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Neoadjuvant Chemotherapy in Locally Advanced and Borderline Resectable Gallbladder Cancer: A PRISMA 2020 Systematic Review and Meta-analysis of Radiologic Response, Resection, R0 Status and Survival

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Abstract

Locally advanced and borderline resectable gallbladder cancer (LA/BR-GBC) has poor outcomes with primary surgery alone, and neoadjuvant chemotherapy (NACT), with or without consolidation chemoradiation, is increasingly used in high-volume hepatobiliary practice. PubMed, Scopus, Web of Science, Cochrane CENTRAL, the International Clinical Trials Registry Platform and ClinicalTrials.gov were searched from 1 January 2010 to 15 May 2026 for studies of adults with cT3/cT4, node-positive, vascular-involved or adjacent-organ-involved gallbladder cancer without distant metastases, treated with platinum-gemcitabine-based neoadjuvant therapy with or without consolidation radiation. Proportions were pooled using a DerSimonian-Laird random-effects model on the Freeman-Tukey double-arcsine scale. Egger testing, leave-one-out sensitivity analysis, subgroup analysis and GRADE certainty assessment were performed. Fifteen studies including 2094 patients were included, and eleven contributed to quantitative synthesis. The pooled radiologic objective response rate was 62.5% (95% CI 53.1-71.5%), the pooled intention-to-treat resection rate was 44.0% (95% CI 33.9-54.3%), and the pooled R0 rate among resected patients was 89.0% (95% CI 80.7-95.2%). The POLCAGB phase III trial reported improved median overall survival with neoadjuvant chemoradiation compared with NACT alone (21.8 versus 10.0 months) and a higher R0 rate (51.6% versus 29.7%; p = 0.01). The available evidence supports NACT as a rational first step in appropriately selected LA/BR-GBC, with selective consolidation chemoradiation and disciplined surgical selection. Multicentre response-adapted randomized trials are still required to define the optimal neoadjuvant regimen and sequencing strategy.

Keywords: Gallbladder Cancer, Meta-analysis, Neoadjuvant Chemoradiation, Neoadjuvant Chemotherapy, PRISMA 2020, R0 Resection.

Introduction

Gallbladder cancer (GBC) is one of the most aggressive malignancies of the biliary tract and is characterized by late presentation, rapid progression and poor overall survival. Surgical resection remains the only potentially curative option, yet fewer than one in five patients are operable at diagnosis, and a proportion of apparently operable patients are found to have occult peritoneal or locoregional spread at exploration. For locally advanced disease, multimodal treatment that adds systemic chemotherapy or radiotherapy to surgery has therefore become essential to improve overall survival. The treatment of locally advanced GBC is changing dynamically, shifting from adjuvant therapy, which is already standardized at many centres, toward neoadjuvant therapy, which is currently being explored for feasibility at a smaller number of high-volume units. Because only a limited number of randomized trials and small cohort studies focused on neoadjuvant treatment are available in the literature, the present systematic review and meta-analysis was undertaken to bridge this evidence gap by synthesizing the available data on

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neoadjuvant therapy and adding pooled estimates to the literature.

GBC has a distinctive geographic distribution, with high-risk belts reported in northern India, Chile, Bolivia, Japan and parts of central and eastern Europe (1, 2). In India, the clinical burden is particularly relevant to hepatobiliary surgeons because many patients present with advanced primary tumours, nodal disease, liver-bed invasion or vascular proximity. For unresectable locally advanced disease, systemic therapy alone has historically produced modest survival, generally in the range of months rather than years (3-5). The management of advanced GBC has consequently moved from a surgery-only decision to a multidisciplinary strategy that integrates systemic treatment, careful restaging, staging laparoscopy and selective radical surgery. A platinum-gemcitabine doublet established the systemic backbone for advanced biliary tract cancer, and later phase III evidence supporting immune-therapy combinations has further reinforced the value of early systemic disease control (5-7). In locally advanced and borderline resectable GBC, neoadjuvant therapy is attractive because it can downstage the primary tumour, reduce nodal burden, increase the likelihood of margin-negative resection and treat micrometastatic disease before a major hepato-biliary operation. It also acts as a biological selection period, because patients who progress during treatment can be spared futile extended cholecystectomy, bile-duct resection or vascular reconstruction.

Earlier reports suggested that neoadjuvant therapy could convert a subset of patients to resection, but the evidence was fragmented. Small prospective and retrospective cohorts reported objective response rates ranging from approximately one-third to more than two-thirds of treated patients, while resection rates varied widely because eligibility criteria, resectability definitions, chemotherapy cycles and restaging protocols were not uniform (8-13). Chemoradiation-based approaches showed promi-sing local response in selected cohorts, but these studies were limited by small sample size, single-centre experience and the absence of randomized comparative evidence (8, 9, 14, 15). More recent Indian and international cohorts have expanded the evidence base, while the POLCAGB randomized trial has provided the first phase III comparison of neoadjuvant chemotherapy versus neoadjuvant chemoradiation in locally advanced GBC (16-20). These developments make it necessary to re-evaluate the field using transparent and reproducible review methods.

