Current perspectives on radiotherapy in hepatocellular carcinoma management: a comprehensive review

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This review examines the transformative role of external beam radiotherapy (EBRT) in managing hepatocellular carcinoma (HCC), spotlighting the progression from traditional EBRT techniques to advanced modalities like intensity-modulated radiotherapy (RT), stereotactic body RT (SBRT), and innovative particle therapy, including proton beam therapy and carbon ion RT. These advancements have significantly improved the precision and efficacy of RT, marking a paradigm shift in the multimodal management of HCC, particularly in addressing complex cases and enhancing local tumor control. The review underscores the synergistic potential of integrating RT with other treatments like transarterial chemoembolization, systemic therapies such as sorafenib, and emerging immunotherapies, illustrating enhanced survival and disease control outcomes. The efficacy of RT is addressed for challenging conditions, including advanced HCC with macrovascular invasion, and RT modalities, like SBRT, are compared against traditional treatments like radiofrequency ablation for early-stage HCC. Additionally, the review accentuates the encouraging outcomes of particle therapy in enhancing local control and survival rates, minimizing treatment-related toxicity, and advocating for continued research and clinical trials. In conclusion, the integration of RT into multimodal HCC treatment strategies, coupled with the emergence of particle therapy, is crucial for advancing oncologic management, emphasizing the need for relentless innovation and personalized treatment approaches. (2024 Mar 25 [online ahead of print])

Keywords: Carcinoma, hepatocellular; Radiotherapy, intensity-modulated; Radiosurgery; Radiotherapy, proton; Radiotherapy, heavy-ion

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for approximately 80% of liver cancer cases.1,2 Most patients with HCC are located in the Asia-Pacific area, and approximately 75% to 90% of these cases are linked to chronic infection with viral hepatitis, predominantly hepatitis B or C.3-5 In recent years, there has been a notable evolution in the treatment of HCC, with developments in external beam radiotherapy (EBRT) contributing substantially to this evolution. Initially perceived as a modality with restricted application because of concerns over radiation-induced liver disease (RILD),6 radiotherapy (RT) has now emerged as an integral element in the multimodal management of HCC. This paradigm shift has been propelled by enhancements in EBRT techniques, such as intensity-modulated RT (IMRT) and stereotactic body RT (SBRT), dramatically improving the precision and efficacy of radiation delivery. Moreover, integrating particle RT, including proton and carbon ion therapy, has expanded therapeutic options, leveraging their unique physical and radiobiological properties to improve outcomes.

HCC presents unique oncologic management challenges because of its complexity and heterogeneity.7 While surgical resection and liver transplantation are preferred for early-stage HCC, these options...
are often unfeasible for most patients who present with advanced disease at diagnosis. Additionally, the liver's complex anatomy and frequent liver function impairment in patients with HCC add to the treatment challenge. In this context, the role of RT has been re-evaluated and expanded, offering new effective treatment avenues for various stages of HCC.

This review aims to offer a comprehensive analysis of the evolving role of RT in HCC treatment. Technical advancements in EBRT will be covered, particularly how IMRT and SBRT have improved treatment outcomes, especially in local tumor control. Additionally, the review will explore the integration of RT with other treatment strategies, such as transarterial chemoembolization (TACE) and systemic therapies, including sorafenib and emerging immunotherapies. The specific application of RT in challenging cases like advanced HCC with macrovascular invasion will also be addressed, underscoring the necessity for ongoing research and future directions in this rapidly developing field. By presenting this review, we aim to highlight the dynamic and crucial role of RT in the multidisciplinary treatment of HCC, emphasizing its importance in enhancing patient outcomes and the necessity for ongoing research and collaboration in this evolving domain.

**Efficacy of RT in HCC**

Historically, the role of EBRT in treating malignant hepatic tumors has been limited owing to the risk of RILD. However, technological advances, such as IMRT and three-dimensional conformal RT, now allow for the delivery of optimized dose distributions in fractionated RT regimens. These techniques utilize three-dimensional images obtained by computed tomography to facilitate precise delineation of the target and avoidance structures, including normal liver tissue, during RT planning. Consequently, in the modern era, EBRT is indicated across all stages of HCC. Furthermore, proton beam therapy (PBT) and carbon ion RT (CIRT) have been proven through various studies to provide outstanding disease control and acceptable toxicity. Recent research has shifted focus toward the combined therapy of EBRT with other modalities or the potential of EBRT as an alternative to conventional local treatments in specific liver locations or depending on the patient’s condition and liver function. Numerous comparative studies are being reported in this area.

**Combined Transarterial Chemo- or Radioembolization with RT**

In many real-world clinical settings, EBRT is often performed in conjunction with TACE for HCC. Several studies have reported comparisons between TACE alone and TACE combined with EBRT. The 1- and 2-year OS rates for TACE combined with EBRT have been reported to range from 50-100% and 23-100%, respectively. In contrast, for TACE alone, the reported 1-year OS rates vary from 31-88.9% and 2-year OS rates from 14-73.6%. Although the survival rate ranges vary across studies, depending on the stage of HCC and the RT modality used, a common finding is that TACE combined with EBRT generally offers a survival advantage over TACE alone. A meta-analysis has shown that combining TACE and EBRT significantly improves the response rate and the 1- and 3-year survival rates compared with TACE alone. Additionally, several studies have reported the effectiveness of using EBRT as a salvage treatment option after incomplete TACE.

