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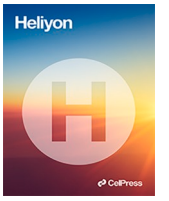

Review article

Design of studies on neoadjuvant therapy for intrahepatic cholangiocarcinoma

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ABSTRACT

The high recurrence rate and dismal prognosis of localized intrahepatic cholangiocarcinoma (ICC) indicate the unmet need for effective adjuvant and neoadjuvant therapy. In recent years, progress has been made in immunotherapy and targeted therapy for the treatment of advanced biliary tract cancer (BTC), leading to clinical exploration of the provision of these therapies in the perioperative period. Based on years of experience in clinical research on hepatobiliary cancers, the authors discuss the design of studies on neoadjuvant therapy for ICC, aiming to provide references for future neoadjuvant studies.

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) accounts for 10 %–15 % of primary liver cases [1], and its incidence is obviously rising worldwide [2]. Radical resection is currently the only curative treatment, but only some patients meet the surgical indications. Furthermore, even if radical resection is performed, approximately 60 % of patients will relapse within 1–2 years [3].

Neoadjuvant therapy [4] refers to preoperative systemic treatment or local treatment for technically resectable ICC with a high risk of recurrence to control the invisible minimal lesions as early as possible or to downstage the tumour to improve the R0 resection rate, increase the possibility of negative surgical margins, and thus reduce the postoperative recurrence rate. A cohort study of >4000 patients demonstrated that neoadjuvant combined surgery reduced the risk of death by 23 % compared with upfront surgery [5].The results of a propensity survival analysis showed that neoadjuvant chemotherapy is associated with improved overall survival (OS) over upfront surgery in patients with resectable ICC and a high risk of treatment failure [5]. These results suggest that neoadjuvant chemotherapy followed by surgery could improve the prognosis of patients with ICC, especially the locally advanced ICC patients. Although there is literature supporting the positive effects of neoadjuvant therapy, there is currently no standard regimen for neoadjuvant therapy for ICC [7]. The NCCN biliary tract cancer guideline recommend that appropriate patients participate in clinical trials of neoadjuvant therapy [8]. Because the concepts of "resectable" and "borderline resectable" ICC commonly depend on the institution and surgeon's experience and there are no clear objective criteria, the target populations for neoadjuvant and conversion therapy partially overlap. Therefore, neoadjuvant studies cover both neoadjuvant and conversion therapies. The 2023 ESMO Congress conducted a biliary tract carcinoma (BTC) neoadjuvant therapy study (DEBATE) [9], which included BTC patients with localized, potentially resectable, nonmetastatic disease determined by surgeons, among whom approximately 10 % were at clinical stage IV.

Systematic chemotherapy is the most frequently employed neoadjuvant therapy for ICC, predominantly utilizing the GemCis

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regimen of gemcitabine and cisplatin [10]. Along with the success of the TOPAZ-1 [11] and KEYNOTE-966 [12] studies, programmed death receptor-l (PD-1)/programmed death ligand 1 (PD-L1) inhibitors have been officially included in the systemic treatment of advanced biliary tract carcinoma (BTC). Especially in TOPAZ-1, the median overall survival and progression-free survival were significantly prolonged in patients receiving durvalumab plus gemcitabine and cisplatin and the confirmed objective response rate was also significantly higher in the durvalumab than in the placebo group. Chinese scholars have explored the innovative use of a "triple combination" (PD-1/PD-L1 inhibitor + chemotherapy + VEGF-TKI) [13–15] therapy to treat locally advanced or metastatic ICC to further improve the ORR, laying a foundation for neoadjuvant therapy for ICC. Although there are several controversies regarding ICC neoadjuvant therapy, based on abundant clinical experience with hepatobiliary carcinomas, the authors discuss thepopulation, intervention,control, outcom and time utilizing the PICOT framework, of studies on neoadjuvant therapy for ICC, expecting to provide additional references for the design of studies about ICC neoadjuvant therapy.

