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Editorial

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# Incorporation of External-Beam Radiotherapy into Barcelona Clinic Liver Cancer Strategy

*Sun Hyun Bae**

*Department of Radiation Oncology, Soonchunhyang University College of Medicine, Korea*

## Keywords

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## Editorial

Hepatocellular Carcinoma (HCC) is the most common cause of primary liver cancer and the leading cause of cancer mortality worldwide. The development of HCC is mainly caused by chronic infection with hepatitis B or C viruses, excessive alcohol consumption, non-alcoholic fatty liver disease, and metabolic dysfunction associated fatty liver disease. Therefore, HCC treatment strategy should take into consideration not only cancer itself, but also underlying liver disease. Now, several staging systems for HCC have been developed and used. Among these, the Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used in the world since it was developed in 1999. The BCLC system incorporates the tumor burden, underlying liver function, and patients' performance status, and provides treatment recommendation and prognosis for the assigned stage of 0-D. The algorithm is simple and easy to use in the clinical setting. However, it has some limitations. Although there are considerable heterogeneities in patients with stage B or C, the treatment algorithm allows rigid treatment modalities and excludes other available and emerging treatment options. In addition, there is a difference between medical resources of the East and the West. In Asia, External-Beam Radiotherapy (EBRT) is commonly applied for HCC patients with BCLC 0-D, but BCLC did not cite EBRT to any stage. This year, the 2025 BCLC strategy is published and firstly incorporate EBRT into staging system [1].

For BCLC-0 (very early stage) and A (early stage), the first treatment option is resection, Liver Transplantation (LT), or ablation. Recently, two phase 3 studies comparing EBRT with radiofrequency ablation (RFA) was published Xi et al. [2] randomly assigned 166 patients with single recurrence HCC ≤ 5 cm to receive Stereotactic Body Radiotherapy (SBRT) (n=83) or RFA (n=83). The 2-year Local Progression-Free Survival (LPFS) rates, the primary endpoint, were 93% in the SBRT group and 76% in the RFA group (Hazard Ratio [HR] 0.45, 95% Confidence Interval [CI]: 0.24–0.87, P = 0.014), respectively. The 2-year Overall Survival (OS) and toxicities are similar between two groups. Kim, et al. [3] randomly assigned 144 patients with ≤ 2 recurrent HCCs <3 cm to receive either Proton Beam Therapy (PBT) (n=72) or RFA (n=72). The 2-year LPFS rates in the per-protocol population, the primary endpoint, were 95% in the PBT group and 84% in the RFA group (HR 0.51, 95% CI: 0.26-1.03, P = 0.114), respectively. This study was designed as non-inferiority and the result means that PBT is not inferior to those of RFA. With the accumulation of clinical studies for SBRT, long-term outcomes with SBRT have been published. International Stereotactic Radiosurgery Society (ISRS) conducted systematic review and meta-analysis about SBRT for HCC, and reported that Local Control (LC) and OS rates were 84% (95% CI: 70-90) and 57% (95% CI: 4-66) at 3-year, and 82% (95% CI: 74-88) and 40% (95% CI, 29-51) at 5-year, respectively [4]. ISRS stated that patients with HCC <3 cm can be considered for SBRT with favorable LC and survival outcomes. SBRT to HCC ≥ 3 cm can be performed with the expectation of durable long-term LC. BCLC 2025 recommends EBRT as an ablative option in BCLC-0 patients. In case of BCLC-A with multifocal lesions, EBRT are considered only in selected and well-compensated patients.

For BCLC-B (intermediate stage), LT, if they meet the institutional extended LT criteria, or Transarterial Chemo-Embolization (TACE) are the standard treatment. Two meta-analyses comparing EBRT with TACE reported conflicting results regarding OS. One meta-analysis compared various locoregional treatments from 40 randomized clinical trials [5]. Among these, six studies were pooled comparing EBRT with other therapies. The subgroup comparison of EBRT with TACE showed a statistical difference on OS (HR 0.35, 95% CI: 0.13-0.97, P = 0.04). Another meta-analysis compared EBRT with TACE from three randomized trials [6]. EBRT was associated with

