potential for heightened systemic inflammatory responses and uncertain hazards. The ultimate treatment selection was guided by each patient's voluntary, educated preference through this collaborative decision-making dialogue, without a preset clinical protocol steering cohort assignment. A collective of 109 individuals meeting the specifications was recruited and allocated into two groups: the LPD-monotherapy cohort (n = 54) and the LPD combined with HIPEC (LPD+HIPEC) cohort (n = 55). A collective 109 individuals meeting

the specifications were recruited and allocated into two groups: the LPD-monotherapy cohort (n=54) and the LPD combined with HIPEC (LPD+HIPEC) cohort (n=55), as detailed in the patient flow diagram **(Figure 1).**

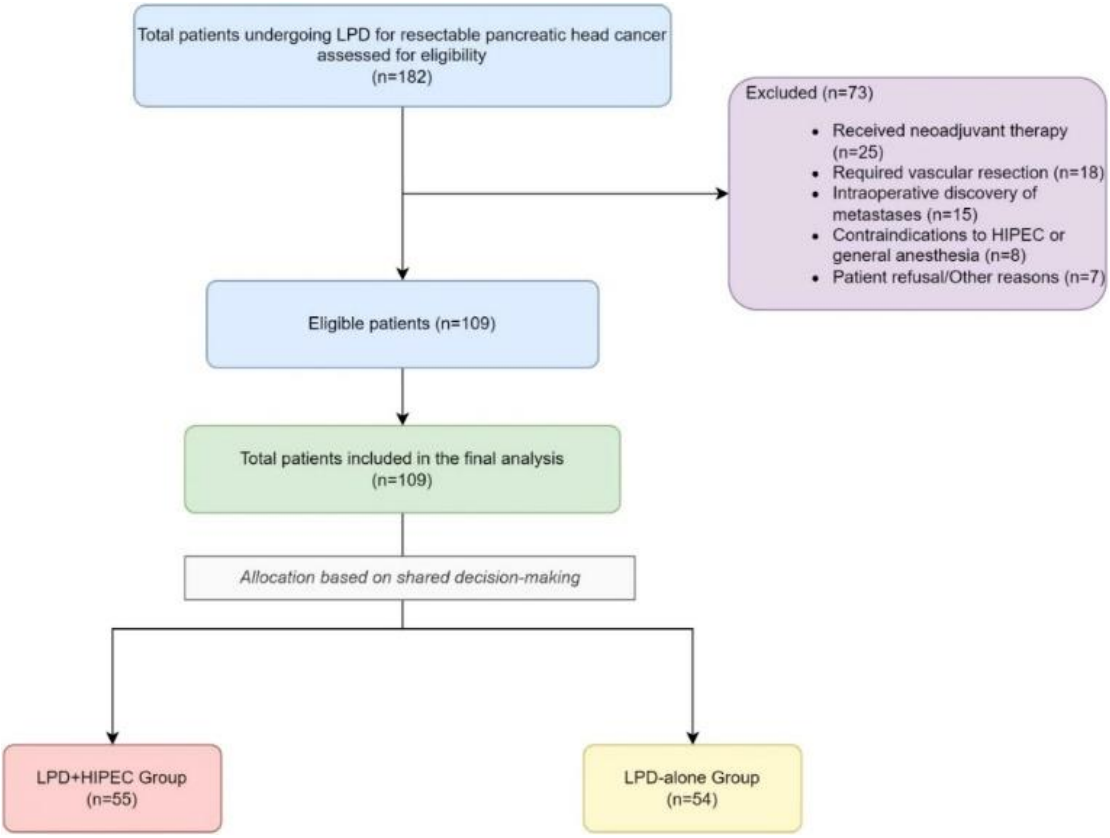

Figure 1. STROBE flow diagram of patient selection. This illustration maps the screening of subjects, rationales for exclusion, and the final assignment of participants to the two study cohorts.

