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Clinical Practice Guideline

External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline

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Noted—An online CME test for this article can be taken at https://academy.astro.org.

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Abstract

Purpose: This guideline provides evidence-based recommendations for the indications and technique-dose of external beam radiation therapy (EBRT) in hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC).

Methods: The American Society for Radiation Oncology convened a task force to address 5 key questions focused on the indications, techniques, and outcomes of EBRT in HCC and IHC. This guideline is intended to cover the definitive, consolidative, salvage, preoperative (including bridge to transplant), and adjuvant settings as well as palliative EBRT for symptomatic primary lesions. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: Strong recommendations are made for using EBRT as a potential first-line treatment in patients with liver-confined HCC who are not candidates for curative therapy, as consolidative therapy after incomplete response to liver-directed therapies, and as a salvage option for local recurrences. The guideline conditionally recommends EBRT for patients with liver-confined multifocal or unresectable HCC or those with macrovascular invasion, sequenced with systemic or catheter-based therapies. Palliative EBRT is conditionally recommended for symptomatic primary HCC and/or macrovascular tumor thrombi. EBRT is conditionally recommended as a bridge to transplant or before surgery in carefully selected patients.

For patients with unresectable IHC, consolidative EBRT with or without chemotherapy should be considered, typically after systemic therapy. Adjuvant EBRT is conditionally recommended for resected IHC with high-risk features. Selection of dose-fractionation regimen and technique should be based on disease extent, disease location, underlying liver function, and available technologies.

Conclusions: The task force has proposed recommendations to inform best clinical practices on the use of EBRT for HCC and IHC with strong emphasis on multidisciplinary care. Future studies should focus on further defining the role of EBRT in the context of liver-directed and systemic therapies and refining optimal regimens and techniques.

Preamble

As the leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, Appendix E1). The complete disclosure policy for formal papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias by selecting a multidisciplinary group of experts with variation in geographic region, gender, ethnicity, race, practice setting, and area of expertise. Representatives from organizations and professional societies with related interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.[1,2] The evidence identified from key questions (KQs) is assessed using the **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO's recommendation grading system. See Supplementary Materials, Appendix E2 for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree." A prespecified threshold of ≥75% (≥90% for expert opinion

recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation (s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE, individual study quality, and panel consensus, all of which inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.

Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	"Recommend/ Should"
Conditional	• Benefits are finely balanced with risks and burden or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	"Conditionally Recommend"

Overall QoE Grade	Type and Quality of Study	Evidence Interpretation
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials **OR** • 2 or more RCTs with some weaknesses of procedure or generalizability **OR** • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.
Low	• 1 RCT with some weaknesses of procedure or generalizability **OR** • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes **OR** • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

* A lower quality of evidence, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden.

Introduction

Background

Primary liver cancers, primarily composed of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC), are one of the most commonly diagnosed cancers and the fourth leading cause of cancer mortality worldwide.[3] In the United States, incidence rates have more than tripled since 1980 and have increased by approximately 2% per year in the last 2 decades, with an estimated 41,810 new cases in 2020.[4] Despite the availability of screening for HCC and improvements in the prevention and treatment of risk factors (hepatitis B and C virus infection and nonalcoholic fatty liver disease), mortality rates continue to rise. Interest in the treatment of HCC and IHC, therefore, remains high.

The optimal management of primary liver cancers relies heavily on a multidisciplinary approach owing to complexities in the diagnosis and staging, the medical comorbidities (particularly the underlying cirrhosis), and the myriad treatment options.[5-8] Input and collaboration from the disciplines of diagnostic radiology, pathology, hepatology, transplant surgery, surgical oncology, medical oncology, radiation oncology, and interventional radiology are critical to achieve individualized and evidence-driven patient care. Multiple treatment approaches are used for the definitive treatment of primary liver cancers. For HCC, orthotopic liver transplantation (OLT), surgery, and thermal ablation (radiofrequency ablation [RFA] and microwave ablation) are standard treatment modalities for curative intent.[9-11] Catheter-based therapies (eg, transarterial bland embolization [TAE], transarterial chemoembolization [TACE], and transarterial radioembolization [TARE]) are considered acceptable treatment options for locoregional tumor control.[12-16] In patients with HCC with metastatic disease and/or macrovascular invasion (MVI), systemic therapy (targeted therapy and/or immunotherapy) is considered standard of care.[17-19] For IHC, a combination of surgery and chemotherapy (with or without radiation) is a standard treatment paradigm.[7]

Historically, external beam radiation therapy (EBRT) for primary liver cancers was cautiously used because of the relative radiosensitivity of liver tissue and technological limitations in tumor delineation and radiation delivery. Advances in imaging and radiation treatment delivery, in addition to improved understanding of normal liver tolerance to radiation, have led to an increasing amount of clinical data on the use of EBRT for primary liver cancers over the last 2 decades.[20] In light of these complexities and rapid growth of EBRT data, ASTRO commissioned a task force to review the published literature on the role and use of EBRT for HCC and IHC and create evidence-based recommendations that address 5 clinical KQs. It must be emphasized that this guideline is not a substitute for evaluation and discussion in the multidisciplinary setting.

Definitions

In this guideline, EBRT includes photon-based approaches (3-dimensional [3-D] conformal radiation therapy and intensity modulated radiation therapy [IMRT]) and proton therapy. Standard fractionation is defined as EBRT with a fraction size of 180 to 200 cGy. The task force adopted modified definitions for hypofractionation as outlined in the ASTRO guideline for prostate hypofractionated radiation therapy,[21] subdividing it into "moderate hypofractionation" and "ultrahypofractionation." These definitions are influenced by the fractionation approaches used in prospective studies described in detail later, considering the dose per fraction and number of fractions. Moderate hypofractionation is defined as EBRT with a fraction size of 300 cGy to 500 cGy and typically involves between 12 and 20 fractions. Ultrahypofractionation is defined as EBRT with a fraction size >500 cGy and typically involves ≤10 fractions. Stereotactic body radiation therapy (SBRT) or stereotactic body ablative radiation (SABR) is included in this fractionation category but is specified as ultrahypofractionation delivered in ≤5 fractions.[22,23]

Methods

Task Force Composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; medical physicists, a hepatologist, a transplant surgeon, and a radiation oncology resident. An interventional radiologist contributed to the discussion during the initial phases of development. This guideline was developed in collaboration with the American Society of Clinical Oncology, American Society of Transplant Surgeons, and the Society of Surgical Oncology, who provided representatives and peer reviewers.

Document Review and Approval

The guideline was reviewed by 13 official peer reviewers (Supplementary Materials, Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment in April 2021. The final guideline was approved by the ASTRO Board of Directors and endorsed by the American Society of Transplant Surgeons, Canadian Association of Radiation Oncology, European Society for Radiotherapy and Oncology, and Society of Surgical Oncology.

Evidence Review

A systematic search of human subject studies retrieved from the Ovid Medline database was conducted. The inclusion criteria required research to involve adults (age ≥18 years), with a diagnosis of HCC or nonmetastatic IHC, published in English, from January 2000 through February 2020. Given that different qualities of evidence were available for each KQ, the search inclusion criteria were further refined. Retrospective studies were restricted to ≥25 patients for KQ2 and ≥50 patients for all other KQs. For KQs 1 to 3, prospective trials required ≥25 participants, whereas there was no minimum patient number required for KQs 4 and 5. For specific subquestions where there were limited data available, expert opinion was relied upon to support recommendations, as reflected in the low-to-moderate quality of evidence cited in these cases.

Table 2 KQs in Population, Intervention, Comparator, Outcome (PICO) format

KQ	Population	Intervention	Comparator*	Outcomes
1	**What is the role of EBRT in the definitive/nontransplant and palliative settings in HCC?**			
	Patients with pathologically or radiologically confirmed HCC	• EBRT • EBRT + other LDTs • EBRT + targeted therapy or immunotherapy	• Non-EBRT LDTs • Targeted therapy or immunotherapy	• Local control • Overall survival • Disease-free survival • Toxicities
2	**What is the role of EBRT in the neoadjuvant setting before surgical resection or OLT for HCC**			
	Patients with pathologically or radiologically confirmed HCC	• Neoadjuvant EBRT • Neoadjuvant EBRT + other LDTs • Neoadjuvant EBRT followed by surgery (resection and/or OLT) • Neoadjuvant EBRT + LDTs followed by surgery (resection and/or OLT)	• Surgery • OLT • Neoadjuvant non-EBRT LDTs	• Local control • Overall survival • Postop complications • Toxicities
3	**In patients receiving EBRT for HCC, what are the preferred techniques, fractionation regimens, and recommended OAR dose constraints?**			
	Patients with pathologically or radiologically confirmed HCC	• IMRT • SBRT • Hypofractionation • Proton therapy • IGRT	• 3-D CRT • Standard fractionation	• Local control • Overall survival • Toxicities
4	**What is the role of EBRT in the definitive and adjuvant setting in IHC?**			

	Patients with pathologically confirmed IHC	• Resectable: postop chemoRT
		• Unresectable:
		  ○ Definitive EBRT or chemoRT
		  ○ Definitive SBRT
			• Surgery alone (resectable patients)
			• Postop chemo alone
			• LDTs
				• Local control
				• Overall survival
				• Disease-free survival
				• Toxicities

5	**In patients receiving EBRT for IHC, what are the preferred techniques, fractionation regimens, and recommended OAR dose constraints?**			
	Patients with pathologically confirmed IHC	• IMRT • SBRT • Hypofractionation • Proton therapy • IGRT	• 3-D CRT • Standard fractionation	• Local control • Overall survival • Toxicities

Abbreviations: 3-D CRT = 3-dimensional conformal radiation therapy; chemoRT = chemoradiation; EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; IGRT = image guided radiation therapy; IHC = intrahepatic cholangiocarcinoma; IMRT = intensity modulated radiation therapy; KQ = key question; LDTs = liver-direct therapies; OAR = organ at risk; OLT = orthotopic liver transplantation; PICO = Population, Intervention, Comparator, Outcome; SBRT = stereotactic body radiation therapy.