The main research gap is not whether neoadjuvant therapy can be delivered, but how consistently it improves clinically meaningful surgical endpoints. Earlier syntheses generally focused on feasibility or narrative survival summaries, and many did not separately pool radiologic response, intention-to-treat resection, R0 resection among operated patients and survival patterns. Survival comparisons are especially difficult because resected patients after neoadjuvant therapy represent a biologically selected subgroup, and simple pooling of survival across single-arm cohorts may overstate the treatment effect. A clinically useful synthesis must therefore present response and resection outcomes with clear denominators and must distinguish the effect of treatment from the effect of post-treatment selection. The present review addresses this gap by synthesizing studies published from 2010 to 2026, a window selected because it reflects the modern gemcitabine-platinum era, wider use of cross-sectional staging, RECIST-based response assessment, multidisciplinary tumour-board decision-making and more consistent radical cholecystectomy standards; studies before 2010 were likely to use older regimens, heterogeneous imaging criteria and less comparable surgical pathways, and their inclusion would have increased clinical indirectness. The novelty of the present work therefore lies in its PRISMA 2020-compliant synthesis of the recent randomized POLCAGB evidence together with the cumulative cohort experience, its use of operational definitions aligned with contemporary resectability and RECIST principles, and its deliberate separation of response, surgical conversion and margin status rather than reliance on a single survival estimate, providing practical quantitative anchors for tumour boards consider-ing neoadjuvant strategies in LA/BR-GBC.

The overarching aim of this systematic review and meta-analysis was to estimate the efficacy and safety of neoadjuvant therapy in adults with locally advanced or borderline resectable GBC without distant metastases. The specific objectives were:

a) to pool the radiologic objective response after neoadjuvant chemotherapy or chemoradiation;
b) to estimate the proportion of patients who proceeded to curative-intent resection using an intention-to-treat denominator;
c) to estimate the R0 rate among resected patients and, where possible, over the intention-to-treat denominator; and
d) to summarize survival, perioperative morbidity and treatment-related toxicity narratively.

Methodology

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) checklist and the Meta-analysis of Observational Studies in Epidemiology guidance (21, 22). A protocol defining eligibility criteria, search strategy, outcomes, extraction fields and statistical methods was prepared before screening and is available from the corresponding author on reasonable request.

Eligible participants were adults aged at least 18 years with histologically or radiologically confirmed locally advanced or borderline resectable GBC. This included cT3 or cT4 primary tumours, clinically suspicious or proven regional nodal disease, tumour extension into adjacent organs, liver-bed involvement beyond 2 cm, hepatoduodenal ligament involvement, or contact with major vascular structures such as the main portal vein, common hepatic artery, proper hepatic artery or coeliac axis, in the absence of distant metastases. Mixed biliary-tract cancer cohorts were eligible only when GBC-specific outcomes were separately available or when patients with GBC formed at least 70% of the cohort.

The intervention of interest was neoadjuvant systemic chemotherapy using a gemcitabine-platinum doublet, with or without subsequent consolidation chemoradiation. A minimum of two cycles before response assessment was required. Eligible comparators included upfront surgery, palliative systemic chemotherapy without resection, NACT alone for studies comparing chemoradiation, or no comparator for single-arm cohorts. The primary outcomes were radiologic objective response rate, post-NACT curative-intent resection rate using the intention-to-treat denominator, and R0 resection rate among resected patients. Secondary outcomes were clinical benefit response, median overall survival, perioperative morbidity and grade 3 or higher treatment-related toxicity.

Randomized trials, prospective cohorts and retrospective cohorts with at least 10 LA/BR-GBC patients were eligible. Case reports, small case series, narrative reviews, editorials and conference abstracts without adequate outcome data were excluded. Operationally, objective response rate was defined as complete plus partial response on RECIST 1.1 (23) or the closest comparable imaging criteria used in the original study. Clinical benefit response comprised complete response, partial response and stable disease at the response-assessment time point. Resection was defined as curative-intent radical cholecystectomy expressed over all patients who started neoadjuvant therapy, and R0 resection denoted histologically negative margins.

PubMed, Scopus, Web of Science Core Collection, Cochrane CENTRAL, the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov were searched from 1 January 2010 to 15 May 2026. The search combined controlled-vocabulary and free-text terms for gallbladder neoplasm, neoadjuvant chemotherapy, neoadjuvant chemoradiation, locally advanced disease, borderline resectable disease, resection, response, R0 status and survival. The 2010-2026 window was chosen to represent the contemporary gemcitabine-platinum and modern imaging era and to avoid clinically indirect older regimens and staging methods. Reference lists of included articles and previous reviews were also screened. The search was limited to English-language studies because reliable extraction of complex surgical and oncological endpoints required full-text interpretability.

Two reviewers independently screened titles and abstracts, assessed full texts and extracted data into a piloted spreadsheet. Disagreements were resolved through discussion with a third author. The extracted variables included year, country, design, sample size, staging definition, regimen, number of cycles, response criteria, response rate, clinical benefit response, resection rate, R0 rate, morbidity, toxicity and survival. When multiple reports from the same centre appeared to overlap, the most recent or methodologically clearest report contributed to the relevant pooled outcome

to avoid double counting, while overlapping articles were retained only for contextual narrative discussion.

Absent or partial outcome data were managed conservatively. If numerators and denominators could be calculated from the text, tables or figures, the data were extracted. If an outcome was reported qualitatively or without a usable denominator, the study was retained in the qualitative synthesis but excluded from that specific pooled estimate. Authors of original studies were not routinely contacted for clarification because most reports were retrospective or already published with fixed outcome reporting, and the review deadline was short. This limitation was considered during GRADE assessment and in the interpretation of imprecision and indirectness.

Observational studies were assessed using the Newcastle-Ottawa Scale, and the randomized trial was assessed using Cochrane RoB 2 (24, 25). Certainty of evidence was assessed with GRADE by considering risk of bias, inconsistency, indirectness, imprecision and possible small-study effects (26). Proportions and 95% confidence intervals were calculated using the Wilson method. Pooled proportions were estimated with a Freeman-Tukey double-arcsine transformation and DerSimonian-Laird random-effects models, with back-transformation using the harmonic mean sample size (27, 28). Heterogeneity was summarized using Cochran Q, I-squared and tau-squared (29). Small-study effects were explored using funnel plot inspection and Egger regression (30). Sensitivity analyses excluded the randomized trial, mixed cohorts and the largest or most influential study. A pooled hazard ratio for overall survival was not calculated because single-arm survival contrasts are strongly affected by post-NACT selection.