In a meta-analysis reported by Yang et al., patients who received EBRT ranging from 37.3 to 150 Gy following incomplete TACE showed 1- and 2-year OS rates of 72.3% and 50.5%, respectively. The pooled response and local control rates were 72.2% and 86.6%, respectively. These findings suggest that EBRT can be a feasible and effective local management strategy for HCC following incomplete TACE.

Identifying the appropriate time interval for effective combined treatment of TACE and EBRT is crucial. Several studies have addressed this; Yu et al. conducted scheduled interval treatment for unresectable HCC, assuming that a 2-week interval between TACE and RT is optimal. This resulted in 70.4% of patients achieving an objective response, with a median OS of 14.7 months. Moreover, grade 3 or higher liver dysfunction, according to the common terminology criteria of adverse events, occurred in only 2.5% of patients, demonstrating the safety and feasibility of a 2-week treatment interval. Additionally, Byun et al. analyzed...
### Table 1. Treatment outcomes for hepatocellular carcinoma treated with external beam radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient number</th>
<th>Study type</th>
<th>Stage/patient characteristic</th>
<th>RT modality</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Treatment outcomes (%)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoon et al.²⁴ (2014)</td>
<td>65</td>
<td>R</td>
<td>UICC stage III or IV-A</td>
<td>IMRT</td>
<td>47.5-60.0</td>
<td>2.5-3.5</td>
<td>1y LC: 72.1, 1y OS: 74.0, 2y OS: 47.1</td>
<td>21</td>
</tr>
<tr>
<td>Huang et al.²³ (2015)</td>
<td>38</td>
<td>R</td>
<td>UICC stage T1-4N0M0, unresectable HCC</td>
<td>IMRT</td>
<td>46.0-71.8</td>
<td>1.8-2.4</td>
<td>1y LC: 88.2, 1y OS: 56.2, 2y OS: 31.7</td>
<td>17.2</td>
</tr>
<tr>
<td>Yeh et al.²² (2015)</td>
<td>106</td>
<td>R</td>
<td>BCLC stage C, HCC with PVTT</td>
<td>IMRT</td>
<td>60-71.8</td>
<td>2</td>
<td>1y OS: 34.7, 2y OS: 11.0</td>
<td>10</td>
</tr>
<tr>
<td>Hou et al.²⁵ (2016)</td>
<td>54</td>
<td>R</td>
<td>BCLC stage C, HCC with PVTT or IVCTT</td>
<td>IMRT</td>
<td>40-66</td>
<td>2.5-4.0</td>
<td>1y OS: 59.3, 2y OS: 32.1</td>
<td>11.8</td>
</tr>
<tr>
<td>Zhang et al.²⁶ (2016)</td>
<td>54</td>
<td>R</td>
<td>UICC stage I-IVA, EBRT following TACE in patients with unresectable HCC</td>
<td>IMRT</td>
<td>44-70</td>
<td>1.8-2.0</td>
<td>1y LC: 84.3, 1y OS: 84.6, 2y OS: 49.7, 3y OS: 36.7</td>
<td>28.7</td>
</tr>
<tr>
<td>Jiang et al.²⁷ (2017)</td>
<td>45</td>
<td>R</td>
<td>Unresectable HCC</td>
<td>IMRT</td>
<td>35-68</td>
<td>2.2-5.5</td>
<td>1y OS: 93.3, 2y OS: 73.3, 3y OS: 50.0</td>
<td>51.9</td>
</tr>
<tr>
<td>Li et al.²⁸ (2018)</td>
<td>76</td>
<td>R</td>
<td>HCC with PVTT</td>
<td>IMRT</td>
<td>50-67</td>
<td>2.0-2.2</td>
<td>1y OS: 38.2, 2y OS: 18.4</td>
<td>11</td>
</tr>
<tr>
<td>Chen et al.²⁹ (2021)</td>
<td>167</td>
<td>R</td>
<td>HCC with HVTT</td>
<td>IMRT</td>
<td>50-67</td>
<td>2.0-2.2</td>
<td>1y OS: 66.8, 2y OS: 29.9</td>
<td>NR</td>
</tr>
<tr>
<td>Sanuki et al.³¹ (2014)</td>
<td>185</td>
<td>R</td>
<td>UICC stage T1-3N0M0</td>
<td>SBRT</td>
<td>35-40</td>
<td>7-8</td>
<td>1y LC: 99.0, 2y LC: 93.0, 2y OS: 83.0</td>
<td>24</td>
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<tr>
<td>Hara et al.³² (2019)</td>
<td>143</td>
<td>R</td>
<td>BCLC stage 0-A, C</td>
<td>SBRT</td>
<td>35-40</td>
<td>7-8</td>
<td>3y LC: 95.6, 3y OS: 63.6</td>
<td>30.2</td>
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<tr>
<td>Kim et al.³³ (2019)</td>
<td>32</td>
<td>P</td>
<td>BCLC stage A, C</td>
<td>SBRT</td>
<td>36-60</td>
<td>9-15</td>
<td>2y LC: 87.0, 2y OS: 81.3</td>
<td>27</td>
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<tr>
<td>Park et al.³⁴ (2020)</td>
<td>290</td>
<td>P</td>
<td>BCLC stage 0-A</td>
<td>SBRT</td>
<td>30-60</td>
<td>10-20</td>
<td>5y LC: 91.3, 5y OS: 44.9</td>
<td>38.2</td>
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<tr>
<td>Mathew et al.³⁵ (2020)</td>
<td>297</td>
<td>R</td>
<td>BCLC stage 0-D</td>
<td>SBRT</td>
<td>27-60</td>
<td>9-10</td>
<td>3y LC: 87.0, 3y OS: 39.0</td>
<td>19.9</td>
</tr>
<tr>
<td>Yoon et al.³⁶ (2020)</td>
<td>50</td>
<td>P</td>
<td>BCLC stage 0-A, small (≤5 cm) HCCs</td>
<td>SBRT</td>
<td>45</td>
<td>15</td>
<td>5y LC: 97.1, 5y OS: 77.6</td>
<td>47.8</td>
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### Table 1. Continued

