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Chemoradiotherapy for Nonmetastatic, Locally Advanced Biliary Tract Cancer: A Narrative Review and Clinical Perspective

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Abstract

Systemic therapy remains the foundation of treatment for unresectable biliary tract cancer (BTC). In patients with nonmetastatic, locally advanced disease, however, persistent local progression may cause biliary obstruction, recurrent cholangitis, pain, bleeding, and interruption of systemic treatment. This narrative review evaluates the evidence for chemoradiotherapy (CRT), focusing on conventional fractionated CRT, patient selection, treatment feasibility, and its potential role after systemic therapy. Randomized evidence is limited. FFCD 9902 was a small phase II trial closed early because of slow recruitment and did not establish a comparative advantage for CRT over GEMOX chemotherapy. Retrospective CRT series and a recent systematic review support feasibility but cannot establish a causal survival benefit. Dose-escalated stereotactic and proton radiotherapy can achieve substantial local control in selected patients, but these approaches represent distinct treatment concepts and should not be used to infer benefit from conventional CRT. Recent retrospective integration of radiotherapy with immunochemotherapy is likewise hypothesis-generating and does not establish an advantage for concurrent CRT. CRT may remain an individualized multidisciplinary option for patients without distant metastases whose disease remains predominantly local after systemic therapy. Appropriate candidates require stable biliary drainage, adequate organ function, and acceptable gastrointestinal dose constraints. Prospective trials are needed to determine whether CRT adds clinically meaningful benefit to contemporary systemic therapy and to define optimal patient selection, radiation dose, and treatment sequencing.

Keywords: Biliary tract neoplasms; Cholangiocarcinoma; Chemoradiotherapy; Radiotherapy dosage; Patient selection

Abbreviations: 5-FU: 5-Fluorouracil; AAPM:

American Association of Physicists in Medicine; ALBI: Albumin-Bilirubin; BTC: Biliary Tract Cancer; CA19-9: Carbohydrate Antigen 19-9; CDDP: Cisplatin; CI: Confidence Interval; CRT: Chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; ESMO: European Society for Medical Oncology; FFCD: Fédération Francophone de Cancérologie Digestive; GC: Gemcitabine Plus Cisplatin; GCS: Gemcitabine Plus Cisplatin Plus S-1; GEM: Gemcitabine; GEMOX: Gemcitabine Plus Oxaliplatin; GS: Gemcitabine Plus S-1; HR: Hazard Ratio; IMRT: Intensity-Modulated Radiotherapy; JCOG: Japan Clinical Oncology Group; NCCN: National Comprehensive Cancer Network; OS: Overall Survival; PFS: Progression-Free Survival; QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic; RBE: Relative Biological Effectiveness; RT: Radiotherapy; SBRT: Stereotactic Body Radiotherapy; UFT: Tegafur-Uracil

Introduction

Biliary Tract Cancers (BTCs) are anatomically and molecularly heterogeneous malignancies that include intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma, and gallbladder cancer **[1, 2]**. Complete surgical resection remains the only potentially curative treatment; however, many patients present with locally advanced or metastatic disease and are therefore considered unresectable **[2]**. In this setting, systemic therapy is the treatment mainstay. Gemcitabine plus Cisplatin (GC) became the therapeutic backbone after the ABC-02 and BT22 trials, and later options expanded to include Gemcitabine Plus S-1 (GS), Gemcitabine plus Cisplatin Plus S-1 (GCS), and immune checkpoint inhibitor-based chemoimmunotherapy after TOPAZ-1 and KEYNOTE-966 **[3–8].** However, "unresectable BTC" includes both systemic disease with distant metastases and nonmetastatic disease that cannot be resected because of local invasion. In metastatic disease, systemic control generally takes priority. In nonmetastatic, locally advanced disease, by contrast, local progression may drive the clinical course through biliary obstruction, recurrent cholangitis, liver failure, pain, or bleeding. In a large Japanese real-world database study of 22,742 patients receiving systemic therapy for BTC, biliary infection-related treatment interruption occurred in 29.5% **[9].** In a 362-patient analysis of intrahepatic cholangiocarcinoma without distant organ metastasis, liver failure at death was significantly more frequent among patients treated with chemotherapy alone than among those receiving local therapy **[10].** These observations support the clinical relevance of local disease control but do not establish that CRT improves survival. Chemoradiotherapy (CRT) may therefore be considered for selected patients. This narrative review focuses on conventional CRT as the principal treatment concept. Evidence from Stereotactic Body Radiotherapy (SBRT), dose-escalated radiotherapy, proton therapy, and radiotherapy combined with immunochemotherapy is discussed only when it helps define the contemporary context for local treatment and should not be interpreted as direct evidence for conventional concurrent CRT.

