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Current Evidence and Future Directions in the Management of Stage II Gallbladder Cancer

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Abstract

Gallbladder cancer (GBC) is an aggressive malignancy with poor overall prognosis, often diagnosed incidentally or at an advanced stage. Optimal outcomes depend on accurate staging, high-quality surgery, and risk-adapted adjuvant therapy. Stage II disease (T2N0M0) remains potentially curable; however, recurrence rates after resection are substantial, highlighting the need for optimized multidisciplinary management. The 8th edition of the American Joint Committee on Cancer TNM staging system subdivided the T2 stage based on tumor location into T2a (peritoneal side) and T2b (hepatic side), reflecting important biological and surgical differences. T2b tumors demonstrate more aggressive biology, with higher rates of lymphatic spread, hepatic micrometastasis, and worse survival compared to T2a tumors. Emerging evidence suggests a potential role for neoadjuvant therapy in selected high-risk patients, although robust prospective data are lacking. Adjuvant chemotherapy with capecitabine for six months remains the current standard of care following R0 resection, based on the Capecitabine for Biliary Cancer (BILCAP) data. Multidisciplinary decision-making is essential, and future studies should focus on refining patient selection for perioperative therapies and integrating new biomarkers and novel therapeutics into clinical practice. This review is intended to document the current evidence and issues for the management strategies for both incidental and non-incidental Stage II GBC. We also discuss the risk-stratified approaches, as no completed Phase III randomized controlled trials specifically dedicated to Stage II incidental GBC currently exist. Furthermore, most of the information relies on retrospective series grouping all biliary tract cancers together, including a limited number of patients with incidentally diagnosed GBC (iGBC).

Categories: General Surgery, Oncology
Keywords: adjuvant chemotherapy, capecitabine, gallbladder cancer, hepatic resection, incidental gallbladder cancer, neoadjuvant chemotherapy, radical cholecystectomy, stage ii, t2a, t2b

Introduction And Background

Gallbladder cancer (GBC) carries high mortality, in part due to late presentation and aggressive biology, with an overall five-year survival rate remaining less than 5%. Symptoms are often nonspecific, and a significant proportion of tumors are discovered incidentally at or after cholecystectomy [1-3].

While GBC has a very poor prognosis overall, patients with early-stage GBC have a far better prognosis, with up to 80% survival at five years [4]. Early GBCs are most often discovered incidentally after cholecystectomy for presumed benign causes at histopathological examination of the surgical specimen [5]. Incidentally diagnosed GBC (iGBC) accounted for up to 60% of surgically removed gallbladder malignancies and ranged from 0.6% to 1.6% after standard cholecystectomies [2,4,6].

The most common stage at presentation in a comprehensive review of more than 2000 iGBCs was pT2, which was followed by pT3 and pT1 [2,6]. Compared to malignancies that manifest symptoms, incidental GBCs have a better prognosis. Thus, incidental GBCs have been subject to investigation regarding further management after the index cholecystectomy [2].

Stage II (T2N0M0) disease has curative potential with surgery, but recurrence risk remains meaningful, providing the rationale for adjuvant therapy to prolong disease-free and overall survival. The National Cancer Institute (NCI) notes that for T2 or greater tumors, extended resection and adjuvant considerations should be reviewed in a multidisciplinary team (MDT) setting, given the risk of relapse despite complete resection [7]. Modifications for T and N categories were provided in accordance with the 8th edition of the American Joint Committee on Cancer (AJCC) staging system for GBC [8]. T2a, or perimuscular invasion on the peritoneal side without serosal involvement, and T2b, or perimuscular invasion on the hepatic side without hepatic invasion, are the specific divisions made within the T2 group [8].

Similarly, Stage II GBC (T2N0M0) was subdivided into IIa (T2a) and IIb (T2b) [8]. This distinction is both biologically and surgically relevant: tumors on the hepatic side lie closer to liver parenchyma and portal structures, which may imply a higher risk of microscopic residual disease and nodal spread even when nodes are pathologically negative. In addition, this more comprehensive staging enables cross-study comparisons

and underpins guideline recommendations and accuracy [9-12]. Conversely, currently an adjustment in the 2025 UICC TNM 9 grouping regarding Stage I has been stated. Stage IA corresponds to T1aN0M0 and Stage IB to T1bN0M0, while T2aN0M0 and T2bN0M0 remain Stage IIA and IIB, respectively [13,14].