2. Population

BTC mainly includes ICC, ECC and GBC. Considering the sample size and recruiting time, the design of advanced BTC studies usually incorporates all three types. ICC patients accounted for 55%–60 % of the population in the newly published TOPAZ-1(11) and KEYNOTES [12] studies. Subgroup analysis showed that the efficacy of the ICC group was better, and the HRs of the ICC group in the two studies were 0.76 (95 % CI: 0.58–0.98) and 0.76 (95 % CI: 0.64–0.91), respectively. Professor Zhou Jian's "triple regimen" study included 100 % of the ICC population, and the final ORR was as high as 80 % [13]. However, BTCs exhibit significant heterogeneity, with distinct molecular characteristics across different anatomical sites. It would be reasonable to select only one site, e.g. ICC, as the target population in a trial.The selection of an ICC population is expected to improve the success rate when designing studies of PD-1/PD-L1 inhibitor-containing regimens for neoadjuvant therapy.

In addition, the target population of each study was set according to its purpose with no uniform standard. The use of ICC neoadjuvant therapy has just started, and the basic inclusion criteria at present are pathologically diagnosed patients with resectable ICC with high risk factors for recurrence and no visible imaging of extrahepatic lesions. In view of the "resectable" and "high risk factors" criteria, there are no clear objective definitions. The determination of "resectable" status usually depends on a multidisciplinary team comprising at least one expert in hepatobiliary surgery, leading to possible subjectivity and bias.

The guidelines for biliary tract cancers (2023 version) issued by the Chinese Society of Clinical Oncology (CSCO) [4] put forward the definition of "unresectable" for the first time considering ICC, hilar cholangiocarcinoma (HCCA), ECC and GBC. For example, unresectable ICC is defined as follows [1]: portal vein, hepatic vein, or main bile duct invasion, which cannot be resected or reconstructed [2]; for patients with decompensated cirrhosis or severe portal hypertension, future liver remnant (FLR) does not conform to the safe hepatectomy decision-making system [3,16] multiple tumours in the left and right liver; and [3] para-aortic lymph node metastasis or distant organ metastasis [5,17,18]. The authors consider this definition controversial, which is not discussed in this article. However, it can be used as a reference for the definition of "resectable" in the design of neoadjuvant therapy studies to help reduce the possibility of subjective bias.

The definition of "high risk factors" refers to the size, number, and distribution of tumours, vascular and nodal invasion, and baseline CA19-9 level. A meta-analysis involving 57 studies (4756 patients) [19] showed that lymph node metastasis, vascular invasion, multifocality, low histological differentiation and tumour size were high risk factors for the postoperative recurrence of locally advanced ICC. The CSCO Guideline [4] proposed the definition of "borderline resectable" biliary malignancy by referring to the definition of "borderline resectable pancreatic cancer". ICC, for example, is defined as follows [1]: a single tumour diameter >5 cm [2]; $\geq$ 3 tumours or tumours combined with satellite lesions [3]; portal vein or hepatic vein invasion [4]; regional lymph node metastasis; and [5] a preoperative CA19-9 level >200 U/ml. The authors believe that although this definition is still controversial, it can be used as a reference for the "high risk factor" criteria in the design of neoadjuvant therapy studies, especially when the goal is to downstage patients with borderline resectable disease to increase the likelihood of R0 resection. The NEO-GAP study [20] is the first prospective study of BTC neoadjuvant therapy, which included oncology patients with technically resectable ICC and high risk factors. The study set the risk factors as follows (confirmed by imaging) [1]: T stage Ib or higher [2]; a solitary lesion >5 cm [3]; multiple lesions or satellite lesions confined to the same lobe as the main lesion but still technically resectable [4]; major vascular invasion but still technically resectable [5]; suspicious or involved regional lymph nodes (N1); and [6] no extrahepatic distant metastasis (M0). The risk factors in this study coincided with the CSCO guideline definition of "borderline resectable" ICC, namely, patients with borderline resectable ICC were included in this study. Several ongoing neoadjuvant ICC studies (NCT04669496, NCT05640791, and NCT04989218) are using similar criteria of high-risk factors, and the results of these studies will further verify the rationality of high-risk criteria.

