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# Locoregional Therapy plus First-Line Systemic Therapy in Unresectable Locally Advanced Intrahepatic Cholangiocarcinoma

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**Research Article**

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# Abstract

### Background and purpose

Whether locoregional consolidation therapy (LCT) adds benefit to first-line systemic therapy in unresectable, locally advanced intrahepatic cholangiocarcinoma (ICC) is unknown.

### Methods

In this single-centre retrospective cohort (2017–2025), 156 patients receiving gemcitabine-based chemotherapy plus a PD-1/PD-L1 inhibitor, with or without a tyrosine kinase inhibitor, were grouped by concomitant LCT (n = 61; radiotherapy 34, non-radiotherapy 27) or systemic therapy alone (n = 95). Stabilised inverse probability of treatment weighting (sIPTW) balanced 13 covariates; weighted Cox models and sensitivity analyses were used.

### Results

At a median follow-up of 37.0 months, after stabilised inverse probability of treatment weighting, LCT was associated with longer progression-free survival (PFS; 17.35 vs 8.67 months; hazard ratio 0.43, 95% confidence interval 0.29–0.62; P < 0.001) and overall survival (OS; 28.91 vs 20.60 months; HR 0.59, 95% CI 0.39–0.91; P = 0.017). Across analytic approaches, hazard ratios were 0.41–0.55 for PFS and 0.49–0.71 for OS. E-values were 3.00 (PFS) and 2.23 (OS). Growth of existing intrahepatic lesions as the first progression was less frequent after radiotherapy-based consolidation (11.8% vs 41.1%; P = 0.002) but not after non-radiotherapy LCT (48.1% vs 41.1%; P = 0.52). Grade ≥ 3 lymphopenia (63.9% vs 33.7%), any-grade thrombocytopenia (82.0% vs 62.1%) and any-grade gastrointestinal ulceration (14.8% vs 2.1%) were more frequent with LCT, the ulcer excess being confined to radiotherapy-based consolidation (20.6% vs 2.1%; P = 0.001).

### Conclusion

In unresectable ICC treated with first-line systemic therapy, consolidative LCT, and radiotherapy-based consolidation in particular, was associated with longer PFS and OS and fewer intrahepatic failures. Randomised confirmation is required.


# Introduction

Intrahepatic cholangiocarcinoma (ICC) accounts for 10–15% of primary liver cancers, and its incidence has risen in both Western and East Asian populations [1, 2]. In East Asia, chronic hepatitis B virus infection and hepatolithiasis account for a substantial share of this burden [3]. Most patients present with locally advanced or metastatic disease that precludes resection, and their prognosis remains poor [4].

Gemcitabine plus cisplatin has been the reference first-line regimen for advanced biliary tract cancer since the ABC-02 trial [5]. Two phase 3 trials established chemoimmunotherapy as the new standard: TOPAZ-1 added durvalumab [6] and KEYNOTE-966 added pembrolizumab [7] to gemcitabine and cisplatin, each significantly prolonging overall survival (OS). Investigator-initiated phase 2 studies from our centre have reported encouraging activity for gemcitabine-based triplet regimens combining a PD-1/PD-L1 inhibitor with lenvatinib, including toripalimab plus GEMOX [8, 9], tislelizumab-based conversion therapy [10], and tislelizumab plus ociperlimab [11]; sintilimab with gemcitabine and cisplatin has shown similar promise [12]. Real-world data confirm these regimens are now widely used [13], and a systematic review of checkpoint inhibition in advanced cholangiocarcinoma concludes that the benefit, although real, remains modest [14]. Nevertheless, median PFS with first-line chemoimmunotherapy remains under one year, and most patients progress within the liver, which provides the rationale for consolidative intensification.

Locoregional therapies are well established in the management of liver-confined ICC. Ablative radiotherapy (RT) doses prolong survival in inoperable disease [15], and hypofractionated proton or photon RT achieves durable local control [16, 17]. Hepatic arterial infusion chemotherapy (HAIC) and transarterial radioembolisation improve outcomes when added to systemic treatment [18, 19, 20]. Preclinical work further suggests that irradiation may prime antitumour immunity and synergise with checkpoint blockade [21, 22]. However, the published evidence consists of single-modality series that were small, mostly unadjusted, and performed before chemoimmunotherapy became standard, and we are not aware of a study that has compared locoregional consolidation with systemic therapy alone within a uniformly treated chemoimmunotherapy cohort. We therefore compared PFS and OS between patients who received LCT during first-line chemoimmunotherapy and those given systemic therapy alone.

## Materials and Methods

# Study design and patients

This single-centre retrospective cohort study included 156 consecutive patients with histologically confirmed, unresectable, locally advanced ICC treated at Zhongshan Hospital, Fudan University, Shanghai, China, between January 2017 and June 2025. Eligibility required first-line gemcitabine-based chemotherapy (gemcitabine-cisplatin or GEMOX) combined with a PD-1/PD-L1 inhibitor, with or without a tyrosine kinase inhibitor, for at least three cycles; complete baseline data including Child-Pugh class, Eastern Cooperative Oncology Group (ECOG) performance status and tumour-node-metastasis (TNM) stage; and at least one post-baseline efficacy assessment. Patients with mixed hepatocholangiocarcinoma, other prior or concurrent malignancies, central nervous system metastases, or fewer than three months of follow-up without an event were excluded. All consecutive eligible patients were included; no sample-size calculation was performed. The study was approved by the Institutional Ethics Committee of Zhongshan Hospital (B2026-405) and conducted in accordance with the

Declaration of Helsinki [23]; informed consent was waived because of the retrospective design. Reporting follows the STROBE statement.