* The initial evidence review included comparators if EBRT was part of the therapeutic approach.

The literature review excluded studies when EBRT was not part of the therapeutic approach. Both Medical Subject Heading (MeSH) terms and key search terms were used, and terms common to all searches included: *primary liver tumor, hepatocellular carcinoma, intrahepatic cholangiocarcinoma, liver neoplasms/radiotherapy, radiation therapy, external beam radiation therapy, intensity modulated radiation therapy, volumetric-modulated arc therapy, local control, overall survival, disease-free survival, and liver toxicity*. Additional terms specific to the KQs and hand searches supplemented the electronic searches.

An additional literature search was also conducted to include meta-analyses and systematic reviews that involved non-EBRT liver-directed therapies (LDTs). The inclusion criteria required research to involve adults (age ≥18 years), with a diagnosis of HCC or nonmetastatic IHC, published in English, from February 2015 to February 2020.

The data used by the task force to formulate recommendations are summarized in evidence tables available in the Supplementary Materials. References selected and published in this document are representative and not all-inclusive. The outcomes of interest are listed in Table 2. Additional ancillary references are included in the text but were not used to support the recommendations. See the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA figure) diagram showing the number of articles screened, excluded, and included for evidence review, and Supplementary Materials (Appendix E3) for the literature search strategy, which includes the evidence search parameters and inclusion/exclusion criteria.

Scope of the Guideline

This guideline addresses only the topics specified in the KQs (Table 2). The scope focuses on the use of EBRT in the management of HCC and IHC, including indications, outcomes, and techniques. It is intended to cover multiple settings for which EBRT may be used, including definitive, preoperative, salvage, consolidative, adjuvant, and as a bridge to OLT. Palliative management as it relates to EBRT for symptomatic primary liver cancers is also addressed.

This guideline is not intended to address the role of surgery, thermal ablation, and catheter-based therapies (eg, TACE and TARE) when used *without inclusion* of EBRT. In accordance with the scope of the guideline, the initial search was restricted to studies with EBRT as part of the therapeutic approach. As a result, clinical outcome data available on non-EBRT LDTs were limited. To address this limitation, an additional literature search (restricted to meta-analyses and systematic reviews) on the use of non-EBRT LDTs for the management of primary liver cancers was performed. Studies from this additional search were not included in the evidence tables but were intended to provide reference data and background context on clinical outcomes of non-EBRT LDTs. However, because of heterogeneity in patient population selection, tumor extension and location characteristics, as well as clinical outcome metrics (eg, radiographic response rate versus local control [LC]), these non-EBRT LDT meta-analyses and systematic reviews did not provide additional meaningful clinical data for comparison.

Outside the scope of this guideline are several related topics, including but not limited to the benefits of recently developed treatment delivery technology, including magnetic resonance imaging-guided EBRT and carbon ion EBRT, and the role of palliative EBRT for extrahepatic metastatic disease sites. These topics are relevant to further the understanding of the role of EBRT in primary liver cancers and may be the subjects of investigation in future guidelines.

Key Questions and Recommendations

KQ1: EBRT in the definitive/nontransplant and palliative settings in HCC (Table 3)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ1 and Figures 1 and 2 for visual representations of the HCC recommendations.

What is the role of EBRT in the definitive/nontransplant and palliative settings in HCC?

Surgery, OLT, and thermal ablation, when appropriate, are considered the mainstays of curative treatments for patients with HCC without MVI.[9-11] Catheter-based therapies have well-established roles in the management of HCC in the nonsurgical, nontransplant setting.[7] EBRT is increasingly being considered as an additional therapeutic option.[12,13,15,16]

Potentially resectable liver-confined HCC without MVI

Multiple retrospective studies as well as phase I and II trials demonstrate similar outcomes to those reported with other LDTs when EBRT is used as a definitive treatment option for carefully selected patients with liver-confined early-stage disease. The vast majority of studies reported 2- to 5-year LC rates of ≥90%, which compare favorably with those reported for other ablative LDTs.[24,26-28,30,36,37] It is important, however, to recognize the context in which patients were selected to receive EBRT. Most of these studies used SBRT in patients with relatively small HCC (1-6 cm in size), with a limited number of lesions (generally 1-5), who were not candidates for

Table 3 EBRT in the definitive/nontransplant and palliative settings in HCC

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with liver-confined HCC who are not candidates for curative options (surgery or thermal ablation) and for whom catheter-based therapies are being considered, EBRT is recommended as *a potential* first-line single therapy option.	Strong	Moderate [24-36]
2. For patients with liver-confined multifocal and/or unresectable HCC, EBRT alone or sequenced with other catheter-based therapies* is conditionally recommended.	Conditional	Moderate [37-42]
3. For patients with liver-confined HCC who had an incomplete response to thermal ablation or catheter-based therapies,* EBRT is recommended as a consolidative treatment option.	Strong	Moderate [38,40,43]
4. For patients with locally recurrent HCC after surgery, thermal ablation, or catheter-based therapies,* EBRT is recommended as a salvage treatment option.	Strong	Low [25,35,44-46]
5. For patients with liver-confined HCC with macrovascular invasion, EBRT is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies.*	Conditional	Moderate [47-53]
6. For patients with symptomatic locally advanced and/or metastatic HCC, palliative hypofractionated EBRT directed to the liver and/or macrovascular tumor thrombus is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies.*	Conditional	Low (locally advanced HCC) [47,53-56] Expert opinion (metastatic HCC)

Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinoma; KQ = key question; TARE = transarterial radioembolization.
* Caution should be used when recommending EBRT after TARE until more data are available.

definitive surgery or ablative procedures and had relatively well-compensated baseline liver function (Child-Pugh [CP] class A5, A6, and B7). One meta-analysis found no statistically significant difference in LC or overall survival (OS) between ultrahypofractionated EBRT and RFA.[31] Another meta-analysis of 32 ultrahypofractionated EBRT studies reported 3-year pooled OS and LC rates of 48.3% and 83.9%, respectively.[32] A body of literature also exists on the use of particle beam therapy, primarily with proton therapy, for HCC. In patients with HCC treated with proton therapy as definitive treatment, prospective and retrospective data have reported 5-year OS and LC rates of 48% to 69%[57-59] and 81% to 94%, respectively.[58,59]

At the time of the evidence review, there were no published randomized controlled trials (RCT) comparing EBRT to thermal ablation for patients with liver-confined HCC without MVI. However, a noninferiority RCT from Korea published in 2021 randomized patients with recurrent HCC (size <3 cm, number ≤2) to either RFA or proton therapy.[60] The results of this trial could not be evaluated because it was published after the guideline's evidence review period, but it will be incorporated into future guideline updates. No randomized data currently exist that directly compare EBRT to catheter-based therapies, other than an interim analysis of proton therapy compared with TACE that showed a trend toward improved 2-year LC (88% versus 45%) and progression-free survival (PFS) (48% versus 31%) favoring proton therapy.[42] Whether a patient with HCC is most appropriate for EBRT or catheter-based therapies depends on a multitude of patient and clinical factors, which should be discussed in a multidisciplinary setting.

In regard to safety of EBRT for patients with HCC, the reported rates of liver toxicity have been highly variable, generally ranging from 0 to 21% in patients with well-compensated liver function.[24-27,30,43-45,53,61,62] The variability in reporting of radiation-induced liver disease (RILD) stems from the heterogeneity in liver toxicity definitions, EBRT regimens used, baseline liver function, and prior LDTs. In contemporary studies, classic RILD (defined as anicteric ascites, hepatomegaly, and elevation of alkaline phosphatase out of proportion to other transaminases) was rarely reported. When studies reported nonclassic RILD (eg, CP class score increases of ≥2), most reported rates of 5% to 15%.[26,27,30,43,44,53,61] For patients with liver cancers treated with ultrahypofractionated EBRT (nearly 50% had HCC), prospective quality-of-life data demonstrate that EBRT is well tolerated with temporary effects on appetite and fatigue, but no significant decline in overall quality of life.[63]

The collective published data, therefore, support the use of EBRT as relatively safe and effective in patients with liver-confined, potentially resectable HCC without MVI who are not candidates for curative strategies (eg, OLT, surgery, or thermal ablation) due to medical comorbidities, poor liver reserve, tumor location or size, and for whom LDT is preferred. Common reasons why thermal ablation would be technically suboptimal include lack of ultrasound echogenicity/visibility, relatively large tumor size (>3 cm), and tumor location in close proximity to the diaphragm, gallbladder, or large vessel that may result in a heat sink effect.[60] In these patients, EBRT alone is recommended as a potential alternative first-line therapy option, along with catheter-based therapies. A typical example is a patient with chronic obstructive pulmonary

disease who cannot tolerate general anesthesia or moderate sedation and has a solitary 4 cm HCC tumor abutting a main portal vein branch.

Multifocal and/or unresectable liver-confined HCC without MVI

For patients with liver-confined HCC but more extensive (multifocal and/or unresectable) disease in the absence of MVI, LDTs are often used in carefully selected patients (eg, noninfiltrative or nondiffuse disease) after multidisciplinary evaluation.[15,37-41] Several studies, including RCTs, have evaluated the potential benefits of combination therapy involving EBRT (primarily with 3-D conformal EBRT techniques) and TACE in patients with unresectable HCC.[37-41] Multiple meta-analyses demonstrated an improvement in OS with TACE plus EBRT compared with TACE alone[39,41,64] as well as superior complete response rates.[39] In a retrospective study of patients with unresectable HCC and a median tumor size of 8.5 cm (5.1-21 cm) treated with SBRT alone or sequenced with TACE, patients who received combination sequenced therapy had a statistically significant 5-year OS rate of 46.9% versus 32.9%.[37] In this study, combination sequential therapy of SBRT and TACE, biologically effective dose assuming an α/β = 10 (BED_{10}) >10,000 cGy, and an equivalent dose in 200 cGy per fraction of ≥7400 cGy were significant prognostic factors for survival outcomes. Therefore, for carefully selected patients with HCC and multifocal and/or unresectable disease for whom locoregional therapies are being considered, combination therapy of EBRT sequenced with TACE is conditionally recommended as a treatment option. Given limited data on the role of EBRT alone versus EBRT in addition to TACE, definitive conclusions cannot be made regarding the role of EBRT alone in this patient population. However, in cases where combination therapy or catheter-based therapies are not feasible, EBRT alone is a reasonable treatment option for similar clinical scenarios. Phase I/II data that included patients with median tumor sizes of 7.2 cm and up to 23.1 cm lend support that acceptable local control (1-year 87%) may be achieved with EBRT alone even for relatively large tumors.[65] Given the increasing use of TARE and SBRT, prospective data evaluating safety and efficacy of the combination are needed. Furthermore, when this guideline was created, significant uncertainties regarding liver dosimetry evaluation still existed when combining both modalities.