In the future, it is necessary to make the criteria of "resectable" more objective on the basis of clinical practice combined with subjective judgement. At the same time, it is necessary to clarify the definition of "high risk", reduce study heterogeneity, improve study reproducibility, and improve study comparability.

3. Intervention

3.1. Systemic thearpy

For neoadjuvant therapy for solid tumours, regimens that have been approved for indications or achieved significant ORRs in the advanced population are usually chosen. The current standard first-line treatment for advanced BTC is a PD-1/PD-L1 inhibitor

combined with a GC regimen (gemcitabine/cisplatin) [11,12], with an ORR ranging from 25 % to 30 %. In addition, a number of phase 2 trials of PD-1/PD-L1 inhibitors + chemotherapy + VEGF-TKIs have achieved a higher ORR [13–15] of approximately 35%–80 %. All of the above regimens can be used for exploratory studies of neoadjuvant therapy for ICC. According to the Clinical Trial website, most

Table 1
Neoadjuvant therapy for stage II/III BTC on the Clinical Trial website (updated as of Sep. 20th, 2023).

Number	Investigated drug	Primary endpoint	Included patients	Sample size	Stage	Design	High risks	Initiation time
NCT03579771	GAP	Treatment completion rate	ICC	31	II	Single arm	T-stage ≥ Ib (Ib-IV); Solitary lesion >5 cm; Multifocal tumours or satellite lesions present confined to the same lobe of the liver as the dominant lesion but still technically resectable; Presence of major vascular invasion but still technically resectable; Suspicious or involved regional lymph nodes (N1)	Sep. 2018 (Completed)
NCT04308174	GC + durvalumab	R0 resection rate	BTC	45	II	Controlled		May. 2020
NCT04523402	GEMOX vs. direct surgery	EFS	ICC	100	II	Controlled	LN metastasis (Probability of LN metastasis ≥50 % as evaluated by radiomics model)	Dec. 2020
NCT04669496	GEMOX + toripalimab + lenvatinib vs. direct surgery	EFS	ICC	178	II/III	Controlled	tumor diameter>5 cm or imaging vascular invasion, multiple tumor nodules or hilar lymph node metastasis or preoperative CA199 > 37U/ml	Jan. 2021
NCT05640791	GAP + durvalumab	Treatment completion rate	BTC	40	II	Single arm	T-stage ≥ Ib (Ib-IV); Solitary lesion >5 cm; Multifocal tumours or satellite lesions present confined to the same lobe of the liver as the dominant lesion but still technically resectable; Presence of major vascular invasion but still technically resectable; Suspicious or involved regional lymph nodes (N1)	Dec. 2022
NCT04989218	GC + durvalumab + tremelimumab	ORR	ICC	20	II	Single arm	Solitary lesion >5 cm; T1b-T4 tumor thought to be technically resectable; Multifocal tumours/a tumor with satellite lesions confined to the same lobe, thought to be technically resectable; Suspicious or involved lymph nodes (N1) thought to be technically resectable; Tumor with any vascular involvement/ invasion considered technically resectable	Jan. 2023
NCT06037655	GC + adebrelimab + mecapegfilgrastim	ORR	BTC	30	II	Single arm		Sep. 2023
NCT06037980	GAP vs. direct surgery	12-m PFSR, PFS	BTC	300	II/III	Controlled	For iCCA: presence of satellitosis or multifocal disease or radiological suspicion of tumoral diaphragmatic adhesion. size of the liver lesion >5 cm.Ca19.9 > 100 U/mL.	Nov. 2023
NCT06017297 (Conversion + neoadjuvant)	GC + durvalumab + tremelimumab	Conversion rate	ICC	28	II	Single arm		Nov. 2023

of the studies currently being carried out are based on the "triple regimen" of addition, reduction and replacement, covering almost all available drugs (Table 1). Chemotherapy drugs, immune drugs and targeted drugs are discussed as follows.