Treatment procedures

Laparoscopic pancreaticoduodenectomy

All LPD operations were completed by highly experienced surgeons matched in credentials and technical skill. The operative methodology was uniform throughout. Following a laparoscopic survey to rule out concealed metastatic deposits, a conventional LPD was undertaken. Steps included Kocherization of the duodenum, mobilization and division of the gastric antrum and proximal jejunum, and separation of the pancreatic neck. The en bloc specimen, which contained the pancreatic head, duodenum, gallbladder, distal common bile duct, and regional lymphatic tissue, was fully freed and extracted. Reconstruction of alimentary tract continuity was accomplished via pancreaticojejunostomy, choledochojejunostomy, and gastrojejunostomy. A variable-caliber pancreatic duct catheter, as previously documented by our group, was used for the pancreaticojejunal anastomosis to mitigate leakage [13].

Modified perioperative HIPEC protocol

For participants assigned to the LPD+HIPEC cohort, a multi-step regimen was deployed.

Step 1 (Intraoperative): Once all anastomoses were finalized and preceding abdominal wall closure, two inflow lines were situated (one positioned ventrally to the pancreaticojejunostomy, one dorsally to the choledochojejunostomy). In comparison, two outflow lines were placed diagonally across the pelvic cavity **(Figure 2).** A 40-minute circulating lavage with warmed normal saline (2000 mL/m²) was delivered. The inflow thermal reading was sustained at 43.0 ± 0.2°C and the outflow at 40.0 ± 0.2°C, with perfusion rates spanning 450–600 mL/min. Gentle manual oscillation of the patient's abdomen was performed to promote homogenous fluid dispersal.

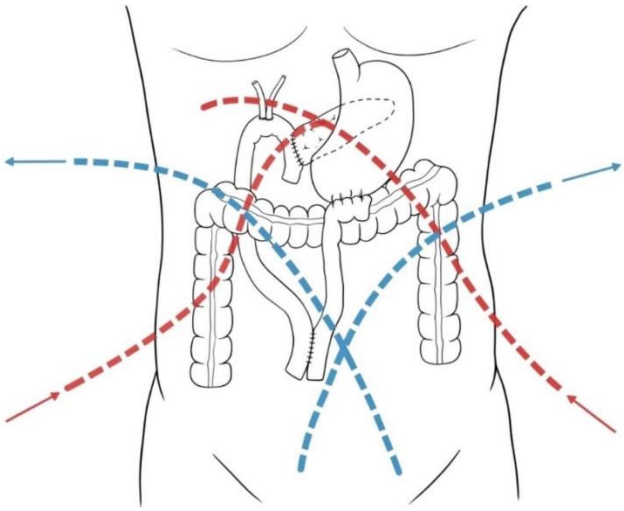

Figure 2. Diagram of catheter arrangement for HIPEC. The red dashed markings indicate the trajectory of the inflow catheters, placed anterior to the pancreaticojejunal connection and posterior to the bilioenteric anastomosis. The blue-dashed line indicates the trajectory of the outflow catheters, arranged diagonally in the pelvis.

Step 2 (Postoperative day 2): A repeat perfusion was conducted on the ward employing gemcitabine (1000 mg/m²) diluted in 2000 mL/m² of normal saline. Both thermal parameters and procedure length replicated the intraoperative delivery.
Step 3 (Postoperative day 4): A terminal 40-minute perfusion using warmed normal saline (2000 mL/m²) was executed as a final peritoneal washout.
Patient well-being during perfusion was safeguarded through uninterrupted monitoring of core temperature, electrocardiographic tracing, and hemodynamic status. Intra-abdominal temperature was corroborated using thermistor probes affixed to both inflow and outflow tubing to verify consistent maintenance of the designated thermal window.

Postoperative management and adjuvant chemotherapy

All participants were managed with a standardized postoperative care pathway. Within an 8-week window from the operation, subjects in both cohorts began a systemic adjuvant chemotherapy course combining gemcitabine and capecitabine, consistent with institutional policy.