## Treatment and grouping

Patients were grouped by whether they received concomitant LCT during first-line systemic treatment: LCT plus systemic therapy (n = 61) or systemic therapy alone (n = 95). The LCT group comprised 34 patients treated with RT (external-beam or stereotactic body RT) and 27 treated with non-RT modalities (ablation, transarterial chemoembolisation [TACE], or HAIC). Treatment decisions were made at a multidisciplinary tumour board and were not protocol-driven. Follow-up comprised contrast-enhanced computed tomography or magnetic resonance imaging and serum tumour-marker assessment every 6–12 weeks during systemic therapy and every 2–3 months thereafter, until death or the data cutoff (July 2026); patients lost to follow-up were censored at the date of last contact. Throughout, this first-line backbone (gemcitabine-based chemotherapy plus a PD-1/PD-L1 inhibitor, with or without a tyrosine kinase inhibitor) is referred to as chemoimmunotherapy, and the comparator as systemic therapy alone.

## Endpoints and assessments

Time zero was the earliest recorded start of first-line treatment: the first chemotherapy cycle in 120 patients, and an earlier immunotherapy, targeted-therapy or locoregional-treatment date in the remaining 36 (median 0.5 months earlier, maximum 8.1 months; in 21 of these the locoregional procedure preceded the first cycle), so that no treated person-time was excluded. The primary endpoint was PFS, defined as the time from time zero to documented progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [24] or death from any cause, whichever occurred first. The secondary endpoint was OS, defined as the time from time zero to death from any cause. Patients alive and progression-free at the last follow-up were censored at the last imaging assessment (PFS) or the last follow-up (OS). For the 22 patients who died without documented protocol-defined PD, death was treated as the PFS event and dated accordingly; PFS end dates were otherwise assigned hierarchically as the date of documented PD or the date of the last imaging assessment. Median follow-up was estimated by the reverse Kaplan-Meier method [25]. Sites of first RECIST-defined progression were recorded. Treatment-related adverse events during first-line systemic therapy were graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

# Statistical analysis

The primary analysis used stabilised inverse probability of treatment weighting (sIPTW). Propensity scores came from a multivariable logistic regression model including 13 pre-treatment covariates: age, sex, ECOG performance status, TNM stage (Tis-IIIA vs IIIB), number of intrahepatic lesions (< 3 vs ≥ 3), portal vein invasion, primary tumour diameter (log-transformed), hepatitis B surface antigen (HBsAg) status, disease status (initially unresectable vs recurrent), chemotherapy regimen, log CA19-9,

concomitant lenvatinib, and PD-L1-class checkpoint inhibitor. Weights were stabilised and truncated at 1/3 and 3 (three patients truncated). Covariate balance was assessed by the standardised mean difference (SMD), with |SMD| < 0.10 indicating adequate balance. The two propensity-score distributions overlapped substantially (Online Resource 1). Treatment effects were estimated by sIPTW-weighted Cox proportional hazards models with robust sandwich variance estimators. Baseline characteristics were compared by the chi-square test, with Yates' continuity correction, or the Fisher exact test, and by the Mann-Whitney U test, as appropriate.

Sensitivity analyses comprised multivariable Cox regression adjusted for all 13 covariates; 1:1 and 1:2 propensity-score matching (nearest neighbour on the logit propensity score, without replacement), retaining 122 and 143 patients; landmark analyses at 3 and 6 months; a common-origin analysis in which time zero was reset to the first chemotherapy cycle for all 156 patients; a start-time analysis in which the survival clock for LCT recipients began at the date of LCT; and complete-case analysis. A time-varying Cox model did not converge because LCT was delivered very early in almost all recipients, producing near-complete separation from survival time. Robustness to unmeasured confounding was quantified by the E-value, computed on the risk-ratio scale after square-root transformation of the hazard ratio because both endpoints were common. Restricted mean survival time (RMST) at 24 months was calculated per arm as a descriptive summary. Pre-specified subgroup analyses estimated sIPTW-weighted hazard ratios (HRs) within six subgrouping variables using the full-cohort weights; interaction P values are reported without adjustment for multiplicity. Analyses used Python 3.12 (lifelines 0.30.3), and two-sided P < 0.05 was considered significant.

## Results

# Patients

Of 6,568 patients screened, 1,173 had histologically confirmed ICC, 578 had unresectable locally advanced disease without distant metastasis, and 278 received gemcitabine-based chemotherapy plus a PD-1/PD-L1 inhibitor with or without lenvatinib. After exclusion of 122 patients who did not meet the remaining criteria, 156 patients were analysed (61 LCT plus systemic therapy, 95 systemic therapy alone; Fig. 1).

## Baseline characteristics

Median age was 60.3 years (interquartile range [IQR] 53.3–68.6); 90 patients (57.7%) were male, 43 (27.6%) were HBsAg-positive, and 97 (62.2%) had TNM stage IIIB disease (Table 1). Before weighting, patients receiving LCT were older (median 62.5 vs 59.7 years) and less often had stage IIIB disease (47.5% vs 71.6%; |SMD| = 0.502) or three or more intrahepatic lesions (34.4% vs 54.7%; |SMD| = 0.415), whereas portal vein invasion was more frequent (73.8% vs 60.0%) and primary tumours were smaller (60.0 vs 66.4 mm). After sIPTW all 13 covariates met the balance criterion, the largest residual

imbalance being log-transformed tumour diameter (|SMD| = 0.096; Online Resource 2). RT was the most frequent LCT modality (34 patients, 55.7%), followed by TACE (21, 34.4%), ablation (12, 19.7%) and HAIC (7, 11.5%); two patients (3.3%) received other modalities. Modalities were not mutually exclusive: 46 patients (75.4%) received one and 15 (24.6%) two. First-line regimens were similar between groups (GEMOX 85.2% vs 89.5%, P = 0.591; median 6 chemotherapy cycles [IQR 5–8] in both; PD-L1-class inhibitor 14.8% vs 12.6%; lenvatinib 86.9% vs 80.0%, P = 0.372; Table 1).

