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MINIREVIEWS

Technical advances in external radiotherapy for hepatocellular carcinoma

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Abstract

Radiotherapy techniques have substantially improved in the last two decades. After the introduction of 3-dimensional conformal radiotherapy, radiotherapy has been increasingly used for the treatment of hepatocellular carcinoma (HCC). Currently, more advanced techniques, including intensity-modulated radiotherapy (IMRT), stereotactic ablative body radiotherapy (SABR), and charged particle therapy, are used for the treatment of HCC. IMRT can escalate the tumor dose while sparing the normal tissue even though the tumor is large or located near critical organs. SABR can deliver a very high radiation dose to small HCCs in a few fractions, leading to high local control rates of 84%-100%. Various advanced imaging modalities are used for radiotherapy planning and delivery to improve the precision of radiotherapy. These advanced techniques enable the delivery of high dose radiotherapy for early to advanced HCCs without increasing the radiation-induced toxicities. However, as there have been no effective tools for the prediction of the response to radiotherapy or recurrences within or outside the radiation field, future studies should focus on selecting the patients who will benefit from radiotherapy.

Key words: Hepatocellular carcinoma; Radiotherapy; 3D-conformal radiotherapy; Intensity-modulated radiotherapy; stereotactic ablative body radiotherapy; Charged particle therapy; Image-guided radiotherapy

Core tip: Radiotherapy techniques have greatly improved in the last two decades. After the introduction of 3-dimensional conformal radiotherapy, the use of radiotherapy for hepatocellular carcinoma (HCC) has increased substantially. Currently, more advanced techniques including intensity-modulated radiotherapy, stereotactic ablative body radiotherapy, charged particle therapy, and image-guided radiotherapy are increasingly used for the treatment of HCCs. These techniques

facilitate the delivery of higher dose radiotherapy for early to advanced HCCs, while minimizing radiation-induced toxicities. This review will cover the technical aspects of modern radiotherapy techniques along with their clinical applications.

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INTRODUCTION

In the past, radiotherapy (RT) had a limited role in the treatment of hepatocellular carcinoma (HCC) due to the poor tolerance of the normal liver and the poor RT technique. As a result, the well-known Barcelona Clinic Liver Cancer guidelines for the treatment of HCC did not recommend RT as a treatment option for all stages of HCC[1]. This guideline recommends surgical treatments or local ablative therapies such as percutaneous ethanol injection or radiofrequency ablation (RFA) for the treatment of early small tumor(s) of stage 0 or A. Transarterial chemoembolization (TACE) is recommended for stage B large or multifocal HCCs and new agents like sorafenib are recommended for advanced stage C HCCs, which includes portal vein invasion or lymph node metastases. However, as many patients are not candidates for curative treatment or are not effectively treated with TACE or sorafenib, the use of other effective local modalities are warranted.

With the advancement of RT technologies, including 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), stereotactic ablative body radiotherapy (SABR), charged particle therapy, and image-guided radiotherapy (IGRT), delivering a higher radiation dose to the tumor in a safer way than before has become possible. To date, many institutions have reported good clinical outcomes for HCC patients receiving high dose radiation[2]. Moreover, increased understanding of the dose-response relationship and radiation-induced liver disease (RILD) facilitates the use of RT for patients with early to advanced HCCs[3-5]. In this topic highlight, we focused on the technical aspects of modern RT techniques for HCC along with their clinical applications.

3D-CRT

In contrast to the conventional 2D-RT technique, which usually uses opposing anterior and posterior radiation fields, 3D-CRT uses multiple coplanar or non-coplanar fields in order to reduce the high-dose exposure of normal tissues including the liver and bowels and to increase the tumor dose coverage (Figure 1). With the use of computed tomography (CT) images for RT planning and a computerized treatment planning system, the tumor and surrounding normal liver can be delineated accurately; the delivered dose and irradiated volume of the tumor and normal liver can be precisely evaluated. As a result, experience in the response of the tumor and normal liver to certain dose levels shapes the current decision making process for the RT regimen.

A high 92% response rate (80% complete response and 12% partial response) was achieved in a French phase 2 trial conducted in 27 patients having Child-Pugh class A or B liver function with a single tumor sized $\leqslant$ 5 cm or 2 tumors sized $\leqslant$ 3 cm after 66 Gy of 3D-CRT delivered in 33 fractions[6]. A Korean multicenter retrospective patterns of care study conducted in 398 HCC patients showed that a biologic effective dose of $\geqslant$ 53.1 Gy_{10} was associated with an improved 2-year overall survival[3]. Seong *et al*[7] treated 158 HCC patients with a dose of 25.2-60 Gy (1.8 Gy per fraction). In their study, the RT dose was identified by multivariate analysis as the only significant factor for survival. The median survival times in patients who received < 40 Gy, 40-50 Gy, and > 50 Gy were 6, 8, and 13 mo, respectively. Other studies also showed that a total RT dose of > 40-50 Gy achieved higher response or survival rates[8-10].

