Review Article
J Liver Cancer 2026;26(1):55-64
pISSN 2288-8128 • eISSN 2383-5001
https://doi.org/10.17998/jlc.2026.03.04

JOURNAL OF LIVER CANCER

The role of radiotherapy in the management of combined hepatocellular-cholangiocarcinoma: current evidence and future perspectives

Seo Hee Choi, Woong Sub Koom, Ik Jae Lee

Department of Radiation Oncology, Heavy Ion Therapy Research Institute, Yonsei Cancer Center, Yonsei University Health System, Yonsei University College of Medicine, Seoul, Korea

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare and highly aggressive hybrid malignancy characterized by a poor prognosis and high recurrence rates due to its dual histological nature. In the absence of established standard-of-care protocols, clinical management strategies are frequently extrapolated from the guidelines for its components, hepatocellular carcinoma and intrahepatic cholangiocarcinoma (iCCA). This review evaluates the evolving role of radiotherapy (RT) as an integral part of the multidisciplinary care for cHCC-CCA. Adjuvant RT may be considered for patients exhibiting high-risk pathological features, such as positive or close resection margins, lymphovascular invasion, and perineural invasion. For unresectable disease unfeasible for surgery or transarterial therapies, definitive RT using intensified doses, analogous to iCCA protocols, is employed to improve local control. High-precision modalities, particularly particle therapies such as proton or carbon ion RT, are emphasized as preferred options for delivering ablative doses while minimizing toxicity and preserving functional liver reserve. Furthermore, preliminary clinical evidence suggests a potential synergy between RT and immune checkpoint inhibitors, with reported cases demonstrating complete responses or successful conversion to curative-intent resection. While current evidence remains limited to retrospective cohorts and case series, the strategic integration of precision RT offers a rational pathway for optimizing outcomes in cHCC-CCA, necessitating further prospective validation. **(J Liver Cancer 2026;26:55-64)**

Keywords: Carcinoma, hepatocellular; Cholangiocarcinoma; Radiotherapy; External beam radiotherapy; Proton therapy

INTRODUCTION

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare and aggressive primary liver malignancy, defined by the unequivocal histomorphological presence of both hepatocytic and cholangiocytic differentiation within a single tumor.[1,2] Although its reported incidence ranges from 0.4% to 14.2% of primary hepatic cancers, its clinical prognosis remains dismal. Outcomes for cHCC-CCA are frequently inferior to those of hepatocellular carcinoma (HCC) and often comparable to or even worse than those of intrahepatic cholangiocarcinoma (iCCA), with 5-year survival rates often failing to reach 30%.[1-3]

Surgical resection with regional lymphadenectomy currently offers the only potential chance for a cure; however, long-term survival is frequently compromised by high rates of locoregional recurrence and distant metastasis, with more than 60% of patients experiencing disease relapse even after curative-intent hepatectomy. For patients with unresectable disease, the current standard of care, gemcitabine and cisplatin-based systemic chemotherapy, has reached a therapeutic plateau, providing limited

Received Feb. 15, 2026 • **Revised** Mar. 2, 2026 • **Accepted** Mar. 4, 2026

Corresponding author: Ik Jae Lee
Department of Radiation Oncology, Heavy Ion Therapy Research Institute, Yonsei Cancer Center, Yonsei University Health System, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
E-mail: ikjae412@yuhs.ac

survival benefit with median overall survival (OS) typically remaining under 1 year. Consequently, there is an urgent clinical imperative to optimize locoregional control strategies to improve clinical outcomes.

The selection of appropriate adjuvant treatment options for cHCC-CCA is uniquely complicated by its biphenotypic nature, exhibiting features resembling both HCC and cholangiocarcinoma (CCA). As patients with cHCC-CCA experiencing poor survival and a heightened likelihood of distant metastasis may stand to benefit from adjuvant therapies, an essential prerequisite is the accurate evaluation and prediction of survival outcomes specific to this subtype. Although external beam radiotherapy (EBRT) is not yet universally established in cHCC-CCA management guidelines, emerging evidence from iCCA underscores that high-dose ablative radiotherapy (RT) and particle therapies, such as proton or carbon-ion RT, can significantly enhance local control and OS.

Given the biological similarities between the biliary component of cHCC-CCA and iCCA, these radiotherapeutic modalities warrant careful investigation through the extrapolation of robust data from iCCA, which is a specific subtype of the broader biliary tract cancer category. This review synthesizes current evidence regarding the multifaceted role of RT in cHCC-CCA, ranging from adjuvant settings for high-risk resections to definitive ablative treatments for advanced disease, and proposes therapeutic strategies by leveraging advances in nodal mapping and dose-escalation to support individualized clinical decision-making.

THERAPEUTIC RATIONALE FOR RADIOTHERAPY

Overcoming the limitations of conventional locoregional therapies

Catheter-based locoregional therapies, including transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), are established treatment options for advanced or recurrent HCC. However, the therapeutic efficacy of TACE and TARE might be constrained by the biological heterogeneity and variable vascularity of cHCC-CCA. Recent evidence indicates that the radiographic appearance and vascular profile of cHCC-CCA are largely determined by the predominant histological component.[2,4] While TACE demonstrates high response rates (approximately 85%) in hypervascular, HCC-dominant tumors, its efficacy drops precipitously to around 10% in hypovascular lesions, which typically exhibit CCA predominance or a dense fibrous stroma.[5] Although TARE has emerged as a promising option for HCC and iCCA, as well as for cHCC-CCA, with response rates reported between 55% and 60%,[6,7] the lack of standardized treatment protocols and the reliance on arterial blood supply remain significant challenges. Consequently, the hypovascular or desmoplastic regions within cHCC-CCA frequently evade the ischemic and cytotoxic effects of chemoembolization, leading to incomplete therapeutic responses. In contrast, RT delivers ionizing radiation that induces DNA damage largely independent of the tumor's vascular architecture or embolic accessibility. This modality offers a distinct advantage by providing a potent cytocidal effect across both the hypervascular HCC and the relatively hypoperfused, desmoplastic CCA components, thereby addressing the intrinsic limitations of catheter-based therapies in these heterogeneous tumors.