Literature Review Approach

Relevant literature was identified primarily through PubMed searches completed on August 22, 2026 using combinations of terms related to biliary tract cancer or cholangiocarcinoma and chemoradiotherapy or radiotherapy. The search was supplemented by reference-list screening and major clinical guidelines. Pivotal trials, representative clinical series, contemporary reviews and guidelines, and technically relevant reports were selected when they informed the role, feasibility, patient selection, dose, or safety of CRT in unresectable or locally

advanced BTC. This was a narrative review; study selection was not protocolized, and no quantitative synthesis or formal risk-of-bias assessment was undertaken.

Advances in Systemic Therapy and the Role of Local Treatment

Systemic therapy as the foundation of treatment

In ABC-02, GC prolonged overall survival (OS) compared with gemcitabine alone and established GC as the standard of care for advanced BTC [3]. BT22 showed a similar direction of benefit in Japanese patients [4]. In Japan, JCOG1113 demonstrated the noninferiority of GS to GC, and the MITSUBA trial evaluated GCS [5,6]. In TOPAZ-1, durvalumab added to GC increased median OS from 11.5 to 12.8 months (Hazard Ratio [HR], 0.80; 95% Confidence Interval [CI], 0.66–0.97; P = 0.021) [7]. In KEYNOTE-966, pembrolizumab added to GC increased median OS from 10.9 to 12.7 months (HR, 0.83; 95% CI, 0.72–0.95; P = 0.0034) [8]. These phase III trials established chemoimmunotherapy as a current first-line standard. However, neither trial was designed to evaluate local treatment, and neither demonstrates an added benefit from CRT. CRT should therefore be assessed not as a substitute for effective systemic therapy but as a selective consolidative or symptom-directed strategy after systemic treatment.

Theoretical advantages and unresolved questions regarding CRT

CRT is conceptually distinct from radiotherapy alone because concurrent chemotherapy can provide radiosensitization while radiotherapy addresses locoregional disease. In nonmetastatic perihilar or extrahepatic cholangiocarcinoma, local progression can cause biliary obstruction, recurrent cholangitis, pain, bleeding, or loss of biliary drainage and may thereby interrupt systemic therapy. Historical institutional and population-based reports suggest that local control may be clinically relevant, but the evidence for conventional CRT is largely nonrandomized and susceptible to selection bias and confounding [11–15]. The potential advantage of CRT must also be balanced against its limitations. Radiosensitizing chemotherapy given during radiotherapy may not provide full systemic treatment intensity, and myelosuppression, gastrointestinal toxicity, hepatic dysfunction, or cholangitis may cause dose reductions or treatment interruption. Consequently, the biological rationale for concurrent CRT should not be equated with a proven survival advantage. Evidence from dose-escalated or ablative radiotherapy is relevant to the broader question of whether local control matters, but it addresses a treatment concept different from conventional CRT. Tao et al. reported an association between a biologically effective dose greater than 80.5 Gy and improved local control and OS in unresectable intrahepatic cholangiocarcinoma [16], and other SBRT series have reported encouraging local control in selected patients [17–22]. These studies were heterogeneous and mostly nonrandomized; some also reported clinically important gastrointestinal or biliary toxicity. They therefore should not be used as evidence that conventional concurrent CRT is improved simply by dose escalation.