Results

The study-selection process is presented in Figure 1. Database searches identified 1325 records, and 22 additional records were obtained through citation tracking and trial registries. After 259 duplicates were removed, 1088 records were screened, 75 full-text articles were assessed, and 60 were excluded, most commonly because the cohort was mixed biliary tract cancer with insufficient GBC-specific data, focused only on the adjuvant setting, or did not report extractable outcomes. Fifteen studies were included in the qualitative synthesis, and 11 contributed data to at least one quantitative pooled outcome.

The 15 included studies enrolled 2094 patients with LA/BR-GBC between 2004 and 2024 across India, the United States and East Asian or international settings (8-20, 31, 32). The designs included one phase III randomized trial, four prospective cohorts and ten retrospective cohorts. Gemcitabine-cisplatin or gemcitabine-carboplatin was the dominant regimen, while gemcitabine-oxaliplatin was used in a minority of cohorts. Median age generally ranged from 50 to 58 years, and women predominated, consistent with the epidemiology of GBC. Most studies defined locally advanced disease by cT3/cT4 status, nodal disease or surgeon-assessed unresectability without distant metastasis, although imaging and surgical criteria differed across reports.

The characteristics of the included studies are summarized in Table 1. The dataset is dominated by retrospective cohorts from Indian high-volume hepatobiliary centres, but it also incorporates one phase III randomized trial and several prospective cohorts, giving a range of evidence levels. The sample sizes vary widely, from small single-centre series to large institutional experiences exceeding 1000 patients. This distribution reflects the concentration of locally advanced gallbladder cancer experience in endemic regions.

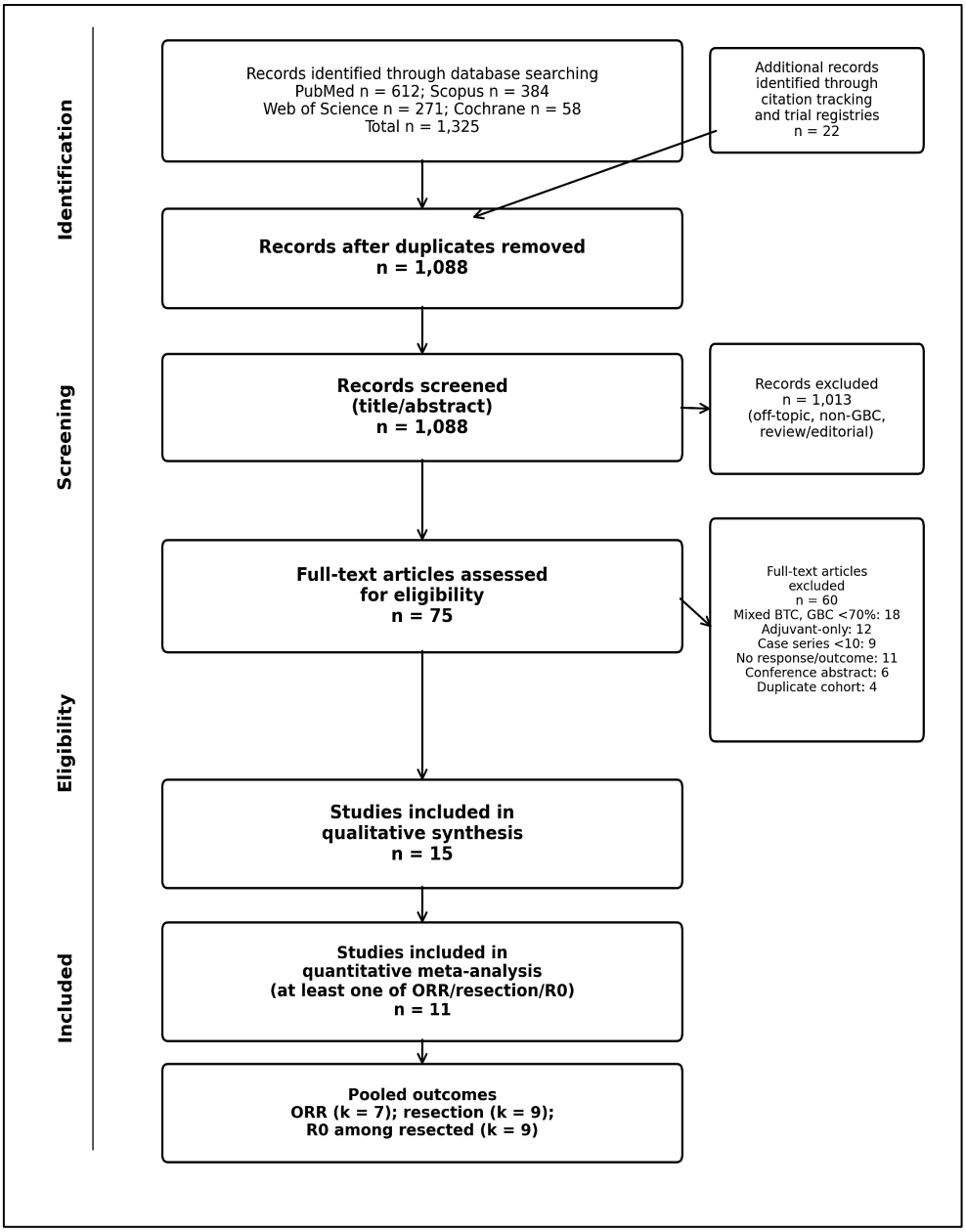

Figure 1: PRISMA 2020 Study-selection Flow Diagram (Adapted from the PRISMA 2020 Statement (21) Under the Creative Commons CC BY 4.0 licence)

