REVIEW

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Conversion and Neoadjuvant Therapy for Intrahepatic Cholangiocarcinoma: Integrating Precision Medicine to Redefine Surgical Curability

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ABSTRACT

Intrahepatic cholangiocarcinoma (ICC) is a type of primary liver cancer that is highly aggressive. In recent years, its incidence has continued to increase around the globe, yet outcomes remain poor and stagnant. Although surgical resection is the only treatment option capable of curing the cancer, most patients present with either advanced disease or unresectable tumors. Over the past decade, our understanding of ICC biology has evolved rapidly, with improved molecular classification and the clinical introduction of targeted therapies and immunotherapies. As a result of these advances, neoadjuvant, conversion, and downstaging strategies have been developed to redefine resectability and improve long-term survival. Patients with selected tumors achieve good control with locoregional approaches, such as transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and radiotherapy. At the same time, the routine use of next-generation sequencing (NGS) has allowed for personalized treatment of tumors with fibroblast growth factor receptor 2 gene (*FGFR2*) fusions, isocitrate dehydrogenase 1 (*IDH1*) mutations, and immunogenic profiles. Even though procedures have come a long way, challenges remain. Treatment protocols differ from one institution to another, and criteria for what constitutes "biological resectability" are not standardized. High-quality prospective evidence exists but is nevertheless limited. As such, it is still unclear when the optimal timing for surgery is after systemic or locoregional therapy. This review focuses on the currently available clinical, molecular, and surgical aspects of intrahepatic cholangiocarcinoma to propose a precision-multimodal treatment algorithm.

Key words: intrahepatic cholangiocarcinoma – ICC – neoadjuvant therapy – conversion therapy —targeted therapy – immunotherapy — next-generation sequencing — precision medicine.

Abbreviations: ALPPS: associating liver partition and portal vein ligation for staged hepatectomy; ARID1A: AT-rich interaction domain 1A; BAP1: BRCA1-associated protein 1 gene; BICC1: bicaudal family RNA binding protein 1; D: durvalumab; DCR: disease control rate; dMMR: mismatch repair deficiency; *FGFR2*: fibroblast growth factor receptor 2 gene; FLR: future liver remnant; GAP: gemcitabine, cisplatin, and nab-paclitaxel; GC: gemcitabine and cisplatin; GEMOX: gemcitabine and oxaliplatin; HAIC: hepatic arterial infusion chemotherapy; ICC: intrahepatic cholangiocarcinoma; IDH1: isocitrate dehydrogenase 1 gene; KRAS: Kirsten rat sarcoma viral oncogene homolog; MAPK: mitogen-activated protein kinase; MDT: multidisciplinary team; MSI-H: high microsatellite instability; NGS: next-generation sequencing; ORR: objective response rate; OS: overall survival; PD-1: programmed cell death protein-1; PFS: progression-free survival; PVE: portal vein embolization; TACC3: transforming acidic coiled-coil containing protein 3; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; TMB-H: high tumor mutational burden; TP53: tumor protein p53; 2HG: 2-hydroxyglutarate.

INTRODUCTION

Epidemiology

Intrahepatic cholangiocarcinoma (ICC) is the second-most frequent type of primary liver cancer, comprising approximately 10% to 15% of all primary liver cancers [1]. The occurrence and death rate from ICC have risen substantially over the past several decades, presenting a significant clinical oncology challenge [2]. The disease develops so slowly that most people do not have any symptoms until it is very advanced. As a result, only 20% to 30% of patients are candidates for a potentially curative surgical resection at diagnosis [3]. For the few patients who undergo surgery, the outlook is still sobering. Even if complete

macroscopic resection is achieved, the disease has a high early recurrence rate (over 60%) and a 5-year overall survival rate of 20-40% [1, 4]. The aggressive biology in this context highlights the great unmet need for ICC management; most patients present with inoperable disease, and even after resection, the risk of recurrence is unacceptably high, indicating the presence of micrometastatic disease even at early stages [1, 3].

Historical Paradigm

Historically, the treatment paradigm for ICC has been rigidly defined by anatomical resectability. Surgical excision with negative margins (R0) has stood as the only potentially curative modality, with long-term survival being exclusively linked to successful resection [1, 3]. Within this framework, the roles of systemic and locoregional therapies were largely confined to the palliative setting for advanced or metastatic disease. Prior to the advent of effective systemic regimens, the therapeutic arsenal was limited, and no standardized neoadjuvant or conversion protocols existed [5, 6]. This left a large cohort of patients with few options, as the binary distinction between "resectable" and "unresectable" was often a final verdict [3, 6].

The Emerging Therapeutic Shift

An unprecedented shift is taking place in the principles of ICC management. This change is the result of two critical developments: the improvement of multimodal treatment strategies and the rise of precision medicine. The traditional definition of resectability as simply anatomical is being replaced by a more dynamic, biology-driven concept. The integration of neoadjuvant therapy for high-risk resectable disease and conversion therapy for initially unresectable ICC has opened new doors to the operating room. Neoadjuvant strategies treat micrometastases to avoid postsurgical recurrence and test the biology of the tumor in vivo, while conversion therapy aims to downstage tumors, rendering them amenable to radical resection [3, 6].

This shift is underpinned by the increasing role of molecular-guided treatment. With the discovery of targetable genetic alterations, such as fibroblast growth factor receptor 2 gene *(FGFR2*) fusions and isocitrate dehydrogenase 1 gene (*IDH1)* mutations—and evidence of the efficacy of immunotherapy in select subsets, we now have the tools to apply these multimodal approaches selectively [7-9]. The paradigm is evolving from a one-size-fits-all surgical strategy to a nuanced, personalized algorithm where systemic and local therapies act as enablers of curative-intent surgery [10].

This review posits that the management of ICC is undergoing a fundamental paradigm shift. The integration of next-generation sequencing (NGS) into routine diagnostic workup is enabling biological stratification which, when combined with multimodal therapeutic strategies, is actively redefining the very concept of "resectability." We argue that NGS-guided neoadjuvant and conversion therapies are no longer experimental ideas, but essential components of contemporary ICC care, capable of unlocking curative-intent surgery in a growing subset of patients who were once considered inoperable. The future of ICC treatment lies in this precision-guided, multimodal approach, in which surgery represents the final step in a carefully orchestrated therapeutic sequence rather than the sole therapeutic intervention.