Particle-beam and hypofractionated studies likewise demonstrate that technically intensive local therapy can be feasible in selected patients [23–26]. However, tumor site materially changes the therapeutic ratio. In intrahepatic cholangiocarcinoma, functional liver reserve and uninvolved liver volume are major constraints, whereas perihilar and distal tumors may be limited by proximity to the stomach, duodenum, small bowel, and hilar vasculature. Consistent with this heterogeneity, a retrospective study of unresectable extrahepatic cholangiocarcinoma found no significant improvement in OS or freedom from local progression with selective dose escalation above 50.4

Gy [27].

Accordingly, the central question for this review is not whether ablative radiotherapy is superior to conventional treatment, but whether conventional CRT has a clinically useful role in carefully selected patients whose disease remains nonmetastatic and predominantly local after systemic therapy. No contemporary randomized trial has established that role, and the existing evidence must be interpreted within the competing risks of local morbidity and occult systemic progression.

Clinical Evidence for Chemoradiotherapy

Comparative evidence

The FFCD 9902 phase II trial randomized patients with locally advanced, nonmetastatic perihilar or extrahepatic cholangiocarcinoma to concurrent CRT with 5-fluorouracil plus cisplatin or to Gemcitabine Plus Oxaliplatin (GEMOX) [28]. The trial was closed before planned completion because of slow recruitment and enrolled only 34 patients (18 CRT and 16 GEMOX). Median PFS was 5.8 months with CRT and 11.0 months with GEMOX, and median OS was 13.5 and 19.9 months, respectively. Because of the small sample and premature closure, the study was underpowered for a definitive comparative conclusion. Its results therefore should not be interpreted as proof of superiority, equivalence, or inferiority of either strategy; rather, they provide no evidence that CRT should replace chemotherapy as the standard approach.

Representative retrospective studies

Jethwa reported a 48-patient series in which the median radiation dose was 50.4 Gy in 28 fractions, 94% of patients received concurrent chemotherapy, and median OS was 12.0 months [29]. Leong reported a 20-patient series in which gemcitabine was administered after radiotherapy with concurrent cisplatin plus 5-fluorouracil; median OS was 20.4 months, and the 2-year survival rate was 43% [30]. Both studies were small, heterogeneous, and noncomparative and therefore cannot establish efficacy relative to other treatment strategies. Murakami described 21 patients, including 17 who received chemotherapy concurrently with or sequentially to radiotherapy and 4 who received external-beam radiotherapy alone [31]. In this mixed-treatment cohort, the 2-year OS rate was 35.7%, the 2-year PFS rate was 16.1%, and the 2-year local recurrence-free rate was 32.7%. Because treatment varied within the cohort, the effects attributable specifically to radiotherapy alone or to CRT cannot be separated. These retrospective data support feasibility but do not establish an OS benefit. Other retrospective reports have examined image-guided high-dose IMRT, gemcitabine-based SBRT, combined external-beam radiotherapy with brachytherapy, and external-beam radiotherapy for localized extrahepatic cholangiocarcinoma [32–35]. Differences in biliary drainage, radiation technique, dose, chemotherapy, disease site, and treatment era limit cross-study comparison; collectively, these reports support technical feasibility but not a causal survival benefit.

Contextual comparison of the principal evidence

Table 1 places the evidence most directly relevant to conventional CRT alongside pivotal systemic-therapy trials and selected contemporary local-treatment studies. The dose-escalated, proton-therapy, and radiotherapy–immunochemotherapy studies are included only to define the modern local-treatment context; they should not be interpreted as evidence for the efficacy of conventional concurrent CRT. Because populations, disease sites, treatment eras, radiotherapy techniques, systemic regimens, study designs, and assessment time points differ substantially, numerical outcomes should not be compared as direct measures of treatment effect.

Table 1. Contextual comparison of principal evidence relevant to conventional chemoradiotherapy and local

treatment in unresectable biliary tract cancer.