Liver-confined HCC after incomplete response to thermal ablation or catheter-based therapies

Thermal ablation and catheter-based therapies are effective at treating liver-confined HCC, with reported initial objective response rates (complete/partial) of up to 61%.[15,16,66,67] Repeat thermal ablation or catheter-based therapies may be considered in those with an incomplete initial response. Consolidative EBRT may also be a treatment option in this setting, particularly when additional thermal ablation or catheter-based therapies may result in suboptimal ablation or are not technically feasible, as previously indicated. In patients who received consolidative SBRT post-TACE, median survival rates ranged from 22.7 to 42 months,[37-39] with 2-year LC rates reported up to 89%.[38,43] In a retrospective study of planned adjuvant versus salvage SBRT post-TACE, superior overall response rates were seen with planned adjuvant SBRT (80% versus 40%).[38] CP class, performance status, and receipt of transplant were associated with improved survival on multivariable analysis.[38,43] Data from a completed RCT presented in abstract form *(NCT02323360)* may better define the role of ultrahypofractionated EBRT after incomplete TAE or TACE.[68]

Locally recurrent liver-confined HCC

In patients with a local recurrence of HCC after surgery, thermal ablation, or catheter-based therapies, further treatment with LDTs is recommended.[25,44-46] The role of EBRT in this setting has been examined in multiple retrospective studies, reporting 2-year OS and LC rates of up to 81.9% and 84.1%, respectively.[25,45,46] Propensity score matching of SBRT versus TACE in medium-sized recurrent HCC demonstrated superior LC at 3 years (75% versus 57.5%) and OS (58.3% versus 5.9%) in favor of SBRT compared with the TACE group.[45] However, it is difficult to generalize these data to all patients with recurrent HCC given the differences in the percentage of patients with recurrent versus primary de novo disease reported in these studies, ranging from 30% to 65%, as well as wide variation in types of initial therapy (primarily after TACE), which were often not explicitly reported.[25,45,46] A multicenter phase II study that only included patients with recurrent HCC treated with salvage 3 fraction SBRT after receiving 1 to 5 TACE sessions reported 3-year LC rate of 95% and OS of 76%.[44] CP class B and albumin-bilirubin score were predictive factors for worsening liver function in this population.[44]

Ultrahypofractionated EBRT has also been studied retrospectively in the setting of incomplete thermal ablation. A study that performed propensity score matching of patients treated with either salvage ultrahypofractionated EBRT or additional RFA after incomplete RFA found that salvage ultrahypofractionated EBRT had superior 2-year PFS (56.9% versus 20.7%) and similar 2-year OS (83.7% versus 88.9%) compared with additional RFA.[35] The task force recommends consideration of salvage EBRT as a treatment option for local recurrences after any LDTs, particularly when additional non-EBRT salvage options are not feasible or are considered suboptimal. If prior LDTs involved EBRT or TARE, caution is recommended when considering reirradiation with salvage EBRT; the benefits must be carefully weighed against the risks of liver and other organ at risk (OAR) toxicity.

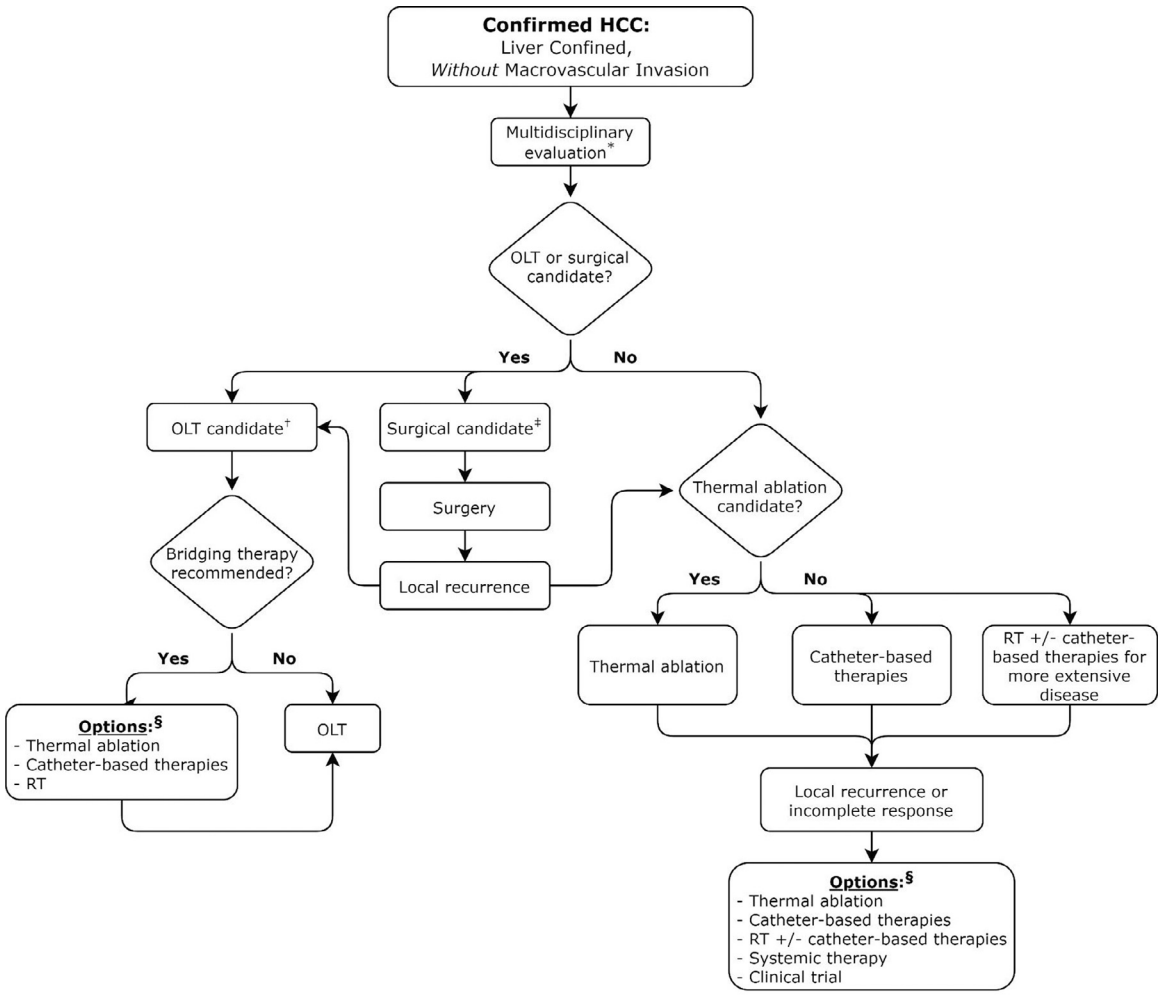


Figure 1 Algorithm for HCC: Liver confined, without macrovascular invasion.
Abbreviations: CP = Child-Pugh; HCC = hepatocellular carcinoma; OLT = orthotopic liver transplantation; RT = radiation therapy; UNOS = United Network for Organ Sharing.
* Enrollment in a clinical trial should be prioritized if available.
† OLT candidate: UNOS criteria (solitary lesion 2-5-cm diameter or 2-3 lesions ≤3 cm each).
‡Surgical candidate: CP class A and selected CP class B (no portal hypertension, adequate location, preserved liver function).
§ Order of listed options does not reflect a particular preference; decision is based on multidisciplinary evaluation.

Liver-confined HCC with MVI

For patients with HCC with liver-confined disease and MVI, a well-known poor prognostic factor, systemic therapies are considered standard of care.[17-19] Multiple other treatments are also available as therapeutic options, including surgery in carefully selected patients (see KQ2) and catheter-based therapies. Growing evidence supports the use of EBRT as a component of LDTs.[48-53] One retrospective study showed a significant improvement in portal vein recanalization with hypofractionation compared with standard fractionated EBRT (33.3% versus 15.1%), in addition to improved objective response rates (62.2% versus 33.9%), median survival (10.9 versus 4.7 months,) and 2-year OS (15% versus 8%).[48] On multivariate analyses, BED_{10} >6500 cGy, alpha-fetoprotein <200 ngmL, single tumors, and Eastern Cooperative Oncology Group performance status all predicted improved OS, which was confirmed in a propensity score-matched analysis. An RCT of treatment-naïve patients with HCC and MVI who received sorafenib versus TACE and EBRT demonstrated significantly improved PFS in the combination arm (median PFS 11.7 versus 31 weeks and OS 43 versus 55 weeks).[50] Retrospective data have shown radiographic response rates (at least 50% necrosis) of 66.2% in patients with liver-confined HCC with MVI treated with EBRT alone or, most commonly, in combination with other LDT.[49] In a retrospective comparison study of sorafenib with or without EBRT, a statistically significant OS benefit was shown with the addition of EBRT.[56] The value of adding EBRT to systemic therapy for HCC with MVI cannot be definitely ascertained until evidence from high-quality RCTs are obtained (eg, Radiation Therapy Oncology Group 1112 [*NCT01730937*]). However,

