

External Beam Radiotherapy for Hepatocellular Carcinoma: a Review of the Current Guidelines in the East and the West

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The incidence of hepatocellular carcinoma (HCC) is geographically heterogeneous depending on the underlying liver disease. Moreover, the decisions and recommendations about standard treatments differ between countries, especially between the East and the West. Because of the complexity of treatment decisions for the management of HCC, a multidisciplinary approach is recommended to maximize the therapeutic efficacy. External beam radiotherapy (RT) has been increasingly used to manage HCC when recommended treatments cannot be applied in real-world clinical practice. However, Western guidelines for the management of HCC do not recommend RT as a treatment option due to the lack of clinical evidence. RT has often been used more in Eastern countries than in Western countries; hence, it is necessary to review both Eastern and Western guidelines for HCC treatment regarding the recommendations about RT. In this study, the comments and potential roles of external beam RT are summarized from several treatment guidelines for the management of HCC. (**J Liver Cancer 2021;21:25-33**)

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INTRODUCTION

Liver cancer is the sixth most common cancer and the fourth leading cause of death from cancer according to the recent global cancer statistics.¹ Hepatocellular carcinoma (HCC) accounts for approximately 80% of cases of liver cancer.^{1,2} The incidence of HCC is geographically heterogeneous and largely depends on the underlying liver disease.³ Moreover, the decisions and recommendations about standard treatments also differ between countries, especially between

countries in the East and West.³

Decisions about the optimal treatment for HCC are complex because many therapeutic options need to be considered based on the tumor burden, underlying hepatic function, patient performance status, and availability or applicability of specific treatment modalities. For example, not all patients with early-stage HCC can undergo curative treatments, such as hepatic resection, radiofrequency ablation (RFA), or liver transplantation (LT), because of various clinical conditions. Moreover, tumor recurrences are frequently observed after initial treatment; however, there are no clear recommendations or guidelines for the management of recurrent HCC. Due to this complexity of treatment decisions, a multidisciplinary approach is recommended to maximize therapeutic efficacy.⁴

In recent times, technologies for external beam radiothera-

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py (RT), including 4-dimensional computed tomography (CT), strategies for management of respiratory motion, intensity-modulated RT, particle therapy, and image-guided RT, have advanced rapidly.^{5,6} Moreover, based on the results of many clinical studies, HCC is considered a radiosensitive malignancy.⁷ Therefore, RT has been increasingly used in the management of HCC when the recommended treatments cannot be applied in real-world clinical practice. Since the purpose of RT can be varied, from curative to palliative depending on the patient's disease status, RT might play a role as a treatment option for all stages of HCC.^{6,8,9} However, the Western guidelines for HCC do not recommend RT as a treatment option because of the lack of clinical evidence.^{10,11} RT has often been used more frequently in Eastern countries than in Western countries. Hence, it is necessary to review the Eastern and Western treatment guidelines for HCC regarding their recommendations for RT to understand the current status of RT in the management of HCC. Here, the comments and potential roles of external beam RT are summarized from several treatment guidelines for the management of HCC.

TREATMENT GUIDELINES IN ASIA

Several guidelines or consensus statements exist for the diagnosis and management of HCC in organizations and countries in the Asian region. In this section, the recently updated recommendations related to external beam RT in these guidelines are summarized in Table 1.

1. Asia-Pacific clinical practice guidelines

The first version of the Asia-Pacific Association for the Study of the Liver (APASL) guidelines on HCC was published in 2010, and a recently updated version was published in 2017,¹² in which the guidelines summarized the background, indications, contraindications, efficacy, complications, and response assessment of RT. This updated version describes the growing evidence of the efficacy of stereotactic body RT (SBRT) for small HCC and charged-particle RT for large HCC or portal vein tumor thrombus.¹³⁻¹⁶ However, be-

cause of the lack of strong evidence to support RT for patients with HCC, the APASL guidelines did not recommend RT as standard therapy, although SBRT and proton beam were reasonable options for patients who had failed to respond to other local therapies (grading of evidence: low or very low quality; grading of recommendation: weak). Nonetheless, RT might be a promising treatment option for HCC because of the radiosensitivity of HCC and recent advancements in RT techniques.¹²