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient number</th>
<th>Study type</th>
<th>Stage/patient characteristic</th>
<th>RT modality</th>
<th>Total dose (Gy)</th>
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<th>Treatment outcomes (%)</th>
<th>Follow-up (months)</th>
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<tr>
<td>Jang et al. (2020)</td>
<td>65</td>
<td>P</td>
<td>BCLC stage 0-C, unresectable HCC</td>
<td>SBRT</td>
<td>60</td>
<td>20</td>
<td>2 yLC: 97.0</td>
<td>41</td>
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<tr>
<td>Durand-Labrunie et al. (2020)</td>
<td>43</td>
<td>P</td>
<td>Early-stage HCC (≤6 cm)</td>
<td>SBRT</td>
<td>45</td>
<td>15</td>
<td>2 yLC: 94.0</td>
<td>48</td>
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<tr>
<td>Kimura et al. (2021)</td>
<td>36</td>
<td>P</td>
<td>BCLC stage 0-C, unresectable HCC</td>
<td>SBRT</td>
<td>40</td>
<td>8</td>
<td>3 yLC: 87.0</td>
<td>21</td>
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<tr>
<td>Kim et al. (2021)</td>
<td>72</td>
<td>P</td>
<td>BCLC stage 0-C</td>
<td>SBRT (proton)</td>
<td>66</td>
<td>6</td>
<td>2 yLC: 92.8</td>
<td>51.6</td>
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<tr>
<td>Kawashima et al. (2005)</td>
<td>30</td>
<td>P</td>
<td>UICC stage I-III</td>
<td>Proton</td>
<td>76</td>
<td>3.8</td>
<td>2 yLC: 96.0</td>
<td>31</td>
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<tr>
<td>Komatsu et al. (2011)</td>
<td>343</td>
<td>R</td>
<td>BCLC stage 0-D</td>
<td>Proton (242)Carbon ion</td>
<td>52.8-84.0 (proton)</td>
<td>3.8-13.2</td>
<td>5 yLC: 90.8</td>
<td>31</td>
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<tr>
<td>Kim et al. (2014)</td>
<td>27</td>
<td>P</td>
<td>BCLC stage A-C</td>
<td>Proton</td>
<td>60-72</td>
<td>3</td>
<td>3 yOS: 56.4</td>
<td>31</td>
</tr>
<tr>
<td>Hong et al. (2016)</td>
<td>83</td>
<td>P</td>
<td>BCLC stage A-C, unresectable HCC</td>
<td>Proton</td>
<td>40.5-67.5</td>
<td>2.7-4.5</td>
<td>2 yLC: 84.8</td>
<td>19.5</td>
</tr>
<tr>
<td>Bush et al. (2016)</td>
<td>69</td>
<td>P</td>
<td>NR</td>
<td>Proton</td>
<td>70.2</td>
<td>4.7</td>
<td>2 yLC: 88.0</td>
<td>28</td>
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<tr>
<td>Kasuya et al. (2017)</td>
<td>124</td>
<td>P</td>
<td>UICC stage II-IVA</td>
<td>Proton</td>
<td>52.8-69.6</td>
<td>5.8-14.5</td>
<td>1 yLC: 94.7</td>
<td>27.1</td>
</tr>
<tr>
<td>Fukuda et al. (2017)</td>
<td>129</td>
<td>R</td>
<td>BCLC stage 0-C</td>
<td>Proton</td>
<td>66.0-77.0</td>
<td>2.2-6.6</td>
<td>5 yLC: 75.0-94.0</td>
<td>55</td>
</tr>
<tr>
<td>Kim et al. (2020)</td>
<td>45</td>
<td>P</td>
<td>BCLC stage A-C</td>
<td>Proton</td>
<td>70</td>
<td>7</td>
<td>3 yLC: 95.2</td>
<td>35.1</td>
</tr>
<tr>
<td>Parzen et al. (2020)</td>
<td>63</td>
<td>P</td>
<td>Unresectable HCC</td>
<td>Proton</td>
<td>32.5-75.0</td>
<td>2.4-10</td>
<td>1 yPFS: 60.3</td>
<td>5.1</td>
</tr>
</tbody>
</table>