Bridging the gap in microscopic disease control

The aggressive nature of the biliary component in cHCC-CCA manifests as a high propensity for microscopic infiltrative spread, which frequently eludes surgical clearance. Pathological hallmarks such as lymphovascular invasion (LVI) and perineural invasion are strong predictors of early locoregional failure and distant metastasis, with recent data identifying LVI as a predominant independent factor for poor survival.[8-10] This prognostic impact aligns with established evidence from iCCA, where vascular and perineural invasion are widely recognized as critical determinants of recurrence and survival.[11-15] Furthermore, the incidence of regional lymph node (LN) metastasis, reported to range from 20% to 40% in cHCC-CCA compared to less than 5% in pure HCC, suggests that subclinical microscopic disease is often present beyond the macroscopically resected area.[15,16] To address these microscopic risk factors, RT provides a targeted cytocidal effect to sterilize potential zones of subclinical disease, thereby compensating for the geographic limitations of surgical resection. Since regional LN involvement is an important predictor of short disease-free survival,[17,18] RT serves as a rational spatial intensifier. By targeting these zones of microscopic persistence in the liver parenchyma and regional lymphatic basins, RT addresses the spatial limitations of surgery and the systemic focus of chemotherapy.

Mitigating mortality from tumor-related liver failure

While distant metastasis is a significant concern in cHCC-CCA, local progression remains a critical driver of mortality. Evidence from iCCA cohorts indicates that approximately 70% of patients with unresectable disease succumb to tumor-related liver failure (TRLF), caused by biliary obstruction, vascular invasion, or extensive parenchymal replacement, rather than extrahepatic tumor burden.[19-21] Consequently, liver-directed RT is hypothesized to provide a significant oncologic benefit by mitigating death due to TRLF.[22-24] Retrospective analyses have demonstrated a clear dose-response relationship in this setting; ablative RT, defined as a biologically effective dose (BED_{10}) >80.5 Gy, significantly prolongs median OS compared to conventional doses (23.7 vs. 12.8 months).[23] Importantly, the benefit of preventing TRLF extends even to patients with metastatic disease.[25] Propensity-matched analysis revealed that definitive liver RT significantly reduced the rate of death attributable to TRLF compared to chemotherapy alone (47% vs. 82%). This local control translated into a substantial survival advantage, with median OS increasing from 9 months to 21 months with the addition of RT. These findings suggest that controlling the dominant liver tumor is essential for altering the natural history of the disease, irrespective of metastatic status.

CURRENT GUIDELINES AND THE CLINICAL GAP IN cHCC-CCA MANAGEMENT

Current international guidelines, primarily established for biliary tract cancers, position RT as a critical option for specific high-risk clinical scenarios. In the adjuvant setting, while the American Society of Clinical Oncology (ASCO) guidelines recommend adjuvant capecitabine as the standard of care,[26] both the National Comprehensive Cancer Network (NCCN)[27] and the American Society for Radiation Oncology (ASTRO)[28] guidelines provide conditional recommendations to consider adjuvant chemoradiotherapy (CRT) specifically for patients with adverse features, such as microscopically positive margins (R1) or regional LN metastases, to enhance local control. In the definitive setting for unresectable disease, NCCN lists EBRT as a locoregional treatment option, and ASTRO strongly supports the use of high-dose or ablative RT (e.g., stereotactic body radiotherapy [SBRT]) for liver-confined disease, where technically feasible and safe for adjacent organs, noting its association with improved survival compared to conventional doses. However, due to the rarity of cHCC-CCA, high-level evidence specific to this histologic subtype remains virtually non-existent. A recent international multicenter survey[29] revealed that only 13% of expert centers have a specific treatment policy for cHCC-CCA, with most decisions relying on institutional preference. Consequently, therapeutic strategies for cHCC-CCA are currently extrapolated from the aforementioned iCCA guidelines, utilizing RT as a rational approach to address locoregional failure in both high-risk postoperative and unresectable settings.

ADJUVANT RADIOTHERAPY FOR RESECTABLE DISEASE

Survival benefit in high-risk populations

While specific data for cHCC-CCA are limited, large-scale population-based analyses of iCCA provide compelling evidence for the survival benefit of adjuvant strategies, often delivered as concurrent CRT (CCRT), which serves as a benchmark for cHCC-CCA management. A surveillance, epidemiology, and end results analysis[30] demonstrated that adjuvant RT significantly improved median OS compared to surgery alone (11 vs. 6 months, P=0.014). Regarding the optimal treatment modality, a nationwide analysis of 599 patients[31] suggested that concurrent CCRT was associated with a reduced mortality risk compared to chemotherapy alone (hazard ratio [HR], 0.67; P=0.001), with the clinical benefit being most pronounced in patients with locally advanced disease or positive surgical margins.

Management of narrow or positive surgical margins

Achieving a wide negative margin (R0≥1 cm) is often challenging in cHCC-CCA due to the tumor's anatomical proximity to major vascular structures. Retrospective and registry analyses consistently demonstrate that adjuvant RT mitigates the oncologic risks associated with incomplete resection. Adjuvant CRT has been reported to significantly improve survival compared to chemotherapy alone in margin-positive patients, regardless of stage (HR, 0.51-0.65).[31] Similarly, National Cancer Database (NCDB) analyses found significant survival advantages for adjuvant therapy in R1/R2 resections, whereas no such benefit was observed in R0 cases with wide margins.[32,33] For technically negative but narrow margins (<1 cm), evidence indicates that adjuvant RT can improve 3-year survival to levels comparable with wide-margin resection (55% vs. 65%), whereas narrow-margin resection alone yields significantly poorer outcomes (20%).[34] These findings support the role of adjuvant RT in "sterilizing" the resection bed in margin-compromised cases.