3.1.1. Chemotherapy

Chemotherapy drug selection should refer to the first-line chemotherapy regimen for advanced BTC. The authors recommend the GemCis regimen as the preferred choice. First, the GC regimen combined with durvalumab or pembrolizumab(Class 1 evidence) is internationally recognized as the first-line treatment for advanced BTC and is listed as the preferred regimen in the NCCN guidelines for cholangiocarcinoma (2024, Version 1) [8], with the most extensive data support. Second, the GC regimen itself is also listed as the preferred regimen in the NCCN guidelines (Class 1 evidence), and multiple phase 3 trials have demonstrated that this regimen maintains an ORR of 20–30 % in treating advanced BTC [11,12,21,22], with stable and repeatable efficacy. Adding more drugs to this regimen can further improve treatment success rates. Third, cisplatin's common toxicities are gastrointestinal reactions, hearing loss, and renal toxicity, while gemcitabine's common toxicities are thrombocytopenia, fever, and rash, and the toxicities of the two drugs do not completely overlap. Other chemotherapy regimens, such as GS (gemcitabine + tegafur/gimeracil/oteracil), FOLFOX (oxaliplatin + fluorouracil), GEMOX (gemcitabine + oxaliplatin), XELOX (oxaliplatin + capecitabine), and GAP (gemcitabine + albumin-bound paclitaxel + cisplatin), are also listed in guidelines [8] as other recommended regimens for advanced BTC, with weaker evidence than the GC regimen. Among these regimens, the GAP regimen achieved an ORR of up to 45 % in a phase 2 trial of first-line treatment for advanced BTC [23]. Unfortunately, the ensuing phase III trial (SWOG 1815) [22] did not demonstrate a statistically significant improvement in overall survival with GAP compared with GC, but the ORR was higher (31 % vs. 22 %), and GAP seemed to be more active in the locally advanced setting than in the metastatic setting (ORR: 28 % vs. 21 %). Although these subset analyses were not adequately powered, it does seem that there may be a place for GAP for localized tumours in the preoperative setting, given the improved response rate. However, the treatment-related adverse events of the GAP regimen were significantly higher than those of the GC regimen. Therefore, studies with designs invoking the GAP protocol need to carefully balance the relationship between efficacy and toxicity.

3.1.2. Immunotherapy

The selection of immunotherapy drugs should be based on the first-line immune therapy regimen for advanced BTC. The preferred choice is durvalumab or pembrolizumab, which have been approved for the treatment of advanced BTC. Second, the CSCO guidelines [4] recommend the use of toripalimab [13] and camrelizumab [24,25] for the treatment of advanced BTC, which have been confirmed to be effective and safe in phase 2 trials. Other PD-1/PD-L1 inhibitors for BTC that have not been studied but have similar mechanisms to the above antibodies, which have been proven to be effective and safe in treating other solid tumours, can also be considered.

Currently, PD-1/PD-L1 inhibitors combined with GC regimens have an ORR of 25 %–30 % in the treatment of advanced BTC (11,12). The DEBATE study [9] combined durvalumab with GC as neoadjuvant treatment for BTC, achieving an ORR of 36 %. Only 68 % of the patients underwent surgical evaluation, and 61 % of the patients underwent R0 or R1 resection, indicating a relatively low overall resection rate. The ORR of chemotherapy combined with immunotherapy cannot support its use as neoadjuvant therapy, and a regimen with a higher ORR, such as combining targeted drugs, is needed.

In addition, the preliminary results of a phase 2 trial of the combination of dual immune drugs for advanced BTC are available. The Medtreme study [26] showed that the GC regimen combined with durvalumab and tremelimumab as first-line treatment for advanced BTC had an ORR of up to 70 %. The anti-PD-L1 antibody SHR-1316 in combination with the anti-CTLA-4 antibody IBI310 was studied in a small-sample phase 2 study of patients with ICC who were naïve or previously treated with ICIs. The results showed that the ORR was 25 % and 15.4 % for the two groups, respectively [27]. Given the ORR of 70 %, a clinical study is currently underway to evaluate the use of the GC regimen combined with durvalumab and tremelimumab as neoadjuvant therapy for BTC (NCT06017297).