The Korean Practice Guidelines for the Management of Hepatocellular Carcinoma recommend RT for HCC patients as follows: (1) RT can be performed in HCC patients if liver functions indicate Child-Pugh class A or superb B and the irradiated total liver volume receiving $\geqslant$ 30 Gy is $\leqslant$ 60% (evidence level B1); (2) RT can be considered for HCC patients ineligible for surgical resection, liver transplantation, RFA, percutaneous ethanol injection, or TACE (C1); (3) RT can be considered for HCC patients who show incomplete response to TACE when the dose-volume criteria in Recommendation 1 are met (B2); (4) RT can be considered for HCC patients with portal vein invasion when the dose-volume criteria in Recommendation 1 are met (C1); and (5) RT is performed to alleviate symptoms caused by primary HCC or its metastases (B1)[11]. In the meta-analysis of 5 randomized and 12 non-randomized trials, TACE combined with RT achieved a better tumor response and survival than TACE alone[12]. Patients with portal vein thrombosis (PVT) responded to RT in about 45% of the cases[13,14].

However, the tolerance dose of the normal liver often limits the use of higher dose RT for HCC despite the availability of the modern 3D-CRT technique. Many factors including poor liver function with a Child-Pugh B or C score, prior TACE, PVT, and hepatitis B carrier status are known to be associated with a higher risk of RILD[15,16]. Nonetheless, these factors are unavoidable when RT is indicated. Radiation dose modification is recommended according to the liver function, the relative size of the tumor to the whole liver, and the normal liver dose[17,18]. Therefore, more advanced RT techniques are warranted to overcome

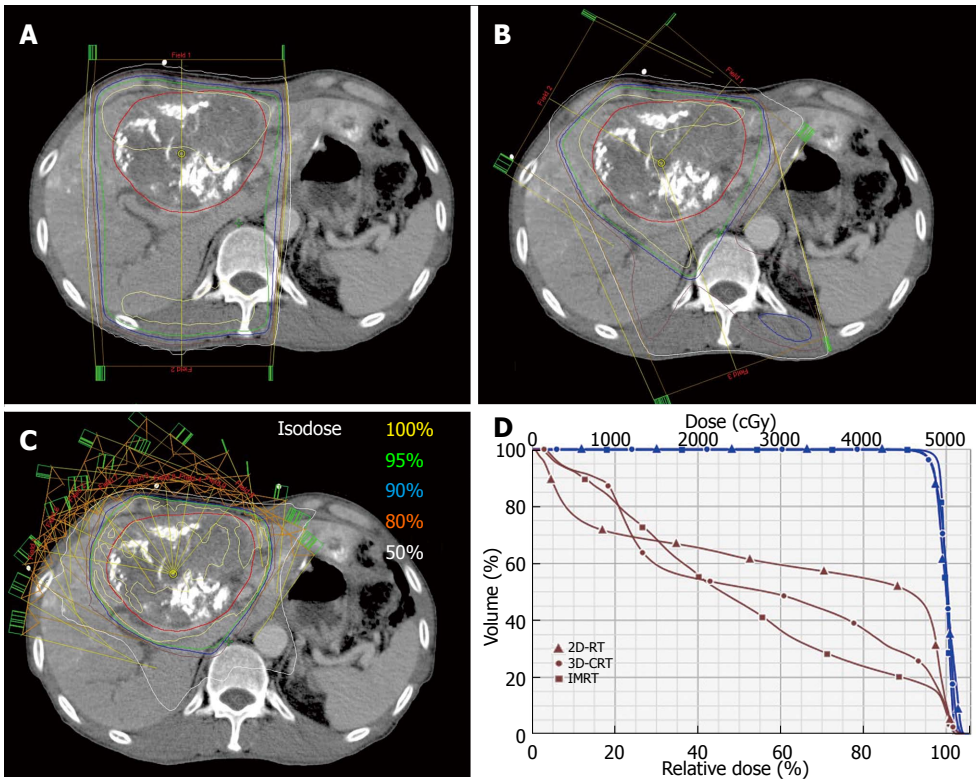

Figure 1 The radiotherapy plans of different radiotherapy techniques for hepatocellular carcinoma. A: 2-dimensional radiotherapy (2D-RT); B: 3-dimensional conformal radiotherapy (3D-CRT); C: Intensity-modulated radiotherapy (IMRT); D: dose volume histogram of the tumor (blue) and normal liver (brown). IMRT plan shows the best liver sparing while 2D-RT shows the worst liver sparing.

these unavoidable obstacles and improve the clinical outcomes in terms of tumor control and normal tissue toxicity.