Liver resection of segments IVb/V and dissection of portal lymph nodes (LNs) is the accepted standard for T2b (hepatic-side) tumors, whereas controversy regarding the benefit of routine liver resection predominantly pertains to T2a (peritoneal-side) disease [11,15]. The National Comprehensive Cancer Network (NCCN) guidelines suggest that at least six LNs need to be examined to ensure the accuracy of staging [16]. Surgery is the only potentially curative treatment for resectable GBC, though not always sufficient in Stage II for disease control and recurrence, justifying adjuvant strategies [7,11,17]. Both locoregional and distant recurrences can occur after R0 resection, supporting the role of adjuvant therapy in selected patients [18]. Population-level Surveillance, Epidemiology, and End Results (SEER) data (American Cancer Society) indicate a five-year relative survival of ~67% for localized GBC (which includes T1-T2N0M0), while institution-level summaries report ~65% for Stages 0-II combined [17]. In addition, studies also indicate survival differences between T2a and T2b cancer stages [19].

These outcomes vary with tumor biology, resection quality, and use of adjuvant therapy. The NCI emphasizes that recurrence risk for T2 disease persists even after complete resection, particularly when unfavorable histopathologic features are present (e.g., perineural or lymphovascular invasion, poor differentiation, resection margins) [7]. Current NCCN guidelines do not recommend routine neoadjuvant chemotherapy (NACT) for resectable disease, despite the fact that these tumors present incidentally during cholecystectomy and urgent re-operation poses higher risks [15,16,20]. There is insufficient data from clinical trials to establish a conclusive benefit; the NCCN guidelines restrict neoadjuvant considerations to locally advanced or borderline resectable tumors as outlined in standard guidelines [16,20].

In addition to highlighting the management of these patients, this narrative review attempts to give a summary of recent research on GBC Stage II. We also discuss the current evidence that either supports or contradicts neoadjuvant treatment for iGBC patients, along with proposing criteria for selecting patients who would derive significant benefit.

Review

The PubMed and Scopus databases were searched for published articles on incidental GBC and GBC Stage II. The search was limited to studies published in the English language between January 2020 and June 2026. The following terms were searched: “incidental gallbladder cancer” AND/OR “gallbladder cancer Stage II," selecting the most relevant primary and review articles from peer-reviewed journals. Finding reviews, meta-analyses, and extensive retrospective investigations was the primary goal of the current search. Case reports and case series articles were excluded.

Post-cholecystectomy assessment

The management of patients with iGBC Stage II relies on the staging determined through histopathological examination of the gallbladder specimen obtained following cholecystectomy for presumed benign disease [21]. Re-resection is the prevailing approach to treating these patients, since 45-60% of re-resection specimens had gross and/or microscopic residual disease after the initial cholecystectomy [22]. However, there is ongoing debate in the literature regarding the requirement of routine hepatectomy for St II GBC (Figure *1*).