Role in node-positive and adverse pathologic features

While regional LN involvement is a known driver of poor outcomes, adjuvant strategies have shown potential to alter this trajectory. A meta-analysis[35] of over 6,700 patients with biliary tract cancers concluded that adjuvant CRT offers a superior survival advantage over surgery alone, particularly for LN-positive and R1-resected populations. Supporting this, retrospective data[36] for node-positive disease indicate that adjuvant RT can nearly double the median OS compared to observation (19.1 vs. 9.5 months, P=0.011). Similarly, a large-scale analysis of the NCDB[37] identified positive LNs status as a key predictor for adjuvant treatment benefit. Furthermore, in a nationwide Taiwanese cohort, Lin et al.[31] demonstrated that adjuvant CCRT significantly reduced mortality risk in patients with stage III/IV disease (often driven by nodal involvement), with an adjusted hazard ratio of 0.55 compared to chemotherapy alone.

Beyond nodal status, specific adverse pathologic features identified in the latest cHCC-CCA research warrant intensified adjuvant strategies. While Kim et al.[38] reported that adjuvant CRT significantly improved recurrence-free survival in R0-resected, node-positive patients (HR, 0.44; P=0.036), recent findings by Chun et al.[8] extend this rationale to LVI. In their cohort, LVI-positive cHCC-CCA patients exhibited a strikingly lower 5-year OS of 35.8% compared to 93.3% in LVI-negative cases. These data suggest that LVI, alongside tumor necrosis and elevated postoperative carbohydrate antigen 19-9, serves as a critical indicator for adjuvant RT to eradicate microscopic residual disease and prevent early locoregional relapse.

DEFINITIVE AND ABLATIVE RADIOTHERAPY FOR UNRESECTABLE DISEASE

The dose-response relationship and ablative radiotherapy

Recent clinical evidence has established a definitive dose-response relationship in iCCA, introducing the concept of ablative RT (A-RT) as a standard for overcoming the intrinsic radioresistance of the biliary component, within safe dose limits for adjacent organs. A landmark retrospective analysis by Tao et al.[39] identified a BED_{10} of >80.5 Gy as a critical threshold for durable local control. Delivering doses above this threshold achieved a 3-year OS of 73%, a substantial improvement compared to the 38% observed with conventional doses. These single-institution findings have been validated by large-scale registry data; in an analysis of the NCDB encompassing 1,112 patients, De et al.[23] demonstrated that A-RT (BED_{10} ≥80.5 Gy) nearly doubled the median OS compared to conventional RT (23.7 vs. 12.8 months, P<0.001). Consistent with these findings, the multi-institutional KROG 20-02 study[40] substantiated that an equivalent dose in 2 Gy fractions (EQD2) of ≥60 Gy serves as a significant independent prognostic factor for improved OS. A recent meta-analysis[41] also demonstrated that A-RT is associated with a superior OS compared to conventional-dose RT (HR, 0.53).

This dose-dependent efficacy, which is drawn primarily from CCA experience in the absence of robust cHCC-CCA data, is consistently observed across modern high-precision modalities such as particle therapy capable of delivering such intensive doses while sparing healthy liver parenchyma (Table 1). High-dose proton beam therapy (PBT) has reported 2-year local control rates as high as 94% (median, 58 GyRBE),[42] while hypofractionated photon RT has yielded a 2-year local control (LC) of 93%.[22] Specifically, among patients treated with PBT, reaching higher dose thresholds has been linked to superior clinical outcomes: a BED >70 GyE was associated with significantly higher 1-year LC rates (83.1% vs. 22.2%, P=0.002),[43,44] and an EQD210 ≥80 GyE led to nearly doubled 2-year OS rates (23.8% vs. 13.2%). The Japan Carbon-Ion Radiation Oncology Study Group (J-CROS) reported that carbon-ion RT achieved a median survival of 14.8 months and a 1-year local control rate of 83% in unresectable iCCA patients, with a favorable toxicity profile. Similarly, a recent meta-analysis[45] underscored the superiority of particle therapy (proton/carbon) and SBRT over conventional approaches. The analysis revealed that particle therapy and SBRT achieved significantly higher 1-year survival rates (71.8% and 59.2%, respectively) compared to conventional 3D-conformal RT (47.2%, P=0.0004), positioning ablative strategies as the preferred definitive locoregional treatment for unresectable disease. While these benchmarks are primarily derived from iCCA cohorts, they provide a critical therapeutic framework for cHCC-CCA, where the cholangiocytic component often dictates the aggressive clinical course and relative resistance to non-ablative therapies.

