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# Perioperative and precision strategies in resectable intrahepatic cholangiocarcinoma

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**Abstract:** Intrahepatic cholangiocarcinoma (ICC) has a poor prognosis, with low rates of surgical eligibility and high recurrence. Effective perioperative strategies are essential. For adjuvant treatment, capecitabine (based on the BILCAP trial) and S-1 (from the ASCOT trial) have become standard regimens. Neoadjuvant therapy using gemcitabine-platinum combinations and locoregional strategies such as hepatic artery infusion chemotherapy (HAIC) and yttrium-90 radioembolization (Y-90 TARE) have improved resectability and survival outcomes. Molecular profiling has revealed actionable alterations in nearly 70% of ICCs. FGFR2 fusions, IDH1 mutations, and BRAF V600E mutations can be targeted with inhibitors such as pemigatinib, ivosidenib, and dabrafenib-trametinib, respectively, showing promising response rates in clinical trials. Immunotherapy has demonstrated efficacy in the microsatellite instability-high (MSI-H) subtype. Combination strategies involving PD-1 inhibitors with radiotherapy or anti-angiogenic agents are further expanding the potential for treatment. Future efforts should focus on standardizing resectability criteria, expanding access to molecular profiling, and accelerating Phase III trials.

***Keywords*:** intrahepatic cholangiocarcinoma (ICC), adjuvant therapy, neoadjuvant therapy

## 1. Introduction

The management of intrahepatic cholangiocarcinoma (ICC) represents one of the most formidable challenges in hepatobiliary oncology (*1*). As the second most common primary liver malignancy, ICC accounts for approximately 20% of hepatic cancers, yet carries a disproportionately poor prognosis (*2*). Surgical resection remains the cornerstone of curative intent, but only 20–30% of patients present with technically resectable disease. Even among those undergoing complete resection, 5-year survival rates linger at 25–40%, with recurrence rates soaring to 50–70% due to micrometastatic spread (*3*). This sobering reality underscores the critical importance of effective perioperative therapies. To improve patient outcomes, surgeries should be performed at centers with extensive surgical experience (*4*). Additionally, recent advances in adjuvant and neoadjuvant approaches are reshaping the therapeutic landscape, though significant controversies persist regarding patient selection, regimen optimization, and biomarker integration.

The determination of surgical candidacy extends beyond traditional TNM staging. While the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual classifies solitary tumors without vascular invasion (T1a/b) as ideal candidates, clinical practice reveals nuanced complexities (*5,6*). Multifocal tumors present particular controversy — some studies suggest comparable outcomes to unimodal disease when completely resected, while others find no survival advantage over systemic therapy alone (*7*). The evaluation of nodal status further complicates decisions; up to 30% of patients deemed clinically node-negative (cN0) harbor occult metastases upon pathological examination, prompting guidelines to mandate routine lymphadenectomy (*8,9*). The 2023 EASL-ILCA criteria introduced quantitative parameters including future liver remnant (FLR) thresholds (> 25% in healthy liver, > 40% in cirrhosis) and emphasize tumor biology assessment. For borderline resectable cases or those with high-risk features (*e.g.*, large tumors abutting vessels

and advanced age), neoadjuvant therapy now serves as a bridge to potential resection (*10,11*).

**2. Adjuvant therapy**

Postoperative systemic therapy has evolved from empirical administration to evidence-based standardization. The landmark capecitabine compared with observation in resected biliary tract cancer (BILCAP) trial established capecitabine as a new backbone, demonstrating a 17-month median overall survival (OS) advantage over observation (53 *vs*. 36 months; hazard ratio [HR]: 0.75) (*12*). This was corroborated by the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in which S-1 resulted in a 9.5% absolute improvement in 3-year OS (77.1% *vs*. 67.6%) (*13*). However, gemcitabine-based regimens show inconsistent results — while some retrospective analyses suggest a benefit, the PRODIGE 12 trial (gemcitabine plus oxaliplatin *vs*. observation after R0 or R1 resection in patients with biliary tract cancer) revealed no survival advantage of gemcitabine plus oxaliplatin (*14*). For patients with high-risk pathological features (R1 resection, lymph node involvement), multimodal approaches are gaining traction. Adjuvant radiotherapy significantly improves outcomes in margin-positive disease (< 1 mm), with the 3-year OS doubling from 20% to 55%, and it provides meaningful survival extension in node-positive patients (median OS of 19.1 *vs*. 9.5 months) (*15*). Transarterial chemoembolization (TACE) demonstrates selective utility in advanced-stage tumors (≥ 5 cm or TNM III/IV), improving the 5-year OS from 6.2% to 21.3%, though it paradoxically increases recurrence risk in early-stage disease (*16,17*).