Data collection and follow-up

Data points were recorded encompassing patient demographics, preoperative clinical profile, intraoperative details, and postoperative events. Postoperative adverse events were recorded and stratified according to the Clavien-Dindo classification [14]. Postoperative pancreatic fistula (POPF) was defined and graded according to the International Study Group on Pancreatic Surgery (ISGPS) 2016 framework [15].
Participant surveillance occurred at 3-month intervals during the initial 2-year period and at 6-month intervals thereafter, continuing until July 2024 or until death. Follow-up examinations comprised physical assessment, measurement of the serum tumor marker CA19-9, and contrast-enhanced computed tomography (CT) of the chest and abdomen. Surveillance was carried out in accordance with a uniform institutional protocol applied to all postoperative pancreatic cancer patients, independent of treatment group assignment. This protocol mandated contrast-enhanced CT imaging of the chest and abdomen every 3–4 months during the first 2 years post-surgery, then every 6 months thereafter. All radiological studies were independently interpreted by two senior radiologists who were masked to the treatment condition. For ambiguous findings, repeat imaging after a 4–6 week interval or PET-CT scanning was recommended to substantiate or exclude recurrent disease. Recurrence was determined by radiological demonstration of novel lesions on contrast-enhanced CT, complemented by biopsy confirmation wherever clinically feasible. Locoregional recurrence was specified as disease reappearance at the surgical margin bed, anastomotic junctions, peritoneal linings (visceral or parietal peritoneum, omentum, and mesentery), or within regional lymph node basins (including peripancreatic, superior mesenteric, and para-aortic nodes

corresponding to AJCC 8th edition nodal designations). Overall survival (OS) was computed from the operative date until death from any cause.

Statistical analysis

All data processing and statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous parameters were summarized as mean ± standard deviation (SD) or median (interquartile range, IQR), and group comparisons were performed using the Student's t-test or the Mann-Whitney U test, depending on the data distribution. Categorical parameters were expressed as frequencies (percentages) and contrasted via the Chi-square test or Fisher's exact test. Standardized mean differences (SMDs) were calculated to verify baseline comparability, with an SMD below 0.2 serving as the benchmark for adequate matching. Survival probabilities were estimated using the Kaplan-Meier method and evaluated statistically using the log-rank test. A multivariate Cox proportional hazards regression framework was constructed to isolate factors independently predictive of OS. The choice of covariates for the multivariable model was informed by both clinical judgment and univariate testing results. More precisely, variables with P-values < 0.10 on univariate screening were candidates for inclusion alongside the principal treatment assignment (LPD+HIPEC versus LPD), yielding a parsimonious model that adjusts for salient confounders while limiting overfitting. The proportional hazards supposition underlying the Cox model was verified by analyzing Schoenfeld residuals, which disclosed no significant departures for any of the model covariates ($P > 0.05$ for each). Hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated. A two-sided P-value falling below 0.05 was interpreted as statistically meaningful. The 109 individuals incorporated in the definitive analysis had no missing observations for either the primary or the secondary endpoints.

Results and Discussion

Patient characteristics

In total, 109 individuals met the entry criteria, with 55 in the LPD+HIPEC cohort and 54 in the LPD-only cohort. The foundational demographic and clinical attributes showed strong concordance between the two study arms, with no meaningful discrepancies in age, sex, BMI, concurrent illnesses, or preoperative CA19–9 titers **(Table 1).** Critically, influential oncologic and surgical determinants with prognostic weight—namely, preoperative tumor dimensions, ECOG performance status, pathological T/N classification, and surgical margin positivity—were also evenly distributed across the cohorts **(Table 2).** This satisfactory alignment was further corroborated by the SMD values, which each registered well below 0.2.

Table 1. Side-by-side summary of demographic and clinical attributes across study arms.