IMRT

IMRT is an advanced form of conformal RT that facilitates the delivery of a higher radiation dose compared to 3D-CRT. A computer-aided automated optimization process, known as inverse treatment planning, modulates the intensity of each beam to gain the desired target coverage while minimizing the dose to the normal organs (Figure 1). At present, various forms of IMRT, including volumetric-modulated arc therapy (VMAT) and helical tomotherapy (HT), are available. VMAT delivers intensity-modulated beams during gantry rotation, and HT delivers the radiation dose in slices with the help of a rotating gantry similar to a helical CT scanner. Furthermore, IMRT can deliver different doses to different targets at the same time, which is called simultaneous integrated boost-IMRT. Using this technique, a higher dose can be delivered to the gross tumor volume concurrently with a lower dose to areas of subclinical disease. Even though radiation oncologists have been reluctant in using IMRT for moving tumors due to the dosimetric and radiobiological uncertainties related to respiratory movement, recent experimental and clinical studies have rationalized its use for the treatment of HCC.

The distortion of calculated dose distribution of the IMRT plan on the static CT images is inevitable if the target moves during the IMRT beam delivery. The difference between the calculated and measured doses of a single IMRT field or a single fraction with doses of multiple IMRT fields was unacceptably high; however, repeated irradiation negated the effect of motion[19-21]. After the delivery of 30 fractions, the mean dose to a moving tumor differed slightly (< 2%-3%) from that of a static tumor[19]. Volumetric dose measurements by Duan *et al*[21] revealed that the 5-fraction isodose line for the moving phantom was fairly well matched with that of the stationary phantom, and the difference between the tumor control probabilities of the stationary and moving tumors for $\geqslant$ 2 fractions was small (< 2.3%). Kuo *et al*[20] reported that this difference was larger at higher amplitudes of tumor motion and higher dose rates of irradiation (500 MU/min *vs* 300 MU/min); however, it did not differ between the IMRT delivery modes (sliding window *vs* step-and-shoot).

The dosimetric advantages of IMRT over 3D-CRT and the importance of the IMRT techniques were previously reported. Early dosimetric studies comparing IMRT to 3D-CRT suggested that IMRT enabled dose escalation without the risk of increased liver toxicity and potentially reduced the normal tissue complication probability in HCC patients previously diagnosed with RILD after 3D-CRT[16,22]. Chen *et al*[23] compared the techniques of

3D-CRT, fixed-angle IMRT, and VMAT in small to large HCCs and suggested that VMAT might carry the lowest risk of RILD with the lowest V20 and V30 compared to 3D-CRT or IMRT for right lobe tumors. However, the results of comparisons between different RT techniques (3D-CRT *vs* fixed-angle IMRT *vs* VMAT *vs* HT) have been variable. Although some studies reported that the mean liver dose was higher for fixed-angle IMRT or VMAT plan compared to 3D-CRT[16,23], these results could be caused by suboptimal IMRT beam configuration or the routine application of constraints to IMRT planning as a planning study. HT has been reported to provide a better uniformity for the target coverage than fixed-angle IMRT; however, the low dose volume of the normal liver that is related to the risk of RILD was higher for HT compared to that of fixed-angle IMRT[24,25]. Park *et al*[26] reported that the dose-volumetric parameters of VMAT *vs* fixed-angle IMRT differed according to the target location within the liver; central tumors showed higher mean liver dose and lower liver volume receiving 30 Gy for VMAT than for IMRT; however, peripheral tumors showed no difference. When using fixed-angle coplanar IMRT, using fields entering the body near the tumor might be better at reducing the normal liver dose by decreasing the length of beam path through the normal liver compared to the equidistant beam array[27].

The clinical outcomes of IMRT have been reported recently. Yoon *et al*[28] reported that IMRT could deliver higher doses (median, 50 Gy in 20 fractions) and achieved higher 3-year overall survival and progression-free survival than 3D-CRT without the increased risk of RILD in stage Ⅲ or ⅣA HCC patients. Hou *et al*[29] reported similar results in advanced HCC patients with portal vein and/or inferior vena cava tumor thrombi with IMRT of a median total dose of 60 Gy with a fraction size of 2.5-4.0 Gy. Several authors reported that delivering a high dose IMRT was feasible in patients with small to large HCCs without a high incidence of RILD. Wang *et al*[30] delivered 45, 60, or 66 Gy in 1.8 or 2.0 Gy per fraction depending on tumor stage, target location, and the sizes of small to large HCCs ineligible for surgery or ablative treatments. The mean normal liver dose was 19.4 ± 6.3 Gy, and nonconventional RILD was observed in 13% of patients. Kang *et al*[31] delivered a median dose of 50.4 Gy to advanced HCCs with an equivalent sphere size of 11.4 ± 2.6 cm. There was no grade ⩾ 3 RILD in patients treated with IMRT without combination with TACE or intra-arterial chemotherapy. McIntosh *et al*[4] conducted an accelerated IMRT with concurrent capecitabine in 20 patients with unresectable HCC with a mean tumor size of 9 cm (range, 1.3-17.4 cm). The prescribed dose was 50 Gy in 20 fractions and there were no grade > 2 acute or late toxicities. Kim *et al*[32] reported that an accelerated RT with simultaneous integrated boost-IMRT was feasible and safe for patients with inoperable HCC. The tumor and the surrounding area with subclinical disease received 66 Gy and 55 Gy in 22 fractions, respectively. When the tumor was located within < 1 cm of the gastrointestinal structures, 55 Gy and 44 Gy in 22 fractions to the tumor and the surrounding area with subclinical disease, respectively, was delivered.

