Review

Application of Radiotherapeutic Strategies in the BCLC-Defined Stagesof Hepatocellular Carcinoma

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Key Words

Hepatocellular carcinoma · Radiotherapy · Treatment guidelines

Abstract

The Barcelona Clinic Liver Cancer (BCLC) staging system is the method currently used to stage hepatocellular carcinoma (HCC) and therefore plays an important role in deciding on an appropriate course of treatment. BCLC takes into consideration the extent of the disease as well as patient factors such as hepatic function and performance status. However, it does not propose solutions for all clinical situations. Although radiotherapy (RT) is not included in the BCLC guidelines, the potent local antitumor effect of RT should be considered seriously as a part of the treatment strategy. Novel RT technologies introduced during the last decade have made it possible to deliver higher doses of radiation to the tumor while avoiding damage to critical normal tissues adjacent to the tumor. Because of the growing interest in using RT for HCC patients unfit for or progressed beyond standard treatments, the role of RT for HCC patients needs to be specified within the BCLC staging system. Curative RT can be used for patients with either very early or early stage BCLC; focal high dose RTs, such as stereotactic body RT, are especially useful. Intermediate or advanced stage disease confined to the liver can be managed safely and effectively by localized RT in conjunction with other treatment modalities such as transarterial chemoembolization or concurrent or adjuvant chemotherapy. In this review, the efficacy of RT in each BCLC stage of HCC will be discussed.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cause of cancer-related death worldwide [1]. Hepatic function is included in many staging systems for HCC because it is widely accepted that the prognosis of HCC is impacted by hepatic function, in addition to tumor-related factors [2–6]. One of the most widely used staging systems is the Barcelona Clinic Liver Cancer (BCLC) system [2]. One major advantage of BCLC is that it provides both tumor staging and treatment recommendations. However, one disadvantage is that the advanced stage disease consists of heterogeneous disease phenotypes with variable prognosis for which there is a single recommended treatment—sorafenib. The majority of HCC patients die of intrahepatic tumor progression; therefore, liver-directed therapies are essential for improving clinical outcomes regardless of the stage [7]. In practice, standard curative local treatment modalities such as liver resection, radiofrequency ablation (RFA), and liver transplantation are offered to a limited number of patients [8]. When these options are limited, transarterial chemoembolization (TACE) is widely used in Asian countries for local control of the disease [9–13]. Nevertheless, local progression or intrahepatic recurrence is common after these therapies [14].

Despite its well-established local antitumor effect, radiotherapy (RT) for HCC has long been overlooked by physicians because even after delivery of sub-therapeutic radiation doses, fatal hepatic injury may develop [15, 16]. With recent developments in RT technology, it is possible to deliver precisely focused, high-dose radiation to partial volumes of the liver [17–29]. This has been incorporated into the National Comprehensive Cancer Network Guidelines, version 2.2012, for HCC, which recommends RT as a locoregional therapy for all tumors irrespective of location [30]. Moreover, RT is considered appropriate for unresectable, locally advanced HCC with hepatic function of Child-Pugh class (CP class) A or B, which is supported by evidence level II in the practice guidelines of the Korean Liver Cancer Study Group [31].

In this review, we will discuss the specific indications for RT in HCC according to the BCLC staging system.

BCLC Very Early Stage Or Early Stage

The treatment of choice for small, solitary HCC at very early BCLC stage and with no portal hypertension is a partial liver resection, whereas liver transplantation is considered for cases with portal hypertension or early BCLC stage and with no contraindication to transplant. For HCC patients at an early BCLC stage and with an inoperable condition, including those refusing surgery, local ablation such as RFA or percutaneous ethanol injection therapy is recommended. However, the lesions near the hepatic dome or adjacent to the main portal vein can be difficult to target with RFA or may be heated improperly because of the heat sink phenomenon and are also susceptible to procedure-related complications [32]. Empirical use of RT for these lesions has resulted in a substantial response (fig. 1).