Variable	SMD	P-value	Statistical test	LPD alone (n = 54)	LPD + HIPEC (n = 55)
Age (years), mean ± SD	0.116	0.548	t = -0.603	60.89 ± 9.07	61.82 ± 6.90
Sex distribution, n (%)	0.207	0.275	$\chi^2 = 1.194$		
Male				35 (64.8)	30 (54.5)
Female				19 (35.2)	25 (45.5)
Body mass index (kg/m²), mean ± SD	0.279	0.146	t = -1.464	23.42 ± 3.27	24.26 ± 2.72
Serum albumin level (g/L), mean ± SD	0.113	0.554	t = -0.594	38.57 ± 4.33	39.02 ± 3.50
Preoperative biliary drainage, n (%)	0.141	0.455	$\chi^2 = 0.559$	16 (29.6)	20 (36.4)
Comorbid conditions, n (%)					
Hypertension	0.169	0.382	$\chi^2 = 0.764$	21 (38.9)	17 (30.9)
Diabetes mellitus	0.245	0.208	$\chi^2 = 1.582$	8 (14.8)	4 (7.3)
Coronary artery disease	0.264	0.206	*	4 (7.4)	1 (1.8)
Preoperative CA19-9 (U/mL), median (IQR)	0.188	0.225	Z = -1.212	44.7 (20.5, 135.8)	60.7 (25.1, 150.3)

LPD, Laparoscopic Pancreaticoduodenectomy; HIPEC, Hyperthermic Intraperitoneal Chemotherapy; SD, Standard Deviation; BMI, Body Mass Index; IQR, Interquartile Range; SMD, Standardized Mean Difference. An SMD < 0.2 was deemed indicative of strong comparability between the two arms.

Fisher's exact test.

Table 2. Side-by-side summary of oncologic and pathological attributes.

Variable	SMD	P-value	Statistical test	LPD alone (n = 54)	LPD + HIPEC (n = 55)
ECOG performance status, n (%)	0.052	0.631	$\chi^2 = 0.231$		
0				38 (70.4)	40 (72.7)
1				16 (29.6)	15 (27.3)
Tumor size on pathological assessment (cm), mean ± SD	0.198	0.327	t = 0.985	3.0 ± 1.1	2.8 ± 0.9
Pathological T stage (AJCC 8th edition), n (%)	0.098	0.646	$\chi^2 = 0.875$		
T1				10 (18.5)	11 (20.0)
T2				31 (57.4)	29 (52.7)
T3				13 (24.1)	15 (27.3)
Pathological nodal status (AJCC 8th edition), n (%)	0.195	0.798	$\chi^2 = 0.452$		
N0				27 (50.0)	23 (41.8)
N1				20 (37.0)	28 (50.9)
N2				7 (13.0)	4 (7.3)
Resection margin status, n (%)	0.059	0.751	*		
R0 (margin-negative)				45 (83.3)	47 (85.5)
R1 (margin-positive)				9 (16.7)	8 (14.5)
Lymphovascular invasion, n (%)	0.126	0.511	$\chi^2 = 0.432$	24 (44.4)	21 (38.2)
Perineural invasion, n (%)	0.089	0.632	$\chi^2 = 0.229$	32 (59.3)	35 (63.6)

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; SMD, Standardized Mean Difference. An SMD < 0.2 was deemed indicative of strong comparability between the two arms.
Fisher's exact test.

Intraoperative and postoperative outcomes

All 109 LPD operations were completed laparoscopically, without any conversions to an open technique. The intraoperative details and postoperative courses are systematically presented in **Table 3**. Neither the mean surgical time nor the median intraoperative blood loss differed appreciably between the cohorts. An itemized inventory of postoperative morbidities, organized according to the Clavien-Dindo grading framework, is presented in **Table 4.** The aggregate incidence of postoperative adverse events remained roughly equivalent. Of particular note, the frequency of clinically meaningful POPF (Grade B/C) did not reach the threshold for statistical significance (5.5% in LPD+HIPEC vs. 9.3% in LPD; P = 0.489). Likewise, the proportion of high-grade morbidity (Clavien-Dindo grade ≥ III) was comparable (5.5% vs. 5.6%; P = 1.000). The two in-hospital deaths documented within the LPD+HIPEC cohort consisted of a 72-year-old man with a background of diabetes and hypertension who died from sepsis arising secondary to a Grade C pancreatic fistula, and a 68-year-old man with coronary artery disease who sustained a catastrophic postoperative bleed. Both cases shared a borderline preoperative performance status (ECOG 1) and mild hypoalbuminemia. The LPD-only cohort had no in-hospital deaths. Participants in the LPD+HIPEC arm exhibited a significantly elevated peak body temperature on the fifth postoperative day (38.28 ± 0.70 °C vs. 37.77 ± 0.51 °C; P < 0.001), consistent with the systemic inflammatory cascade elicited by hyperthermic perfusion. Markers of systemic inflammation underwent a transient upswing in the LPD+HIPEC arm, which registered significantly higher maximal C-reactive protein readings (185 ± 42 mg/L vs. 132 ± 35 mg/L, P < 0.001) and leukocyte counts (14.5 ± 3.1 x10⁹/L vs. 11.8 ± 2.5 x10⁹/L, P < 0.001) relative to the LPD arm. In typical cases, these laboratory derangements resolved within 5–7 days. Other self-limiting side effects linked to HIPEC were minimal.