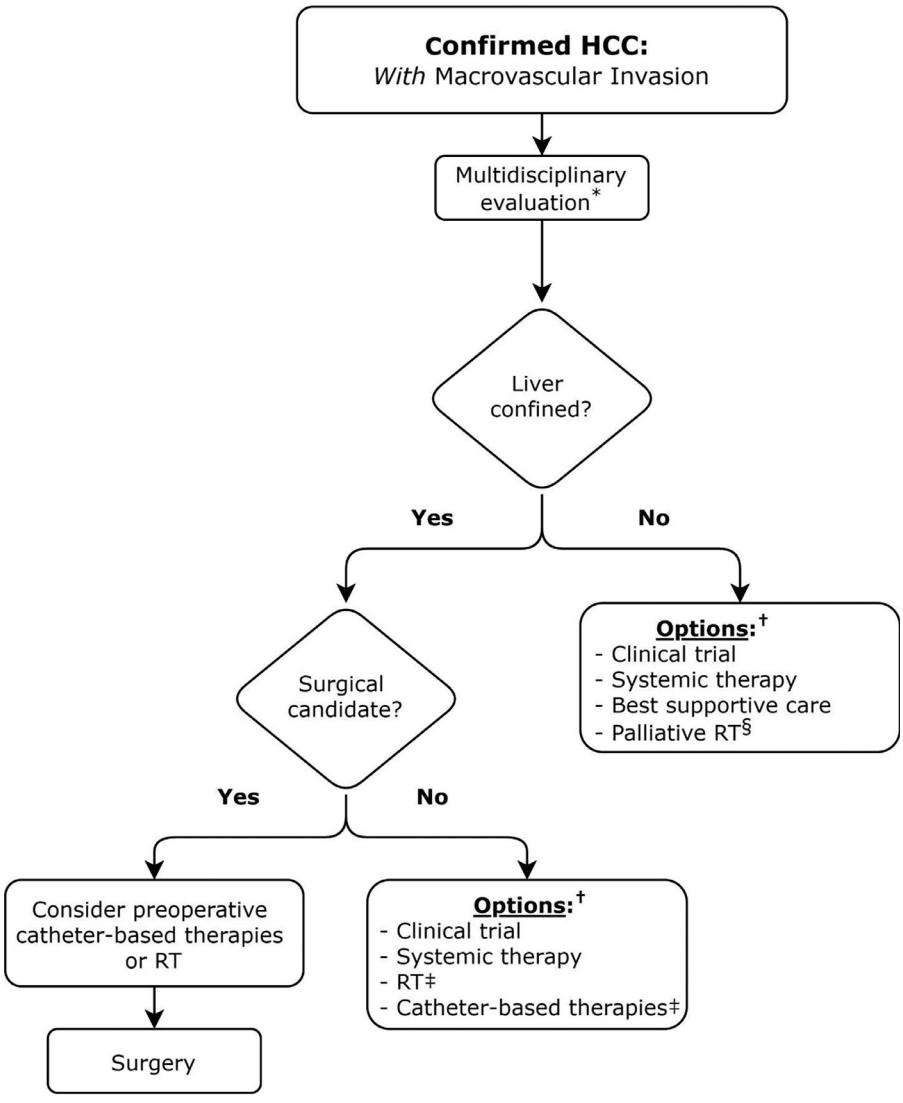


Figure 2 Algorithm for HCC with macrovascular invasion.
Abbreviations: HCC = hepatocellular carcinoma; RT = radiation therapy.
* Enrollment in a clinical trial should be prioritized if available.
† Order of listed options does not reflect a particular preference; decision is based on multidisciplinary evaluation.
‡ Consider alone or in sequential combination.
§ To liver tumor(s) and/or large vessel tumor thrombus if symptomatic.

sufficient evidence exists that supports the conditional recommendation to consider EBRT as a treatment option in these patients, alone or sequenced with systemic or catheter-based therapies.[48-53] The concurrent combination of systemic therapy (eg, sorafenib) with EBRT should be used with caution because of limited available data and concern for excessive gastrointestinal and hepatic toxicities.[69,70]

Symptomatic locally advanced and/or metastatic HCC

Prospective data support the use of palliative EBRT to help alleviate pain in patients with HCC and symptomatic liver lesions. A phase II trial of single fraction (800 cGy) palliative liver EBRT in symptomatic patients with extensive HCC demonstrated an improvement at 1 month in pain symptoms according to the brief pain inventory (48% improvement on average).[71] The presence of large vascular tumor thrombi may affect portal blood flow and cause progression of liver dysfunction and ascites. As previously mentioned, EBRT is capable of re-establishing portal vein flow by recanalization in 15.1% to 33.3% of patients, depending on the EBRT technique employed.[48] Data also exist for the use of EBRT in patients with more extensive MVI. Prospective and meta-analyses of hypofractionated EBRT to vascular tumor thrombi involving the inferior vena cava and/or right atrium have exhibited LC rates of >90% at 1 year and radiologic response rates of nearly

60%.[47,54,55] Based on these studies, palliative EBRT directed to symptomatic primary HCC tumors and/or macrovascular tumor thrombus is conditionally recommended, alone or sequenced with systemic therapy or catheter-based therapies in the setting of patients with locally advanced and metastatic HCC.

KQ2: Neoadjuvant EBRT before surgery or OLT for HCC (Table 4)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ2 and Figures 1 and 2 for visual representations of the HCC recommendations.

What is the role of EBRT in the neoadjuvant setting before surgical resection or OLT for HCC?

The rationale for the use of EBRT as an LDT for patients being considered for OLT is to provide tumor downstaging or stabilization of disease while waiting for organ availability or completion of transplant eligibility. The selection of EBRT as a potential bridge to transplant has generally been made in the setting of ineligibility for other LDTs (eg, tumor located in close proximity to a large vessel, which would be unfavorable for thermal ablation), once the patient has been evaluated by the multidisciplinary team. Various dose-fractionation regimens and EBRT modalities in the bridge to transplant setting have been used, primarily with SBRT regimens.[38,42,72-77] Multiple retrospective series have reported that approximately 63% of patients successfully receive an OLT after SBRT, indicating that SBRT may be safe and effective as a bridge to transplant.[75,76] Outcomes for patients who receive an OLT after EBRT as part of their bridge to transplant regimen are favorable, with 5-year OS ranging from 61% to 72.7%, with no significant difference between bridging LDT techniques (eg, TACE, TARE, or RFA).[72-74,77]

Pathologic complete responses after EBRT were highly variable across studies, ranging from 8.6% to 63%.[73-77] One potential explanation for this variability may be related to the time to transplant from completion of EBRT. As the time to transplant increased, the pathologic complete response rates tended to increase: 8.6% to 14% for median time to transplant of 4 to 6 months compared with 45% to 63% for median time to transplant of 8 to 12 months.[72-77] Although some studies compared bridging EBRT to other bridging LDTs, no definitive conclusions can be made in terms of superiority of any of the currently used bridging LDT regimens.[42,73,74] RILD rates of any grade in these series using EBRT (mainly SBRT) were relatively low, ranging from 0 to 8.7%.[38,42,72-77] Based on these low-quality data of small observational studies, EBRT using moderate or ultrahypofractionation is conditionally recommended as a potential bridge to transplant option alongside other bridging therapies (eg, thermal ablation and catheter-based therapies).

The management of patients with liver-confined HCC with MVI is challenging, with multiple treatment options. Although not routinely performed in these patients, surgical resection is recognized as a potential treatment approach in carefully selected patients after multidisciplinary discussion.[7] The rationale for neoadjuvant EBRT before surgical resection in patients with HCC with portal vein tumor thrombus is to reduce tumor burden, particularly of the tumor thrombus component, for patients who are otherwise surgically resectable to undergo hepatectomy. This is typically performed for patients with Cheng type II (involving the right/left portal vein) and type III tumor thrombus (involving the main portal vein).[78,79,81] It is noteworthy that nearly all the literature for this combination approach is from Asian countries,[51,78-80] and that this practice paradigm is not routinely used in Western countries. The highest quality evidence is from a Chinese RCT that assessed the value of hypofractionated neoadjuvant EBRT to 1800 cGy in 5 fractions in patients with Cheng type II and III portal vein tumor thrombus. It demonstrated a significant improvement in 2-year OS from 9.4% to 27.4% and disease-free survival from 3.3% to 13.3% with neoadjuvant EBRT before hepatectomy versus hepatectomy alone.[79] Neoadjuvant EBRT appeared to be well-tolerated, with reported radiation-induced liver toxicities grade ≥3 ranging from 0 to 2.4%.[51,78-80] Based on this

Table 4 Neoadjuvant EBRT before surgery or OLT for HCC

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (refs)
1. For patients with HCC who are potential candidates for OLT, ultra- or moderately hypofractionated EBRT is conditionally recommended as a bridge to transplant or as a downstaging intervention.	Conditional	Low [38,42,72-77]
2. For patients with HCC with portal vein tumor thrombus that are potentially resectable, neoadjuvant EBRT is conditionally recommended.	Conditional	Low [51,78-80]

Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinomas; KQ = key question; OLT = orthotopic liver transplantation.

low-quality data, neoadjuvant EBRT is conditionally recommended as a treatment option for patients with HCC presenting with portal vein tumor thrombus.

Reported dose-fractionation regimens and EBRT modalities in the neoadjuvant setting before partial hepatectomy were varied, but generally included moderate hypofractionation to 1800 to 4500 cGy in 300 cGy fractions (BED_{10} 2340-5850 cGy).[51,78-80] Close collaboration with surgery is critical to discuss issues such as adequate functional future liver remnant and anticipated fibrosis after neoadjuvant EBRT. Although many of these earlier studies relied on older technologies and low-dose radiation therapy (RT), there is an ongoing need for high-quality data to evaluate the role of ultrahypofractionation before hepatectomy in patients with portal vein thrombus. It is also noted that these studies had a high proportion of patients with hepatitis B, who may have had minimal to no baseline cirrhosis and did not include patients with CP class B8 or greater cirrhosis. Therefore, caution should be applied when extrapolating these recommendations to those with moderate-to-severe underlying liver cirrhosis outside the clinical trial setting.

