Review Article | Palliative Medicine and Palliative Care for Incurable Cancer

Palliative radiotherapy for hepatic tumors: a narrative review of indications and recommendations※

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Background and Objective: Primary and metastatic liver cancer presents heterogeneously. New radiotherapy techniques have reduced toxicity concerns, leading to increased use of liver radiotherapy. This review synthesizes available evidence and offers recommendations for palliative radiotherapy for liver cancer.

Methods: PubMed, Ovid Medline, Embase, Cochrane Central, and Web of Science were searched from inception to December 28th, 2022. Articles reporting local control (LC), survival, toxicity, symptom control, and response after stereotactic body radiotherapy (SBRT), partial-liver, or whole-liver radiotherapy (WLRT) techniques were reviewed. We also identified nomograms identifying patients who may benefit from radiotherapy.

Key Content and Findings: Nine randomized-controlled trials were found, in addition to many retrospective, feasibility, and phase I or II studies. Patients with favorable prognosis may receive SBRT using 30–50 Gray (Gy) in 3–5 fractions for primary cancer and up to 60 Gy for metastases, provided normal-tissue constraints are met. Select patients with multiple (>5) or large (>10 cm) lesions or macrovascular invasion (MVI) may be considered, but with potentially reduced LC and increased toxicity. Lower SBRT doses (i.e., 25 Gy in 5 fractions) can be considered on a cautionary basis for patients with poorer liver function or health. Patients with larger tumor burden, poor performance status (PS), or inability to tolerate SBRT positioning or motion-management can consider partial-liver three-dimensional conformal radiotherapy (3DCRT). For patients with extremely guarded prognosis and/or extremely poor performance, WLRT provides pain and symptom relief over several weeks. Combining radiotherapy and systemic therapy may allow radiotherapy de-escalation while maintaining good outcomes.

Conclusions: Radiotherapy has a definite role for palliation of liver cancer with practical research providing guidance in the use of techniques and different regimens in various patient subgroups. Future investigation, including randomized trials, is needed to optimize patient selection, radiotherapy techniques, and integration with other therapies.

Keywords: Liver cancer; liver metastases; radiotherapy; palliation; narrative review

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Introduction

Background

Primary and secondary liver cancer carries a poor prognosis, so there is active investigation to identify better management options. Modalities such as chemotherapy, immunotherapy, ablation, and radiation have shown rapid advances recently. Much of this work has focused on patients in the curative setting. Despite these significant advances, most patients will succumb to disease or are not eligible for curative treatment. Here, we provide a review of the evidence focusing on palliative radiotherapy.

The liver is a common site of metastases, especially via portal venous drainage from the gastrointestinal tract. Approximately 20% of patients with colorectal cancer (CRC) present with liver metastasis at diagnosis, with 70% of recurrences found in the liver (1-3). Resection is feasible in patients with good liver function, adequate platelet count (>100 bil/L), good performance status (PS), no portal venous thrombosis (PVT), no portal hypertension, normal bilirubin, and no extra-hepatic disease with liver remnant of >40% of total liver volume. Unfortunately, 85–95% of patients with liver metastases (4) cannot undergo curative resection, and up to 50% cannot undergo palliative resection (4). Median survival (MS) for patients with liver metastases is 2–6 months (1), or 6–20 weeks if left untreated (1,3), so additional treatment options are needed (1,5-7).

Rationale and knowledge gap

Hepatocellular carcinoma (HCC), the most common primary liver cancer, is a leading global cause of death. A total of 80–90% of HCC patients (8,9) cannot undergo curative resection. Risk factors include hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol abuse, non-alcoholic steatohepatitis, and cirrhosis. Patients are often asymptomatic at diagnosis, with disease found incidentally and at advanced stages. Classic imaging findings of arterial-phase enhancement and venous-phase "washout" in patients with lesions >2 cm are diagnostic for HCC without biopsy (2). HCC tends to remain in the liver, but multi-focality and macrovascular invasion (MVI) commonly develop (2). The American Association for the Study of Liver Disease guidelines suggest 6-month ultrasound screening for patients at-risk for HCC, with 3-month ultrasound screening for lesions <1 cm, and multi-phasic computed tomography (CT) scan and/or magnetic resonance imaging (MRI) for lesions >1 cm (10,11).

Standard curative-intent treatment modalities for non-metastatic primary liver cancers include resection, orthotopic liver transplantation (OLT), thermal ablation (radiofrequency or microwave), or catheter-based therapies (transarterial bland embolization or chemoembolization) (12-15). Effective palliation remains an unmet need in liver cancer patients, as one-third of patients report inadequate symptom control at presentation (16), including abdominal pain, night sweats, and nausea (17). Common medications, like opioids, may present excessive sedation risk due to reduced liver clearance, and may even exacerbate symptoms (18). Published guidelines, such as Barcelona Clinic Liver Cancer (BCLC) system for HCC, can help select appropriate management although it has primarily been applied to earlier-stage disease rather than palliative or emergent care settings (10,11). There are no classification systems for liver metastases.

Early treatment, even for asymptomatic patients, should be considered since progression can rapidly lead to organ failure, deleterious symptoms, and death. Advances in radiotherapy (RT), including stereotactic body radiotherapy (SBRT), have improved local control (LC) and reduced RT-induced liver toxicity (19). Recent American Society of Radiation Oncology (ASTRO) guidelines recommended first-line RT for all patients with liver-confined HCC who are not curative-treatment candidates, with conditional recommendations for RT alone or combined with catheter-based or systemic therapy as palliation for HCC with MVI, symptomatic lesions, or metastases (20,21). Dose-escalation for all liver-confined tumors was recommended via SBRT, hypofractionation with intensity-modulated radiotherapy (IMRT), or heavy-particle techniques combined with respiratory management and daily image-guidance (20-25). Recently, the RTOG 1112 randomized clinical trial compared the combination of SBRT and sorafenib, a multi-kinase inhibitor, to sorafenib alone for patients with advanced HCC. This multi-center trial demonstrated improved overall survival (OS) and progression-free survival (PFS) by adding SBRT to sorafenib with no difference in toxicity (26), providing level I evidence that SBRT can significantly improve clinical outcomes and palliation in advanced liver cancer.

Objective

The role of liver RT is rapidly evolving, with multiple guidelines and options published in parallel that include definitive and palliative patients. We present a narrative review synthesizing available literature focusing on palliative liver RT and provide evidence-based recommendations for

Table 1 The search strategy summary

Items	Specification
Date of search	2/26/2022, 5/14/2022, 6/26/2022, 7/28/2022, 10/28/2022, 12/28/2022
Databases and other sources searched	Ovid Medline, Embase, Cochrane Central Register of Controlled Trials, PubMed, Web of Science
Search terms	Liver, hepatocellular carcinoma, metastases, radiotherapy, tumor, cancer, palliation, combination therapy, definitive, systemic
Timeframe	Inception to December 28th, 2022
Inclusion and exclusion criteria	Adults (>18 years old) with primary or secondary liver malignancy were included who received RT (any technique), other local-regional treatment, or systemic therapy, with any CP score or BCLC stage and treatment for palliative intent. Included designs were randomized controlled trials, retrospective analyses, treatment guideline recommendations, feasibility, phase I, phase II, QOL, dose-escalation, meta-analyses, and abstracts that led to publications. We excluded case reports, cohorts with <10 patients, reviews, letters, errata, commentaries, and studies published only as abstracts
Selection process	We tabulated author, year, histology, tumor size and volume, number of lesions, primary or secondary cancer, presence of cirrhosis or MVI, PS, and type of treatment: local, regional, systemic, and/or RT. For RT patients, we recorded dose, fractionation, amount of normal liver spared, and technique. Outcomes were also tabulated, including LC, toxicity, disease progression, DM, response rates, symptom control, OS, and PFS

RT, radiotherapy; CP, Child-Pugh; BCLC, Barcelona Clinic; QOL, quality of life; MVI, macrovascular invasion; PS, performance status; LC, local control; DM, distant metastases; OS, overall survival; PFS, progression-free survival.

RT to improve quality of life (QOL) and clinical outcomes in liver cancer patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-965/rc).

Methods

Search methods are summarized in *Table 1*. We searched PubMed, Ovid Medline, Embase, Cochrane Central, and Web of Science from inception to December 28th, 2022. Included reports studied adults who received RT (any technique) or other anti-cancer therapy for primary or secondary liver cancer. Recorded data includes disease factors (histology, tumor number, tumor size), patient factors [cirrhosis, Child-Pugh (CP) score, hepatitis], and treatment factors (modalities, RT technique, RT dose/fractionation). Case reports, studies of <10 patients, abstract-only publications, and commentaries that did not present new data were excluded. Outcomes of interest were LC, mortality, toxicity, progression, symptom control, response rates, patient reported outcomes (e.g., QOL), and survival.

Discussion

Literature review results

We found nine phase III randomized controlled trials (26-34). The remainder were retrospective, quality or committee recommendations, feasibility, phase I or II studies. We also identified nomograms for identifying which patients may benefit from radiotherapy.

Non-radiation local and regional therapy options

Techniques such as radiofrequency ablation (RFA), electroporation, light-activated drug therapy, and Yttrium-90 (Y-90) radioembolization are recommended for patients with potentially-curable early-stage HCC and liver metastases who cannot undergo surgical resection (35). Intrahepatic Y-90 also provides effective palliation, with symptomatic improvement demonstrated in 54% of patients and mean survival 5–14 months in mixed HCC and liver metastasis populations (36-38). RFA is commonly used for tumors <3 cm and far from large vessels with mostly retrospective or small prospective data suggesting LC up to 90% for HCC (39); decreasing LC is suggested for larger tumors or those close

to large vessels (40). Variable 5-year survival (15–55%) and complication outcomes (6–9%, including mortality up to 2%) may limit its applicability, particularly in the palliative setting (2,35,41).

Transarterial chemoinfusion (TAI), image-targeted delivery of chemotherapy directly to the tumor (42), may act as an effective bridge to liver transplantation for HCC (43). Transarterial chemoembolization (TACE) combines chemoembolization with drug-eluting beads (42) and may improve survival for HCC and liver metastases (44,45). Usually, TACE is recommended for intermediate-stage primary HCC (BCLC-B), but guidelines vary, including the "up to seven" criteria (45) or BCLC-B3/B4 patients with good PS and low tumor burden (e.g., solitary nodule, or ≤3 nodules that measure ≤3 cm). Only 10% of HCC patients meet accepted TACE guidelines (46) so many TACE treatments are applied to patients outside of established criteria (46). TACE is less effective for large HCC (>10 cm) or with major PVT and is not recommended for extra-hepatic or metastatic disease (15). Despite evidence of OS improvement, death from liver failure remains frequent (30). Given limitations of TACE and other treatments, investigation of new techniques is a priority.

RT

Toxicity considerations

Given poor prognosis of liver cancers, selecting patients and appropriate treatment intent is critical (47). Factors to consider include liver function, PS, tumor histology, size, stage, local invasion (e.g., PVT), underlying liver disease, comorbidities, potential RT interactions with other therapies or anatomical structures (e.g., nearby gastrointestinal tissues), and patient's goals of care (48). The multi-disciplinary team, along with the patient and their loved ones, should develop a comprehensive therapeutic approach. Patients often present with advanced disease and significant comorbidities, so early treatment is critical to avoid future problems, as well as improve chances of effective palliation. Even with low expectation of cure, aggressive pre-emptive treatment can provide significant palliative benefit by preventing symptoms like pain, nausea, night sweats, jaundice, or bleeding to improve or maintain patient QOL (17).

Historically, liver RT was avoided due to perceived risk of RT-induced toxicity, as fatal hepatitis can result from whole-liver radiotherapy (WLRT) of 30–36 Gray (Gy) in daily 2 Gy fractions. Classic radiation-induced liver disease (RILD) is a clinical syndrome of anicteric hepatomegaly, elevated liver enzymes, and ascites occurring 2 weeks to 3 months after RT (48-50). Classic RILD may cause tissue damage, cytotoxic chemical and antigen release, inflammation, and eventual fibrosis (51). However, patients with poorer baseline liver function and underlying liver disease usually develop non-classical RILD which includes any other liver toxicity, including hepatitis reactivation (52), elevation of liver enzymes, or decline in liver function (49). Acute toxicity from liver RT includes nausea and vomiting, usually well-managed with anti-emetics such as prochlorperazine (53), or serotonin antagonists like ondansetron (50). Antiretroviral therapy is recommended before initiating RT for patients with HBV due to risk of reactivation (52). Nearby non-hepatic normal structures (such as duodenum and bowel) also need to be protected to avoid toxicity (54).

Selecting patients for radiotherapy

Several systems may help select patients for RT and estimate outcomes, including Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging, the Okuda staging system for HCC (55), and others. The CP classification stratifies HCC patients with liver cirrhosis by perioperative mortality risk. Scores (1–3 points per category, depending on severity) are based on: ascites, bilirubin, serum albumin, international normalized ratio (INR), and encephalopathy. In total, 5–6 points (CP-A) suggests 2-year OS of 85%; score 7–9 (CP-B) yields 2-year OS of 60%; and ≥10 points (CP-C) yields 2-year OS of 35%. CP score is prognostic for survival in patients with cirrhosis from chronic liver diseases (56), but has variable reliability due to subjectivity of ascites and encephalopathy (57). Both TACE and SBRT can be pursued in HCC patients with CP-A status, CP-B status with caution, lesions <10 cm, no metastases or extra-hepatic sites, and no MVI. Because CP score correlates with toxicity from RT (58), CP ≤7 points has been recommended for RT in current ASTRO guidelines (20). For liver-directed therapy, including RT for cure or palliation, CP score is an important decision factor.