MOLECULAR LANDSCAPE AND PRECISION MEDICINE

We are witnessing a fundamental reshaping of how we manage ICC, driven entirely by our deepening grasp of its molecular underpinnings. To truly leverage precision medicine, we must move beyond the old histology-based approach and embrace a classification system rooted in genetics. This shift is the only way to ensure we are selecting the optimal therapeutic pathway for each individual patient.

Key Genetic Drivers

Comprehensive genomic profiling has taught us that ICC is not a single entity, but a highly heterogeneous collection of somatic alterations [11]. Within this diverse landscape, two specific mutation classes stand out for their clinical significance: *FGFR2* fusions and *IDH1/2* mutations. Each of these appears in roughly 10–20% of cases [12-16]. The *FGFR2* fusions, including variants such as FGFR2 – bicaudal family RNA binding protein 1 (BICC1) and FGFR2 – transforming acidic coiled-coil containing protein 3 (TACC3), define a unique subtype where constitutive mitogen-activated protein kinase (MAPK) signaling pathway activation drives the tumor, making them highly sensitive to FGFR inhibitors [12, 15]. The story is different for *IDH1/2* mutations. These act as oncogenic drivers not through standard signaling pathways, but by churning out the oncometabolite 2-hydroxyglutarate (2-HG). This metabolite wreaks havoc on the cell's epigenetic machinery via DNA hypermethylation—a process we can now effectively block with drugs like ivosidenib [13, 16]. Outside of these targets, we frequently see mutations in chromatin-remodeling genes such as BRCA1-associated protein 1 gene (*BAP1)* and AT-rich interaction domain 1A (*ARID1A)* (found in 10–15% of ICCs), alongside the more difficult Kirsten rat sarcoma viral oncogene homolog (KRAS) and tumor protein p53 (TP53) alterations that typically signal aggressive, treatment-refractory disease [11, 13, 17]. The molecular landscape of ICC is depicted in Fig 1.

Molecular Subtypes and Tumor Biology

Integrative molecular analyses have begun to stratify ICC into distinct subtypes with biological and clinical relevance. One seminal study proposed a classification into two broad classes: an "inflammation" class, characterized by immune and inflammatory pathway activation, and a "proliferation" class, marked by enhanced growth factor signaling and cell cycle activation, with the inflammation class generally associated with a more favorable prognosis [11]. In addition, current consensus, including the EASL-ILCA Clinical Practice Guidelines, emphasizes that the histological distinction between small duct and large duct intrahepatic cholangiocarcinoma remains relevant and is associated with characteristic molecular patterns [18].

From a therapeutic standpoint, supported by NGS, ICC can be conceptualized into the following clinically actionable groups:

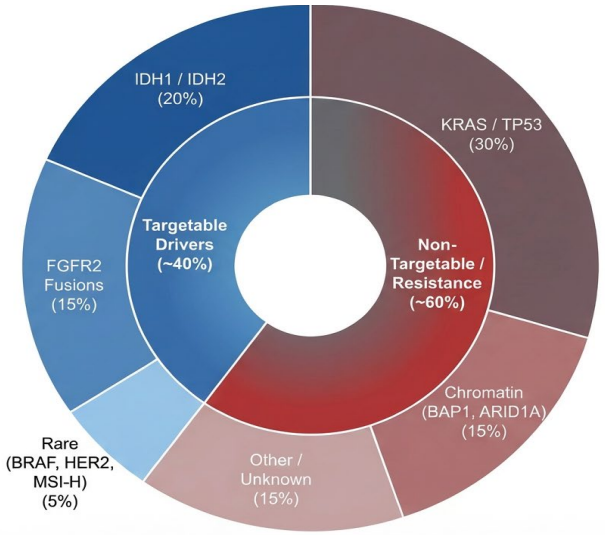

Fig. 1. The molecular landscape of intrahepatic cholangiocarcinoma (ICC). A schematic representation of the genomic heterogeneity in ICC. The inner ring categorizes patients based on therapeutic eligibility, while the outer ring details specific genetic alterations. Approximately 40% of patients harbor an actionable driver (Blue/Green section), necessitating routine NGS. *IDH1/2* mutations (~20%) and *FGFR2* fusions (~15%) represent the dominant targetable subgroups. The remaining 60% (Grey/Red section) comprise tumors driven by currently non-targetable mutations, including *KRAS* and *TP53* (associated with aggressive biology) and chromatin remodelers like *BAP1* and *ARID1A*. Percentages are approximate estimates derived from aggregated genomic profiling data [1, 10, 15, 16].

• *Targetable ICC:* Defined by the presence of actionable drivers such as *FGFR2* fusions/rearrangements and *IDH1* mutations, alterations more frequently observed in the small duct subtype [7, 8, 12-16].

• *Immunogenic ICC:* Encompasses tumors with mismatch repair deficiency (dMMR) / high microsatellite instability (MSI-H) and/or high tumor mutational burden (TMB-H), which may predict response to immune checkpoint inhibition; although these are pan-tumor biomarkers, their identification is important for selecting ICC patients for immunotherapy [9, 19, 20].

• *Proliferation/Resistance Clusters:* Often enriched for *KRAS* and/or *TP53* alterations, which are more often associated with the large duct subtype and aggressive tumor behavior; these subtypes currently lack established targeted therapies and typically rely on systemic chemotherapy and clinical-trial enrollment [11, 13, 17].

NGS as a Standard Tool

In this evolving landscape, NGS has transitioned from a research tool to a clinical necessity. Given the high molecular heterogeneity and the observation that a substantial fraction of ICCs, commonly estimated at around 30–40%, harbor potentially actionable alterations [1, 10, 15, 16], routine NGS testing on tumor tissue is recommended for all patients with advanced disease [3, 10]. The utility of NGS extends beyond simply identifying common mutations; it can detect rare fusions and alterations that would be missed by single-gene tests, comprehensively informing therapy selection. This approach directly influences conversion potential, as identifying a targetable alteration can allow for the use of highly effective, well-tolerated systemic agents that are more likely to induce significant tumor regression and enable surgery [3, 6-8]. Consequently, in the current therapeutic era, omitting comprehensive molecular profiling effectively results in an incomplete diagnostic workup and may deny some patients access to highly active, potentially downstaging therapies.