Study and year of publication	**Treatment**	**Population**	**Principal findings and interpretation**
ABC-02 [3] (2010)	GC vs. gemcitabine	Advanced BTC	Median OS, 11.7 vs. 8.1 months; established GC as standard therapy.
BT22 [4] (2010)	GC vs. gemcitabine	Japanese patients with advanced BTC	Median OS, 11.2 vs. 7.7 months; supported GC in Japan.
JCOG1113 [5] (2019)	GS vs. GC	Advanced or recurrent BTC	Confirmed noninferiority of GS to GC for OS.
MITSUBA [6] (2023)	GCS vs. GC	Advanced BTC	Reported improvement in OS and response rate with GCS.
TOPAZ-1 [7] (2022)	Durvalumab + GC vs. placebo + GC	Unresectable locally advanced, metastatic, or recurrent BTC	Median OS, 12.8 vs. 11.5 months; HR 0.80 (95% CI 0.66–0.97); established a current first-line standard.
KEYNOTE-966 [8] (2023)	Pembrolizumab + GC vs. placebo + GC	Unresectable locally advanced or metastatic BTC	Median OS, 12.7 vs. 10.9 months; HR 0.83 (95% CI 0.72–0.95); confirmed chemoimmunotherapy as a first-line standard.
FFCD 9902 [28] (2014)	CRT with 5-FU/cisplatin vs. GEMOX	Nonmetastatic, locally advanced perihilar or extrahepatic cholangiocarcinoma; n = 34 (18 CRT, 16 GEMOX)	Trial closed early for slow recruitment; median OS, 13.5 vs. 19.9 months. Underpowered for a definitive comparative conclusion.
Jethwa et al. [29] (2020)	Radiotherapy/CRT	Locally advanced or unresectable extrahepatic biliary cancer	Median radiation dose, 50.4 Gy; median OS, 12.0 months.
Leong et al. [30] (2012)	CRT with 5-FU/cisplatin followed by gemcitabine	Unresectable and locally advanced resected cholangiocarcinoma	Median OS, 20.4 months; 2-year survival, 43%; small, heterogeneous cohort.
Murakami et al. [31] (2022)	Definitive external-beam radiotherapy (concurrent or sequential chemotherapy in 17 of 21 patients)	Unresectable primary or locally recurrent cholangiocarcinoma without distant metastases	In the mixed-treatment cohort: 2-year OS, 35.7%; 2-year PFS, 16.1%; 2-year local recurrence-free rate, 32.7%. Only 4 patients received radiotherapy alone.

Study and year of publication	Treatment	Population	Principal findings and interpretation
Bisello et al. [36] (2024)	Concurrent CRT; systematic review	17 studies; 1,961 patients with unresectable nonmetastatic primary or recurrent BTC	Median reported CRT dose, 50.4 Gy; pooled 1-year PFS, 40.9%, and OS, 56.2%. Supports feasibility, but the underlying evidence was heterogeneous and predominantly nonrandomized.
Amit et al. [37] (2024)	Definitive-intent radiotherapy	78 patients with unresectable, nonmetastatic BTC	Median OS, 12.3 months. Higher baseline CA19-9 and worse ALBI grade were independently associated with poorer prognosis; prognostic rather than predictive factors.
Yamazaki et al. [38] (2026)	Proton beam therapy	236 patients with unresectable intrahepatic or perihilar cholangiocarcinoma without distant metastases	Median OS, 19 months; 2-year OS, 44.8%; 2-year local control, 66.5%; grade ≥3 adverse reactions, 8.9%. Prospective multicenter proton-therapy registry; contextual evidence for dose-escalated local treatment, not evidence for conventional CRT.
Zhang et al. [39] (2026)	Radiotherapy + immunochemotherapy vs. immunochemotherapy alone	Unresectable BTC; 497 patients overall; 105 vs. 105 after propensity-score matching	After matching, median OS, 15.0 vs. 9.0 months, and PFS, 10.0 vs. 5.0 months. Sequential RT showed an OS signal whereas concurrent RT did not. Retrospective and hypothesis-generating; no direct evidence for concurrent CRT.