The Model for End-Stage Liver Disease (MELD) score can predict 3-month mortality in HCC or metastatic patients considered for liver transplant or trans-jugular intrahepatic portosystemic shunt (TIPS). It uses serum bilirubin, creatinine, sodium, and INR, while the updated MELD-Plus adds additional serum markers (59). Using a cut-off of 7.5, MELD may be more effective than CP in predicting toxicities for patients receiving RT (60).

The albumin-bilirubin (ALBI) grade, based on serum albumin and bilirubin, is the only score validated for predicting RILD. It may predict survival better than MELD in HCC patients (61-63), but has not been evaluated in the setting of liver metastases. Adding platelet count produces the platelet-ALBI (PALBI) score (64), which may be more prognostic, but requires validation. Volume of irradiated liver (to equivalent dose of 40 Gy) may predict post-RT decline in liver function as measured by ALBI or CP score (61). The CRAFITY score, based on serum C-reactive protein and alpha-fetoprotein (AFP), was studied in several HCC cohorts receiving PD-L1 immunotherapy, but not RT. The score was associated with radiological response and OS, and was validated among subgroups divided by CP score and PS (65).

Practical nomograms are being developed for prognostic and predictive information, and to select patients who may benefit from treatments like liver RT. One model has accurately predicted 3-month mortality [area under the curve (AUC), 0.961]: CP score and tumor size (>5 cm) predicted survival for HCC patients; serum albumin, extra-hepatic disease, and colorectal primary were predictive for metastatic patients; and CP score, Eastern Cooperative Oncology Group (ECOG) PS, ascites, serum albumin, previous resection, and presence of extrahepatic disease were predictive for the combined HCC and metastatic cohort (66,67). Another system for patients treated with SBRT uses number of lesions (0–1 or >1), active systemic disease, and PS (Karnofsky >80). Allocating 1 point for each factor, scores of 0, 1, 2, and 3 yielded median MS of 34, 12.5, 7.6, and 2.8 months, respectively (68). Another nomogram based on age, normal-liver volume, cancer stage, cirrhosis, hemoglobin, and AFP level also demonstrated favorable (AUC, 0.74) survival prediction (69). Further validation of these techniques is required. No single nomogram has been uniformly accepted as best in liver RT patients.

Another promising approach is a normal-tissue complication probability (NTCP) model incorporating dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) changes before and after RT along with cytokine biomarkers, CP score, ALBI score, and liver enzyme changes for patients with HCC and cirrhosis undergoing RT (70). Technetium-99m galactosyl human serum albumin (99mTc-GSA) single-photon emission computed tomography (SPECT) imaging may also be able to assess extent of functional liver tissue; a small feasibility study observed correlation between SPECT-detected functional liver volume, lesion size, and risk of RILD, but needs further validation (71).

SBRT

Sometimes referred to as stereotactic ablative radiotherapy (SABR), SBRT is delivered in few (usually 5 or fewer) relatively-large doses of highly-conformal RT using advanced techniques like strict immobilization (e.g., via Vac-lock device) and daily cone-beam computed tomography (CBCT) for image-guidance to reduce setup variation between fractions (72); four-dimensional computed tomography (4DCT) (73) or tumor tracking via implanted fiducial markers (74,75) to evaluate physiological tumor motion; and multiple beams (including non-co-planar beams) to achieve steep dose gradients and minimize dose to normal tissues (76,77). Planning for SBRT generally uses CT with intravenous contrast, positron emission tomography (PET) and/or contrast-enhanced MRI to precisely define targets (78,79). To undergo liver SBRT, patients must be able to lie comfortably on their back for at least 30–40 min and produce consistent breathing patterns or breath-holds.

Proper SBRT allows safe delivery of ablative RT for liver cancer, previously contraindicated due to toxicity risk. Prospective data suggest significant OS advantage for SBRT over conventional RT for patients with HCC and liver metastases, with SBRT improving 2-year OS to 42% from 27% in one large study, with no difference by tumor histology (80). Different strategies have been developed to select SBRT doses while sparing normal liver such as individualizing RT doses based on maintaining the same predicted RILD risk (81) or using NTCP models and ensuring ≥700 cc of uninvolved liver is spared (20,23,82,83). Given the excellent safety profile of SBRT protocols, which resemble curative-intent plans, they can also be used effectively for palliative treatment. *Table 2* lists studies of SBRT for both primary liver cancer and metastases. These studies suggest excellent LC rates of 57–100% at 1 year, up to 95% at 5 years, and 2-year OS from 30–83% (81,89,94,95,97,99,105-109,113,114). However, critical appraisal is needed since most used retrospective or early-phase prospective designs, aside from one phase III trial (26). Many of these pioneering SBRT studies had radical treatment intent, but most patients were end-stage and not eligible for interventions such as surgery or TACE.

SBRT allows treatment for patients who experience disease recurrence after loco-regional therapies like TACE or RFA (2,15,30,35-41,43-46,115), whereas previously only supportive care was available. HCC patients treated with SBRT after TACE have seen response rates of 67% with 14 months median OS (116). Patients with liver

Table 2 SBRT for liver tumors

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Median follow up (months)	Tumor volume (cc)	Tumor diameter (cm)	Lesion number (per patient)	Dose (Gy)	Fractions	Survival					Toxicity (grade ≥3) (%)	Response		LC, 1-year (%)	Metastases (%)	Comments
				CP/BCLC	Hepatitis							Median OS (months)	1-year OS (%)	>1-year OS (%)	Median PFS (months)	PFS (%)		Response rate (%)	Complete response (%)			
Primary liver tumors																						
Tse, 2008 (84)	41	HCC	–	CP-A	–	36	173 [9–1,913]	–	–	36 [24–54] dose per NTCP	6	12	48	–	–	–	29 (3-month)	–	–	65	Intrahepatic out-of-field: 34, DM: 12	Patients with MVI had 6% complete response rate; phase I
Koo, 2010 (85)	71, TACE, CRT	HCC, IVCTT	–	60% CP-A, 40% CP-B; 40% BCLC-B, 61% BCLC-C	83% HBV	–	–	Thrombus and/or tumor within 2 cm, median 10–13	1	45 [28–50]	10–15	TACE + CRT: 12	TACE + CRT: 48	–	–	TACE + CRT: 71	0	43	–	–	–	MVI, CP-B status, IVCTT progression, and treatment type predicted mortality; phase II
Andolino, 2011 (24)	60	HCC	10% TACE	60% CP-A, 40% CP-B	13% HBV, 50% HCV	27	29 [2–112]	3.2 [1–7]	–	CP-A: 44 [30–48], CP-B: 40 [24–48]	CP-A: 3, CP-B: 5	44	–	67 (2-year)	20	48 (2-year)	0	–	–	90 (2-year)	Median TTP: 48 months, regional: 47, DM: 18	Retrospective
Price, 2012 (86)	26	HCC	–	54% CP-A, 46% CP-B	12% HBV, 58% HCV	13	–	≤6	1–3	42 [24–48]; CP-A: 36–48, CP-B: 26–42	CP-A: 4, CP-B: 3–5	–	77	60 (2-year)	–	–	–	–	–	73	–	There was increased toxicity for CP-B patients; prospective phase I/II
Bujold, 2013 (87)	102	HCC	52%	–	38% HBV, 38% HCV	31	117 [1–1,913]	7	–	36 [24–54]	6	17	55	–	–	–	30 (1-year)	–	–	87	–	Phase I/II
Que, 2014 (88)	22	HCC, inoperable, large	–	–	–	12	–	≥10	–	26–40	5	11	50	–	–	–	4.5 (1-year)	86	23	56	Regional: 53 (1-year)	SBRT dose was prognostic for survival; CP was borderline prognostic; phase I/II
Su, 2016 (89)	132	HCC	–	86% CP-A, 14% CP-B; 55% BCLC-A, 45% BCLC-B	88% HBV	21	–	1–5	–	28–30 in 1 fraction; 42–46 in 3–5 fractions	1 [3–5]	–	94	74 (2-year), 64 (3-year)	–	83 (1-year), 58 (2-year), 36 (3-year)	8	–	–	90	–	CP-B predicted worse OS; multiple lesions predicted worse PFS
Matsuo, 2016 (90)	43 SBRT, 54 3DCRT)	HCC, MVI	>90% (no prior RT)	50% CP-A, 45% CP-B, 5% CP-C	25% HBV, 50% HCV	7	–	Thrombus	1	SBRT dose: 50.4 [45–55]; 3DCRT dose: 45 [39–50]	10–15	–	SBRT: 49; 3DCRT: 29	–	–	–	0	SBRT: 67; 3DCRT: 46	–	SBRT: 80; 3DCRT: 56	Local 20: (1-year)	SBRT enabled higher biologically effective RT dose. better OS, and LC for advanced HCC with MVI; phase I/II
Lazarev, 2018 (21)	53	HCC, central lesions	–	62% CP-A, 38% CP-B; 68% BCLC-A or -B	18% HBV, 62% HCV	12	106 [24–506]	3 [1–14]	–	Median BED_{10} 72	–	–	–	53 (2-year DSS), 40 (2-year)	–	–	17	76 (2-year)	–	88 (2-year); 97 if BED_{10} >70 Gy	–	–
Yoon, 2018 (27)	90, TACE, RT *vs*. sorafenib	HCC, MVI	–	100% CP-A	84% HBV, 1% HCV	5–32	–	10 [7–12]	–	45 with TACE	15–18	–	–	TACE + RT: 55 (5-month)	–	TACE + RT: 87 (3-month), 33 (6-month)	TACE + RT: 16	TACE+RT: 33 (5-month)	–	–	Median TTP: TACE-RT 31 weeks	Phase III RCT
Yeung, 2019 (91)	31	HCC, 10% PVT	84% local therapy	90% CP-A, 10% CP-B	52% HBC, 29% HCV	18	–	3 [1–5]	–	45	3–5	–	84	–	–	49 (1-year)	32: 19 had reduced CP-status	–	–	94	–	Small tumor size predicted improved OS

Table 2 *(continued)*

Table 2 *(continued)*

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Median follow up (months)	Tumor volume (cc)	Tumor diameter (cm)	Lesion number (per patient)	Dose (Gy)	Fractions	Survival					Toxicity (grade ≥3) (%)	Response		LC, 1-year (%)	Metastases (%)	Comments
				CP/BCLC	Hepatitis							Median OS (months)	1-year OS (%)	>1-year OS (%)	Median PFS (months)	PFS (%)		Response rate (%)	Complete response (%)			
Yang, 2019 (92)	45 SBRT, 59 3DCRT	HCC, MVI	–	–	–	6	–	–	–	3DCRT: 51.5 [45–54]; SBRT: 45 [40–48]	3DCRT: 15–30; SBRT: 3–8	–	SBRT: 35; 3DCRT: 16	–	–	SBRT: 70; 3DCRT: 32 (1-year)	SBRT: 2; 3DCRT: 5	SBRT: 62; 3DCRT: 34	–	SBRT: 69; 3DCRT: 32	–	Late RILD incidence was not different between groups, even after pooling RILD types (SBRT 16.7% *vs.* 3DCRT 19.8%, P=0.6)
Durand-Labrunie, 2020 (22)	43	HCC, 12% MVI	–	88% CP-A, 12% CP-B	25% HBV or HCV	48 [12–55]	–	3 [1–6]	–	45	3	42	–	72 (18-month)	24	65 (18-month), 48 (2-year)	31	–	–	98 (18-month)	Intrahepatic out-of-field: 26, DM: 5	Outcomes after SBRT for untreated solitary HCC were excellent for patients unfit for transplant or local therapy; phase II
Liu, 2020 (93)	96	HCC, 21% MVI	48%	88% CP-A, 12% CP-B; 61% BCLC-0/A, 31% BCLC-B/C	40% HCV	13	–	4 [1.5–17]	1–5, 112 total	35–45 median BED_{10}: 86 for BCLC-0/A, 60 for BCLC-B/C	3–5	–	BCLC-0/A: 95, BCLC-B/C: 71	–	–	BCLC-0/A: 80 (1-year), BCLC-B/C: 40 (1-year)	1; 13 acute self-resolving labs	–	–	BCLC-0/A: 94, BCLC-B/C: 74 (1.5-year)	Intrahepatic out-of-field: 33, DM: 5	SBRT is effective for early HCC with low toxicity. Lower-dose SBRT can provide palliation for advanced patients; retrospective
Park, 2020 (25)	290	HCC	–	86% CP-A	74% HBV, 13% HCV	38	–	2 [1–6]	1–3	30–60	3–4	–	–	45 (5-year)	–	–	4	–	–	91 (5-year)	Intrahepatic out-of-field: 72, DM: 22 (5-year)	Age, CP-status, tumor size >3 cm, and albumin levels predicted LC
Dawson, 2023 (26)	92 sorafenib, 85 SBRT + sorafenib	HCC, 74% MVI, 50% ECOG 1–2, 4% metastases	–	82% BCLC-C	19% HBV, 41% HCV	13	–	8 [0.1–19]	40% had single lesion	27.5–50	1–5	SBRT + sorafenib: 16	SBRT + sorafenib: 59	43 (18-month), 33 (2-year); MVI: 9 (2-year)	SBRT + sorafenib: 9	–	SBRT + sorafenib: 3.5	–	28 (18-month)	37	Median TTP: SBRT + sorafenib 9.5 months	SBRT improved outcomes over sorafenib alone; phase III RCT
Metastatic liver tumors																						
Hoyer, 2006 (94)	64	Metastases: 100% colorectal	33% liver-directed therapy	–	–	50	–	3.5 [1–9]	2 [1–6]	45	3	19	67	38 (2-year), 22 (3-year), 13 (4-year)	–	19 (2-year)	3	–	–	Tumor: 80 (2-year); patient: 64 (2-year)	Median TTP: 6.5 months, DM: 14	Prospective trial
Katz, 2007 (95)	69	Metastases: 29% colorectal, 23% breast, 13% pancreas, 7% lung, 7% HCC, 7% carcinoid	–	–	–	15	–	3 [1–12]	2.5 [1–6]	48 [30–55]	5	14.5	–	–	–	46 (6-month), 24 (1-year)	0	–	–	76 (10-month), 57 (20-month)	Intrahepatic out-of-field: 75, DM: 4	Retrospective
Milano, 2008 (96)	121	Metastases: 30% colorectal, 29% breast, 13% lung, 3% pancreas or biliary, 2% HCC	–	–	–	–	–	<6–8	1–5, 293 total	30–60	1–6	–	–	–	–	–	–	–	–	77 (2-year), 73 (4-year)	–	Larger tumors lead to worse LC. Primary pancreatic, biliary, colorectal, or liver cancer exhibited significantly poorer LC, whereas metastatic breast lesions were better controlled; prospective