Table 1
Baseline characteristics of the study cohort by treatment group

| Characteristic | LCT + systemic (n = 61) | Systemic alone (n = 95) | SMD before | SMD after | P |
|---|---|---|---|---|---|
| Age, years | 62.5 (53.7–70.7) | 59.7 (53.0–67.1) | 0.256 | 0.038 | 0.099 |
| Female sex | 28 (45.9) | 38 (40.0) | 0.119 | -0.006 | 0.574 |
| ECOG performance status ≥ 1 | 30 (49.2) | 59 (62.1) | -0.261 | -0.033 | 0.154 |
| TNM stage IIIB | 29 (47.5) | 68 (71.6) | -0.502 | -0.002 | 0.004 |
| Intrahepatic lesions ≥ 3 | 21 (34.4) | 52 (54.7) | -0.415 | 0.023 | 0.021 |
| Portal vein invasion | 45 (73.8) | 57 (60.0) | 0.294 | 0.018 | 0.111 |
| Primary tumour diameter, mm | 60.0 (40.0–85.0) | 66.4 (54.5–99.0) | -0.379 | -0.096 | 0.044 |
| log10 CA19-9, U/mL | 1.7 (1.2–2.4) | 1.8 (1.0–2.9) | -0.104 | -0.080 | 0.737 |
| HBsAg positive | 17 (27.9) | 26 (27.4) | 0.011 | -0.057 | 1.000 |
| Recurrent disease | 8 (13.1) | 6 (6.3) | 0.229 | 0.050 | 0.245 |
| GEMOX regimen | 52 (85.2) | 85 (89.5) | -0.127 | 0.032 | 0.591 |
| Concomitant lenvatinib | 53 (86.9) | 76 (80.0) | 0.185 | -0.046 | 0.372 |
| PD-L1-class checkpoint inhibitor | 9 (14.8) | 12 (12.6) | 0.061 | 0.022 | 0.890 |

Values are median (interquartile range) or n (%) of the observed cohort. SMD, standardised mean difference; LCT, locoregional consolidation therapy; ECOG, Eastern Cooperative Oncology Group; TNM, tumour-node-metastasis; CA19-9, carbohydrate antigen 19 − 9; HBsAg, hepatitis B surface antigen; GEMOX, gemcitabine-oxaliplatin. For tumour diameter the SMD is on the log scale and for CA19-9 on the log10 scale, matching the covariates used in the propensity model. P values are for the unadjusted comparison between the two groups ($\chi^2$ test with Yates' continuity correction for categorical variables, Mann-Whitney U test for continuous variables) and are therefore not a test of balance; balance was judged by the standardised mean difference. One missing ECOG record was assigned performance status 0, one missing CA19-9 value was imputed to 200 U/mL, and six not-tested HBsAg results were merged with the negative category, so all 13 covariates were complete.

## Survival

At a median follow-up of 37.0 months, 136 PFS events (46 LCT, 90 systemic) and 109 deaths (34, 75) had occurred. Median PFS was 17.35 months with LCT plus systemic therapy versus 8.67 months with systemic therapy alone (unadjusted HR 0.408, 95% CI 0.289–0.576; P < 0.001), unchanged after sIPTW (HR 0.426, 95% CI 0.294–0.617; P < 0.001; Fig. 2) and concordant across the four analytic approaches (HR 0.41–0.48; Fig. 3). Median OS was 29.41 versus 20.60 months (unadjusted HR 0.537, 95% CI 0.357–0.807; P = 0.003) and 28.91 versus 20.60 months after sIPTW (HR 0.592, 95% CI 0.385–0.910; P = 0.017; Fig. 2), again concordant across approaches (HR 0.54–0.59; Fig. 3).

The weighted PFS benefit was consistent for RT-based and non-RT consolidation (HR 0.33, 95% CI 0.22–0.50, weighted median 21.6 vs 8.7 months; and HR 0.56, 95% CI 0.36–0.87, 13.3 vs 8.7 months; Online Resource 3 and Online Resource 4), although the two modalities were not formally compared. OS estimates were less precise (RT HR 0.59, 95% CI 0.36–0.95, P = 0.031; non-RT HR 0.60, 95% CI 0.33–1.10, P = 0.098). PFS HRs across the 12 subgroups of the six pre-specified variables all lay below 1 (0.26–0.65) and 11 were nominally significant; only the number of chemotherapy cycles showed a nominally significant interaction (PFS P = 0.043; OS P = 0.047), with a lower HR below six cycles (0.26, 95% CI 0.13–0.54) than at six or more (0.48, 0.31–0.74) (Online Resource 5), although no interaction survived correction for the four tests performed per endpoint.