The results discussed thus far indicated that IMRT has the potential of dose escalation for HCC without an increased risk of RILD, which signals the potential for improved survival and quality of life in patients with HCC. However, because there is no standard technique for IMRT delivery and because the IMRT plan is not always better than the 3D-CRT plan, it is important to individualize the treatment plan for every patient.

SABR

SABR is generally defined as a treatment method for delivering a high dose of radiation to the target in a few fractions (typically 1-5 fractions) with a high degree of precision. SABR with a common linear accelerator usually utilizes multiple coplanar or noncoplanar static beams or multiple arc beams (Figure 2). The CyberKnife system (Accuray, Inc., Sunnyvale, CA, United States) and the VERO system (BrainlLab AG, Feldkirchen, Germany) are specialized machines for SABR, and HT is also used for SABR. To irradiate the tumor more accurately and to increase the sparing of the normal organs, SABR is performed in combination with at least one kind of IGRT technique integrated into the treatment machine; the different IGRT techniques are described in the subsequent section. During the last decade, the use of SABR for HCC has increased substantially and the practice guidelines from the National Cancer Center and Korean Liver Cancer Study Group recommend SABR as an alternative to the ablation/embolization techniques, or when these therapies have failed or are contraindicated[11,33].

Since the reporting of the first clinical experience with SABR by Blomgren *et al*[34] in 1995, many prospective and retrospective studies have been conducted (Table 1). Generally, SABR was used for the treatment of a few, small HCCs (< 5-6 cm) in patients with Child-Pugh class A or B disease. Local control rates at 2-3 years were 84%-100%, excluding two studies in which a relatively low dose was used[35] or large tumors were treated[36]. However, the overall survival and the incidence of severe hepatic toxicities varied due to the heterogeneity of patient and tumor characteristics such as liver function, tumor location, and tumor size. The most recent study by Wahl *et al*[37] showed comparable results between SABR (249 tumors in 161 patients) and RFA (83 tumors in 63 patients) in 224 patients with inoperable, nonmetastatic HCC. The rates of freedom from local progression at 1 and 2 years were 83.6% and 80.2% for RFA *vs* 97.4% and 83.8% for SABR. Notably, increase in tumor size was a predictor of local progression in patients who underwent RFA, but not in patients who underwent SABR.

Although there have been no prospective trials comparing SABR to other ablative modalities, recent