Table 2 *(continued)*

Table 2 *(continued)*

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Median follow up (months)	Tumor volume (cc)	Tumor diameter (cm)	Lesion number (per patient)	Dose (Gy)	Fractions	Survival					Toxicity (grade ≥3) (%)	Response		LC, 1-year (%)	Metastases (%)	Comments
				CP/BCLC	Hepatitis							Median OS (months)	1-year OS (%)	>1-year OS (%)	Median PFS (months)	PFS (%)		Response rate (%)	Complete response (%)			
Ambrosino, 2009 (97)	27	Metastases: 41% colorectal, 37% pancreas, 7% breast, 100% inoperable	–	–	–	13	69 [20–165]	1–6	1–3	36 [25–60]	3	–	–	–	–	–	0	74	26	74	Intrahepatic out-of-field: 11, DM: 15	No relationship was found between age, tumor volume, irradiated volume, or dose and post-treatment LC; phase I/II
Lee, 2009 (81)	68	Metastases: 59% colorectal, 18% breast, 23% other, 100% inoperable	–	–	–	11	75 [1–3,100]	<6–8	1–5	42 [28–60]	6	18	–	47 (18-month)	4	–	9 acute, 3 late (grade 4–5)	–	–	71	Intrahepatic out-of-field: 32, DM: 50	6-fraction SBRT is safe and effective; phase I
Rusthoven, 2009 (98)	47	Metastases: 32% colorectal, 21% lung, 8.5% breast, 6% ovarian, 6% esophageal, 45% extrahepatic disease	69% chemo	–	–	16	–	3 [0.5–6]	1–3, 63 total	Phase I: 36–60 escalation; phase II: 60	3	20.5	–	–	95 (median 7.5 months)	–	2	–	–	95; 92 (2-year); 100 (<3 cm)	–	Phase I/II
van der Pool, 2010 (99)	20	Metastases: 100% colorectal; not candidates for surgery or RFA	–	–	–	26	–	2.5 [1–6]	1–3, 31 total	37.5–45	3	34	100	83 (2-year)	–	–	10	–	–	100, 74 (2-year)	–	Size did not predict outcome. Prospective trial
Rule, 2011 (100)	27	Metastases: 44% colorectal, 11% carcinoid, 7% pancreas, 7% renal, 7% melanoma, 4% gastric, 4% ovary, 37% extrahepatic disease	44% liver-directed therapy, 81% prior chemo	–	–	20	–	>10	1–5	30–60	3–5	37	–	2-year: 50 (60 Gy), 67 (50 Gy), 56 (30 Gy)	–	–	0	–	–	100 (60 Gy), 89 (50 Gy), 56 (30 Gy)	–	700 cc of normal liver was constrained to <21 Gy. No DLT was observed. Phase I dose-escalation
Chang, 2011 (101)	65	Metastases: 100% colorectal	72% prior chemo	–	–	1.2 years	30 [0.5–3,088]	–	1–4, 102 total	42 [22–60]	1-3	–	72	38 (2-year)	–	–	3 acute, 6 late	–	–	90 (46–52 Gy in 3 fractions); 84 (≥42 Gy); 48 (<42 Gy)	–	Extra-hepatic disease predicted OS. Dose and dose-per-fraction predicted LC
Scorsetti, 2013 (102)	61	Metastases: 46% colorectal, 18% breast, 36% other	46% prior liver-directed therapy, 83% prior chemo	–	–	12	–	≤6	1–3, 76 total, 79% with 1 lesion	75	3	19	84	–	–	95	2 late	–	–	94	Intrahepatic out of field: 41, DM: 54	Phase II
Aitken, 2014 (82)	34	Metastases: 79% colorectal, 12% breast	40% prior liver-directed therapy, 80% prior chemo	–	–	15	73 [2–614]	5 [2–13]	1–3, 46 total	30–60 dose guided by liver-toxicity risk	10	14.5	60	38 (2-year)	–	29 (1-year), 16 (2-year)	0%	–	–	64, 45 (2-year)	Median time to distant progression: 5 months; DM: 76	Tumor size ≤60 cm and BED_{10} >50 Gy improved time to local failure. GTV size ≤60 cc and liver-only disease improved OS; retrospective

Table 2 *(continued)*

Table 2 *(continued)*

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Median follow up (months)	Tumor volume (cc)	Tumor diameter (cm)	Lesion number (per patient)	Dose (Gy)	Fractions	Survival					Toxicity (grade ≥3) (%)	Response		LC, 1-year (%)	Metastases (%)	Comments
				CP/BCLC	Hepatitis							Median OS (months)	1-year OS (%)	>1-year OS (%)	Median PFS (months)	PFS (%)		Response rate (%)	Complete response (%)			
Stintzing, 2013 (103)	60, single-fraction SBRT or RFA	Metastases: 100% colorectal	57% surgery, 72% chemo	–	–	23	–	3 [0.7–5]	1–2, 70 total	–	–	34	–	–	34 (DFS)	–	0	–	–	SBRT: 85, 80 (2-year)	SBRT: median FFDR: 7 months	Prospective trial
Andratschke, 2015 (104)	74	Metastases: 50% colorectal, 16% breast, 7% esophageal, 27% other, 47% extrahepatic	48% chemo	–	–	15	123 [11–1,074]	1 [1–4]	1–2, 91 total	15–62	3–5	27	77	30 (3-year), 27 (5-year)	–	–	0	–	–	75 (1-year), 48 (3-year)	DM: 55	BED (>120 Gy) was prognostic for better LC. Tumor volume predicted survival; retrospective
Mixed liver tumors																						
Herfarth, 2001 (105), 2004 (106)	37	2% HCC, 5% IHC, 93% metastases: 53% colorectal, 25% breast, 7% lung, 7% sarcoma	–	–	–	6	10 [1–132]	<6–8	1–4, 60 total	14–26	1	–	72	–	–	–	0%	79 (6-month)	16 (6-month)	81 (18-month)	–	Tumor size predicted LC; phase I/II
Méndez Romero, 2006 (107)	25	32% HCC, 68% metastases: 88% colorectal, 6% breast, 6% lung. Unsuitable for other treatment, 38% PVT	–	HCC: 62% CP-A, 38% CP-B	–	13	22 [1–322]	3 [0.5–7]	2, total: 34 metastases, 11 HCC	Group 1: metastases, HCC without cirrhosis, or HCC <4 cm w/cirrhosis: 37.5; group 2: HCC ≥4 cm and cirrhosis: 25 or 30	Group 1: 3; group 2: 5 or 10	–	Metastases: 85; HCC: 75	Metastases: 62 (2-year); HCC: 40 (2-year)	–	Metastases: 94 (1-year); HCC: 82 (1-year)	Acute 16%; 4% grade 5; 12% of mets with grade 3 toxicity	–	–	94, 82 (2-year)	–	Use extreme caution with CP-B patients because of high toxicity risk; phase I/II
Wulf, 2006 (108)	44, low dose SBRT, (11% HCC, 89% metastases), high dose SBRT (7% HCC, 93% metastases	11% HCC, 89% metastases: 45% colorectal, 21% breast, 8% ovarian, 25% other	–	–	–	15	–	–	Total: 5 HCC, 51 metastases	Low dose: 30 in 3 fractions or 28 in 4 fractions; high dose: 36 in 3 fractions, 37.5 in 3 fractions, or 26 in 1 fraction	1–4	–	72	32 (2-year)	–	–	0	–	–	HCC: 100 (1- and 2-year). Metastases: 92, 66 (2-year). Low dose: 86, 58 (2-year). High dose: 100, 82 (2-year)	HCC: 60% intrahepatic out-of-field: 60, freedom from systemic progression: 35 (1-year), 19 (2-year)	Higher dose was the only factor that predicted LC. 2 local failures (ovarian cancer, breast cancer) were marginal and 7 local failures were in-field (1 kidney cancer, 6 CRC). All colorectal local failures were in the low dose group. Retrospective
Goodman, 2010 (109)	26	35% HCC, 19% IHC, 73% metastases: 32% colorectal, 16% pancreatic, 10% ovarian, 10% gastric	–	–	–	17	33 [1–147]	≤5	1–2, 40 total	18–30	1	29	71 (primary liver); 62 (metastases)	54 (primary liver, 2-year); 50 (metastases, 2-year)	–	–	0	–	–	64	Intrahepatic out-of-field: 30, DM: 26	Single-fraction SBRT is safe, effective, and feasible for lesions ≤5 cm; phase I dose-escalation

Table 2 *(continued)*

Table 2 *(continued)*

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Median follow up (months)	Tumor volume (cc)	Tumor diameter (cm)	Lesion number (per patient)	Dose (Gy)	Fractions	Survival					Toxicity (grade ≥3) (%)	Response		LC, 1-year (%)	Metastases (%)	Comments
				CP/BCLC	Hepatitis							Median OS (months)	1-year OS (%)	>1-year OS (%)	Median PFS (months)	PFS (%)		Response rate (%)	Complete response (%)			
Lanciano, 2012 (110)	30	23% HCC, 77% metastases: 65% colorectal, 13% breast, 9% lung, 13% other	37% liver-directed therapy, 87% chemo	–	–	22	25 [0.5–316]	–	1–4	36–60,700 cc of normal liver ≤15 Gy	3	20	73	31 (2-year); 2-year: 21 (low-dose), 42 (high-dose)	–	–	4	–	–	64; 81 for BED >100 Gy, 45 for BED ≤100 Gy; 2-year LC: 75 for BED >100 Gy, 38 for BED ≤100 Gy	DM: 73	BED predicted LC
Dewas, 2012 (111)	120	35% HCC, 5% IHC, 60% mixed metastases, 100% ineligible for local therapy	26% surgery, 52% chemo	HCC: 86% CP-A, 14% CP-B	–	15	32 [0.2–500]	3 [0.5–11]	1–2, 153 total	27–45	3–4	–	–	–	–	–	0	–	–	84, 75 (2-year); IHC: 100, HCC: 90 (1- and 2-year), metastases: 81 (1-year), 72 (2-year)	Median time to recurrence: HCC: 4 months, metastases: 7 months, IHC: 14 months; intrahepatic out-of-field: HCC: 7, metastases: 25, IHC: 33	Dose >45 Gy, tumor diameter <5 cm, and volume were prognostic for LC; phase I/II
Klein, 2015 (112)	222	48% HCC, 10% IHC, 42% mixed metastases	–	95% CP-A, 5% CP-B	18% HBV, 19% HCV	1–5 years	133 [1–3,115]	–	–	24–60	6	17; IHC: 12, HCC: 17, metastases: 18	58	34 (2-year)	–	–	–	–	–	–	–	SBRT temporarily worsens appetite and fatigue, not overall QOL, with symptom recovery at 3 months. At 1-year, 21% of patients improved QOL, while 46% maintained stable QOL, both relative to baseline. Tumor size and QOL influenced survival. OS and QOL did not differ by pathology. prospective

Data are presented as median, median [range], or n. SBRT, stereotactic body radiotherapy; CP-A/B, Child-Pugh A/B; BCLC, Barcelona Clinic Liver Cancer; Gy, Gray; OS, overall survival; PFS, progression-free survival; LC, local control; HCC, hepatocellular carcinoma; NTCP, normal tissue complication probability; DM, distant metastases; MVI, macrovascular invasion; TACE, transarterial chemoembolization; CRT, chemoradiotherapy; IVCTT, inferior vena cava tumor thrombus; HBV, hepatitis B virus; HCV, hepatitis C virus; TTP, time to progression; 3DCRT, three-dimensional conformal radiotherapy; RT, radiotherapy; BED, biologically effective dose; DSS, disease-specific survival; RCT, randomized controlled trial; PVT, portal vein thrombosis, ECOG, Eastern Cooperative Oncology Group; chemo, chemotherapy; RFA, radiofrequency ablation; DLT, dose-limiting toxicity; GTV, gross tumor volume; DFS, disease-free survival; FFDR, freedom from distant recurrence; IHC, intrahepatic cholangiocarcinoma; mets, metastasis; CRC, colorectal cancer; QOL, quality of life.

metastases, including many who received prior treatment, have also shown good outcomes using a range of SBRT doses (36–60 Gy in 1–6 fractions), with higher doses associated with improved LC (2-year LC 75–95% *vs.* 38% for lower doses) as long as ≥700 cc of normal liver was preserved for non-cirrhotic patients (81,87,91,94,96,98,101,103,106,110). Higher LC was also observed with higher doses in HCC, leading to the most recent ASTRO guidelines recommending a biologically effective dose (BED) of 65 Gy (20,21,117).

For patients with many prior treatments (91), advanced comorbidities, or liver disease (e.g., BCLC-B/C, CP-B, or vascular invasion), durable LC (up to 74% at 1 year) and effective palliation may still be achieved with lower SBRT doses (93). For example, CP-B patients (107) have seen tumor responses with SBRT doses of 24–28 Gy in 5 fractions (24,86).

