CT evaluations of focal liver reactions following stereotactic body radiotherapy for small hepatocellular carcinoma with cirrhosis: relationship between imaging appearance and baseline liver function

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ABSTRACT. This study aimed to assess the imaging appearances of focal liver reactions following stereotactic body radiotherapy (SBRT) for small hepatocellular carcinoma (HCC) and to examine relationships between imaging appearance and baseline liver function. We retrospectively studied 50 lesions in 47 patients treated with SBRT (30–40 Gy in 5 fractions) for HCC, who were followed up for more than 6 months. After SBRT, all patients underwent regular follow-ups with blood tests and dynamic CT scans. At a median follow-up of 18.1 months (range 6.2–43.7 months), all lesions but one were controlled. 3 density patterns describing focal normal liver reactions around HCC tumours were identified in pre-contrast, arterial and portal-venous phase scans: iso/iso/iso in 4 patients (Type A), low/iso/iso in 8 patients (Type B) and low/iso (or high)/high in 38 patients (Type C). Imaging changes in the normal liver surrounding the treated HCC began at a median of 3 months after SBRT, peaked at a median of 6 months and disappeared 9 months later. Liver function, as assessed by the Child–Pugh classification, was the only factor that differed significantly between reactions to treatment showing “non-enhanced” (Type A and B) and “enhanced” (Type C) appearances in CT. Hence, liver tissue with preserved function is more likely to be well enhanced in the delayed phase of a dynamic contrast-enhanced CT scan. The CT appearances of normal liver seen in reaction to the treatment of an HCC by SBRT were therefore related to background liver function and should not be misread as recurrence of HCC.

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The incidence of hepatocellular carcinoma (HCC) has been rising recently because of an increased incidence of hepatitis viral infections [1]. Because of the underlying cirrhosis and the presence of multiple simultaneous lesions, curative treatments, such as surgery or percutaneous ablation, are not feasible for some patients, who can benefit only from options such as transarterial chemoembolisation (TACE) [2]. Historically, conventional radiotherapy has not been considered to be a definitive treatment for liver tumours because of the low radiation tolerance of the liver [3], but recent developments in three-dimensional (3D) treatment planning for conformal radiotherapy permit both high-dose delivery to the tumours with normal liver sparing and a quantitative description of the dose delivered to the normal liver [4]. Nevertheless, significant toxicities, such as radiation-induced liver disease (RILD), are often observed, especially when large target volumes are irradiated [4–7].

By contrast, hypofractionated stereotactic body radiotherapy (SBRT) enables the accurate delivery of much higher doses of radiation to a confined target [5, 8, 9]. Clinically apparent toxicity occurs only rarely with SBRT, but the normal liver tissue surrounding a tumour presents unique pathophysiological reactions to SBRT and its imaging appearance may be mistakenly interpreted as tumour recurrence [10].

In our institution, solitary HCC, for which treatment modalities such as resection or other ablation therapies are not indicated, was treated with hypofractionated SBRT after TACE [11]. After several months of follow-up by three-phase enhancement CT scans, we often found a focal liver reaction in an area around the tumour consistent with findings published by others [10, 12–14].

Dynamic CT has been an important modality for the detection and post-treatment evaluation of HCC [2, 15]. Some reports have described radiographic findings of radiation-induced hepatic injury resulting from treatments involving conventional doses and fractionation [14, 16, 17], and a few reports have described radiographic findings after SBRT for patients with liver metastasis who

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have normal liver function [10, 12, 13, 16, 18]. There are few detailed reports, however, especially relating to patients with HCC who have liver cirrhosis.

Our experience with SBRT for liver tumours suggests that this treatment is associated with distinctive features on follow-up scans, especially on dynamic-enhanced CT scans, and that baseline liver function may influence the image appearance. To our knowledge, our series is the largest ever reported for liver SBRT for patients with limited liver function. The purpose of our study was to describe the long-term imaging appearance of hepatic injuries following hypofractionated SBRT for the treatment of HCC with cirrhosis. We looked at the reactions of normal liver after SBRT, sorting the imaging findings by changes that occurred between the phases of the CT scans. We also focused on background liver function, which is often diminished in patients with HCC.

