Special Contribution
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Stereotactic body radiation therapy for hepatocellular carcinoma: 2026 expert consensus-based practical recommendation of the Korean Liver Cancer Association

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Stereotactic body radiation therapy (SBRT) is a noninvasive, high-precision radiation technique that delivers a high dose to the tumor in a limited number of fractions, typically five or fewer, and is increasingly used as a curative-intent option for hepatocellular carcinoma (HCC), particularly when surgical resection, liver transplantation, or local ablative therapies are not feasible. Although domestic and international guidelines have incorporated SBRT into the treatment algorithm for HCC, the lack of comprehensive evidence and expert opinion regarding patient selection, pretreatment evaluation, treatment planning and delivery, complication management, and post-treatment follow-up has resulted in substantial variation in clinical practice. Accordingly, expert consensus-based practical recommendations for SBRT were developed by a group of radiation oncologists, hepatologists, and radiologists from the Research Committee of the Korean Liver Cancer Association, based on expert surveys, a comprehensive review of evidence-based literature, and a modified Delphi process. Encompassing the entire clinical workflow of liver SBRT, these recommendations are intended to provide practical guidance for the safe and effective implementation of SBRT in patients with HCC. **(J Liver Cancer 2026;26:182-204)**

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INTRODUCTION

Stereotactic body radiation therapy (SBRT) is an advanced radiation therapy (RT) technique characterized by the delivery of high-dose radiation to a tumor over a limited number of fractions, typically five or fewer. To achieve high-precision treatment, SBRT integrates cutting-edge technologies, including image-guided radiation therapy (IGRT), intensity-modulated radiation therapy, and respiratory motion management. These capabilities distinguish SBRT from conventional RT by enabling the delivery of curative doses to the target tumor while minimizing damage to the surrounding normal liver parenchyma and adjacent critical organs.[1]

The clinical significance of SBRT is increasingly recognized in both domestic and international clinical practice guidelines. The 2022 Korean Liver Cancer Association (KLCA)-National Cancer Center (NCC) Korea practice guidelines for management of hepatocellular carcinoma (HCC) recommend RT as an alternative treatment option when surgical resection, liver transplantation, or local ablative therapies are not feasible.[2] Furthermore, the guidelines highlight SBRT as a potential subsequent treatment for recurrent HCC following primary interventions such as resection, local ablative therapies, or transarterial chemoembolization (TACE). Similarly, major guidelines from the United States, Europe, and Japan have incorporated SBRT into their treatment algorithms, establishing it as a key pillar of curative intent strategies.[3-6]

The KLCA has consistently provided practical clinical guidance by publishing expert consensus-based practical recommendations on major therapeutic modalities, including TACE in 2023, local ablation in 2024, and surgical treatment in 2025.[7-9] As an extension of these systematic efforts, the current practical recommendations aim to provide specific and practical guidance for the safe and effective implementation of SBRT. This consensus was developed based on expert surveys, a comprehensive review of the available evidence, and multidisciplinary panel discussions. It encompasses the entire clinical workflow of SBRT, ranging from patient selection and treatment preparation to delivery techniques, complication management, and post-treatment follow-up.

EXPERT CONSENSUS

The Research Committee of the KLCA formed an expert committee consisting of radiation oncologists (n=8), hepatologists (n=3), and radiologists (n=2). To provide practical guidance for the clinical implementation of SBRT in patients with HCC, the committee established and developed eight core domains: patient selection, pretreatment imaging and liver function assessment, simulation, treatment planning, treatment delivery, post-treatment patient management and follow-up, and tumor response assessment. Through qualitative literature analysis across these eight domains, the expert committee derived 21 recommendations, which were validated by an external expert panel using a modified Delphi survey method. The expert panel consisted of 42 HCC specialists recommended by the KLCA and the Korean Society for Radiation Oncology, including specialists in radiation oncology, hepatology, surgery, and radiology.

The level of agreement among the expert panel for each recommendation was collected on a scale of 0 (strongly disagree) to 100 (strongly agree) and classified into five stages. Anonymity was maintained throughout the survey process so that all panelists participating in the Delphi survey were unaware of each other's responses; the survey results were collected and analyzed by the Chair and the Secretary. Recommendations that received more than 75% agreement in the first Delphi round were considered to have reached a consensus. As a result of the first round, 20 of the 21 proposed recommendations reached a consensus, while one failed to do so. According to predefined criteria, the recommendation that did not reach consensus in the first round was partially revised and subjected to a second Delphi round. In this process, the individual responses of the panelists remained anonymous and were not identifiable by anyone except the Chair and the Secretary. In the second Delphi round, recommendations with more than 80% agreement were deemed to have reached a consensus. Following the second Delphi survey, one final recommendation failed to reach a consensus (Fig. 1).

PATIENT SELECTION

According to the international clinical guidelines, including the 2022 revised HCC treatment guidelines by the KLCA and NCC Korea, RT is a treatment modality applied for various purposes across different stages of HCC.[2-5,10] SBRT is an RT method that maximizes treatment efficacy by delivering high-dose radiation to a tumor over a limited number of fractions with high treatment accuracy. Although definitions vary slightly depending on the country and the primary tumor, in the Republic of Korea, SBRT is typically defined as high-dose therapy consisting of five or fewer treatment sessions. Compared to liver resection and local ablative therapies, SBRT is non-invasive, can be administered on an outpatient basis, and can be applied relatively safely even in patients who are elderly or have comorbid chronic conditions.

Due to these advantages, it is being utilized as an alternative curative treatment for HCC.[1] This expert consensus focuses primarily on the role of SBRT as a curative treatment modality for HCC.

For liver SBRT, treatment is generally feasible provided that the prescribed dose can be delivered while respecting the dose constraints of the remaining liver and surrounding organs at risk, irrespective of tumor size or number. In particular, treatment can be performed relatively safely compared with other local therapies, even in cases where the tumor is located in the hepatic dome adjacent to the diaphragm or near intrahepatic vessels and bile ducts.[11] However, the use of high-dose SBRT may be limited in cases where it is difficult to avoid radiation damage due to proximity to the gastrointestinal tract, where baseline liver function is insufficient to tolerate RT, or where the patient's general condition is poor and cooperation with treatment is deemed difficult due to irregular breathing.[1,12-14] In a survey regarding the optimal tumor size for SBRT, 89% and 42% of the expert panel selected ≤3 cm and ≤5 cm, respectively, as the optimal upper size limit.

Risk factors for major adverse events should also be considered when selecting HCC patients for SBRT. The most important adverse event after SBRT is deterioration of liver function. Since most HCCs develop in patients with liver cirrhosis caused by chronic hepatitis B, chronic hepatitis C, alcohol, and metabolic dysfunction-associated steatotic liver disease, it is essential to consider both the natural decline in liver function associated with cirrhosis progression and SBRT-induced hepatic toxicity when assessing liver function after SBRT.[15,16] In general, patients with Child-Pugh class A or B7 liver function represent the optimal indication for SBRT. For patients with Child-Pugh class B8 or higher, or those with uncontrolled ascites or hepatic encephalopathy, SBRT can be considered using more stringent dose-volume constraints.[1-3,10] Gastrointestinal toxicity is another major adverse event following SBRT; therefore, the feasibility of SBRT should be thoroughly assessed when a tumor is adjacent to the gastrointestinal tract.[3,4] Existing data suggest that combining SBRT with sorafenib or bevacizumab increases the risk of severe gastrointestinal toxicity, and greater caution is required when determining the dose-volume constraints in this clinical setting.[17] In cases where an elevated risk of major adverse events is anticipated with SBRT, modification of the treatment strategy, including a reduction in dose per fraction and an increase in the number of fractions, should be considered.

The combination of SBRT and TACE should be considered for patients with HCC who have an incomplete response to TACE or in whom an inadequate response is anticipated. SBRT can be performed following the resolution of acute adverse events associated with TACE.[18,19]

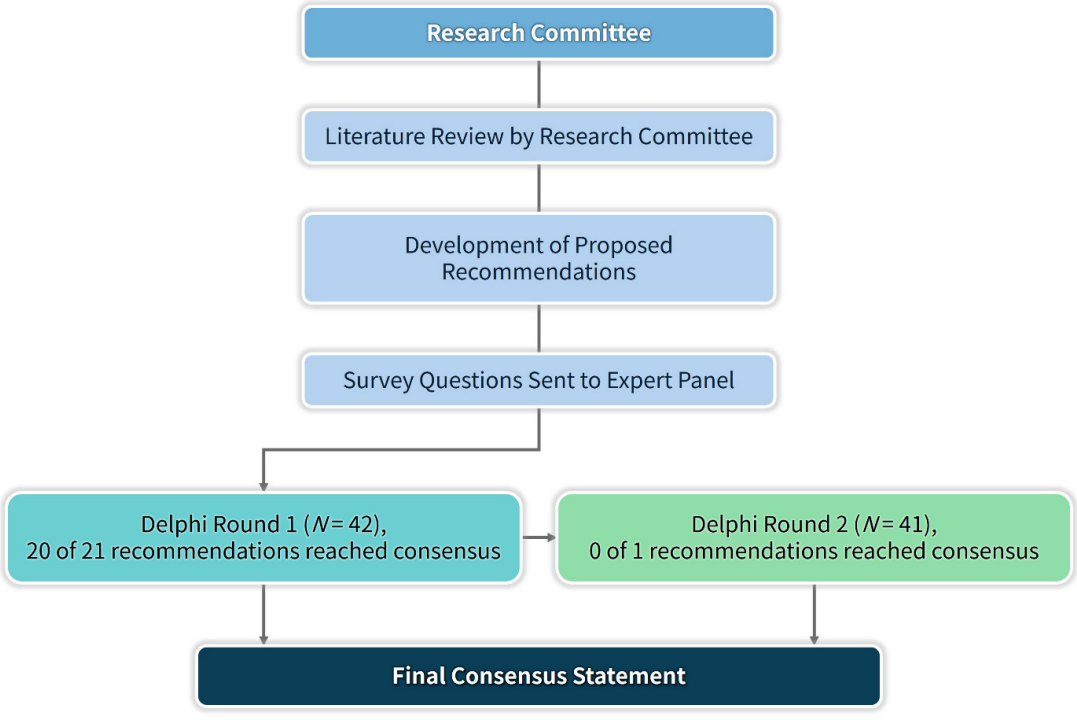


Figure 1. Workflow of the recommendation development and expert consensus process.