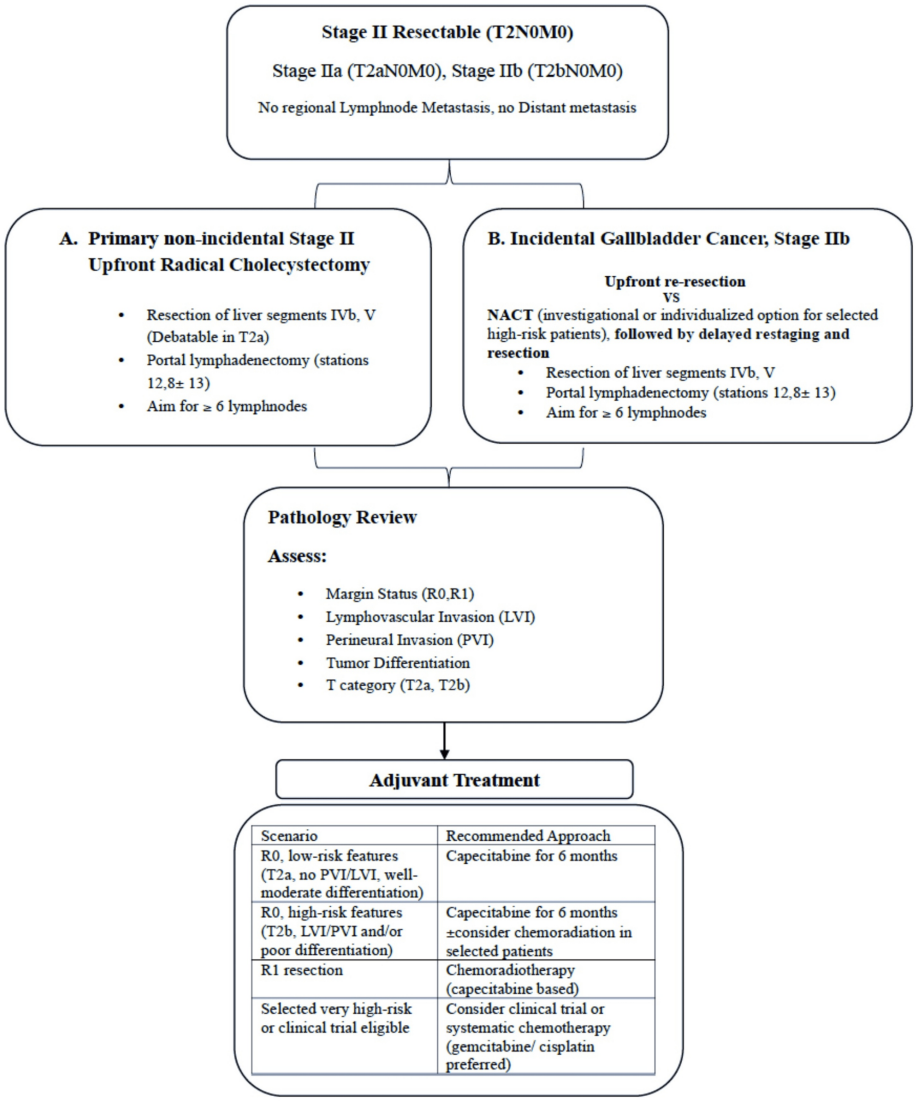


FIGURE 1: Treatment algorithm for Stage II gallbladder cancer

Data adapted from [2,7,9,11,16,21].

In a large multicenter retrospective cohort study (Operative Management of Gallbladder Cancer (OMEGA)) on 3767 patients, liver resection did not improve long-term survival for any T-stage (including T1b) and increased morbidity/mortality [23]. Although there were very few patients in the groups without liver resection, in a comprehensive review and meta-analysis by Alrawashdeh et al. of survival outcomes in T2a and T2b gallbladder tumors, liver resection was linked to improved five-year overall survival (OS) in all T2 patients (82.9% vs. 59.3%). The survival benefit of liver resection was primarily observed in T2b disease, whereas its routine omission or necessity remains debated in T2a. Despite these findings, the review has certain limitations because all of the included studies had moderate to severe bias [23,24].

In regard to the time interval from index cholecystectomy to re-resection, it is defined with considerable variation among studies, with a median usually at two to three months and a range between one and 11 months, although the timing of surgery remains disputed [9,25,26]. Several studies have shown that patients presented with recurrences as soon as one month post re-resection, with 85% of recurrences being distant disease and a median time to recurrence of approximately 11 months [21,22].

Therefore, patients experiencing early recurrences following re-resection probably had pre-existing systemic disease [21]. Hence, surgical decision-making must take into consideration that this malignancy is characterized by poor tumor biology, and distant recurrence is the most common cause of surgical failure [22]. For instance, poorer differentiation and increased rates of vascular and perineural invasion are linked to T2b malignancies [11,27]. Furthermore, nodal staging (N) cannot be performed since most uncomplicated cholecystectomies do not include LN samples [28]. Besides, even in cases when the cystic node is not involved, adjacent nodes may exhibit tumor spread, making the cystic LN alone unsuitable for nodal staging

[2,28].

Although retrospective, recent research indicates improved outcomes in patients undergoing reoperation between four to eight and 10-14 weeks following the initial cholecystectomy, compared to those who underwent reoperation immediately afterward [20,21]. These results call for reevaluating surgical approaches and the consideration of the potential advantages of administering neoadjuvant systemic treatment to these patients before re-resection [21,22]. This four- to 14-week interval could be utilized to administer several cycles of NACT before re-resection in high-risk patients, who likely have micrometastases at diagnosis, and we could theoretically improve outcomes [20-22,29,30].

The systemic therapy-first approach may be taken into consideration due to the potential advantages of early treatment of micrometastases, even if there is no evidence supporting the use of NACT prior to re-resection [21,28,31]. Additionally, it may evaluate in vivo tumor chemosensitivity, enhance patient selection for curative resection, and downstage the residual tumor if present [20-22,28]. The morbidity of major surgery can be avoided for patients who develop distant metastases during systemic treatment, potentially preventing unnecessary major surgery for individuals whose disease advances or recurs during the neoadjuvant period [21,22,28]. Therefore, we must seriously consider NACT for individuals who have residual disease, even though we utilize the eradication of residual disease to support resection [22].