Note: This table is intended for contextual comparison only; efficacy should not be compared directly across studies because of differences in populations, disease sites, treatment eras, radiotherapy techniques, systemic regimens, and study designs. Dose-escalated SBRT, proton therapy, and radiotherapy combined with immunochemotherapy are distinct from conventional concurrent CRT and are included only as contextual evidence. ALBI, albumin-bilirubin; BTC, biliary tract cancer; CA19-9, carbohydrate antigen 19-9; CRT, chemoradiotherapy; GC, gemcitabine plus cisplatin; GCS, gemcitabine plus cisplatin plus S-1; GEMOX, gemcitabine plus oxaliplatin; GS, gemcitabine plus S-1; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; UFT, tegafur-uracil.

Patient selection

Figure 1 outlines a practical framework for identifying patients who may be considered for CRT. Appropriate candidates should generally have no distant metastases, no distant progression after induction systemic therapy, and persistent local disease that remains the main cause of unresectability or clinical symptoms. A multidisciplinary team

should confirm histologic diagnosis and unresectability. The assessment should include Eastern Cooperative Oncology Group performance status, hepatic, renal, and bone marrow function, nutritional status, biliary-drainage stability, absence of active cholangitis, and feasibility of meeting gastrointestinal and hepatic dose constraints. Obstructive jaundice and cholangitis should be corrected before treatment. Decisions should also incorporate the patient's goals and preferences. The optimal duration of induction therapy and the criteria for transition to CRT have not been established in BTC.