The recent randomized RTOG 1112 trial evaluated the addition of SBRT (27.5–50 Gy in 5 fractions, individualized by normal-liver dose) to sorafenib for patients with BCLC-B (intermediate) or C (advanced) HCC, with 82% categorized as BCLC-C, and 4% having metastases outside the liver. In the trial, OS (median 16 months SBRT and sorafenib *vs.* 12 months sorafenib) and PFS (median 9 months SBRT and sorafenib *vs.* 5 months sorafenib) was improved by adding SBRT to sorafenib with no difference in toxicity (3.5% *vs.* 5% sorafenib alone), with particular benefit noted in patients with more advanced disease, suggesting SBRT can be considered for advanced or poor-prognosis HCC patients (26). Combining RT or SBRT with other therapies may be more effective than either treatment alone and aggressive treatments may improve palliation and survival in this population.

Studies of QOL also suggest that liver SBRT is well-tolerated. Common effects included temporary worsening of appetite and fatigue, with symptom severity generally recovering to baseline levels within 3 months after SBRT completion (112). Other potential adverse effects of SBRT can include nausea and vomiting, decline in liver function, esophagitis (16–18%), and gastroesophageal bleeding or ulceration (10,81,89,118).

Based on available evidence, SBRT can be considered primarily in settings of good liver function (CP ≤ B7) with up to 3 lesions with the sum of diameters ≤6 cm. This recommendation reflects the recent ASTRO guidelines which recommend selecting SBRT regimens for HCC patients based on CP score: CP-A patients should receive 40–50 Gy in 3–5 fractions, while 30–40 Gy in 5 fractions is recommended for CP-B7 patients (20,22,24). Given the increased risks from SBRT for patients with poor liver function or other risk factors, de-intensification modifications like longer fractionations, different dosing, or non-stereotactic techniques (discussed further below) may be considered.

SBRT and PVT

Vascular tumor invasion (also known as MVI), such as PVT or into the inferior vena cava, is common with HCC (10–40% at initial diagnosis) (12,20,34,119,120). Invasion may cause portal hypertension, ascites, tumor spread, reduced liver function, and destruction of collateral circulation, thereby limiting local therapies like TACE, TAI, Y-90, or surgery, precluding patients from lying flat for any RT. Some affected patients may require diuretics, drainage, or shunt before they can be considered for RT (121-123). Prognosis with PVT or MVI is poor, with MS <4 months without treatment (92,124-127), and systemic therapies are currently considered standard of care (12,20,34,119,120).

SBRT has shown good outcomes for HCC patients with PVT, with LC rates >80% and 1-year OS 43–50% with rates of grade 3 toxicity <10% (mostly bilirubin elevation or bone marrow suppression) (69,83,87,90,126). Another analysis suggested BED >65 Gy, AFP <200 ng/mL, single tumors, and ECOG PS predicted for OS, so these factors may be used to help select treatment for patients (92).

Given the severity of symptoms from PVT (large vascular tumor thrombi block portal blood flow and cause progression of liver dysfunction and ascites), recanalization and LC are important palliative outcomes in these patients. Studies suggest significant improvement in portal vein recanalization with SBRT compared with conventionally-fractionated RT (33% *vs.* 15%), as well as improved MS (11 *vs.* 5 months), and 2-year OS (15% *vs.* 8%) (92). Higher dose and better thrombus targeting may further improve survival rates (128), as may combining therapies like TACE and hypofractionated RT, which significantly improved median PFS (12 *vs.* 31 weeks) and OS (43 *vs.* 55 weeks) when compared with sorafenib alone in a randomized trial (27).

As mentioned previously, 74% of HCC patients in the RTOG 1112 randomized trial had MVI, and OS, PFS, and time to progression (TTP) were significantly improved by adding SBRT to sorafenib with no difference in toxicity. Patients with PVT saw an estimated 24-month OS rate of 28% [95% confidence interval (CI): 16–41%] when receiving sorafenib plus SBRT (*vs.* 9% when receiving sorafenib alone). This provides compelling evidence that incorporating SBRT into therapy for patients with advanced

liver cancer not only provides effective LC, but also extends survival (26). Other combination therapies, such as RT with catheter-based therapies, are being investigated for patients with poor-prognosis or palliative-intent treatments, leading to conditional recommendations in recent ASTRO guidelines (20,27,129). Goals of care and willingness to risk potential toxicity (e.g., gastrointestinal) should inform any consideration of SBRT in combination with other treatments (130,131).

SBRT and large lesions

Larger liver tumors (e.g., ≥10 cm) present challenges in all pathologies for minimizing dose to normal liver and adjacent structures. Large lesions may also be RT-resistant due to hypoxia and therapy-resistant clonogens (82,102,111,132). Nevertheless, as shown in *Table 2*, good outcomes have been reported treating large lesions with SBRT doses of 26–54 Gy in 5–6 fractions: 1-year LC up to 90%, 1-year OS up to 50%, and grade 3 toxicity around 12%. Local and regional recurrence remain the major failure patterns, however, SBRT remains a palliative and definitive option for select patients with large liver tumors as long as sufficient liver volumes (≥700 cc) are spared (66,84,88,100,104,133).

SBRT recommendations

Although not currently endorsed by multi-disciplinary guidelines such as the National Comprehensive Cancer Network (NCCN), we believe that SBRT can be considered as a treatment option alongside RFA, systemic therapy, and TACE for definitive or palliative HCC patients with unresectable disease who are not candidates for liver transplantation. For HCC patients with intra-hepatic tumors <3 cm and away from large vessels, SBRT and RFA have demonstrated similar outcomes. However, with larger or multiple lesions, or those close to blood vessels, we recommend SBRT due to higher LC and lower toxicity (134,135). Surgery, RFA, or SBRT may be considered for smaller lesions. TACE may be considered for HCC patients with CP-A or CP-B liver function without metastases, extra-hepatic disease, or vascular invasion.

SBRT can also be considered for patients with recurrence after TACE (20), and represents the best palliative option for larger lesions that are still amenable to SBRT (20,22). As lesions become larger, more numerous, involve MVI, or as prognosis or liver function worsens, SBRT can still be considered for definitive or palliative treatment, as this is a spectrum of disease in which the improved control and survival benefits of SBRT can benefit the patient.

When treating with SBRT, doses should be individualized with a total dose of 30–50 Gy given in 3–5 fractions for HCC (20-22,24,25,117), and up to 60 Gy in 3-5 fractions for liver metastases. These doses should be considered for maximum benefit in palliative or symptomatic patients if they can tolerate it and normal-tissue liver constraints are met. Single-fraction SBRT (18–30 Gy) may be considered for lesions ≤5 cm if patients cannot tolerate a multi-fraction course. SBRT should be considered on a cautionary basis for patients with poor liver function, such as CP-B in HCC. These patients may still benefit from lower doses, such as 25 Gy in 5 fractions or 30–35 Gy in 3 fractions.

For patients with multiple (>5) or large volume (>10 cm) lesions, SBRT may still be considered for palliative treatment if liver function is adequate (e.g., CP-A). Tumor size >60 cc may be associated with worse LC. In these cases, systemic therapy may be preferred, such as atezolizumab [anti-programmed death ligand 1 (PD-L1) agents], bevacizumab [anti-vascular endothelial growth factor (VEGF) agents], or sorafenib for HCC, or other appropriate systemic therapy depending on cancer histology for metastatic disease. TACE is not recommended for HCC >10 cm or with PVT; SBRT can be considered in these conditions, but with potentially increased toxicity and lower LC rates. Conditional ASTRO recommendations suggest combination therapy with TACE. Combining SBRT and systemic therapy may improve outcomes for this relatively-common, high-risk subgroup.

Respiratory-motion management and image-guided daily treatment should be used (20), and understanding these set-up requirements is crucial for selecting appropriate SBRT patients. Regardless of indication, when planning liver SBRT, care must be taken to spare sufficient normal liver from radiation exposure. One popular method is to ensure that least 700 cc of normal-liver tissue, sometimes called "liver minus gross tumor volume (GTV)", receives a maximum BED of 30–32 Gy in 2 Gy fractions (20,23). Alternatively, radiobiology-guided dose escalation based on mean liver dose may be used, as pioneered by Dawson *et al.* and used in RTOG 1112 (136).

Treatment as part of clinical trials should be encouraged where possible. Multi-disciplinary decision making is key when attempting to utilize definitive techniques to maximize palliation and clinical outcomes in palliative or poor-prognosis patients.

Charged particle radiotherapy (CPRT)

CPRT, such as protons or carbon ions, may improve liver sparing compared with photon SBRT techniques, permitting dose escalation. These techniques employ the Bragg peak, a phenomenon whereby dose is deposited within a narrow range and specific depth based on initial energy, with minimal dose deposited beyond the target (137). This phenomenon can allow better sparing of uninvolved liver and nearby critical organs (138). Given potential for improved normal-liver sparing, CPRT may also allow safer treatment of patients with compromised liver function (e.g., CP-B or CP-C).

Prospective CPRT trials have suggested favorable outcomes with 5-year OS approximately 50% for one HCC cohort treated with conventional-fractionation proton therapy, including around 25% for poor-prognosis CP-B and CP-C patients (139,140). Another study of poor-prognosis HCC patients (47% CP-B; 24% CP-C) treated with hypofractionated proton therapy demonstrated median PFS and OS of 36 and 18 months, respectively (141).

Proton therapy has demonstrated efficacy in HCC patients with large tumors >5 cm or multiple tumors >3 cm each, with prospective data suggesting median PFS 36 months without grade ≥3 toxicities (141). Randomized data comparing hypofractionated proton therapy (70.2 Gy in 15 fractions) to TACE alone in HCC patients showed fewer hospitalizations and re-treatments, and trends to better LC (88% *vs.* 35%, P=0.06) and PFS (48% *vs.* 31%, P=0.06) without significant difference in OS for proton therapy (142). Across a variety of fractionation schemes, including SBRT, similar outcomes have been shown with proton therapy and carbon-ion therapy for CP-B and CP-C HCC patients, with 5-year LC of 90–93% and OS 36–38% (143).

As with photon RT, dose and fractionation for CPRT must be tailored based on goals of care and proximity to normal structures and uninvolved liver-tissue volume. A phase II multi-institutional trial delivered hypofractionated proton therapy to doses of 67.5 Gray equivalents (GyE) in 15 fractions for peripheral tumors and 58.05 GyE in 15 fractions for central tumors, while keeping mean liver dose ≤24 GyE. Treatment was well tolerated with this risk-adjusted dosing approach in a population of patients with large primary liver tumors (diameter range, 2–12 cm) and PVT in 30% of patients. Two-year OS rates were 63% for HCC, and 2-year LC 95%. Only 4% of patients saw a decline in liver function from CP-A to CP-B, and only 5% of patients experienced grade ≥3 toxicity (144). More randomized trials and cost-effectiveness data are needed before further recommendations can be made regarding CPRT for palliative patients.

Partial-liver and WLRT

Some patients who may benefit from dose-escalated tumor RT are not good candidates for SBRT. These include patients with guarded prognosis, poor PS, extensive disease, small normal-liver volumes, need for urgent RT start, or inability to tolerate SBRT setup requirements. Partial-liver RT with conventional fractionation (i.e., smaller daily fraction-sizes that allow normal-tissue recovery, usually 1.8–2 Gy, delivered over a longer treatment course to a total dose that provides tumor control) may be a better option for these patients.

Table 3 summarizes studies that suggest reasonable rates of portal-vein recanalization for conventional RT, although worse than with SBRT (92). These studies employed either hypofractionated RT (2–5 Gy per fraction to balance patient convenience, more dose per fraction, and normal-tissue healing) or conventional (1.8–2 Gy per fraction) planning techniques and fractionations. Using a range of total doses (35.4–71.5 Gy), most studies suggest radiologic response and 1-year LC rates up to 90% and 1- and 2-year OS rates around 50% and 25%, with low toxicity (grade ≥3 1–10%). These are favorable results for a population that historically has been without good treatment options due to poor prognosis from factors including CP-B liver function, limited liver reserve, elevated AFP (≥400 μg/L), multiple tumors, distant metastases, severe symptoms, poor PS, or other factors (117,153,156). Studies support better responses using higher doses for HCC patients treated with partial-liver 3DCRT with 2-year OS rates of 31% for doses >53.1 Gy *vs.* 22% for lower doses (47,145,149-151,154). Palliative 3DCRT to symptomatic primary HCC tumors and/or symptomatic MVI is now conditionally recommended by ASTRO "alone or sequenced with systemic therapy or catheter-based therapies in the setting of locally advanced and metastatic HCC" (20,117,153,156).