In the real-world clinical setting, repeated liver SBRT is sometimes applied to patients with HCC who have previously undergone SBRT; however, evidence on the safety and efficacy of re-irradiation to guide clinical practice remains scarce. Few studies suggest that re-irradiation can be safely administered to patients with a long treatment interval since the previous SBRT, preserved liver function (Child-Pugh class A or B7), and sufficient remaining liver volume. However, the feasibility of re-irradiation is limited when high-dose volumes overlap with previously irradiated areas of the gastrointestinal organs or the central biliary tract.[20,21] A survey was conducted on the optimal timing of re-irradiation following the initial SBRT in patients with a new intrahepatic recurrence that was sufficiently distant from the previous SBRT field. The results showed that 41.5% of the expert panel responded that repeated SBRT could be performed "immediately," while 24.4% each suggested waiting 3 and 6 months, respectively. In a survey on whether re-irradiation with SBRT can be performed using the same dose-volume constraints as the initial SBRT in the absence of overlap with the previous SBRT field, 24.4% of the expert panel responded with "strongly agree" and 29.3% with "agree." However, 46.3% of the panel opted for "depends on the situation," suggesting that various clinical factors related to the patient and the tumor may influence the decision-making process for re-irradiation. Therefore, further research is warranted to define the optimal indication for re-irradiation of the liver with SBRT and to establish standardized recommendations for its clinical application.

[Recommendations]

1. The indications for SBRT should be based on the KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Furthermore, both the patient's performance status and the risk factors for major adverse events, including underlying liver function and tumor location, should be thoroughly evaluated.

PRETREATMENT IMAGING FOR STEREOTACTIC BODY RADIATION THERAPY

SBRT is a highly precise, image-guided local treatment modality; therefore, pretreatment imaging is essential for accurate and safe treatment planning. Pretreatment imaging also serves as the baseline for post-treatment response assessment, extending its role beyond diagnostic evaluation alone. Appropriate and timely imaging contributes not only to improving treatment efficacy and safety but also to evaluating the anatomical relationship between the tumor and adjacent structures, such as vessels, bile ducts, and the gastrointestinal tract. This information is important for determining the feasibility of SBRT and anticipating potential treatment-related complications.

For diagnostic evaluation prior to SBRT, dynamic contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) are recommended as complementary imaging modalities. CT provides accurate anatomical assessment and can be readily registered with treatment planning CT because both are based on the same imaging modality. CT also offers high spatial resolution and wide scan coverage, making it useful for evaluating extrahepatic metastases, while offering advantages in cost-effectiveness.[22] MRI complements CT by providing superior soft tissue contrast and multiparametric lesion characterization. MRI may be performed using either extracellular contrast agents (e.g., gadopentetate dimeglumine) or hepatocyte-specific contrast agents (e.g., gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid), depending on clinical needs. In particular, hepatobiliary phase (HBP) imaging using a hepatocyte-specific contrast agent is useful for accurately delineating tumor margins by maximizing the signal intensity contrast between the tumor and the surrounding liver parenchyma. Diffusion-weighted imaging (DWI) can also improve the detection of small intrahepatic lesions and may be helpful for evaluating the target lesion and detecting additional lesions before SBRT (Fig. 2).[22-25] Meanwhile, treatment planning CT alone may not provide sufficient information regarding arterial phase hyperenhancement, portal venous washout, and tumor margins of HCC. Therefore, diagnostic dynamic contrast-enhanced CT or MRI should be obtained before treatment planning. These diagnostic images can be integrated with the treatment planning CT through image registration to improve the accuracy of target delineation and treatment planning.[26,27]

Although the optimal timing of pretreatment imaging for SBRT has not been established due to a lack of direct evidence, based on expert consensus informed by clinical experience, an interval within 1 month between imaging and treatment initiation may be appropriate, considering the potential for tumor progression. Imaging obtained within 2 months may still be acceptable for treatment planning; however, if the interval exceeds 2 months, changes in tumor size or margins may reduce the accuracy of target delineation and the appropriateness of baseline imaging for treatment response assessment. In such cases, additional imaging before SBRT may be considered. Further studies are needed to establish evidence-based guidance on the optimal timing of pretreatment imaging.

[Recommendations]

1. For pretreatment imaging prior to SBRT, dynamic contrast-enhanced CT and MRI are recommended as complementary modalities.
2. To support accurate treatment planning and reliable baseline imaging for response assessment, it is appropriate to keep the interval between imaging and SBRT within 1 month when feasible. If the interval exceeds 2 months, additional imaging may be considered.

PRETREATMENT LIVER FUNCTION ASSESSMENT AND CONCOMITANT MEDICATIONS FOR STEREOTACTIC BODY RADIATION THERAPY

Liver function assessment prior to stereotactic body radiation therapy

Most patients with HCC have underlying cirrhosis or hepatitis, which can increase the risk of deterioration of liver function after treatment.[28] Therefore, liver function assessment prior to SBRT is essential, both to prevent post-treatment hepatic decompensation and to determine an appropriate radiation dose for each patient. Rather than relying on a single parameter, liver function should be evaluated by integrating multiple indicators, including clinical findings, laboratory tests, and imaging studies (Fig. 3).

Routine laboratory tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, and platelet count, are useful for predicting the risk of post-treatment hepatic deterioration, and several composite models combining these parameters have been clinically applied. The Child-Pugh score and class are the most widely used indices for assessing liver function and stratify patients into three classes: A (5-6), B (7-9), and C (10-15).[29] Among Child-Pugh class B patients, those with a score of B7 are likely to have compensated cirrhosis, whereas those with B8-9 frequently exhibit features of decompensation such as ascites, hepatic encephalopathy, or jaundice, and are therefore at higher risk of hepatic deterioration following HCC-directed treatment.[30] Multiple studies have demonstrated

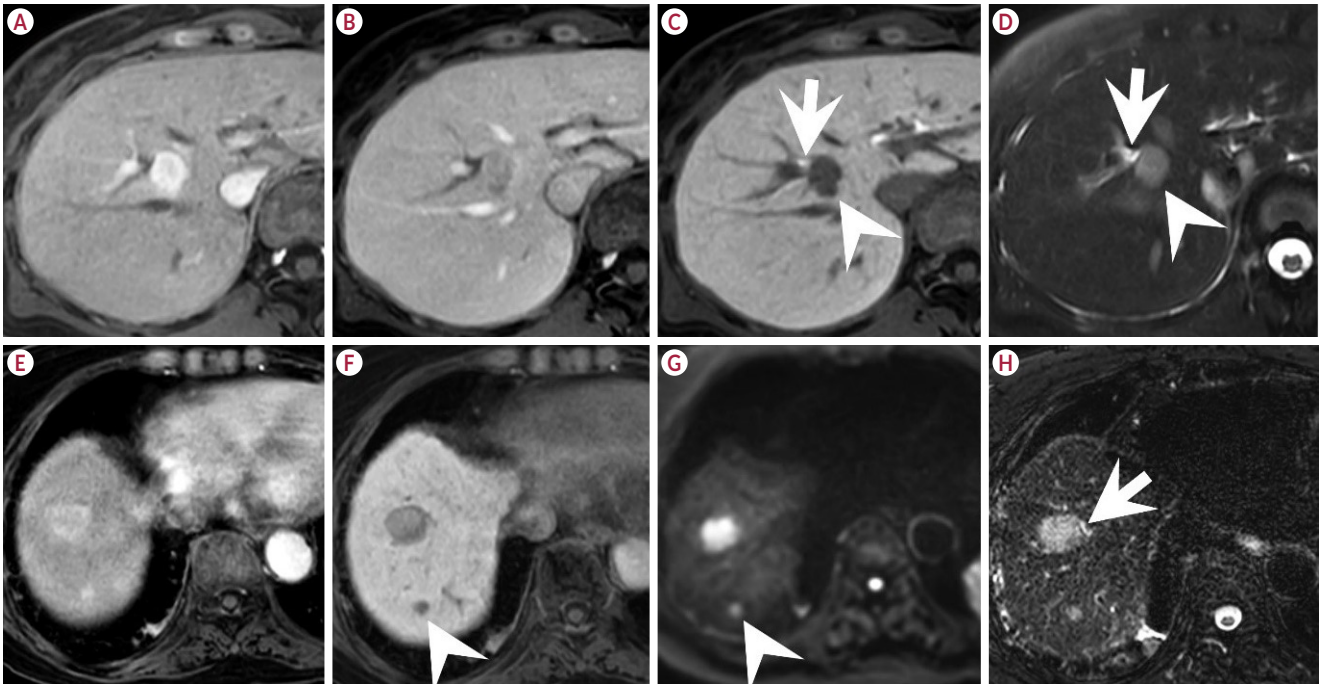


Figure 2. Two representative examples of dynamic contrast-enhanced MRI using a hepatocyte-specific contrast agent (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid) applied to the diagnosis of HCC and SBRT. (A-D) A 1.8-cm nodule in hepatic segment 8. (A) Arterial phase and (B) portal venous phase images show typical arterial phase hyperenhancement and portal venous washout, allowing a diagnosis of definite HCC. (C) The hepatobiliary phase image most clearly delineates the extent of the lesion (arrowhead). (C, D) The hepatobiliary phase and T2-weighted images demonstrate a bile duct (arrow) adjacent to the lesion, suggesting that the lesion is located in an anatomical position unfavorable for local treatment such as radiofrequency ablation. (E-H) A 2.8-cm nodule in hepatic segment 8. (E) The arterial phase image shows an enhancing lesion, and (F) the hepatobiliary phase and (G) diffusion-weighted imaging are useful for detecting an additional 0.8-cm lesion in hepatic segment 7 (arrowhead) that could be easily overlooked on conventional imaging. (H) The T2-weighted image shows a bile duct (arrow) running adjacent to the lesion. Such multisequence MRI aids in precise target delineation and safe treatment planning for SBRT. MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy.

the efficacy and safety of SBRT in Child-Pugh class A patients, and comparable outcomes have been reported in carefully selected Child-Pugh B7 patients.[31] However, some studies have reported an elevated risk of hepatic deterioration in patients with Child-Pugh scores of B8 or higher; thus, the radiation dose should be determined by considering the risk of liver disease progression, the expected therapeutic benefit, and the remaining liver volume. It should also be noted that the Child-Pugh score relies on subjective parameters such as ascites and hepatic encephalopathy.