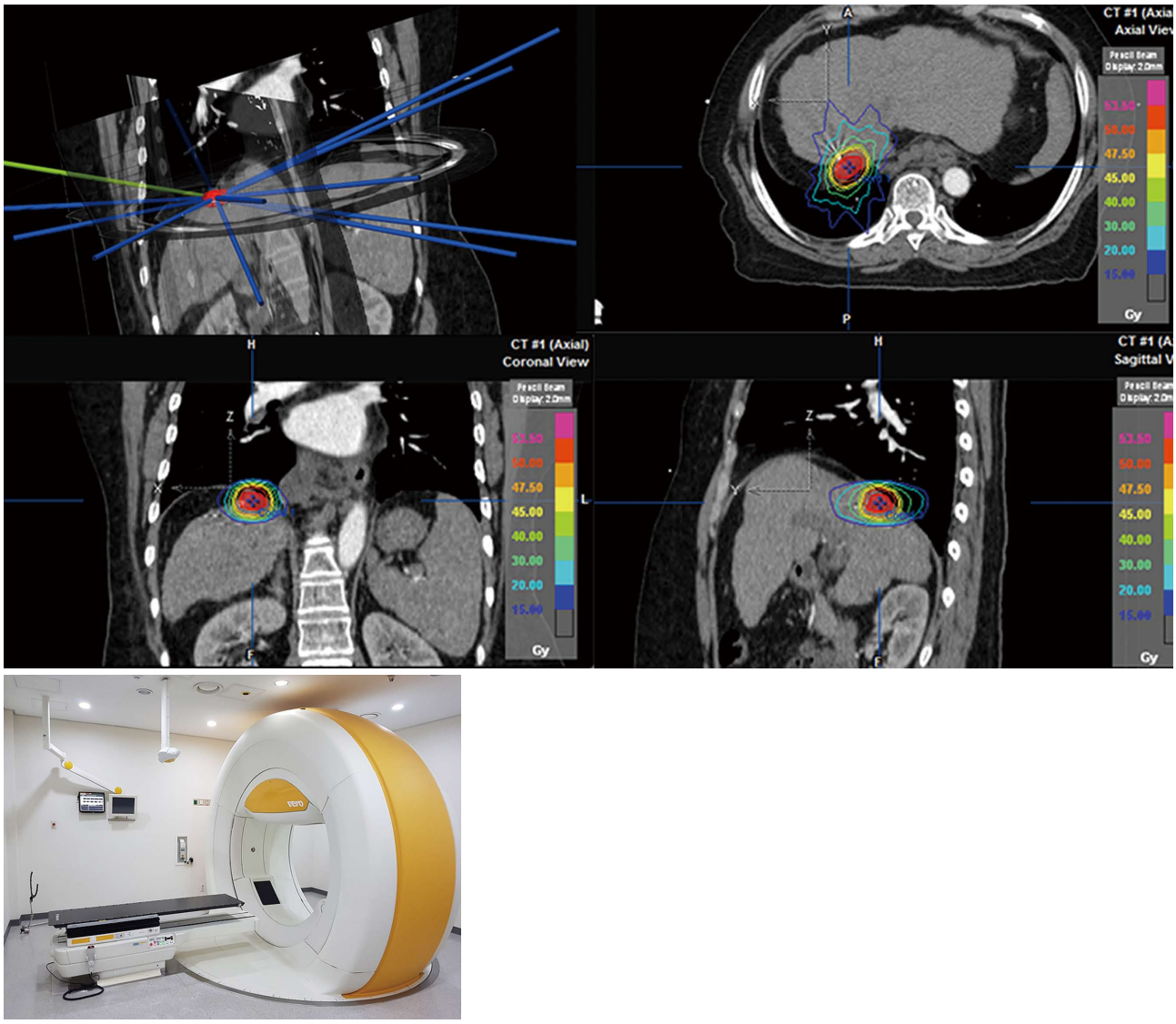

Figure 2 The stereotactic ablative body radiotherapy plan using the VERO system.

Table 1 The summary of the trials conducted using stereotactic ablative body radiotherapy for hepatocellular carcinoma

Study	Year	*n*	Dose/fraction (Gy/Fr)	Local control	Overall survival	Severe hepatic toxicity
Cárdenes *et al*[65]	2010	17	36–48 Gy/3 or 5 Fr	2-yr, 100%	2-yr, 60%	27% in CPC-B
Kwon *et al*[35]	2010	42	30–39 Gy/3 Fr	3-yr, 68%	3-yr, 59%	Gr ⩾ 3, 2%
Andolino *et al*[5]	2011	60	40–48 Gy/3 or 5 Fr	2-yr, 90%	2-yr, 67%	Gr ⩾ 3, 0%
Bujold *et al*[36]	2013	102	24–54 Gy/6 Fr	2-yr, 74%	2-yr, 34%	Gr ⩾ 3, 17%
Kang *et al*[66]	2012	47	42–60 Gy/3 Fr	2-yr, 95%	2-yr, 69%	Gr ⩾ 3, 19%
Yoon *et al*[67]	2013	93	30–60 Gy/3-4 Fr	3-yr, 92%	3-yr, 54%	Gr ⩾ 3, 7%
Sanuki *et al*[68]	2014	185	35–40 Gy/5 Fr	3-yr, 91%	3-yr, 70%	Gr 5, 7% in CPC-B
Kimura *et al*[69]	2015	65	48 Gy/4 Fr	2-yr, 100%	2-yr, 76%	Gr ⩾ 3, 23%
Wahl *et al*[37]	2016	63	27–60 Gy/3 or 5 Fr	2-yr, 84%	2-yr, 46%	Gr ⩾ 3, 2%

CPC-B: Child-Pugh class B; Gr: Grade.

data supports the use of SABR as an alternative ablative treatment option for the treatment of inoperable HCC. However, because SABR cannot be repeated unlike the other treatment modalities and because RILD occurs more frequently in patients with poor liver function, the decision on the best ablative modality should be made using a multidisciplinary approach.