Role in metastatic disease

The benefits of definitive liver RT extend even to patients with iCCA with extrahepatic metastases (M1), challenging the traditional dogma that local therapy is futile in the metastatic setting. Controlling the dominant intrahepatic tumor burden is critical because local progression is a primary driver of mortality in this population. De et al.[25] reported that definitive liver RT signifi-

Table 1. Summary of particle therapy outcomes for unresectable intrahepatic cholangiocarcinoma as clinical evidence for cHCC-CCA management

Study	Design	Country	Modality	Number of patients	Dose/fractionation	2-year LC (%)	2-year OS (%)	Toxicity ≥G3 (%)	Main findings
Hong et al.[42] (2016)	Ph II	USA	PBT	37	Peripheral 67.5 GyE/15fr Central 58.05 GyE/15 fr	94	47	8	Multicenter phase II study: high LC, low toxicity
Smart et al.[22] (2020)	R	USA	PBT or Photon	66	Median 58.05 GyE (BED 80.5)/15 fr	93	62	11	Proton (vs. photon): improve OS
Tao et al.[39] (2016)	R	USA	PBT or Photon	79	Median 58.05 GyE (BED 80.5)/15 fr	45	61	No RILD	BED_{10} >80.5 Gy: 3-year LC increased (78% vs. 45%, *P*=0.04), 3-year OS increased (73% vs. 38%, *P*=0.017)
Makita et al.[43] (2014)	R	Japan	PBT	6	Median 68.2 GyE (BED 75.8)	68*	49*	Acute 1 Late 2	BED_{10} >70 GyE: 1-year LC increased (83.1% vs. 22.2%, *P*=0.002)
Shimizu et al.[55] (2019)	R	Japan	PBT	37	66-74 GyE/10-37 fr	72	52	Acute 0 Late 3	
Hung et al.[56] (2020)	R	Taiwan	PBT	18	66.0-72.6 GyE/10-22 fr	88*	32	RILD 6.7	
Kim et al.[44] (2022)	R	Korea	PBT	47	45-80 GyE/10 fr	87	43	9	$EQD2_{10}$ ≥80 GyE: 2-year OS increased (23.8% vs. 13.2%)
Ohkawa et al.[57] (2015)	R	Japan	PBT	20	55.0-79.2 GyE/10-35 fr	60	61	Acute 1 Late 2	
Kasuya et al.[58] (2019)	R	Japan	CIRT	56	52.8-76.0 GyE/4-20 fr	58	41 (iCCA 53, PHC 26)	G3 CIRT-related bile duct stenosis 1, RILD-related death 1	Poor prognostic factors: pre-RT cholangitis, CPB

LC, local control; OS, overall survival; G3, grade 3; Ph II, phase II; PBT, proton beam therapy; GyE, Gray equivalent; fr, fractions; R, retrospective; BED, biologically effective dose; RILD, radiation-induced liver disease; Gy, Gray; EQD2, equivalent dose in 2-Gy fractions; CIRT, carbon ion radiotherapy; iCCA, intrahepatic cholangiocarcinoma; PHC, perihilar cholangiocarcinoma; RT, radiotherapy; CPB, Child-Pugh B.
*One-year rate results.

cantly reduced the incidence of death due to TRLF compared to chemotherapy alone (47% vs. 82%) and improved median OS from 9 to 21 months. This finding is corroborated by an NCDB analysis by Sebastian et al.,[20] which found that adding liver-directed therapy (surgery or RT≥45 Gy) to chemotherapy significantly improved OS compared to chemotherapy alone (HR, 0.57; *P*<0.001). Given that the biliary component of cHCC-CCA frequently leads to catastrophic complications such as obstructive jaundice or hepatic insufficiency, prioritizing intrahepatic control through RT is a rational strategy to prevent terminal liver failure, even in the presence of extrahepatic spread.

Downstaging and conversion to resectability

Beyond survival prolongation, integrating RT with systemic therapy serves as a strategic bridge to curative surgery for initially unresectable disease.[46] Specifically, Sumiyoshi et al.[47] reported that 71.4% of locally advanced iCCA patients achieved downstaging following CRT, with 80% of those reaching R0 resection status. Similarly, Cho et al.[48] observed successful conversion in 12.5% of patients after concurrent CRT. The KROG 22-02 study[40] recently substantiated the role of dose escalation in this setting. High-dose RT (EQD2≥60 Gy) combined with sequential gemcitabine-cisplatin significantly improved resectability, achieving a 28% conversion rate compared to 8.6% in the low-dose group and 0% with RT alone. Notably, patients who successfully underwent curative resection following conversion achieved a 3-year OS of 75%, illustrating that effective downstaging can fundamentally alter the clinical trajectory. Given that achieving an R0 margin represents the only definitive pathway to long-term survival for cHCC-CCA, these conversion strategies are particularly vital. High-dose RT can induce significant tumor regression in locally advanced disease, thereby expanding the eligibility for curative-intent surgery among patients initially considered for palliative management only.

FUTURE PERSPECTIVE

A fundamental challenge in standardizing treatment for cHCC-CCA is its evolving pathological definition across successive