Sensitivity analyses were directionally consistent (PFS HR 0.41–0.55, significant throughout; OS 0.49–0.71; Fig. 3). OS remained significant after 1:2 matching (0.49), at 3- and 6-month landmark analyses (0.59 and 0.63) and in the complete-case analysis (0.57) (Online Resource 6). Anchoring time zero at the first chemotherapy cycle for all 156 patients, rather than at the earliest treatment date, gave HRs of 0.479 (95% CI 0.333–0.689) for PFS and 0.622 (0.400–0.969; P = 0.036) for OS, so the primary estimates do not depend on the follow-up accrued before the first cycle in 36 patients. Only the start-time analysis, in which the LCT clock begins at the locoregional procedure while the comparator remains on the systemic-therapy clock, was attenuated (HR 0.71, 95% CI 0.46–1.11; P = 0.13); because that analysis places the arms on different time scales, it is reported as a descriptive post-LCT summary rather than as a test of the primary estimate. E-values were 3.00 for PFS (2.14 for the confidence limit closest to the null) and 2.23 for OS (1.34). RMST at 24 months was 16.7 versus 10.3 months for PFS and 20.6 versus 17.9 months for OS. In the multivariable model, LCT remained associated with PFS (adjusted HR 0.424, 95% CI 0.287–0.627) and OS (0.568, 0.358–0.901); only log CA19-9 was independently associated with both endpoints (PFS 1.321, 95% CI 1.084–1.609; OS 1.531, 1.237–1.895).

# Response

Response was assessed at 3, 6, 9 and 12 months with the full cohort retained as the denominator, so patients without an assessment at a given landmark were not counted as responders (Online Resource 7). Objective response rates (18, 23, 26 and 19 of 61 with LCT versus 22, 28, 21 and 12 of 95 with systemic therapy alone) were 29.5%, 37.7%, 42.6% and 31.1% versus 23.2%, 29.5%, 22.1% and 12.6%, and

disease control rates (56, 52, 47 and 33 of 61 versus 84, 58, 32 and 18 of 95) were 91.8%, 85.2%, 77.0% and 54.1% versus 88.4%, 61.1%, 33.7% and 18.9%. These proportions are cross-sectional descriptions; no between-group tests were applied.

# Patterns of first progression

Patterns of first progression are shown in Fig. 4 and expressed as the proportion of all patients in each arm; progression was documented in 36 of 61 patients receiving LCT, 13 of 34 in the RT subgroup, 23 of 27 in the non-RT subgroup, and 78 of 95 receiving systemic therapy alone. Growth of existing intrahepatic lesions was less frequent after RT-based consolidation (11.8% vs 41.1%; P = 0.002) and, at the margin of significance, new intrahepatic lesions were also less frequent (17.6% vs 35.8%; P = 0.055). The corresponding estimates for the whole LCT cohort (27.9% vs 41.1%, P = 0.12; 27.9% vs 35.8%, P = 0.38) and for non-RT LCT (48.1% vs 41.1%, P = 0.52; 40.7% vs 35.8%, P = 0.66) showed no reduction. Extrahepatic patterns did not differ between arms (all P > 0.15). Failure modes were not mutually exclusive.

# Toxicity

Adverse events were graded in all 156 patients; percentages use all patients per arm as the denominator and the 24 events were compared without correction for multiple testing (Table 2). Any-grade cytopenias were near-universal (lymphopenia 98.4% vs 98.9%), but grade ≥ 3 lymphopenia was almost twice as frequent with LCT (63.9% vs 33.7%; P < 0.001). Thrombocytopenia was more frequent at any grade (82.0% vs 62.1%; P = 0.012) without an excess of grade ≥ 3 events (13.1% vs 15.8%). Gastrointestinal ulceration was more frequent with LCT (14.8% vs 2.1%; P = 0.004), a difference concentrated in the radiotherapy subgroup (20.6% vs 2.1%; P = 0.001) rather than in the non-radiotherapy subgroup (7.4% vs 2.1%; P = 0.21) and consistent with incidental irradiation of the stomach or duodenum; grade ≥ 3 ulceration and diarrhoea each occurred in 4.9% versus 0% (P = 0.058). Liver investigations diverged in opposite directions without reaching significance: grade ≥ 3 alanine aminotransferase (16.4% vs 8.4%) and aspartate aminotransferase (13.1% vs 6.3%) increases were more frequent with LCT, whereas grade ≥ 3 blood bilirubin increase was less frequent (6.6% vs 11.6%; all P > 0.15). Immune-related, vascular and other events, including hypothyroidism (49.2% vs 35.8%), did not differ (all P > 0.15).

Table 2
Treatment-related adverse events

| Adverse event | Any grade, LCT (%) | Any grade, systemic (%) | Grade ≥ 3, LCT (%) | Grade ≥ 3, systemic (%) | P, any grade | P, grade ≥ 3 |
|---|---|---|---|---|---|---|
| Leukopenia | 80.3 | 66.3 | 21.3 | 13.7 | 0.069 | 0.271 |
| Neutropenia | 65.6 | 64.2 | 24.6 | 20.0 | 1.000 | 0.553 |
| Lymphopenia | 98.4 | 98.9 | 63.9 | 33.7 | 1.000 | < 0.001 |
| Thrombocytopenia | 82.0 | 62.1 | 13.1 | 15.8 | 0.012 | 0.818 |
| Anaemia | 85.2 | 73.7 | 11.5 | 5.3 | 0.112 | 0.218 |
| Proteinuria | 9.8 | 4.2 | 4.9 | 2.1 | 0.191 | 0.380 |
| Hypothyroidism | 49.2 | 35.8 | 0.0 | 0.0 | 0.133 | 1.000 |
| Myocarditis | 3.3 | 5.3 | 1.6 | 2.1 | 0.706 | 1.000 |
| Pericardial effusion | 0.0 | 1.1 | 0.0 | 0.0 | 1.000 | 1.000 |
| Heart failure | 4.9 | 4.2 | 1.6 | 0.0 | 1.000 | 0.391 |
| Left ventricular systolic dysfunction | 0.0 | 0.0 | 0.0 | 0.0 | 1.000 | 1.000 |
| Hypertension | 16.4 | 16.8 | 6.6 | 8.4 | 1.000 | 0.766 |
| Rash | 19.7 | 21.1 | 11.5 | 10.5 | 1.000 | 1.000 |
| Hand-foot syndrome | 13.1 | 13.7 | 0.0 | 1.1 | 1.000 | 1.000 |
| Gastrointestinal ulcer | 14.8 | 2.1 | 4.9 | 0.0 | 0.004 | 0.058 |
| Pneumonitis | 3.3 | 4.2 | 1.6 | 0.0 | 1.000 | 0.391 |
| Nausea | 52.5 | 42.1 | 1.6 | 0.0 | 0.250 | 0.391 |
| Vomiting | 19.7 | 21.1 | 3.3 | 0.0 | 1.000 | 0.151 |
| Fever | 14.8 | 15.8 | 3.3 | 0.0 | 1.000 | 0.151 |
| Weakness | 52.5 | 43.2 | 3.3 | 2.1 | 0.324 | 0.644 |
| Diarrhoea | 18.0 | 15.8 | 4.9 | 0.0 | 0.826 | 0.058 |
| Alanine aminotransferase increase | 65.6 | 69.5 | 16.4 | 8.4 | 0.725 | 0.198 |

