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Review Article

Neoadjuvant treatment for incidental gallbladder cancer: A systematic review

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Incidental gallbladder cancer (iGBC) diagnosed post-histopathological examination of gallbladders removed assuming benign gallstone disease constitutes a significant proportion of GBC patients. Most iGBC patients present with early-stage disease. The standard care for localized (non-metastatic) iGBC includes a reoperation for complete extended (radical) cholecystectomy involving liver resection and lymphadenectomy, followed by postoperative adjuvant systemic therapy. However, a major drawback of this approach is the high recurrence rate within six months post-radical surgery, which undermines the benefits of the extensive procedure; notably, most recurrences are distant, highlighting the efficacy of systemic therapy. Similar to other gastrointestinal cancers, there appears to be a potential for neoadjuvant systemic therapy (chemotherapy) before reoperative surgery in iGBC cases. The premise that neoadjuvant systemic therapy aids in selecting diseases with more favorable biological characteristics and addresses micro-metastatic disease appears applicable to iGBC as well. This systematic review examines the current evidence supporting or refuting neoadjuvant therapy and discusses criteria for selecting patients who would derive significant benefit, along with proposing an optimal chemotherapy regimen for iGBC patients. Improved outcomes have been reported in patients undergoing reoperation after 4 to 14 weeks following the initial cholecystectomy compared to immediate reoperation. Limited, yet promising, evidence supports the use of 3 to 4 cycles of gemcitabine-based neoadjuvant chemotherapy prior to reoperative surgery in select high-risk iGBC cases.

Key Words: Gallbladder neoplasms; Drug therapy; Neoadjuvant therapy; Cholecystectomy; Radiotherapy

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INTRODUCTION

Many gallbladder cancers (GBC) are diagnosed upon histopathological examination of gallbladders removed for conditions initially presumed to be benign biliary diseases, such as cholelithiasis. These are termed incidental GBCs (iGBC); they are typically diagnosed at an early stage without involvement of adjacent structures, organs, or major vessels and thus are more likely to undergo resection with curative intent (32% vs 14%), resulting in a more favorable prognosis compared to

non-iGBC, diagnosed preoperatively [1]. The standard treatment for iGBC involves revision surgery, determined by the depth of invasion into the gallbladder wall and the presence or absence of lymph nodes or distant metastases [2]. A non-R0 resection for GBC yields outcomes analogous to those of metastatic disease. For intraoperatively diagnosed GBC, the current National Comprehensive Cancer Network (NCCN) guidelines advise against immediate radical resection and recommend comprehensive staging prior to surgical intervention [3]. The management strategy for postoperatively diagnosed iGBC likewise begins with surgical staging. Simple cholecystectomy is the contemporary standard for tumor in situ and pT1a tumors [4]. Extended, also known as radical, cholecystectomy that includes adjacent liver tissue and regional lymphadenectomy, remains the standard-of-care for T1b and higher-grade tumors. Major hepatic resections, while considered for certain cases, are seldom performed initially and generally necessitate some form of neoadjuvant systemic therapy [5]. The timing of surgery for iGBC is under debate, with survival rates dependent on the cancer stage and the completeness of the revision surgery [6]. Additionally, over the last decade, most gastrointestinal malignancies have shifted towards some form of neoadjuvant therapy, offering various benefits such as improving tumor-related symptoms, treating micro-metastatic disease, providing insights into tumor biology and chemotherapy responsiveness, selecting tumors with favorable biology for surgery, enhancing treatment adherence, and downstaging the disease. We have investigated whether these advantages might be extendable to patients with iGBC as well.

METHODS

References for this review were identified through searches of PubMed/Scopus using the search terms "Incidental Gallbladder Cancer" AND "Neo-adjuvant" AND/OR "Chemotherapy/Radiotherapy" OR "Systemic Therapy" from January 2000 to January 2024. The searches yielded a total of 52 results. Only papers published in the English Language were reviewed. The final reference list was generated based on the originality and relevance of the articles to the extensive scope of this review, focusing specifically on the role of neoadjuvant therapy in iGBC (Fig. 1).