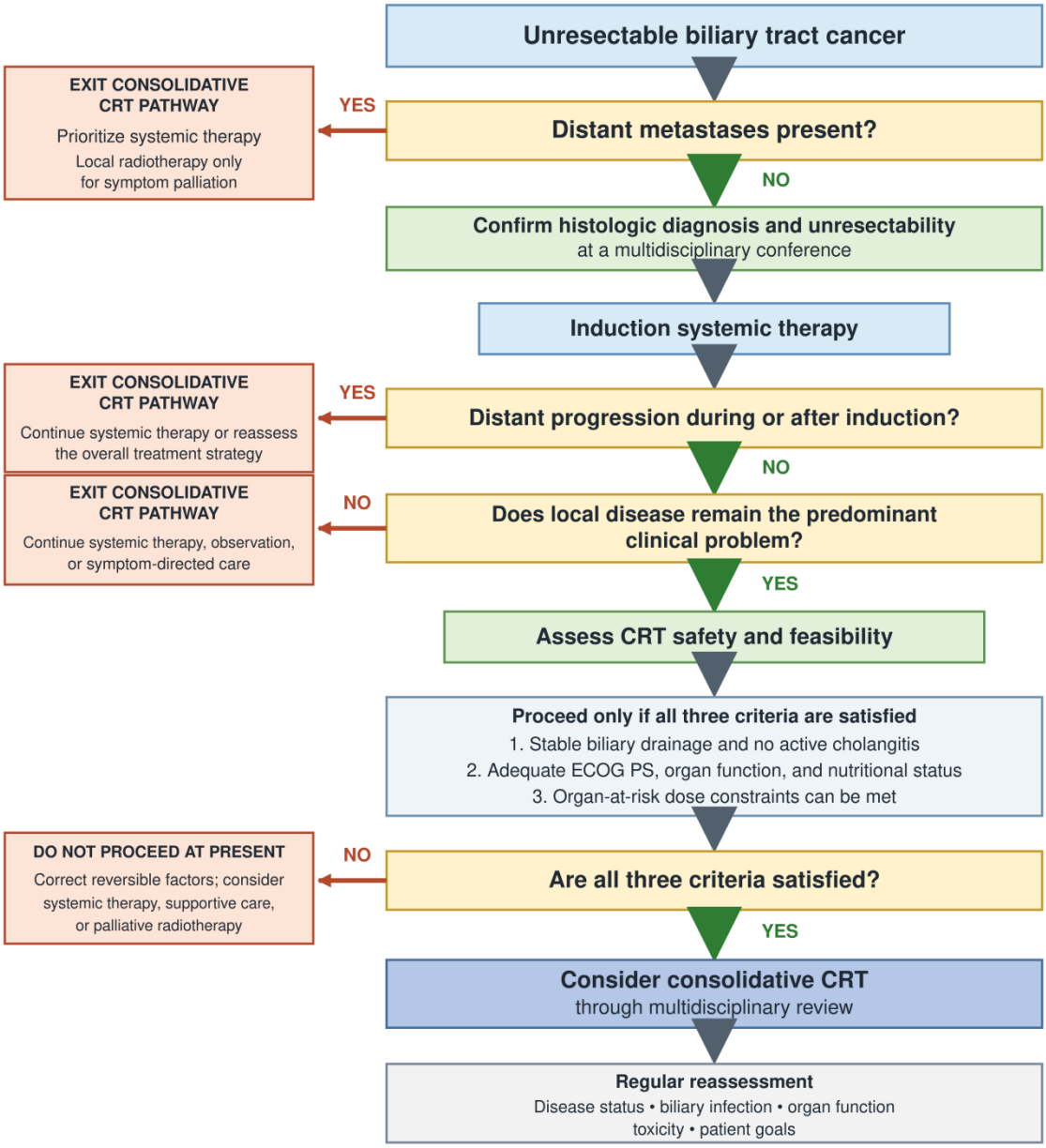

Figure 1: Patient-selection algorithm for chemoradiotherapy.

Note: At each decision node, the labeled downward arrow continues the CRT-assessment pathway, whereas the labeled leftward arrow ends it. This algorithm provides a practical framework for nonmetastatic, locally advanced disease and does not represent validated eligibility criteria or demonstrate a survival benefit from CRT. Treatment decisions should be individualized through multidisciplinary review and should incorporate resectability, treatment goals, and patient preferences. CRT, chemoradiotherapy.

Treatment Planning and Safety

Conventional CRT technique and dose

Most reports of conventional CRT used external-beam radiotherapy in the range of approximately 45–60 Gy, typically in 1.8–2.0-Gy fractions **[28–32,35]**. Polistina combined gemcitabine with Stereotactic Body Radiotherapy (SBRT) **[33],** whereas Deodato et al. incorporated brachytherapy into combined-modality treatment **[34];** these studies therefore should not be used to define the conventional fractionation range. For conventional CRT, dose selection should be individualized according to tumor location and extent, biliary drainage or stent status, hepatic reserve, uninvolved liver volume, and relevant gastrointestinal, renal, and spinal cord dose constraints. Fractionation-appropriate QUANTEC reviews provide dose-volume guidance for liver **[40],** stomach and small bowel **[41],** kidneys **[42],** and spinal cord **[43].** Particular caution is required for the stomach and duodenum when the target abuts the upper gastrointestinal tract. AAPM TG-101 is an SBRT-specific report and is therefore relevant to hypofractionated/SBRT planning **[44],** not to conventional 1.8–2.0-Gy fractionation. Intensity-modulated radiotherapy and image-guided radiotherapy may improve conformality, but respiratory motion and day-to-day gastrointestinal anatomy must be considered. Evidence from dose-escalated SBRT and proton therapy should be interpreted separately from conventional concurrent CRT: higher-dose associations in selected series **[16,22]** and prospective proton-therapy outcomes **[38]** support the broader importance and feasibility of local treatment but do not establish that increasing dose within a conventional CRT strategy improves survival. Indeed, selective escalation above 50.4 Gy was not associated with improved OS or freedom from local progression in a retrospective extrahepatic cholangiocarcinoma cohort **[27].**

Concurrent systemic agents

Reported concurrent agents include 5-fluorouracil, capecitabine, cisplatin, and gemcitabine, but no optimal concurrent regimen has been established for unresectable BTC **[11–13,28,30,32–35].** Standard systemic doses may not be safe when delivered with radiotherapy, and radiosensitizing schedules should not be assumed to provide the same systemic control as full-dose contemporary therapy. Drug selection and dose should therefore account for bone marrow, hepatic, and renal function, infection risk, and gastrointestinal dose exposure. A phase II protocol has evaluated the rationale for nivolumab with SBRT after induction chemotherapy **[45],** but modern prospective evidence specifically supporting concurrent CRT with an immune checkpoint inhibitor is insufficient. The recent Zhang study **[39]** evaluated radiotherapy integrated with immunochemotherapy and showed a signal with sequential rather than concurrent radiotherapy; it should therefore not be used as evidence for contemporary concurrent CRT.