The albumin-bilirubin (ALBI) grade is a more objective and continuous index that complements the subjective limitations of the Child-Pugh score and is particularly useful for predicting prognosis and determining treatment indications in patients with borderline liver function (Child-Pugh A6-B7). Previous studies have shown that the ALBI score outperforms the Child-Pugh score in predicting overall survival and adverse events among Child-Pugh class A patients,[32] and patients with ALBI grade 1 or 2 have demonstrated favorable efficacy and safety outcomes after SBRT.[33] In patients with ALBI grade 3, SBRT may be considered on a limited basis, only for localized lesions when no other treatment is feasible, given the elevated risk of post-treatment hepatic failure and radiation-induced liver disease associated with reduced hepatic reserve.

Vibration-controlled transient elastography is a noninvasive imaging modality with high accuracy for the diagnosis of hepatic fibrosis and cirrhosis and has potential for liver function assessment; however, evidence specifically addressing its use prior to SBRT remains limited.[34] In addition, CT is useful for evaluating the presence of cirrhosis, ascites, and remaining liver volume.

In patients with a history of prior HCC-directed treatment, remaining liver volume may be reduced and liver function compromised; therefore, more meticulous evaluation of the risk of hepatic deterioration is required, and treatment decisions are best made through multidisciplinary discussion. In summary, prior to SBRT, liver function should be assessed by integrating multiple indicators rather than relying on a single tool, and treatment indications and radiation dose should be determined accordingly.

[Recommendations]
1. Liver function should be assessed prior to SBRT by integrating clinical findings, laboratory tests, and imaging studies.
2. The Child-Pugh score and the ALBI score may be used to assess liver function prior to SBRT.

Medication management during stereotactic body radiation therapy

During SBRT, medications should be used appropriately to prevent reactivation of viral hepatitis and to minimize adverse events, while drugs that may aggravate liver function should be avoided whenever possible.

Prophylactic antiviral therapy

Patients with HCC undergoing SBRT may experience immune suppression and hepatocellular injury, which can predispose to re-

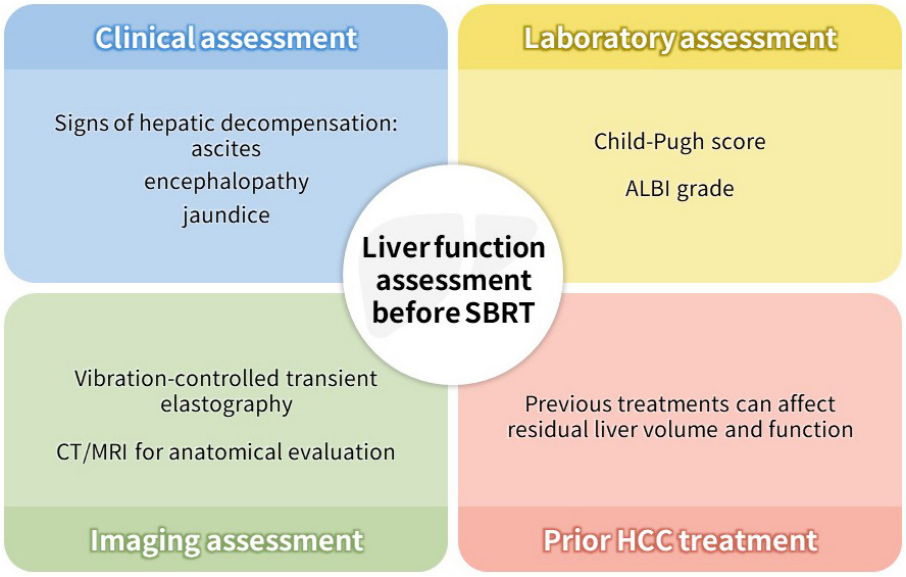


Figure 3. Integrated assessment of liver function before stereotactic body radiation therapy. ALBI, albumin-bilirubin; SBRT, stereotactic body radiation therapy; CT, computed tomography; MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma.

activation of viral hepatitis. In previous studies, the incidence of chronic hepatitis B reactivation during external-beam radiation therapy (EBRT) has been reported as 22.2-24.6%, classifying EBRT as a high-risk treatment, with the dose-volume relationship of the irradiated liver identified as a risk factor.[35,36] Furthermore, the risk of hepatitis B virus (HBV) reactivation has been reported to be more than two-fold higher when EBRT is combined with TACE than with EBRT alone.[37,38]

In HCC patients undergoing EBRT, HBV reactivation rates were reported to be 21.8% in the control group and 0% in the lamivudine prophylaxis group, with corresponding ALT elevation rates of 12.5% vs. 2.3%, respectively, indicating a significantly higher rate in the control group.[39] Another multicenter retrospective study of 133 patients receiving EBRT alone similarly reported HBV reactivation rates of 29.4% and 0% in patients without and with antiviral therapy, respectively.[40] Accordingly, prophylactic antiviral therapy is recommended for hepatitis B surface antigen (HBsAg)-positive patients undergoing SBRT. The KLCA-NCC HCC clinical practice guidelines also recommend prophylactic antiviral therapy for HBV-infected patients receiving high-risk anticancer treatments, including EBRT.[2] Although prospective data specifically addressing the risk of HBV reactivation after SBRT remain limited, the consistent evidence from EBRT and combination therapy supports consideration of prophylactic antiviral therapy in HBsAg-positive patients undergoing SBRT.

In hepatitis C virus (HCV)-related HCC, increases in HCV replication or hepatitis flares may occur after cancer treatment, although progression to hepatic failure or death is rare. A prospective observational study reported that elevations in HCV RNA may occur after cancer therapy, but, unlike HBV, the course is generally indolent and no association with hepatic failure or liver-related mortality has been established.[41] Nevertheless, monitoring of HCV RNA titers and the development of hepatitis flares is warranted during the treatment of HCV-related HCC.

Premedication and supportive medications prior to stereotactic body radiation therapy

Because adverse events during SBRT are infrequent, specific premedications are generally not required, in contrast to systemic chemotherapy. However, systemic symptoms such as fatigue, anorexia, and nausea may occur during treatment; in such cases, supportive measures, including adequate nutritional support and symptomatic therapy with antiemetics, may be considered. Such supportive care can help maintain quality of life and improve treatment continuity.

Management of hepatotoxic medications during stereotactic body radiation therapy

The use of potentially hepatotoxic agents during SBRT may increase the risk of hepatic deterioration and should therefore be discontinued or substituted whenever feasible (Table 1). When concomitant medications are used, regular evaluation of their efficacy and adverse effects is necessary, as radiation therapy may cause pharmacokinetic and pharmacodynamic alterations.

The risk of hepatic deterioration during SBRT may be increased by underlying liver disease and concomitant medications. Therefore, prophylactic antiviral therapy before and after SBRT, appropriate supportive care, and close monitoring of hepatotoxic medications are required. A multidisciplinary approach is essential to establish a treatment plan that maximizes the preservation of liver function and the safety of the procedure.

Table 1. Medications requiring caution during stereotactic body radiation therapy

Drug class	Recommendation
Acetaminophen	In patients with cirrhosis, high-dose administration may increase the risk of hepatotoxicity; daily dose should be limited to ≤2-3 g.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Caution is required in patients with cirrhosis owing to the risk of hepatotoxicity and gastrointestinal bleeding.
Statins	Caution is required in patients with decompensated cirrhosis; temporary discontinuation should be considered if AST or ALT levels increase significantly during SBRT.
Anti-tuberculosis agents	Caution is required when used concomitantly in patients with impaired liver function, given the potential for cytochrome P450 induction and hepatotoxicity.

AST, aspartate aminotransferase; ALT, alanine aminotransferase; SBRT, stereotactic body radiation therapy.

CONSIDERATIONS PRIOR TO TREATMENT PLANNING FOR STEREOTACTIC BODY RADIATION THERAPY

Respiratory motion management in stereotactic body radiation therapy

Methods of respiratory motion–managed radiation therapy

When SBRT for HCC is performed without accounting for respiratory motion, the positions of the tumor and the liver become uncertain throughout the breathing cycle. This not only reduces treatment accuracy but may also increase the risk of toxicity to the liver and adjacent organs. Accordingly, respiratory motion management is essential when SBRT is performed for HCC. The available methods for respiratory motion management are summarized in Table 2.[42-44]

In the expert survey on respiratory motion management practice (multiple responses allowed), free-breathing with internal target volume (ITV) and respiratory gating were the most frequently used techniques, each used by 66.7% of respondents, followed by breath-hold (30.3%) and tumor tracking (9.1%). A small proportion (6.1%) reported not performing respiratory motion management.