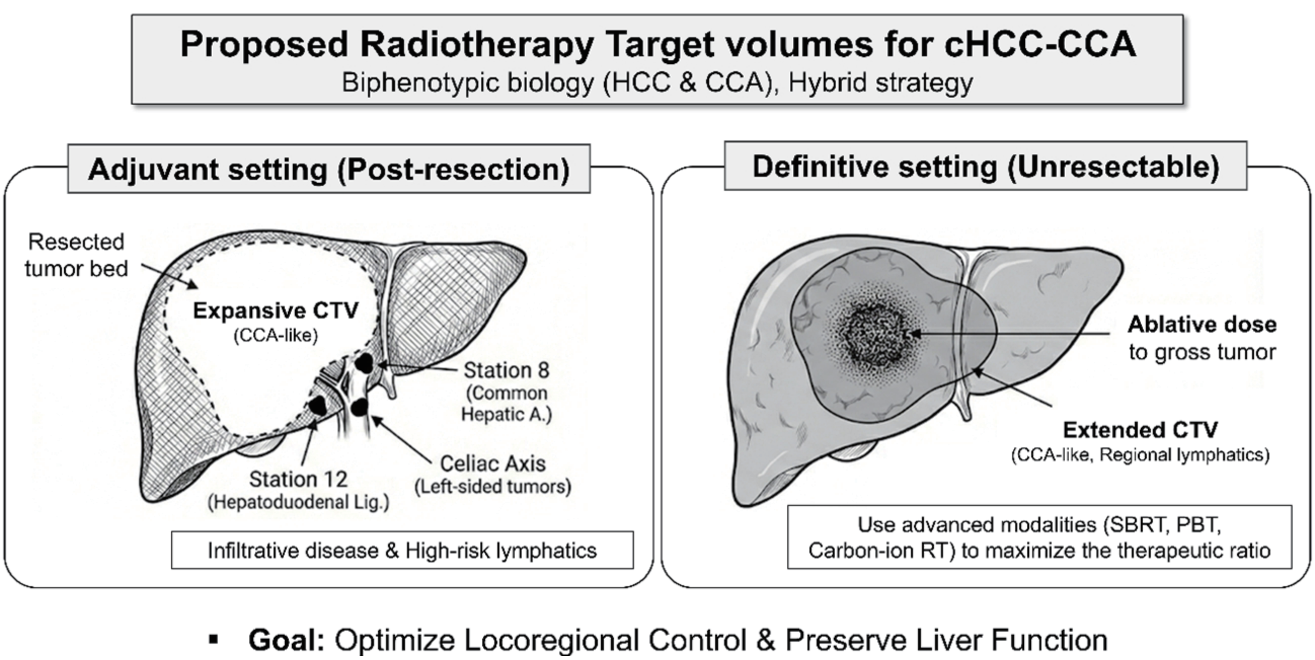

Figure 1. Proposed radiotherapy target volume strategies for combined hepatocellular-cholangiocarcinoma (cHCC-CCA). The framework integrates biphenotypic biology by tailoring target volumes to anatomical recurrence patterns. In the adjuvant setting, the proposed framework suggests an expansive clinical target volume (CTV) that may optionally incorporate elective nodal irradiation (ENI) to address the infiltrative biliary component. This strategy targets high-risk nodal stations (e.g., stations 8 and 12) based on potential recurrence patterns, with laterality-based individualization, such as the celiac axis for left-sided tumors. For definitive cases, the strategy combines ablative-dose delivery to the primary tumor (HCC-like) with extended CTV for regional lymphatics (CCA-like). High-precision modalities (SBRT, PBT, and carbon-ion RT) are essential to maximize the therapeutic ratio by achieving robust locoregional control while preserving functional liver reserve. HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; SBRT, stereotactic body radiotherapy; PBT, proton beam therapy; RT, radiotherapy.

World Health Organization (WHO) classifications and its inherent biological ambiguity, which remains insufficiently understood as to whether it behaves more similarly to HCC, iCCA, or a distinct entity. Due to this biological complexity and the paucity of disease-specific data, standardizing target volumes for cHCC-CCA remains a significant clinical challenge.

Refining radiotherapy target volumes for cHCC-CCA

A risk-adapted framework is proposed here, integrating anatomical recurrence patterns with the disease's unique biphenotypic biology to move toward a hybrid targeting strategy (Fig. 1). Regarding the extent of the target volume, particularly in the adjuvant setting, evidence from recent nodal mapping, most notably by Yang et al.,[49] suggests that elective nodal irradiation should prioritize the common hepatic artery (station 8) and the hepatoduodenal ligament (station 12), where recurrence rates frequently exceed 30%. However, the clinical benefit of elective nodal irradiation remains a hypothesis-driven strategy. Given that the survival benefit of LN dissection is still a matter of controversy even within the iCCA literature, the necessity and impact of regional nodal coverage in cHCC-CCA, both in postoperative and locally advanced settings, require further prospective validation. Regarding the specific margins of the target volume, in contrast to the focal margins utilized in HCC, a more expansive clinical target volume (CTV) is recommended, analogous to biliary cancer atlases,[50] to address the infiltrative nature of the biliary component. This volume should be further individualized based on tumor laterality;[51] left-sided tumors may exhibit a higher propensity for spread toward the celiac axis and lesser curvature stations. For definitive cases, a multifaceted approach is suggested: delivering ablative doses to the primary tumor to overcome intrinsic radioresistance, leveraging the dose-response relationship, while extending the CTV to include regional lymphatic echelons. This represents a strategic departure from the gross tumor volume-only approach common in HCC SBRT. Given the high prevalence of underlying cirrhosis in cHCC-CCA patients, this intensification must be balanced against the risk of radiation-induced liver disease. Consequently, advanced modalities such as PBT or carbon-ion RT may be uniquely suited to navigate this narrow therapeutic window, preserving functional liver reserve and host immunity while achieving robust locoregional control.

Synergistic potential of immuno-radiotherapy in cHCC-CCA

While the systemic therapeutic landscape for cHCC-CCA remains limited, the integration of RT with immune checkpoint inhibitors (ICIs) is being explored as a potential strategy to overcome treatment resistance. Although large-scale prospective evidence is currently lacking, preliminary case series[52-54] have noted instances where SBRT combined with programmed cell death protein-1 inhibition facilitated complete remission or enabled conversion surgery for unresectable disease. Interestingly, these responses have been observed even in tumor mutational burden-low or programmed cell death-ligand 1-negative cases, suggesting a possible role for RT in sensitizing immune-cold microenvironments. Mechanistically, it is hypothesized that RT may

Table 2. Proposed indications and strategies for radiotherapy in cHCC-CCA

Disease status	RT aim	Indications and clinical considerations
Resectable	Adjuvant	Presence of high-risk features (analogous to iCCA)
		Positive or close RM
		LVI
		PNI, tumor necrosis, or other high-risk nodal features
Unresectable	Definitive	Disease unfeasible for surgery, transplantation, or transarterial therapies (analogous to HCC)
		Delivery of higher radiation doses (analogous to iCCA)
		Technical options are IMRT, SBRT, or particle therapy (proton/carbon ion)
Metastatic	Palliative	Symptomatic management of lesions causing pain, biliary obstruction, or neurological deficits
	Ablative/curative*	Management of oligometastatic disease or durable intrahepatic local control†