Re-resection as the standard-of-care for iGBC

Re-resection has been associated with improved surgical outcomes in iGBC in various studies [7-10]. For T1a tumors, cholecystectomy alone is generally sufficient. However, for T1b to T3 tumors, re-resection involving partial hepatectomy of the liver in the gallbladder bed and regional lymphadenectomy is advised [11-13]. The primary aim of reoperation is to eliminate any macroscopic or microscopic residual disease. T4 tumors typically exhibit invasion of the main portal vein, the proper hepatic artery, or two or more adjacent organs, and patients with these conditions generally do not benefit from reopera-

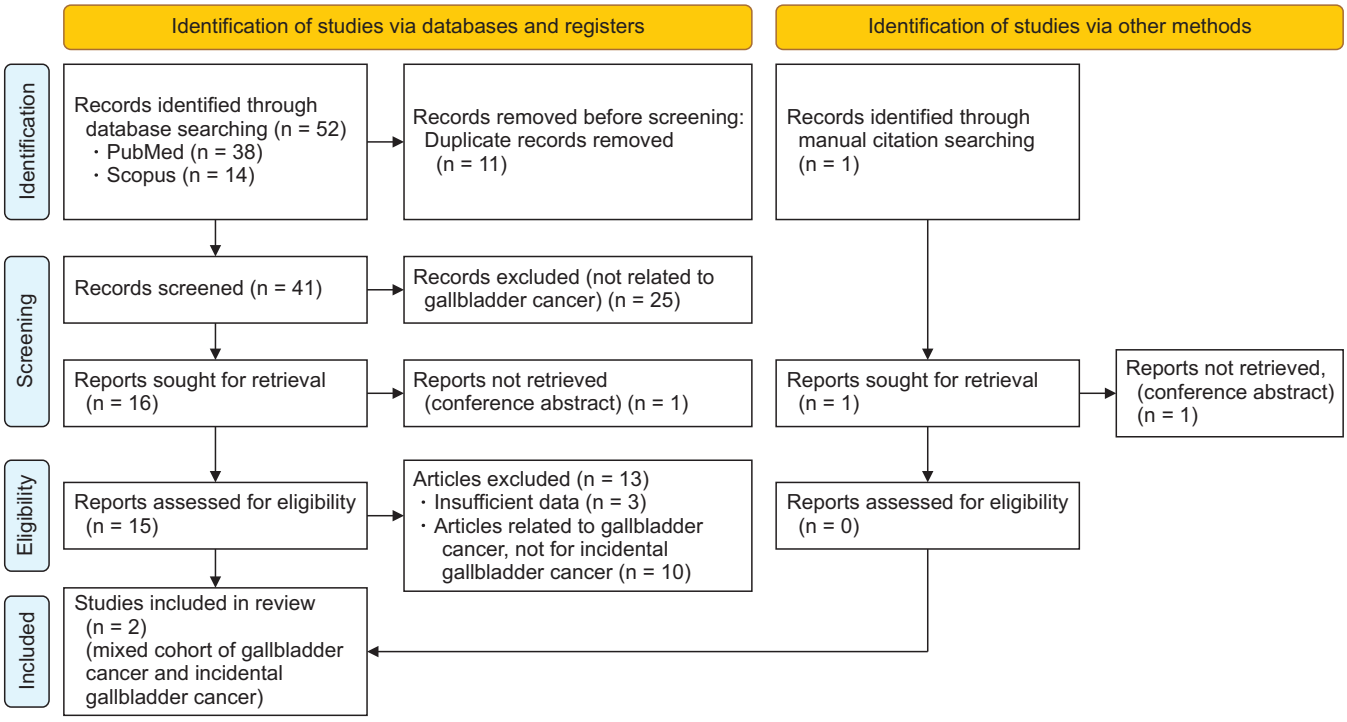

Fig. 1. PRISMA diagram.

tion. A Japanese study reported a 5-year overall survival (OS) rate of 42% for patients who underwent re-resection, compared to 15% for those who received non-surgical management in the form of systemic therapy alone [14]. An Memorial Sloan Kettering Cancer Center, New York (MSKCC) series indicated a disease-specific survival (DSS) of 42 months for a cohort of patients who underwent re-resection for iGBC [15].

Is there a role for neoadjuvant (after the initial cholecystectomy but before reoperation) therapy? If so, in which cases?

Although re-resection is linked with improved oncological outcomes in terms of survival for iGBC, it carries a theoretical risk of peritoneal dissemination due to violation of the subserosal plane during the original cholecystectomy. Additionally, bile spillage, often unmentioned in operative notes, is a significant factor that may lead to microscopic dissemination of tumor cells at the time of the initial cholecystectomy [16]. These factors are associated with adverse outcomes and early distant recurrences, which appear after re-resection. Studies have documented recurrences as soon as one month post reoperation, with a median time to recurrence of approximately 11 months, with the majority (85%) of recurrences being distant disease [17,18]. These early recurrences suggest that these were likely overlooked during imaging assessments for re-resection, thereby negating any potential benefits of the surgery (local therapy) undergone by these patients in the form of completion extended (radical) cholecystectomy. Thus, patients experiencing early recurrences after re-resection likely had pre-existing systemic disease. These findings urge a reconsideration of our surgical strategies and the exploration of the potential benefits of integrating neoadjuvant systemic treatment for such patients prior to re-resection.