Patient respiratory monitoring and breath control techniques

Patient respiratory monitoring and breath control techniques should be selected based on the regularity of the patient's breathing pattern, level of cooperation, ability to sustain breath-hold, lesion location and magnitude of motion, and the available equipment. Currently used techniques are summarized in Table 3.[42-45]

In the expert survey on respiratory monitoring techniques (multiple responses allowed), marker-based optical tracking systems were the most frequently used technique (67.7%), followed by surface-guided systems (25.8%) and pressure sensor-based systems (12.9%). Contact-based displacement sensors and MRI guidance were each used by 3.2% of respondents, and 19.4% reported not performing respiratory monitoring. In a separate survey on the use of active breath control techniques other than free-breathing (multiple responses allowed), abdominal compres-

Table 2. Respiratory motion management methods applicable in stereotactic body radiation therapy

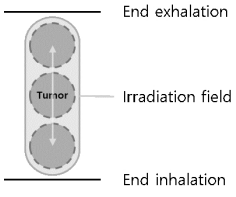
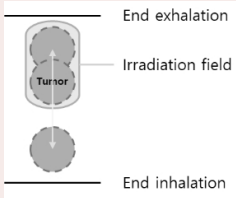
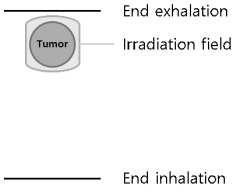
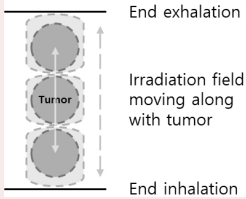
Method	Description	Image	Advantages	Disadvantages
Free-breathing with internal target volume	Encompasses the entire range of tumor motion throughout the respiratory cycle within the treatment volume.		Technically simple. Broad patient eligibility and relatively short treatment time.	The dose to the remaining liver may be relatively higher than with other methods.
Respiratory gating	Delivers radiation only during a predefined phase of the respiratory cycle.		Relatively favorable normal tissue sparing.	Requires patients who are capable of regular breathing. Treatment time may be prolonged.
Breath-hold	Delivers radiation while the patient holds breath at a predefined respiratory level.		Relatively favorable normal tissue sparing.	Requires patients capable of maintaining a stable breath-hold for a sufficient duration. Limited patient eligibility.
Tumor tracking	Delivers radiation while continuously tracking the tumor position in real time.		Highest geometric accuracy. Excellent normal tissue sparing.	Requires specialized equipment. Technically complex.

Table 3. Respiratory monitoring and breath control techniques used in stereotactic body radiation therapy

Category	Technique	Principle	Main applications	Considerations
Respiratory monitoring	Marker-based optical tracking	Generates a respiratory signal by tracking external markers attached to the chest/abdomen with infrared cameras.	Monitoring during free-breathing, gating, and breath-hold.	Potential discrepancy between external signals and internal organ motion should be considered.
	Pressure sensor-based system	Tracks the respiratory pattern using an abdominal pressure sensor.	Monitoring during free-breathing and gating.	Uncertainty arising from signal latency or offset should be considered.
Breath control	Abdominal compression	Compresses the upper abdomen to limit diaphragmatic motion and chest/abdominal expansion.	Reduction of treatment volume during free-breathing therapy; improvement of respiratory regularity in patients with irregular breathing.	Abdominal organ motion may paradoxically increase in some patients. Compression-related patient discomfort may also occur.
	Active breath-hold control	Controls the patient's breath-hold at a predefined respiratory level.	Adjunct for breath-hold delivery.	Patient cooperation is essential. May be difficult to apply in patients with pulmonary disease, ascites, anxiety/panic disorders, or active infection.

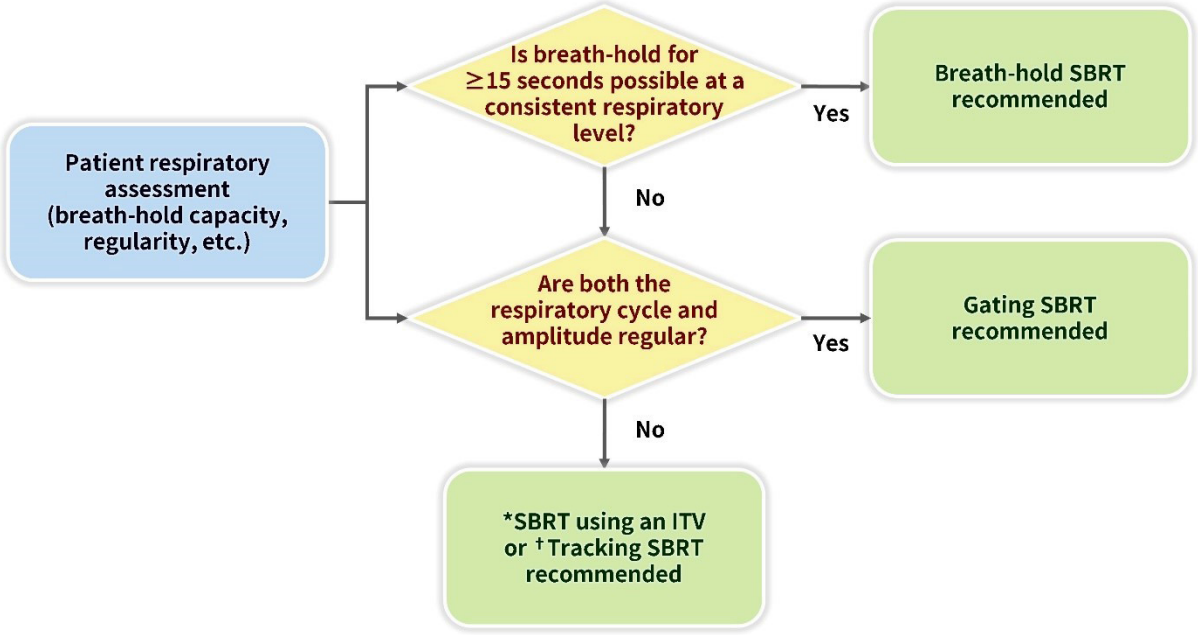


Figure 4. Example of a patient-tailored respiratory motion management strategy. *If the respiratory motion amplitude is large, abdominal compression may be used to reduce the amplitude. †Tracking SBRT may be recommended under any respiratory condition; however, the decision should consider equipment availability and the need for internal fiducial markers. SBRT, stereotactic body radiation therapy; ITV, internal target volume.

sion was used by 60% of respondents and active breath-hold control devices by 10%, while 33.3% reported not implementing any active breath control technique.

Patient-tailored selection of respiratory motion management strategy

The optimal respiratory motion management strategy should be selected by comprehensively considering the patient's respiratory characteristics, level of cooperation, and lesion location. Figure 4 illustrates an example of a decision-making algorithm for patient-tailored respiratory motion management.

Preparation prior to stereotactic body radiation therapy planning

Determination of image guidance surrogates

During image-guided SBRT for HCC, accurately identifying the location of intrahepatic lesions can be challenging. To overcome this limitation, the use of image guidance surrogates is essential. Representative examples and methods of commonly used image guidance surrogates are illustrated in Figure 5 and Table 4.

Basic preparation for treatment planning

For patients in whom intravenous contrast media will be used during treatment planning CT, fasting for at least 4-6 hours prior to simulation is recommended.[46] Even when contrast media are not used, fasting for at least 4-6 hours prior to simulation may be recommended if the position and shape of the stomach are expected to significantly influence the tumor location during treatment. To ensure reproducible patient positioning, immobilization devices such as vacuum cushions and arm supports may be used

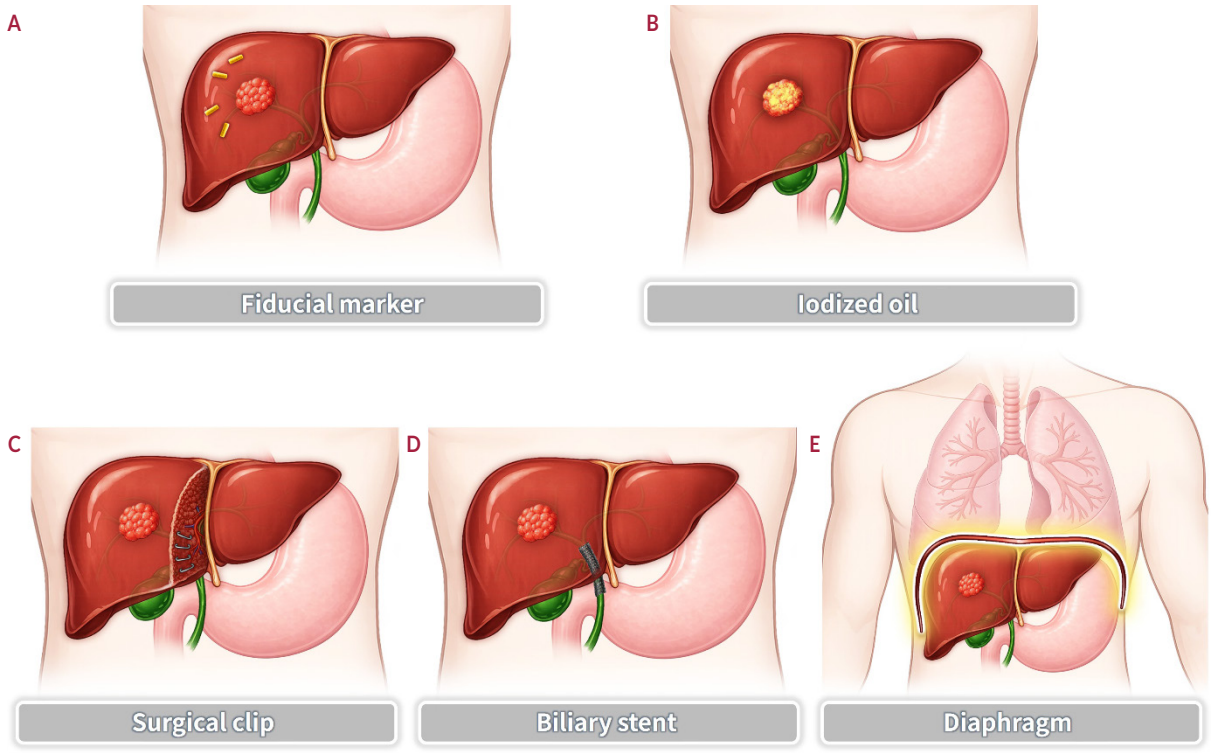


Figure 5. Representative examples of image guidance surrogates.