Values are the percentage of all patients in each arm (LCT plus systemic therapy, n = 61; systemic therapy alone, n = 95) and were compared by Fisher exact test without correction for multiple comparisons. Adverse events were graded by the Common Terminology Criteria for Adverse Events version 5.0 during first-line systemic therapy. LCT, locoregional consolidation therapy.

| Adverse event | Any grade, LCT (%) | Any grade, systemic (%) | Grade ≥ 3, LCT (%) | Grade ≥ 3, systemic (%) | P, any grade | P, grade ≥ 3 |
|---|---|---|---|---|---|---|
| Aspartate aminotransferase increase | 72.1 | 65.3 | 13.1 | 6.3 | 0.386 | 0.162 |
| Blood bilirubin increase | 42.6 | 31.6 | 6.6 | 11.6 | 0.175 | 0.407 |

Values are the percentage of all patients in each arm (LCT plus systemic therapy, n = 61; systemic therapy alone, n = 95) and were compared by Fisher exact test without correction for multiple comparisons. Adverse events were graded by the Common Terminology Criteria for Adverse Events version 5.0 during first-line systemic therapy. LCT, locoregional consolidation therapy.

# Discussion

In this cohort of patients with unresectable, locally advanced ICC receiving first-line chemoimmunotherapy, consolidative LCT was associated with an approximately twofold increase in median PFS (17.35 vs 8.67 months) and a clinically meaningful improvement in OS (28.91 vs 20.60 months; sIPTW HR 0.592, 95% CI 0.385–0.910). Point estimates remained below 1 across all sensitivity analyses, with E-values of 3.00 (PFS) and 2.23 (OS). The effect was not uniform across modalities: RT-based consolidation was associated with less intrahepatic failure, whereas non-RT modalities showed no clear reduction.

Our results extend the published experience with locoregional treatment in ICC in three ways. First, earlier series established a dose-response relation for RT [15] and durable local control with hypofractionated or proton RT [16, 17], but they predated effective systemic therapy and could not separate the effect of consolidation from that of patient selection. Second, HAIC and radioembolisation have improved outcomes when combined with chemotherapy [18, 19, 20], and contemporary reviews position arterial therapy within multimodal algorithms [26]; our data suggest that the incremental value of these modalities over modern chemoimmunotherapy may be smaller than their historical comparisons implied. Third, the failure-pattern analysis offers a mechanistic reading: RT delivers ablative doses to a defined volume and was associated with a fall in in-field intrahepatic progression from 41.1% to 11.8%, whereas TACE and HAIC act through perfusion-dependent delivery and delay rather than prevent intrahepatic progression. The immunomodulatory effects of irradiation described experimentally [21, 22] provide a further rationale for concurrent checkpoint blockade, although our design cannot isolate them.

These findings support a practical framework already implicit in multidisciplinary practice. For patients with oligo-intrahepatic disease amenable to target-volume delineation, consolidative RT can be discussed once a response to chemoimmunotherapy has been established; the toxicity profile in our cohort was consistent with the irradiated liver volume, with grade ≥ 3 lymphopenia, any-grade thrombocytopenia and gastrointestinal ulceration as the main excess events, and no excess of grade ≥ 3

hepatic or immune-related toxicity. For patients whose disease burden precludes RT planning, non-RT modalities remain an option but should not be expected to prevent intrahepatic failure. This position is consistent with the broader move towards conversion-oriented and multimodal strategies in biliary tract cancer [27, 28], and with ongoing trials combining arterial therapy with checkpoint inhibition [29].

Several limitations apply. The cohort came from a single high-volume Asian centre with a high prevalence of HBsAg positivity (27.6%) and was enriched for Child-Pugh class A disease, so the results may not transfer to other populations or to less RT-experienced centres. Treatment was not randomised, and although sIPTW balanced 13 covariates, the largest residual SMD was 0.096 for tumour diameter and unmeasured confounding cannot be excluded; the E-values indicate that an unmeasured confounder would need associations of 3.00 (PFS) and 2.23 (OS) with both treatment and outcome to explain the estimates away. Subgroup analyses reused the full-cohort weights, so residual imbalance persisted within the RT and non-RT subsets (maximum |SMD| 0.56 for both; Online Resource 8), and the subgroups were small (34 and 27 patients); these results are exploratory. The OS estimate was attenuated and no longer significant in the start-time analysis (HR 0.71, 95% CI 0.46–1.11), which reflects the weight of the early post-LCT period and argues for caution. Finally, PFS and response were assessed by institutional imaging without central review, and immune checkpoint inhibitor exposure was heterogeneous.