Methods and materials

Patient eligibility

Patients treated with SBRT at our institution all had solitary HCC that was inoperable or for which surgery would be difficult, and for which percutaneous ablative therapies were not feasible. They also met the following criteria: liver function with Child–Pugh score of A or B; a tumour ≤ 4 cm in diameter; target located at a distance so that the dose to the bowels did not exceed 25 Gy in five fractions; curative intent; and informed consent. Among these patients, those who were followed up for more than 6 months after the treatment with regular dynamic CT scans were eligible for the current imaging study. Pre-treatment evaluation included dynamic three-phase CT scans, ultrasonography and angiography. The diagnosis of HCC was confirmed by the characteristic findings of these images [2].

Treatment

Prior to SBRT, TACE was planned for all patients to obtain a synergistic local treatment effect, as well as to visualise the position of the target with non-contrast-enhanced CT scanning by the deposition of lipiodol. When lipiodol in the surrounding tissue obscured the tumour, SBRT was postponed until the lipiodol had been washed out. When CT showed only a slight accumulation of lipiodol in the tumour, SBRT was initiated within a few days of TACE. SBRT was performed with dynamic conformal multiple arc irradiation [19]. Details of the treatment procedures have been reported previously [11]. In brief, planning CT images that were used to determine the internal target volume (ITV) were obtained using a long scan time technique [20] with a CT simulator (CT port, Toshiba Medical Systems, Tokyo, Japan). When calculating planning target volume (PTV), individualised treatment margins of 5–8 mm were applied around the ITV. A stereotactic, multi-arc dynamic conformal radiation procedure, designed by a radiation treatment planning system (FOCUS XiO version 4.2.0–4.3.3, Computerized Medical Systems, St Louis, MO), was performed using X-ray beams from a

6 MV linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA). The treatment plans, including the dose and fraction size, were approved by a radiation oncologist (AT). A total dose of 30–40 Gy was delivered in 5 fractions over 5–9 days. The dose depended on the patient's liver function and the dose to the normal liver: 40 Gy for Child–Pugh score A, 35 Gy for Child–Pugh score B, with a further reduction of 5 Gy if more than 20% of the normal liver volume would otherwise receive a dose of 20 Gy.

Treatment was planned to enclose the PTV by the 80% isodose-line with 80% of the maximum dose equated to the prescribed dose. Using this method, a prescribed dose of 40 Gy total at the PTV periphery to be administered in 5 fractions essentially corresponds to D95 (the minimal dose delivered to 95% of the target volume) [19]. Dose calculations used a superposition algorithm [21].

Patient follow-up

After treatment the patients were seen monthly. Laboratory tests were done to evaluate liver function and blood cell counts. Measurements of alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonists-II (PIVKA-II) were included in these tests. Treatment responses and local recurrences were evaluated with dynamic CT at 1 month and every 3 months after treatment.

Imaging evaluation

A CT examination was performed with a four-channel-detector row helical CT scanner (Light Speed, GE, Milwaukee, WI) with a reconstructed slice width of 5 mm and a slice interval of 5 mm. Scanning parameters were 120 kV, 440 mA, 2.5 mm section thickness, 6.0 helical pitch (1.5 beam pitch) and 0.5 s rotation speed. Dynamic CT scans were done over the range of the diaphragmatic dome to the inferior edge of the liver. Images were obtained before contrast enhancement, and at 25 s (early arterial phase), 40 s (late arterial phase) and 63 s (portal-venous phase) after injection of 100 ml of non-ionic contrast medium at a rate of 4 ml s⁻¹.

