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Stereotactic Body Radiotherapy Based on ^{99m}Tc-GSA SPECT Image-guided Inverse Planning for Hepatocellular Carcinoma

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Abstract. *Background/Aim: A recent planning study suggested that ^{99m}Tc-labelled diethylene triamine pentaacetate-galactosyl human serum albumin (^{99m}Tc-GSA) single-photon emission computed tomography (SPECT) image-guided inverse planning (IGIP) shows dosimetric superiority to conventional planning in sparing liver function. Here, we report the first clinical translation of ^{99m}Tc-GSA SPECT IGIP for stereotactic body radiotherapy (SBRT) in a patient with hepatocellular carcinoma (HCC). Case Report: A 60-year-old male developed obstructive jaundice caused by recurrent HCC in segment 1 after hepatic resection. He underwent repeated radiotherapy (RT) consisting of 45 Gy in 15 fractions 8 years ago and 30 Gy in 5 fractions 2 years ago. We performed SBRT consisting of 40 Gy in 8 fractions using ^{99m}Tc-GSA SPECT-IGIP. We confirmed the dosimetric superiority of functional IGIP to conventional planning. He achieved complete response as assessed using the target volume. The patient has remained alive without recurrence for 18 months. He did not experience radiation-induced liver disease. Conclusion: Recurrent HCC was successfully and safely salvaged via re-irradiation with SBRT using ^{99m}Tc-GSA SPECT-IGIP.*

Hepatocellular carcinoma (HCC) has a high recurrence rate, which is reported to reach 70% after hepatic resection (1). Transarterial chemoembolisation (TACE), radiofrequency ablation (RFA) and/or radiotherapy (RT) are repeated to treat recurrent HCC (2-6). These treatment modalities lead to regional damage of the liver function; therefore, the distribution of liver function in patients with HCC is frequently heterogeneous (7). Recently, intensity-modulated radiotherapy (IMRT) based on the inverse planning technique using a dose-volume histogram (DVH) has been initiated into RT for HCC (8). Some groups have suggested that IMRT provides a better target dose conformity with a lower surrounding normal organ dose compared to the 3-dimensional (3D) conformal RT in the planning study (8). However, heterogeneity of liver function is not reflected in RT planning because DVH calculation is performed based on computed tomography (CT) morphological images (7).

^{99m}Tc-labelled diethylene triamine pentaacetate-galactosyl human serum albumin (^{99m}Tc-GSA), which specifically binds to the asialoglycoprotein receptor of the liver, is used to evaluate liver function (9). The combined use of ^{99m}Tc-GSA and single-photon emission computed tomography (SPECT) yields 3D information regarding the distribution of liver function (7). Our recent planning study suggested that ^{99m}Tc-GSA SPECT image-guided inverse planning (IGIP) shows dosimetric superiority to conventional planning in sparing liver function (10). In this case report, we discuss the first clinical translation of ^{99m}Tc-GSA SPECT-IGIP for stereotactic body radiotherapy (SBRT) in a patient with HCC.

Case Report

Clinical findings. A 60-year-old man was diagnosed with hepatitis B virus-associated HCC 17 years ago. He underwent hepatic resection of the right posterior section and segment 8 16 years ago and the left lateral section 4 years ago. He also underwent repeated TACE and RFA for recurrent intrahepatic lesions. For the lesion that relapsed after TACE in segment 1, he received repeated RT with 45 Gy in 15 fractions 8 years ago and 30 Gy in 5 fractions 2

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years ago (Figure 1). He developed obstructive jaundice because of recurrence of the lesion after RT (Figure 2). An endoscopic retrograde biliary drainage tube was inserted, and the patient had a Child-Pugh score of 6 points. We offered re-irradiation as a treatment option in addition to observation. After obtaining fully informed consent, we performed SBRT according to his wishes.

RT treatment planning. Figure 3 presents the fused planning CT and SPECT/CT image, which was created using Velocity AI (version 3.0.2; Varian Medical Systems, Palo Alto, CA, USA) as described elsewhere (7). The functional liver structure (FLS) for optimisation was decided using a threshold in SPECT at 55% of the maximum pixel value, which creates a gap in the FLS around the target volume (10). The planning CT images with FLS were transferred to the RT treatment planning system (Monaco version 3.3; Elekta Oncology Systems, Crawley, UK). The structures of the target volume and organs at risk (OARs) were delineated on the planning CT images. A clinical target volume (CTV) margin of 3 mm was added to the gross tumour volume (GTV). Planning target volume (PTV) margins of 5 mm for the superior-inferior direction, 4 mm for the left-right direction and 2 mm for the anterior-posterior direction were added to the CTV to cover for the internal motion of the target volume and setup errors. Internal motion of the target volume was estimated on the basis of pre-treatment CBCT (11). A functional image-guided SBRT plan (plan F) was generated for treating the patient with photon energy of 6 MV using single arc volumetric modulated arc therapy. A total RT dose of 40 Gy was prescribed to the PTV in 8 fractions. Plan F was optimised to reduce FLS volume receiving >15 Gy. A linear accelerator (Synergy; Elekta Oncology Systems) equipped with a 5-mm multi-leaf collimator was used for the treatment. We evaluated liver function in relation to the irradiation dose based on the dose-function histogram (DFH) (7). DFH parameters were calculated for 5-50 Gy as follows:

Fx=(sum of the counts within the liver volume receiving a dose of >x Gy/sum of the counts within the whole liver volume)×100 (7).