**3. Neoadjuvant therapy**

The paradigm of preoperative treatment has transformed from an experimental approach to an essential strategy for high-risk resectable and borderline resectable ICC. Beyond facilitating tumor downstaging, neoadjuvant therapy eradicates micrometastases and enables better patient selection for aggressive surgery. Contemporary data suggest potential superiority over adjuvant approaches, with a propensity-matched analysis revealing a 7.5-month median OS advantage (40.3 *vs*. 32.8 months) for neoadjuvant chemotherapy (*18*). Gemcitabine-platinum combinations serve as the current backbone, achieving resection in 73% of initially unresectable patients in small-scale phase II studies (*19*). Locoregional strategies amplify this potential — hepatic artery infusion chemotherapy (HAIC) combined with systemic gemcitabine-oxaliplatin extends the median OS to 30.8 months compared to 18.4 months with systemic therapy alone in advanced cases (*20*). Emerging techniques like yttrium-90 radioembolization (Y-90 TARE) demonstrate significant tumor volume reduction in 42.7% of patients, with ongoing trials evaluating combinatorial approaches (*21*).

**4. Molecularly targeted therapies**

The genomic landscape of ICC reveals actionable alterations in nearly 70% of tumors, ushering in an era of biomarker-directed therapy (*22,23*). Fibroblast growth factor receptor 2 (FGFR2) fusions (10–15% prevalence) are effectively targeted by selective inhibitors — pemigatinib achieves a 35.5% objective response rate (ORR) in refractory disease, while futibatinib results in a 34% ORR and 9.1-month median progression-free survival (PFS) (*24*). For IDH1-mutant ICC (10–20% prevalence), ivosidenib more than doubles the PFS compared to a placebo (2.7 *vs*. 1.4 months) with a manageable toxicity profile (*25*). BRAF V600E mutations (5–7%) respond to dabrafenib-trametinib combinations (41% ORR), though efficacy varies across non-V600E alterations (*26*). Despite the promising activity of molecularly targeted therapies, challenges remain regarding their optimal integration with locoregional therapies, management of acquired resistance, and the accessibility of comprehensive genomic profiling.

**5. Immunotherapy**

ICC is a highly desmoplastic cancer with abundant tumor stroma. Studies have revealed that pembrolizumab achieves response rates exceeding 40% in the microsatellite instability-high (MSI-H) subtype (*27*). Thus, immunotherapy for ICC represents a highly promising therapeutic strategy. Recent combination strategies show greater promise — PD-1 inhibitors coupled with radiotherapy yield an impressive 61.1% ORR and 22-month median OS in unresectable disease (*28*). Anti-angiogenic combinations (*e.g*., PD-1 inhibitors with lenvatinib) demonstrate a disease control rate of 80.6%, albeit with significant toxicity (50.5% grade 3–4 adverse events) (*29*).

**6. Future directions**

The current standard of care for resectable ICC emphasizes a multimodal treatment approach (Figure 1). Three critical barriers are impeding progress: heterogeneous resectability criteria, limited access to molecular profiling, and the scarcity of phase III data. Artificial intelligence-assisted surgical planning may standardize FLR assessment, while liquid biopsy platforms offer cost-effective alternatives for dynamic biomarker monitoring (92.3% sensitivity for micrometastasis detection) (*30*). Global efforts like the ICC-RFC Project aim to accelerate trial enrollment, with innovative studies exploring TGF-β inhibition to overcome fibrotic barriers, neoantigen