In a review study involving 1040 patients, including 542 (52.1%) cases of iGBC, Patkar et al. reported superior outcomes in patients who underwent radical resection after NACT (n = 235), compared to those who had inoperable disease (n = 97) [32]. In a retrospective study by Kunte et al., NACT was administered in a subset of patients with Stage II GBC undergoing a curative resection. The authors stated that NACT should only be administered to those patients with high-risk histologic characteristics, despite the fact that the study's findings indicate no additional advantage to the standard use of chemotherapy in Stage II GBCs [33].

Adjuvant therapy: evidence and guidelines

Evidence from node-positive cohorts translates to Stage II (N0) disease, focusing on high-risk features that justify adjuvant therapy [11,34]. Capecitabine for six months is the recommended adjuvant standard after R0 resection of GBC per the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline for resected biliary tract cancer [35]. Although debatable, this recommendation, drawing from Capecitabine for Biliary Cancer (BILCAP) evidence and consensus, allows dose tailoring to institutional practice and patient tolerance with the goal of improving disease-free survival (DFS) and potentially OS over observation [36,37]. GBCs, however, accounted for just a small portion of the BILCAP population, accounting for roughly one-third of all biliary tract malignancies [2,38]. Gemcitabine was the preferred medication in the examined trials, and overall, adjuvant chemotherapy seemed to be linked to improved survival for all biliary tract malignancies as well as for a number of iGBC [2,26,39]. More recent prospective data from India (GECCOR-GB, Phase II) in resected Stage II/III GBC reported that both gemcitabine/cisplatin (GC) and capecitabine with subsequent chemoradiotherapy (CRT) achieved promising one-year DFS (~89% for GC; ~78% for capecitabine+CRT) and similar two-year DFS (~75%) in both arms [40]. While not designed to compare directly against capecitabine monotherapy after R0, these data suggest multiple active adjuvant options may exist. However, Phase III confirmation and Stage II-specific stratification are required before changing standards [40].

In outline, for Stage II GBC (IIa/IIb) after R0 resection, capecitabine for six months remains the most evidence-supported adjuvant therapy, consistent with ASCO guidelines. After R1 resection or in the presence of high-risk features (e.g., T2b hepatic-side anatomy and unfavorable histology), chemoradiation can be considered to enhance locoregional control. Phase II data suggest activity for gemcitabine/cisplatin and capecitabine-based CRT in resected Stage II/III disease, but Phase III confirmation with stage-specific stratification is needed. Risk stratification using clinicopathological factors and biomarkers (CA 19-9/CEA) can support individualized adjuvant choices and follow-up. Multidisciplinary management and clinical trial enrollment are strongly encouraged to strengthen the evidence base and improve outcomes [7,35,40,41].

Practical considerations

Regimen Choice

Capecitabine remains first-line after R0 resection. GC may be considered in trial settings or specific scenarios (e.g., highly adverse biology), but it is not an established Stage II standard.

Toxicity and Monitoring

Capecitabine commonly causes hand-foot syndrome, diarrhea, and mucositis; GC is associated with myelosuppression, nephrotoxicity, and nausea. Close monitoring, supportive care, and open communication with healthcare providers are essential to manage these side effects [42].

Chemoradiotherapy (CRT) and radiotherapy (RT)

ASCO advises that adjuvant CRT may be considered for GBC with R1 margins or other high-risk features, using shared decision-making given the balance of potential benefit and toxicity [35]. Biological plausibility is supported by patterns-of-failure data showing that ~70-75% of recurrences after surgery occur within potential postoperative radiotherapy (PORT) volumes (tumor bed and regional lymphatics). Frequently involved nodal stations include para-aortic (No.16), hepatoduodenal ligament (No.12), retropancreatic head (No.13), and celiac axis (No.9) nodes, informing target delineation to improve locoregional control in high-risk cases [41]. Including station 16 in radiation targets is extrapolated from advanced recurrence patterns rather than standard regional irradiation for Stage II disease.

Indications for CRT/RT in Stage II

Patients with R1 margins, perineural/lymphovascular invasion, or T2b (hepatic-side) anatomy with high suspicion of microscopic residual disease should be considered for CRT [41]. Patients at material risk of locoregional relapse but without robust evidence for universal RT benefit should be discussed in an MDT approach and, where possible, enrolled in trials.