Some advanced or poor-prognosis patients may be better served by low-dose WLRT (51), a palliative-intent regimen that can lead to symptom relief and tumor debulking, and has rapid planning and treatment times (136,157-159). These considerations must be balanced with sufficient RT dose for durable disease or symptom control, since mean liver doses (in 2 Gy fractions) of 28 Gy for primary liver cancer and 32 Gy for metastases are associated with 5% classic RILD risk (136,158-162). *Table 4* summarizes WLRT studies, which suggest effective palliation for primary and metastatic

Table 3 Partial-liver 3DCRT for liver tumors

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Follow-up (months)	Tumor diameter (cm)	Dose (Gy)	Fractions, n	Survival				Toxicity (grade ≥3) (%)	Response		LC, 1-year (%)	Metastases (%)	Comments
				CP/BCLC	Hepatitis					Median OS (months)	1-year OS (%)	>1-year OS (%)	PFS (%)		Response rate (%)	Complete response (%)			
Primary liver cancer																			
Seong, 2000 (116)	27	HCC, inoperable, 27% multi-nodular, 18% MVI	100% TACE	63% CP-A, 37% CP-B	74% HBV	9–48	7±3	52±8	25–33	14	56	36 (2-year), 21 (3-year)	–	0	66.7	–	63	Intrahepatic out-of-field: 37, extrahepatic: 15	RT induced a substantial tumor response; phase II
Guo, 2003 (145)	165, TACE, 3DCRT	HCC, large, inoperable, 33% multifocal, 22% PVT	–	83% CP-A, 17% CP-B	–	26	Tumor: liver volume ratio <0.7:1	30–50	15–28	–	TACE + RT: 64	TACE + RT: 29 (3-year), 19 (5-year)	–	0	TACE + RT: 47	–	–	–	Tumor extension, RT, and CP-status predicted survival; retrospective
Liu, 2004 (146)	44	HCC, 32% PVT, 72% massive (>5 cm)	100% TACE	73% CP-A, 27% CP-B, 48% Okuda I, 50% Okuda II, 2.3% Okuda III	79% HBV, 20% HCV	8.3	16 (36%) <5, 16 (36%) 5–10, 12 (27%) >10	50 [40–60]	22–33	15	61	40 (2-year), 32 (3-year)	–	0	61	–	–	Intrahepatic out-of-field: 43, DM: 14	Okuda stage, PVT, pretreatment AFP, and total RT dose predicted survival
Zeng, 2004 (147)	203, TACE, 3DCRT	HCC, inoperable	–	–	–	–	–	–	–	–	TACE + RT: 72	TACE + RT: 42 (2-year), 24 (3-year)	–	0	TACE + RT: 76	–	–	–	Intrahepatic failure lower in TACE + RT; retrospective
Mornex, 2006 (47)	27	HCC, cirrhotic, not suitable for other curative treatment	100%	60% CP-A, 40% CP-B	11% HBV, 33% HCV	29±9	1 nodule ≤5 cm, or 2 nodules ≤3 cm	66	33	–	–	41% (3-year)	–	CP-A: 19, CP-B: 22	92	80	78 (3-year)	Intrahepatic out-of-field: 41 (7-month)	3DCRT was well-tolerated in cirrhotic patients, but with caution for CP-B; prospective, phase II
Zhou, 2007 (148)	50, 3DCRT, TACE	HCC	–	–	–	16 [3–57]	–	43±6, mean dose to normal liver 19 ±6	18–25	17	60	38 (2-year), 28 (3-year)	74 (1-year), 57 (2-year), 38 (3-year)	6	18	0	–	DM: 15 (1-year), 21 (2-year), 40 (3-year)	Dose, T-stage, and cirrhosis predicted survival; phase II
Seong, 2009 (149)	398	HCC, 41% PVT	100%; 78% TACE	59% CP-A, 22% CP-B, 0.5% CP-C, 50% Okuda III, 28% Okuda IV	–	12 [0.4–42]	6 [1–24]	≥45; 247 (62%) >45	–	12	–	28 (2-year), high dose: 31 (2-year), low dose: 22 (2-year)	–	0	–	–	–	Intrahepatic out-of-field: 34, DM: 7	CP-A, tumor <5 cm, node-negative, and greater dose improved prognosis; retrospective
Oh, 2010 (150)	40, 3DCRT	HCC, inoperable, 25% PVT	100%	90% CP-A, 10% CP-B	–	18 [4–32]	–	54	18	–	72	46 (2-year)	–	0	63	21	78	Intrahepatic out-of-field: 40, extrahepatic: 33	Tumor size <5 or ≥5 cm and AFP levels predicted survival; phase II
Ren, 2011 (151)	40, 3DCRT or IMRT with TACE	HCC	–	100% CP-A	93% HBV	13	10 [5–16]	62 (<10), 52 (>10)	26–31	–	72	62 (2-year)	In-field: 93 (2-year), local 44 (2-year)	0	–	–	–	DM: 6 (1-year), 15 (2-year)	No DLT was reached. RT dose was safely escalated in HCC using 3DCRT or IMRT; phase I/II
Yoon, 2018 (27)	90, TACE + 3DCRT, sorafenib	HCC, poor prognosis, 100% PVT, 79% multiple lesions	0%	100% CP-A	84% HBV	≤32	10	45	15–18	14	55	–	87 (12-week)	1	33 (24-week)	–	–	–	Curative surgical resection was conducted for 11.1% of the TACE-3DCRT group owing to downstaging. MVI was a route for distant spread; phase III randomized controlled trial
Kim, 2019 (152)	639, TACE, 3DCRT	HCC, 100% MVI, 63% multiple lesions, 26% extra-hepatic disease	0%	62% CP-A, 38% CP-B, 100% BCLC-C	87% HBV	–	10 [1–23]	39 [24–50]	5–25	11, low-risk: 85, high-risk: 6	46	24 (2-year)	–	10	–	–	–	–	Tumor size >10 cm, extrahepatic metastasis, CP-B status, AFP >150,000 ng/mL, and RT dose ≤40 Gy were significant survival predictors; retrospective

Table 3 *(continued)*

Table 3 *(continued)*

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Follow-up (months)	Tumor diameter (cm)	Dose (Gy)	Fractions, n	Survival				Toxicity (grade ≥3) (%)	Response		LC, 1-year (%)	Metastases (%)	Comments
				CP/BCLC	Hepatitis					Median OS (months)	1-year OS (%)	>1-year OS (%)	PFS (%)		Response rate (%)	Complete response (%)			
Lou, 2019 (153)	75, 3DCRT	HCC, 100% MVI to inferior vena cava or right atrium	100%	88% CP-A, 12% CP-B, 100% BCLC-C	92% HBV	12 [3–40]	–	38 [30–48]	8–16	10, 87% of deaths from intrahepatic tumor progression	38	13 (2-year), 5 (3-year)	–	0	96	23	24	Intrahepatic out-of-field: 24	Factors predicting poor survival were CP-B liver function, AFP ≥400 μg/L, intrahepatic multiple tumors, distant metastases, only the TT as the target, a BED <55 Gy and no chance of further RT; retrospective
Rim, 2020 (117)	49, 3DCRT	HCC, poor-prognosis, MVI—inferior vena cava or right atrium	0%	84% CP-A	78% HBV, 12% HCV	9 [1–12]	10 [1–20]	47 [35–72]	17–36	10	43	30 (2-year)	–	–	–	–	89, 74 (2-year)	Intrahepatic out-of-field: 35, DM: 43	Significant factors affecting OS were AFP ≥300 ng/mL, tumor multiplicity, and patient volume of institutions; phase II
Metastatic liver tumors																			
Robertson, 1995 (154)	22, 3DCRT, intrahepatic floxureidine	Metastases: 100% colorectal, ineligible for other local therapy, 37% >3 lesions	64%	–	–	42	>10	48–73, per normal liver spared	31–49	20, 14 if extrahepatic disease at presentation	60	35 (2-year)	–	Acute: 18, late: 60	–	–	–	–	There was risk of increased toxicity for CP-B or CP-C patients. Response was not durable, and hepatic progression was frequent; phase I/II
Mixed liver tumors																			
Ben-Josef, 2005 (155)	128, NTCP-adapted 3DCRT, intra-hepatic floxuridine	Metastases: 36%, all colorectal, primary: 27%, HCC, 36%, cholangiocarcinoma, inoperable, life expectancy >12 weeks	–	–	–	16	Large	61 [40–90] per NTCP RILD risk	27–60 BID	16, 14 primary, 17 metastases	57	17 (3-year)	–	30	–	–	–	–	Higher doses (≥75 Gy) were associated with increased survival for all pathologies. There was no significant survival differences by pathology, only by dose; phase II

Data are presented as mean ± standard deviation or median [range]. CP-A/B, Child-Pugh A/B; BCLC, Barcelona Clinic Liver Cancer; Gy, Gray; OS, overall survival; PFS, progression-free survival; LC, local control; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; TACE, transarterial chemoembolization; HBV, hepatitis B virus; RT, radiotherapy; 3DCRT, three-dimensional conformal radiotherapy; PVT, portal vein thrombosis; HCV, hepatitis C virus; DM, distant metastases; AFP, alpha-fetoprotein; IMRT, intensity-modulated radiotherapy; DLT, dose-limiting toxicity; TT, tumor thrombus; BED, biologically effective dose; NTCP, normal tissue complication probability; RILD, radiation-induced liver disease; BID, twice a day.

liver tumors (55–95% at 2 weeks post-treatment) and 3–9 months response durations using a range of doses (e.g., 10 Gy in 2 fractions, 8 Gy in 1 fraction, or 20–33 Gy in 1.5–3 Gy fractions) (17,28,29,158,159,161,163-168,171-174). A dose-response relationship has been suggested with lower rates (~50%) of symptom improvement reported with doses 8–10 Gy and up to 90% for higher doses. Better response to RT may also predict longer response duration and clinical outcomes (161). Treatment with 33 Gy was associated with a 10% rate of late liver injury (171).

Combining WLRT with radiosensitizing agents to sensitize hypoxic cancer cells to radiation has been hypothesized to improve palliation. A phase I trial evaluating dose-escalated sorafenib combined with SBRT (30–60 Gy in 6 fractions) and WLRT (21.6 Gy in 6 fractions) for extensive liver metastases suggested that full-dose sorafenib can sometimes be combined safely with SBRT, but not with WLRT (175). A large, multi-institutional, prospective study assessing WLRT (21 Gy in 7 fractions) with or without the radiosensitizer misonidazole found no differences in clinical outcomes, with misonidazole significantly increasing nephropathy rates (29). Another phase I trial for patients with advanced cancer treated with WLRT found that intravenous amifostine increased liver tolerance, suggesting utility but future trials are needed to confirm these findings (176).

Partial-liver and WLRT recommendations

Palliative patients of any liver pathology who cannot undergo SBRT may be considered for 3DCRT or WLRT for symptomatic or local disease control. Multi-disciplinary discussion is critical to determine appropriate treatment, goals of care, and patient tolerance for RT setup requirements. Partial-liver 3DCRT attempts tumor dose-escalation and normal-tissue sparing via fractionation and planning techniques for advanced patients with large or multiple tumors or poor-prognosis features, but who can still tolerate extended treatment courses. Conversely, WLRT is reserved for patients with more advanced disease, significantly reduced PS, pain from liver-capsule stretch or rupture, emergency symptom relief, extensive and diffuse liver involvement, wish to minimize treatment time, diffuse infiltration of the liver refractory to systemic treatment, or extremely-guarded prognosis (e.g., <3 months) (177).

WLRT and partial-liver techniques may be faster to initiate than SBRT due to less intense dosimetry requirements and require less treatment time (<20 min), as they do not require breath-hold or motion management. Minimal immobilization and slight head elevation further improve palliative patient comfort. For partial-liver 3DCRT, mean dose to the liver outside the tumor should be kept <28 Gy with ≤30% liver volume exceeding 35 Gy. WLRT is simple to plan (usually 2 RT fields) and generally provides durable pain relief over several weeks. Recommended doses include 8 Gy in 1 fraction, 10 Gy in 2 fractions, or 20–30 Gy in 2–3 Gy per fraction (17,28,29,136,158,159,161,163-168,171-174,178). Recently, ASTRO guidelines conditionally endorsed palliative WLRT to 8 Gy in 1 fraction for pain alleviation and symptom improvement for HCC (20,158).

CPRT is promising but requires further evidence, given relative lack of availability and direct evidence comparing the modalities. If no RT techniques are tolerable or consistent with goals of care, alternatives include systemic therapy (with possible RT later, if disease responds), regional therapies, or hospice/supportive care alone.

Combination therapy with RT

Combining RT with regional or systemic therapy may provide synergy, which has been demonstrated in metastatic renal-cell carcinoma (179). Phase III trials support combining RT with TACE for MVI in HCC (27) and systemic treatments with palliative WLRT (28,29), but evidence should be interpreted with caution and decisions adapted to patient goals and treatment tolerability.

Combining therapies like TACE with SBRT (30–60 Gy in 5–15 fractions) has demonstrated excellent results and favorable toxicity (<10% grade ≥3 toxicity rates) (20,58,85,123,124,152). These studies suggest that combining TACE and partial-liver 3DCRT holds promise for patients with good PS and liver function who are ineligible for SBRT; studies for HCC patients suggest response rates up to 90%, 1-year OS 47–72%, 2-year OS 25–62%, and <20% grade ≥3 toxicity rates (47,117,145-148,150-153,155). Patients with liver metastases treated with partial-liver 3DCRT combined with TACE or chemotherapy have seen response rates of 50–60%, 1-year OS 55–60%, 2-year OS 30–35%, and <13% grade 3 toxicity (145,147,148,150,151,154,155,180). RTOG 1112 demonstrated improved OS, PFS, and TTP by combining SBRT with sorafenib with no toxicity difference, with particular benefit noted in more advanced disease (26).