Actionable Targets

The translation of molecular discoveries into clinical practice has been rapid. Pemigatinib, an FGFR1-3 inhibitor, received FDA approval for advanced cholangiocarcinoma with *FGFR2* fusions based on the FIGHT-202 trial, which demonstrated an objective response rate (ORR) of 35.5% [7, 21]. Similarly, the *IDH1* inhibitor, ivosidenib significantly improved overall survival in the ClarIDHy trial, leading to its approval for *IDH1*-mutated advanced ICC [8, 16]. For patients with HER2 amplifications (more common in extrahepatic disease) or NTRK fusions (rare), targeted therapies like trastuzumab and larotrectinib, respectively, have shown efficacy [22, 23]. Furthermore, biomarkers such as MSI-H, TMB-H, and PD-L1 expression can identify candidates for immunotherapy, forming the basis for the integration of checkpoint inhibitors into treatment regimens [19, 20, 24].

Actionable molecular alterations and therapeutic implications in ICC are detailed in Table I.

NEOADJUVANT THERAPY FOR ICC

Neoadjuvant therapy represents a decisive break from the traditional "upfront surgery" model in ICC management. This strategy involves administering systemic or local treatment prior to resection, specifically to improve long-term outcomes in patients who face a high risk of recurrence.

Rationale

The rationale for this approach is multifaceted. Its primary goal is to confront the high rate of postoperative recurrence, which currently exceeds 60% [4]. By initiating treatment before surgery, clinicians can target occult micrometastases early, potentially eradicating microscopic disease before it disseminates [3]. Furthermore, neoadjuvant therapy can shrink the primary tumor and downstage locally advanced features, thereby increasing the odds of achieving a complete (R0) resection, the single strongest predictor of long-term survival [1, 3]. A critical, often underappreciated advantage is the *in vivo* test of tumor biology; a tumor that fails to respond to preoperative therapy reveals its aggressive nature early, prompting a necessary reconsideration of the risks versus benefits of major surgery [3]. Crucially, this biological "stress test" can act as a filtration mechanism, identifying patients with chemo-refractory biology and potentially sparing them the morbidity of a major resection that is unlikely to provide durable benefit.

Table I. Actionable molecular alterations and therapeutic implications in intrahepatic cholangiocarcinoma (ICC)

Genetic alteration	Frequency in ICC	Typical context / notes	Therapeutic class	Example agents
FGFR2 fusions	~10–15%	Enriched in "small duct" ICC; often non–flukeassociated; defines a distinct molecular subtype	FGFR inhibitors	Pemigatinib, Futibatinib, Infigratinib, Derazantinib
IDH1 / IDH2 mutations	~10–20%	Non–flukeassociated ICC; epigenetically driven subtype via 2HG	IDH inhibitors	Ivosidenib (IDH1); IDH2 inhibitors under investigation
MSIHigh / dMMR	~1–2%	Sporadic; occasionally related to Lynch syndrome; hypermutated/immunogenic	Immune checkpoint inhibitors	Pembrolizumab, Dostarlimab
TMBHigh	Small subset	Immunogenic phenotype; not always MSIH	Immune checkpoint inhibitors	Pembrolizumab (tissueagnostic)
PDL1–positive	Variable	Reflects immune microenvironment; predictive role still evolving	Immune checkpoint inhibitors	Durvalumab, Pembrolizumab, Nivolumab
HER2 amplification	2–5%	More relevant in extrahepatic BTC, but present in a minority of ICC	HER2targeted antibodies / TKIs	Trastuzumab ± Pertuzumab; TrastuzumabFOLFOX
BRAF V600E	~1–5%	Associated with aggressive disease; found across BTC subtypes	BRAF/MEK inhibitors	Dabrafenib + Trametinib
KRAS / TP53	~20–40%	Associated with aggressive biology and resistance; currently nondruggable	Prognostic / resistance markers	No approved targeted therapy; emphasizes need for systemic chemo

ICC: intrahepatic cholangiocarcinoma; FGFR: fibroblast growth factor receptor; IDH: isocitrate dehydrogenase; MSI-H: microsatellite instability-high; TMB: tumor mutational burden; TKI: tyrosine kinase inhibitor; BRAF: B-Raf proto-oncogene; KRAS: Kirsten rat sarcoma viral oncogene homolog; TP53: tumor protein p53.

Evidence Overview

The evidence for neoadjuvant therapy is still evolving, although more data is now available, especially for systemic regimens.

The gemcitabine and cisplatin (GC) regimen forms the backbone of many neoadjuvant approaches and has become the established first-line standard in advanced disease. According to a meta-analysis of five studies, neoadjuvant chemotherapy may improve 5-year overall survival (OS) without increasing postoperative complications. This finding provides a rationale upon which to base clinical practice [25].

The NEO-GAP study tested the gemcitabine, cisplatin, and nab-paclitaxel (GAP) regimen for the treatment of high-risk ICC [26]. This study showed feasibility, with 73% of patients completing chemotherapy and proceeding to surgery. However, there was no survival benefit from GAP versus GC in the unresectable setting in the Phase III SWOG 1815 trial, which dampened enthusiasm for a broad neoadjuvant role until further data is available.

A recent field of research studies combinations of immune checkpoint inhibitors with conventional cytotoxic chemotherapy. In a phase II study, researchers tested durvalumab (D) plus GC (D+GC) versus GC alone in cholangiocarcinoma. The ORR was dramatically higher at 36% versus 7%. The R0 resection rate was also promising at 48% in the D+GC group [NCT04308174]. This implies that chemoimmunotherapy may create surgical opportunities in potentially resectable cases. Locoregional therapy, including TACE, HAIC, and radiotherapy, remains relevant, especially for localized disease control or in combination with systemic therapy to enhance the pathologic response [27-29].

Patient Selection

It is a difficult and nuanced task to ascertain which patients with resectable ICC will benefit most from neoadjuvant therapy. Patients who exhibit high-risk features are the group that should be targeted.

"High-risk" is defined by expert consensus and clinical trials as:

- A tumor with a single diameter larger than 5 cm.
- The presence of multiple tumors or satellite lesions.
- Radiologic evidence of major vascular invasion.
- Regional lymph node metastasis.
- Preoperative CA19-9 (Carbohydrate antigen 19-9) > 200 U/mL [3, 26].

Formal staging systems can also guide selection. Using the NCDB database, propensity score analyses demonstrated that neoadjuvant chemotherapy did not notably improve the prognosis for patients with AJCC stage I disease, but it did improve long-term survival for patients with AJCC stage II to III disease [30]. In addition, sophisticated tools like nomograms and radiomics models are being developed to predict early recurrence (within 6 months), which will allow for a more personalized approach to candidate selection for preoperative treatment [31, 32].