Table 4. Image-guidance surrogates applicable in stereotactic body radiation therapy

Image-guidance surrogate	Description
Fiducial marker	Small metallic markers implanted in the liver parenchyma surrounding the HCC. They serve as reference points for respiratory tracking and positional correction in cone-beam CT, fluoroscopy, and the CyberKnife system. The patient's general condition and coagulation status should be evaluated before insertion, and the location and number of markers should be determined through multidisciplinary consultation. During treatment, marker positions can be continuously verified using image-guidance to ensure accurate patient positioning.
Internal surrogate	Pre-existing structures identifiable on imaging (e.g., iodized oil retained after TACE, surgical clips, or biliary stents) are used as reference points without additional procedures. Although there is no procedural risk, positional stability may be somewhat lower; therefore, the decision to use them should be made by the treating physician based on the patient's situation and lesion characteristics. Their position should be continuously monitored throughout treatment.
Anatomical surrogate	When neither fiducial markers nor internal surrogates are available, anatomical structures such as the diaphragm or major vessels may be used as references for correction. Although these carry no procedural risk, their accuracy may be limited depending on tumor location, and their use should be judged on a case-by-case basis.

HCC, hepatocellular carcinoma; CT, computed tomography; TACE, transarterial chemoembolization.

during simulation. The supine position is the standard, and raising both arms above the head is recommended to maximize the range of beam angles.[47]

Treatment planning computed tomography acquisition

Treatment planning CT should be performed by comprehensively considering the patient's respiratory motion, lesion location, general condition, and available institutional resources. Applicable CT acquisition techniques are summarized in Table 5.[48]

In addition, because HCC lesions are characterized on dynamic contrast-enhanced CT through the arterial, portal venous, and delayed phases, the use of contrast media during treatment planning CT is recommended; the contrast phase that provides the most informative depiction for target delineation should be selected according to the chosen respiratory motion management technique and the imaging characteristics of the tumor.[48] Contrast use during treatment planning CT may be limited in patients with reduced renal function and should be avoided in patients with a previous immediate-type hypersensitivity reaction to iodinated contrast media or with concurrent acute thyrotoxic crisis; in such cases, alternative contrast agents or emergency-response preparations, including antihistamine premedication, may be required.[46] In patients with severe renal impairment (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), acute kidney injury, or a history of moderate-to-severe contrast hypersensitivity, premedication such as intravenous hydration and antihistamine administration should be considered.[46] For patients taking metformin who also have impaired renal function, metformin should be withheld for up to 48 hours after contrast administration.[46] When contrast use is contraindicated and target delineation must be performed using non-contrast CT alone, it is first necessary to verify whether the low-density tumor is clearly visible. However, since the boundaries of the lesion are often difficult to distinguish, options such as image registration with diagnostic CT or MRI should be considered to assist in tumor volume delineation. In cases where such image registration is required, examination schedules must be adjusted to keep the interval between diagnostic imaging and treatment planning CT as short as possible to ensure accurate tumor volume definition.

In addition, four-dimensional (4D) CT may be performed during simulation so that respiratory-induced tumor motion is incorporated into the treatment plan. Because of its repeated image acquisition, 4D CT increases patient radiation exposure compared with conventional CT by approximately 60% based on the volumetric CT dose index, although the dose generally remains less than twice that of conventional CT. The scan range and number of repeat acquisitions should therefore be minimized to the extent clinically necessary.[49]

In the expert survey on treatment planning CT practice for SBRT (multiple responses allowed), 4D CT was used by 96.8% of respondents, whereas breath-hold CT and slow CT were used by 16.1% and 6.5%, respectively. None of the respondents reported acquiring CT without considering respiratory motion.

Treatment planning magnetic resonance imaging acquisition

MRI provides superior soft-tissue contrast among the tumor, remaining liver parenchyma, and vascular structures compared with CT, making it valuable for target delineation.[26] When institutional equipment permits, obtaining both CT and MRI at the simulation stage may be considered.[26,50,51] Acquiring MRI immediately after the treatment planning CT in the same patient position helps reduce CT-MRI registration error.[50] Planning MRI enables precise target delineation according to lesion characteristics through the use of various sequences; in particular, T2-weighted imaging and DWI are useful for delineating tumor borders and detecting additional lesions.[51] The use of gadolinium-based contrast agents enhances the contrast between the lesion and the remaining liver and aids tumor visualization, but caution is required in patients with reduced renal function. When the eGFR is <30 mL/min/1.73 m^2, gadolinium-based contrast administration should be avoided owing to the increased risk of

Table 5. Treatment planning computed tomography acquisition techniques

Type	Acquisition method	Applicable respiratory motion management technique
4D CT	Acquires images while tracking the patient's respiratory cycle with external markers and reconstructs the images according to respiratory phase.	Free-breathing ITV-based SBRT, gating SBRT
Slow CT	Acquires axial images by slowing the table feed so that the entire respiratory cycle is encompassed.	Free-breathing ITV SBRT
BH CT	Acquires images while the patient holds breath at a predefined respiratory level (typically end-expiration or end-inspiration).	BH SBRT

4D, 4-dimensional; CT, computed tomography; ITV, internal target volume; SBRT, stereotactic body radiation therapy; BH, breath-hold.

nephrogenic systemic fibrosis.[46] Premedication with antihistamines or corticosteroids is recommended in patients with a previous history of contrast hypersensitivity.[46]

In the expert survey on treatment planning MRI practice, 12.1% of respondents reported performing treatment planning MRI in all patients prior to SBRT, while 27.3% performed it selectively in specific patients. The remaining 60.6% reported not performing treatment planning MRI.

[Recommendations]
1. During SBRT for HCC, an appropriate respiratory motion management technique tailored to the patient's respiratory characteristics and equipment resources is recommended.
2. During SBRT for HCC, an appropriate image guidance surrogate that adequately represents the tumor position is recommended.
3. Contrast-enhanced CT is recommended for SBRT simulation; however, the use of contrast media should be tailored to the patient's clinical condition.

TREATMENT PLANNING FOR STEREOTACTIC BODY RADIATION THERAPY

Required equipment specifications

SBRT utilizes ultra-hypofractionation with high doses per fraction; therefore, high-precision radiotherapy equipment is essential. While specific requirements may vary depending on tumor size, intensity modulation is generally recommended to ensure reliable, high-precision, and high-dose radiation delivery. To achieve this, high-resolution multileaf collimators are necessary to create a steep dose gradient between the target and the surrounding healthy tissues. Furthermore, image guidance systems, including kV fluoroscopy, CT, or MRI, are required to identify and compensate for changes in tumor position, patient movement, and respiratory-induced tumor motion before and during treatment. Additionally, a high dose rate of 1,000 monitor units/min or more is preferred to shorten beam-on time. This helps maintain consistency in dose delivery by reducing uncertainties associated with patient discomfort, general condition, and variations in respiratory patterns.

Particle beam therapy, including proton and carbon-ion therapy, can reduce the volume of the remaining liver exposed to moderate or low radiation doses. Therefore, particle beam therapy may be used for SBRT in patients with HCC, who often have underlying liver disease.[52,53] However, it should be noted that uncertainties in range, tissue heterogeneity, intestinal gas, and the use of contrast agents can affect the range and position of the Bragg peak. If accurate positioning of the Bragg peak, a defining characteristic and advantage of particle beam therapies, cannot be ensured, there is a higher risk of both reduced tumor control and increased toxicity compared to photon radiotherapy.[54,55]

Image registration and fusion for treatment planning

Image registration for treatment planning CT should be performed using end-exhalation CT acquired during free breathing, breath-hold CT, or 4D CT scans acquired during simulation, according to the respiratory motion management strategy selected for each patient. If necessary, diagnostic CT, MRI, or positron emission tomography/CT images may be fused with the treatment planning CT to assist in target volume delineation. If the tumor identified on the treatment planning CT shows significant changes compared to pretreatment diagnostic images, additional diagnostic CT or MRI scans should be acquired. Then, these images should be registered to the treatment planning CT to ensure a more accurate assessment of the current tumor extent.

Target volume definition

The gross tumor volume (GTV) is defined based on findings from dynamic CT and MRI, particularly arterial phase hyperenhancement and portal venous or delayed phase washout. The clinical target volume is generally considered identical to the GTV because preserving the remaining liver is critical, and additional margins are already accounted for by respiratory motion.[52,53,56,57] When treating a site after TACE, consideration should be given to including both the residual HCC and the iodized oil-retaining lesions within the GTV.[58] The ITV is established by expanding the GTV to encompass the specific respiratory cycle range identified on 4D CT. Finally, the planning target volume (PTV) is typically defined by adding a 5-10 mm margin to the ITV, accounting for patient-specific setup variations and institution- or device-specific uncertainties.

Definition of organs at risk

The primary organs at risk (OARs) include the whole liver (or remaining liver) and the adjacent gastrointestinal tract (esophagus, stomach, duodenum, small intestine, and large intestine). Additional OARs include the spinal cord, kidneys, skin, chest wall, lungs, and heart. To define the liver volume accurately, contrast-enhanced CT should be used to clearly delineate the hepat-

ic vascular structures and tumor boundaries.