RT, radiotherapy; R, retrospective study; UICC, Union for International Cancer Control; IMRT, intensity-modulated radiotherapy; y, year(s); LC, local control; OS, overall survival; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; IVCTT, inferior vena cava tumor thrombus; EBRT, external beam radiotherapy; TACE, transarterial chemoembolization; HVTT, hepatic vein tumor thrombus; NR, not reported; SBRT, stereotactic body radiotherapy; P, prospective study; PFS, progression-free survival.
### Table 2. Treatment outcomes of combined TACE and radiotherapy versus TACE monotherapy in the treatment of hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient number</th>
<th>Study type</th>
<th>Stage/patient characteristic</th>
<th>RT modality</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Treatment outcomes* (%)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng et al.26 (2000)</td>
<td>17 (TACE+RT) 16 (TACE alone)</td>
<td>R</td>
<td>UICC stage I-IV, unresectable HCC</td>
<td>3D</td>
<td>36.0-61.6</td>
<td>1.8-2.0</td>
<td>1 y OS: 84 vs. 68</td>
<td>23</td>
</tr>
<tr>
<td>Guo et al.27 (2003)</td>
<td>76 (TACE+RT) 89 (TACE alone)</td>
<td>R</td>
<td>Okuda stage I-III, unresectable large HCC</td>
<td>3D</td>
<td>30-50</td>
<td>1.8-2.0</td>
<td>1 y OS: 64.0 vs. 39.9</td>
<td>26</td>
</tr>
<tr>
<td>Zeng et al.27 (2004)</td>
<td>54 (TACE+RT) 149 (TACE alone)</td>
<td>R</td>
<td>Unresectable HCC</td>
<td>2D</td>
<td>36-60</td>
<td>2</td>
<td>1 y OS: 71.5 vs. 59.6</td>
<td>NR</td>
</tr>
<tr>
<td>Wu et al.26 (2004)</td>
<td>41 (TACE+RT) 40 (TACE alone)</td>
<td>R</td>
<td>Okuda stage I-II</td>
<td>3D</td>
<td>48-60</td>
<td>4-8</td>
<td>1 y OS: 90.2 vs. 89.7</td>
<td>37</td>
</tr>
<tr>
<td>Shim et al.25 (2005)</td>
<td>38 (TACE+RT) 35 (TACE alone)</td>
<td>R</td>
<td>UICC stage III, IVA</td>
<td>3D</td>
<td>36.0-594</td>
<td>1.8</td>
<td>1 y OS: 70 vs. 33</td>
<td>NR</td>
</tr>
<tr>
<td>Koo et al.24 (2010)</td>
<td>42 (TACE+RT) 29 (TACE alone)</td>
<td>P</td>
<td>BCLC stage B or C HCC with IVCTT</td>
<td>3D</td>
<td>28-50</td>
<td>2.5-5.0</td>
<td>1 y OS: 50 vs. 17</td>
<td>NR</td>
</tr>
<tr>
<td>Honda et al.22 (2013)</td>
<td>30 (TACE+RT) 38 (TACE alone)</td>
<td>R</td>
<td>Small (&lt;3 cm) HCC without PVTT or extrahepatic metastases</td>
<td>SBRT</td>
<td>48-60</td>
<td>6-12</td>
<td>1 y OS: 100.0 vs. 88.9</td>
<td>12.31</td>
</tr>
<tr>
<td>Kim et al.23 (2014)</td>
<td>35 (TACE+RT) 49 (TACE alone)</td>
<td>R</td>
<td>BCLC stage B or C, unresectable HCC</td>
<td>3D, IMRT, tomosurgery</td>
<td>36-60</td>
<td>1.8-3.0</td>
<td>1 y OS: 68 vs. 31</td>
<td>27.8</td>
</tr>
<tr>
<td>Chen et al.20 (2014)</td>
<td>78 (TACE+RT) 80 (TACE alone)</td>
<td>P</td>
<td>UICC stage III, IV</td>
<td>3D</td>
<td>50-62</td>
<td>2.0-2.5</td>
<td>1 y OS: 78.5 vs. 58.8</td>
<td>27.5</td>
</tr>
</tbody>
</table>

TACE, transarterial chemoembolization; RT, radiotherapy; R, retrospective study; UICC, Union for International Cancer Control; HCC, hepatocellular carcinoma; 3D, three-dimensional conformal radiotherapy; y, year(s); OS, overall survival; 2D, two-dimensional radiotherapy; NR, not reported; P, prospective study; BCLC, Barcelona Clinic Liver Cancer; IVCTT, inferior vena cava tumor thrombus; PVTT, portal vein tumor thrombus; SBRT, stereotactic body radiotherapy; IMRT, intensity-modulated radiotherapy.

*TACE+RT vs. TACE alone; †TACE+SBRT; ‡TACE alone.
treatment outcomes based on various intervals between TACE and RT, finding that groups receiving early RT within 5 weeks exhibited the highest local failure-free rate. As EBRT is increasingly applied for consolidation or salvage purposes following TACE in HCC cases, it becomes imperative to conduct additional research and validation studies to determine its optimal timing.

Radiation can also be effectively delivered to HCC via transarterial radioembolization (TARE), in addition to EBRT. TARE has been demonstrated to offer superior objective response rates, exceptional local tumor control, and a favorable toxicity profile. This technique involves administering \(^{90}\)Y microspheres into the hepatic artery branches that supply the tumor. Despite the proven therapeutic success of TARE in HCC treatment, the application of TARE following EBRT is met with concerns regarding the risk of RILD. Furthermore, there is a scarcity of research on using EBRT after TARE. Hardy-Abeloos et al. compared the outcomes of SBRT following TARE and SBRT post-TACE. SBRT post-TARE did not demonstrate significant differences in local control and OS compared with post-TACE, although the objective response rate was worse post-TARE. Additionally, grade 3 or higher toxicity and liver decompensation did not show significant differences between the two groups. Conversely, Lam et al. conducted a safety analysis in patients who underwent TARE after previously receiving EBRT. The results indicated that prior exposure of the liver to EBRT increased the risk of hepatotoxicity. However, the cumulative liver dose was not an independent predictor, and a dose-volume histogram analysis revealed that the fraction of liver exposed to >30 Gy (V30) was the strongest predictor of hepatotoxicity. These findings provide insight into the combined therapy of EBRT and TARE, yet all studies are retrospective and involve a limited number of patients, necessitating further validation.