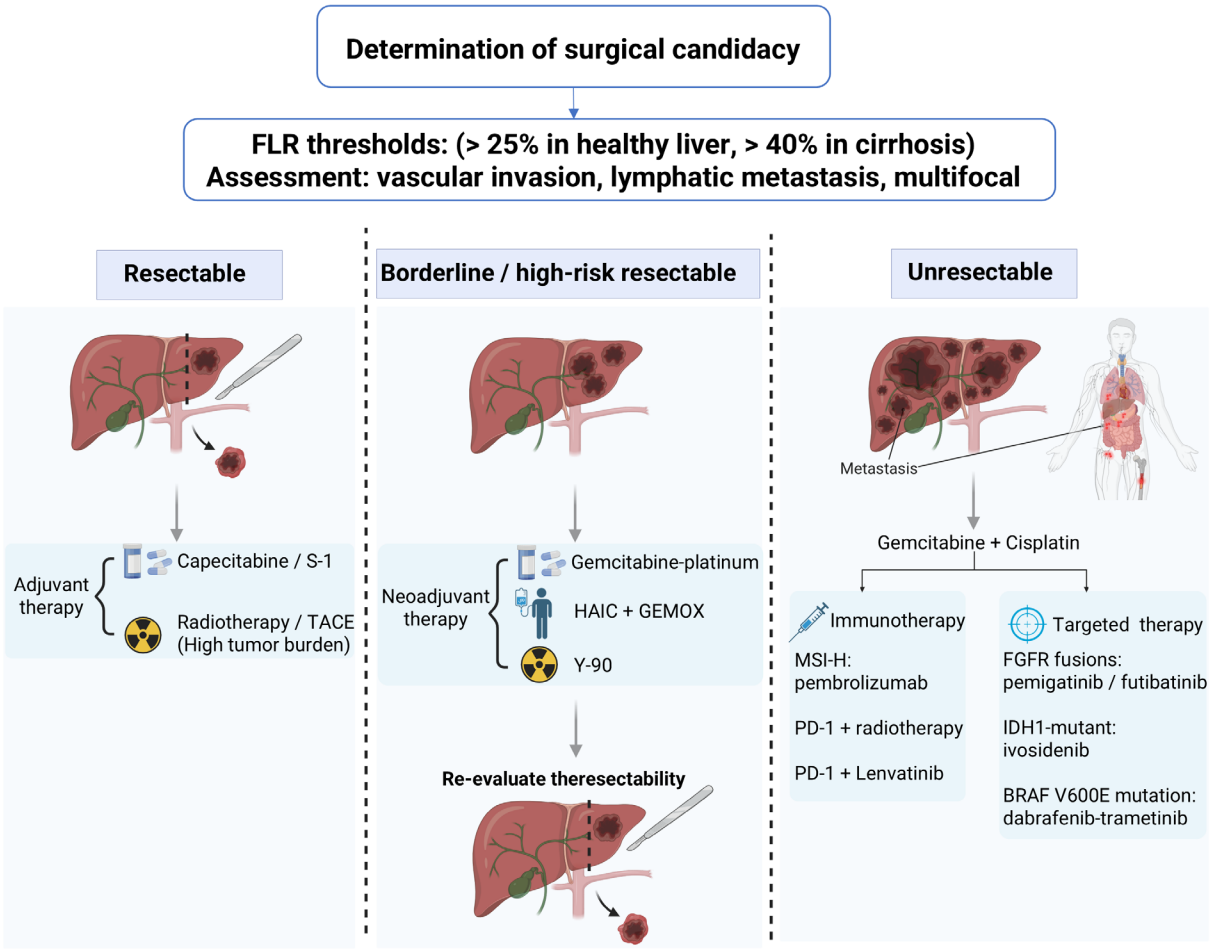


**Figure 1. Diagnostic and therapeutic approaches for intrahepatic cholangiocarcinoma (ICC).** This figure stratifies patients with ICC into three categories: resectable, borderline/high-risk resectable, and unresectable. The top section illustrates schematic diagrams of each category, while the bottom section outlines the corresponding recommended treatment strategies. *Abbreviations*: FLR, future liver remnant; HAIC, hepatic artery infusion chemotherapy; GEMOX, gemcitabine-oxaliplatin; Y-90, yttrium-90; MSI-H, microsatellite instability-high; PD-1, programmed cell death protein 1; FGFR, fibroblast growth factor receptor; IDH1, isocitrate dehydrogenase 1; BRAF, B-Raf proto-oncogene.

vaccines, and FGFR2-directed cellular therapies. The ongoing ACTICCA-1 trial, which evaluates adjuvant chemotherapy with gemcitabine and cisplatin *vs*. standard of care after curative-intent resection of biliary tract cancer, and the PRODIGE 57 trial, which investigates durvalumab plus tremelimumab with or without paclitaxel in advanced biliary tract cancer after platinum-based chemotherapy, will provide much-needed level I evidence for chemotherapy and targeted neoadjuvant approaches.

## 7. Conclusion

The therapeutic approach for resectable ICC has transformed from isolated surgical intervention to integrated multimodal strategies. Fluoropyrimidine-based adjuvant therapy is now the standard care for patients undergoing resection. while neoadjuvant approaches expand curative opportunities for borderline resectable disease. Molecular stratification enables targeted therapy integration, though barriers to accessibility persist. As ongoing trials address existing evidence gaps, the future promises increasingly personalized pathways combining optimized local control with systemic precision — moving closer to the ultimate goal of a robust cure for this complex malignancy.

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