Recently, various artificial intelligence-based auto-segmentation technologies have been introduced, improving efficiency and reproducibility in the field of radiotherapy. Auto-segmentation results, however, must be verified by an experienced radiation oncologist before being applied to the actual treatment planning of individual patients.

Additionally, for appropriate image guidance and respiratory motion management, internal surrogates should be selected and defined. This typically involves contouring the diaphragm or liver dome, iodized oil deposits, surgical clips, or other implanted fiducial markers.[57,59]

Treatment planning

In SBRT for HCC, the evidence regarding the dose-response relationship for local control is not yet fully established. The target dose is generally a biologically effective dose (BED_{10}) of 80-100 Gy or higher, assuming an α/β ratio of 10 for HCC, delivered in 3-5 fractions.[1] Here, BED_{10} is a standardized metric that allows for the comparison of actual biological effects on tissues on a uniform scale, regardless of variations in fractionation schedules or physical doses. When establishing the plan, the pretreatment liver function must be prioritized. To preserve remaining liver function, it is recommended that at least 700 mL of the remaining liver receive ≤15 Gy, or that the mean liver dose (MLD) be limited to 10-15 Gy or less.[47,56,57]

Dose constraints for all other critical OARs, including the gastrointestinal tract, spinal cord, and kidneys, should be set based on international guidelines. The radiation oncologist must verify that all constraints are met prior to treatment (Table 6). Furthermore, since many HCC patients suffer from underlying liver disease such as cirrhosis, which may be accompanied by portal hypertension-related gastrointestinal complications, it should be noted that the risk of radiation-induced gastrointestinal toxicity may increase even when standard OAR dose constraints are strictly followed.[60,61] Finally, given that intrahepatic recurrence is common and may necessitate additional treatments, including re-irradiation, the treatment plan should be designed to maximize sparing of the remaining liver.[52,53,56,62]

Table 6. Organ-specific dose constraint for stereotactic body radiation therapy (Task group-101)

Organ at risk	Maximum point dose	Number of fractions
Liver (normal)	≥700 mL <9.1 Gy/19.2 Gy/21 Gy	1/3/5 fractions
Stomach/duodenum	12.4 Gy/22.2 Gy/32 Gy	1/3/5 fractions
Bowel (small/large)	12.4 Gy/22.2 Gy/35 Gy	1/3/5 fractions
Esophagus	15.4 Gy/25.2 Gy/35 Gy	1/3/5 fractions
Spinal cord	14 Gy/21.9 Gy/30 Gy	1/3/5 fractions
Heart/pericardium	22 Gy/30 Gy/38 Gy	1/3/5 fractions
Skin	26 Gy/33 Gy/39.5 Gy	1/3/5 fractions
Kidneys	≥200 mL <8 Gy/16 Gy/17.5 Gy	1/3/5 fractions

Gy, gray.

Dose prescription

The primary objective of dose prescription in SBRT is to ensure that the PTV is covered by the 95% isodose line of the prescribed dose, following standard radiotherapy principles. However, "hot spots" within the target volume, even those exceeding 150% of the prescribed dose, may be acceptable, provided they do not extend into the surrounding normal tissues.[63-65] Furthermore, the simultaneous integrated boost technique can be utilized to deliver a higher dose to the core of the GTV while tapering to a lower dose at the PTV periphery. Conversely, the simultaneous integrated protection technique can be applied to modulate and reduce the dose in areas immediately adjacent to critical OARs, thereby improving normal tissue sparing.[66-68]

Quality assurance

Due to the high-dose and hypofractionated nature of SBRT, even minor errors can directly impact patient safety and therapeutic efficacy. Therefore, it is essential to perform regular quality assurance (QA) of equipment performance, image guidance systems, and respiratory motion management, to ensure that they remain within the tolerance limits recommended by international guidelines.[69] Additionally, to verify that each patient's specific treatment plan can be accurately reproduced on the delivery system prior to the start of treatment, patient-specific QA is required. This involves measuring the actual dose distribution, using film, electronic portal imaging devices, or detector arrays, and comparing the measured dose distribution with the calculated dose distribution.

[Recommendations]

1. It is essential to use equipment equipped with image guidance systems and high-dose-rate irradiation capabilities.
2. It is necessary to define OARs, including the whole or remaining liver, adjacent gastrointestinal tract (esophagus, stomach, duodenum, small intestine, and large intestine), and when appropriate, the spinal cord, kidneys, skin, chest wall, lungs, and heart.
3. To preserve remaining liver function, the treatment plan should aim to limit the dose to ≤15 Gy for at least 700 mL of the remaining liver or limit the MLD to the remaining liver to ≤10-15 Gy. While satisfying dose constraints for surrounding organs such as the gastrointestinal tract, the prescribed dose should aim for a BED10 of at least 80 to 100 Gy.
4. Prior to SBRT, patient-specific quality assurance should be conducted to ensure that the established treatment plan can be accurately delivered on the delivery system.

DELIVERY OF STEREOTACTIC BODY RADIATION THERAPY

Methods of image-guided radiation therapy

Necessity of image-guided radiation therapy

Because the liver undergoes significant positional changes due to respiration and internal motion, accurate verification and correction through pretreatment and intrafraction image guidance are necessary during SBRT. This enhances treatment reproducibility and minimizes unnecessary radiation exposure to critical organs, such as the remaining liver and the gastrointestinal tract. The IGRT strategy may vary depending on the type of equipment, respiratory control method, lesion location, and whether fiducial markers are used.[42-45,70-72]

Image-guided radiation therapy equipment and techniques

The methods used for image guidance in SBRT can be classified as shown in Table 7 and should be selected according to the characteristics of each treatment device, treatment site, and the patient's condition.

According to the survey results on the image guidance methods used during SBRT (multiple responses allowed), all respondents reported using one or more image guidance methods. Regarding the equipment used, all respondents reported using cone-beam CT (CBCT), and 25% also used fluoroscopy. In addition, 6.3% reported using MRI guidance, and 3.1% reported using surface-guided systems.

Intrafraction monitoring and decisions on treatment discontinuation

Necessity of real-time intrafraction monitoring

Due to the characteristics of SBRT as a high-dose, hypofractionated treatment, even minute positional changes during treatment can significantly impact treatment outcomes; therefore, continuous verification through pretreatment and intrafraction IGRT and respiratory monitoring is essential.[73-76] Particularly when applying respiratory control techniques, predefined criteria for treatment interruption in the event of respiratory abnormalities should be established, and rapid communication among medical staff is required.

Monitoring during respiratory motion-managed radiation therapy

In SBRT for HCC, respiratory motion should be monitored in real time to ensure accurate radiation delivery within the planned

Table 7. Image-guided radiation therapy techniques used in stereotactic body radiation therapy

IGRT technique	Utilized treatment equipment	Process	Advantages	Disadvantages
Fluoroscopy	LINAC, CyberKnife	2D tracking based on fiducial markers or bony anatomy.	Real-time monitoring and tracking are possible.	Limited 3D anatomical information. Direct tumor verification is not possible.
Cone-beam CT	LINAC	Positional correction through 3D image acquisition before treatment.	Easy daily verification and correction of anatomical positions.	Radiation exposure exists. Soft tissue contrast is low.
MR guidance	MR-LINAC	Positional verification and tracking using real-time MRI.	Excellent soft tissue contrast. No radiation exposure.	Requires specialized equipment. Treatment time can be prolonged.
In-room CT	Separate CT installed in the treatment room	Uses high-resolution diagnostic CT scanner installed in the treatment room.	Excellent for evaluating anatomical structures.	Requires additional installation space and cost. Patient transfer is required.

IGRT, image-guided radiation therapy; LINAC, linear accelerator; 2D, 2-dimensional; 3D, 3-dimensional; CT, computed tomography; MR, magnetic resonance; MRI, magnetic resonance imaging.

treatment volume. To achieve this, a combination of external respiratory signal monitoring (e.g., marker-based optical tracking and pressure sensor-based systems), image guidance surrogates (e.g., fiducial markers, internal surrogates, and anatomical surrogates), and IGRT equipment (e.g., CBCT and fluoroscopy) should be used based on the equipment available at each institution. Such real-time monitoring is essential for maintaining treatment accuracy and minimizing unnecessary radiation exposure to surrounding OARs.[42-45,70,71,77] Monitoring during respiratory motion-managed radiation therapy is generally performed according to the following principles.

- Position verification: the position of the tumor or internal surrogates should be verified using pretreatment and intrafraction imaging (CBCT, fluoroscopy, etc.) to confirm that the motion remains within the planned range.
- Maintaining respiratory stability: external respiratory signals should be monitored for changes in the respiratory cycle, amplitude, and phase. If irregular breathing is detected, treatment should be temporarily interrupted and resumed once a stable respiratory pattern has been re-established.
- Ensuring reproducibility: the reproducibility of the planned respiratory state or treatment position should be verified throughout treatment according to the selected respiratory control technique, such as breath-hold, gating, or tumor tracking.
- Positional correction: If displacement of the tumor or adjacent organs is detected, treatment should be resumed only after positional correction has been performed and the position has been re-verified.

Decisions on treatment interruption

If respiration becomes irregular during treatment or if the target position deviates from the planned range, treatment should be temporarily interrupted, and the patient's respiratory status and treatment plan should be re-evaluated. In the following situations, treatment may be resumed after respiratory retraining or a short period of rest if respiratory stability is restored. However, if the problem persists or is considered clinically significant, treatment for that fraction may need to be discontinued, and a new treatment plan should be developed beginning with the simulation process.