Table 3. Comparative account of intraoperative and overarching postoperative outcomes.

Parameter	P-value	Statistical Test	LPD Alone (n = 54)	LPD + HIPEC (n = 55)
Operative duration (min), mean ± SD	0.503	t = 0.672	326.78 ± 51.13	319.85 ± 56.20
Estimated intraoperative blood loss (mL), median (IQR)	0.556	Z = -0.588	300 (200, 400)	300 (200, 500)

Peak body temperature on postoperative day 5 (°C), mean ± SD	<0.001	t = -4.290	37.77 ± 0.51	38.28 ± 0.70
Length of postoperative hospitalization (days), median (IQR)	0.064	Z = -1.852	13 (10, 16)	14 (11, 19)

POD, Postoperative Day.

Table 4. Detailed postoperative morbidity tabulated per the Clavien-Dindo classification.

Adverse event category	P-value	LPD Alone (n = 54), n (%)	LPD + HIPEC (n = 55), n (%)
Grade I complications			
Postoperative ileus (resolved spontaneously)	0.748	4 (7.4)	5 (9.1)
Grade II complications (pharmacologic treatment required)			
Urinary tract infection	0.679	2 (3.7)	3 (5.5)
Superficial surgical site infection	0.615	1 (1.9)	2 (3.6)
Grade IIIa (intervention without general anesthesia)			
Percutaneous drainage of an intra-abdominal collection	1.000	1 (1.9)	1 (1.8)
Grade IIIb (intervention under general anesthesia)			
Reoperation due to postoperative bleeding	1.000	1 (1.9)	1 (1.8)
Reoperation for anastomotic leakage	0.495	1 (1.9)	0 (0)
Grade IVa (single-organ dysfunction)	0.495	1 (1.9)	0 (0)
Grade V (in-hospital mortality)	0.242	0 (0)	2 (3.6)
Any postoperative complication (all grades)	0.676	11 (20.4)	13 (23.6)
Severe complications (Clavien–Dindo ≥ III)	0.748	4 (7.4)	5 (9.1)

Values rendered in bold signify statistical significance (P < 0.05).

Adjuvant therapy and follow-up

Specifics regarding the delivery of adjuvant chemotherapy are outlined in **Table 5.** The share of participants who initiated and completed the prescribed adjuvant regimen was nearly identical between the LPD+HIPEC and LPD cohorts (85.5% vs. 83.3%, P = 0.748), suggesting that the addition of HIPEC did not compromise tolerance to subsequent systemic treatment. The median length of surveillance across the entire study population was 15 months (spanning 1–36 months). The median surveillance period extended further in the LPD+HIPEC cohort (18 months) than in the LPD cohort (12 months).

Table 5. Comparative account of postoperative adjuvant chemotherapy delivery.

Variable	P-value	Statistical Test	LPD Alone (n = 54)	LPD + HIPEC (n = 55)
Time to initiation of adjuvant therapy (weeks), mean ± SD	0.408	t = -0.831	5.9 ± 1.3	6.1 ± 1.2
Patients who started adjuvant therapy, n (%)	1.000	*	50 (92.6)	51 (92.7)
Patients completing planned adjuvant therapy, n (%)	0.748	$\chi^2 = 0.103$	45 (83.3)	47 (85.5)
Reasons for treatment discontinuation, n				
Toxicity or intolerance			4	3
Patient refusal or other causes			1	1

Fisher's exact test.