Limitations

Neoadjuvant therapy in ICC shows potential but is limited in many ways. The most prominent is the lack of standardized protocols. There is wide variability in chemotherapy regimens, number of cycles, and criteria for surgery across institutions, leading to heterogeneity in practice and outcomes [3, 6]. This is compounded by a lack of prospective data, with most evidence coming from retrospective series or small single-arm phase II trials [3, 24](3, 2. Due to the absence of large randomized phase III studies comparing neoadjuvant therapy followed by surgery versus upfront surgery, we cannot definitively confirm the survival benefit of this approach. Finally, determining the optimal duration of therapy and timing of surgery remains

more art than science; studies typically use anywhere from 3 to 6 cycles and perform surgery 4-8 weeks after therapy, based largely on institutional experience [3, 26].

CONVERSION THERAPY

For patients presenting with unresectable ICC, conversion therapy represents a beacon of hope, aiming to transcend the traditional limits of inoperability. This strategy utilizes intensive multimodal treatment to downstage tumors, transforming them from unresectable to resectable and offering a chance for curative-intent surgery.

Concept and Indications

Conversion therapy is quite different from palliative care; it is an aggressive, active treatment aimed at radical resection [6]. The significance of this approach is profound. Research shows that patients who successfully undergo conversion therapy and subsequent surgery achieve dramatically improved outcomes, with a reported two-year survival rate of 88% and a median OS reaching 46 months in this selected subset. In contrast, the median OS with palliative chemotherapy alone is typically less than 12 months [33]. This approach can extend survival as well as relieve symptoms by shrinking the tumor.

Indications for conversion therapy include patients who are unresectable for anatomical or biological reasons. Key criteria include:

Anatomical/biological unresectability: Invasion of the main portal vein, hepatic veins, or bile duct which cannot be reconstructed; multiple tumors in both liver lobes; insufficient future liver remnant (FLR); or distant lymph node metastases [6, 34].

Role of a multidisciplinary team (MDT): A MDT discussion is essential for assessing the reasons for unresectability, planning an individualized conversion strategy, and periodically reassessing resectability [6, 34, 35].

Systemic Approaches

Most conversion regimens primarily rely on systemic therapy, while combination approaches offer superior results.

Chemotherapy: The GC regimen remains a backbone, although more intensive regimens demonstrate higher conversion rates. In the KHBO1401-MITSUBA trial, the addition of S-1 to GC resulted in an ORR of 41.5%, and three patients successfully underwent conversion surgery [36]. Similarly, the GAP regimen achieved a conversion rate of 20% in a phase II trial [37].

Immunotherapy combinations: Research indicates that combining immune checkpoint inhibitors with chemotherapy is incredibly effective. Findings from a phase II trial showed an ORR of 80% with the combination regimen of toripalimab, lenvatinib, and gemcitabine and oxaliplatin (GEMOX), resulting in a 10% conversion rate [38]. Real-world evidence further supports this strategy. In a retrospective study, chemotherapy combined with lenvatinib and programmed cell death protein-1 (PD-1) blockade achieved an ORR of 54.7% [disease control rate (DCR) 96.2%] with a median OS of 39.6 months [median progression-free survival (PFS) 23.4 months], outperforming chemotherapy alone [39]. While these responses and early tumor shrinkage suggest potential for radiographic downstaging in selected patients, conversion to curative-intent surgery was not reported as a primary endpoint and should be interpreted cautiously [39].

Molecular targeted therapy: Targeted therapy is an excellent option for patients with actionable mutations, offering high efficacy and tolerability. In the pivotal FIGHT-202 trial, pemigatinib achieved an ORR of 35.5% in patients with FGFR2 fusions or rearrangements [7]. Because conversion to curative-intent surgery was not a prespecified endpoint in this trial, the findings should be interpreted as evidence of radiographic activity; nevertheless, substantial tumor regression may facilitate consideration of locoregional therapy or resection in highly selected responders following multidisciplinary evaluation. Similarly, a single-arm phase II study of lenvatinib plus PD-1 inhibitors in unresectable biliary tract cancer BTC reported an ORR of 42% and a DCR of 76.3%; notably, 13/38 (34.2%) patients achieved downstaging and underwent surgery [40]. However, these impressive response rates must be interpreted with caution: radiographic regression does not automatically translate into long-term survival, and clinicians must carefully balance aggressive conversion attempts against cumulative treatment toxicity.

Key clinical trials supporting systemic and conversion strategies relevant to ICC are detailed in Table II.

Locoregional Conversion Tools

Locoregional therapies can be powerfully combined with systemic treatment to maximize tumor control and conversion potential.

Transarterial chemoembolization (TACE): When combined with systemic GC, drug-eluting bead TACE (DEB-TACE) achieved an ORR of 68% and successfully converted 25% of patients to surgery, with a median OS of 33.7 months [27]. TACE combined with lenvatinib demonstrated a remarkable 63.6% downstaging rate to surgical resection [42].

Hepatic arterial infusion chemotherapy (HAIC): HAIC delivers high local concentrations of chemotherapy. HAI of floxuridine plus systemic GEMOX resulted in an 11% conversion rate [28]. Modern HAIC-based triple therapy (e.g., lenvatinib + durvalumab + FOLFOX-HAIC) shows ORRs of 65.2% (mRECIST) and conversion rates of 13% [43].

Transarterial radioembolization (TARE/Y-90): TARE provides highly focused internal radiation. Y-90 combined with chemotherapy has demonstrated conversion rates of 20-22%, with post-resection median OS reaching 46 months [33, 44].

Evaluating Response

Judging the right time for surgery depends on an accurate assessment of treatment response. While standard anatomic imaging using RECIST 1.1 criteria represents the baseline, it has some deficiencies. More recently, functional imaging with PET/CT has proven very useful, allowing for the detection of metabolic responses or persistent activity that a CT scan might miss [45].