**COMPARISON OF SBRT AND RADIOFREQUENCY ABLATION**

In cases of early-stage HCC where surgery is not feasible, the current guidelines predominantly recommend radiofrequency ablation (RFA) as the treatment option of choice. However, recent studies have brought to light that the local control rates of SBRT are comparably effective to those of RFA. Emerging data increasingly substantiate the effectiveness of SBRT in managing early-stage HCC, evidenced by a 2-year local control rate reaching 90%. In various prospective clinical trials, SBRT has consistently demonstrated robust local control, achieving rates between 87% and 100% over a period of 1 year to 3 years. In the multinational study conducted by Kim et al., SBRT was shown to have superior local control rates compared with RFA for small-sized tumors (≤3 cm). Significantly, SBRT demonstrated remarkable treatment outcomes for large-sized tumors located in challenging areas, such as the subphrenic regions, where RFA is typically less effective. Additionally, a recent meta-analysis reported that the pooled 1- and 2-year survival rates for HCC studies were 91.8% and 77.7% after RFA and 89.0% and 76.0% after SBRT, respectively. The pooled grade ≥3 complication rates were 2.9% for RFA and 2.8% for SBRT. The meta-analysis further revealed that SBRT can be more effective than RFA for tumors larger than 2-3 cm or specific sublocations in the liver, such as the subphrenic or perivascular sites. These findings imply that SBRT can be considered a comparable alternative to RFA in treating early-stage HCC, considering factors such as tumor size, location, and the patient's condition and history.

This emerging evidence suggests a potential re-evaluation of SBRT’s role in the treatment paradigm for early-stage HCC. Additionally, SBRT has been reported in several studies as a successful alternative to TACE and RFA for recurrent tumors. Moreover, for HCC lesions that recurred after TACE, SBRT markedly outperformed RFA in achieving better outcomes. Consequently, the American Society of Radiation Oncology guidelines have officially recognized SBRT as a viable treatment option.

**EBRT IN ADVANCED HCC WITH MACROVASCULAR INVASION**

EBRT has also been demonstrated as a viable and safe option for treating advanced HCC with macrovascular invasion. Studies have indicated that the overall tumor response rate following EBRT ranges from 30% to 96%, with patients experiencing a median survival time of 7 to 34.4 months. This response rate varies depending on the tumor’s location. Specifically, patients with portal vein tumor invasion exhibited response rates between 30% and 83%. In contrast, those with tumor invasion into the inferior vena cava and right atrium had response rates of 43% to 96%. Notably, the median survival period post-EBRT for HCC patients with invasion of the inferior vena cava and right atrium was recorded at 12.1 months and 9.3 months, respectively. Hou et al. compared treatment outcomes based on the location of the tumor thrombus in patients with HCC and macrovascular invasion, reporting that patients with inferior vena cava tumor thrombi showed significantly better response rates to EBRT than those with portal vein tumor thrombi. Additionally, Wu et al. conducted a meta-analysis on the treatment outcomes in patients with HCC and macrovascular invasion, according to the RT modality. They reported that proton therapy showed significantly
better 1-year and 2-year OS compared with conventional RT or SBRT (proton therapy vs. conventional RT, P=0.005 for 1-year OS, P=0.001 for 2-year OS; proton therapy vs. SBRT, P=0.002 for 1-year OS, P=0.004 for 2-year OS).

A retrospective cohort analysis conducted in multiple centers across Korea showed that 66.7% of patients with HCC and portal vein invasion who underwent EBRT also received a combination treatment involving TACE or hepatic arterial infusion chemotherapy (HAIC).103 Further supporting this approach, a recent meta-analysis highlighted that this combination therapy (TACE or HAIC with EBRT) notably enhances the objective response and OS in these patients, as opposed to the results achieved through monotherapies like TACE, HAIC,104 or sorafenib.105 Additionally, both retrospective series analyses and a recent randomized controlled trial underscored the superior survival rates achieved in patients with HCC and portal vein invasion when treated with the combined regimen of TACE and EBRT, in contrast to those undergoing sorafenib monotherapy.106-109

PARTICLE THERAPY FOR HCC

With the advancement of RT techniques, there has been a significant increase in reported studies on meaningful particle therapy in HCC (Table 3).19,22,25,47-63 PBT is characterized by its exceptional dose concentration, enabling the safe delivery of high doses directly to tumors. This is particularly advantageous in treating large lesions, which are often challenging to manage with SBRT.110 Additionally, PBT offers effective local control of tumors.111 PBT is also effective for HCC with portal vein tumor thrombosis or inferior vena cava tumor thrombosis, conditions that are challenging to treat with surgery or RFA.28,112 Substantial clinical evidence exists for PBT, particularly when comparing outcomes with various treatment modalities.113 In a multi-institutional prospective study conducted in Japan, PBT for unresectable HCC showed promising results.114 Over a median follow-up period of 39 months, local recurrence was observed in only 7.8% of cases. Furthermore, the median OS and progression-free survival (PFS) were reported as 48.8 months and 14.7 months, respectively. The 3-year OS and PFS rates were 58.8% and 30.2%, respectively. Additionally, in the most recent study by Bush et al.111 on untreated HCC, a comparison between TACE and PBT showed nearly identical 2-year OS rates at 68% in both groups (P=0.08), with PBT demonstrating significantly better outcomes in terms of median PFS and local control. Tamura et al.112 compared treatment outcomes between surgical resection and PBT in HCC cases where the lesion was less than 10 cm and without vessel invasion. Across all patients, the median survival time was superior in the surgery group compared with PBT. However, no significant difference was observed in relapse-free survival between the two groups. Additionally, results from propensity-score matching analysis indicated no significant difference in OS between the two groups. In a recent phase III randomized controlled trial by Kim et al.114 in Korea, PBT for HCC lesions ≤3 cm showed comparable efficacy to RFA, the standard treatment. This single-center, non-inferiority trial revealed PBT’s local control rate was not inferior, with locoregional PFS rates at 92.8% vs. 83.2% for RFA. No significant differences were noted in PFS, OS, or toxicity rates. PBT has similar efficacy and an excellent safety profile, evidenced by stable Child-Pugh scores, and has been established as a viable, curative option for small HCC.