2. Practice guidelines for the management of HCC in Korea

The first version of the Korean Liver Cancer Study Group (KLCSG)-National Cancer Center (NCC) Korea practice guidelines for the management of HCC was announced in 2003, and the 4th version of the Korean Liver Cancer Association (KLCA, formerly KLCSG)-NCC Korea practice guidelines was published in 2018.¹⁷ According to the guidelines, there are six recommendations related to the use of RT in the management of HCC.

First, external beam RT requires computerized RT planning using CT and is feasible for patients with HCC if their liver function is Child-Pugh class A or B7 and the irradiated total liver volume receiving ≤ 30 Gy is $\geq 40\%$ (quality of evidence: moderate; strength of recommendation: strong).^{17,18} Second, RT can be considered for patients with HCC ineligible for surgical resection, LT, other local modalities, and transarterial chemoembolization (TACE) (quality of evidence: low; strength of recommendation: strong). In this category, hypofractionated RT, such as SBRT or particle therapy, can be actively considered based on recent favorable clinical results if the tumor burden is not widespread.^{15,16,19-22} Third, RT can be performed in patients with HCC who show an incomplete response to TACE (quality of evidence: moderate; strength of recommendation: weak). The addition of RT after incomplete TACE resulted in a complete response rate of 20-25%.^{23,24} Fourth, RT can be performed in patients with HCC with portal vein tumor thrombus when the dose-volume criteria are met (quality of evidence: moderate; strength of recommendation: weak) with those reported in

many previous retrospective studies.²⁵⁻³⁰ Moreover, the combination therapy with conventional TACE and RT was strongly recommended (quality of evidence: moderate; strength of recommendation: strong) for patients with localized tumors and portal vein tumor thrombus, based on the results of a recent single-center randomized controlled trial in Korea.³¹ Fifth, RT can be performed to alleviate symptoms caused by metastases (quality of evidence: moderate; strength of recommendation: strong) according to many studies on

the role of RT in patients with lymph node metastases,³²⁻³⁴ adrenal metastases,³⁵ lung metastases,³⁶ brain metastases,^{37,38} and bone metastases, including spinal cord compression.³⁹⁻⁴² Finally, the updated guidelines also included second-line therapies for recurrent HCC: RT can be considered in patients with HCC who have recurrent or refractory disease after local therapy in this regard (quality of evidence: low; strength of recommendation: strong).¹⁷

Although the quality of evidence is moderate to low, the

Table 1. Summary of the recommendations regarding radiotherapy in the guidelines and consensus statements for the management of hepatocellular carcinoma

Affiliation	Country	Year	Evidence of RT	Recommendation of RT	Potential role of RT in clinical situations
APASL	Multinational (Asia)	2017	Low/very low	Weak	<ul style="list-style-type: none"> • SBRT for small HCC • Particle therapy for large HCC or PVTT
KLCA-NCC	Korea	2018	Low/moderate	Weak/strong	<ul style="list-style-type: none"> • RT for HCC ineligible for surgery, LT, other LRTs • RT for incomplete response to TACE • RT for HCC with PVTT (combined with TACE) • Palliative RT for metastases
JSH	Japan	2017	-	Weak	<ul style="list-style-type: none"> • SBRT for HCCs not indications for other LRTs • Particle therapy for HCCs not eligible for other LRTs • 3D-CRT when SBRT and particle therapy are not eligible (PVTT, unresectable HCC)
TLCA	Taiwan	2015	Level 2	Recommended	<ul style="list-style-type: none"> • Medically inoperable, refusal of standard treatment, bridge to transplant, unsuitable/refractory to TACE, localized HCC with symptoms, PVTT, symptomatic metastasis or oligo-metastasis in all BCLC stages
NHFPC	China	2017	Level 3	-	<ul style="list-style-type: none"> • RT for PVTT, IVCTT or extrahepatic metastases, bridge to LT, relieving symptoms • Adjuvant RT for centrally located tumors with narrow surgical margins
	Hong Kong	2015	Level 4/5	-	<ul style="list-style-type: none"> • RT for effective local control, a viable portion for unresectable HCC, combined with TACE for unresectable HCC • SBRT as an alternative to ablation and a bridging therapy before LT
AASLD	United States	2018	Level 2	-	<ul style="list-style-type: none"> • SBRT as an alternative to thermal ablation
EASL	Multinational (Europe)	2018	Low	Weak	<ul style="list-style-type: none"> • RT in combination with TACE • SBRT as a bridge to LT • RT for PVTT • Palliative RT for pain, impending fracture
ESMO	Multinational (Europe)	2018	Level 3	B/C	<ul style="list-style-type: none"> • SBRT as alternatives for the ablation • Palliative RT for bone metastases