KQ3: EBRT technique, fractionation, and OAR constraints for HCC (Table 5)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ3 and Figures 1 and 2 for visual representations of the HCC recommendations.

In patients receiving EBRT for HCC, what are the preferred techniques, fractionation regimens, and recommended OAR dose constraints?

Across multiple prospective trials and large retrospective series examining the role of EBRT for HCC, various dose and fractionation regimens, techniques, and modalities have been used. However, there are no published RCTs comparing them. The topic of optimal tumor dose for patients with HCC is an important one, as higher tumor doses must be balanced with the risk of hepatic decompensation of the underlying cirrhotic liver, which is often irreversible and potentially fatal, as demonstrated in the phase I/II setting.[65,86] The potential benefit of dose escalation for HCC has been extrapolated from published prospective and retrospective studies, primarily from the SBRT literature.[24,30,32,34,36,46,57,58,82-86] Regarding the recommended radiation dose for the treatment of liver-confined HCC, data on the dose threshold for optimal LC and OS are conflicting and complicated by inherent biases. The optimal dose-response relationship is not clearly defined in the available literature. There are data showing a potential clinical benefit in terms of improved LC when using dose escalation (minimum BED_{10} 6500-10,000 cGy), provided OAR constraints can be met.[32,34,43,48,96,97] Some studies suggest a minimum BED_{10} of 6500 to 7900 cGy,[34,48,54,95,96] while dose escalation beyond BED_{10} of 10,000 cGy has been questioned.[98] Additionally, an association between LC and tumor size has been demonstrated, with decreasing LC as a function of increasing tumor size, suggesting a potential need for more intense dose escalation for tumors >3 to 5 cm in size.[43,97]

Table 5 EBRT technique and fractionation for HCC

KQ3 Recommendations	Strength of Recommendation	Quality of evidence (refs)
1. For patients with liver-confined HCC, for whom EBRT is recommended, dose-escalated ultra- or moderately hypofractionated EBRT is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology (Table 6).	Strong	Moderate 24,30,32,34,36,46,57,58,82-86
2. For patients with HCC with macrovascular invasion for whom EBRT is delivered in combination with other catheter-based therapies, moderately hypofractionated EBRT is conditionally recommended (Table 6).	Conditional	Moderate 39,50,52,53,87
3. For patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology.	Strong	Moderate 24,28,30,36,46,57-59, 65,84,86,88,89
4. For patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT, respiratory motion management and daily image guidance are recommended.	Strong	Low 36,43,44,90,91
5. For patients with HCC, radiation dose to the liver minus the gross tumor volume should be evaluated and minimized to reduce the risk of radiation-induced liver disease (Table 7).	Strong	Moderate 61,65,92-95

Abbreviations: EBRT = external beam radiation therapy; HCC = hepatocellular carcinomas; IMRT = intensity modulated radiation therapy; KQ = key question.

The selection of EBRT dose and safety profile are highly dependent on the patient's baseline liver function, typically defined by their CP class. Much of the data on liver decompensation after EBRT for HCC are derived from the SBRT literature, which mostly excluded patients with CP class B (score 8) or C liver dysfunction.[27,30,43,44,61,86,92,93] The definition of liver toxicity has evolved from classic RILD, which is rarely reported in contemporary studies, to a nonclassic RILD definition of increase in CP class of ≥2 points in the first 3 to 6 months post-EBRT.[92,93,99] Patients who have baseline CP class A liver function can generally be treated safely with EBRT, if the dose to the normal liver is not exceeded (see Table 7 for suggested EBRT dose constraints). The risk of nonclassic RILD in patients with CP class A liver function when meeting liver tolerance constraints ranges from 5% to 15%.[26,27,30,43,44,53,61] CP class B patients (score 8) are more sensitive than CP class A patients to liver decompensation. The highest quality prospective study that illustrates the need to stratify CP class A and B patients was published by Indiana University.[86] This trial differentially determined the delivered dose based on the patients' baseline CP class (4800 cGy in 3 fractions for CP class A, 4000 cGy in 5 fractions for CP class B). Among the CP class A patients, 50% progressed to a higher CP class (42% to CP class B and 8% to CP class C), whereas among the CP class B patients, 33.3% progressed to CP class C, demonstrating the need for stringent dose constraints to the residual normal liver. Doses as low as 250 cGy to the liver have been shown to be relevant, particularly in patients with liver dysfunction.[86] Progression of the CP class was also found to be related to OS, mainly when OLT was not an available option. These data suggest that the total dose and dose per fraction should be selected differently for CP class A and B7 patients, particularly in light of different normal liver dose constraints between these patients (Table 7).[86,91-93] Because data on patients with CP class B8 and worse liver function are limited, EBRT for these patients should be used with caution.

In addition to SBRT, there have also been hypofractionated trials using 10 to 15 fractions.[46,59,62,90,100] Much of the prospective literature included proton therapy with an individualized approach of different fractionation regimens based on tumor location relative to gastrointestinal (GI) structures. For tumors that were located closer to a GI structure, the number of fractions increased and the dose per fraction decreased. The highest quality data for de novo proton therapy for definitive treatment of unresectable HCC comes from Japan in which 266 patients were treated with doses stratified by tumor proximity to GI structures, which yielded a 5-year LC rate of 95%: peripheral tumors >2 cm from GI structures were treated to 6600 cGy in 10 fractions, tumors <2 cm from the porta hepatis were treated to 7260 cGy in 22 fractions, and central tumors located <2 cm from GI structures were treated to 7700 cGy in 35 fractions.[58,59] North American data for 15 fraction moderate hypofractionation have also been published using 6750 cGy in 15 fractions for peripheral tumors and 5805 cGy in 15 fractions for central tumors, which demonstrated a 2-year LC rate of 94%.[46]

Given the existing prospective data and a plethora of retrospective studies, ultrahypofractionation or moderately hypofractionated regimens are recommended as feasible treatment regimens for patients with HCC, with the choice of fractionation regimen dependent on tumor location, underlying liver function, available technology, and meeting of dose constraints. Table 6 includes various dose-fractionation regimens with the supportive references noted. Expert consensus highlights the 3 to 5 fraction regimens for ultrahypofractionation and the 15 fraction regimen for moderate hypofractionation as preferred regimens based on prospective trials.[24,46,62,86]

For patients with HCC, a high degree of dose conformality is desired to ensure optimal tumor dose delivery while minimizing dose to the surrounding OARs, particularly to the normal uninvolved liver. Various conformal treatment techniques (eg, step-and-shoot IMRT and volumetric-modulated arc therapy) have been used for patients with HCC treated with EBRT, primarily in the setting of ultra- or moderately hypofractionated regimens.[44,48,58,65,86,101] The use of proton therapy for HCC is of particular interest as an EBRT modality, given its potential for improved normal liver sparing at low-to-moderate doses.[102] A single institution retrospective study of patients with HCC that compared outcomes between photon and proton therapies showed a potential signal of clinical benefit for protons, with improved survival and less CP class score increases of ≥2.[62] However, given the limitations of retrospective analyses and lack of randomized data, there are insufficient data to recommend one technique or modality over another. The potential benefit of protons over photons is currently the subject of an ongoing RCT, NRG GI-003 trial (*NCT03186898*). Although there is a paucity of data comparing different treatment techniques and modalities, use of conformal techniques (either IMRT or proton therapy) for the treatment of patients with HCC in the setting of dose-escalated ultra- or moderately hypofractionated regimens is recommended based on consensus of the task force. Until higher quality evidence is available, the choice of treatment modality and technique should be based on tumor location, underlying liver function, and available technology.

When EBRT is used in combination with TACE to treat patients with HCC with MVI, moderately hypofractionated regimens are the most commonly used fractionation approach.[39,50,52,53,87] The highest quality data using moderate hypofractionation are from the previously discussed RCT that demonstrated OS superiority of TACE plus hypofractionated EBRT (3000-4500 cGy in 10-15 fractions) over sorafenib alone in CP class A patients with MVI.[50] It should be noted that there are multiple studies using standard

Table 6 Recommended EBRT doses and fractionation for HCC and IHC*

Fractionation Regimen	Total dose/fractionation	BED_{10}	References
Ultrahypofractionation	**Noncirrhotic (primarily IHC): 4000-6000 cGy/3-5 fx**†	7200-18,000 cGy	110
	CP class A: 4000-5000 cGy/3-5 fx	7200-12,500 cGy	24,27,28,30,34,43,44,61,86,101,111
	CP class B7: 3000-4000 cGy/5 fx	4800-7200 cGy	28,36,86,94,101
	4000-5400 cGy/6 fx	6700-10,300 cGy	65,93
	5000-6600 cGy/10 fx	7500-11,000 cGy	57,59,83,90,100,112
Moderate hypofractionation	4800 cGy/12 fx	6720 cGy	110
	4500-6750 cGy/15 fx	5900-9800 cGy	42,46,50,62,90,113,114
	6000 cGy/20 fx	7800 cGy	57
	6600-7200 cGy/22 fx	8600-9600 cGy	57-59,112
Standard fractionation	**5040 cGy/28 fx**‡	5947 cGy	114,115
	6000 cGy/30 fx‡	7200 cGy	114,115
	7700 cGy/35 fx	9400 cGy	58,59

Abbreviations: BED_{10} = biologically effective dose assuming an $\alpha/\beta = 10$; CP = Child-Pugh; EBRT = external beam radiation therapy; fx = fractions; HCC = hepatocellular carcinoma; IHC = intrahepatic cholangiocarcinoma.

* Bolded regimens are the most common prescriptions used, based on consensus of the task force. Dose constraints in Table 7 pertain to these most common dose fractionations.

† Lower doses recommended for central lesions in which the maximum point dose to central bile duct(s) cannot be met.

‡ For IHC when combined with concurrent systemic therapy.

fractionated EBRT with concurrent hepatic arterial infusion or systemic chemotherapy in the Asian literature for HCC with favorable clinical outcomes.[103-106] Given the concerns for increased toxicity, concurrent combination of EBRT and targeted therapy should be used in the context of a clinical trial.