IDENTIFYING HIGH-RISK PATIENTS

The management of iGBC primarily relies on the staging determined through histopathological examination of the gallbladder specimen obtained during the index cholecystectomy. The T stage is available by default and, occasionally, the nodal status may be assessed if the cystic lymph node is submitted along with the gallbladder specimen. An advanced T stage is associated with poor outcomes, as evidenced by multiple retrospective studies [15,19-21]. A French study reported 5-year OS rates of 100%, 62%, 19%, and 0% for T1, T2, T3, and T4 stages, respectively [22]. Recent evidence also indicates survival differences between T2a and T2b cancer stages [23,24]. Node-positive disease has similarly been linked to poor oncological outcomes across various series [15,21,25]. A study from the MSKCC reported a 5-year DSS rate of 51% for node-negative disease versus 17% for node-positive disease [21]. Therefore, submission of even a single cystic lymph node with the cholecystectomy specimen could provide prognostic significance and aid in identifying high-risk patients. Other factors linked to poor oncological outcomes include the grade of differentiation, lymphovascular invasion (LVI), perineural invasion (PNI), involvement of the common bile duct, jaundice, bile spill during the index cholecystectomy, and macroscopic residual disease post-cholecystectomy [16-23]. Early identification of these factors can stratify high-risk patients who may benefit from neoadjuvant systemic treatment and guide patient selection, thus potentially avoiding unnecessary surgery for those whose disease progresses or recurs during the neoadjuvant period.

NEOADJUVANT CHEMOTHERAPY

There is limited research addressing the indications for neoadjuvant chemotherapy (NACT) or adjuvant chemotherapy in iGBC; the management strategy for iGBC is extrapolated from that of non-iGBC.

CHEMOTHERAPY REGIMENS

In both iGBC and non-iGBC, adjuvant therapy is commonly utilized in patients with muscle-invasive (T1b and beyond), node-positive or margin-positive diseases [24,26-28]. The ABC-02 trial established the regimen of gemcitabine and cisplatin (GC) as the standard-of-care for patients with advanced biliary tract cancers (BTC), including GBC, demonstrating that this combination was associated with a survival benefit (11.7 months vs. 8.1 months; hazard ratio, 0.64; 95% confidence interval [95% CI], 0.52 to 0.80; $p < 0.001$) compared to single-agent gemcitabine. Furthermore, the tumor control rate in the GC group was significantly higher (81.4% vs. 71.8%, $p = 0.049$) [29]. The phase III study, SWOG 1815, evaluated the role of adding Nab-paclitaxel to the GC regimen in locally advanced and metastatic BTC, including 16% of patients with GBC [30]. Although it demonstrated better efficacy than historical data in an initial phase II single-arm study, subsequent studies from the same group [31] and an Indian study [32] failed to establish statistical significance of the triplet over the standard GC regimen in randomized trials. Similarly, the phase II PRODIGE 38 AMEBICA study randomized patients to the modified FOLFIRINOX (5-fluorouracil/leucovorin [5-FU/LV] plus irinotecan plus oxaliplatin) or standard-of-care GC regimen [33]. There was no statistically significant difference in median progression-free survival (PFS) or median OS between these two regimens, with 6.2 and 11.7 months for modified FOLFIRINOX, and 7.4 and 13.8 months for GC, respectively. Consequently, GC continues to be the backbone of chemotherapy for BTCs including GBC, as well as for studies integrating chemotherapy with immunotherapy in the first-line setting. The phase III trials, TOPAZ-1 and KEYNOTE-966, confirmed the PFS and OS benefits of adding immunotherapy—durvalumab or pembrolizumab—to the standard GC chemotherapy in an advanced set-

ting, thereby establishing it as the new standard-of-care [34,35]. However, the effectiveness of this combination treatment in the neoadjuvant setting remains to be tested. As immunotherapy may demonstrate a delayed benefit, its potential to improve response rates when added to chemotherapy as neoadjuvant therapy is still under investigation (Table 1).