In HCC treatment, CIRT has recently been recognized as a noteworthy therapeutic approach.115 CIRT, a form of particle RT, leverages carbon ion beams for precise targeting and eradication of cancer cells.116 The primary advantages of CIRT lie in its distinctive physical and biological characteristics.117 These carbon ions can deposit concentrated energy within a limited tissue volume, inflicting greater damage to cancer cells with superior biological effectiveness than photons or protons. Additionally, the unique dose distribution of carbon ions facilitates administering a high radiation dose directly to the tumor while substantially reducing the impact on adjacent normal organs.118 Several prospective phase I and II studies have rigorously examined the efficacy and feasibility of CIRT for HCC. In a landmark 2004 phase I trial by the National Institute of Radiological Sciences in Japan, dose escalation from 49.5 Gy (relative biological effectiveness [RBE]) to 79.5 Gy (RBE) in 15 fractions exhibited no severe adverse effects or deaths, achieving an 81% local control rate at 3 and 5 years.119 The institute’s 2017 combined phase I and II trial results identified maximum tolerated doses at 69.6, 58.0, and 52.8 Gy (RBE) for 12, eight, and four fractions, respectively, with 52.8 Gy (RBE) in four fractions recommended for phase II studies.120 In two prospective trials led by Shibuya et al.121 where doses of 52.8 Gy and 60 Gy (RBE) were administered in four fractions, the local control rates achieved were 92.3% at the 2-year mark and 76.5% at 4 years. These studies observed only late-grade 3 hepatobiliary toxicity, indicating a favorable safety profile for this treatment regimen. In a recent phase I trial from China, where doses ranged from 55 to 70 Gy (RBE) in 10 fractions, no dose-limiting toxicity was observed. The trial achieved a 5-year OS and local control rates of 67.1% and 94.4%, respectively.122 Limited retrospective studies exist comparing CIRT with other treatment modalities for HCC. According to Shibata et al.,123 CIRT was compared with TACE for a single HCC lesion. Analysis of 17 matched pairs revealed significantly better 3-year