Although modern conformal treatment techniques have the advantage of a high degree of dose conformity required for target dose escalation while minimizing dose to OARs, they are less robust when there is variability in patient setup and respiratory motion. Image guidance is essential for the safe and effective delivery of highly conformal treatment dose to account for inter- and intrafractional motion. Respiratory motion assessment and management techniques allow appropriate design of internal tumor volume margin and accurate beam delivery with respect to intrafractional organ motion. Although there are no studies that specifically address the value of daily image guidance or respiratory motion management, prospective and retrospective trials of EBRT for HCC routinely reported using daily image guidance (eg, orthogonal kilovoltage, computed tomography [CT] on rails, cone beam CT) and respiratory motion management (eg, breath hold, gating, tracking, abdominal compression) to reduce tumor motion when possible. The use of fiducial markers or presence of residual ethiodol/lipiodol from prior intra-arterial administration for tumor localization and image guidance was variable across studies and was institution-dependent.[36,43,44,90,91]

In patients with primary liver cancers treated with EBRT, greater volumes of uninvolved liver (liver minus the gross tumor volume) exposed to increasing doses of RT increase the risk of RILD, most notably in patients with cirrhosis.[107] Therefore, it is critical to evaluate and minimize RT dose to uninvolved liver, specifically at the low-dose range, to reduce the risk of RILD.[86,90] Other potential modifying factors that may increase the risk of RILD include underlying liver function, extent of tumor, and use of current and/or prior chemotherapy.[107] Significant heterogeneity in liver dose constraints exist among published studies without standardized consensus. Table 7 provides recommended liver constraints for commonly used fractionation regimens, based on a combination of available data, including prospective studies that focused on constraints, and consensus of the task force. Key elements that were considered included baseline liver function and type of fractionation regimen. Both mean liver dose and volume of liver spared constraints are included. Toxicity was defined as CP score increase ≥ 2 at 3 months and beyond.[92,93,99,108] The moderate hypofractionation literature using >10 fractions has not historically separated patients out by these criteria, although most patients in these studies were CP class A patients. It is emphasized that the selection of fractionation

Table 7 Recommended dose constraints for uninvolved liver and bowel structures*

OARs/ References	Ultrahypofx 3 fx	Ultrahypofx 5 fx	Moderate hypofx 15 fx	Standard fx ≥20 fx	Toxicity endpoint
Uninvolved liver, noncirrhotic (MLD)[22,109]	Mean <1200-1500 cGy ≥700 cc <1900 cGy	Mean <1500-1800 cGy ≥700 cc <2100 cGy	Mean <2400 cGy	Mean <3200 cGy	RILD
Uninvolved liver, CP class A (MLD)[46,83,86,93,116]	Mean <1000-1200 cGy	Mean <1300-1500 cGy ≥700 cc <1500 cGy	Mean <2000 cGy	Mean <3000 cGy	CP increase ≥2 at 3 mo RILD
Uninvolved liver, (MLD) CP class B7[46,83,86,93,116,117]	N/R†	Mean <800-1000 cGy ≥500 cc <1000 cGy	Mean <1600 cGy	Mean <2400 cGy	CP increase ≥2 at 3 mo RILD
Central bile ducts[109]	D0.03 cc <3570 cGy	D0.03 cc <4050 cGy	—	—	Stenosis
Stomach[22,46,109]	D0.03 cc <2200 cGy D10 cc <1650 cGy	D0.03 cc <3200 cGy D10 cc <1800 cGy	D0.03 cc <4200 cGy	D0.03 cc <5400 cGy V45 Gy <33.3% V40 Gy <66.7%	Ulcer
Duodenum[22,46,109]	D0.03 cc <2200 cGy D5 cc <1650 cGy	D0.03 cc <3200 cGy D5 cc <1800 cGy	D0.03 cc <4500 cGy	D0.03cc <5400 cGy	Ulcer
Small bowel[22,46,109]	D0.03 cc <2500 cGy D5 cc <1800 cGy	D0.03 cc <3200 cGy D5 cc <1950 cGy	D0.03 cc <4500 cGy	D0.03cc <5400 cGy V45 Gy <195 cc	Ulcer
Large bowel[22,46,109]	D0.03 cc <2800 cGy D20 cc <2400 cGy	D0.03 cc <3400 cGy D20 cc <2500 cGy	D0.03 cc <4500 cGy	D0.03cc <6000 cGy V55 Gy <5 cc V45 Gy <60 cc V35 Gy <150 cc V30 Gy <200 cc	Ulcer

Abbreviations: CP = Child-Pugh; D = dose to; fx = fraction; hypofx = hypofractionation; MLD = mean liver dose; N/R = not recommended; OARs = organs at risk; RILD = radiation-induced liver disease; SBRT = stereotactic body radiation therapy; V = volume that received.

* This table is a combination of evidence-based constraints and expert opinion; dose constraints are for the most common fractionations. It is meant as a starting point to keep the doses as low as possible to OARs while still achieving a tumoricidal dose.

† CP class B patients are at very high risk of decompensation. The task force does not recommend 3 fraction SBRT; a 5 fraction SBRT regimen or hypofractionated approach to keep the MLD as low as possible is preferred.

regimen and degree of dose escalation must be carefully balanced against the dose to the uninvolved liver and risk of RILD. Careful consideration of baseline liver function and tailoring the fractionation regimen and liver dose constraints are critical to the safe EBRT treatment of patients with HCC. Dose constraints for GI OARs are also included and were based upon published prospective studies, QUANTEC (Quantitative Analyses of Normal Tissue Effects in the Clinic), and American Association of Physicists in Medicine recommendations.[22,46,109]

KQ4: EBRT in the definitive and adjuvant setting in IHC (Table 8)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations

Table 8 EBRT in the definitive and adjuvant setting in IHC

KQ4 Recommendations	Strength of Recommendation	Quality of evidence (refs)
1. For patients with unresectable IHC, induction chemotherapy followed by consolidation with EBRT, alone or in combination with chemotherapy, is recommended. Implementation remark: For patients who are not candidates for induction chemotherapy, EBRT alone or in combination with chemotherapy should be considered.	Strong	Moderate[46,110,113,114,118-120]
2. For patients with IHC who underwent curative surgical resection and have high-risk features, adjuvant EBRT with concurrent chemotherapy, alone or sequenced after systemic chemotherapy, is conditionally recommended. Implementation remark: High-risk clinical features include positive lymph nodes and/or R1 resection.	Conditional	Low[121,122]

Abbreviations: EBRT = external beam radiation therapy; IHC = intrahepatic cholangiocarcinoma; KQ = key question; R1 = microscopic positive resection margins.

for KQ4 and Figures 3 and 4 for visual representations of the IHC recommendations.

What is the role of EBRT in the definitive and adjuvant setting in IHC?

In patients with IHC, surgical resection is the only potentially curative treatment. Among patients with unresectable disease, systemic therapy is the mainstay of treatment.[123] However, historical median OS and intrahepatic PFS rates are <1 year after chemotherapy alone.[115,118,120] After induction chemotherapy, the rationale for consideration of consolidative EBRT in unresectable IHC, therefore, is to improve LC and intrahepatic PFS and to mitigate tumor-related liver failure.[115,118,120] Liver failure results from portal or hepatic venous vascular obstruction and/or biliary obstruction from tumor progression.[115,120] LC and OS rates among patients with unresectable IHC treated with EBRT in retrospective and prospective studies support its effectiveness for consolidative treatment and for salvage after disease progression.[46,113,114,120] Among patients without distant metastatic disease or multifocal progression after initial systemic therapy, multiple retrospective studies strongly support EBRT with or without concurrent fluoropyrimidine chemotherapy for consolidation.[46,113-115,119,120] Across the range of studies, among patients treated with EBRT, 1-year OS ranged from 39% to 70%.[46,110,115,119] Multiple contemporary studies using moderately hypofractionated EBRT regimens demonstrate favorable LC after treatment.[114,124] In one retrospective cohort study of patients who received photon or proton therapy to 3750 to 6750 cGy or cGy (relative biological effectiveness [RBE]) in 15 fractions for unresectable or locally recurrent IHC, 84% 2-year LC and 58% 2-year OS were achieved.[113] In a prospective cohort of patients who received proton therapy with a target dose of 5805 to 6570 cGy (RBE) in 15 fractions for unresectable IHC, 94% 2-year LC was achieved.[46] The main limitations of these studies are the absence of randomized data evaluating the role of EBRT, the paucity of data to directly compare outcomes of EBRT versus systemic or other therapies, and the potential selection bias among treatment groups when treatments are compared in observational study designs. These limitations emphasize the importance of multidisciplinary discussion for optimal management of IHC and balancing the goals and risks/benefits of EBRT. For patients with unresectable IHC that are not candidates for upfront systemic therapy, definitive EBRT alone or with concurrent chemotherapy should be considered when EBRT can be safely delivered.

For patients with resectable IHC who undergo curative resection, high-risk prognostic factors, including positive surgical margin status and involvement of lymph nodes, are associated with worse LC and OS.[125,126] The rationale for adjuvant treatment in this setting is to optimize locoregional control and potentially OS. There are no prospective studies evaluating adjuvant EBRT after curative resection in patients with IHC. Limited low-to-moderate quality retrospective data provide support that adjuvant EBRT, primarily in combination with concurrent chemotherapy, improves locoregional control and relapse-free survival with trends in OS improvement.[121,122] In one retrospective study, among patients with higher risk "narrow" (<1.0 cm) margin status, adjuvant EBRT was associated with improved 3-year intra- and extrahepatic tumor control compared with surgery alone (64% versus 33% and 57% versus 35%, respectively).[122] Another study demonstrated that compared with surgery alone, adjuvant EBRT combined with concurrent chemotherapy yielded superior recurrence-free survival.[121] In the presence of high-risk clinical features, the use of postoperative EBRT with concurrent chemotherapy is conditionally recommended, after multidisciplinary discussion, to reduce local recurrence risk related to postsurgery residual disease.[121,122] An important component of multidisciplinary discussion is timing and sequencing of the radiation course relative to any planned adjuvant chemotherapy, as well as the chemotherapy agent to be used in combination with EBRT, if so recommended.[120]

KQ5: EBRT technique, fractionation, and OAR constraints for IHC (Table 9)

See evidence tables in Supplementary Materials, Appendix E4 for the data supporting the recommendations for KQ5 and Figures 3 and 4 for visual representations of the IHC recommendations.