Retrospective studies

Although no single-institution case series exclusively examines the outcomes of NACT in iGBC, there are case series that report outcomes of NACT in non-iGBC (resectable/locally advanced/borderline). Among these, two series specify the number of iGBC cases.

A study of 160 consecutive patients from India with locally advanced or borderline resectable GBC, including several cases of iGBC (specific number not mentioned), suggested that NACT using a combination of gemcitabine and platinum can be effective for patients categorized under the Tata Memorial Hospital, Mumbai, India (TMH) criteria. This NACT regimen shows added potential for downstaging tumors to resectable status. After NACT, 41.2% of patients were eligible for curative-intent resection. These patients exhibited significantly improved OS of 49 months vs. 7 months (p = 0.0001) and enhanced event-free survival of 25 months vs. 5 months (p = 0.0001), compared to those who did not receive NACT [36]. Another study from the MSKCC investigated the role of NACT in 74 patients with GBC, including 25 with iGBC. At the initial response assessment, approximately one-fourth experienced disease progression. Half of the patients maintained stable disease, and the remaining one-fourth achieved a partial response. The median OS for the entire cohort was 14 months (95% CI, 11.3–17.9). Among those undergoing surgery, patients who achieved definitive resection (constituting one-third of the study population) had a median OS of 51 months (95% CI, 11.7–55.3), vs 11 months (95% CI, 4.1–23.6) for those who were unresectable (p = 0.003) [37]. Two additional studies demonstrated tumor downsizing in 36% of patients and a resectability rate of 67% following NACT [24,25]. Drawing on data from the BilCap study, which included 447 patients and approximately 18% with muscle-invasive GBC, no improvement in OS was observed in the intention-to-treat analysis after administration of 8 cycles of capecitabine in the adjuvant setting [38]. Collectively, these data highlight the potential of systemic chemotherapy predominantly in the neoadjuvant rather than the adjuvant setting.

Systematic review and meta-analysis (GBC)

Although no systematic review or meta-analysis specifically addressing NACT in iGBC exists in the literature to date, a systematic review by Naveed et al. [39] explored the role of NACT

Table 1. Summary of studies with systemic therapy in gallbladder cancer

Study	Year	Phase	Number of GBC patients	Setting	Treatment regimen	0RR (%)	p value (ORR)	MedianPFS (mon)	MedianOS (mon)	HR; p value (OS)
ABC-02 [29]	2010	III	149	Advanced	GC vs. Gem	37.7 vs. 21.4 (GBC)	NS	8 vs 5	11.7 vs 8.1	HR = 0.64; p < 0.001
Engineer et al. [45]	2019	II	243	Advanced	GEMOX vs. BSC vs. FUFA	30.8 vs. 0 vs. 13.3	< 0.001	8.5 vs 3.5 vs 2.5	9 vs 4.5 vs 4.6	HR = 0.44; p = 0.03
MyPathway basket [49]	2021	II	16	Advanced	Pertuzumab plus trastuzumab	31	NA	4	10.8	NA
Das et al. [50]	2021	II	21	Advanced	Trastuzumab + chemotherapy vs. chemotherapy	70 vs. 16	< 0.01	9.7 vs 4.1	14 vs 6	HR = 0.08; p = 0.001
TOPAZ-1 [34]	2022	III	171	Advanced	Durvalumab + GC vs. GC	26.7 vs. 18.7	NS	7.2 vs. 5.7	12.8 vs. 11.5 (all patients)	HR = 0.94 (GBC)
SWOG 1815 [30]	2023	III	70	Advanced	GAP vs. GC	50 vs. 24 (GBC)	0.09	8.2 vs 6.4 (all patients)	17.0 vs. 9.3	HR = 0.74; p = 0.33
Gedela et al. [32]	2023	II	116	Advanced	GAP	67.6	NA	9.92	NA	NA
KHBO1401-MITSUBA [31]	2023	III	82	Advanced	GC + S1 vs. GC	41.5 vs. 15.0	< 0.001	7.4 vs 5.5	13.5 vs. 12.6	HR = 0.791; p= 0.046
KEYNOTE-966 [35]	2023	III	233	Advanced	Pembrolizumab + GC vs. GC	29 vs. 29	NS	6.5 vs 5.6 (all patients)	12.7 vs. 10.9 (all patients)	HR = 0.96
GECCOR-GB [47]	2024	III	90	Resected stage II/III (R0/R1 resection)	GC vs. capecitabine concurrent with chemoradiation (CCRT)	NA	NA	88.5% vs 74.5 % (1-year DFS)	26.7 vs. 11.4	NA