Complete response (CR) was defined as the disappearance of contrast enhancement in the tumour for the arterial phase. For tumours with dense lipiodol deposits, CR was also defined as persistent lipiodol deposition lasting for at least 3 months. A reduction in the volume of an enhanced area in the arterial phase or of a low-density area in the portal-venous phase that persisted for more than 6 months after the treatment was judged to be a partial response (PR). Tumours without any of these changes or with an increase in the volume of an enhanced area were designated as no change (NC) or progressive disease (PD), respectively.

A local recurrence was defined as the appearance of a new enhanced lesion within the site of the treated volume, defined as the 80% isodose line. Conversely, a new appearance of a tumour outside the treated volume was judged to be an intrahepatic recurrence. When no tumour enhancement was detected within the PTV on enhanced dynamic CT at ≥ 6 months after treatment, patients were considered to have had no relapse.

Focal liver reactions in the normal liver around the tumour were also evaluated by visual comparisons of consecutive CT scans. HU was measured in each representative CT scan to evaluate the liver tissue density in the irradiated and non-irradiated liver. A difference of at least 10 HU between a non-contrast enhanced and an enhanced CT was defined as a significant difference in tissue density.

The reactions of normal liver tissue to SBRT as assessed by radiological findings were characterised and sorted by changes over the course of the scans. Factors that influenced the imaging appearance were also analysed.

Statistical analysis

χ^2 tests were performed using SPSS 17 software (SPSS, Chicago, IL) to compare the characteristics of lesions showing "enhanced" and "non-enhanced" CT appearances (see Results) after SBRT. A *p*-value <0.05 was considered statistically significant. Characteristics that were analysed in this way included Child-Pugh score, sex, tumour size (<2 cm *vs* ≥2 cm), cause of cirrhosis (viral *vs* non-viral), dose and location (central *vs* peripheral).

Results

Eligible patients

Between March 2005 and July 2008, 57 patients received SBRT for the treatment of solitary HCCs. Among these, 50 tumours in 47 patients were eligible for this study. The baseline characteristics of the eligible patients are listed in Table 1. There were 34 men and 16 women with a median age of 71 years (range 45–86 years). All patients had underlying liver cirrhosis with either good or moderately impaired liver function: 41 patients were Child-Pugh A and 9 were B. Among these, one patient who received SBRT twice was initially classified as Child-Pugh A, then as Child-Pugh B for the second SBRT. Cirrhosis was related to either hepatitis B virus infection (*n*=2), hepatitis C virus infection (*n*=35), alcoholic hepatitis (*n*=8), non-alcoholic steatohepatitis (*n*=1) or cryptogenic origin (*n*=4).

Table 1. Patient characteristics

Characteristics	<i>n</i>
Lesions (patients)	50 (47)
Sex, male/female	34/16
Median age (range)	71 (45–86) years
Tumour size, median (range)	2.0 (0.9–3.6) cm
Child-Pugh score, A/B	41/9
Type of chronic hepatitis	
HBV infection	2
HCV infection	35
Alcoholic	8
Cryptogenic	4
NASH	1

HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis.

The median tumour size was 2.0 cm (range 0.9–3.6 cm) and the median ITV size was 2.7 cm (range 1.2–4.2 cm). The prescribed doses were 30 Gy for 2 lesions, 35 Gy for 21 lesions and 40 Gy for 27 lesions, administered in all cases in 5 fractions.

Treatment outcomes and objective responses

At the median follow-up time of 18.1 months (range 6.2–43.7 months), all lesions but one were controlled; a relapse adjacent to the treated volume developed in one patient, who had already had multiple intrahepatic recurrences, 9.4 months after the treatment. Intrahepatic recurrences outside the treated volumes developed in 22 patients during follow-up. Distant metastases were observed in five patients (three had distant failure only, two had distant failures after intrahepatic metastases). Eight patients (17%) died during the follow-up period as a result of either progression of intrahepatic recurrence (*n*=2), liver failure with hepatic decompensation (*n*=5) or a non-hepatic-related cause (*n*=1, ileus).