3.1.3. Targeted therapy

Targeted therapy is currently not a first-line standard treatment for advanced BTC. Phase 2 small-sample trials have shown that VEGF-TKIs combined with chemotherapy and PD-1 inhibitors as first-line treatment for advanced BTC have improved ORRs compared to GC chemotherapy [13–15]. A phase 3 confirmatory study (NCT05342194) has been initiated. The CSCO guidelines for cholangiocarcinoma [4] recommend lenvatinib [13], anlotinib [28], Surufatinib [29], and regorafenib [30], all of which have been proven to be effective and safe in phase 2 trials. As targeted drugs are not yet standard treatments for advanced BTC, their use in neoadjuvant therapy requires consideration of both toxicity and efficacy.

The large molecule bevacizumab has also been explored regarding advanced BTC treatment. The phase 2 IMbrave151 trial [31] included patients with advanced BTC in the first-line treatment population, and patients were randomly assigned to the GC + atezolizumab + bevacizumab group (79 patients) and the GC + atezolizumab group (83 patients). Finally, there was no difference in the ORR between the two groups (24.1 % vs. 25.3 %). Given the results of the IMbrave151 trial and the need to discontinue bevacizumab for 6 weeks prior to surgery, it is recommended to use bevacizumab in ICC neoadjuvant therapy with caution unless new efficacy data become available.

With the advancement of genetic testing technology and the development of precision medicine concepts, the genomic profiling of BTC and the identification of specific molecular alterations that can be used as therapeutic targets are being studied. Multiple targeted drugs have been studied and have shown good efficacy in BTC, including FGFR2 inhibitors (pemigatinib, infigratinib, and futibatinib), IDH1 inhibitors (ivosidenib), and HER-2 inhibitors (zanidatamab), and many other targets, such as BRAF, NTRK, KRAS G12C, RET, PI3K, and c-MET, are also being studied. Among these targets, FGFR2 inhibitors have an ORR as high as 30–50 % [32–35]. Currently, infigratinib combined with chemotherapy is being studied in patients with FGFR2 fusions/rearrangements in the OPTIC trial

(NCT05514912). In the future, precision medicine will be further explored in the field of neoadjuvant therapy, including combination therapy and single-agent therapy. It should be noted that the ORR and safety remain the cornerstones of neoadjuvant therapy.

3.2. Local treatment

The local treatment in neoadjuvant therapy is mainly used for locally advanced or potentially resectable ICC, including transcatheter arterial chemoembolization (TACE), hepatic artery infusion (HAI), transcatheter arterial radioembolization (TARE), and radiotherapy. By combining local and systemic treatment, the local control rate can be improved, and the staging can be reduced to improve surgical resection rates. It should be noted that the operational process of local treatment is closely related to the surgeon, and standardization and homogenization are difficult. In addition, in the neoadjuvant study of ICC, it is necessary to clarify the contribution of each treatment method to the overall treatment and balance the relationship between efficacy and toxicity.

3.2.1. TACE

ICCs are tumours with little blood supply, so the response to TACE is poor. Since most deaths related to ICC are caused by liver failure, TACE, especially Drug-Eluting Bead (DEB)-TACE, can be used to control locally advanced ICC. There are also some studies on the neoadjuvant treatment of cholangiocarcinoma with TACE. Most patients can only reach disease stabilization after TACE treatment, and there are relatively few reports of overall conversion to resectable status. Future combined regimens may need to be considered to improve response rates.