BSC, best supportive care; FUFA, 5-fluorouracil + folinic acid; GAP, gemcitabine + cisplatin + nab-Paclitaxel; GBC, gallbladder cancer; GC, gemciatbine + cisplatin; ORR, odds ratio; OS, overall survival; GEMOX, gemcitabine + oxaliplatin; PFS, progression-free survival; HR, hazard ratio.

in GBC. This review encompassed six published studies involving 420 patients who received NACT, wherein over 30% experienced disease progression despite treatment. Notably, while 67% displayed a favorable response to chemotherapy, only 33% (half of the responsive group) underwent curative surgery. For those achieving R0 resection, the OS ranged between 18.5 and 50.1 months, compared to 5.0 to 10.8 months for non-operated patients, underlining that only a minority substantially benefited from chemotherapy. Defining the advantages of NACT in treating resectable or borderline resectable GBC remains to be accomplished.

Randomized trial

To evaluate the necessity of NACT in iGBC, the ongoing GAIN study [40]—a multicenter, randomized, controlled, open-label phase III trial—is randomizing patients with resectable or borderline resectable iGBC to undergo either perioperative chemotherapy (GC; 3 cycles before and 3 cycles after surgery) or surgery alone followed by adjuvant therapy, at the discretion of the investigator. The inclusion criteria include histologically confirmed iGBC (T2–3, N-ve or T1-3, N+ve post simple cholecystectomy) without prior chemotherapy exposure. The results are anticipated to define the neoadjuvant management of iGBC. The current phase III GAIN study aims to ascertain whether induction chemotherapy, followed by radical resection in intrahepatic cholangiocarcinoma (ICC)/extrahepatic cholangiocarcinoma (ECC), and subsequent re-resection in iGBC (and, if feasible, postoperative chemotherapy) extends OS compared to radical surgery alone for iGBC and cholangiocarcinoma that is either resectable or borderline resectable.

In the USA, the recently activated OPT-IN trial (EA2197; ClinicalTrials.govidentifier: NCT04559139) compares perioperative (neoadjuvant) gemcitabine plus cisplatin with postoperative (adjuvant) treatment using the same regimen in patients with pT2 and pT3 iGBC. The outcomes of this trial are highly anticipated.

Neoadjuvant chemoradiotherapy

Despite the absence of definitive literature regarding the role of radiotherapy (RT) in iGBC, and its unclear role in GBC generally, RT is frequently administered alongside chemotherapy following an R1 or R2 resection. A meta-analysis by Ma et al. [26] demonstrated that OS in patients receiving adjuvant chemotherapy surpassed those undergoing chemoradiotherapy (CRT) or RT alone. Conversely, the SWOG0809 single-arm prospective trial indicated a potential benefit of adjuvant CRT over historical outcomes for patients with GBC and ECC following R1 resection. Currently, however, the evidence is not robust enough to endorse RT for any subset of GBC [41]. In a systematic review, Hakeem et al. [42] analyzed eight studies of NACT and neoadjuvant chemoradiotherapy (NACRT) in GBC but did not make comparisons between the two types of treatment. The review concluded that only those with advanced GBC, who subsequently underwent an R0 resection, may benefit from neoadjuvant therapy—representing merely one-third of the entire cohort. A handful of older studies report limited success with NACRT [43,44]. A phase III randomized clinical trial, POLCAGB, examining perioperative therapy (NACT vs. NACRT) in locally advanced GBC, is underway and is expected to clarify the role of NACRT in GBC [45].

What therapy (chemotherapy alone, radiotherapy alone, or chemoradiotherapy)?

The type of adjuvant therapy is determined by the tumor's sensitivity and the pattern of recurrence. Distant metastases account for approximately 85% of recurrences in GBC [46]. The recurrence pattern in GBC indicates that systemic neoadjuvant/adjuvant treatment may offer more effective control than radiation, which primarily serves a local consolidative function; this is likely applicable to iGBC as well. The GAIN study, POLCAGB trial, and OPTIN EA2197 trial may further elucidate the role of neoadjuvant therapy in GBC and iGBC.

For how long?

Although there is no high-quality data to recommend neoadjuvant therapy initially, even less evidence exists regarding its duration—ongoing trials suggest 3 (GAIN) or 4 (OPT-IN) cycles of NACT prior to surgery.