In conclusion, in patients with unresectable, locally advanced ICC receiving first-line chemoimmunotherapy, consolidative LCT was associated with longer PFS and OS, and RT-based consolidation in particular with fewer intrahepatic failures. These observational findings are hypothesis-generating and warrant prospective randomised evaluation to define the optimal modality, timing and patient selection.

## Declarations

# Competing interests:

The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval:**

This study was approved by the Institutional Ethics Committee of Zhongshan Hospital, Fudan University (approval number B2026-405) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Consent to participate:**

The requirement for informed consent was waived by the Institutional Ethics Committee because of the retrospective and observational nature of the study.

**Consent for publication:**

Not applicable.

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# Author contributions:

All authors contributed to the study conception and design. Data collection was performed by Qianqian Zhao and Kehao Liu; statistical analysis by Qianqian Zhao and Zhaochong Zeng; the first draft was written by Qianqian Zhao and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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# Data availability:

The de-identified dataset analysed during the current study is available from the corresponding author on reasonable request and subject to institutional data-sharing policy.

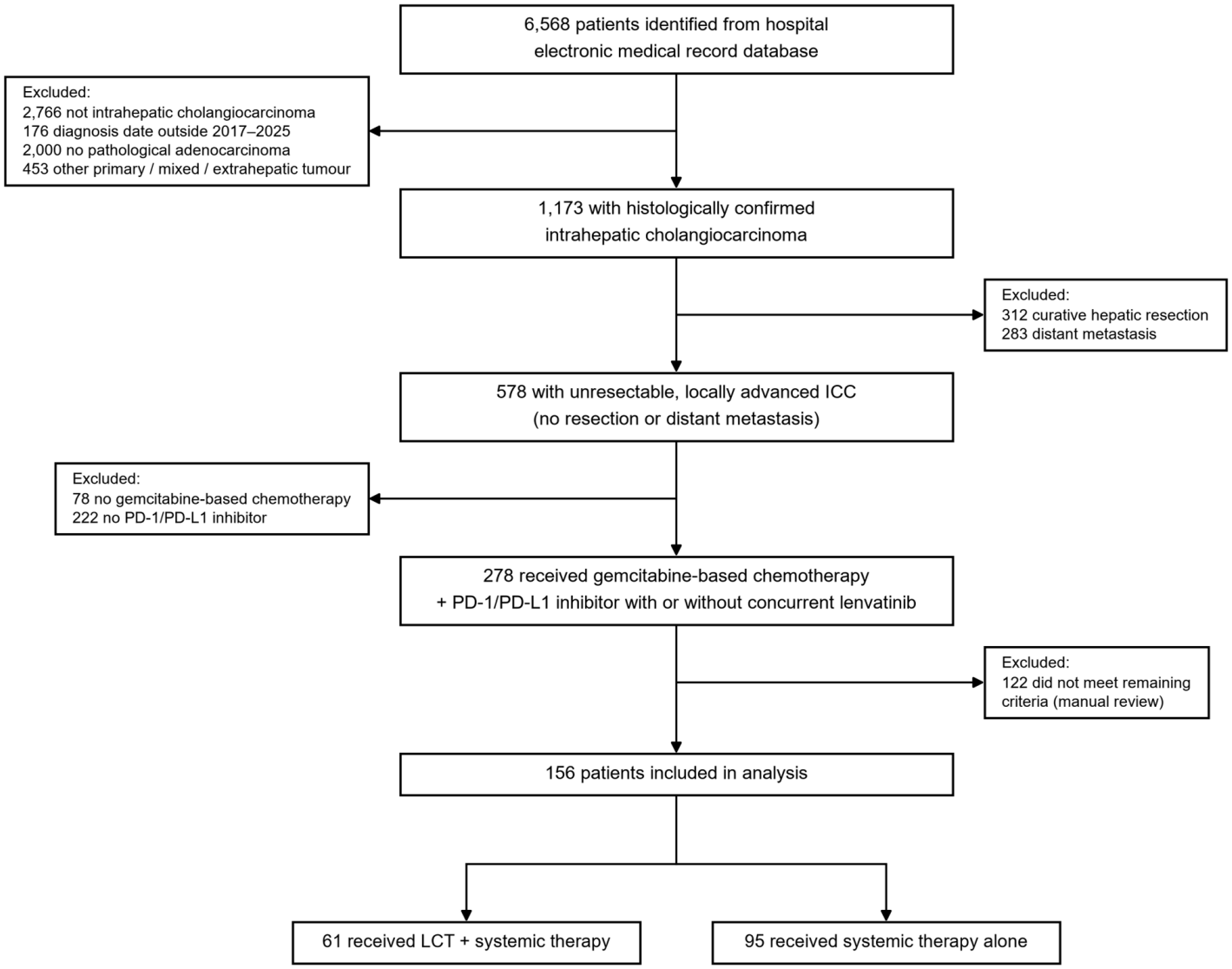
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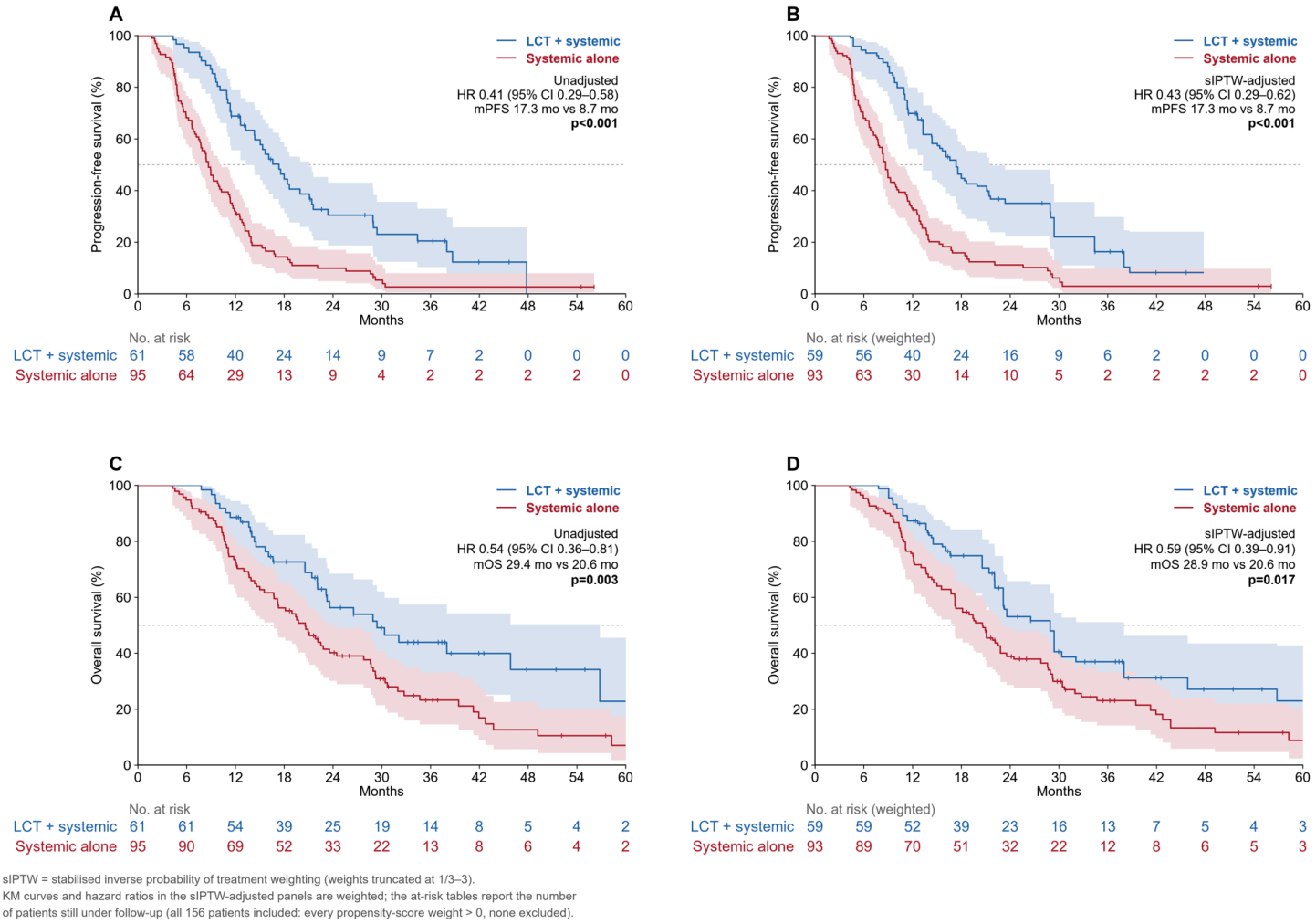
# Figures