3.2.2. HAI

HAI has been used for locally advanced ICC for 20 years. Multiple prospective and retrospective studies have shown that the ORR of HAI is higher than that of intravenous administration during the same period [36,37]. A phase 2 clinical trial published in 2020 showed that patients with unresectable ICC who received combined HAI fluorouracil + gemcitabine + oxaliplatin achieved a PFS of 11.8 months and an OS of 25.0 months, with 10.5 % of patients achieving R0 resection [38]. To further improve the drug therapy response rate, Wang et al. [39] used HAI chemotherapy (FOLFOX regimen) combined with bevacizumab and trifluridine/tipiracil for advanced BTC, including 32 patients. The ORR reached up to 82.3 %. The ASCO GI conference in 2024 reported a Hai pump chemotherapy in patients with advanced intrahepatic cholangiocarcinoma confirmed to the liver phase 2 pump II trial for the treatment of advanced ICC, which showed an orr of 46 %, a surgical resection rate of 8 %, and a pathological complete response rate of 1 % [40].Neoadjuvant treatment urgently needs a high ORR regimen; therefore, the use of HAI to improve efficacy is a good choice. Common side effects of HAI include hepatic and renal impairment. It is important to monitor liver and kidney function during treatment and before and after surgery.

3.2.3. TARE

Through the local internal irradiation effect, TARE can effectively deliver radioactive material to the tumour area, destroying tumour cells and reducing damage to healthy tissue as much as possible. TARE improves tumour downstaging in some ICC patients, which has the potential for neoadjuvant therapy. Yttrium-90 (Y-90) is used to treat locally advanced ICC, which can reduce a patient's stage to a surgically resectable level. Al-Adra et al. [41] conducted a pooled analysis of studies on the use of Y-90 in patients with unresectable ICC and found that the partial response rate after Y-90 treatment was 28 %. Although TARE provides good local regional control, when used alone, the low response rate limits the downstaging effect of neoadjuvant therapy. The combination of TARE with systemic therapy is a current research direction, and multiple studies (NCT06058663, NCT04238637) have been launched. Another advantage of Y-90 is that the overall incidence of complications following radioembolization is low, with significant adverse events occurring in less than 9 % of patients [42], but its high cost has limited its clinical application.

3.2.4. Neoadjuvant radiotherapy

Stereotactic radiotherapy has the advantages of high accuracy, the precise delivery of high-dose radiation, a rapid treatment process, a wide application range, low toxicity and few side effects, and it has good prospects in the conversion treatment of ICC. In a study on neoadjuvant chemoradiotherapy for BTC [43], 60 % of patients underwent pancreaticoduodenectomy, 32 % of patients underwent hemihepatectomy due to cholangiocarcinoma or gallbladder cancer (GBC), and 96 % of patients achieved R0 resection. This study confirmed that neoadjuvant therapy is feasible and may improve survival by controlling regional progression. A retrospective study [44] found that chemotherapy combined with radiotherapy can be used as a neoadjuvant therapy option. The 3-year recurrence-free survival (RFS) rates for patients who did and did not receive neoadjuvant therapy were 78 % and 58 % ($P = 0.0263$), respectively, and neoadjuvant therapy improved OS. Locally advanced BTC may be treated with preoperative neoadjuvant chemoradiotherapy to achieve the purpose of downstaging and improving surgical resection rates. However, radiotherapy may increase the difficulty of surgery and the risk of related complications due to damage to liver tissue and portal vessels. The impact of neoadjuvant radiotherapy on the safety of surgery needs more clinical trial data to confirm.

3.3. Adjuvant therapy

The BILCAP [45] and ASCOT [46] studies demonstrate that, following radical resection of BTC, patients can reap significant benefits from adjuvant treatments with capecitabine and S1(Tegafur, Gimeracil and Oteracil Potassium Capsules). Two other phase-III randomized clinical trials failed to show whether adjuvant chemotherapy based on gemcitabine [47] or gemcitabine plus oxaliplatin

[48] improves the OS or RFS in patients with BTC. In the NEO-GAP study [23], patients underwent 4 cycles of preoperative GAP chemotherapy, followed by postoperative observation. In the DEBATE study [9], patients underwent 4 cycles of preoperative GC chemotherapy combined with durvalumab, followed by no further chemotherapy but 6 cycles of durvalumab treatment postoperatively. The GAIN study [49] included patients with resectable or borderline resectable cholangiocarcinomas scheduled to receive perioperative chemotherapy (gemcitabine + cisplatin for 3 cycles pre- and postsurgery) or undergo surgery alone followed by a therapy of the investigator's choice. In the Neotorch study for lung cancer [50], patients underwent 3 cycles of preoperative chemotherapy, followed by 1 cycle of postoperative chemotherapy, and PD-1 inhibitor treatment was administered for approximately 1 year before and after surgery.