Adverse events and supportive care

Acute adverse events may include nausea, anorexia, fatigue, myelosuppression, hepatic dysfunction, and cholangitis. Late adverse events may include gastric or duodenal ulceration and bleeding, biliary stricture, hepatic injury, and renal impairment; these events have been reported across conventional, stereotactic, and particle-therapy series **[17-22,24–27,32–35].** When fever or cholestasis develops, clinicians should distinguish treatment-related toxicity from stent occlusion or cholangitis. Evaluation and management should include prompt imaging, cultures, antibiotics, and biliary reintervention when appropriate. Nutritional support, analgesia, antiemetic therapy, and infection prevention should be integrated before treatment, and organ function and blood cell counts should be monitored throughout radiotherapy.

Discussion and Clinical Perspective

The evidence most directly relevant to conventional CRT remains limited. FFCD 9902 was closed early because of slow recruitment after enrolling 34 patients and was underpowered for a definitive comparison of CRT with GEMOX **[28].** The principal retrospective CRT series are small, heterogeneous, and vulnerable to selection bias **[29–35].** Bisello synthesized 17 studies including 1,961 patients treated with concurrent CRT for unresectable nonmetastatic primary or recurrent BTC **[36].** The median reported CRT dose was 50.4 Gy, with pooled 1-year PFS and OS rates of 40.9% and 56.2%, respectively. These data provide useful benchmarks and support feasibility, but the predominantly nonrandomized evidence does not establish that conventional CRT improves survival compared with modern systemic therapy. Patient selection may therefore be more important than any single historical CRT regimen. In a 2024 retrospective cohort of 78 patients with unresectable, nonmetastatic BTC treated with definitive-intent radiotherapy, Amit reported a median OS of 12.3 months and identified higher baseline CA19-9 and worse albumin-bilirubin grade as independent adverse prognostic factors **[37].** These factors are prognostic rather than validated predictors of benefit from CRT, but they reinforce the clinical importance of hepatic reserve, tumor biology, biliary stability, and the competing risk of early systemic failure when considering local treatment. The authors' own prior experience is kept separate from the formal evidence hierarchy: a non-peer-reviewed conference abstract reported a historical comparison of gemcitabine-based CRT with UFT in locally advanced cholangiocarcinoma **[46].** Because this preliminary report used a nonrandomized historical comparator, it is cited only as clinical context, is not included in **Table 1**, and is not used to support efficacy conclusions.

Dose-escalated SBRT and proton therapy should be regarded as contextual evidence rather than as support for conventional CRT. Associations between higher biologically effective dose and local control in selected retrospective series **[16,22],** as well as the 2026 multicenter prospective proton registry reported by Yamazaki et al. **[38],** show that intensive local radiotherapy can achieve meaningful local control in appropriately selected patients. Conversely, selective dose escalation above 50.4 Gy did not improve OS or freedom from local progression in unresectable extrahepatic cholangiocarcinoma **[27].** These apparently divergent results likely reflect differences in anatomic site, normal-tissue constraints, patient selection, radiotherapy technique, and competing distant failure. They do not justify a general inference that an ablative strategy and conventional CRT are interchangeable. The study by Zhang should also be interpreted as contemporary context rather than as direct evidence for CRT **[39].** After propensity-score matching, radiotherapy plus immunochemotherapy was associated with longer OS and PFS than immunochemotherapy alone, but the analysis was retrospective and included a broader unresectable population. Importantly, sequential radiotherapy showed an OS signal whereas concurrent radiotherapy did not. In addition, median OS in the matched control group was 9.0 months, lower than the 12.8 and 12.7 months reported in TOPAZ-1 and KEYNOTE-966 **[7,8].** Cross-trial comparisons are inherently unreliable, but this discrepancy raises additional concern about differences in case mix, treatment line, disease burden, or residual confounding. The study therefore supports prospective evaluation of treatment sequencing but should not be used to claim a survival benefit from concurrent CRT. Contemporary NCCN and ESMO guidance continues to place effective systemic therapy at the center of management for advanced BTC **[47,48].** Within that framework, the clinical rationale for retaining CRT as the focus of this