Table 1: Studies Included in the Systematic Review and Meta-analysis

Year	Country	Design	n	Setting	References
2015	India	Prospective cohort	37	NACT	(8)
2015	India	Retrospective cohort	21	NACT	(9)
2016	India	Prospective cohort	28	NACRT	(10)
2017	USA	Retrospective cohort	74	NACT with surgery in selected patients	(11)
2018	India	Retrospective cohort	160	NACT	(12)
2019	India	Randomized trial protocol	124 planned	NACT versus NACRT	(13)
2019	India	Retrospective cohort	25	NACT in neuroendocrine subtype	(31)
2021	India	Retrospective cohort	32	Portal vein embolization plus NACT	(32)
2022	India	Retrospective cohort	26	NACRT	(14)
2022	India	Retrospective cohort	145	NACT with or without cCTRT	(15)

2023	India	Retrospective cohort	234	Stage IV disease with selective surgery	(16)
2023	India	Retrospective cohort	1040	Perioperative chemotherapy experience	(17)
2025	India	Retrospective cohort	401	Clinical benefit response analysis	(18)
2025	India	Phase III randomized trial	124	NACT versus NACRT	(19)
2026	India	Prospective cohort	226	NACT	(20)

Note: NACT= Neoadjuvant Chemotherapy; NACRT=Neoadjuvant Chemoradiation; cCTRT=Consolidation Chemoradiation; N= Number of Patients; USA=United States of America.

The treatment and assessment details of each cohort are presented in Table 2. A gemcitabine-platinum doublet was the predominant systemic backbone, delivered for a median of three to six cycles, while a smaller number of cohorts used gemcitabine-based chemoradiation. RECIST 1.1 was the most frequently applied response criterion, sometimes supplemented by carbohydrate antigen 19-9 (CA 19-9) trends. The variability in cycle number and response definitions across studies is an important source of clinical heterogeneity.

Table 2: Study Characteristics, Regimen and Response Criteria

Year	Period	Regimen	Cycles	Response criteria	References
2015	2010-2013	Gemcitabine-cisplatin or gemcitabine-carboplatin	4-6	RECIST 1.1	(8)
2015	2004-2010	Gemcitabine-cisplatin	3-6	Imaging plus clinical criteria	(9)
2016	2010-2013	Weekly gemcitabine with 57 Gy/25 fractions	NACRT	RECIST 1.1	(10)
2017	2004-2014	Gemcitabine-platinum, varied	At least 2	Surgical/pathologic assessment	(11)
2018	2010-2017	Gemcitabine-cisplatin primarily	4-6	RECIST 1.1 plus CA 19-9	(12)
2022	2014-2018	Gemcitabine-based NACRT	NACRT	RECIST 1.1	(14)
2022	2014-2016	Gemcitabine-cisplatin with or without cCTRT	6 plus cCTRT	RECIST 1.1	(15)
2023	2010-2019	Gemcitabine-cisplatin or gemcitabine-oxaliplatin	3-6	RECIST plus CA 19-9	(17)
2025	2010-2023	Gemcitabine-platinum	3-6	RECIST 1.1 and CBR composite	(18)
2025	2016-2024	Gemcitabine-cisplatin versus chemoradiation	4 plus RT	RECIST 1.1	(19)
2026	2018-2023	Gemcitabine-platinum	4-6	RECIST 1.1	(20)

Note: CA 19-9=Carbohydrate Antigen 19-9; CBR=Clinical Benefit Response; cCTRT= Consolidation Chemoradiation; Gy=Gray; NACRT=Neoadjuvant Chemoradiation; RECIST= Response Evaluation Criteria in Solid Tumours; RT= Radiotherapy.

The primary efficacy outcomes of each contributing study are presented in Table 3, comprising the objective response rate, the intention-to-treat resection rate, the R0 rate among patients and the median overall survival pattern, together with the corresponding pooled estimates. Response and resection outcomes varied widely across cohorts, whereas the R0 rate among patients who reached surgery was consistently high. The pooled values are displayed in the final row of the table for direct comparison with the individual studies.

Table 3: Primary Efficacy Outcomes

n	ORR (%)	Resection % (ITT)	R0 among resected (%)	mOS pattern	Reference
37	67.5	46	Not stated	Cohort mOS 13.4 months; higher after surgery	(8)
21	Qualitative downstaging	66.7 (14/21)	100 (14/14)	42.8 versus 6.6 months	(9)

28	71	50	100	Curative resection feasible	(10)
74	Not stated	14 (10/74)	80 (8/10)	51 versus 11 months for R0 versus not	(11)
160	52.5	41.2	Approximately 85	49 versus 7 months	(12)
26	77	46	92	Not separately reported	(14)
145	65 PR; CBR 77	Approximately 7 (10/145)	NR	14 versus 7 months for cCTRT versus CT	(15)
332 NACT	Not stated	70.8 (235/332)	NR	Propensity-matched outcomes comparable to upfront surgery	(17)
401	CBR 75.5	86 of CBR group	NR	CBR 25 versus 8.5 months	(18)
39	35	45.3	Approx. 61 of explored	mOS 10.0 months	(19)
53	74	65	Approx. 79 of explored	mOS 21.8 months	(19)
226	Not stated	36.2	95.1	27 versus 13 months	(20)
—	62.5 (53.1-71.5)	44.0 (33.9-54.3)	89.0 (80.7-95.2)	—	Pooled

Note: ORR= Objective Response Rate; ITT= Intention-To-Treat; R0= Histopathologically Negative Resection Margin; mOS= Median Overall Survival; CBR= Clinical Benefit Response; cCTRT= Consolidation Chemoradiation; CT= chemotherapy; CI= Confidence Interval; NR= Not Reported; PR= Partial Response; n= Number of Patients.