For patients who have received neoadjuvant therapy, the need for postoperative adjuvant therapy is still uncertain. Given the complexity of ICC surgery, whether postoperative adjuvant therapy is needed should be decided by the investigator. The investigator can decide whether to use adjuvant therapy based on the surgical resection and pathological response to treatment, without affecting the study endpoint ORR and MPR, but it may affect the outcomes of event-free survival (EFS) and OS. Due to the physical condition of patients after surgery, continuing with preoperative chemotherapy regimens may not be tolerable. Therefore, the authors recommend considering 6 months of postoperative adjuvant capecitabine treatment, which also facilitates cohort studies with patients who undergo surgery directly. AstraZeneca has registered a Phase III ARTEMIDE Biliary01 (NCT06109779) clinical trial on ClinicalTrials.gov, evaluating the efficacy and safety of Rilvegostomig (TIGIT/PD1 bispeciantibody) combined with chemotherapy for adjuvant therapy of BTC. VEGF-TKI has not been approved for indications in advanced BTC, and there are no ongoing prospective adjuvant studies that include targeted therapy. Whether targeted and immune therapies should be used postoperatively is not currently known and should be evaluated carefully based on efficacy and safety before application.

Circulating tumour cells and DNA are expected to become novel markers for diagnosis, treatment efficacy and prognosis. The DYNAMIC study [51] used ctDNA to guide postoperative adjuvant chemotherapy in patients with stage II colon cancer, with the decision to use adjuvant chemotherapy based on the ctDNA detection results. This approach allowed nearly half of the patients to avoid adjuvant chemotherapy. Future postoperative adjuvant therapy for ICC will be designed based on tumour biology for personalized treatment.

4. Control

The control should be designed based on the research purpose. If a new regimen is being explored for the first time, a small sample, single-arm study can be started. Further cohort studies or randomized controlled trials can be carried out based on single-arm studies. The experimental group is the neoadjuvant therapy group, and the current standard treatment can be chosen for the control group. The standard treatment for the perioperative period is adjuvant chemotherapy after surgery for ICC, and these patients can be included as a control group to compare the advantages and disadvantages of neoadjuvant therapy and postoperative adjuvant therapy. Randomized, controlled phase II/III trials of neoadjuvant therapy for BTC, conducted by Niger (Italy) and Fan (China), selected patients who underwent direct surgery combined with postoperative capecitabine chemotherapy as the control group (NCT04669496, NCT06037980).

5. Outcome

The study endpoint should match the research purpose, and there is no unified standard. For example, in the NEO-GAP study [20], the primary endpoint was set as the treatment completion rate, defined as the percentage of patients who completed all preoperative and surgical treatments. As neoadjuvant therapy for ICC is still in the exploratory stage, we must first establish the safety and feasibility of such an approach. Therefore, the treatment completion rate and safety are the primary observation indicators, followed by commonly used endpoints such as the ORR, OS, EFS, the MPR, and the pathological complete response (pCR). Due to the brief duration of neoadjuvant therapy and the ORR of approximately 30 %, its correlation with OS is uncertain. Therefore, ORR is not suitable as the primary study endpoint. OS is most commonly used as the primary endpoint in advanced BTC trials [11,12]. However, patients undergoing surgery have longer survival times, and subsequent treatment after recurrence can impact OS. Hence, it is unsuitable as the primary endpoint for neoadjuvant therapy. MPR can be identified by the ratio of viable tumor cells (RVTCs) in pathological specimens, calculated by dividing the remaining viable tumor area by the total tumor area. However, there is still a lack of experience in the pathological evaluation of the MPR threshold for ICC neoadjuvant therapy. It is recommended to report in the form of levels of $\leq$10 %,>10 %–30 %,>30 %–50 %,>50 % to accumulate more data.Interim analyses or futility analyses must be conducted to ensure that patients are not being harmed, which would mandate termination of the trial.