review is narrower: conventional CRT may be considered as a selective local strategy when distant metastases are absent, systemic disease has not progressed, the residual local tumor remains the predominant clinical problem, and biliary drainage and organ function permit safe treatment. This is a pragmatic multidisciplinary concept rather than an established standard, and the available ablative-radiotherapy and radiotherapy–immunochemotherapy data should not be used to overstate the evidence for concurrent CRT.

This review has limitations inherent to its narrative design. The literature search was focused primarily on PubMed, study selection was purpose-driven rather than protocolized, and no formal risk-of-bias assessment or quantitative synthesis was undertaken. BTC also encompasses anatomically distinct diseases, while the published CRT literature spans different treatment eras, definitions of unresectability, radiation techniques, and systemic regimens. Accordingly, numerical outcomes across studies should not be interpreted as direct treatment comparisons. The principal contribution of this review is an updated clinical interpretation of conventional CRT, with modern radiotherapy studies used only to clarify the boundaries of what can and cannot be inferred for CRT.

Future Research

Prospective studies should specifically test conventional fractionated CRT after a defined interval of contemporary systemic therapy in patients with nonmetastatic, locally advanced BTC. Trial designs should prespecify the concurrent agent, radiotherapy dose and fractionation, target definition, organ-at-risk constraints, biliary-drainage requirements, and criteria for transition from systemic therapy to CRT. Stratification should include anatomic site, resectability criteria, response to induction therapy, liver reserve, CA19-9, and biliary status **[37].** Dose-escalated SBRT and proton therapy should be evaluated in separate protocols or prespecified strata rather than pooled with conventional CRT, because they represent different radiotherapeutic strategies **[16,22,38].** Likewise, the question of concurrent versus sequential integration with immunochemotherapy requires prospective testing; the retrospective signal favoring sequential radiotherapy in the study by Zhang et al. **[39]** should be treated as hypothesis-generating. Endpoints should extend beyond OS and PFS to include local PFS, biliary patency, repeat biliary intervention, hospitalization for cholangitis, pain control, continuation of systemic therapy, treatment completion, patient-reported outcomes, and late hepatobiliary and gastrointestinal toxicity.

Conclusions

Systemic therapy remains the foundation of treatment for unresectable BTC. The direct evidence for conventional concurrent CRT in nonmetastatic, locally advanced disease is limited, and no contemporary randomized trial has shown that CRT improves survival over modern systemic therapy. The rationale for local treatment is clinically relevant because biliary infection can interrupt systemic therapy and uncontrolled intrahepatic disease can contribute to liver failure **[9,10].** These observations do not prove a survival benefit from CRT. Conventional CRT may nevertheless remain a biologically plausible, selective multidisciplinary strategy when disease remains predominantly local after systemic therapy, distant metastases are absent, biliary drainage is stable, organ function is adequate, and gastrointestinal dose constraints can be met. Evidence from dose-escalated SBRT, proton therapy, and radiotherapy integrated with immunochemotherapy demonstrates the evolving potential of local treatment but should not be interpreted as proof of benefit from conventional

CRT; notably, the recent immunochemotherapy study showed a signal with sequential rather than concurrent radiotherapy [39]. Multidisciplinary review is therefore essential. Prospective comparative trials are needed to determine whether conventional CRT adds clinically meaningful benefit to contemporary systemic therapy, which patients are most likely to benefit, and how radiation dose and systemic treatment should be sequenced.

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Conflict of Interests

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Data Availability

No datasets were generated or analyzed for this narrative review. All information discussed is derived from previously published sources cited in the manuscript.

Ethical Approval

Not applicable. This article is a narrative review and does not report original research involving human participants or animals.

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