Seven studies reporting objective response by RECIST or near-RECIST criteria contributed 488 patients. The pooled radiologic objective response rate was 62.5% (95% CI 53.1-71.5%; I-squared = 74.7%; tau-squared = 0.012). Heterogeneity was substantial and appeared to reflect differences between NACT-only and neoadjuvant chemo-radiation strategies. In subgroup analysis, the pooled response rate was 53.9% (95% CI 45.5-62.2%) for NACT-only cohorts and 75.7% (95% CI 67.8-82.8%) for neoadjuvant chemoradiation cohorts. The Egger intercept was not statistically significant (intercept = 1.62, p = 0.47).

The pooled radiologic objective response rate is displayed in the forest plot in Figure 2. Individual study estimates and their 95% confidence intervals are shown alongside the random-effects pooled proportion. The plot illustrates the higher response observed in chemoradiation cohorts relative to chemotherapy-only cohorts, which contributed to the substantial between-study heterogeneity.

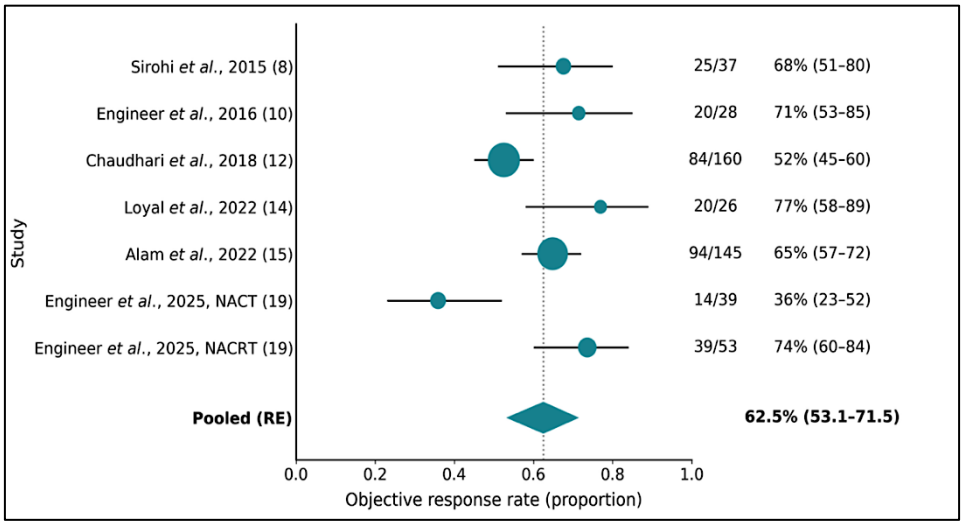

Figure 2: Forest Plot of the Pooled Radiologic Objective Response Rate After Neoadjuvant Chemotherapy or Chemoradiation. (DerSimonian–Laird Random-effects Model on the Freeman–Tukey Double-arcsine Scale; k = 7; n = 488)

Nine studies including 664 patients contributed to the pooled intention-to-treat resection outcome. The pooled curative-intent resection rate was 44.0% (95% CI 33.9-54.3%; I-squared = 83.9%;

tau-squared = 0.020). Study-level estimates ranged from 14% in a stringent intention-to-treat cohort to 67% in a smaller selected cohort. Exclusion of the most conservative low-resection study increased the pooled estimate to 47.4% (95% CI 40.8-54.0%), while exclusion of the neoadjuvant chemoradiation arm of the randomized trial yielded 41.9% (95% CI 32.2-52.0%). The Egger test was not significant (intercept = 2.43, p = 0.23).

The pooled curative-intent resection rate on an intention-to-treat basis is shown in the forest plot in Figure 3. The plot demonstrates a wide spread of study-level estimates, from a stringent intention-to-treat cohort with the lowest resection rate to smaller selected cohorts with substantially higher rates. The random-effects pooled estimate is presented in the final row.

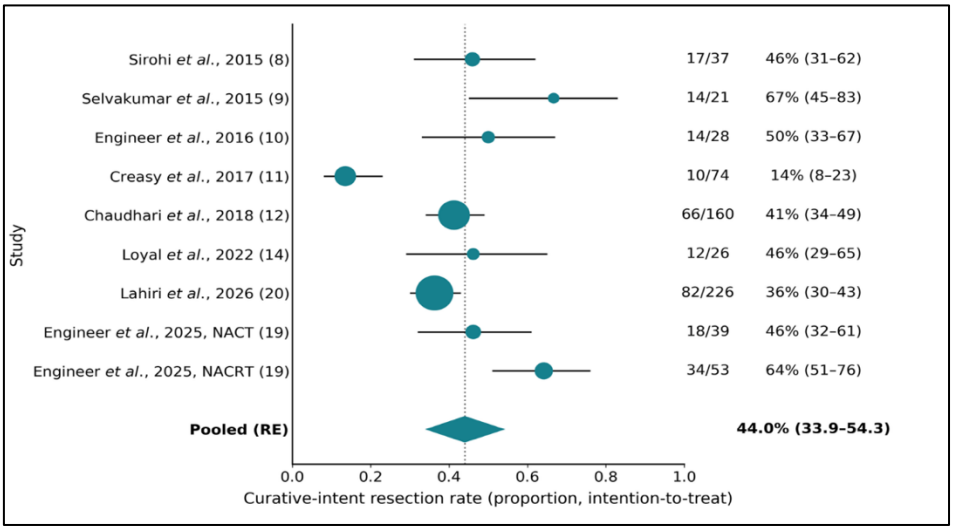

Figure 3: Forest Plot of the Pooled Post-neoadjuvant Curative-intent Resection Rate using the Intention-to-treat Denominator. (k = 9; n = 664)

A funnel plot of the resection-rate analysis is provided in Figure 4 to assess small-study effects. The study estimates are distributed broadly symmetrically about the pooled proportion, and the Egger test showed no significant asymmetry (intercept = 2.43, p = 0.23). This argues against substantial publication bias for this outcome, although the limited number of studies reduces the sensitivity of the test.