Recurrence and survival outcomes

Patterns of disease relapse are consolidated in **Table 6**. At the time of last follow-up, the LPD+HIPEC arm demonstrated a strikingly lower incidence of locoregional disease recurrence compared with the LPD arm (14.6% vs. 31.5%, P = 0.035). When dissecting the locoregional recurrence category, nodal failure was identified in 9 subjects (16.7%) assigned to the LPD arm and in 4 subjects (7.3%) assigned to the LPD+HIPEC arm **(Table 6).**

The frequencies of metastatic spread to the liver or lungs did not diverge meaningfully between the two study arms.

Table 6. Comparative account of postoperative surveillance and recurrence distributions.

Variable	P-value	Test Statistic	LPD Alone (n = 54)	LPD + HIPEC (n = 55)
Postoperative CA19-9 (U/mL), median (IQR)	0.911	Z = -1.112	29.54 (13.71, 39.72)	29.16 (11.62, 44.53)
Recurrence patterns, n (%)				
Locoregional recurrence (overall)	0.035	$\chi^2 = 4.422$	17 (31.5)	8 (14.6)
Nodal recurrence (subset of locoregional)	0.141	*	9 (16.7)	4 (7.3)
Liver metastasis	0.513	$\chi^2 = 0.429$	10 (18.5)	13 (23.6)
Lung metastasis	0.527	$\chi^2 = 0.401$	4 (7.4)	6 (10.9)

CA19-9 level obtained at the 3-month postoperative time point.
Fisher's exact test.

The Kaplan-Meier survival analysis highlighted a significant advantage for the LPD+HIPEC arm **(Figure 3).** The median OS was 27 months (95% CI, 24.1–29.9 months) among those receiving LPD+HIPEC, compared with 23 months (95% CI, 20.5–25.5 months) among those receiving LPD alone (log-rank P = 0.045). Landmark OS probabilities at 1, 2, and 3 years for the LPD+HIPEC arm were estimated at 84.9%, 58.2%, and 26.3%, respectively. For the LPD arm, the parallel estimates stood at 74.6%, 40.0%, and 15.0%.

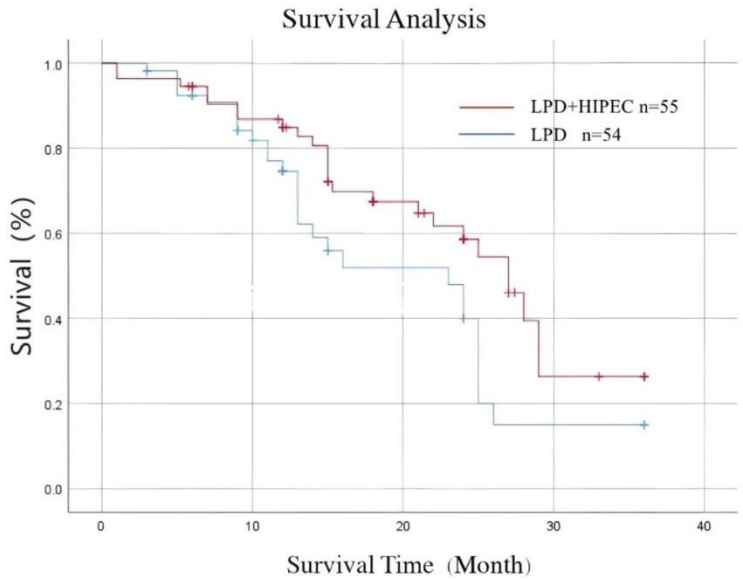

Figure 3. Kaplan-Meier survival plots for overall survival. Head-to-head depiction of overall survival between the LPD+HIPEC arm (n = 55) and the LPD-only arm (n = 54). The median overall survival equaled 27 months in the LPD+HIPEC arm and 23 months in the LPD arm (Log-rank test, P = 0.045).

When evaluated through multivariate Cox regression, three variables were found to independently confer a survival advantage: allocation to the LPD+HIPEC arm (HR 0.58, 95% CI 0.35–0.97, P = 0.038), pathologically confirmed node-negative disease (HR 0.45, 95% CI 0.26–0.78, P = 0.004), and the achievement of a margin-negative (R0) excision (HR 0.51, 95% CI 0.27–0.95, P = 0.034) **(Table 7).**

Table 7. Multivariate Cox regression delineating independent determinants of overall survival.