RT, radiotherapy; APASL, Asia-Pacific Association for the Study of the Liver; SBRT, stereotactic body radiotherapy; HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center; LT, liver transplantation; LRT, locoregional therapy; TACE, transarterial chemoembolization; JSH, Japan Society of Hepatology; 3D-CRT, 3-dimensional conformal radiotherapy; TLCA, Taiwan Liver Cancer Association; BCLC, Barcelona Clinic Liver Cancer; NHFPC, National Health and Family Planning Commission; IVCTT, inferior vena cava tumor thrombus; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; ESMO, European Society for Medical Oncology.

recommendation of external beam RT for several clinical situations as a treatment modality for HCC is strong according to the KLCA-NCC Korea practice guidelines. Interestingly, RT alone (stage II by the modified Union for International Cancer Control [UICC] staging) and combined TACE and RT (stage III by the modified UICC staging) were described as some of the best treatment options in the first-line treatment recommendations from the 2018 KLCA-NCC Korea practice guidelines for patients with HCC, Child-Pugh class A, no portal hypertension, and Eastern Cooperative Oncology Group performance status 0 or 1.¹⁷

3. Clinical practice guidelines for HCC in Japan

The first edition of the clinical practice guidelines for HCC was compiled by the Japan Society of Hepatology (JSH) in 2005. The 4th version of the JSH-HCC guidelines was published on the JSH website (<https://www.jsh.or.jp/English/>) and in a recent article that highlighted the important revisions in the recommendation and algorithms.⁴³ They classified RT for HCC into ablative RT for achieving local cure, such as SBRT and particle therapy, and adjuvant RT for supporting surgery and TACE, such as 3-dimensional conformal RT (3D-CRT).⁴⁴ From this perspective, the guidelines used clinical questions related to SBRT, particle therapy, and 3D-CRT in their chapter on RT with the background, scientific statement, and explanation for each clinical question.

In the clinical question about whether SBRT can be recommended as a treatment for HCC, the guidelines mentioned that SBRT might be performed for HCC lesions in which other types of locoregional therapies are not indicated and for recurrent HCC after various locoregional therapies (grading of recommendation: weak). In the second clinical question about the efficacy of particle therapy in HCC, the guidelines stated that particle therapy (proton therapy and heavy particle therapy) might be performed for HCC for which other types of locoregional therapies are not indicated (grading of recommendation: weak). For the last question, which was about the recommendation for 3D-CRT, the guidelines mentioned that 3D-CRT might be performed when SBRT and particle therapy are difficult to perform in

patients who are not candidates for other standard treatments because of the presence of portal vein tumor thrombus, unresectable HCC, or internal complications (grading of recommendation: weak).⁴⁴ Unfortunately, the guidelines recommend RT as an alternative treatment only when other locoregional therapies cannot be performed in various situations. In their special report of the 2019 update, the guidelines described that RT is recommended for the management of painful bone metastasis and brain metastasis.⁴³

4. Consensus guidelines for HCC in Taiwan

The Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan initiated work on the management consensus for HCC using a multidisciplinary and evidence-based approach and presented the final statement in 2015.⁴⁵ There are four statements about the recommendations of RT in patients with HCC.