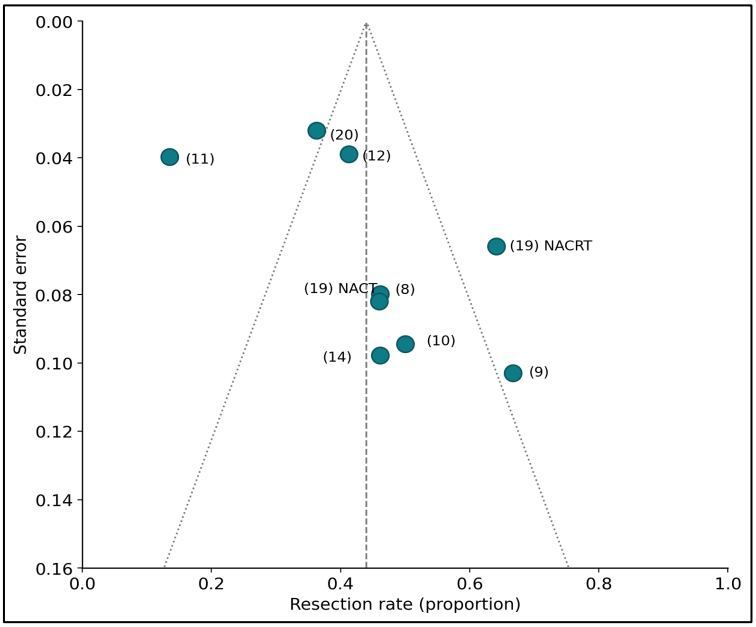

Figure 4: Funnel Plot for the Pooled Resection Rate. (Egger Intercept = 2.43, p = 0.23, Indicating no Significant Asymmetry) Study Labels Denote Reference Numbers in Brackets

Nine cohorts reported R0 status among resected patients, with 267 R0 resections among 300 assessable operations. The pooled R0 rate among resected patients was 89.0% (95% CI 80.7-95.2%; I-squared = 68.8%; tau-squared = 0.020). When recalculated using the intention-to-treat denominator, the pooled R0-of-intention-to-treat rate was 36.8% (95% CI 28.1-46.0%; I-squared = 81.9%), reflecting attrition at restaging and surgical exploration.

Median overall survival among patients converted to resection after neoadjuvant therapy was consistently higher than that among patients who remained unresected, but these comparisons were interpreted narratively because of biological selection. Across cohorts, median survival in resected patients generally ranged from approximately 19 to 51 months, while survival in unresected counterparts ranged from 5 to 13 months. The randomized POLCAGB evidence provided the strongest comparative signal, with median overall survival of 21.8 months after neoadjuvant chemoradiation compared with 10.0 months after NACT alone, alongside better event-free survival, objective response and R0 resection outcomes (19).

The within-study comparative survival findings are summarized in Table 4, contrasting patients who achieved resection or clinical benefit with those who did not. A consistent and often large survival advantage was reported in favour of patients who underwent curative-intent resection after neoadjuvant therapy. These contrasts are descriptive, however, because the resected groups represent a biologically selected population rather than the result of randomized allocation.

Table 4: Within-study Comparative Survival

Comparison	mOS / effect pattern	p-value	References
Surgery versus no surgery	Cohort mOS 13.4 months; surgery better than no surgery	Reported NS	(8)
R0 versus inoperable	42.8 versus 6.6 months	< 0.01	(9)
R0 versus not resected	Curative resection achieved in 50%	Reported significant	(10)
R0 versus no resection	51 versus 11 months	< 0.001	(11)
Resected versus unresected	49 versus 7 months; EFS 25 versus 5 months	0.0001	(12)
cCTRT versus chemotherapy alone	14 versus 7 months	0.04	(15)
Radical versus palliative approach	19 versus 12 months	< 0.01	(16)
CBR versus no CBR	25 versus 8.5 months	Reported significant	(18)
NACRT versus NACT	21.8 versus 10.0 months	Significant	(19)
Resectable versus unresectable after NACT	27 versus 13 months	< 0.001	(20)

Note: mOS= Median Overall Survival; EFS= Event-Free Survival; cCTRT= Consolidation Chemoradiation; CBR= Clinical Benefit Response; NACT= Neoadjuvant Chemotherapy; NACRT= Neoadjuvant Chemoradiation; NS= Not Significant; R0= Histopathologically Negative Resection Margin.

Safety reporting was heterogeneous. In seven studies with usable safety data, grade 3 or higher treatment-related adverse events occurred in approximately 9-22% of treated patients, mainly neutropenia, fatigue and gastrointestinal toxicity. Treatment-related mortality during neoadjuvant therapy was uncommon, reported around 1-2% where available. Among patients who underwent resection, perioperative mortality ranged from 0% to 4%, and major morbidity ranged from 13% to 25%, which is broadly comparable with contemporary radical cholecystectomy series in carefully selected patients.

Risk-of-bias and certainty assessments are summarized in Table 5. The randomized trial was assessed as low risk overall, with some concerns related to open-label design and surgical endpoint assessment. Newcastle-Ottawa scores for observational studies ranged from 6 to 9 stars, with most downgrading arising from incomplete comparability adjustment for stage, performance status or treatment selection. GRADE certainty was moderate for objective response rate, resection rate and R0 among resected patients, mainly downgraded for inconsistency. Certainty for comparative survival was low because of risk of bias and post-treatment selection.