Several reports of RT in these patient populations have been published recently. Updated results from the French RTF-1 trial, a prospective phase II trial including CP class A or B cirrhotic patients with small size HCC unsuitable for curative treatments, showed an 80% complete response (CR) rate and 12% partial response (PR) rate after administering 33 fractions of 3-dimensional conformal RT (3D CRT) at 66 Gy [33]. Grade 3 toxicities were observed in 19% patients but were all asymptomatic. Grade 4 toxicities were observed in 22% patients, and all patients had hepatic function of CP class B. Kwon et al. [34] reported the results of stereotactic body RT (SBRT) for 42 HCC patients with tumors ≤100 cc who were

Fig. 1. A HCC (black dotted circle and white arrow) at the liver dome and near a great vessel. A total of 90 Gy of hypofractionated RT in 18 fractions was delivered. This patient was disease-free 2 years after RT. (**a**) Computed tomography (CT) image before RT, (**b**) CT image 2 years after RT.
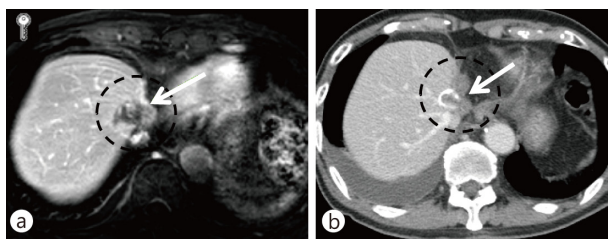
ineligible for local ablation or surgical resection; total doses of 30–39 Gy were administered in 3 fractions. The overall in-field CR and PR rates were 59.6 and 26.2%, respectively, and the 1- and 3-year overall survival rates were 92.9 and 58.6%, respectively. Patients with smaller tumors (<32 cc) had superior in-field progression-free and overall survival rates, and major toxicity was observed in only 1 patient. A prospective, phase I dose escalation study of SBRT for primary HCC conducted at Indiana University reported the 1- and 2-year overall survival rates of 75 and 60%, respectively [35]. The radiation dose was escalated to 48 Gy (16 Gy/fraction) in Child-Turcotte-Pugh's class A patients. For Child-Turcotte-Pugh's class B patients, a regimen of 5 fractions starting at 40 Gy (8 Gy/fraction) was administered; 1 patient experienced progressive liver failure. The Child-Turcotte-Pugh score was the only factor related to more than a single grade 3 or greater liver toxicity event or death within 6 months. Takeda et al. [36] suggested that a combination of TACE and SBRT could be considered for solitary tumors ≤100 cc that are not close to the gastrointestinal tract or kidneys. According to their preliminary report, all patients were alive at the end of a median follow-up of 20 months. Fifty percent of the patients showed CR and 44% showed stable disease. No serious treatment-related toxicity was observed. Seo et al. [37] also reported on the toxicity and efficacy of SBRT after TACE for the treatment of localized HCC. They administered SBRT at 33–57 Gy in 3 or 4 fractions, according to the tumor volume (median, 40.5 cc). Three months after SBRT, they reported a 2-year overall survival rate of 61.4%, local progression-free survival rate of 66.4%, and local response rate of 63%. They found the high radiation dose to be independently related to survival. They also reported a decline in hepatic function in 6 patients (16%) and Grade 3 musculoskeletal toxicity in 1 patient (2.7%).

Taken together, the studies reviewed above suggest that SBRT could be used as a curative treatment modality for selected patients, either alone or in combination with TACE. In cases with large tumors or tumors close to radiosensitive organs, efforts should be made to deliver sufficient dose within an acceptable range of expected toxicities [38]. In addition, conventional fraction schedules or precise RT techniques, such as intensity-modulated RT (IMRT), breath control, and tumor tracking should be considered [39, 40].

BCLC Intermediate Stage HCC

Although TACE is recommended for the BCLC intermediate stage on the basis of studies reporting a survival benefit [11, 41, 42], the beneficial effects are limited to cases with vascular shunting, recanalization around the tumor, or multiple feeding vessels [43, 44]. In addition, efficacy is decreased and procedural morbidity is increased in tumors >10 cm [45]. These effects are well documented in the pathological evidence from patients who underwent resection after TACE [43, 44]. Even after complete necrosis of the main tumor, the presence of microsatellite lesions and microvascular invasion around the tumor may cause subsequent local recurrence [46]. To overcome these limitations, TACE is typically performed repeatedly;

Fig. 2. A HCC following incomplete TACE. A total of 54 Gy of conventional RT in 30 fractions was delivered. This patient gained complete response after RT. (**a**) CT image after TACE and before RT, (**b**) CT image after RT.
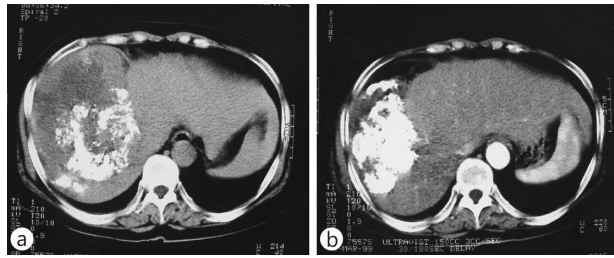
however, the final outcome in the majority of patients is outgrowth of HCC that is refractory to TACE.