CHARGED PARTICLE THERAPY

Charged particle therapy such as proton and carbon ion therapy offers distinct physical properties. The

Table 2 The summary of trials conducted using charged particle therapy for hepatocellular carcinoma

Study	Year	Particle	*n*	Dose/fraction (Gy/fr)	Local control	Overall survival	Grade ⩾ 3 Liver toxicity
Nakayama *et al*[38], retrospective	2009	Proton	318	55–79.2 CGE/10–22 Fr	NA	5-yr, 45%	None
Komatsu *et al*[40], retrospective	2011	Proton	242	52.8–84 CGE/4–38 Fr	5-yr, 90%	5-yr, 38%	1%
		Carbon	101	52.8–76 CGE/4–20 Fr	5-yr, 93%	5-yr, 36%	3%
Hata *et al*[39], retrospective	2006	Proton	19	50–84 Gy/10–24 Fr	1 failure	2-yr, 42%	None
Bush *et al*[70], phase 2	2011	Proton	76	63 Gy/15 Fr	NA	3-yr, 60%[1]	None
Hong *et al*[42], phase 2	2016	Proton	44	58.05–67.5 CGE/15 Fr	2-yr, 95%	2-yr, 63%	2%
Bush *et al*[43], randomized	2016	Proton	33	70.2 Gy/15 Fr	2-yr, 88%	2-yr, 48%[1]	None

[1]Progression-free survival. CGE: Cobalt gray equivalent; NA: Not available.

absorbed dose rapidly increases and suddenly rises to a peak before the proton is ultimately stopped, called the "Bragg peak effect". This facilitates increased sparing of normal tissues surrounding the tumor compared to conventional photon beam therapy, and thus, dose escalation for HCC can be achieved.

Some retrospective[38-40] and prospective[41-43] studies have reported encouraging outcomes with proton or carbon beam therapy in patients with HCC (Table 2). Local control rates were 88%-98% at 2-5 years with a very low incidence of severe toxicity. Hata *et al*[39] reported that patients with Child-Pugh C cirrhosis also showed no therapy-related toxicity of grade ⩾ 3. Bush *et al*[41] reported that 6 patients showed pathologic complete response and 7 patients showed microscopic residual disease in 18 patients who underwent liver transplantation after proton beam therapy. Recently, the interim analysis of a randomized trial comparing proton beam therapy to TACE for HCC was reported[43]. At the time of analysis, 36 patients in the TACE group and 33 patients in the proton group were available for analysis. Pathologic complete response was achieved in 10% of the 10 patients from the TACE group and 25% of the 12 patients from the proton group, who underwent liver transplantation after treatment. There was a trend toward improved 2-year local control (88% *vs* 45%, $P = 0.06$) and progression-free survival (48% *vs* 31%, $P = 0.06$) favoring proton beam therapy.

Charged particle therapy generally showed better local control and survival rates than the photon-based RT series, although a direct comparison is impossible due to the differences in patient characteristics. Moreover, a recent interim analysis of a randomized trial comparing TACE and proton beam therapy favored the proton beam therapy. Although the facilities for charged particle therapy have been limited thus far, it is anticipated that the use of charged particle therapy will increase in the near future.

IGRT

IGRT is defined as RT that employs imaging to maximize accuracy and precision throughout the whole process, which includes target and normal tissue delineation, radiation delivery, and adaptation of therapy to anatomic and biological changes over time in individual patients[44]. Of these, accurate target delineation, target relocalization to allow proper patient repositioning, and respiratory motion management have been the most challenging in patients with HCC.

Target delineation

The initial step of IGRT is precise tumor delineation. The specific enhancement pattern of HCC (enhancement in arterial phase and washout in portal venous or late delayed phase) can help radiation oncologists delineate gross tumor volume. A radiologic-pathologic correlation study showed that microscopic invasion from HCC was observed up to 4 mm from the gross tumor, and the distance was correlated with the alpha-feto protein level, tumor size, PVT, and TNM stage[45]. This study suggested that a margin of < 5 mm from the gross tumor volume is required for the clinical target volume. The planning target volume (PTV) is defined as the volume that is used for the RT planning to ensure the tumor dose in the presence of breathing motion and set-up uncertainties. The PTV margin from the clinical target volume ranges 5-10 mm or more, depending on the methods of simulation and in-room IGRT.

For the tumor delineation of HCC, 4D-CT images, which are synchronized with the patient's respiratory cycle, are usually acquired to capture the whole trajectory of the moving tumor. Brock[46] recommended the acquisition of contrast breath-hold CT scans followed by 4D-CT in the HCC patients to capture both the early enhancement and washout phases. However, 4D-CT cannot acquire the same quality achieved with the diagnostic scans[47] and have many artifacts preventing accurate tumor delineation[48]. Therefore, diagnostic CT or magnetic resonance imaging (MRI), which shows the extent of HCC better, should be used for tumor delineation. Rigid or deformable registration between the diagnostic and RT planning images can be used. Based on our experience of rigid registration, it is important to match the fiducial markers (*e.g.*, lipiodol) or anatomical landmarks (*e.g.*, liver contour and vessels) near the tumor, instead of the whole liver. Although a difference in target size by a few millimeters was observed after the deformable registration between MRI and CT images[49], deformable registration

between diagnostic MRI and RT planning images could be helpful for target delineation; however, it is still at the investigational phase.