In patients receiving EBRT for IHC, what are the preferred techniques, fractionation regimens, and recommended OAR dose constraints?

Patients with unresectable IHC have been treated with a range of dose-fractionation regimens when EBRT was used as definitive local therapy,[46,110,113-115,119] but there is a lack of randomized comparisons between these regimens. The studies with the highest quality data used ultra- or moderately hypofractionated regimens.[46,113,114] A prospective phase II trial using moderately hypofractionated proton therapy prescribed doses according to tumor location in 15 fractions (5805 cGy [RBE] for central tumors within 2 cm from the porta-hepatis and 6750 cGy [RBE] for peripheral tumors) and yielded 2-year LC, PFS, and OS of 94.1%, 25.7%, and 46.5%, respectively.[46]

Retrospective series have shown similarly high rates of LC when using hypofractionated regimens.[46,110,114,119] Dose escalation potentially improves LC, with one series demonstrating superior LC and OS when prescribing a BED_{10} of >8050 cGy.[114,119] One multi-institutional retrospective series reported results using SBRT, in which 42% of patients were treated with 3- and 5-fraction approaches.[110] In this study, treatment doses within the target volume were heterogeneous relating to the SBRT

Table 9 EBRT technique and fractionation regimens for IHC

KQ5 Recommendations	Strength of Recommendation	Quality of evidence (refs)
1. For patients with unresectable IHC receiving EBRT, dose-escalated ultra- or moderately hypofractionated EBRT is conditionally recommended with fractionation based on tumor location, underlying liver function, and available technology (Table 6). Implementation remark: Concurrent systemic therapy should not be used with ultrahypofractionated EBRT.	Conditional	Low 46,110,113,114,119
2. For patients with resected IHC receiving postoperative EBRT, standard fractionation is conditionally recommended (Table 6).	Conditional	Low 121,122
3. For patients with unresectable IHC receiving dose-escalated ultra- or moderately hypofractionated EBRT, IMRT or proton therapy is conditionally recommended with choice of regimen based on tumor location, underlying liver function, and available technology.	Conditional	Low 46,110,113-115,119
4. For patients with IHC receiving dose-escalated ultra- or moderately hypofractionated EBRT, respiratory motion management and daily image guidance are recommended.	Strong	Low 46,110,113-115,119
5. For patients with IHC, radiation dose to the liver minus the gross tumor volume should be evaluated and minimized to reduce the risk of radiation-induced liver disease (Table 7).	Strong	Low 46,110,113,119

Abbreviations: EBRT = external beam radiation therapy; IHC = intrahepatic cholangiocarcinoma; IMRT = intensity modulated radiation therapy; KQ = key question.

treatment planning approach, and higher maximum BED_{10} values (>91 Gy_{10}) were associated with improved LC and OS. High-grade toxicities were uncommon in all of these series. Although the quality of evidence is considered low given the limited quantity of data and lack of randomized data, well-designed prospective study data were sufficient to conditionally recommend dose escalated ultra- or moderately hypofractionated EBRT for patients with unresectable IHC.[46,119] There are no data that compared fractionation regimens, so the specific choice of hypofractionated EBRT regimen should be based on the tumor location, the underlying liver function, consideration of the ability to meet normal tissue constraints, and the technology available to deliver the treatment course, with a goal of safely delivering an escalated prescription dose while meeting OAR constraints. Although concurrent systemic therapy has been used with moderately hypofractionated regimens,[114] use of systemic therapy concurrently with ultrahypofractionation is not appropriate.

Available data regarding the potential clinical benefits of adjuvant EBRT included standard fractionated regimens.[121,122] This approach is further supported by the Southwest Oncology Group S0809 trial, which was a phase II study of postoperative chemotherapy followed by EBRT (4500 cGy to regional lymphatics and 5250-5940 cGy to tumor bed in 25-33 fractions) with concurrent chemotherapy in patients with resected extrahepatic cholangiocarcinoma.[127] Although patients with IHC were excluded from this trial, the clinical context and EBRT nodal target volumes are similar to those of postoperative treatment for IHC, with the exception of potentially needing to treat the liver resection margin of the liver remnant for R1 margins in patients with IHC. This regimen was well tolerated and was associated with a low risk of local recurrence. Therefore, standard fractionation is conditionally recommended for patients with resected IHC receiving postoperative EBRT.[121,122] An adjuvant dose of 4500 to 6000 cGy is reasonable to consider depending on the clinical scenario, surgical margin status, postoperative imaging, and dose to OARs.

As with patients with HCC, normal tissue sparing is a major concern for patients with unresectable IHC treated with EBRT, which requires a high degree of dose conformity to ensure optimal tumor dose escalation while minimizing dose to the surrounding OARs. Various conformal treatment techniques (eg, static field IMRT, volumetric-modulated arc therapy, and proton therapy) have been reported in clinical studies of patients with unresectable IHC.[46,110,113,114,119] However, there is insufficient evidence to evaluate and compare the outcome and toxicity profiles of these different treatment techniques. Given the paucity of data directly evaluating different treatment techniques, conformal techniques are conditionally recommended for treatment of patients with unresectable IHC. Until randomized data regarding the benefits of these techniques are available, choice of appropriate conformal techniques should be based on tumor location, underlying liver function, and resource and technology availability.

Similar to patients with HCC, image guidance and motion management techniques are critical to the safe and effective delivery of highly conformal EBRT for patients with IHC. Daily image guidance based on in-room imaging (eg, orthogonal kV, cone beam CT, CT on

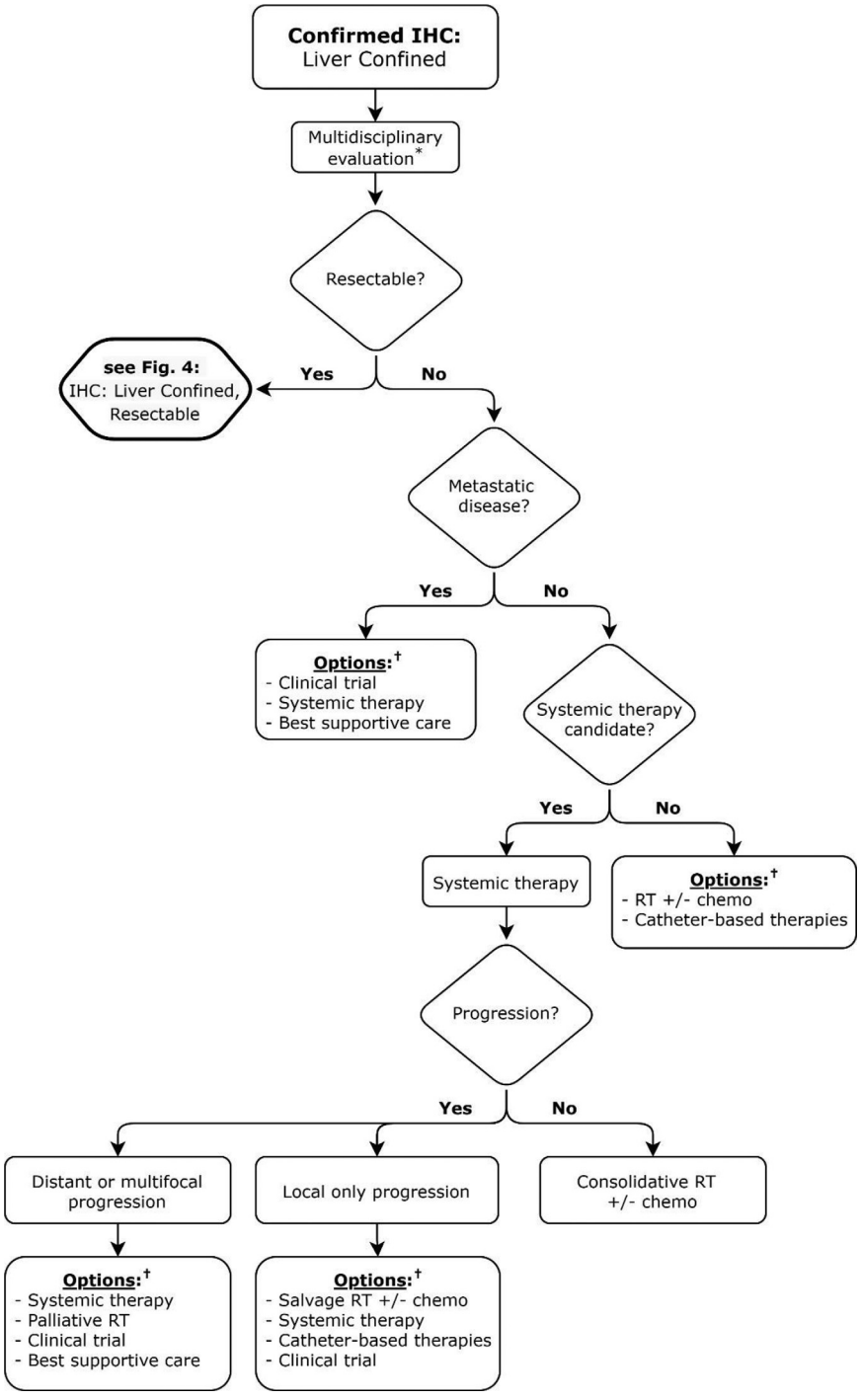


Figure 3 Algorithm for IHC: Liver confined, unresectable.
Abbreviations: chemo = chemotherapy; IHC = intrahepatic cholangiocarcinoma; RT = radiation therapy.
* Enrollment in a clinical trial should be prioritized if available.
† Order of listed options does not reflect a particular preference; decision is based on multidisciplinary evaluation.

rails) was used in most clinical studies of patients with unresectable IHC.[46,110,113,114,119] Various motion assessment and management techniques were reported for patients with unresectable IHC in clinical studies, including patient-specific respiratory assessment (eg, 4-D CT, abdominal compression, voluntary or forced breath-hold, and respiratory gating). Many of these studies permitted mixed motion management and were selected on an individual patient basis.[110,113,114,119] Respiratory motion control and daily image guidance are strongly recommended for patients receiving ultra- or moderately hypofractionated EBRT.