Sergio et al. [47] found that patient survival was affected by elevation in angiogenic factors and invasive parameters observed after incomplete TACE. Therefore, the antivascular and antitumor activities of RT can ameliorate the limitations of TACE [48]. After encouraging results of combination treatment of TACE and radiation [20], Seong et al reported in more detail the treatment outcomes of patients who underwent TACE alone or TACE plus RT [21]. Of 105 patients with tumors of ≥5 cm in diameter, TACE was incomplete in 73 patients (69.5%). Of these, 38 patients received local RT and 35 patients received repeated TACE. The 2-year survival rate of patients receiving RT was significantly higher than that of patients receiving repeated TACE (37% vs. 14%, respectively, p = 0.001). The survival benefit was greater in patients with large tumors (>8 cm). Meta-analysis of 17 trials involving 1476 patients of unresectable HCC showed that TACE and RT combination therapy significantly improved 1-, 2-, 3-, and 5-year survival rates compared with TACE alone [49]. Choi et al. [50] reported the outcomes of 16 HCC patients with tumors >5 cm (median, 9 cm) who had received TACE and RT combination therapy followed by hepatic resection. TACE was performed three times on average, and the median radiation dose was 45 Gy. The degree of tumor necrosis was >90% in 87.5% of the patients. Five patients survived >2 years, and 2 of these patients survived >5 years; median survival time was 13.3 months. This study showed the possibility of long-term survival in patients who became eligible for tumor resection following TACE and RT combination therapy. Fig. 2 shows images of tumors in patients with incomplete TACE and RT, who eventually achieved CR.

BCLC Advanced Stage HCC—Intrahepatic Lesion

The BCLC advanced stage consists of heterogeneous disease categories, including portal vein invasion, lymph node metastasis, and distant metastasis in patients with performance 0–2. Sorafenib is an orally available multikinase inhibitor that blocks the serine-threonine kinase Raf-1 as well as the activity of receptor tyrosine kinases of vascular endothelial growth factor receptors. Sorafenib is recommended as the standard treatment in the BCLC guidelines on the basis of demonstration of improved survival in advanced HCC patients in phase III randomized trials in United States and Asia-Pacific region [51, 52]. However, the recommendations regarding sorafenib in the Asian-Pacific region have some differences [31, 53]. At the workshop on the multidisciplinary management of nonresectable HCC under the 1st Asia-Pacific Primary Liver Cancer Expert Meeting, although there was a consensus agreement to recommend sorafenib for HCC with extrahepatic spread [54], the strategies to treat either HCC confined to the liver in the BCLC advanced stage or patients who stopped sorafenib because of adverse events or disease progression remained unfinalized.

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Fig. 3. A HCC with portal vein thrombosis (white arrow). The patient was treated with concurrent intra-arterial chemotherapy and IMRT by helical tomotherapy. A total of 50 Gy of radiation in 20 fractions was delivered. After treatment, the patient received a year of adjuvant intra-arterial chemotherapy. The patient was disease-free 2 years after RT. (**a**) Positron emission tomography (PET)CT images before RT, (**b**) PET-CT images 2 years after RT.
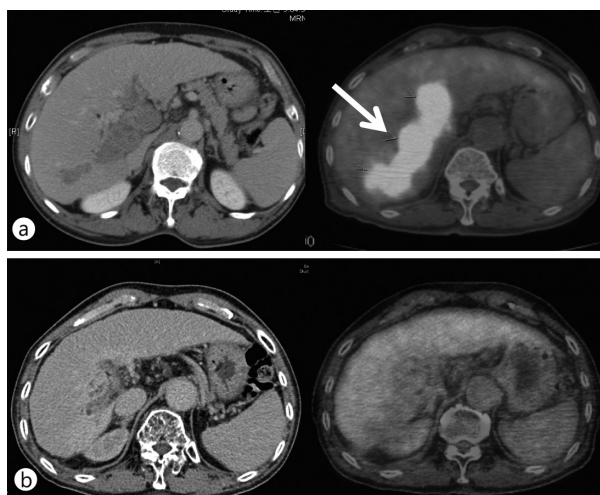
For patients with disease confined to the liver but with portal vein invasion and thrombosis (PVT), promising objective response rates after RT combined with other modalities have been reported [55–58]. Han and Seong et al. [59] reported the outcome of localized concurrent chemoradiotherapy (CCRT) with intra-arterial chemotherapy followed by hepatic arterial infusion chemotherapy in advanced HCC patients with portal vein invasion and well-reserved hepatic function. An objective response was observed in 18 of 40 patients (45%), and the 3-year overall survival rate was 24.1%. Fig. 3 shows the tumor response in a patient with massive portal vein invasion who received CCRT and gained CR with a survival of >2 years. Yoon et al. [60] reported 1- and 2-year survival rates of 42.5 and 22.8%, respectively, in 412 patients with portal vein invasion receiving TACE or transarterial tumor chemoinfusion followed by RT for PVT. Median 40 Gy (range, 21–60 Gy) in 2–5 fractions was delivered. Overall and PVT objective response rates were 27.9 and 85.6%, respectively. There is no agreement on the radiation field for treating HCC with PVT, specifically regarding whether to include the tumor and PVT or the PVT alone. The published reports show a slight survival benefit when the radiation field includes the tumor and PVT [59, 61–64]; however, further investigation is needed. To identify the optimal RT technique for the typical advanced intrahepatic HCC, a large mass with vascular invasion, Lee et al. [58] compared tumor coverage and normal organ doses of 3D CRT, linac-based IMRT, and helical tomotherapy for the delivery of 60 Gy in 30 fractions". Helical tomotherapy achieved the best tumor coverage as well as lower dose to the remaining normal liver, whereas linac-based IMRT showed better stomach sparing in cases of separated lesions in both liver lobes. This study [65] suggests that tumor location should be considered when determining the RT technique.