Timing of reoperation

Although retrospective, recent studies have reported improved outcomes in patients undergoing reoperation between 4–8/10–14 weeks after the initial cholecystectomy compared to those reoperated on immediately afterward; this may reflect the selection of cases with more favorable biology for reoperation [12,47,48]. This 4 to 14 week interval could be utilized to administer several cycles of NACT.

Immunotherapy and checkpoint inhibitors

Despite its poor survival rates following systemic therapy, GBC has been slower than other gastrointestinal cancers in advancing research and developing targeted therapy and immunotherapy. Researchers have focused on targets such as Her2/neu and DNA repair gene alterations including TP53, CDKN2A/B, ERBB2, PIK3CA, which occur in approximately 10% to 15% of GBC patients [49,50]. Although a few studies and trials have explored their potential in a therapeutic role, particularly in the locally advanced or metastatic settings in conjunction with chemotherapeutic agents, none have demonstrated the superiority of this approach. There have been no studies conducted in the neoadjuvant setting, making it difficult to assess their benefits for iGBC [51,52].

Keynote-158 (NCT02628067) is a significant phase II study that enrolled approximately 104 patients with incurable BTC, more than half of whom (58%) tested positive for program death ligand (PD-L1+). This study reported a PFS of 5.3 months

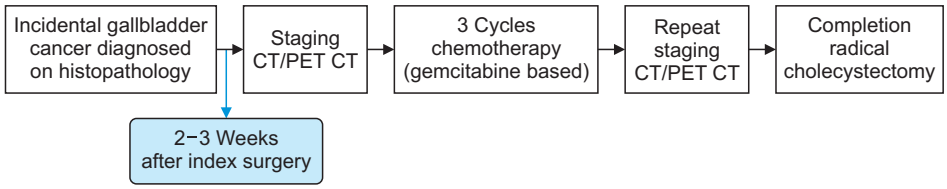

Fig. 2. Proposed treatment sequence. CT, computed tomography; PET, positron emission tomography.

for the Pembrolizumab + GEMOX (gemcitabine + oxaliplatin) regimen compared to 4.4 months for the control group [53]. A phase I study involving Nivolumab, either alone or combined with cisplatin and gemcitabine, included 30 Japanese patients with unresectable or recurrent BTC and demonstrated a 37% response rate and an OS of 15 months with a manageable safety profile [54]. In another phase II study, the combination of durvalumab, an anti-PD-L1 antibody, and tremelimumab, an anti-CTLA-4 antibody, with chemotherapy, was assessed in 121 patients with metastatic biliary tract cancer. It reported a median PFS of 13 months and concluded that PD-L1 analysis prior to treatment showed no correlation with PFS or OS [55].

Future studies

In the context of precision oncology, many solid tumors are increasingly treated with targeted or immunotherapy along with NACT. Future studies should be designed to integrate tailored treatment strategies based on comprehensive genomic profiling, while administering neoadjuvant therapy for GBC and iGBC.

Consensus statement

Distant recurrence remains the primary cause of mortality following surgery for GBC. Patients with iGBC often present with early-stage disease and are likely to benefit significantly from reoperative interventions. However, many iGBC patients present with disease beyond T2 stage and possibly with node-positive status. Outcomes could improve through the identification of high-risk patients likely to have micrometastases at the time of initial iGBC diagnosis and managing them with NACT prior to re-resection. The evidence supporting the role of neoadjuvant therapy in iGBC remains limited and has not yet been universally validated for routine clinical application. Additionally, the adverse effects of chemotherapy can diminish the functional status, rendering the patient unfit for surgery, while a suboptimal response to NACT increases the risk of local disease progression to unresectability. Hence, selecting the optimal treatment strategy for iGBC, whether it be immediate reoperation or NAT, necessitates a meticulous evaluation of both risks and benefits. The ongoing AIO/ CALGP/ ACO-GAIN-Trial may provide further insights into the optimal management strategies for iGBC [40].

Based on the current evidence, which is limited and preliminary, certain patients with iGBC, particularly those at high risk of recurrence—such as those who experienced intraoperative gallbladder perforation and bile spill during the initial cholecystectomy, those with advanced T stage (T3 or T4), node-positive disease, higher differentiation grade, or other histopathological features including PNI, LVI, pericapsular invasion, or tumor budding—may be considered for 3 or 4 cycles of preoperative NACT (using a gemcitabine-based regimen) after the index cholecystectomy and before reoperation. They should only be offered reoperation for re-resection if there is no progression of the disease; those exhibiting disease progression may instead continue with definitive chemotherapy, without reoperation (Fig. 2).

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CONFLICT OF INTEREST

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