Another way to measure response is to monitor tumor markers like CA19-9. Generally, a continuous drop in CA19-9 is a positive sign; this decline often precedes imaging changes and indicates the therapy is effective. Looking ahead, circulating tumor DNA (ctDNA) is becoming increasingly valuable as a sensitive biomarker. Studies suggest that ctDNA

Table II. Key clinical trials supporting systemic and conversion strategies relevant to intrahepatic cholangiocarcinoma (ICC)

Study / trial	Regimen	Population (BTC subtype)	Key findings / efficacy (selected)	Ref
ABC-02 (Valle et al.)	Gemcitabine + Cisplatin vs Gemcitabine	Advanced / metastatic BTC (includes ICC)	Established gemcitabine–cisplatin as firstline standard of care; median OS 11.7 vs 8.1 months with Gem alone.	[5]
TOPAZ1 (Oh et al.)	Gem/Cis + Durvalumab vs Gem/Cis + placebo	Advanced / metastatic BTC	Improved OS with chemoIO (median 12.9 vs 11.3 months); established Gem/Cis + durvalumab as a widely adopted firstline regimen.	[9]
KEYNOTE966 (Kelley et al.)	Gem/Cis + Pembrolizumab vs Gem/Cis + placebo	Advanced / metastatic BTC	Confirmed benefit of adding pembrolizumab to Gem/Cis; median OS 12.7 vs 10.9 months. Validates chemoIO as a firstline strategy.	[41]
NEOGAP (Maithel et al.)	Gem/Cis + Nabpaclitaxel	Highrisk resectable ICC (neoadjuvant)	73% completed neoadjuvant therapy and proceeded to surgery; demonstrated feasibility and acceptable toxicity of neoadjuvant triplet in ICC.	[26]
Shi et al. (Phase II, 2023)	Toripalimab + Lenvatinib + GEMOX	Unresectable / advanced ICC (conversion intent)	ORR 80.0%; DCR 93.3%; a subset of initially unresectable patients underwent curativeintent resection after response.	[38]
Edeline et al. (Phase II)	TARE (Y90) + Gem/Cis	Locally advanced / unresectable ICC	Conversion to resection in ~22% of patients; among resected patients, median OS ~46 months. Supports combined locoregional–systemic approach.	[33]
FIGHT202 (AbouAlfa et al.)	Pemigatinib	Unresectable/advanced CCA with *FGFR2* fusions	ORR 35.5%; durable disease control in many patients; established a role for FGFR2targeted therapy.	[7]
ClarIDHy (Zhu et al.)	Ivosidenib vs placebo	IDH1mutant unresectable/ advanced CCA	Improved PFS and adjusted OS; supports IDH1 inhibition as a standard option in this molecular subset.	[8]

BTC: biliary tract cancer; ICC: intrahepatic cholangiocarcinoma; OS: overall survival; ORR: objective response rate; DCR: disease control rate; Gem/Cis: gemcitabine and cisplatin; GEMOX: gemcitabine and oxaliplatin; TARE: transarterial radioembolization; IO: immunotherapy; SOC: standard of care.

can detect residual tumor burden long before it becomes clinically visible, making it a promising tool for identifying minimal residual disease [46].

Surgical Considerations After Conversion

Successfully converting a tumor is only the first step; the subsequent surgery presents unique challenges.

Timing: Surgery is typically performed 4-8 weeks after the last dose of neoadjuvant therapy to allow for recovery from treatment-related toxicities and adequate tumor response assessment [3, 26].

Managing fibrosis: Intensive preoperative therapy, especially regimens containing anti-angiogenic agents like lenvatinib, can induce significant peritumoral fibrosis and make dissection planes more challenging.

FLR optimization: For patients with insufficient future liver remnant, techniques to induce hypertrophy are essential. Portal vein embolization (PVE) is a standard method, while associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) offers a more rapid and potent hypertrophy, particularly for locally advanced ICC, and has been associated with significantly improved OS compared to palliative chemotherapy [47].

INTEGRATED PRECISION-MULTIMODAL TREATMENT ALGORITHM

The evolving landscape of ICC management necessitates a structured yet flexible approach that integrates diagnostic findings, molecular data, and therapeutic modalities. The following algorithm provides a practical, evidence-based framework for clinical decision-making, designed to maximize the potential for curative-intent outcomes by leveraging the principles of precision medicine and multimodal therapy.

Workflow Overview

A robust initial workup serves as the cornerstone of effective patient stratification; without this foundation, the implementation of specific treatment pathways is impossible.

Diagnostic foundation: The process begins with a comprehensive evaluation, necessitating high-quality cross-sectional imaging [computed tomography (CT) / magnetic resonance imaging (MRI)] and definitive histopathological confirmation.

Molecular profiling: In the current era, the diagnostic workup must extend beyond histology. Routine NGS of tumor tissue is strongly recommended,particularly for locally advanced or metastatic disease - to identify actionable alterations such as *FGFR2* fusions or *IDH1* mutations. Furthermore, concurrent testing for immune biomarkers (PD-L1, MSI, TMB) provides the necessary data to inform a comprehensive therapeutic strategy [10, 48].

Multidisciplinary evaluation: Complex treatment decisions should not be made in isolation. A dedicated MDT discussion, convening hepatobiliary surgeons, medical and radiation oncologists, interventional radiologists, and pathologists, is critical. This forum allows for the synthesis of anatomical, biological, and functional data, ensuring that the patient's disease is accurately categorized and assigned to the optimal treatment track [49, 50]. Thus, the MDT functions

not merely as a logistical planning body, but as the key forum in which technical resectability is weighed against likely oncological benefit.

Detailed Clinical Pathways

Based on the MDT assessment and biomarker profile, patients should be stratified into the following clinical pathways, which are designed to be dynamic, with regular re-evaluation for surgical candidacy. Where available, the distinction between small duct and large duct subtypes should be considered, as it is associated with characteristic molecular patterns and may inform the likelihood of actionable alterations [18].

Pathway A - Actionable Mutation Present

This pathway prioritizes the use of targeted therapy for patients with identified driver alterations (more frequently observed in the small duct subtype).

A1: *FGFR2* fusion

→ Targeted *FGFR* inhibition (e.g., Pemigatinib): This targeted approach is supported by the FIGHT-202 trial, which demonstrated an ORR of 35.5% in this population [7, 21].

→ Re-evaluate: Assess response every 2-3 cycles using imaging and tumor markers.

→ Surgery: If significant downstaging is achieved and resection becomes feasible, proceed with curative-intent surgery.

A2: IDH1 Mutation

→ *IDH1* inhibitor (e.g., ivosidenib) **:** Based on the ClarIDHy trial, which showed a survival benefit for ivosidenib in patients with IDH1-mutant advanced cholangiocarcinoma [8, 16].

→ Re-evaluate: Monitor for response and resectability.

→ Surgery: Proceed to resection if conversion is successful.

Pathway B - no driver mutation but immunotherapy candidate

For patients without a targetable driver but with features suggesting sensitivity to immunotherapy. Although these are pan-tumor characteristics, their identification is crucial for selecting ICC patients eligible for immune checkpoint inhibition.

▪ Biomarkers: dMMR/MSI-H and/or TMB-H (PD-L1 positivity may be considered supportive, acknowledging its imperfect predictive value in biliary tract cancer).