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patient number</th>
<th>Study type</th>
<th>Stage/patient characteristic</th>
<th>RT modality</th>
<th>Total dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>Treatment outcomes (%)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shibata et al. (2018)</td>
<td>29</td>
<td>R</td>
<td>UICC stage T1-4N0M0</td>
<td>Proton</td>
<td>66.0-80.5</td>
<td>2.0-6.6</td>
<td>2 y LC: 95, 2 y OS: 61</td>
<td>27</td>
</tr>
<tr>
<td>Tamura et al. (2020)</td>
<td>31</td>
<td>R</td>
<td>Single HCC, &lt;10 cm, without vessel invasion</td>
<td>Proton</td>
<td>66-76</td>
<td>2.0-6.6</td>
<td>3 y OS: 62.2</td>
<td>56.3</td>
</tr>
<tr>
<td>Chadha et al. (2019)</td>
<td>46</td>
<td>R</td>
<td>Unresectable HCC</td>
<td>Proton</td>
<td>24.0-91.0</td>
<td>1.6-6.1</td>
<td>1 y LC: 95, 1 y OS: 73</td>
<td>14</td>
</tr>
<tr>
<td>Kim et al. (2019)</td>
<td>243</td>
<td>R</td>
<td>BCLC stage A-C</td>
<td>Proton</td>
<td>50-66</td>
<td>5.0-6.6</td>
<td>3 y LPFS: 88.6, 3 y OS: 61.8</td>
<td>31.5</td>
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<tr>
<td>Kim et al. (2020)</td>
<td>45</td>
<td>P</td>
<td>BCLC stage A-C</td>
<td>Proton</td>
<td>70</td>
<td>7</td>
<td>3 y LPFS: 95.2, 3 y OS: 86.4</td>
<td>35.1</td>
</tr>
<tr>
<td>Yoo et al. (2020)</td>
<td>167</td>
<td>R</td>
<td>BCLC stage 0-D</td>
<td>Proton</td>
<td>66.0 or 72.6</td>
<td>6.6 or 3.3</td>
<td>2 y LC: 86.5, 2 y OS: 86.6</td>
<td>14</td>
</tr>
<tr>
<td>Iwata et al. (2021)</td>
<td>45</td>
<td>P</td>
<td>UICC stage I</td>
<td>Proton</td>
<td>66.0 or 72.6</td>
<td>6.6 or 3.3</td>
<td>2 y LC: 95, 2 y OS: 84</td>
<td>53</td>
</tr>
<tr>
<td>Iizumi et al. (2021)</td>
<td>30</td>
<td>R</td>
<td>HCC in the caudate lobe</td>
<td>Proton</td>
<td>55-77</td>
<td>2.0-5.5</td>
<td>1 y LC: 100.0, 1 y OS: 86.6</td>
<td>37.5</td>
</tr>
<tr>
<td>Bhangoo et al. (2021)</td>
<td>37</td>
<td>R</td>
<td>HCC without metastatic disease</td>
<td>Proton</td>
<td>58.5 or 67.5</td>
<td>3.9 or 4.5</td>
<td>1 y LC: 94, 1 y OS: 78</td>
<td>21</td>
</tr>
<tr>
<td>Iizumi et al. (2023)</td>
<td>15</td>
<td>R</td>
<td>HCC with bile duct invasion</td>
<td>Proton</td>
<td>72.6</td>
<td>3</td>
<td>1 y LC: 93.3, 1 y OS: 80.0</td>
<td>23.4</td>
</tr>
<tr>
<td>Kato et al. (2004)</td>
<td>24</td>
<td>P</td>
<td>UICC stage II-IVA</td>
<td>Carbon ion</td>
<td>49.5-79.5</td>
<td>3.3-5.3</td>
<td>1 y LC: 92, 1 y OS: 92</td>
<td>71</td>
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<tr>
<td>Komatsu et al. (2011)</td>
<td>101</td>
<td>R</td>
<td>BCLC stage 0-D</td>
<td>Carbon ion</td>
<td>52.8-76.0</td>
<td>3.8-13.2</td>
<td>5 y LC: 93.0, 5 y OS: 36.3</td>
<td>31</td>
</tr>
<tr>
<td>Shiba et al. (2017)</td>
<td>31</td>
<td>R</td>
<td>BCLC stage A-C</td>
<td>Carbon ion</td>
<td>52.8-60.0</td>
<td>5-15</td>
<td>2 y LC: 89.2, 2 y OS: 82.3</td>
<td>23.2</td>
</tr>
<tr>
<td>Kasuya et al. (2017)</td>
<td>126</td>
<td>P</td>
<td>BCLC stage A-C</td>
<td>Carbon ion</td>
<td>52.8-69.6</td>
<td>5.8-13.2</td>
<td>1 y LC: 94.7, 1 y OS: 90.3</td>
<td>27.1</td>
</tr>
<tr>
<td>Okazaki et al. (2021)</td>
<td>9</td>
<td>R</td>
<td>HCC in the caudate lobe</td>
<td>Carbon ion</td>
<td>52.8 or 60.0</td>
<td>5-15</td>
<td>No local recurrence, five patients died</td>
<td>18.3</td>
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<tr>
<td>Shiba et al. (2020)</td>
<td>11</td>
<td>R</td>
<td>BCLC stage A, C</td>
<td>Carbon ion</td>
<td>52.8 or 60.0</td>
<td>5-15</td>
<td>3 y LC: 78, 3 y OS: 64</td>
<td>36.4</td>
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<tr>
<td>Shibuya et al. (2021)</td>
<td>35</td>
<td>P</td>
<td>NR</td>
<td>Carbon ion</td>
<td>52.8 or 60.0</td>
<td>13.2 or 15.0</td>
<td>2 y LC: 92.6, 2 y OS: 82.8</td>
<td>49</td>
</tr>
<tr>
<td>Hong et al. (2023)</td>
<td>23</td>
<td>P</td>
<td>BCLC stage 0, B, C</td>
<td>Carbon ion</td>
<td>55-70</td>
<td>5.5-7.0</td>
<td>1 y LC: 100.0, 1 y OS: 91.3</td>
<td>56.1</td>
</tr>
</tbody>
</table>

RT, radiotherapy; R, retrospective study; UICC, Union for International Cancer Control; y, year(s); LC, local control; OS, overall survival; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; LPFS, local progression-free survival; P, prospective study; NR, not reported.
outcomes for CIRT, with higher OS (88% vs. 58%), local control (80% vs. 26%), and PFS (51% vs. 15%) than TACE. Fujita et al. also compared CIRT with RFA as initial treatments for early-stage HCC. In a cohort of 560 patients, those undergoing CIRT showed significantly lower cumulative intrasubsegmental recurrence rates at 2 years (12.6% vs. 31.7%) and 5 years (15.5% vs. 49.6%). Nevertheless, local control, PFS, and OS rates were similar between the groups. Importantly, the CIRT group experienced no grade 3 or higher adverse events, as opposed to a 1.2% rate in the RFA group.

**SYSTEMIC THERAPY COMBINED WITH EBRT**

With the advancement of EBRT technology, superior local control in various stages of HCC, including the early stage, has been demonstrated. Nevertheless, RT faces certain limitations in managing advanced HCC. Achieving local tumor control through RT does not consistently result in prolonged patient survival, mainly because of its limitations in addressing liver dysfunction and the risk of metastasis or progression in other organs. Consequently, integrating local and systemic treatments for HCC may offer enhanced survival benefits for patients. In advanced HCC, sorafenib is a crucial option for systemic therapy. This agent gained approval following the results of two significant randomized controlled trials specifically targeting HCC. Currently, sorafenib is recognized as the primary systemic treatment for HCC in patients with preserved liver function (classified as Child-Pugh class A), in cases of advanced-stage HCC (Barcelona Clinic Liver Cancer-C), and HCC cases exhibiting progression post-locoregional therapy. Recent studies, however, have shown that combination therapy of atezolizumab and bevacizumab offers superior OS rates compared with sorafenib alone. While new therapeutic options for HCC have emerged, including lenvatinib as a first-line treatment and nivolumab, regorafenib, ramucirumab, and cabozantinib as second-line treatments, sorafenib retains its significance in treating advanced HCC. This is because other first-line treatments, besides the atezolizumab-bevacizumab combination, have not demonstrated superiority over sorafenib. Moreover, most second-line therapies are considered in scenarios where sorafenib has not yielded the desired outcomes.