Variable	P-value	95% confidence interval (CI)	Hazard ratio (HR)
Treatment group (LPD+HIPEC vs. LPD)	0.038	0.35 – 0.97	0.58
Age (≥ 65 vs. < 65 years)	0.471	0.72 – 2.03	1.21

Pathological T stage (T3 vs. T1–T2)	0.105	0.91 – 2.64	1.55
Pathological nodal status (N+ vs. N0)	0.004	1.30 – 3.76	2.21
Resection margin status (R1 vs. R0)	0.034	1.03 – 3.58	1.92
Lymphovascular invasion (present vs. absent)	0.138	0.88 – 2.49	1.48

Bold formatting marks statistically significant associations ($P < 0.05$).

This two-center retrospective investigation set out to determine whether supplementing standard LPD with an adapted perioperative HIPEC protocol would influence outcomes for resectable pancreatic head adenocarcinoma. The key takeaway is that patients receiving the dual-modality approach experienced a meaningful extension of overall survival and a marked reduction in locoregional disease recurrence compared with those treated with LPD alone. Reassuringly, these oncologic improvements were not accompanied by a discernible rise in serious postoperative adverse events.

The scientific premise supporting intraperitoneal chemotherapy in pancreatic cancer rests on firm ground. The steep propensity for peritoneal tumor reseeding after radical surgery underscores the pressing need for an effective cavity-directed treatment. Our observations reinforce this reasoning, documenting a greater than halving of locoregional relapse rates among subjects who received HIPEC. This result implies that perioperative instillation of heated chemotherapy can effectively eliminate microscopic tumor deposits dislodged intraoperatively, thereby delaying or preventing peritoneal failure. These data echo prior reports that similarly credit intraperitoneal chemotherapy with improved local disease suppression [10, 16].

A distinguishing feature of the present work is the unconventional, multi-step HIPEC schedule. Classic HIPEC delivers a single intraoperative dose of cytotoxics. Our approach, by contrast, commenced with an intraoperative hyperthermic saline lavage and deferred the gemcitabine instillation until the second postoperative day. In its design, this schedule bridges classical HIPEC and the principles of early postoperative intraperitoneal chemotherapy (EPIC). The initial intraoperative heated lavage mechanically flushes the abdominal compartment, while the thermal component can induce cancer cell apoptosis and enhance the tissue penetration of any subsequently delivered drug [17, 18]. Holding the chemotherapeutic agent back until POD 2 provides a window for hemodynamic convalescence following the stress of major resection, potentially enhancing tolerability—a concept lent support by early EPIC experiences in other malignancies [19, 20]. Crucially, this timing still precedes the phase of dense postoperative adhesion formation, which, if established, would impede uniform drug distribution and curtail therapeutic reach. The choice of gemcitabine rested on its proven clinical activity in pancreatic adenocarcinoma and preclinical evidence of a supra-additive cell-killing effect when combined with thermal stress [21, 22].

The feasibility of pairing HIPEC with a technically demanding reconstruction such as LPD, especially regarding anastomotic healing, represents a legitimate safety question. Postoperative pancreatic fistula remains among the most severe procedure-specific complications. In our series, the emergence of clinically significant POPF was not statistically more frequent in the LPD+HIPEC cohort, nor did we observe a surge in other major morbidities. This suggests that, within the high-volume surgical practice ecosystem, our modified regimen is both technically deliverable and acceptably safe. The extensive institutional proficiency—over 2,000 LPD cases completed since 2013—likely contributed to the modest baseline event rates. Nevertheless, the two postoperative deaths cataloged in the HIPEC arm, although not reaching formal statistical significance at this sample size, constitute a stark warning regarding the regimen's potential toxicity and must factor into any risk-benefit deliberation. This reality underscores the need for rigorous patient vetting when considering such an intensive multimodal strategy.