Studies of chemotherapy and WLRT are generally small and non-randomized, reporting good results for CRT using different systemic therapies combined with a range of doses and fractionations, but with increased toxicity, as seen in *Table 4* (29,154,155,164-167,169,170,181,182). Most studies

Table 4 WLRT for liver tumors

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Follow-up (months)	Dose (Gy)	Fractions	MS (months)	Toxicity (grade ≥3) (%)	Symptom response (%)	Lab response (%)	Radiological response (%)	LC (%)	Response duration (months)	Comments
				CP/BCLC	Hepatitis											
Primary liver cancer																
Yeung, 2020 (161)	52	HCC, inoperable, symptomatic, expected survival ≥1 month, 65% tumor encased >50% liver, 46% extrahepatic disease, 44% PVT	100% TACE	62% CP-A, 39% CP-B; 98% BCLC-C, I, or D	73% HBV, 2% HCV	5 [0.4–30]	8 WLRT	1	4.5 overall, 6.5 for patients who received post-RT treatment	4 (3-month)	52 (1-month): 65 (pain), 35 (abdominal discomfort)	49 (1-month AFP)	15 (3-month)	55 (3-month)	3	WLRT improves QOL for patients with poor prognosis. PVT and ALBI predicted OS. Better symptom responders to RT enjoy a better response duration. retrospective
Metastatic liver tumors																
Turek, 1975 (163)	11	Symptomatic metastases: 36% breast, 27% sarcoma, 18% reticulum cell sarcoma, 9% colorectal, 9% Wilm's tumor; 81% nausea, 36% jaundice, 36% vomit	–	–	–	–	25 WLRT	16–17	–	–	73	–	–	–	9 [2–38]	WLRT, an old technique, offers valuable, tolerable symptom palliation. prospective
Sherman, 1978 (164)	55	Symptomatic metastases: 45% colorectal, 18% breast, 2% lung, 35% unknown primary	25% chemo	–	–	–	24 [15–30] WLRT	8	4.5; 9 for patients who experienced symptom relief	9	90	–	93	–	–	MS with excellent response to RT was comparable to that of regional arterial chemo at the time, but with fewer complications
Herbsman, 1978 (165)	13, intrahepatic 5-FU ± methotrexate, WLRT	Symptomatic metastases: 100% colorectal	–	–	–	–	24–25 WLRT	12	16	0	69	–	–	–	–	Phase I
Webber, 1978 (166)	48, hepatic artery floxuridine infusion ± WLRT	Symptomatic metastases: 50% colorectal, 10% breast, 8% lung, 2% esophagus, 2% pancreas, 2% ovary, 2% gallbladder, 2% carcinoid	–	–	–	–	25 WLRT	10	Median: WLRT: 4.5, chemo: 9, WLRT + chemo: 12; responders lived significantly longer than non-responders	0	WLRT: 28, chemo: 25, WLRT + chemo: 33	–	–	–	–	Primary tumor site, disease duration, and degree of abnormality of liver function had no relationship to the response to treatment. Response lead to better survival. Grade 2 toxicities were mostly related to chemo prospective, uncontrolled, non-randomized
Friedman, 1979 (167)	22, WLRT, intra-hepatic 5-FU and adriamycin	Symptomatic metastases: 86% colorectal, 14% unknown primary	67% chemo	–	–	–	13.5–21 WLRT	4–7	3.5	27	69	–	48	–	3	Phase I
Borgelt, 1981 (168)	109	Symptomatic metastases: 38% colorectal, 25% lung, 13% other gastrointestinal, 24% unknown	–	–	–	–	WLRT: 30.4 or 30 solitary metastases; WLRT: 30, 25.6, 20, or 21 multiple metastases	19 or 15, solitary metastasis; 15, 16, 10, or 7 multiple metastases	2.5	16	7–34 complete; 19–55 partial; 77 within 2 weeks	40	–	–	65–80% of patients: remainder of their lives	74% completed treatment. 25% improved PS. Higher pre-treatment bilirubin levels predicted reduced pain responses and survival. prospective, uncontrolled, non-randomized, feasibility
Barone, 1982 (169)	18, WLRT, intra-hepatic 5-FU or floxuridine	Symptomatic metastases: 100% colorectal	22% chemo	–	–	–	30 WLRT	4 every 4 weeks for 3 cycles, alternate with chemo	8: 26 (LFT's <2× normal, 6 (LFT's >2× normal), P=0.02	28	56; 22 complete	–	–	9 (50%) DM within 12 months of starting therapy	12 (LFT's <2× normal) *vs.* 1.5 (LFT's >2× normal)	Phase I
Byfield, 1984 (170)	28, WLRT intra-hepatic floxuridine	Symptomatic metastases: 100% colorectal, 27% extrahepatic disease at presentation	36% chemo	–	–	–	20–30 WLRT	4 every 2–3 weeks for 3 cycles, alternate with chemo	26 (LFT's <2× normal), 8 (LFT's >2× normal)	3.6 (grade 5)	–	–	–	–	–	Liver dysfunction at initiation of treatment predicted survival. phase I

Table 4 *(continued)*

Table 4 *(continued)*

Author, year	Patients	Diagnosis	Prior treatment	Liver function		Follow-up (months)	Dose (Gy)	Fractions	MS (months)	Toxicity (grade ≥3) (%)	Symptom response (%)	Lab response (%)	Radiological response (%)	LC (%)	Response duration (months)	Comments
				CP/BCLC	Hepatitis											
Leibel, 1987 (29)	187, WLRT ± miso	Symptomatic metastases: 60% colorectal, 15% lung, 7% breast, 18% other	–	–	–	Up to 36	21 WLRT	7	4; WLRT + miso: 7; WLRT: 6	0	54 complete	–	–	–	3: WLRT + miso: 87%, WLRT: 74%	PS improved in 28%. phase III, randomized clinical trial
Wiley, 1989 (28)	37, regional 5-FU ± WLRT	Metastases: 100% colorectal	86% resection, 68% chemo	–	–	–	25.5 WLRT	–	WLRT + 5-FU: 6; 5-FU: 8	Acute: 10 WLRT + 5-FU, 6 5-FU; late: WLRT + 5-FU: 30, 5-FU: 0	–	–	WLRT + 5-FU: 37; 5-FU: 50	–	–	Tumor vascularity and histology grade predicted survival. Low-dose WLRT does not offer a survival advantage and should be for symptom control. randomized, controlled trial
Russell, 1993 (171)	173	Metastases: 75% colorectal, 9% pancreas, 9% stomach; 40% estra-hepatic metastases	–	–	–	–	27–33 WLRT	18–22 BID	4 for 27-, 30-, and 33-Gy arms	Acute: 11, 33-Gy arm only; late: 10, 33-Gy arm only (6-month)	–	–	–	–	–	Larger total RT doses did not prolong survival or decrease progression. PS predicted survival. 33 Gy in BID fractions of 1.5 Gy is unsafe. multi-institutional, dose-escalation, phase I/II
Bydder, 2003 (17)	28	Symptomatic metastases: 96% pain, 68% abdominal distension, 64% nausea, 43% night sweats, 28% vomiting; 56% ECOG ≥2	76% chemo	–	–	–	10 WLRT	2	2.5; 93% (2-week), 57% (6-week), 43% (10-week)	7	54 (2-week); 66 complete (2-week)	–	–	100% died from progressive disease	–	WLRT was simple and effective for symptom palliation. 14% of patients experienced symptom worsening
Edyta, 2015 (172)	27	Symptomatic, massive metastases (each ≥4 cm): 96% pain, 22% weight loss, 77% lack of appetite, 4% night sweats	63% chemo	–	–	At least 24	WLRT: 9–17	5–12	5; 1-year OS 39%	3	100 (4-week), 40 (2-month), 28 (3-month)	–	–	–	–	This simple treatment using older techniques is effective and has current utility for palliation. retrospective
Mixed liver tumors																
Soliman, 2013 (158)	41	51% HCC; 49% metastases; 20% PVT; 25%: liver involved more than 75% of liver	44% chemo, 17% surgery	83% CP-A, 17% CP-B	24% HBV, 5% HCV	12	8 WLRT	1	3-month: 63% overall: 59% HCC, 70% metastases; 6-month: 26% overall: 24% HCC, 35% metastases	2	1-month: 48 overall: 47 HCC, 50 metastases; improvement in symptoms at their worst: 53 HCC, 50 metastases	–	–	–	–	Symptoms improved within 1 month of WLRT for most patients. There were no differences in symptom response by pathology. prospective, phase II, QOL

Data are presented as median, median [range], or n. WLRT, whole-liver radiotherapy; CP-A/B, Child-Pugh A/B; BCLC, Barcelona Clinic Liver Cancer; Gy, Gray; MS, median survival; LC, local control; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis; TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; RT, radiotherapy; AFP, alpha-fetoprotein; QOL, quality of life; ALBI, albumin-bilirubin; OS, overall survival; chemo, chemotherapy; 5-FU, 5-fluorouracil; PS, performance status; LFT, liver function test; DM, distant metastases; miso, misonidazole; BID, twice a day; ECOG, Eastern Cooperative Oncology Group.

of WLRT and systemic therapy report generally favorable results (165-167,170,182). However, one small randomized trial found that adding chemotherapy to WLRT did not improve outcomes (28). Improvements in LC or palliation may still be achievable with radiosensitization, as suggested in a study of NTCP-based RT for large tumors with concurrent hepatic arterial floxuridine (60% response and 17 months MS for metastatic patients) (155). Further data is required to fully evaluate the role of combined RT and systemic therapy in the palliative setting for liver RT.

Conclusions

Prevalence of primary and secondary liver cancer is growing, both of which carry a poor prognosis. Many patients present asymptomatically but may have advanced and/or rapidly progressing disease. Effective treatment is often indicated for symptomatic control or to prevent future symptoms.

New modalities like SBRT allow ablative doses to be safely delivered, including for palliation. Favorable outcomes have been demonstrated for patients with limited tumor burden, good PS, and adequate liver function. The randomized RTOG 1112 trial recently reported significant improvements in clinical outcomes with SBRT and sorafenib for patients with advanced HCC. As prognosis worsens with more advanced disease or if goals of care are palliative or less-intensive treatment modalities, partial-liver or WLRT techniques can be considered for rapid response and symptom relief.

In order to better optimize patient selection, RT techniques, and integration with other therapies, treatment as part of clinical trials, especially randomized studies, should be prioritized. However, the current body of evidence is robust enough to recommend RT alongside other established therapies for primary and secondary liver cancer in palliative settings.

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Footnote

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References

1. Jaffe BM, Donegan WL, Watson F, et al. Factors influencing survival in patients with untreated hepatic metastases. Surg Gynecol Obstet 1968;127:1-11.
2. Befeler AS, Di Bisceglie AM. Hepatocellular carcinoma: diagnosis and treatment. Gastroenterology 2002;122:1609-19.
3. Williams GR, Manjunath SH, Butala AA, et al. Palliative Radiotherapy for Advanced Cancers: Indications and Outcomes. Surg Oncol Clin N Am 2021;30:563-80.
4. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 2006;244:254-9.

5. Nordlinger B, Rougier P. Liver metastases from colorectal cancer: the turning point. J Clin Oncol 2002;20:1442-5.
6. Lochan R, White SA, Manas DM. Liver resection for colorectal liver metastasis. Surg Oncol 2007;16:33-45.
7. Malik HZ, Gomez D, Wong V, et al. Predictors of early disease recurrence following hepatic resection for colorectal cancer metastasis. Eur J Surg Oncol 2007;33:1003-9.
8. Kulik L, El-Serag HB. Epidemiology and Management of Hepatocellular Carcinoma. Gastroenterology 2019;156:477-491.e1.
9. Roayaie S, Jibara G, Tabrizian P, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology 2015;62:440-51.
10. Barry A, Knox JJ, Wei AC, et al. Can Stereotactic Body Radiotherapy Effectively Treat Hepatocellular Carcinoma? J Clin Oncol 2016;34:404-8.
11. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.
12. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-73.
13. Lobo L, Yakoub D, Picado O, et al. Unresectable Hepatocellular Carcinoma: Radioembolization Versus Chemoembolization: A Systematic Review and Meta-analysis. Cardiovasc Intervent Radiol 2016;39:1580-8.
14. Truty MJ, Vauthey JN. Surgical resection of high-risk hepatocellular carcinoma: patient selection, preoperative considerations, and operative technique. Ann Surg Oncol 2010;17:1219-25.
15. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002;359:1734-9.
16. Zhu AX. Hepatocellular carcinoma: are we making progress? Cancer Invest 2003;21:418-28.
17. Bydder S, Spry NA, Christie DR, et al. A prospective trial of short-fractionation radiotherapy for the palliation of liver metastases. Australas Radiol 2003;47:284-8.
18. Smith HS. Opioid metabolism. Mayo Clin Proc 2009;84:613-24.
19. Lock MI, Hoyer M, Bydder SA, et al. An international survey on liver metastases radiotherapy. Acta Oncol 2012;51:568-74.
20. Apisarnthanarax S, Barry A, Cao M, et al. External Beam Radiation Therapy for Primary Liver Cancers: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2022;12:28-51.
21. Lazarev S, Hardy-Abeloos C, Factor O, et al. Stereotactic body radiation therapy for centrally located hepatocellular carcinoma: outcomes and toxicities. J Cancer Res Clin Oncol 2018;144:2077-83.
22. Durand-Labrunie J, Baumann AS, Ayav A, et al. Curative Irradiation Treatment of Hepatocellular Carcinoma: A Multicenter Phase 2 Trial. Int J Radiat Oncol Biol Phys 2020;107:116-25.
23. Su TS, Luo R, Liang P, et al. A prospective cohort study of hepatic toxicity after stereotactic body radiation therapy for hepatocellular carcinoma. Radiother Oncol 2018;129:136-42.
24. Andolino DL, Johnson CS, Maluccio M, et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e447-53.
25. Park S, Jung J, Cho B, et al. Clinical outcomes of stereotactic body radiation therapy for small hepatocellular carcinoma. J Gastroenterol Hepatol 2020;35:1953-9.
26. Dawson LA, Winter KA, Knox JJ, et al. NRG/RTOG 1112: Randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC). J Clin Oncol 2023;41:abstr 489.
27. Yoon SM, Ryoo BY, Lee SJ, et al. Efficacy and Safety of Transarterial Chemoembolization Plus External Beam Radiotherapy vs Sorafenib in Hepatocellular Carcinoma With Macroscopic Vascular Invasion: A Randomized Clinical Trial. JAMA Oncol 2018;4:661-9.
28. Wiley AL Jr, Wirtanen GW, Stephenson JA, et al. Combined hepatic artery 5-fluorouracil and irradiation of liver metastases. A randomized study. Cancer 1989;64:1783-9.
29. Leibel SA, Pajak TF, Massullo V, et al. A comparison of misonidazole sensitized radiation therapy to radiation therapy alone for the palliation of hepatic metastases: results of a Radiation Therapy Oncology Group randomized prospective trial. Int J Radiat Oncol Biol Phys 1987;13:1057-64.
30. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002;35:1164-71.
31. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet

Oncol 2022;23:77-90.
32. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
33. Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821-9.
34. Hack SP, Spahn J, Chen M, et al. IMbrave 050: a Phase III trial of atezolizumab plus bevacizumab in high-risk hepatocellular carcinoma after curative resection or ablation. Future Oncol 2020;16:975-89.
35. Lencioni R. Loco-regional treatment of hepatocellular carcinoma. Hepatology 2010;52:762-73.
36. Ariel IM, Padula G. Treatment of symptomatic metastatic cancer to the liver from primary colon and rectal cancer by the intraarterial administration of chemotherapy and radioactive isotopes. J Surg Oncol 1978;10:327-36.
37. Grady ED. Internal radiation therapy of hepatic cancer. Dis Colon Rectum 1979;22:371-5.
38. Mantravadi RV, Spigos DG, Tan WS, et al. Intraarterial yttrium 90 in the treatment of hepatic malignancy. Radiology 1982;142:783-6.
39. Sherman M, Burak K, Maroun J, et al. Multidisciplinary Canadian consensus recommendations for the management and treatment of hepatocellular carcinoma. Curr Oncol 2011;18:228-40.
40. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 2010;28:493-508.
41. Garcea G, Lloyd TD, Aylott C, et al. The emergent role of focal liver ablation techniques in the treatment of primary and secondary liver tumours. Eur J Cancer 2003;39:2150-64.
42. Lewandowski RJ, Geschwind JF, Liapi E, et al. Transcatheter intraarterial therapies: rationale and overview. Radiology 2011;259:641-57.
43. De Luna W, Sze DY, Ahmed A, et al. Transarterial chemoinfusion for hepatocellular carcinoma as downstaging therapy and a bridge toward liver transplantation. Am J Transplant 2009;9:1158-68.
44. Shimose S, Kawaguchi T, Iwamoto H, et al. Indication of suitable transarterial chemoembolization and multikinase inhibitors for intermediate stage hepatocellular carcinoma. Oncol Lett 2020;19:2667-76.
45. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. J Hepatol 2015;62:1187-95.
46. Park JW, Sherman M, Colombo M, et al. Observations of hepatocellular carcinoma (HCC) management patterns from the global HCC bridge study: First characterization of the full study population. J Clin Oncol 2012;30:abstr 4033.
47. Mornex F, Girard N, Beziat C, et al. Feasibility and efficacy of high-dose three-dimensional-conformal radiotherapy in cirrhotic patients with small-size hepatocellular carcinoma non-eligible for curative therapies--mature results of the French Phase II RTF-1 trial. Int J Radiat Oncol Biol Phys 2006;66:1152-8.
48. Klein J, Dawson LA. Hepatocellular carcinoma radiation therapy: review of evidence and future opportunities. Int J Radiat Oncol Biol Phys 2013;87:22-32.
49. Guha C, Kavanagh BD. Hepatic radiation toxicity: avoidance and amelioration. Semin Radiat Oncol 2011;21:256-63.
50. Priestman TJ. Controlling the toxicity of palliative radiotherapy: the role of 5-HT3 antagonists. Can J Oncol 1996;6 Suppl 1:17-22.
51. Ferris FD, Bezjak A, Rosenthal SG. The palliative uses of radiation therapy in surgical oncology patients. Surg Oncol Clin N Am 2001;10:185-201.
52. Kim JH, Park JW, Kim TH, et al. Hepatitis B virus reactivation after three-dimensional conformal radiotherapy in patients with hepatitis B virus-related hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2007;69:813-9.
53. Henriksson R, Bergström P, Franzén L, et al. Aspects on reducing gastrointestinal adverse effects associated with radiotherapy. Acta Oncol 1999;38:159-64.
54. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10-9.
55. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918-28.
56. Cholongitas E, Papatheodoridis GV, Vangeli M, et al. Systematic review: The model for end-stage liver disease--should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther 2005;22:1079-89.
57. Farnsworth N, Fagan SP, Berger DH, et al. Child-Turcotte-Pugh versus MELD score as a predictor of outcome after elective and emergent surgery in cirrhotic

patients. Am J Surg 2004;188:580-3.
58. Lasley FD, Mannina EM, Johnson CS, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child-Pugh class A and B enrolled in a phase 1-2 trial of stereotactic body radiation therapy. Pract Radiat Oncol 2015;5:e443-9.
59. Kartoun U, Corey KE, Simon TG, et al. The MELD-Plus: A generalizable prediction risk score in cirrhosis. PLoS One 2017;12:e0186301.
60. Okazaki E, Yamamoto A, Nishida N, et al. Three-dimensional conformal radiotherapy for locally advanced hepatocellular carcinoma with portal vein tumour thrombosis: evaluating effectiveness of the model for end-stage liver disease (MELD) score compared with the Child-Pugh classification. Br J Radiol 2016;89:20150945.
61. Toesca DAS, Osmundson EC, von Eyben R, et al. Assessment of hepatic function decline after stereotactic body radiation therapy for primary liver cancer. Pract Radiat Oncol 2017;7:173-82.
62. Feng D, Wang M, Hu J, et al. Prognostic value of the albumin-bilirubin grade in patients with hepatocellular carcinoma and other liver diseases. Ann Transl Med 2020;8:553.
63. Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol 2015;33:550-8.
64. Liu PH, Hsu CY, Hsia CY, et al. ALBI and PALBI grade predict survival for HCC across treatment modalities and BCLC stages in the MELD Era. J Gastroenterol Hepatol 2017;32:879-86.
65. Scheiner B, Pomej K, Kirstein MM, et al. Prognosis of patients with hepatocellular carcinoma treated with immunotherapy - development and validation of the CRAFITY score. J Hepatol 2022;76:353-63.
66. Lock M, Callan L, Gaede S, et al. 92: Identification of Patients that will not Benefit from Hepatic Radiation. Radiother Oncol 2016;1:S36.
67. Vickress J, Lock M, Lo S, et al. A multivariable model to predict survival for patients with hepatic carcinoma or liver metastasis receiving radiotherapy. Future Oncol 2017;13:19-30.
68. Kress MA, Collins BT, Collins SP, et al. Scoring system predictive of survival for patients undergoing stereotactic body radiation therapy for liver tumors. Radiat Oncol 2012;7:148.
69. Li X, Ye Z, Lin S, et al. Predictive factors for survival following stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumour thrombosis and construction of a nomogram. BMC Cancer 2021;21:701.
70. El Naqa I, Johansson A, Owen D, et al. Modeling of Normal Tissue Complications Using Imaging and Biomarkers After Radiation Therapy for Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2018;100:335-43.
71. Shirai S, Sato M, Noda Y, et al. Distribution of functional liver volume in hepatocellular carcinoma patients with portal vein tumor thrombus in the 1st branch and main trunk using single photon emission computed tomography-application to radiation therapy. Cancers (Basel) 2011;3:4114-26.
72. Dawson LA, Eccles C, Bissonnette JP, et al. Accuracy of daily image guidance for hypofractionated liver radiotherapy with active breathing control. Int J Radiat Oncol Biol Phys 2005;62:1247-52.
73. Wunderink W, Méndez Romero A, de Kruijf W, et al. Reduction of respiratory liver tumor motion by abdominal compression in stereotactic body frame, analyzed by tracking fiducial markers implanted in liver. Int J Radiat Oncol Biol Phys 2008;71:907-15.
74. Shirato H, Shimizu S, Kitamura K, et al. Four-dimensional treatment planning and fluoroscopic real-time tumor tracking radiotherapy for moving tumor. Int J Radiat Oncol Biol Phys 2000;48:435-42.
75. Wunderink W, Méndez Romero A, Seppenwoolde Y, et al. Potentials and limitations of guiding liver stereotactic body radiation therapy set-up on liver-implanted fiducial markers. Int J Radiat Oncol Biol Phys 2010;77:1573-83.
76. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2010;76:326-32.
77. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. J Clin Oncol 2007;25:938-46.
78. Wurm RE, Gum F, Erbel S, et al. Image guided respiratory gated hypofractionated Stereotactic Body Radiation Therapy (H-SBRT) for liver and lung tumors: Initial experience. Acta Oncol 2006;45:881-9.
79. Kirilova A, Lockwood G, Choi P, et al. Three-dimensional motion of liver tumors using cine-magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2008;71:1189-95.
80. Lock M, Chow R, Jayatilaka A, et al. Does stereotactic body radiation improve outcomes compared to conventional radiation for liver cancer patients? Clin Transl Radiat Oncol 2022;35:17-20.

81. Lee MT, Kim JJ, Dinniwell R, et al. Phase I study of individualized stereotactic body radiotherapy of liver metastases. J Clin Oncol 2009;27:1585-91.
82. Aitken KL, Tait DM, Nutting CM, et al. Risk-adapted strategy partial liver irradiation for the treatment of large volume metastatic liver disease. Acta Oncol 2014;53:702-6.
83. Xi M, Zhang L, Zhao L, et al. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. PLoS One 2013;8:e63864.
84. Tse RV, Hawkins M, Lockwood G, et al. Phase I study of individualized stereotactic body radiotherapy for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol 2008;26:657-64.
85. Koo JE, Kim JH, Lim YS, et al. Combination of transarterial chemoembolization and three-dimensional conformal radiotherapy for hepatocellular carcinoma with inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys 2010;78:180-7.
86. Price TR, Perkins SM, Sandrasegaran K, et al. Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. Cancer 2012;118:3191-8.
87. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol 2013;31:1631-9.
88. Que JY, Lin LC, Lin KL, et al. The efficacy of stereotactic body radiation therapy on huge hepatocellular carcinoma unsuitable for other local modalities. Radiat Oncol 2014;9:120.
89. Su TS, Liang P, Lu HZ, et al. Stereotactic body radiation therapy for small primary or recurrent hepatocellular carcinoma in 132 Chinese patients. J Surg Oncol 2016;113:181-7.
90. Matsuo Y, Yoshida K, Nishimura H, et al. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: evaluation by comparison with conventional three-dimensional conformal radiotherapy. J Radiat Res 2016;57:512-23.
91. Yeung R, Beaton L, Rackley T, et al. Stereotactic Body Radiotherapy for Small Unresectable Hepatocellular Carcinomas. Clin Oncol (R Coll Radiol) 2019;31:365-73.
92. Yang JF, Lo CH, Lee MS, et al. Stereotactic ablative radiotherapy versus conventionally fractionated radiotherapy in the treatment of hepatocellular carcinoma with portal vein invasion: a retrospective analysis. Radiat Oncol 2019;14:180.
93. Liu HY, Lee Y, McLean K, et al. Efficacy and Toxicity of Stereotactic Body Radiotherapy for Early to Advanced Stage Hepatocellular Carcinoma - Initial Experience From an Australian Liver Cancer Service. Clin Oncol (R Coll Radiol) 2020;32:e194-202.
94. Hoyer M, Roed H, Traberg Hansen A, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol 2006;45:823-30.
95. Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. Int J Radiat Oncol Biol Phys 2007;67:793-8.
96. Milano MT, Katz AW, Schell MC, et al. Descriptive analysis of oligometastatic lesions treated with curative-intent stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2008;72:1516-22.
97. Ambrosino G, Polistina F, Costantin G, et al. Image-guided robotic stereotactic radiosurgery for unresectable liver metastases: preliminary results. Anticancer Res 2009;29:3381-4.
98. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. J Clin Oncol 2009;27:1572-8.
99. van der Pool AE, Méndez Romero A, Wunderink W, et al. Stereotactic body radiation therapy for colorectal liver metastases. Br J Surg 2010;97:377-82.
100. Rule W, Timmerman R, Tong L, et al. Phase I dose-escalation study of stereotactic body radiotherapy in patients with hepatic metastases. Ann Surg Oncol 2011;18:1081-7.
101. Chang DT, Swaminath A, Kozak M, et al. Stereotactic body radiotherapy for colorectal liver metastases: a pooled analysis. Cancer 2011;117:4060-9.
102. Scorsetti M, Arcangeli S, Tozzi A, et al. Is stereotactic body radiation therapy an attractive option for unresectable liver metastases? A preliminary report from a phase 2 trial. Int J Radiat Oncol Biol Phys 2013;86:336-42.
103. Stintzing S, Grothe A, Hendrich S, et al. Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases. Acta Oncol 2013;52:971-7.
104. Andratschke NH, Nieder C, Heppt F, et al. Stereotactic radiation therapy for liver metastases: factors affecting local control and survival. Radiat Oncol 2015;10:69.
105. Herfarth KK, Debus J, Lohr F, et al. Stereotactic single-dose radiation therapy of liver tumors: results of a phase I/II trial. J Clin Oncol 2001;19:164-70.
106. Herfarth KK, Debus J, Wannenmacher M. Stereotactic