- Respiratory instability: when the respiratory amplitude persistently exceeds the predefined tolerance limit (e.g., 3-5 mm or the predefined gating window).
- Excessive treatment time: when the total treatment time exceeds the planned duration by 1.5- to 2-fold because of repeated setup and positional corrections, or when the beam-on ratio decreases substantially during the treatment session.
- Image discrepancy: when in-room imaging (e.g., CBCT) demonstrates target displacement beyond the PTV margin, or when there is concern that dose constraints for adjacent OARs may be exceeded.

These criteria should not be applied as absolute numerical values, but rather by comprehensively considering the patient's respiratory stability, immobilization, and general condition. In cases of temporary instability, treatment may be resumed after respiratory retraining and setup correction. However, simple positional correction alone may not be sufficient in some cases. This includes situations in which substantial changes in the shape of the tumor or adjacent organs are observed on images acquired during treatment. In such cases, adaptive planning or repeat simulation CT may also be considered.

According to the survey on the clinical implementation of adaptive radiotherapy (ART), 77.4% of valid respondents reported that they do not implement additional ART when a stable setup is maintained, indicating that ART is not routinely performed in most cases if appropriate setup correction is achieved. Conversely, 22.6% reported implementing ART to improve treatment precision even when a stable setup is maintained. Specifically, 22.6% responded using interfraction adaptive radiotherapy (offline ART) based on periodic repeated CT, whereas 3.2% reported using real-time adaptive radiotherapy (online ART) on the day of treatment, suggesting that some institutions periodically incorporate interfraction anatomical changes into the treatment process.

[Recommendations]

1. During SBRT, appropriate pretreatment and intrafraction IGRT should be applied, taking into account the patient's respiratory characteristics and the equipment available at each institution.
2. When SBRT is performed using respiratory control techniques, treatment safety and accuracy should be ensured through real-time intrafraction monitoring.
3. The decision to interrupt treatment should be based on predefined criteria, including respiratory instability, excessive treatment time, and image discrepancy. In cases of persistent or repeated deviation, deferral of the treatment fraction and corrective procedures should be considered.

POST-TREATMENT PATIENT MANAGEMENT AND FOLLOW-UP AFTER STEREOTACTIC BODY RADIATION THERAPY

Post-treatment patient care

Treatment-related complications

SBRT for HCC is generally associated with a relatively low incidence of severe treatment-related complications in patients with preserved liver function. In a study evaluating quality of life (QoL) in 222 patients enrolled in phase 1/2 clinical trials, SBRT did not significantly affect overall QoL. Fatigue and decreased appetite worsened transiently at 1 month after treatment but returned to baseline by 3 months.[78]

Potential acute complications (within 3 months of treatment completion) following SBRT for intrahepatic lesions include systemic symptoms (e.g., fatigue and anorexia), gastrointestinal symptoms (e.g., nausea, vomiting, and abdominal pain), and laboratory abnormalities, including elevations in liver enzymes (AST and ALT), hyperbilirubinemia, and hematologic toxicities (e.g., leukopenia and thrombocytopenia).[56,57] Reported late complications (beyond 3 months after treatment) include elevations in liver enzymes, deterioration of liver function (e.g., worsening of the Child-Pugh score or ALBI grade), gastrointestinal toxicities (e.g., gastric or duodenal ulcers), radiation pneumonitis (predominantly involving the right lower lobe), rib fractures, intercostal neuritis, and biliary strictures.[56,57,79] However, these severe late complications are largely preventable through appropriate patient selection and meticulous treatment planning. Therefore, the risk of treatment-related complications should be assessed comprehensively, taking into account tumor location and size, the prescribed radiation dose, and other relevant treatment parameters.

Management of complications

Most complications following SBRT for HCC are mild, corresponding to common terminology criteria for adverse events grade 1 or 2, and typically resolve with conservative management and/or spontaneously over time.[80,81] Rarely, gastrointestinal bleeding may require endoscopic hemostasis or blood transfusion. In cases where biliary stricture results in secondary complications such as jaundice, interventions including biliary drainage or biliary stent placement may be considered.

Prevention of complications is of paramount importance. Strict adherence to OAR dose constraints and careful patient selection based on a comprehensive pretreatment assessment of liver function are essential. In patients with compromised liver function, dose de-escalation and/or adjustments to the total prescribed dose or dose per fraction should be considered.[44,82,83]

Follow-up management after stereotactic body radiation therapy

Surveillance for recurrence and liver function

After SBRT for HCC, radiologic imaging (CT or MRI) and serum tumor markers, including alpha-fetoprotein and protein induced by vitamin K absence-II, are used to assess disease status and detect recurrence. Regular laboratory tests should also be performed to assess liver function and monitor treatment-related complications, including AST/ALT, bilirubin, alkaline phosphatase, albumin, prothrombin time, and complete blood count. Additional evaluations may be performed as clinically indicated based on the patient's symptoms.

Hepatocellular carcinoma recurrence

Recurrence after curative-intent treatment for HCC is most frequent during the first year after treatment and decreases thereafter. After 2 years, the risk of developing de novo HCC has been reported to exceed the risk of recurrence from the treated lesion.[84] The 2022 KLCA-NCC practice guidelines for HCC recommend post-treatment evaluations at 6 to 8-week intervals. In patients who achieve a complete response, follow-up evaluations every 2-6 months are recommended until 2 years after treatment. Although studies specifically addressing tumor marker kinetics and post-SBRT surveillance strategies are limited, given the high complete response rates of treated lesions and the evidence that radiologic responses may take several months to fully manifest, it is reasonable to follow the KLCA-NCC surveillance schedule for monitoring intrahepatic recurrence after SBRT.

Post-treatment liver function monitoring

Elevations in liver enzymes and deterioration of liver function after SBRT have been reported in approximately 5%–35% of patients, depending on the study.[44,56,85] When assessed using the Child–Pugh score, changes are most pronounced at approximately 3 months after treatment. While mild deterioration may persist up to 12 months, it is generally of limited clinical significance.[86-88] However, in patients with impaired baseline liver function, the risk of post-treatment liver enzyme elevation or hepatic functional deterioration is higher, and recovery may be delayed.[89] Therefore, close monitoring for acute hepatic complications is warranted during the first 3 months after treatment, and liver

function should be assessed serially using both the Child–Pugh score and ALBI grade.

Imaging surveillance

Imaging surveillance after SBRT should be guided by the post-treatment imaging findings of the lesion.[90] When masslike enhancement that has increased in size compared with pretreatment imaging, or newly developed masslike enhancement, is observed, it should be considered suggestive of clinically significant tumor activity, and subsequent treatment strategies should be determined through multidisciplinary discussion. In such cases, the timing of repeat imaging should be individualized according to the planned treatment strategy. For masslike enhancing lesions that remain stable or have decreased in size, as well as those in which enhancement has completely disappeared, follow-up imaging at approximately 3-month intervals is recommended. The use of the same imaging modality is recommended whenever feasible to ensure accurate comparison. However, alternative imaging modalities or contrast agents may be used when a diagnostic benefit is anticipated. In addition, when other intrahepatic lesions are present outside the lesion treated with SBRT, the follow-up imaging interval may be adjusted accordingly.

In the expert survey, 95.2% of respondents agreed that the interval for post-treatment imaging follow-up should be individualized based on the imaging findings of the treated lesion and the development of new lesions. Accordingly, this consensus recommends that the imaging follow-up interval for tumor response assessment after SBRT be individualized according to the post-treatment imaging findings of the lesion.

[Recommendations]

1. Radiologic imaging and serum tumor marker assessments for surveillance of HCC recurrence after SBRT are recommended every 2-3 months for up to 2 years after treatment and every 6 months thereafter.
2. In patients with impaired liver function before SBRT, defined as Child-Pugh class B or higher, close and continuous monitoring for post-treatment deterioration of liver function is recommended.
3. The imaging follow-up interval for tumor response after SBRT should be individualized based on the post-treatment imaging findings of the treated lesion and the development of new lesions.

TUMOR RESPONSE ASSESSMENT AFTER STEREOTACTIC BODY RADIATION THERAPY

Considerations in tumor response assessment after stereotactic body radiation therapy

SBRT is a treatment modality that induces tumor cell death through the delivery of high-dose radiation. The death of HCC cells after SBRT occurs gradually over several months through delayed cell death and radiation-induced cellular senescence rather than immediate necrosis.[91-94] According to the literature, tumor enhancement generally diminishes over 6-12 months,[57,95-99] and tumor size gradually decreases over 3-12 months (Fig. 6).[97-100] Some studies have reported cases in which lesion enhancement persisted for up to 24 months after treatment but were ultimately confirmed as pathologic complete necrosis without additional treatment.[98] Furthermore, considering the high local control rates of SBRT reported in the literature, masslike enhancement observed on imaging shortly after treatment does not necessarily indicate clinically significant tumor viability. These unique response characteristics should be taken into account when assessing tumor response after SBRT.

In addition, a focal liver reaction may be observed in the hepatic parenchyma surrounding the SBRT irradiation field, representing the imaging manifestation of radiation-induced hepatitis. The most common finding is geographic arterial phase hyperenhancement around the treated lesion, which appears 3-6 months after treatment and may persist for up to 12 months (Fig. 7).[97,101-103] This finding is thought to result from a compensatory increase in arterial blood flow due to small venous occlusion. Subsequently, progressive fibrosis may lead to chronic radiation-induced changes, including delayed enhancement, capsular retraction, and liver atrophy.[103] Because these changes may mimic the imaging features of residual or recurrent HCC, it is essential to recognize them as part of the normal post-radiation course and to interpret them by comprehensively considering their morphologic characteristics and evolution over time.