As established standard protocols for cHCC-CCA are currently lacking, these clinical strategies are largely extrapolated from retrospective cohorts or management guidelines for HCC and iCCA.
cHCC-CCA, combined hepatocellular-cholangiocarcinoma; RT, radiotherapy; iCCA, intrahepatic cholangiocarcinoma; RM, resection margin; LVI, lymphovascular invasion; PNI, perineural invasion; HCC, hepatocellular carcinoma; IMRT, intensity-modulated radiotherapy; SBRT, stereotactic body radiotherapy.
*Selected cases; †Evidence for this setting remains limited.

induce immunogenic priming by reprogramming the immune landscape and enhancing antigen presentation, thereby potentially increasing sensitivity to ICIs.[2,3] Results from ongoing trials investigating novel agents like camrelizumab are anticipated to clarify this paradigm.[46] However, since the synergy of immuno-radiotherapy is still under evaluation even in pure HCC and iCCA, its application in cHCC-CCA, harboring both components, involves even greater clinical uncertainty. Identifying the optimal systemic backbone remains a significant knowledge gap, emphasizing the need for prospective trials to resolve these complexities.

CONCLUSION

In conclusion, cHCC-CCA is a rare hybrid malignancy for which no established standard treatment currently exists. Due to the lack of prospective evidence and standardized protocols, clinical decisions regarding RT must be largely extrapolated from the management strategies of HCC and iCCA. As summarized in Table 2, RT remains a viable therapeutic option across the clinical spectrum: it can be utilized as an adjuvant treatment for high-risk surgical cases with features such as LVI or positive margins, as a definitive modality for unresectable disease unfeasible for surgery or transplantation, and as a palliative or curative-intent tool in metastatic settings. Moving forward, prospective trials are essential to establish high-level evidence and refine tailored dose-fractionation schemes based on specific tumor biology. Furthermore, the investigation of RT in combination with immunotherapy and advanced particle therapies represents a promising future direction for achieving personalized and optimized care for patients with cHCC-CCA.

Conflicts of Interest

The authors have no conflicts of interests to declare.

Ethics Statement

This review article is fully based on articles which have already been published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

Funding Statement

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2025-16072367).

Data Availability

Not applicable.

ORCID

Seo Hee Choi https://orcid.org/0000-0002-4083-6414
Woong Sub Koom https://orcid.org/0000-0002-9435-7750
Ik Jae Lee https://orcid.org/0000-0001-7165-3373

Author Contributions

Conception: SHC, IJL
Manuscript preparation: SHC
Critical revision: WSK, IJL
Writing - review & editing: SHC, WSK, IJL
Approval of final manuscript: SHC, WSK, IJL

REFERENCES

1. Beaufrère A, Calderaro J, Paradis V. Combined hepatocellular-cholangiocarcinoma: an update. J Hepatol 2021;74:1212-1224.
2. Chu KJ, Kawaguchi Y, Wang H, Jiang XQ, Hasegawa K. Update on the diagnosis and treatment of combined hepatocellular cholangiocarcinoma. J Clin Transl Hepatol 2024;12:210-217.
3. Zhang YZ, Liu YC, Su T, Shi JN, Huang Y, Liang B. Current advances and future directions in combined hepatocellular and cholangiocarcinoma. Gastroenterol Rep (Oxf) 2024;12:goae031.
4. Gigante E, Ronot M, Bertin C, Ciolina M, Bouattour M, Dondero F, et al. Combining imaging and tumour biopsy improves the diagnosis of combined hepatocellular-cholangiocarcinoma. Liver Int 2019;39:2386-2396.
5. Kim JH, Yoon HK, Ko GY, Gwon DI, Jang CS, Song HY, et al. Nonresectable combined hepatocellular carcinoma and cholangiocarcinoma: analysis of the response and prognostic factors after transcatheter arterial chemoembolization. Radiology 2010;255:270-277.
6. Chan LS, Sze DY, Poultsides GA, Louie JD, Mohammed MAA, Wang DS. Yttrium-90 radioembolization for unresectable combined hepatocellular-cholangiocarcinoma. Cardiovasc Intervent Radiol 2017;40:1383-1391.
7. Malone CD, Gibby W, Tsai R, Kim SK, Lancia S, Akinwande O, et al. Outcomes of yttrium-90 radioembolization for unresectable combined biphenotypic hepatocellular-cholangiocarcinoma. J Vasc Interv Radiol 2020;31:701-709.
8. Chun SJ, Jung YJ, Choi Y, Yi NJ, Lee KW, Suh KS, et al. Prognostic evaluation and survival prediction for combined hepatocellular-cholangiocarcinoma following hepatectomy. Cancer Res Treat 2025;57:229-239.
9. Wang X, Wang W, Ma X, Lu X, Li S, Zeng M, et al. Combined hepatocellular-cholangiocarcinoma: which preoperative clinical data and conventional MRI characteristics have value for the prediction of microvascular invasion and clinical significance? Eur Radiol 2020;30:5337-5347.
10. Lee SD, Park SJ, Han SS, Kim SH, Kim YK, Lee SA, et al. Clinicopathological features and prognosis of combined hepatocellular carcinoma and cholangiocarcinoma after surgery. Hepatobiliary Pancreat Dis Int 2014;13:594-601.
11. Guglielmi A, Ruzzenente A, Campagnaro T, Pachera S, Valdegamberi A, Nicoli P, et al. Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. World J Surg 2009;33:1247-1254.
12. Hu LS, Weiss M, Popescu I, Marques HP, Aldrighetti L, Maithel SK, et al. Impact of microvascular invasion on clinical outcomes after curative-intent resection for intrahepatic cholangiocarcinoma. J Surg Oncol 2019;