radiation therapy of liver metastases: update of the initial phase-I/II trial. Front Radiat Ther Oncol 2004;38:100-5.
107. Méndez Romero A, Wunderink W, Hussain SM, et al. Stereotactic body radiation therapy for primary and metastatic liver tumors: A single institution phase i-ii study. Acta Oncol 2006;45:831-7.
108. Wulf J, Guckenberger M, Haedinger U, et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. Acta Oncol 2006;45:838-47.
109. Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. Int J Radiat Oncol Biol Phys 2010;78:486-93.
110. Lanciano R, Lamond J, Yang J, et al. Stereotactic body radiation therapy for patients with heavily pretreated liver metastases and liver tumors. Front Oncol 2012;2:23.
111. Dewas S, Bibault JE, Mirabel X, et al. Prognostic factors affecting local control of hepatic tumors treated by Stereotactic Body Radiation Therapy. Radiat Oncol 2012;7:166.
112. Klein J, Dawson LA, Jiang H, et al. Prospective Longitudinal Assessment of Quality of Life for Liver Cancer Patients Treated With Stereotactic Body Radiation Therapy. Int J Radiat Oncol Biol Phys 2015;93:16-25.
113. Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients. Acta Oncol 1995;34:861-70.
114. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009;27:1579-84.
115. Raoul JL, Forner A, Bolondi L, et al. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev 2019;72:28-36.
116. Seong J, Park HC, Han KH, et al. Local radiotherapy for unresectable hepatocellular carcinoma patients who failed with transcatheter arterial chemoembolization. Int J Radiat Oncol Biol Phys 2000;47:1331-5.
117. Rim CH, Jeong BK, Kim TH, et al. Effectiveness and feasibility of external beam radiotherapy for hepatocellular carcinoma with inferior vena cava and/or right atrium involvement: a multicenter trial in Korea (KROG 17-10). Int J Radiat Biol 2020;96:759-66.
118. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. J Clin Oncol 2016;34:452-9.
119. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
120. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
121. Lu J, Zhang XP, Zhong BY, et al. Management of patients with hepatocellular carcinoma and portal vein tumour thrombosis: comparing east and west. Lancet Gastroenterol Hepatol 2019;4:721-30.
122. Yuan J, Yin X, Tang B, et al. Transarterial Chemoembolization (TACE) Combined with Sorafenib in Treatment of HBV Background Hepatocellular Carcinoma with Portal Vein Tumor Thrombus: A Propensity Score Matching Study. Biomed Res Int 2019;2019:2141859.
123. Wang JC, Xia AL, Xu Y, et al. Comprehensive treatments for hepatocellular carcinoma with portal vein tumor thrombosis. J Cell Physiol 2019;234:1062-70.
124. Wang J, Luo J, Yin X, et al. Jiedu Granule Combined with Transcatheter Arterial Chemoembolization and Gamma Knife Radiosurgery in Treating Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. Biomed Res Int 2019;2019:4696843.
125. Cerrito L, Annicchiarico BE, Iezzi R, et al. Treatment of hepatocellular carcinoma in patients with portal vein tumor thrombosis: Beyond the known frontiers. World J Gastroenterol 2019;25:4360-82.
126. Shui Y, Yu W, Ren X, et al. Stereotactic body radiotherapy based treatment for hepatocellular carcinoma with extensive portal vein tumor thrombosis. Radiat Oncol 2018;13:188.
127. Kang J, Nie Q, DU R, et al. Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis. Mol Clin Oncol 2014;2:43-50.
128. Iwamoto H, Nomiyama M, Niizeki T, et al. Dose and Location of Irradiation Determine Survival for Patients with Hepatocellular Carcinoma with Macrovascular Invasion in External Beam Radiation Therapy. Oncology 2019;96:192-9.
129. Hamaoka M, Kobayashi T, Kuroda S, et al. Hepatectomy after down-staging of hepatocellular carcinoma with portal vein tumor thrombus using chemoradiotherapy: A retrospective cohort study. Int J Surg 2017;44:223-8.
130. Brade AM, Ng S, Brierley J, et al. Phase 1 Trial of Sorafenib and Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys

2016;94:580-7.
131. Chen SW, Lin LC, Kuo YC, et al. Phase 2 study of combined sorafenib and radiation therapy in patients with advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2014;88:1041-7.
132. Brown JM, Diehn M, Loo BW Jr. Stereotactic ablative radiotherapy should be combined with a hypoxic cell radiosensitizer. Int J Radiat Oncol Biol Phys 2010;78:323-7.
133. Guckenberger M, Allgäuer M, Appold S, et al. Safety and efficacy of stereotactic body radiotherapy for stage 1 non-small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. J Thorac Oncol 2013;8:1050-8.
134. Yu J, Kim DH, Lee J, et al. Radiofrequency Ablation versus Stereotactic Body Radiation Therapy in the Treatment of Colorectal Cancer Liver Metastases. Cancer Res Treat 2022;54:850-9.
135. Jeong Y, Lee KJ, Lee SJ, et al. Radiofrequency ablation versus stereotactic body radiation therapy for small (≤ 3 cm) hepatocellular carcinoma: A retrospective comparison analysis. J Gastroenterol Hepatol 2021;36:1962-70.
136. Dawson LA, Ten Haken RK. Partial volume tolerance of the liver to radiation. Semin Radiat Oncol 2005;15:279-83.
137. Skinner HD, Hong TS, Krishnan S. Charged-particle therapy for hepatocellular carcinoma. Semin Radiat Oncol 2011;21:278-86.
138. Wang X, Krishnan S, Zhang X, et al. Proton radiotherapy for liver tumors: dosimetric advantages over photon plans. Med Dosim 2008;33:259-67.
139. Nakayama H, Sugahara S, Tokita M, et al. Proton beam therapy for hepatocellular carcinoma: the University of Tsukuba experience. Cancer 2009;115:5499-506.
140. Mizumoto M, Okumura T, Hashimoto T, et al. Proton beam therapy for hepatocellular carcinoma: a comparison of three treatment protocols. Int J Radiat Oncol Biol Phys 2011;81:1039-45.
141. Bush DA, Kayali Z, Grove R, et al. The safety and efficacy of high-dose proton beam radiotherapy for hepatocellular carcinoma: a phase 2 prospective trial. Cancer 2011;117:3053-9.
142. Bush DA, Smith JC, Slater JD, et al. Randomized Clinical Trial Comparing Proton Beam Radiation Therapy with Transarterial Chemoembolization for Hepatocellular Carcinoma: Results of an Interim Analysis. Int J Radiat Oncol Biol Phys 2016;95:477-82.
143. Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. Cancer 2011;117:4890-904.
144. Hong TS, Wo JY, Yeap BY, 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;34:460-8.
145. Guo WJ, Yu EX, Liu LM, et al. Comparison between chemoembolization combined with radiotherapy and chemoembolization alone for large hepatocellular carcinoma. World J Gastroenterol 2003;9:1697-701.
146. Liu MT, Li SH, Chu TC, et al. Three-dimensional conformal radiation therapy for unresectable hepatocellular carcinoma patients who had failed with or were unsuited for transcatheter arterial chemoembolization. Jpn J Clin Oncol 2004;34:532-9.
147. Zeng ZC, Tang ZY, Fan J, et al. A comparison of chemoembolization combination with and without radiotherapy for unresectable hepatocellular carcinoma. Cancer J 2004;10:307-16.
148. Zhou ZH, Liu LM, Chen WW, et al. Combined therapy of transcatheter arterial chemoembolisation and three-dimensional conformal radiotherapy for hepatocellular carcinoma. Br J Radiol 2007;80:194-201.
149. Seong J, Lee IJ, Shim SJ, et al. A multicenter retrospective cohort study of practice patterns and clinical outcome on radiotherapy for hepatocellular carcinoma in Korea. Liver Int 2009;29:147-52.
150. Oh D, Lim DH, Park HC, et al. Early three-dimensional conformal radiotherapy for patients with unresectable hepatocellular carcinoma after incomplete transcatheter arterial chemoembolization: a prospective evaluation of efficacy and toxicity. Am J Clin Oncol 2010;33:370-5.
151. Ren ZG, Zhao JD, Gu K, et al. Three-dimensional conformal radiation therapy and intensity-modulated radiation therapy combined with transcatheter arterial chemoembolization for locally advanced hepatocellular carcinoma: an irradiation dose escalation study. Int J Radiat Oncol Biol Phys 2011;79:496-502.
152. Kim YJ, Jung J, Joo JH, et al. Combined transarterial chemoembolization and radiotherapy as a first-line treatment for hepatocellular carcinoma with macroscopic vascular invasion: Necessity to subclassify Barcelona Clinic Liver Cancer stage C. Radiother Oncol 2019;141:95-100.
153. Lou J, Li Y, Liang K, et al. Hypofractionated radiotherapy as a salvage treatment for recurrent hepatocellular carcinoma with inferior vena cava/right atrium tumor thrombus: a multi-center analysis. BMC Cancer 2019;19:668.

154. Robertson JM, Lawrence TS, Walker S, et al. The treatment of colorectal liver metastases with conformal radiation therapy and regional chemotherapy. Int J Radiat Oncol Biol Phys 1995;32:445-50.
155. Ben-Josef E, Normolle D, Ensminger WD, et al. Phase II trial of high-dose conformal radiation therapy with concurrent hepatic artery floxuridine for unresectable intrahepatic malignancies. J Clin Oncol 2005;23:8739-47.
156. Rim CH, Kim CY, Yang DS, et al. External beam radiation therapy to hepatocellular carcinoma involving inferior vena cava and/or right atrium: A meta-analysis and systemic review. Radiother Oncol 2018;129:123-9.
157. Minsky BD, Leibel SA. The treatment of hepatic metastases from colorectal cancer with radiation therapy alone or combined with chemotherapy or misonidazole. Cancer Treat Rev 1989;16:213-9.
158. Soliman H, Ringash J, Jiang H, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. J Clin Oncol 2013;31:3980-6.
159. Soliman H, Wong R, Ringash J. Preliminary results of a phase II study of single fraction palliative radiotherapy for symptomatic hepatocellular carcinoma and liver metastases. Radiother Oncol 2010;88:S17-8.
160. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991;21:109-22.
161. Yeung CSY, Chiang CL, Wong NSM, et al. Palliative Liver Radiotherapy (RT) for Symptomatic Hepatocellular Carcinoma (HCC). Sci Rep 2020;10:1254.
162. Dawson LA, Normolle D, Balter JM, et al. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int J Radiat Oncol Biol Phys 2002;53:810-21.
163. Turek-Maischeider M, Kazem I. Palliative irradiation for liver metastases. JAMA 1975;232:625-8.
164. Sherman DM, Weichselbaum R, Order SE, et al. Palliation of hepatic metastasis. Cancer 1978;41:2013-7.
165. Herbsman H, Hassan A, Gardner B, et al. Treatment of hepatic metastases with a combination of hepatic artery infusion chemotherapy and external radiotherapy. Surg Gynecol Obstet 1978;147:13-7.
166. Webber BM, Soderberg CH Jr, Leone LA, et al. A combined treatment approach to management of hepatic metastases. Cancer 1978;42:1087-95.
167. Friedman M, Cassidy M, Levine M, et al. Combined modality therapy of hepatic metastasis. Northern California Oncology Group Pilot Study. Cancer 1979;44:906-13.
168. Borgelt BB, Gelber R, Brady LW, et al. The palliation of hepatic metastases: results of the Radiation Therapy Oncology Group pilot study. Int J Radiat Oncol Biol Phys 1981;7:587-91.
169. Barone RM, Byfield JE, Goldfarb PB, et al. Intra-arterial chemotherapy using an implantable infusion pump and liver irradiation for the treatment of hepatic metastases. Cancer 1982;50:850-62.
170. Byfield JE, Barone RM, Frankel SS, et al. Treatment with combined intra-arterial 5-FUdR infusion and whole-liver radiation for colon carcinoma metastatic to the liver. Preliminary results. Am J Clin Oncol 1984;7:319-25.
171. Russell AH, Clyde C, Wasserman TH, et al. Accelerated hyperfractionated hepatic irradiation in the management of patients with liver metastases: results of the RTOG dose escalating protocol. Int J Radiat Oncol Biol Phys 1993;27:117-23.
172. Edyta WR, Jakub L, Jerzy W. Whole Liver Palliative Radiotherapy for Patients with Massive Liver Metastases. Asian Pac J Cancer Prev 2015;16:6381-4.
173. Wirtanen GW, Wiley AL, Vermund H, et al. Intraarterial iododeoxyuridine infusion combined with irradiation. A pilot study. Am J Clin Oncol 1990;13:320-3.
174. Leibel SA. Radiation Therapy of Hepatobiliary Tumors. In: Bottino JC, Opfell RW, Muggia FM. editors. Liver Cancer. Boston: Springer, 1985:297-312.
175. Brade AM, Kim J, Brierley J, et al. Phase I study of sorafenib and whole-liver radiation therapy (WLRT) or stereotactic body radiation therapy (SBRT) for liver metastases. Int J Radiat Oncol Biol Phys 2012;84:S11-2.
176. Feng M, Smith DE, Normolle DP, et al. A phase I clinical and pharmacology study using amifostine as a radioprotector in dose-escalated whole liver radiation therapy. Int J Radiat Oncol Biol Phys 2012;83:1441-7.
177. Mendez Romero A, Høyer M. Radiation therapy for liver metastases. Curr Opin Support Palliat Care 2012;6:97-102.
178. Ingold JA, Reed GB, Kaplan HS, et al. Radiation hepatitis. Am J Roentgenol Radium Ther Nucl Med 1965;93:200-8.
179. Staehler M, Haseke N, Stadler T, et al. Feasibility and effects of high-dose hypofractionated radiation therapy and simultaneous multi-kinase inhibition with sunitinib in progressive metastatic renal cell cancer. Urol Oncol 2012;30:290-3.
180. Lawrence TS, Robertson JM, Anscher MS, et al. Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31:1237-48.
181. McIntosh A, Hagspiel KD, Al-Osaimi AM, et al. Accelerated treatment using intensity-modulated radiation

therapy plus concurrent capecitabine for unresectable hepatocellular carcinoma. Cancer 2009;115:5117-25.
182. Lokich J, Kinsella T, Perri J, et al. Concomitant hepatic radiation and intraarterial fluorinated pyrimidine therapy: correlation of liver scan, liver function tests, and plasma CEA with tumor response. Cancer 1981;48:2569-74.

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