Table 5: Risk-of-bias and GRADE Certainty Summary

Design group	Selection	Comparability	Outcome	Overall Judgement	Reference
Prospective cohort	3/4	1/2	3/3	7/9	(8)
Retrospective cohort	3/4	1/2	2/3	6/9	(9)
Prospective cohort	3/4	1/2	3/3	7/9	(10)
Retrospective cohort	4/4	1/2	3/3	8/9	(11)
Retrospective cohort	3/4	2/2	3/3	8/9	(12)
Retrospective cohort	3/4	1/2	2/3	6/9	(14)
Retrospective cohort	3/4	1/2	3/3	7/9	(15)
Retrospective cohort	3/4	2/2	3/3	8/9	(16)
Retrospective cohort	4/4	2/2	3/3	9/9	(17)
Retrospective cohort	4/4	2/2	3/3	9/9	(18)
Prospective cohort	4/4	1/2	3/3	8/9	(20)
Randomized trial	—	—	—	Low risk overall; some concerns due to open-label design	(19)

Note: GRADE, Grading of Recommendations Assessment, Development and Evaluation; NOS, Newcastle-Ottawa Scale; RoB 2, revised Cochrane risk-of-bias tool for randomised trials. Cohort scores are shown as points achieved out of the maximum for each domain (Selection /4, Comparability /2, Outcome /3, Overall /9). GRADE certainty: objective response rate, moderate; resection rate, moderate; R0 among resected patients, moderate; comparative survival, low.

Discussion

This systematic review and meta-analysis provide three clinically useful quantitative anchors for the multidisciplinary management of LA/BR-GBC. Approximately 63% of patients achieved a radiologic objective response after neoadjuvant therapy, 44% proceeded to curative-intent resection on an intention-to-treat basis, and 89% of resected patients achieved R0 margins. These findings support the clinical impression that neoadjuvant therapy can convert a meaningful subgroup of locally advanced or borderline resectable GBC patients to potentially curative surgery, while also preventing futile surgery in patients with early progression.

The response and resection rates observed in this synthesis are broadly consistent with earlier Indian cohort experience, but the pooled estimates are more conservative than some single-centre reports. Smaller series tended to report higher conversion and R0 rates, likely because of stricter referral selection, better performance status and exclusion of early progressors. Larger intention-to-treat cohorts produced lower resection estimates, which may better reflect routine practice. This contrast explains why the pooled resection rate settled near 44%, even though individual surgical cohorts reported much higher rates. A realistic message for clinical practice is therefore that neoadjuvant therapy should not be presented as a guaranteed route to surgery; rather, it identifies the subgroup most likely to benefit from radical resection. These pooled estimates are concordant with contemporary high-volume experience. A large single-institution series of perioperative chemotherapy reported propensity-matched outcomes comparable to upfront surgery in selected patients (17), and a recent prospective study found that resectable patients after neoadjuvant therapy had substantially better survival than those who remained unresectable, at 27 versus 13 months (20). In a stringent stage IV cohort with limited metastatic burden, by contrast, prolonged survival was largely confined to the minority who underwent radical resection (16), reinforcing that the benefit is concentrated in carefully selected responders. A recently described clinical benefit response framework may help to identify this subgroup prospectively and to standardize the definition of treatment response across centres (18).

Compared with earlier narrative reviews and smaller meta-analyses, the present work adds a clearer distinction between radiologic response, surgical conversion and margin status. Earlier reviews generally concluded that neoadjuvant therapy was feasible but emphasized the paucity of randomized evidence and the variability of definitions (8-13). The present pooled response estimate supports those conclusions but also clarifies that the main attrition occurs before surgery, whereas the likelihood of R0 status is high once patients reach resection. This pattern

suggests that multidisciplinary selection, restaging and staging laparoscopy are as important as the chemotherapy regimen itself.

The finding that neoadjuvant chemoradiation produced higher response than NACT alone is biologically plausible because radiation can intensify local control in the gallbladder fossa and hepatoduodenal ligament. This interpretation is strengthened by the POLCAGB randomized trial, which showed improved survival and R0 outcomes with neoadjuvant chemoradiation compared with chemotherapy alone (19). This is concordant with observational consolidation-chemoradiation data, in which the addition of radiation in responders to first-line chemotherapy improved survival relative to chemotherapy alone (15), although the associated toxicity profile underlines the need for careful patient selection (14). However, the result should be applied carefully because chemoradiation requires expertise, may increase perioperative complexity and may not be appropriate for patients with borderline functional reserve or early systemic progression. The evidence therefore supports selective intensi-fication rather than universal chemoradiation for all LA/BR-GBC patients.

The survival differences reported in resected versus unresected patients were large and directionally consistent, but they should not be interpreted as pure treatment effects. Patients who underwent surgery after neoadjuvant therapy had already demonstrated favourable biology, absence of early metastatic progression, adequate functional status and technical resectability, and these selection factors probably explain part of the survival gap. For this reason, a pooled hazard ratio was intentionally avoided. The more defensible interpretation is that successful conversion to R0 resection after neoadjuvant therapy is associated with substantially better survival, while the magnitude of any causal benefit requires randomized and response-adapted studies.

Several contextual factors may explain the heterogeneity across studies. First, locally advanced and borderline resectable GBC were not uniformly defined, with some studies using cT3/cT4 or nodal disease and others using surgeon-defined unresectability or vascular contact. Second, response assessment differed by timing and criteria, with some studies using RECIST 1.1 and others using combined imaging, clinical judgment and CA 19-9 trends. Third, surgical thresholds varied between centres, especially regarding vascular resection, extrahepatic bile-duct resection and the management of para-aortic or interaortocaval nodes. Fourth, the availability of staging laparoscopy and high-volume hepatobiliary expertise likely influenced resection and R0 outcomes.