Selection of imaging modality

Dynamic contrast-enhanced CT is widely used as the standard imaging modality for post-treatment surveillance of HCC and is useful for evaluating tumor size and enhancement patterns. However, after SBRT, accurate assessment of actual changes in lesion size may be challenging because of radiation-induced pa-

renchymal changes in the liver.[102,104,105] Dynamic contrast-enhanced MRI generally provides higher sensitivity than CT for the diagnosis of HCC; however, evidence regarding its utility for response assessment after SBRT remains limited. Furthermore, contrast-enhanced MRI shares similar limitations with CT, as evaluation of the treated lesion may be hindered by radiation-induced changes in the surrounding hepatic parenchyma.[95] In MRI using hepatocyte-specific contrast agents, the HBP, which provides the highest sensitivity for HCC detection, is also limited for response assessment after SBRT, as the signal intensity of the hepatic parenchyma surrounding the lesion is concomitantly reduced. In contrast, T2-weighted imaging and DWI, which are uniquely available with MRI, may aid in assessment, as new high signal intensity and a decrease in the apparent diffusion coefficient may suggest significant tumor viability.[106] In addition, MRI offers the advantage of detecting newly developed intrahepatic lesions with high sensitivity while also facilitating tumor response assessment.

To date, no clear evidence indicates which imaging modality is superior for response assessment after SBRT. In the expert survey, the majority of respondents (71.4% strongly agree and 26.2% agree) supported the complementary use of dynamic contrast-enhanced CT and MRI. Accordingly, the complementary use of both imaging modalities is recommended for tumor response assessment after SBRT.

Response assessment guidelines

The conventional response assessment criteria, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, are based

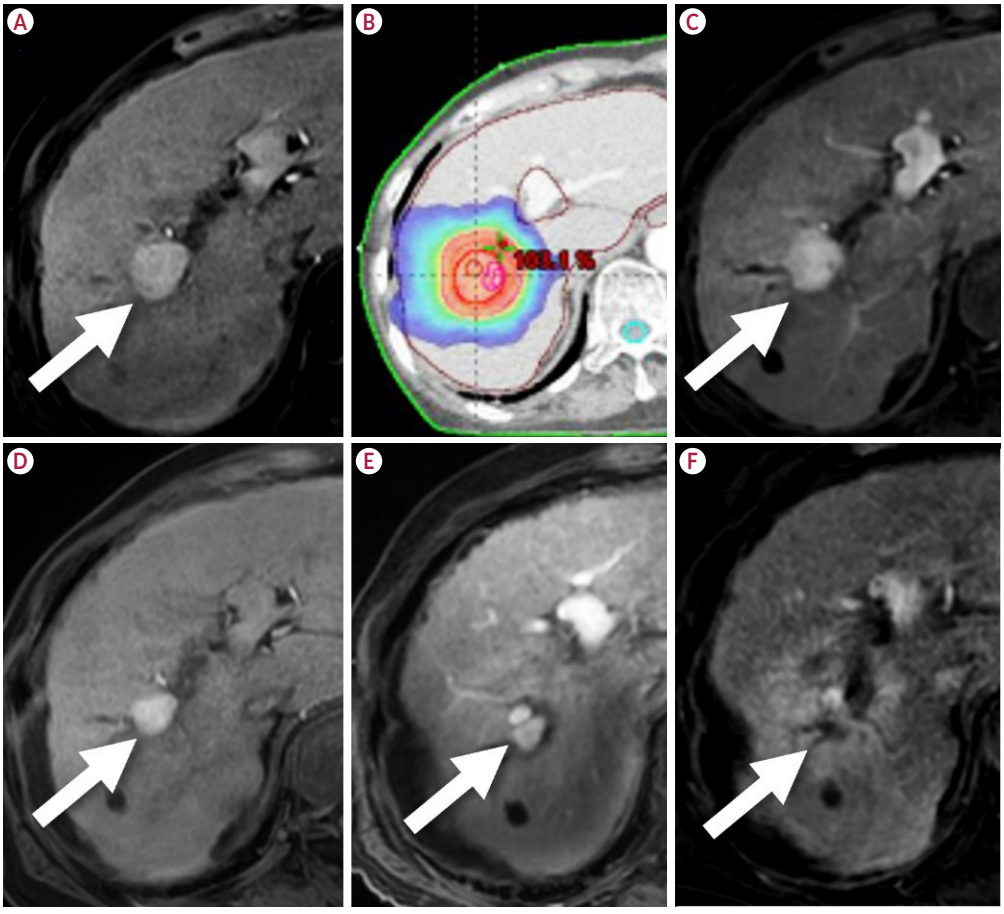


Figure 6. Temporal changes in tumor size and enhancement after SBRT for HCC. (A) A 78-year-old woman presented with a 2.3-cm HCC (arrow) in hepatic segment 8, which showed arterial phase enhancement on MRI. (B) The lesion was treated with SBRT of 42 Gy in 3 fractions. Follow-up arterial phase MRI obtained at (C) 1 day, (D) 2 months, (E) 5 months, and (F) 8 months after treatment showed a gradual decrease in lesion size, with persistent arterial phase hyperenhancement (arrow) observed until complete resolution. (F) At 8 months after treatment, no measurable lesion (arrow) remained. Without additional treatment, the lesion ultimately showed a complete response, and no local tumor recurrence within the treated field was observed on subsequent follow-up imaging. SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

solely on changes in tumor size and therefore do not adequately reflect the delayed tumor necrosis that occurs after SBRT.[95,104] The modified RECIST and European Association for the Study of the Liver criteria define areas of arterial phase enhancement as viable tumor, providing an HCC-specific assessment of treatment response. However, these criteria may interpret the persistent arterial phase enhancement commonly observed after SBRT as viable residual tumor, potentially leading to unnecessary additional treatment.[95,97,98]

The Liver Imaging Reporting and Data System (LI-RADS) CT/MRI radiation treatment response algorithm (LR-TRA) version 2024 provides a lesion-based response assessment system for radiation-treated lesions, classifying evaluable lesions into three categories: viable, nonprogressing, and nonviable.[90,107] Even when masslike enhancement persists after treatment, lesions that remain stable or have decreased in size compared with pretreatment imaging are classified as nonprogressing and are not regarded as clinically significant tumor activity, allowing continued surveillance. If masslike enhancement disappears during follow-up, the lesion may be reclassified as nonviable. Conversely, if new masslike enhancement develops or existing enhancement increases in size, the lesion is classified as viable, and additional treatment for this lesion should be considered. In addition, when newly developed or increased diffusion restriction or mild-to-moderate T2 hyperintensity is observed on MRI, the lesion may be upgraded from nonprogressing to viable, even when masslike enhancement remains stable or has decreased. Although the LR-TRA is a response assessment system that accounts for the unique imaging features observed after radiation therapy, it has not yet been sufficiently validated, and further studies are warranted.

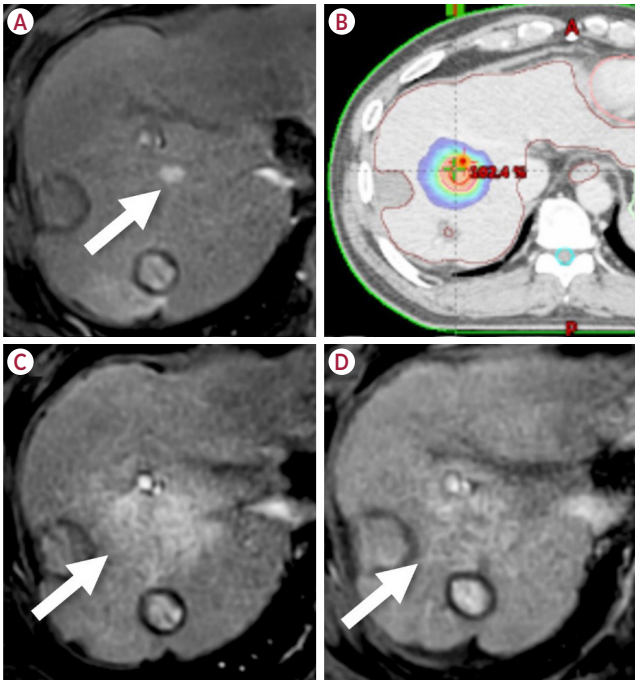


Figure 7. Peritumoral arterial phase hyperenhancement after SBRT. (A) A 60-year-old man with a history of radiofrequency ablation for HCC was found to have a recurrent 1.2-cm HCC (arrow) in hepatic segment 8. (B) The lesion was treated with SBRT of 42 Gy in 3 fractions. (C) Follow-up MRI performed 45 days after treatment showed ill-defined arterial phase hyperenhancement (arrow) distributed along the radiation field, surrounding the treated lesion. This peritumoral enhancement obscured clear delineation of the tumor, making it difficult to assess changes in the size of the treated tumor. (D) This peritumoral arterial phase hyperenhancement (arrow) persisted on follow-up imaging up to 8 months after treatment. SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

In the expert survey, 78.6% of respondents agreed that follow-up observation without additional treatment is feasible when there is no increase in lesion size or development of new masslike enhancement after treatment. Accordingly, this consensus recommends that, during response assessment after SBRT, when there is no increase in lesion size and no new masslike enhancement within the lesion, any residual masslike enhancement should not be considered clinically significant residual tumor. In such cases, surveillance should be prioritized over additional treatment.

[Recommendations]

1. Dynamic contrast-enhanced CT and MRI may be used complementarily for tumor response assessment after SBRT.
2. In response assessment after SBRT, residual masslike enhancement should not be regarded as clinically significant residual tumor when there is no increase in lesion size or new masslike enhancement within the lesion. In such cases, surveillance without additional treatment is recommended as the initial approach.

Conflicts of Interest

Jinhong Jung, Han Ah Lee, Gyu Sang Yoo, and Sang Min Yoon are Editorial Board members of *Journal of Liver Cancer*. They were not involved in the review, evaluation, or decision-making process for this manuscript.

Ethics Statement

Not applicable.

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Data Availability

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