6. Time

6.1. Duration of the intervention

The duration of neoadjuvant therapy for ICC is currently not standardized, and it is generally recommended that patients undergo surgery after 3–4 cycles of treatment. A study on neoadjuvant therapy using camrelizumab combined with nab-paclitaxel and capecitabine in the treatment of locally advanced oesophageal squamous cell carcinoma [52] included 43 patients who received 3 cycles of neoadjuvant therapy, followed by CT and endoscopy after the second and third cycles. The results showed that compared to patients who received 2 cycles, patients who received 3 cycles of treatment had a higher ORR and an increased tumour downstaging rate. Last

year at the ASCO Congress, there was also a controlled study of NSCLC patients receiving neoadjuvant therapy (neoSCORE) [53], which found that 3 cycles of neoadjuvant therapy resulted in a higher major pathological response (MPR) rate than 2 cycles. Looking at phase 3 registered studies of neoadjuvant immunotherapy for lung cancer (CheckMate816 [54], AEGEAN [55], and Neotorch [50]), the preoperative administration of 3–4 cycles resulted in approximately 15–20 % of subjects not needing to undergo surgery.

Due to the high malignancy of ICC and the lack of effective drugs, the authors do not recommend a long duration of neoadjuvant therapy, avoiding tumour progression and losing the opportunity for surgery while ensuring the safety of invasive surgery after neoadjuvant therapy. Several studies that focused on conversion surgery for colorectal LM showed that the administration of long-term chemotherapy, including 5-FU and oxaliplatin, increased the incidence of liver failure from sinusoidal injury [56,57]. There are also studies reporting a slight degree of hepatic fibrosis caused by gemcitabine combined with cisplatin [58]. It is recommended that the overall preoperative treatment duration should not exceed 4 months. Evaluation should be conducted every 2–3 cycles, taking into account imaging results, tumor markers, and the patient's overall physical condition.

6.2. Follow-up period

The follow-up time should be aligned with the outcomes to confirm sufficient time over which participants are observed after the intervention The follow-up period is critical for assessing both short term and long term outcomes of the treatment Neoadjuvant therapy usually focuses on evaluating short term outcomes, but it is recommended to continue follow-up to evaluate long-term outcomes such as OS, and sufficient follow-up time can better observe safety.

7. Conclusion

Neo-adjuvant therapy for ICC presents several knowledge gaps, such as determining the most effective treatment regimens, identifying patients who would benefit most, and establishing reliable biomarkers for therapy response. Current research efforts are focused on addressing these gaps through clinical trials that compare different therapy combinations, alongside advances in molecular profiling to predict treatment outcomes. Looking forward, the next five years are expected to see significant developments in personalized medicine for ICC, with treatments increasingly tailored to the genetic profiles of individual tumours.

The design of neoadjuvant therapy for ICC is crucial and needs to be closely aligned with the outcomes, including the selection of the target population, choice of investigational drugs, involvement of local treatment, and implementation of specific protocols, all of which require sufficient data support, clinical practicality, and seamless interplay to ensure the smooth progress of the study. Risk management must be conducted throughout the entire study process, with dynamic tracking of competing studies and timely adjustment or even termination of the study.

Finally, not every study can be successfully completed with positive results, but negative results can also address some clinical needs. Studies can be patient-centred and research-oriented, designed from the top level with a layout considering diversified clinical studies.

CRediT authorship contribution statement

Yuan Cheng: Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation. **Xiangcheng Li:** Methodology, Conceptualization.

Ethical approval and consent to participate

Not applicable.

Data availability statement

Data associated with this study is not available in public repository because this is a review article and no original data have been used.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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