Every effort should be taken to delineate the target precisely using the currently available imaging modalities, and further research is required for the combination of these modalities in order to make the whole trajectory of the tumor more clearly visible on the RT planning system.

Target relocalization and tumor surrogates

Before the radiation beam is turned on, bony landmarks are usually used to position the tumor to its original location at the time of simulation. However, as HCC moves during the respiratory cycle and is often invisible on in-room images, surrogates for the tumor are required for the application of IGRT. High-density materials (*e.g.*, inserted fiducial markers, packed lipiodol, surgical clips), the diaphragm, large vessels, and the entire liver can be used as surrogates. With the help of these surrogates, PTV margins can be reduced and normal tissue doses can be further spared.

Various techniques involving 2D or 3D volumetric image guidance are now available to verify and reposition the location of surrogates[46]. Kilovoltage (kV) or megavoltage (MV) radiography can help visualize the location of diaphragm or fiducial markers, which is subsequently compared to their location on the planning CT image at the specific phase of respiration (*e.g.*, breath-hold or gated). The kV fluoroscopic imaging can show the tumor motion during respiration or breath-hold. Using volumetric imaging by a CT scanner in the treatment room, soft tissues, including the liver, adjacent structures, or fiducial markers, can be used for image guidance. Because the long acquisition time for CT images can lead to image blurring, breath-hold or respiration sorting techniques can be used as well. The specific technique for the target relocalization can be chosen according to the RT delivery technique (free-breathing, breath-hold, gated, or tracking). Recently, non-invasive MRI has been used for IGRT[50,51].

Gold fiducial markers are preferred over other surrogates because they provide better visibility on a standard MV imaging device as well as on kV X-ray images. They can be used for real-time tumor tracking (for gated or tracking treatment) as well as for confirming PTV margins in 2D or 3D images. Interestingly, Wahl *et al*[37] reported that the local failure rate was higher in SABR-treated patients without fiducial markers compared to those with fiducial markers (10% *vs* 0%, respectively, $P = 0.15$), which highlights the importance of using an accurate IGRT technique.

The management of respiratory motion

Another issue in RT for HCC is the control of the respiratory motion, because the liver moves in a significant range during respiration[52]. The ways to treat a moving tumor can be classified into motion-encompassing, forced shallow breathing with abdominal compression, respiratory gating, and real-time tumor tracking[53]. The motion-encompassing method refers to the covering of all possible positions of the moving tumor through the whole breathing cycle and subsequently a large volume of normal tissue may be irradiated. Although breath-hold and forced shallow breathing can reduce the respiratory motion for liver tumors, this might result in significant patient discomfort or inconvenience during treatment. Presently, respiratory gating and real-time tumor tracking are the most advanced techniques. Figure 3 shows the dose distribution for the three techniques of motion management.

The respiratory gating method involves turning on the radiation beam when the tumor is at a given location, which leads to a smaller PTV volume. The current commercially available Real-time Position Management system (Varian Medical system, Palo Alto, CA) detects the respiratory signal *via* the movement of the surrogate on the abdominal surface, which can be correlated with the respiratory movement of the tumor inside the body. The position and width of the gate within a patient's respiratory cycle are determined by monitoring the tumor's respiratory motion that was captured on 4D-CT images. This gating method using an external breathing signal is easy, noninvasive, and radiation-free; however, a potential error might be that the signal does not accurately correlate with the internal target position[54-56]. For this reason, the Hokkaido group developed the real-time tumor tracking radiation therapy system that combines both the external breathing signals and the internal tumor motion signals *via* implanted fiducial markers[57]. Kubo *et al*[58] reported the feasibility of gated IMRT as well. A disadvantage of the gating techniques is the reduced efficiency of radiation delivery, resulting in a prolonged treatment time (or reduced duty cycle). For SABR, where a larger dose is delivered at each treatment, this prolonged treatment time could decrease the patient compliance.

An alternative strategy is to reposition the radiation beam while tracking the tumor's changing position dynamically. Ideally, this method can eliminate the need to compensate for the movement of the tumor and achieve a 100% duty cycle for dose delivery. Iizuka *et al*[59] showed that the tracking technique could reduce the PTV volume by 35% in 11 liver cases, compared to the motion-encompassing method. Currently, there have been two treatment machines capable of tumor tracking: the CyberKnife system and the VERO system. The clinical feasibility of the CyberKnife system has been shown in several studies[60-63]. The CyberKnife system consists of a pair of fluoroscopes in the ceiling coupled to a small X-band linear accelerator mounted on a robotic arm, which can move according to the movement of the inserted fiducial markers. The VERO