BCLC Advanced Stage HCC—Extrahepatic Lesion

In patients with BCLC advanced stage extrahepatic disease, RT effectively controlled local lesions. For HCC with lymph node metastases, Yoon et al. [66] reported an overall response rate to RT of 76%. In addition, they showed that the total radiation dose, time dose fractionation values, and the biologically effective dose are all important factors related to response. They also suggest using radiation doses of ≥45 Gy to achieve a significant response (response rate of 93% vs. 57%, p = 0.003). Gastrointestinal bleeding or ulceration was observed in 15.7% of their patients, and toxicities of ≥grade 3 were observed in 5.9% patients.

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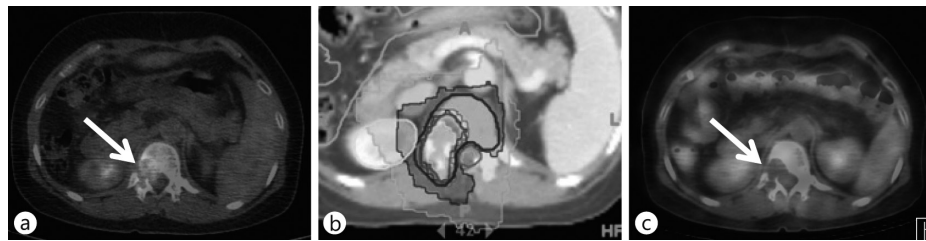www.karger.com/lic

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Fig. 4. A HCC with solitary spinal metastasis (white arrow). Hypofractionated IMRT by helical tomotherapy was performed to protect the spinal cord and kidney. The patient was disease-free 2 years after RT. (**a**) PET-CT images before RT, (**b**) axial isodose distribution of RT, (**c**) PET-CT images 2 years after RT.

A history of chronic gastritis or ulceration, with the inclusion of the whole circumference of the gastric antrum, was an important factor for the development of bleeding [66]. Some studies have analyzed prognostic factors in patients receiving RT for HCC with lymph node metastases. After adjustments using multivariate analysis, one study reported that CP class B and the presence of symptoms were significantly associated with inferior overall survival [67], whereas another study found that the absence of other concurrent distant metastasis and controllable primary HCC were significant [68].

RT is also effective in patients with localized distant metastases [69]. HCC metastases are frequently found in the skeletal system, particularly vertebrae, and are accompanied with severe pain, neuropathic pain, and possible spinal cord compression. In patients with solitary paraspinal metastases, RT can effectively achieve disease control that frequently translates into long-term survival. However, precision technology is strongly recommended to spare the radiosensitive spinal cord whilst delivering a sufficiently high-dose radiation for tumor control. Intensity modulated technology is useful (fig. 4).

BCLC Terminal Stage HCC

To determine a detailed treatment plan for patients with distant metastases, the systemic tumor burden and disease symptoms should be considered. Effective supportive care and full symptomatic palliation are important for patients in the BCLC terminal stage. Therefore, regardless of the location, tumor lesions inducing pain or specific symptoms are an indication for RT.