→ First-line Chemo + Immunotherapy: The current standard, based on Level 1 evidence from the TOPAZ-1 and KEYNOTE-966 trials, is GC + D or Pembrolizumab [9, 41]. For highly selected cases or in clinical trials, more intensive regimens like Toripalimab + Lenvatinib + GEMOX (ORR 80%) may be considered [38].

→ Re-evaluate: Assess for radiologic and biologic response.

→ Surgery: If downstaged to resectability, surgical intervention is recommended.

Pathway C - locally advanced without actionable drivers

For patients with locally advanced, biomarker-negative disease (often enriched for KRAS/TP53 alterations and more commonly associated with large duct biology), where locoregional control is a key component of conversion strategy.

→ **Systemic Chemotherapy + Locoregional Therapy:** First-line treatment with Gemcitabine/Cisplatin should be combined with a locoregional modality such as TARE (Y-90), HAIC/HAIP, or TACE in appropriate candidates. This approach is supported by studies showing conversion rates of 10-25% and superior tumor control when combining systemic and local therapies [27, 28, 33].

→ **Re-evaluate:** Monitor closely with imaging (including mRECIST criteria for locoregional therapy response) and tumor marker trends (CA19-9, CEA).

→ **Surgery:** Proceed with resection if the tumor is successfully downstaged and adequate FLR can be achieved.

Special Pathway: perihilar cholangiocarcinoma (pCCA) meeting strict transplant criteria

It is crucial to distinguish this pathway, which is specific to a highly selected subset of perihilar, not intrahepatic, cholangiocarcinoma.

→ Neoadjuvant Chemoradiation (Mayo Protocol): A rigorous regimen of external-beam radiation therapy with radiosensitizing chemotherapy (5-FU/Capecitabine), often supplemented with brachytherapy; tumor-marker trends (e.g., CA19-9 when interpretable) may support biologic selection, although values can be confounded by biliary obstruction or cholangitis [51, 52].

→ Staging Laparotomy: A mandatory exploratory surgery to rule out occult peritoneal or nodal metastases before proceeding; this step excludes approximately 25% of patients [53, 54].

→ Liver Transplantation: For patients who successfully complete neoadjuvant therapy and have a negative staging laparotomy, liver transplantation offers excellent long-term outcomes, with 5-year recurrence-free survival rates of 65% [53, 55]. The success of this protocol raises a provocative question: can the "transplant paradigm" be extended beyond perihilar disease? Whether a similar biology-driven transplant strategy could be safely offered to carefully selected patients with intrahepatic cholangiocarcinoma-particularly those achieving sustained disease control after conversion therapy-remains an open and controversial issue.

Fig. 2 provides an integrated precision-multimodal treatment algorithm for locally advanced and unresectable ICC.

PERIOPERATIVE MANAGEMENT

Successful surgery after neoadjuvant or conversion therapy is an important milestone in the patient's journey. This phase requires careful planning and management to navigate the anatomical and physiological changes caused by the treatment.

Preoperative Assessment: A comprehensive preoperative workup is essential to confirm the feasibility and safety of resection after downstaging therapy.

Radiologic Response: High-quality cross-sectional imaging (contrast-enhanced CT or MRI) is mandatory to reassess tumor anatomy, vascular relationships, and the extent of residual disease. This evaluation confirms that an R0 resection is achievable based on the new post-treatment anatomy.

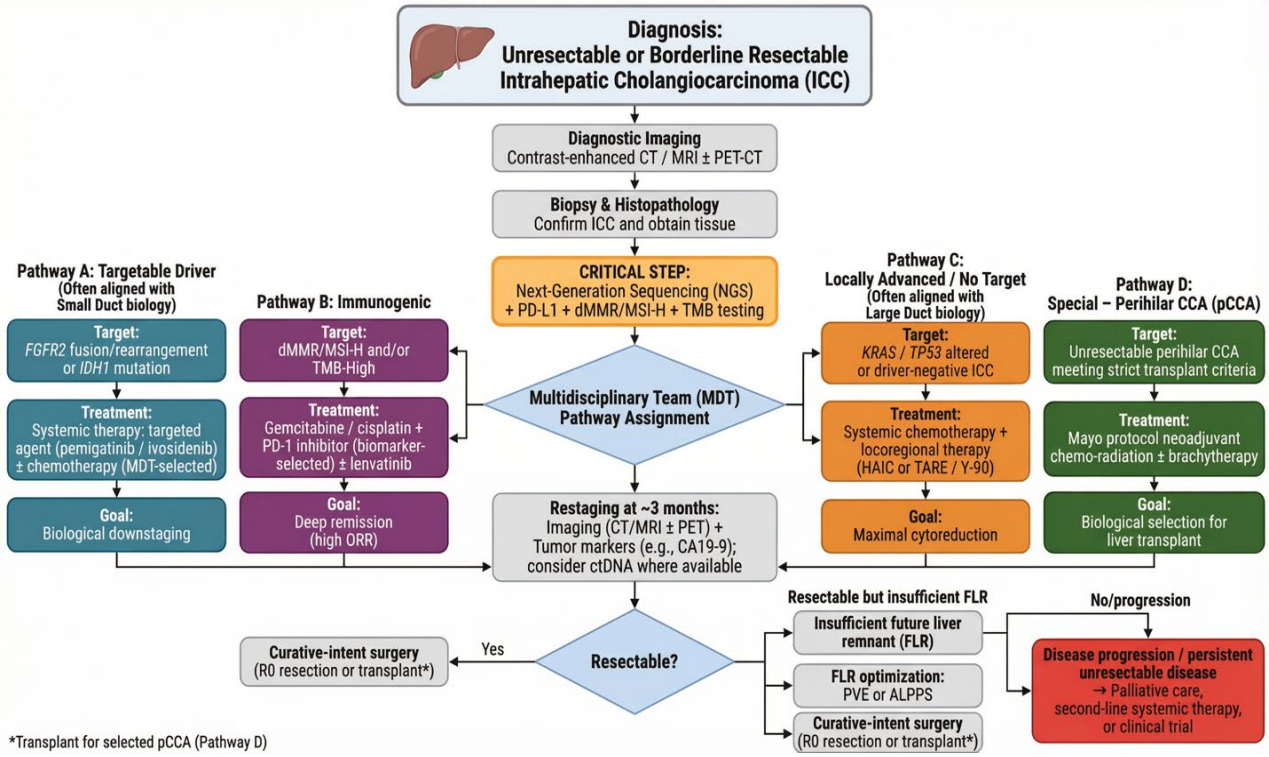

Fig. 2. Integrated precision-multimodal treatment algorithm for locally advanced and unresectable ICC. The workflow mandates upfront molecular profiling (NGS) to stratify patients into distinct therapeutic pathways. Pathway A (often aligned with Small Duct biology) utilizes targeted inhibition for actionable drivers such as FGFR2 fusions/rearrangements and IDH1 mutations. Pathway B leverages biomarker-selected immunotherapy-based regimens for pan-tumor immunogenic subsets (e.g., dMMR/MSI-H and/or TMB-H). Pathway C (often aligned with Large Duct biology) combines systemic chemotherapy with locoregional therapies (HAIC/TARE) for bulk tumor control in biomarker-negative disease. Pathway D represents the specific transplant protocol for perihilar cholangiocarcinoma (pCCA). Regular MDT re-evaluation is crucial to identify the window of opportunity for surgical conversion.