119:21-29.
13. Bartsch F, Heuft LK, Baumgart J, Hoppe-Lotichius M, Margies R, Gerber TS, et al. Influence of lymphangio (L), vascular (V), and perineural (Pn) Invasion on recurrence and survival of resected intrahepatic cholangiocarcinoma. J Clin Med 2021;10:2426.
14. Lurje G, Bednarsch J, Czigany Z, Lurje I, Schlebusch IK, Boecker J, et al. The prognostic role of lymphovascular invasion and lymph node metastasis in perihilar and intrahepatic cholangiocarcinoma. Eur J Surg Oncol 2019;45:1468-1478.
15. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. JAMA Surg 2014;149:565-574.
16. Wakizaka K, Yokoo H, Kamiyama T, Ohira M, Kato K, Fujii Y, et al. Clinical and pathological features of combined hepatocellular-cholangiocarcinoma compared with other liver cancers. J Gastroenterol Hepatol 2019; 34:1074-1080.
17. Endo I, Gonen M, Yopp AC, Dalal KM, Zhou Q, Klimstra D, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. Ann Surg 2008;248:84-96.
18. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. J Clin Oncol 2013;31:1188-1195.
19. Yamashita S, Koay EJ, Passot G, Shroff R, Raghav KP, Conrad C, et al. Local therapy reduces the risk of liver failure and improves survival in patients with intrahepatic cholangiocarcinoma: a comprehensive analysis of 362 consecutive patients. Cancer 2017;123:1354-1362.
20. Sebastian NT, Tan Y, Miller ED, Williams TM, Noonan AM, Hays JL, et al. Association of liver-directed local therapy with overall survival in adults with metastatic intrahepatic cholangiocarcinoma. JAMA Netw Open 2019;2:e1911154.
21. Koay EJ, Odisio BC, Javle M, Vauthey JN, Crane CH. Management of unresectable intrahepatic cholangiocarcinoma: how do we decide among the various liver-directed treatments? Hepatobiliary Surg Nutr 2017;6: 105-116.
22. Smart AC, Goyal L, Horick N, Petkovska N, Zhu AX, Ferrone CR, et al. Hypofractionated radiation therapy for unresectable/locally recurrent intrahepatic cholangiocarcinoma. Ann Surg Oncol 2020;27:1122-1129.
23. De B, Tran Cao HS, Vauthey JN, Manzar GS, Corrigan KL, Raghav KPS, et al. Ablative liver radiotherapy for unresected intrahepatic cholangiocarcinoma: Patterns of care and survival in the United States. Cancer 2022; 128:2529-2539.
24. De B, Abu-Gheida I, Patel A, Ng SSW, Zaid M, Thunshelle CP, et al. Benchmarking outcomes after ablative radiotherapy for molecularly characterized intrahepatic cholangiocarcinoma. J Pers Med 2021;11:1270.
25. De B, Upadhyay R, Liao K, Kumala T, Shi C, Dodoo G, et al. Definitive liver radiotherapy for intrahepatic cholangiocarcinoma with extrahepatic metastases. Liver Cancer 2023;12:198-208.
26. Shroff RT, Kennedy EB, Bachini M, Bekaii-Saab T, Crane C, Edeline J, et al. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. J Clin Oncol 2019;37:1015-1027.
27. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: biliary tract cancers [Internet]. Plymouth Meeting (US): National Comprehensive Cancer Network; [cited 2026 Feb 1]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1517.
28. Apisarnthanarax S, Barry A, Cao M, Czito B, DeMatteo R, Drinane M, et al. External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. Pract Radiat Oncol 2022;12:28-51.
29. Claasen MPAW, Ivanics T, Beumer BR, de Wilde RF, Polak WG, Sapisochin G, et al. An international multicentre evaluation of treatment strategies for combined hepatocellular-cholangiocarcinoma. JHEP Rep 2023; 5:100745.
30. Shinohara ET, Mitra N, Guo M, Metz JM. Radiation therapy is associated with improved survival in the adjuvant and definitive treatment of intrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 2008;72:1495-1501.
31. Lin YK, Hsieh MC, Wang WW, Lin YC, Chang WW, Chang CL, et al. Outcomes of adjuvant treatments for resectable intrahepatic cholangiocarcinoma: chemotherapy alone, sequential chemoradiotherapy, or concurrent chemoradiotherapy. Radiother Oncol 2018;128:575-583.
32. Sur MD, In H, Sharpe SM, Baker MS, Weichselbaum RR, Talamonti MS, et al. Defining the benefit of adjuvant therapy following resection for intrahepatic cholangiocarcinoma. Ann Surg Oncol 2015;22:2209-2217.
33. Hammad AY, Berger NG, Eastwood D, Tsai S, Turaga KK, Christian KK, et al. Is radiotherapy warranted following intrahepatic cholangiocarcinoma resection? The impact of surgical margins and lymph node status on survival. Ann Surg Oncol 2016;23(Suppl 5):912-920.
34. Zheng X, Chen B, Wu JX, Jia AY, Rong WQ, Wang LM, et al. Benefit of adjuvant radiotherapy following narrow-margin hepatectomy in patients with intrahepatic cholangiocarcinoma that adhere to major vessels. Cancer Manag Res 2018;10:3973-3981.
35. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol 2012;30:1934-1940.
36. Jiang W, Zeng ZC, Tang ZY, Fan J, Zhou J, Zeng MS, et al. Benefit of radiotherapy for 90 patients with resected intrahepatic cholangiocarcinoma and concurrent lymph node metastases. J Cancer Res Clin Oncol 2010; 136:1323-1331.
37. Lee GC, Ferrone CR, Tanabe KK, Lillemoe KD, Blaszkowsky LS, Zhu AX, et al. Predictors of adjuvant treatment and survival in patients with intrahepatic cholangiocarcinoma who undergo resection. Am J Surg 2019;218: 959-966.
38. Kim YS, Oh SY, Go SI, Kang JH, Park I, Song HN, et al. The role of adjuvant therapy after R0 resection for patients with intrahepatic and perihilar cholangiocarcinomas. Cancer Chemother Pharmacol 2017;79:99-106.
39. Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: a retrospective dose response analysis. J Clin Oncol 2016;34:219-226.
40. Im JH, Yu JI, Kim TH, Kim TG, Kim JW, Seong J. Combined high-dose radiotherapy with sequential gemcitabine-cisplatin based chemotherapy increase the resectability and survival in locally advanced unresectable intrahepatic cholangiocarcinoma: a multi-institutional cohort study. Cancer Res Treat 2024;56:838-846.
41. Lee IJ, Bang JI, Choi SH, Im JH. Optimizing radiotherapy in unresectable or metastatic intrahepatic cholangiocarcinoma: systematic review and meta-analysis of the literature. Radiat Oncol 2025;21:13.
42. Hong TS, Wo JY, Yeap BY, Ben-Josef E, McDonnell EI, Blaszkowsky LS, et al. Multi-institutional phase II study of high-dose hypofractionated proton beam therapy in patients with localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2016;34: 460-468.
43. Makita C, Nakamura T, Takada A, Takayama K, Suzuki M, Ishikawa Y, et al. Clinical outcomes and toxicity of proton beam therapy for advanced cholangiocarcinoma. Radiat Oncol 2014;9:26.
44. Kim TH, Woo SM, Lee WJ, Chun JW, Cho YR, Kim BH, et al. Clinical efficacy of hypofractionated proton beam therapy for intrahepatic cholangiocarcinoma. Cancers (Basel) 2022;14:5561.
45. Mizumoto M, Shibuya K, Terashima K, Murakami M, Murakami M, Shioyama Y, et al. Particle therapy for intrahepatic cholangiocarcinoma: a multicenter prospective registry study, systematic review and meta-analysis. Liver Cancer 2024;14:211-222.
46. Thonglert K, Chuong MD, Herrera R, Apisarnthanarax S. Advanced and emerging radiation therapy approaches for intrahepatic cholangiocarcinoma. Hepatoma Res 2023;9:40.
47. Sumiyoshi T, Shima Y, Okabayashi T, Negoro Y, Shimada Y, Iwata J, et al. Chemoradiotherapy for initially unresectable locally advanced cholangiocarcinoma. World J Surg 2018;42:2910-2918.
48. Cho Y, Kim TH, Seong J. Improved oncologic outcome with chemoradiotherapy followed by surgery in unresectable intrahepatic cholangiocarci-