Technical aspects: PORT typically includes the tumor bed, cystic duct stump, hepatoduodenal ligament, porto-caval region, and nodal stations No. 8/9/11/12/13/14/16a2-16b1. Common adjuvant doses are 45-50.4 Gy in 1.8-2.0 Gy fractions; capecitabine may be used concurrently as a radiosensitizer [35,41]. Including station 16 in radiation fields increases the risk of serious toxicity and is extrapolated from recurrence patterns of advanced disease rather than standard treatment for Stage II (N0) disease.

Evidence gaps, selection, and biomarkers

Stage II-specific evidence remains limited because many studies pool mixed biliary tract sites and stages. Biomarkers may assist selection: CA 19-9 and CEA are associated with recurrence risk after resection; normalization from preoperative elevation may carry prognostic value for early relapse. An international multi-institutional analysis found both markers informative for recurrence-free survival and one-year recurrence prediction after GBC resection, supporting risk-adapted adjuvant decisions and surveillance [43].

Challenges and controversies

Heterogeneous Evidence Base

Most recommendations for GBC are extrapolated from broader biliary cohorts or retrospective series; robust subgroup analyses for Stage IIA vs. IIB are uncommon. ASCO's endorsement of capecitabine after R0 is the most consistently supported approach, but direct head-to-head data against observation in a pure Stage II cohort are limited [35].

Regional Practice Variation

In parts of Asia, more aggressive adjuvant approaches (GC, combined CRT) are used based on local data and experience; in Western practice, capecitabine after R0 and selective CRT after R1 are typical. Phase II results from GECCOR-GB support feasibility and activity for both GC and capecitabine-based CRT in resected Stage II/III, yet implementation outside trials varies [40].

Toxicity and Quality of Life

Regimen choice must balance recurrence risk against toxicity. Capecitabine's dose-limiting hand-foot syndrome and RT-related gastrointestinal effects/fatigue underline the need for shared decision-making and proactive supportive care [35,42].

Surgical Determinants

Long-term outcome analyses emphasize that R0 resection and nodal negativity largely determine the chance of cure; R1 margins or N+ disease greatly diminish cure probability. This underscores the primacy of optimal surgery and thoughtful, risk-adapted adjuvant therapy rather than reflexive intensification post hoc [35,44].

Future directions

Immunotherapy and Targeted Agents

Multiple trials are evaluating PD-1/PD-L1 inhibitors and targeted therapies in biliary cancers (including GBC) in adjuvant or perioperative settings. Translating benefits from the metastatic setting to adjuvant use requires stage-specific evidence in GBC. High expression of programmed death-ligand 1 (PD-L1) has been found in 8.6% of biliary tract malignancies [45].

Precision Oncology and Biomarkers

Dynamics of CA 19-9/CEA pre-/post-op may refine risk stratification and identify Stage II patients who could benefit most from intensified adjuvant therapy or surveillance. Prospective validation is necessary before biomarker-guided adjuvant therapy becomes standard [43].

Optimizing RT Fields and Dose

Patterns of failure data justify attention to the tumor bed and specific nodal stations. Future trials should randomize RT vs. no RT in well-characterized Stage II cohorts (IIA vs. IIB) and evaluate modern techniques such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) to limit toxicity [41].

Trial Design Priorities

Multicenter trials should stratify by IIa vs IIb, margin status (R0/R1), histopathology, and biomarker levels, with standardized surveillance. Validation of neoadjuvant therapy before re-resection versus upfront surgery warrants a randomized trial [28]. Endpoints should include DFS, OS, patient-reported outcomes, and cost-effectiveness.

Conclusions

Despite being uncommon, GBC is the most prevalent and aggressive biliary tract cancer. The majority of patients receive an incidental diagnosis, as the number of cholecystectomies for presumed benign diseases is steadily increasing. The most common stage of incidentally diagnosed GBC is Stage II (T2). An incidental diagnosis does not exclude advanced-stage disease or aggressive pathological features, and an accurate post-index cholecystectomy staging is needed before an appraisal for re-resection. Current NCCN guidelines do not recommend routine neoadjuvant chemotherapy for resectable Stage II disease based on surgical risks; however, there was not complete consensus on this recommendation. Multidisciplinary management and clinical trial enrollment are likely to provide much-needed evidence in this regard. Standard adjuvant capecitabine alongside selective CRT may be considered post-resection in patients with R1 margins or other high-risk features.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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