Our findings are broadly congruent with limited earlier data on HIPEC administered during open pancreatic surgery. For example, Tentes *et al*. [16] described encouraging survival signals associated with intraoperative HIPEC during pancreatoduodenectomy. What sets our report apart is its exclusive focus on a laparoscopic approach combined with a delayed, multi-component chemotherapy schedule, an innovation that may possess a distinct safety and efficacy character. The primary endpoint—a 4-month improvement in median OS that persisted as an independent predictor in the multivariable model—represents a clinically meaningful gain in a disease notorious for its therapeutic recalcitrance. Even so, this survival signal must be weighed against the study's inherent limitations.

The level of statistical certainty surrounding the primary endpoint, overall survival, was modest ($P = 0.045$) and warrants restrained interpretation. This marginal significance likely reflects the limited statistical power due to a relatively small cohort. A substantially larger study population might have yielded a more emphatic separation.

Nonetheless, the absolute 4-month prolongation of median OS, in the context of a hazard ratio of 0.58 on multivariable testing, translates to a clinically relevant effect magnitude for this aggressive cancer, where hard-fought survival gains are typically measured in weeks rather than years [23]. The survival advantage is further buttressed by the pronounced and statistically robust reduction in locoregional failure—the mechanistic target endpoint against which a cavity-directed intervention such as HIPEC would be expected to demonstrate activity [24]. Accordingly, although the survival P-value hovers near the conventional threshold, the triangulation of survival and recurrence data suggests a genuine biological effect that merits further rigorous exploration.

Limitations

Several important constraints encumber this work. First and most critically, its retrospective, non-randomized structure leaves it exposed to selection bias. Although the two groups showed close alignment across numerous demographic and prognostic tumor characteristics, and although our multivariable model adjusted for identified confounders, the influence of unmeasured variables cannot be ruled out. Treatment allocation relied on a shared decision-making framework that could have subtly steered heartier patients toward the HIPEC arm. We deliberated the application of propensity score matching (PSM) as a supplementary strategy to address potential selection bias. However, given the limited overall enrollment, deploying PSM would have markedly reduced analytic power and risked introducing instability into the effect estimates. Thus, we elected to rely on multivariate Cox regression for confounder control while transparently acknowledging its limitations. Second, the cohort's modest size curtails the statistical power to detect smaller between-group differences in complication rates and cautions against interpreting P-values of borderline significance. Third, a disparity in median follow-up length existed between the arms, with shorter surveillance in the control group. This asymmetry could, in theory, lead to an undercount of late recurrences among LPD-only recipients. However, the early and sustained divergence of the Kaplan-Meier curves provides strong evidence of a genuine treatment-related effect. Furthermore, the dependence on radiological rather than uniformly biopsy-confirmed recurrence introduces the possibility of diagnostic misclassification. Finally, these data emanate from a single institutional experience with a non-standardized HIPEC protocol, and their applicability to centers with differing treatment regimens or lower operative throughput remains uncertain.

Future directions

Drawing on the current findings, we surmise that the best-suited candidates for this demanding multimodal regimen are those under 70 years of age who exhibit an excellent performance status (ECOG 0), carry a low comorbid disease burden, and have preserved nutritional parameters. Moreover, patients whose tumors harbor biological features portending a high risk of peritoneal spread—such as T3 classification or malignant peritoneal washings—may experience the greatest incremental benefit. Our immediate research trajectory includes a prospective Phase II study designed to substantiate the safety profile and therapeutic impact of this protocol within a more stringently defined patient population, leveraging biomarkers such as circulating tumor DNA (ctDNA) to refine risk stratification and dynamically monitor treatment response.

Conclusion

In summary, this dual-center retrospective cohort analysis suggests that LPD integrated with a modified perioperative HIPEC schedule is associated with superior overall survival and reduced locoregional recurrence burden in patients undergoing resection for pancreatic head adenocarcinoma, while maintaining an acceptable toxicity profile in a high-volume practice setting. Although these results are encouraging, they are best viewed as hypothesis-generating groundwork. Definitive validation through rigorously structured, multi-institutional randomized controlled studies is indispensable before this combined-modality approach can be endorsed as a standard-of-care option in pancreatic cancer management.

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