noma. Strahlenther Onkol 2017;193:620-629.
49. Yang Z, Wang L, Zhai Y, Zhao J, Ye F, Wang S, et al. Nodal recurrence mapping and clinical target volumes after resection of intrahepatic cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma. Clin Transl Radiat Oncol 2024;45:100749.
50. Bisello S, Renzulli M, Buwenge M, Calculli L, Sallustio G, Macchia G, et al. An atlas for clinical target volume definition, including elective nodal irradiation in definitive radiotherapy of biliary cancer. Oncol Lett 2019;17: 1784-1790.
51. Zhang XF, Xue F, Weiss M, Popescu I, Marques HP, Aldrighetti L, et al. Lymph node examination and patterns of nodal metastasis among patients with left- versus right-sided intrahepatic cholangiocarcinoma after major curative-intent resection. Ann Surg Oncol 2023;30:1424-1433.
52. Liu X, Yao J, Song L, Zhang S, Huang T, Li Y. Local and abscopal responses in advanced intrahepatic cholangiocarcinoma with low TMB, MSS, pMMR and negative PD-L1 expression following combined therapy of SBRT with PD-1 blockade. J Immunother Cancer 2019;7:204.
53. Liu ZL, Liu X, Peng H, Peng ZW, Long JT, Tang D, et al. Anti-PD-1 immunotherapy and radiotherapy for stage IV intrahepatic cholangiocarcinoma: a case report. Front Med (Lausanne) 2020;7:368.
54. Zhao Q, Chen Y, Du S, Yang X, Chen Y, Ji Y, et al. Integration of radiotherapy with anti-PD-1 antibody for the treatment of intrahepatic or hilar cholangiocarcinoma: reflection from four cases. Cancer Biol Ther 2021; 22:175-183.
55. Shimizu S, Okumura T, Oshiro Y, Fukumitsu N, Fukuda K, Ishige K, et al. Clinical outcomes of previously untreated patients with unresectable intrahepatic cholangiocarcinoma following proton beam therapy. Radiat Oncol 2019;14:241.
56. Hung SP, Huang BS, Hsieh CE, Lee CH, Tsang NM, Chang JT, et al. Clinical outcomes of patients with unresectable cholangiocarcinoma treated with proton beam therapy. Am J Clin Oncol 2020;43:180-186.
57. Ohkawa A, Mizumoto M, Ishikawa H, Abei M, Fukuda K, Hashimoto T, et al. Proton beam therapy for unresectable intrahepatic cholangiocarcinoma. J Gastroenterol Hepatol 2015;30:957-963.
58. Kasuya G, Terashima K, Shibuya K, Toyama S, Ebner DK, Tsuji H, et al. Carbon-ion radiotherapy for cholangiocarcinoma: a multi-institutional study by and the Japan carbon-ion radiation oncology study group (J-CROS). Oncotarget 2019;10:4369-4379.