First, RT might be recommended for patients with Barcelona Clinic Liver Cancer (BCLC) stage A in the following situations: 1) HCC inaccessible for percutaneous ablative therapies; 2) medically inoperable status; 3) refusal to receive standard treatment; and 4) as a bridge therapy until liver transplant (agreement: 96%; evidence: 2; recommendation: B).^{8,46-48} Second, RT might be recommended for patients with BCLC stage B in the following situations: 1) HCC inaccessible/unsuitable for TACE; 2) refractory to TACE; 3) consolidate TACE (under conditions 1) and 2)); 4) as a bridge therapy until liver transplant (under conditions 1) and 2)); and 5) localized tumor (of multiple) with symptoms or threat to the liver reserve (agreement: 95.8%; evidence: 2; recommendation: B).^{49,50} Third, RT might be recommended for patients with BCLC stage C in the following situations: 1) presence of portal vein tumor thrombus (combined modalities with TACE or sorafenib); 2) HCC unsuitable/refractory to TACE; and 3) localized tumor (of multiple) with symptoms or threat to liver reserve (agreement: 100%; evidence: 2; recommendation: B).^{28,51,52} Finally, RT might be recommended for patients with BCLC stage D with symptomatic metastasis or oligo-metastasis (agreement: 100%; evidence: 2; recommendation: B).^{36,53} The guidelines also mentioned radiation-in-

duced damages to the liver and adjacent luminal gastrointestinal structures and recommended a fine balance of an adequate radiation dose to control HCC while avoiding toxicity after RT.⁴⁵

5. Guidelines for primary liver cancer in China

Guidelines for the diagnosis and treatment of primary liver cancer in China (2017 edition) included the official recommendations by the National Health and Family Planning Commission of the People's Republic of China about the surveillance, diagnosis, staging, and treatment of HCC.⁵⁴ They suggested the following indications for external beam RT: 1) palliative RT for patients with stage IIIa and IIIb (staging by the Chinese staging system) HCC with tumor emboli in the portal vein/inferior vena cava or extrahepatic metastases; 2) bridge to LT; 3) relief of symptoms, such as pain, obstruction, or bleeding, and controlling tumor progression in patients with extrahepatic metastases; 4) postoperative adjuvant RT for centrally located tumors with narrow surgical margins (≤ 1 mm); these were based on published references.^{34,39,50,55,56} However, all the suggested indications had a low level of clinical evidence (evidence level 3). Interestingly, the guidelines also described how to define the target volumes in various circumstances, evaluation of respiratory liver motion, and use of multimodal imaging tools during the simulation process.⁵⁴ Moreover, the prescription and tolerance doses of the liver and surrounding gastrointestinal tracts were also mentioned in the guidelines.⁵⁴ However, there is no consensus on the target volume delineation or radiation dose prescription in RT for HCC, and careful determination of the target volume and radiation dose are necessary during RT in patients with HCC.

6. Consensus recommendations on the management of HCC in Hong Kong

A multidisciplinary group of Hong Kong clinicians published a consensus of treatment recommendations on the management of HCC considering the most current evidence pertaining to treatment modalities for HCC and the latest

opinion of practicing clinicians engaged in treating HCC in 2015.⁵⁷ In the section on external RT, three statements were summarized as follows: 1) high-precision RT offers effective local control of selected HCC confined to the liver, with an acceptable toxicity profile in patients with Child-Pugh A cirrhosis (level 4 according to the 2011 Oxford criteria); 2) high-precision RT is a viable option for unresectable HCC, ineligible for or refractory to TACE or other locoregional therapies (level 4); 3) high-precision RT may be combined with TACE for unresectable HCC; however, the optimal sequencing and timing are not known, and the survival benefit is uncertain (level 4).⁵⁷ This consensus cited some relevant references in the section on external RT.^{28,58-62} All statements contained slightly unspecific comments about the role of RT.