Seong et al. [70] reported an overall response rate of 73% in HCC patients receiving palliative RT for painful bone metastasis. Patients receiving >43 Gy in a biological effective dose had a response rate of 96%, and objective reduction of tumor size was observed in 13 of the 15 available sites. Nakamura et al. [71] evaluated the therapeutic effects of RT on spinal HCC metastases by retrospective analysis of 24 ambulatory patients and reported an ambulatory rate of 85% after 3 months and 63% after 6 months, a local progression-free survival rate of 53% after 3 months and 47% after 6 months. They suggested that a biological equivalent dose of 39–50.7 Gy (median 44.8 Gy) was not sufficiently low to prevent paralysis and that dose escalation with a highly precise radiation technique should be evaluated further.

Despite the rarity of brain metastasis from HCC—0.9% of 6,919 patients [72], these lesions are an important cause of morbidity and mortality and are associated with extremely poor survival. In a retrospective analysis of 62 patients with brain metastasis, 17 were treated with only whole-brain RT (WBRT), 10 with only gamma knife surgery (GKS), 6 patients with only surgical resection, and 5 patients with surgical resection followed by WBRT. The
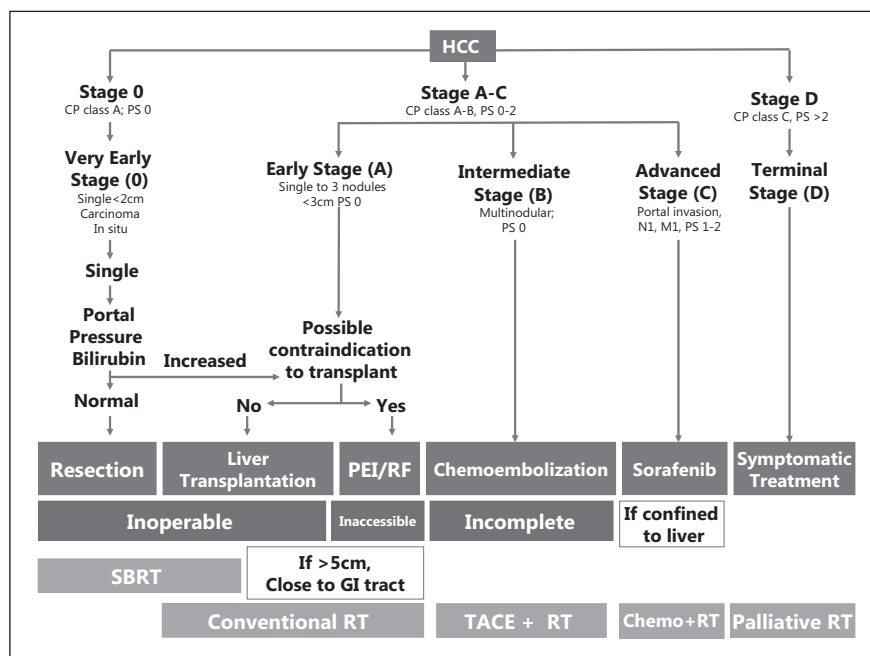
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Fig. 5. RT according to the Barcelona Clinic Liver Cancer stage. Patients who cannot receive recommended treatment at each stage can be managed using RT. Solitary tumors distant from the gastrointestinal tract and kidneys with tumors volume <100 cc are indicated for stereotactic body RT.
PS = performance status; PEI = percutaneous ethanol injection; RF = radiofrequency.

median survival time was only 6.8 weeks (95% confidence interval, 3.8–9.8 weeks) after a diagnosis of brain metastasis was made. Treatment modality (resection or GKS and/or WBRT vs. steroid alone), number of brain lesions, and hepatic function were all associated with survival with statistical significance.

Conclusions

RT is applicable for HCC patients at each BCLC stage (fig. 5). For patients at a very early or early stage of BCLC, RT may be an alternative to surgery, especially SBRT. However, for patients with tumors >5 cm or tumors that are very close to radiosensitive organs, conventional RT should be used to deliver safe treatment. For the intermediate stage, RT combined with TACE could have a greater benefit over repeated TACE. Advanced stage disease confined to the liver can be managed effectively by localized RT in combination with other treatment modalities, such as concurrent or adjuvant chemotherapy. In addition, RT can provide good palliation of symptoms in patients with extrahepatic metastases. Further clinical studies using novel radiation technologies and multidisciplinary approaches are necessary to specify treatment options for HCC patients.

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