Resectability Reassessment: The MDT must reconvene to reassess the patient's status using post-therapy imaging and overall clinical condition, confirming that the original barriers to resection have been adequately resolved [34, 49, 50].

Liver Function Evaluation: A thorough assessment of hepatic functional reserve is paramount. This includes standard liver function tests, volumetric analysis for FLR calculation, and functional tests such as indocyanine green (ICG) clearance. If the FLR is less than 25-30% in a healthy liver, or less than 40% in a compromised liver, there is a high risk of post-hepatectomy liver failure (PHLF). In these cases, techniques such as PVE or ALPPS are necessary to induce hypertrophy and mitigate this risk [56, 57].

Surgical Complexity After Treatment

The introduction of neoadjuvant and conversion therapies, while enabling surgery, can create significant technical difficulties.

Fibrosis: Systemic and locoregional treatments, particularly those involving anti-angiogenic agents like lenvatinib or radiation, can induce a dense peritumoral fibrotic reaction. As this fibrosis obliterates normal tissue planes, dissection becomes more difficult, increasing the risk of bleeding and injury to adjacent structures.

Vascular management: Treatment-related changes can complicate vascular control. As emphasized in the pCCA transplant experience, neoadjuvant radiotherapy is associated with substantially higher rates of hepatic artery (21%) and portal vein (22%) complications - such as thrombosis or stenosis - requiring specialized reconstructive techniques and vigilant monitoring [58, 59].

Biliary reconstruction: Radiation can render the bile ducts fibrotic and fragile, compromising anastomotic healing. In the pCCA transplant protocol, the standard biliary reconstruction must often be modified due to radiation effects on the duodenum. Furthermore, routine intraoperative frozen section analysis of the bile duct margin is essential to ensure oncologic clearance [52, 59].

Postoperative Therapy

Preoperative treatment and pathological findings guide the management strategy after successful resection.

Adjuvant pptions: For patients who receive neoadjuvant or conversion therapy, the choice of adjuvant treatment is not standardized. Clinicians may choose to continue the preoperative regimen if it was well-tolerated and effective, or switch to an evidence-based adjuvant therapy like capecitabine. This decision should be personalized based on the degree of pathological response, the preoperative regimen used, and patient tolerance [34, 60]. However, a critical uncertainty remains regarding how the adjuvant setting should be managed after intensive preoperative therapy. It is unknown whether additional cytotoxic chemotherapy improves outcomes in this group, or whether continuation of effective targeted or

immunotherapy (e.g., *FGFR* inhibition) in the adjuvant setting would yield higher cure rates.

Continuing targeted therapy: Researchers are actively investigating the role of continuing targeted therapies (such as *FGFR* or *IDH* inhibitors) after resection. While eradicating minimal residual disease is theoretically attractive, the benefits must be weighed against the risks of long-term toxicity and the current lack of prospective data supporting this practice.

Thromboprophylaxis: Given the elevated risk of thrombotic complications—particularly after major hepatectomy and in pCCA patients post-transplantation - long-term aspirin therapy is recommended for thromboprophylaxis in this specific population [59].

CHALLENGES, CONTROVERSITIES AND GAPS

The advances made in neoadjuvant and conversion therapy for ICC are promising. However, many challenges remain unresolved, and substantial evidence gaps persist. Recognizing and addressing these limitations is imperative for guiding future research and refining clinical practice.

Evidence Gaps

The biggest hurdle to establishing standardized protocols is the absence of high-level evidence. The current body of literature is dominated by retrospective series, small single-arm Phase II trials, and subgroup analyses, all of which are inherently subject to selection bias [3, 6]. There is a critical lack of large, randomized Phase III trials comparing modern conversion therapy followed by surgery against continued systemic therapy alone. Furthermore, the strict selection criteria of established curative pathways, such as the pCCA transplant protocol, limit their application to only a small subset (~2%) of patients, highlighting a significant accessibility gap [52, 53].

Biological vs. Anatomical Resectability

A central controversy in modern oncology is the definition of resectability. The traditional, purely anatomic definition (based on tumor location, vascular involvement, and FLR) is increasingly being challenged by the concept of biological resectability. The latter considers tumor behavior and responsiveness to therapy. The pCCA transplant protocol ingeniously incorporates a „biological test" by enforcing a waiting period after neoadjuvant therapy; patients whose disease progresses are excluded, thereby selecting those with more favorable tumor biology for the definitive transplant procedure [53]. However, no universal criteria exist to integrate radiological, metabolic (e.g., PET), and molecular responses into a standardized definition of biological resectability for ICC. This raises a fundamental question: how should "biological resectability" be defined? Future consensus will need to determine whether composite measures - such as radiologic response, CA19-9 normalization, and ctDNA clearance - should be incorporated into a formal definition, and whether ctDNA negativity might reasonably become a prerequisite for surgery in selected high-risk patients.

Optimal Timing

Determining the optimal timing for surgical intervention following successful conversion therapy remains one of the most significant clinical controversies. The question of how long to treat before deciding on surgery lacks a definitive answer, with studies using 3 to 6 cycles based on protocol rather than robust evidence [26, 61]. Similarly, the timing of surgery post-therapy balances the risk of tumor reprogression against the need for recovery from treatment-related toxicities and adequate tumor response. This decision is predominantly contingent upon the physician's experience and MDT discussion, as clear guidelines are absent [3, 6]. The observation that a longer interval between neoadjuvant therapy and transplantation in pCCA is associated with lower recurrence rates offers a compelling, though not directly transferable, rationale for a deliberate approach [52]. Research is urgently needed to define a rational "washout" period that allows resolution of treatment-related toxicities (including immune-related adverse events) while minimizing the risk of tumor regrowth during the interval before surgery.