Recently, they published a new consensus document to update the 2015 recommendations with a focus on the treatment of unresectable HCC.⁶³ In this update, the statement on external RT focused mainly on SBRT as follows: 1) SBRT is an acceptable option for unresectable HCC (up to five lesions) (level 4); 2) SBRT can be considered in patients with limited liver reserve (up to Child-Pugh grade B8); 3) SBRT can be an alternative to ablation for tumors close to the major blood vessels or biliary tract (level 5); 4) local control can be achieved by SBRT with limited toxicity (level 4); 5) SBRT can be considered as a bridging therapy before LT (level 4).⁶³

TREATMENT GUIDELINES IN WESTERN COUNTRIES

The recently updated guidelines for the diagnosis and management of HCC from organizations in Western countries are reviewed below to summarize the recommendations of external beam RT for HCC (Table 1).

1. Practice guidance by the American Association for the Study of Liver Diseases

The updated 2018 practice guidance by the American Association for the Study of Liver Diseases (AASLD) provided a data-supported approach to the diagnosis, staging, and treatment of patients with HCC.¹¹ Although the committee

classified SBRT as a noncurative therapy, it was considered as an alternative to thermal ablation in patients, mostly those within the Milan criteria with the relevant references.^{16,22,64} In addition, SBRT was also included as a therapeutic option for BCLC stage A patients in the treatment recommendations diagram (level of evidence: 2).¹¹ This can be considered as a significant change in the perception of RT compared to the previous 2010 AASLD practice guidelines.⁶⁵

2. Practice guidelines by the European Association for the Study of the Liver

An updated version of practice guidelines for the management of HCC by the European Association for the Study of the Liver was published in 2018.¹⁰ There is a short review of the potential role of RT in combination with TACE or other intra-arterial treatments in the external RT section.^{66,67} SBRT can be used as a bridge to LT with drop-out and survival rates comparable to those of TACE and RFA from the time of listing.⁶⁴ In addition, it has been mentioned that patients with portal vein tumor thrombus are considered a good target with some cases of secondary LT.^{26,68} However, the guidelines conclude that external beam RT is under investigation, and there is no robust evidence to support this therapeutic approach in the summary of recommendations (evidence low; recommendation weak).¹⁰ There is also a short comment in the palliative and best supportive care section about palliative RT for pain caused by well-identified bone metastasis or lytic bone metastasis, which is considered at high risk of spontaneous fracture, especially due to body weight.¹⁰

3. European Society for Medical Oncology clinical practice guidelines

In the high conformal, high dose rate radioablation section, there are two short comments about RT in the management of HCC.⁶⁹ First, SBRT might be considered as an alternative for the ablation of tumors with a high risk of local failure after thermal ablation due to the location (level of evidence: III; grades of recommendation: C). Second, RT can be used to control pain in patients with bone metastases (lev-

el of evidence: III; grades of recommendation: B). However, there is no recommendation for RT in the management of advanced-stage HCC.

CONCLUSION

External beam RT has been frequently used in the Asian region, and observations on the use of RT are described in much more detail in Asian guidelines. RT is not considered an established treatment modality for HCC because of the low level of clinical evidence. Despite this low level of evidence, it is noteworthy that SBRT is mentioned as an alternative to thermal ablation and a bridge to LT in the recent Western treatment guidelines. The recommendation levels for the use of RT are weak in the Western guidelines. Even in the Asian guidelines, the recommendations are not consistent according to the consensus of any organization or country. The utility of RT in all stages of HCC might increase in the future because of the recent advances in RT techniques and clinical studies on RT for HCC. In addition, studies focusing on detailed clinical situations can also provide good evidence to support the role of RT in HCC. A more definitive role of external beam RT in HCC will be identified from the results of several ongoing prospective trials.

ETHICS APPROVAL

This review was exempted from the Institutional Review Board approval in accordance with the regulations.

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AUTHOR CONTRIBUTIONS

The author contributed solely to this article.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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