Changes in the size of the tumour began at a median of 6 months (range 1–10 months) after irradiation. 36 lesions (72%) had CR with complete disappearance of an enhanced tumour. Because SBRT was performed shortly after TACE for 44 lesions, 5 of these lesions (10%) showed no tumour enhancement on the pre-treatment dynamic CT because dense lipiodol accumulation surpassed tumour enhancement. None of these five lesions showed changes in appearance that corresponded to CR. 7 lesions (14%) were judged as PR. The remaining 2 (4%) were NC. SBRT caused no clinically apparent toxicities such as RILD.

Reactions of normal liver to radiation

Three density patterns describing focal normal liver reactions around the HCC tumours were identified in pre-contrast, arterial and portal-venous phase scans: iso/iso/iso in 4 patients (Type A), low/iso/iso in 8 patients (Type B) and low/iso (or high)/high in 38 patients (Type C) (Table 2; Figure 1). The numbers of lesions associated with focal normal liver reactions of Types A, B and C were 4, 8 and 38, respectively.

For Type C reactions, the liver appearances were differentiated most clearly in the portal vein phase on contrast-enhanced CT, but were sometimes observed also in the arterial phase. The median time for detection of a demarcated radiation reaction in surrounding normal liver was 3 months (range 1–6 months) after SBRT. Reactions increased and peaked at a median of 6 months (range 3–12 months) after SBRT. 20 (53%) of the reactions disappeared at a median of 9 months (range 3–21 months), but reactions persisted in the areas surrounding 10 lesions (26%) even after 12 months (maximum 30 months). The remaining 8 lesions (21%) were also associated with persistent reactions at their maximum follow-up at a median of 9 months (maximum 12 months). A typical time-course for Type C reactions of normal liver after SBRT is shown in Figure 2.

For Type B reactions, the median time after which a low-attenuation area was detected was 3 months (range 1–3 months) after SBRT, with a peak at a median of 6

Table 2. Density change in the high-dose area around the tumour

Type of reaction	n	Phase		
		Pre-contrast	Arterial	Portal-venous
Type A	4	Iso	Iso	Iso
Type B	8	Low	Iso	Iso
Type C	38	Low	Iso or high	High

months (range 3–8 months). Because of the short follow-up time for Type B reactions, however, the absolute durations of the changes were not assessed. As for Type A responses, 2 out of 4 lesions that were associated with a Type B response also had a short follow-up time (6 months), although the low-attenuation change remained for more than 12 months in the area surrounding the remaining 2 lesions.

Factors associated with the types of reactions

After Type A and B reactions were combined as a “non-enhanced group”, their characteristics were compared with those of Type C reactions (“enhanced group”) to identify possible factors that might influence their appearances on CT. These included Child–Pugh score, sex, tumour size (<2 cm *vs* ≥2 cm), cause of cirrhosis (viral *vs* non-viral), dose and location (central *vs* peripheral). χ^2 tests determined significant differences between the two image groups (enhanced and non-enhanced) in Child–Pugh score ($p<0.001$) and irradiated dose ($p=0.006$) (Table 3). However, the irradiated dose was partially dependent on Child–Pugh classification because the prescribed dose was decided upon according to liver function and the dose received by normal liver. Therefore, liver function as classified by Child–Pugh scores was considered to be the only significant factor identified as being related to patterns of image changes after SBRT.

Discussion

Recently, SBRT for extra-cranial targets has emerged as a promising new field for radiotherapy. Compared with 3D conformal radiotherapy (CRT), which delivers a high dose by conventional fractionation, SBRT is advantageous because it allows the delivery of higher doses to a confined area of the liver [22, 23]. However, most reports on SBRT concerned patients with metastatic liver tumours who had normal baseline liver functions. By contrast, most patients with HCC have liver cirrhosis and have a tolerance to radiation different to those with metastatic liver tumours and normal baseline liver function [24]. To our knowledge, our series is the largest yet reported for liver SBRT and with cirrhosis.