Patients were identified from the hospital electronic medical record database who had a pathological diagnosis of adenocarcinoma or cholangiocarcinoma after liver biopsy or surgical resection, a diagnosis date between 1 January 2017 and 30 June 2025, and either gemcitabine recorded among administered medications or 'GEMOX' (gemcitabine plus oxaliplatin) / 'GP' (gemcitabine plus cisplatin) recorded in the medical records. LCT, locoregional consolidation therapy.

**Figure 1**

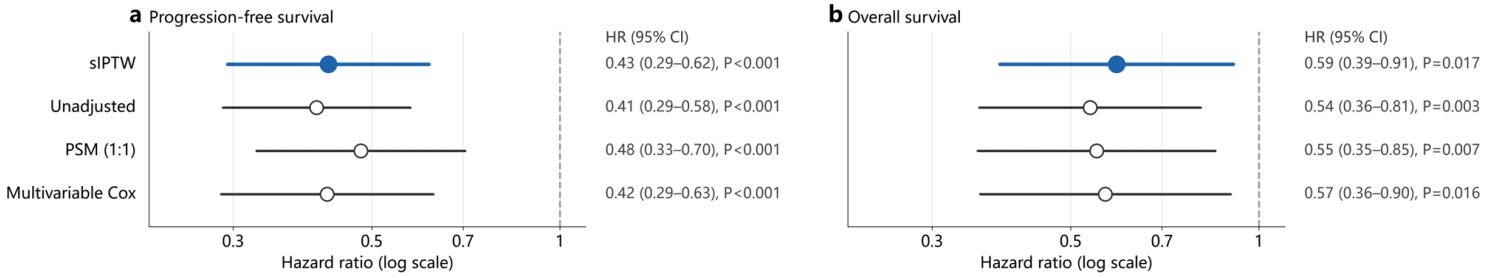
STROBE participant flow diagram. Between January 2017 and June 2025, 6,568 patients were identified, of whom 1,173 had histologically confirmed intrahepatic cholangiocarcinoma, 578 had unresectable locally advanced disease, and 278 received gemcitabine-based chemotherapy plus a PD-1/PD-L1 inhibitor with or without lenvatinib; 156 patients were analysed after exclusion of 122 who did not meet the remaining eligibility criteria




sIPTW = stabilised inverse probability of treatment weighting (weights truncated at 1/3–3).
KM curves and hazard ratios in the sIPTW-adjusted panels are weighted; the at-risk tables report the number of patients still under follow-up (all 156 patients included: every propensity-score weight > 0, none excluded).