Numerous studies have established the survival benefits of combining sorafenib with EBRT. A multicenter study in Korea demonstrated that concurrent administration of sorafenib and EBRT significantly improved OS compared with sorafenib monotherapy. Additionally, a nationwide cancer-registry-based study in Taiwan reported that patients receiving sorafenib plus RT had significantly better 1-year survival than those treated with sorafenib alone. Conversely, a propensity score-matching analysis conducted in Korea indicated that sorafenib administered before or concurrently with EBRT did not significantly impact OS. However, administering EBRT after sorafenib was associated with a significant improvement in OS. Additionally, a Chinese study using a propensity score-matching analysis found that HCC with macrovascular invasion treated with IMRT and TACE combined with sorafenib showed longer PFS but no significant difference in OS compared with a group without sorafenib.

**FUTURE DIRECTIONS AND ONGOING RESEARCH**

In the most recent phase 3, multicenter randomized controlled trial (NRG/RTOG 1112) for locally advanced HCC, the treatment outcomes of sorafenib monotherapy were compared with those of a combination therapy involving SBRT (27.5-50 Gy in five fractions) followed by sorafenib. The results revealed that the combination therapy significantly enhanced OS and PFS. Additionally, there was no significant difference in grade 3 or higher toxicity between the two groups. These findings underscore the safety and considerable survival benefits of adding SBRT to sorafenib, a commonly used systemic therapy agent in advanced HCC, suggesting a more prominent role for SBRT in future clinical applications.

While immunotherapy has emerged as a primary treatment approach for advanced HCC, its effectiveness varies owing to innate or acquired resistance mechanisms. This variation highlights the critical need for research into combined therapies, integrating immunotherapy with other treatment methods to enhance effectiveness in HCC management. Pursuing such research is vital for advancing patient care and addressing the current limitations of immunotherapy strategies in HCC. RT can modify the tumor microenvironment, influencing immune response and potentially synergizing with immunotherapies. With the proven efficacy of anti-PD-1/PD-L1 and anti-CTLA-4 antibodies in malignant tumors, researchers are actively exploring their combination with RT modalities, including SBRT or proton therapy in HCC treatment. A multicenter phase 2 trial in Korea investigated the concurrent use of nivolumab and EBRT in advanced HCC with macrovascular invasion, reporting promising PFS and safety. Similarly, a study in Hong Kong comparing SBRT with nivolumab to TACE alone in locally advanced HCC found significantly better survival and reduced treatment toxicity with the combined approach. Furthermore, an ongoing prospective phase 2 study is evaluating the efficacy and safety of atezolizumab/bevacizumab with PBT in...
HCC with portal vein invasion. While numerous trials have explored various immunotherapies and RT types across HCC stages, there is still a significant need for data on their synergistic use. These ongoing studies are crucial, as the integration of RT and immunotherapy represents a substantial shift in HCC treatment paradigms. This approach opens new avenues for comprehensive strategies, targeting the tumor and leveraging the body’s immune response, potentially improving patient outcomes in HCC management.

CONCLUSION

This review has thoroughly explored the dynamic role of RT, including advanced modalities like IMRT, SBRT, and particle therapy, in managing HCC. The advancements in RT, particularly with the introduction of particle therapy such as PBT and CIRT, mark a significant leap forward in treating HCC. These techniques offer unique advantages, including precision targeting and reduced risk to surrounding healthy tissue, making them especially valuable in treating complex cases like HCC with macrovascular invasion or in challenging anatomical locations.

The integration of RT with other treatments, such as TACE and systemic therapies, including sorafenib and immunotherapies, has shown enhanced outcomes regarding OS and disease control. This multimodal approach is particularly relevant in advanced HCC, where treatment options were previously limited. The synergistic potential of combining RT with emerging treatments like immunotherapy opens new avenues for comprehensive cancer care, offering hope for better patient outcomes and personalized treatment strategies.

Moreover, the developing field of particle therapy in HCC treatment, demonstrated by the promising outcomes of PBT and CIRT, highlights the necessity for continued research and clinical trials. These advanced RT modalities have yielded promising results, showing improved local control, enhanced survival rates, and diminished treatment-related toxicity, particularly in scenarios where traditional treatments are less effective or unviable.

In conclusion, the role of RT in HCC has expanded significantly, moving beyond traditional limitations to become a cornerstone of modern oncologic management. The continuous advancements in RT techniques, including the emerging field of particle therapy, coupled with the integration of RT into multimodal treatment regimens, are crucial in improving the prognosis and quality of life for patients with HCC. As we progress, the focus on personalized medicine, backed by robust clinical research, will be vital to optimizing treatment strategies and outcomes in HCC management.

Conflicts of Interest
The authors have no conflicts of interest to disclose.

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Author Contribution
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Writing - review & editing: DK, JSK

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