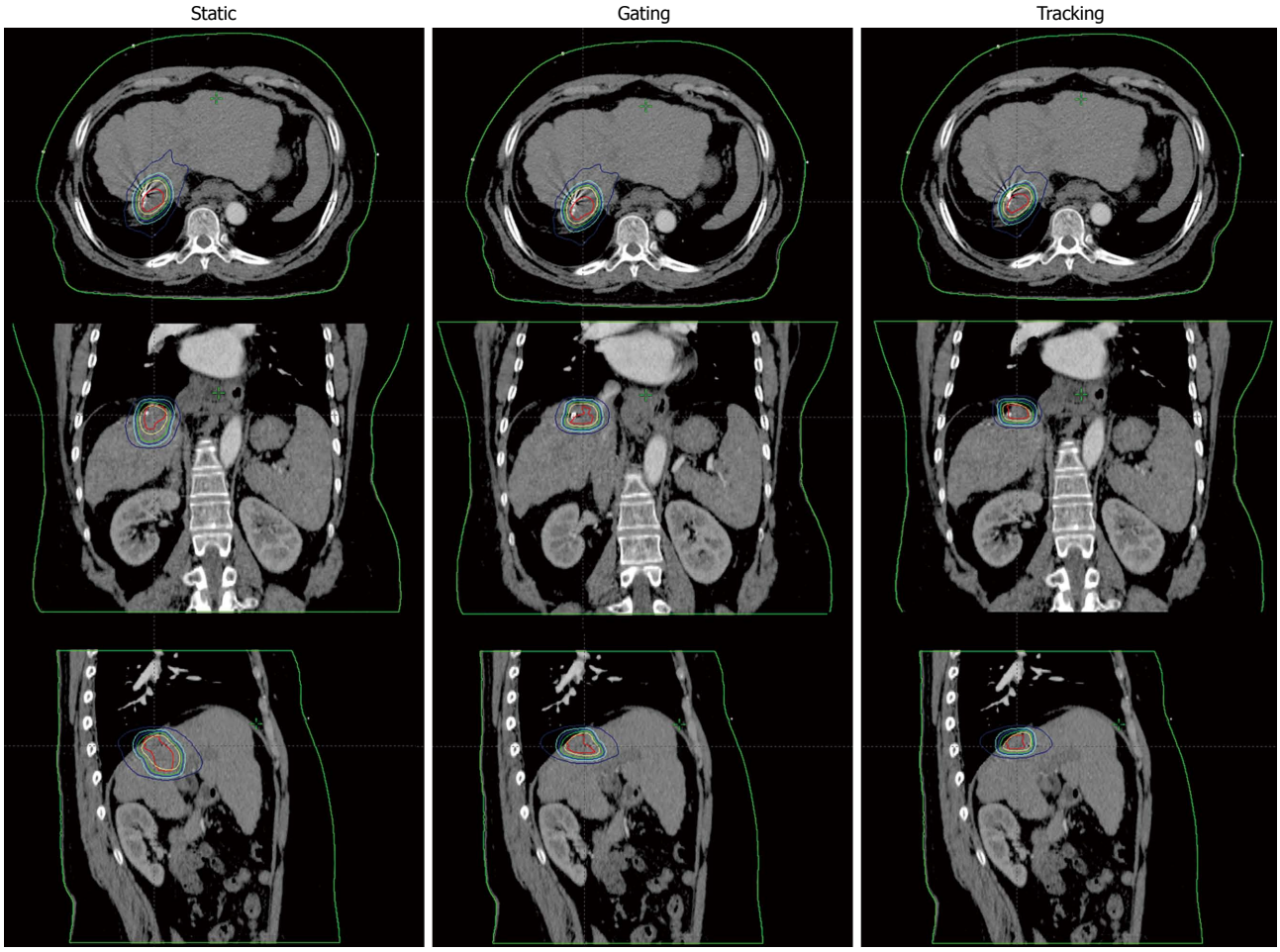

Figure 3 The comparison of dose distributions in 3 stereotactic ablative body radiotherapy plans for a representative case. The static plan using the motion encompassing technique is shown in the left column. The gating and tracking plans are shown in the middle and right column, respectively.

system uses a pair of fluoroscopes mounted in the machine to monitor the movement of inserted fiducial markers and allows the treatment head, gimbal, to pivot in two dimensions according to the movement of the fiducial markers[64].

CONCLUSION

Recent advances in the RT techniques facilitate dose escalation for small to large tumors with the hope of improved local tumor control without increasing normal tissue toxicity. However, local failure is still problematic, especially in advanced HCCs, and intrahepatic or distant metastases often develop, which could offset the impact of increased local control and render the given treatments meaningless. Unfortunately, reliable methods that can predict the tumor response to RT or recurrences within or outside the RT field have not been developed. Therefore, future research should focus on the prediction of the outcomes after treatment to determine the patients who will benefit from RT as well as the novel biologic agents that can prevent recurrences outside the RT field.

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