The practical consequence is that neoadjuvant therapy should be embedded within a structured pathway. Patients with LA/BR-GBC should be discussed in a multidisciplinary tumour board before treatment, undergo baseline contrast-enhanced imaging, receive gemcitabine-platinum-based systemic therapy when fit, and undergo restaging after three to four cycles. Favourable criteria for exploration include radiologic response or sustained stable disease, falling CA 19-9, no new metastatic disease, an acceptable liver remnant and a realistic prospect of R0 resection. Staging laparoscopy should be considered before laparotomy because peritoneal or liver-surface disease may remain radiologically occult.

This review has limitations. Most included evidence was observational, retrospective and centre-heavy, and several reports originated from high-volume Indian institutions with overlapping practice patterns. The number of randomized trials remains small, the reporting of partial outcome data limited pooling for some endpoints, and author contact was not undertaken. Heterogeneity was substantial for response and resection outcomes, the English-language restriction may have excluded relevant non-English studies, and survival could not be validly pooled because of strong post-NACT selection bias. These limitations mean that the results should guide multidisciplinary discussion rather than function as definitive treatment-policy evidence.

Future research should prioritize multicentre randomized trials with standardized resectability criteria, response-adapted treatment sequencing and central radiology review. The role of immunotherapy-based chemotherapy combinations in the neoadjuvant setting is a logical next question because advanced biliary tract trials have shown benefit with immune checkpoint inhibitor combinations (6, 7). Future studies should also validate predictive models using tumour stage, CA 19-9 kinetics, inflammatory markers, radiomics

and circulating tumour DNA, and individual-participant-data meta-analysis would help separate treatment effect from selection effect and identify which patients benefit most from chemotherapy alone, chemoradiation or early surgery after response.

Conclusion

This PRISMA 2020 systematic review and meta-analysis shows that neoadjuvant therapy for locally advanced and borderline resectable gallbladder cancer produces a radiologic response in about three of five patients, enables curative-intent surgery in about four of ten patients who start treatment, and achieves R0 resection in nearly nine of ten patients who reach surgery. By pooling 2094 patients from 15 studies, including the first phase III randomized comparison of neoadjuvant chemotherapy and chemoradiation, the analysis provides quantitative benchmarks that can be applied directly when counselling patients and planning multidisciplinary care.

The principal contribution of this synthesis is the deliberate separation of radiologic response, intention-to-treat resection, R0 status and survival, which prevents the overinterpretation of survival among a biologically selected group of surgical responders and locates the main point of attrition before, rather than at, surgery. The practical consequence is a default neoadjuvant approach for fit patients with LA/BR-GBC, embedded within structured restaging and staging laparoscopy, with selective consolidation chemo-radiation reserved for situations in which local control and margin clearance are the dominant concerns. In practical terms, these benchmarks can be quoted directly when counselling patients about the realistic probability of reaching surgery and of achieving a margin-negative resection, and they provide reference values against which individual centres can audit their own neoadjuvant pathways.

These conclusions are tempered by substantial heterogeneity, a predominance of retrospective and centre-heavy data, and unavoidable post-treatment selection bias, so the present estimates should inform tumour-board discussion rather than serve as definitive treatment policy.

The clearest research priority is a new generation of multicentre randomized trials using standardized resectability criteria, response-adapted designs, central radiology review and modern systemic regimens, including immuno-therapy combinations, to define the optimal neoadjuvant pathway and to distinguish true treatment effect from selection. Future studies should also incorporate predictive biomarkers such as CA 19-9 kinetics, inflammatory indices, radiomics and circulating tumour DNA, and individual-participant-data meta-analysis would help to clarify which patients benefit most from chemotherapy alone, from added chemoradiation or from early surgery after response.

Abbreviations

CA 19-9: carbohydrate antigen 19-9, CBR: clinical benefit response; GBC: gallbladder cancer, GRADE: Grading of Recommendations Assessment, Development and Evaluation, LA/BR-GBC: locally advanced or borderline resectable gallbladder cancer, NACRT: neoadjuvant chemoradiation, NACT: neoadjuvant chemotherapy, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, R0: histopathologically negative resection margin, RECIST: Response Evaluation Criteria in Solid Tumours.

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Author Contributions

Aditya C: Conceptualization, Study Design, Literature Search, Data Extraction, Statistical Analysis, Manuscript Draft Preparation, Naveen Kumar A: Surgical Oncology Interpretation, Clinical Validation, Critical Revision, K G Sruthi: Evidence Synthesis, Data Screening, Data Extraction, Anita M: Study Supervision, Critical Revision, Pavani Duppada: Study Supervision, Critical Revision, Savitha Lakshmi Raghavan: Study Supervision, Critical Revision, Rajkumar Manoharan: Data Interpretation, Methodological Review, V Priya: Data Interpretation, Methodological Review, Suganya P: Data Verification, Manuscript Editing. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability

All data analysed in this study are derived from publicly available published articles cited in the reference list. The extracted dataset and analysis code are available from the corresponding author on reasonable request.

Declaration of Artificial Intelligence (AI) Assistance

Generative AI and AI-assisted technologies were used only to refine language, improve grammar and assist formatting of the revised manuscript and response letter. They were not used for study design, eligibility decisions, data extraction, statistical analysis or clinical interpretation. All authors critically reviewed and verified the manuscript and accept full responsibility for its content.

Ethics Approval

This study is a systematic review and meta-analysis of previously published, publicly available data and did not involve new studies of human or animal participants performed by the authors. Ethics approval was therefore not required.

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