Treatment Toxicities and Practical Limitations

The aggressive multimodal regimens required for conversion therapy introduce a distinct spectrum of toxicities that can jeopardize surgical eligibility.

Fibrosis: As previously discussed, effective downstaging often induces a dense fibrotic reaction around the tumor and vasculature. This biological response, while indicative of treatment effect, significantly increases the technical complexity of the subsequent resection.

Immune-Related Events: The integration of immunotherapy presents new challenges. Immune-related adverse events (irAEs), such as colitis or pneumonitis, occur unpredictably. These complications can necessitate prolonged steroid use or surgical delay, and in severe instances, may permanently preclude a patient from undergoing curative resection.

Accessibility: Beyond biology, practical barriers remain substantial. Global access to NGS testing and high-cost targeted agents is uneven. Furthermore, specialized locoregional therapies like HAIC and TARE are often restricted to high-volume centers, creating disparities in care delivery.

Long-term Oncologic Outcomes

While conversion rates and short-term survival data are increasingly reported, there remains a critical gap in long-term oncologic outcomes. Data on 3-year and 5-year overall and recurrence-free survival for patients who have undergone resection after conversion therapy are very limited. Retrospective studies suggest surgery after conversion has better outcomes than continued medication, but prospective long-term data are essential to validate the durability of this approach and justify its associated risks and costs [62]. Ultimately, it remains unclear whether "conversion" is equivalent to cure. We lack prospective evidence confirming whether conversion surgery truly cures more patients or primarily selects those with favorable biology; randomized trials comparing surgery with continued modern systemic therapy in responders will be required to resolve this fundamental uncertainty.

Molecular Heterogeneity and Biomarker Development

The molecular diversity of ICC presents a complex paradox. While this heterogeneity opens the door to personalized medicine, it also complicates the search for a universal biomarker [63]. We still lack a clear map of which specific molecular subtypes drive postoperative recurrence, and many proposed biomarkers have yet to prove their worth in clinical practice [64]. Beyond the established immunotherapy panel, PD-L1, MSI, and TMB, newer candidates are generating significant interest. Emerging markers such as ARID1A, BAP1, ctDNA, and Interleukin-6 show promise; however, until they are validated in prospective trials, they cannot be reliably integrated into routine decision-making for patient stratification [65-67].

FUTURE DIRECTIONS

The future of ICC management will be defined by the refinement of existing strategies and the integration of novel technologies.

Novel Therapies

Therapeutic development is moving beyond single-target inhibition to address resistance mechanisms. Next-generation inhibitors, such as futibatinib, are showing efficacy in patients who progress on first-line FGFR inhibitors, representing a critical salvage option for the „Targetable" pathway [15]. Simultaneously, combination immunotherapy strategies are evolving. Trials evaluating dual checkpoint inhibition (CTLA-4 + PD-1 blockade) and combinations with novel agents (e.g., CD40 agonists) aim to turn immunologically „cold" tumors „hot," potentially expanding the population eligible for Pathway B conversion [10, 68].

Emerging Biomarkers

Liquid biopsy (ctDNA) is poised to revolutionize perioperative decision-making. It offers a non-invasive method to monitor minimal residual disease (MRD) and distinguish true pathologic complete response from radiologic scar tissue, potentially sparing patients from futile surgery or guiding adjuvant therapy duration [46]. Additionally, multi-omics approaches integrating genomics with radiomics and proteomics are identifying „high-risk" signatures that predict early recurrence more accurately than traditional staging, allowing for better selection of neoadjuvant candidates [32, 64].

Integrating Artificial Intelligence

Artificial intelligence holds the potential to synthesize complex datasets, imaging, genomics, and clinical variables, to predict treatment response. Machine learning algorithms are being developed to predict outcomes after resection and response to immunotherapy, which could eventually power real-time, dynamic clinical decision support tools for the MDT [32].

Global Implementation

The difficulty in accessing these advanced modalities represents a substantial challenge. Currently, access to NGS testing, targeted agents, and complex procedures like liver transplantation is largely restricted to high-volume academic centers in developed nations. Moving forward, efforts must concentrate on democratizing access to precision medicine and establishing simplified, cost-effective protocols suitable for implementation in diverse healthcare settings [2, 10].

CONCLUSIONS

The management of intrahepatic cholangiocarcinoma is evolving from a static, anatomy-based framework to a dynamic, biology-driven model. This transition, driven by the integration of precision medicine and multimodal therapy, challenges established concepts of resectability.

Comprehensive molecular profiling has become a central entry point for biological stratification. By identifying the approximately 40% of patients with actionable alterations—including FGFR2 fusions and IDH1 mutations—clinicians can deploy targeted therapies that offer a well-tolerated path to tumor control. Concurrently, biomarker assessment for immunotherapy facilitates the use of chemoimmunotherapy regimens, which have delivered unprecedented response rates in non-driver mutated populations.

Building on this molecular foundation, neoadjuvant and conversion therapies have expanded the surgical candidate pool. For high-risk resectable disease, neoadjuvant therapy targets micrometastases to improve R0 resection rates. For initially unresectable ICC, intensive conversion therapy (utilizing triplets of chemotherapy, targeted agents, and immunotherapy) often augmented by locoregional modalities, can successfully downstage tumors to an operable status. Survival outcomes for these converted patients far exceed those achieved with palliative care alone.

Success in this new era depends on a structured integrated treatment algorithm and the central role of the multidisciplinary team. From diagnosis to re-evaluation, the MDT ensures that patients navigate the appropriate pathway, whether it involves targeted therapy, chemoimmunotherapy, or a combined systemic-locoregional approach.

Despite these advances, the field faces constraints, including a lack of standardized protocols and high-level evidence from randomized trials. Resolving controversies regarding surgical timing and managing treatment-related complexities remains a priority. Furthermore, addressing the gap in long-term oncologic outcomes after conversion therapy requires prospective validation.

Ultimately, the future of ICC management will be defined by next-generation therapeutics, the integration of real-world data, and the validation of dynamic biomarkers like ctDNA. The objective remains clear: refining patient selection and standardizing protocols to deliver the full promise of precision-guided therapy. Through these efforts, curative-intent surgery is becoming a realistic goal for a broadening population of patients.

Conflicts of interest: None to declare.

Authors' contribution: F.S. and J.L conceived the study, designed the methodology and collected the data. F.S. drafted the manuscript. J.L. revised the manuscript. Both authors read and approved the final version of the manuscript.

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