Imaging changes after high-dose focal irradiation

The earliest imaging studies to evaluate the liver by CT after radiation therapy were performed by Jeffrey et al

[25] and showed low-attenuation parenchymal changes with straight margins corresponding to the radiation portal. In terms of high-dose irradiation to the liver, a typical appearance is a low-attenuation area identical to the irradiated volume on the non-contrast phase scan and highly enhanced areas on delayed scans [12, 14, 16]. MRI shows that the low-density area on CT has high signal on the T_2 weighted image, indicating necrotic liver parenchyma or oedema [26, 27].

Reports on CT appearance after radiation therapy have been limited to patients with normal liver function, as most of the studies included patients with metastatic liver tumours with no hepatitis virus infections. In addition, the CT evaluation methods used to detect liver metastasis are different from those used for HCC. For the diagnosis of HCC, a dynamic three-phase CT is recommended [2], whereas a delayed enhancement is often performed for metastatic liver tumours.

In the current study, we classified the CT findings of focal normal liver reactions around HCC tumours after SBRT for patients with liver cirrhosis. Table 4 compares our study with three other reports that showed three CT patterns after liver irradiation. Herfarth et al [10], who also assessed 31 patients with focal liver reactions after single fraction SBRT, classified the CT appearances into three patterns. The series by Herfarth et al [10] is almost comparable to ours as SBRT was performed in both; there were however differences in fractionation (Herfarth et al used a single fraction *vs* five fractions), in CT evaluation methods, in the use of delayed enhancement rather than dynamic enhancement scans and in assessing mostly metastatic liver tumours with preserved liver function (only one patient had an HCC in Herfarth et al's series) rather than HCC with liver cirrhosis. Chiou et al [12] described 3 different types of reaction in terms of liver density on dynamic enhancement CT scans for 18 patients with HCC who were treated with high-dose conventional radiation therapy. Types 1 and 2 from the reports by Herfarth et al [10] and Chiou et al [12] and Types 1 and 2 from the report by Wada et al [13] correspond to our Types A and B, while type 3 reactions from both reports appear to be applicable to our Type C.

Influence of liver function and blood flow on image appearance

In our study, various factors were compared statistically between the “non-enhanced group” (Types A and B) and the “enhanced group” (Type C). The Child–Pugh classification was the only significant factor that differed between these two groups. Hence, liver tissue with preserved function is more likely to be well enhanced in the delayed phase of a dynamic contrast-enhanced CT scan.

As far as we know, our report is the first to assess factors that are associated with image appearance after liver irradiation. Gender was an insignificant factor ($p=0.70$) in our study, although Ahmadi et al [16], who investigated imaging appearances of hepatic injury following proton beam irradiation in 46 patients, claimed that the early appearance of radiation-induced hepatic injury was gender dependent, with a tendency to occur with higher irradiated doses.

Figure 1. Three types of CT appearances seen 6 months after stereotactic body radiotherapy treatment. The four CT images in each row, from left to right, show the dose distribution (the red line corresponds to the 80% isodose level, which encompasses the planning target volume) and the pre-contrast, arterial and portal-venous phases. (a) Type A shows a density pattern of iso/iso in the pre-contrast/arterial and portal-venous phases, respectively; (b) Type B shows a density pattern of low/iso/iso; and (c) Type C shows a density pattern of low/iso (or high)/high.