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***Correspondence:***

*Sun Hyun Bae, Department of Radiation Oncology, Soonchunhyang University College of Medicine, Bucheon, 170 Jomaru-ro, Wongmi-gu, Bucheon-si, Gyeonggi-do, 14584, Korea, Fax: +82 32 621 6950; Tel: +82 32 621 5877;*

*E-mail: gurigurihaia@hanmail.net*

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significantly improved LC than TACE (HR 0.16, 95% CI: 0.08-0.34), whereas, there was no significant difference in OS (risk ratio 0.79, 95% CI: 0.51-1.22). Because OS data on EBRT are not robust enough to replace TACE, BCLC 2025 stated that EBRT may be considered for patients who are not candidate for TACE, and that the current BCLC strategy still does not support EBRT as first line alternative to TACE. Another applicable strategy is combination of EBRT and TACE, although this combined treatment is not considered in BCLC 2025. A meta-analysis reported that patients receiving EBRT and TACE showed significantly better 1- to 5-year OS that patients receiving TACE alone [7]. A recent phase 3 study randomly assigned 40 HCC patients with incomplete response to the first course of TAE/TACE to receive either SBRT (n=21) or TAE/TACE continuance (n = 19) [8]. The 1-year LC, the primary endpoint, was significantly superior in the SBRT group (HR 0.19, 95% CI: 0.04-0.40, P <0.001). OS was similar in both groups. The combination of EBRT and TACE is considered as a promising treatment modality if insufficient response after TACE is anticipated.

For BCLC-C (advanced stage), systemic treatment is the first treatment option. Since the introduction of sorafenib, various antiangiogenic agents and immunotherapies, as well as novel combination regimens are available and investigating for advanced HCC. From a EBRT perspective, two different approaches can be considered. The first way is to apply EBRT alone or combined treatment of EBRT and TACE. This can serve to delay the initiation of systemic treatment or preserve it. Yoon et al. [9] reported a phase 2 randomized study comparing EBRT plus TACE with sorafenib alone for liver-confined HCC with Macrovascular Invasion (MVI). The 12-week progression-free survival rate, the primary endpoint, was significantly higher in the EBRT plus TACE group than the sorafenib group (87% *vs.* 34%, P <0.001). The objective response rate and OS were significantly higher in the EBRT plus TACE group. The second way is to combine EBRT and systemic treatment. RTOG 1112 phase 3 study randomly assigned 177 patients with advanced HCC to receive either SBRT and sorafenib (n=85) or sorafenib alone (n = 92) [10]. MVI was seen in 74%. Unfortunately, this study was early closure due to a change in standard-of-care systemic treatment. The median OS, the primary endpoint, was 15.8 months in the SBRT and sorafenib group and 12.3 months in the sorafenib group (HR 0.77, 90% CI: 0.59–1.01, P=0.06). Adjusting for stratification factors, OS was improved with SBRT (HR 0.72; 95% CI: 0.52-0.99, P=0.04). BCLC 2025 suggested EBRT can be considered in appropriate patients with MVI and should be investigated in further trials that incorporate modern systemic treatment. Currently, a lot of prospective clinical studies for combination of EBRT and systemic treatment are ongoing. These would give us some answers on the best treatment option. For BCLC-D (end stage), BCLC 2025 considered EBRT as palliative modality for metastases.

The 2025 BCLC update maintains evidence-based first treatment option for each stage. It also introduces the concept of CUSE framework (Complexity, Uncertainty, Subjectivity, Emotion) to person-centered decision making when evidence on alternatives is non-comparable or lacking. Hereby, EBRT firstly incorporate into BCLC strategy for the treatment of HCC. A lot of studies on EBRT for HCC has published and shown the efficacy and safety. Most of them are retrospective or phase 1- or 2- design. Non-randomized study design is susceptible to the heterogeneity and selection bias. To minimize these weaknesses, radiation oncologists are trying consistently to undergo multicenter or international studies, adjust by using several statistical analyses, and conduct systematic review and meta-analysis. Of course, various prospective clinical studies for HCC also are undergoing. I hope the role of EBRT will more expand in the next version of BCLC strategy as evidence accumulates.

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