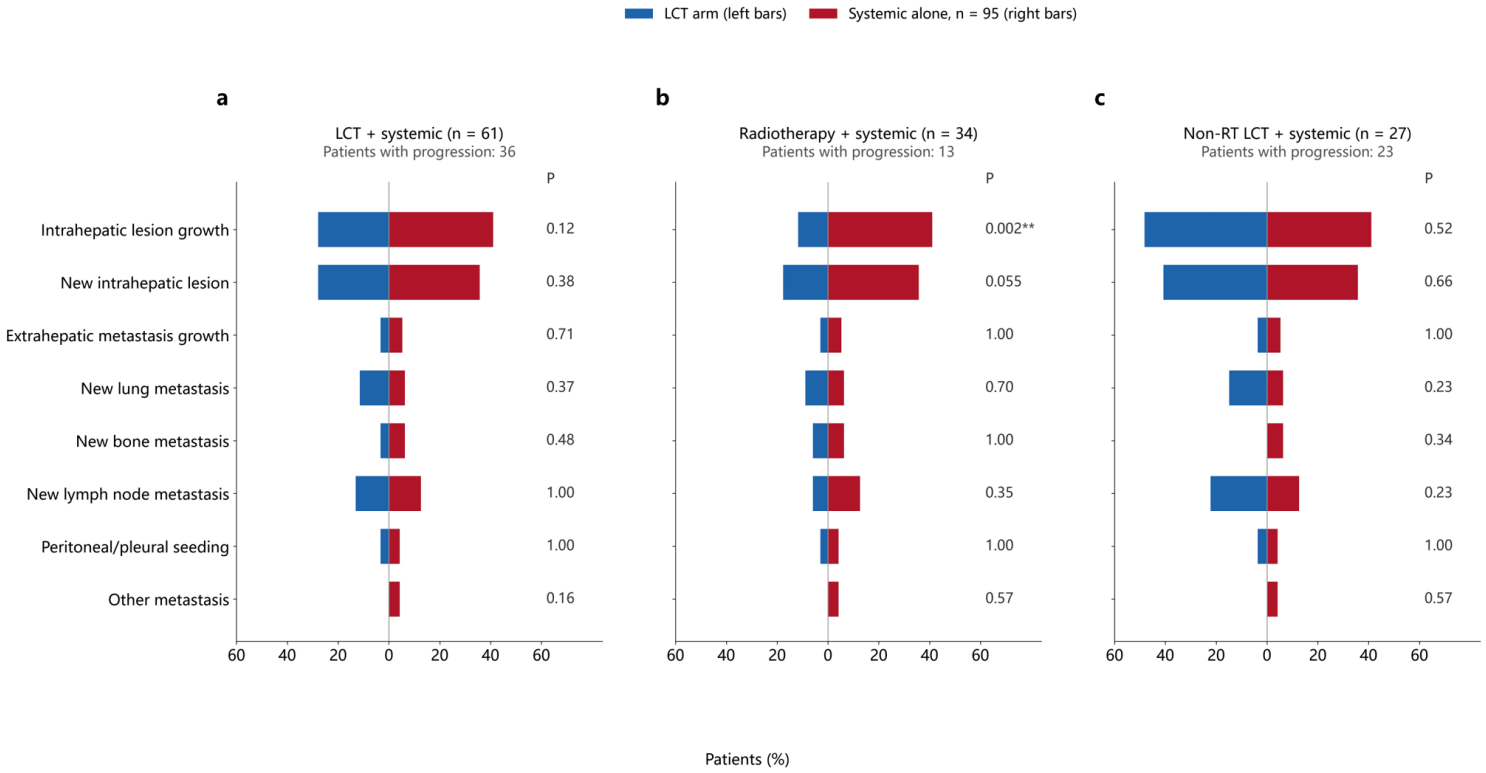
## Figure 2

Kaplan-Meier estimates of progression-free survival (a, b) and overall survival (c, d) for locoregional consolidation therapy plus systemic therapy versus systemic therapy alone. The left column shows unadjusted estimates and the right column stabilised inverse probability of treatment weighted estimates. Shaded bands are 95% confidence intervals, vertical ticks censored observations and the dashed line 50% survival. Hazard ratios are from Cox models with robust sandwich variance estimators, unadjusted in a and c and weighted in b and d; P values are two-sided Wald tests from the same models




## Figure 3

Hazard ratios for progression-free survival (a) and overall survival (b) estimated by four analytic approaches: unadjusted Cox regression, stabilised inverse probability of treatment weighted Cox regression, multivariable Cox regression and 1:1 propensity-score matching. The weighted estimate is highlighted; squares are hazard ratios and horizontal lines 95% confidence intervals on a logarithmic axis




Percentages are the proportion of all patients in each arm who developed that pattern; arms are not mutually exclusive, so rows need not sum to 100%.
P values are two-sided Fisher's exact tests, each LCT arm versus systemic therapy alone; * P<0.05, ** P<0.01. Adrenal, pleural and brain metastases were not recorded as a first progression site in any arm.

**Figure 4**

Patterns of first disease progression. Prevalence of eight failure modes among all patients in (a) locoregional consolidation therapy plus systemic therapy (n = 61), (b) radiotherapy plus systemic therapy (n = 34) and (c) non-radiotherapy locoregional consolidation therapy plus systemic therapy (n = 27), each compared with systemic therapy alone (n = 95). Percentages are the proportion of all patients in each arm, arms are not mutually exclusive and P values are two-sided Fisher exact tests

# Supplementary Files

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