The underlying mechanism of radiation-induced liver change and the associated findings on imaging have not yet been fully investigated, but severe congestion of the sinusoids in the central portion of the lobules and decreasing flow towards the portal areas, referred to as a form of "veno-occlusive disease (VOD)", is suggested as a possible mechanism of pathology. Willemart et al [17] evaluated changes in normal liver after focal abdominal irradiation for epidural spread of non-Hodgkin's lymphoma using a triphasic CT scan and by hepatic biopsy, which showed changes typical of VOD. Unger et al [26] performed CT angiography and demonstrated increased attenuation owing either to increased accumulation of or

to retention of contrast medium within the region of radiation-induced hepatic injury. They concluded that this phenomenon reflected vascular congestion and relative stasis with slow clearance of contrast material from the irradiated area [26].

As regards changes in the liver after SBRT for metastatic liver tumours, Olsen et al [18] reported microscopic tumour parenchymal effects of liver SBRT after examining liver samples from two cases obtained by surgery (one 2 months and the second 8 months after treatment). In these samples, the central area of the treated volume was replaced by necrotic tissue, which was surrounded by fibrosis, and the circumference of this central area had

Figure 2. Type C treatment response in a 57-year-old male with hepatitis C virus infection and Child-Pugh score A cirrhosis receiving stereotactic body radiotherapy (SBRT) at a dose of 40 Gy in five fractions. (a) Dose distribution and pre-treatment dynamic CT. The tumour was well enhanced in the arterial phase. (b) 3 months after SBRT. The tumour size has begun to decrease and a slight enhancement has started to appear in the portal-venous phase. (c) 6 months after SBRT, the well-demarcated enhancement area around the tumour has peaked in both the arterial and portal-venous phases. (d) The reaction has decreased gradually but persists 12 months after treatment; it was not observed at 24 months. The four CT images in (a), from left to right, show the dose distribution (the red line corresponds to the 80% isodose level, which encompasses the planning target volume) and the pre-contrast, arterial and portal-venous phases. The three images in (b–d) show the pre-contrast, arterial and portal-venous phases.

Table 3. Factors affecting CT appearance

	Non-enhanced group	Enhanced group	p-value
	Type A + B	Type C	
Cirrhosis			
Child-Pugh score A	5	36	<0.001
Child-Pugh score B	7	2	
Sex			
Male	8	26	0.586
Female	4	12	
Cause of cirrhosis			
Viral infection	7	30	0.256
Others	5	8	
Tumour size			
<2 cm	6	9	0.503
≥2 cm	6	29	
Tumour location			
Central	7	22	0.624
Peripheral	5	16	
Dose			
40 Gy	2	25	0.006
35 Gy or less	10	13	

VOD with marked sinusoidal congestion. The authors concluded that these areas were radiographically Herfarth Type I and II reactions. They postulated that Type 1 hyperdensity reactions in the late contrast phase were probably explained by progressive fibrin deposition and occlusion of the central veins that caused stasis and pooling (leading to reduced contrast clearance). They also speculated that the Type 2 isodense portal-venous appearance and the hyperdensity in late contrast phase were caused by progressive fibrosis, which was associated with worsened pooling and stasis of contrast. This resulted in a greater decrease in venous drainage than that seen in Type 1. These findings suggest that a focal liver reaction may correspond to RILD. On the basis of these considerations, it is possible that there is a gradual

pattern to the enhancement: (1) delayed enhancement for patients with normal baseline liver function; (2) relatively early, arterial/portal-phase enhancement for patients with relatively compensated cirrhosis (Child-Pugh A); and (3) no enhancement for patients with Child-Pugh B. The first pattern (1) is applicable to the enhancement patterns described by Olsen et al [18] and by Herfarth et al [10]; patterns ((2) and (3)) correspond to our Type C and Type A and B, respectively.

In chronic liver disease, the portal fraction of liver perfusion decreases as a result of the increase in intrahepatic vascular resistance, which is partially compensated by an increase in arterial inflow [28–30]. In cirrhosis, however, the increase in arterial perfusion is often not sufficient to maintain total liver perfusion owing to high extrahepatic portosystemic shunting [28, 31]. Hashimoto et al [32] assessed the utility of CT perfusion for the quantitative evaluation of liver function and showed that the hepatic arterial fraction for patients without liver disease was significantly lower than for those with Child-Pugh scores B and C, although tissue blood flow tended to decrease with the severity of the chronic liver disease.