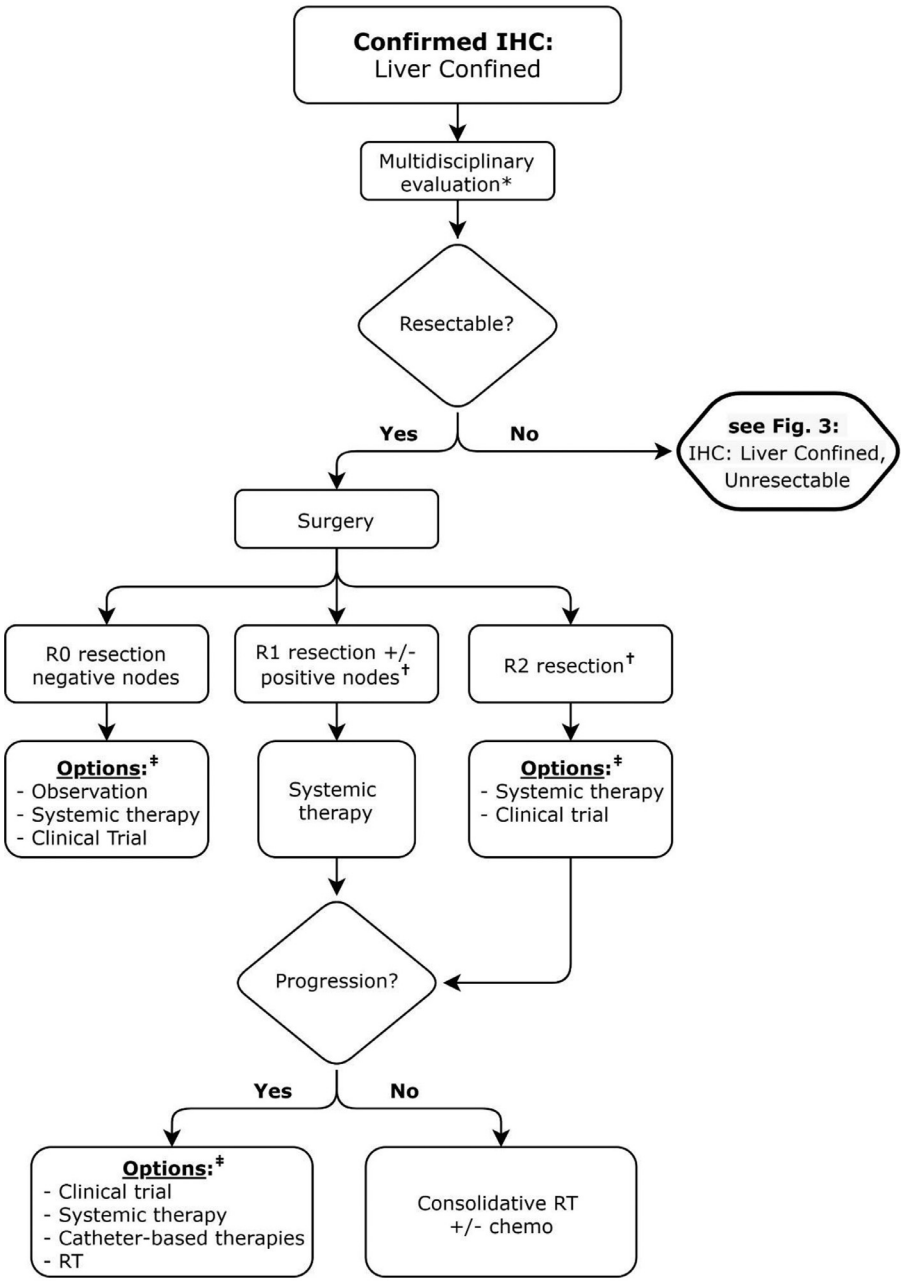
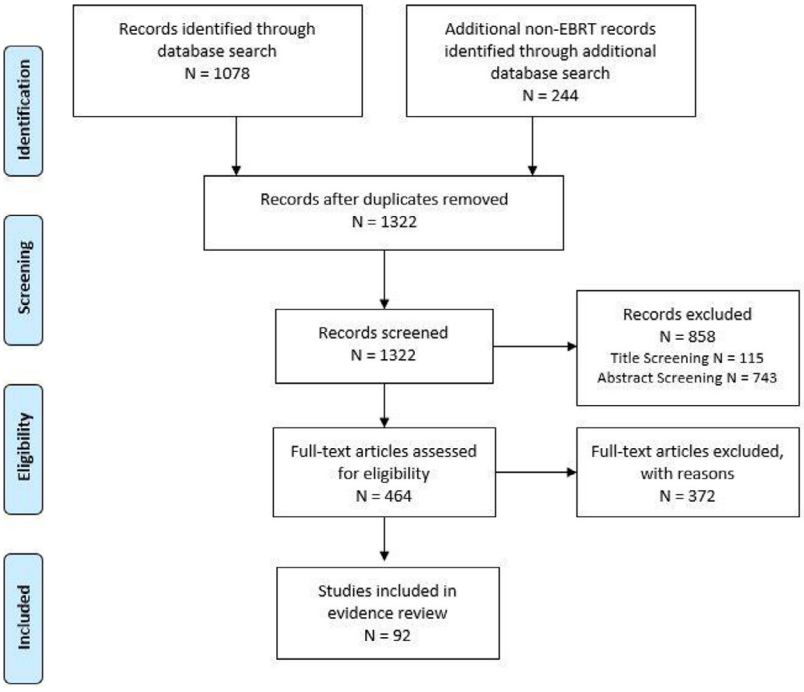


Figure 4 Algorithm for IHC: Liver confined, resectable.
Abbreviations: chemo = chemotherapy; IHC = intrahepatic cholangiocarcinoma; RT = radiation therapy.
* Enrollment in a clinical trial should be prioritized if available.
† Consider additional surgical resection when feasible before adjuvant therapy.
‡ Order of listed options does not reflect a particular preference; decision is based on multidisciplinary evaluation.

Although many patients with IHC may not have cirrhosis, the importance of minimizing RT dose to the normal liver is still critical to minimize the risk of RILD. In most published series of patients with IHC treated with EBRT, the reported rates of RILD were low.[46,113-115,119] This is likely due to patient selection (limiting to patients without cirrhosis or with well-compensated CP class A or B cirrhosis) and prespecified treatment planning goals for reducing radiation dose to uninvolved liver.[46,119] Some studies have incorporated individualized prescription dosing based on dose to uninvolved liver determined during the treatment planning process.[46,113,119] The specific goals for dose to uninvolved liver are dependent on the fractionation schedule used and potentially the patient's underlying liver function (typically CP class). Table 7 includes examples of dose-volume constraints for patients with primary liver cancers, including IHC.



PRISMA diagram, based on Moher et al.[128]

Abbreviations: EBRT = external beam radiation therapy; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Conclusions/Future Directions

The treatment of patients with HCC and IHC is complex and requires a multidisciplinary approach intended to select not only the most appropriate upfront therapy but to determine the risk and benefits of appropriately combining or sequencing potential available modalities. Currently, high-quality evidence to guide the use of EBRT in patients with liver-confined HCC and IHC disease is limited. However, low-to-moderate quality evidence from observational and prospective studies published at the time of the literature review support the consideration of EBRT as a reasonable potential treatment option in various clinical settings for HCC and IHC, including definitive, consolidative, salvage, and adjuvant therapy. In certain clinical scenarios, EBRT may also be combined or sequenced with other LDTs. Data from RCTs published after the guideline's literature review end date (eg, the Korean phase III trial comparing proton therapy with thermal ablation),[60] completed RCTs presented in abstract form (eg, the Italian phase III study [*NCT02323360*] that compared ultrahypofractionation to additional TAE or TACE after incomplete TAE or TACE),[68] and ongoing RCTs (eg, ABC-07 [*CRUK/14/029*], which is comparing systemic therapy with and without EBRT in IHC) will provide further clarification on the role of EBRT in HCC and IHC. Because the number and quality of comparative studies between EBRT and other LDTs are limited, definitive conclusions cannot be made on the role and effectiveness of EBRT in comparison to other LDTs.

The choice of dose-fractionation regimens, technique, and modality should ultimately depend on tumor location, underlying liver function, and available technologies given the lack of published RCTs directly comparing the preferred technical aspects of EBRT for HCC and IHC. Whenever possible, moderate dose escalation in the form of ultra- or moderate hypofractionation is recommended when OAR constraints can be safely met. Careful consideration of baseline liver function and tailoring the fractionation regimen and liver dose constraints are critical to the safety of EBRT in the treatment of patients with HCC and IHC. It is imperative to minimize the risk of liver toxicity, particularly in patients with cirrhosis because it is often irreversible and potentially life-threatening, unless salvage OLT becomes an option.

In addition to conducting more high-quality clinical trials, particularly RCTs comparing different LDTs, several important topics and areas of research are needed to fully understand the role of EBRT for HCC and IHC. Some of the most relevant include (1) refinement of optimal tumor dose and normal liver dose constraints; (2) consensus in reporting radiologic response and liver toxicity metrics; (3) serum and functional liver imaging biomarkers for improved risk stratification, identification of early response and toxicity, and individualized adaptive treatment; (4) integration of EBRT with systemic therapies, including molecular targeted therapy and immunotherapy; (5) clinical benefit of magnetic resonance imaging-guided EBRT; and (6) patient selection and indications for EBRT versus TARE and potential interactions when used sequentially.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.prro.2021.09.004.

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