With regard to altered blood flow from the normal liver during progression from Child-Pugh score A to B, we speculate that radiation injury to the normal liver causes worsened pooling and decreased venous drainage due to fibrosis. For those with Child-Pugh score A, there is poorer venous drainage with earlier pooling; and for those with Child-Pugh score B, poor blood flow in both the portal vein and artery results in a decreased enhancement effect.

Time course after liver irradiation in patients with liver cirrhosis

RILD typically occurs 4–8 weeks after the completion of treatment, although it has been described as early as 2 weeks and as late as 7 months [3]. After 6 months, there is little congestion and cell plates are re-established, and the injury recovers within several months. However, the

Table 4. Reported types of CT appearance

Studies	Objectives (n)	Dose/fraction (fr)	Types	Phase			
	Enhancement timing	Radiation method		Pre-contrast	Arterial	Portal-venous	Late
Our study	HCC (n=50) 40/63 s	40 Gy/5 fr SBRT	Type A	Iso	Iso	Iso	–
			Type B	Low	Iso	Iso	–
			Type C	Low	Iso or high	High	–
Chiou et al	HCC (n=18) 30–35/80–100 s	41.4–65.6 Gy Conventional radiation therapy	Type 1	Low	Low	Low	–
			Type 2	Low	Iso	Iso	–
			Type 3	Low-iso	Iso or high	High	–
Herfarth et al	Metastatic tumour (n=35) HCC (n=1) 70 s/4 min	22 Gy/1 fr SBRT	Type 1	Low	–	Low	Iso
			Type 2	Low	–	Low	High
			Type 3	Low	–	High	High
Wada et al	HCC (n=6), others (n=9) 30 /120 s	45 Gy/3 fr 60 Gy/8 fr SBRT	Type 1	Iso	–	Low	Iso
			Type 2	Low	–	Low	High
			Type 3	Low	–	Iso or high	High

HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy.

imaging changes in our study began at a median of 3 months, peaked at a median of 6 months and had mostly disappeared after 9 months, although some of the changes in tissue enhancement persisted even after 12 months.

Herfarth et al [10] detected radiation reactions at a median of 1.8 months (range 1.2–4.6 months) after single-dose SBRT, slightly earlier than the changes seen in our series. They also pointed out that Type 1 and 2 reactions gradually shifted to Type 3. In our series, however, no difference was observed in the timing of appearance of each pattern. For Types A and B (non-enhancement group), however, the relatively long follow-up may result in a shift to Type C, as was observed with Herfarth's series. However, we again place special emphasis on the differences in background liver function: longer follow-ups do not appear to result in the pattern shift seen in Herfarth's series; instead the cirrhosis might have caused irreversible changes in hepatic structure.

Future directions

A number of results on liver irradiation have emerged recently. Owing to the relatively limited experience, however, insufficient knowledge is available regarding toxicity to the normal liver resulting from irradiation. Baseline liver function, as well as doses and volumes, is one possible factor that influences liver toxicity [24]. Understanding the underlying pathophysiological mechanism and elucidating the dosimetric parameters that are predictive of liver toxicity will help to preserve remaining liver function for patients with baseline liver dysfunction.

Conclusions

The imaging appearances of normal liver reactions after SBRT for HCC patients with cirrhosis were classified into three patterns. The imaging changes began at a median of 3 months, peaked at 6 months and in most patients disappeared at about 9 months after treatment. These appearances remained for more than 12 months in at least one-third of the patients. These patterns of focal liver reactions were significantly related to background liver function. This reaction following SBRT to the liver must be recognised, and it should not be misinterpreted as local recurrence of HCC. More detailed investigations will provide useful information for preservation of liver function after SBRT.

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