Treatment plan comparison. In addition to plan F, we created another RT plan that was optimised without FLS (conventional SBRT plan: plan C) to evaluate the dosimetric benefit of plan F. Figure 4 presents the dose distributions of plans F and C. The low-to-medium dose to the FLS was reduced in plan F compared to that in plan C. Figure 5 presents the DVH of the non-cancerous liver parenchyma (liver − GTV) and DFH of the liver for plans F and C, and Table I shows their parameters. Although the DVH parameters of the PTV, spinal cord, oesophagus and duodenum were similar in both treatment plans, F_{10} and F_{15} of the liver were smaller in plan F compared to plan C.

Patient outcome. After SBRT, the target volume completely disappeared, and the treatment response was considered a complete response (Figure 2). The patient survived without recurrence of the target volume for 18 months. During this period, his Child-Pugh score remained at 6 points, and he did not experience radiation-induced liver disease (RILD).

Discussion

Functional image-guided RT has been clinically introduced for treating non-small cell lung cancer (12, 13); however, it is rarely used in patients with HCC. This paper reports the first clinical translation of ^{99m}Tc-GSA SPECT-IGIP for HCC. In this case, inverse planning, based on SPECT image, provided dosimetric superiority to conventional planning in sparing liver function while maintaining the DVH parameters of the PTV and OARs as previously reported in our planning study (10). Some groups have investigated the introduction of functional images of ^{99m}Tc-sulphur colloid SPECT, which reflects the Kupffer cell distribution, into treatment planning and assessment of functional liver damage after RT (14, 15). Meanwhile, the main feature of ^{99m}Tc-GSA, which binds the asialoglycoprotein receptor in hepatocytes, is that it enables the direct evaluation of liver function (16).

Re-irradiation for recurrent HCC is extremely challenging. Huang *et al*. have retrospectively evaluated patients who underwent re-irradiation for recurrent HCC. Of the 36 patients who received two courses of RT, 13 (36%) experienced RILD within 3 months, and 9 (25%) died of RILD (17). Sophisticated RT techniques are feasible for HCC, especially in cases of re-irradiation. Although our patient previously underwent radiotherapy twice, his recurrent HCC was successfully and safely salvaged *via* re-irradiation with SBRT using ^{99m}Tc-GSA SPECT-IGIP. Our technique may facilitate the expanded use of RT in patients with HCC, classically considered to have a relatively high risk of RILD.

In summary, we have reported the first clinical translation of SBRT based on ^{99m}Tc-GSA SPECT-IGIP for HCC. We confirmed the dosimetric superiority of functional IGIP to conventional planning in a real clinical setting. Recurrent HCC was successfully and safely salvaged *via* re-irradiation with SBRT using ^{99m}Tc-GSA SPECT-IGIP. Our technique may facilitate the expanded use of RT in HCC patients with a relatively high risk of RILD.

Conflicts of Interest

The Authors declare no conflicts of interest.

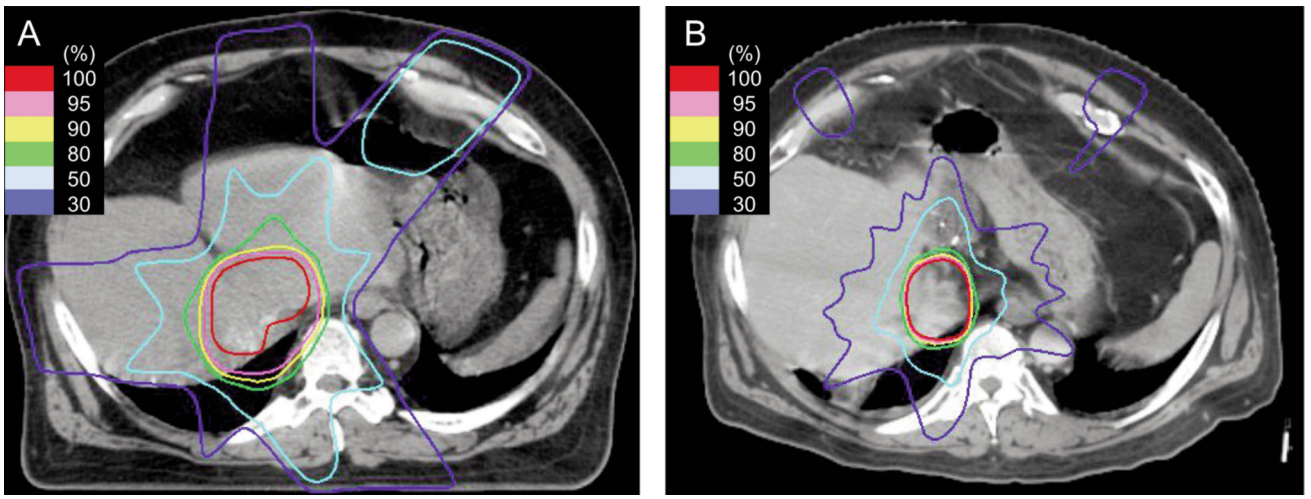

Figure 1. *Dose distributions of previous radiotherapy consisting of (A) 45 Gy in 15 fractions and (B) 30 Gy in 5 fractions. Coloured areas illustrate the relative doses to the prescribed doses.*

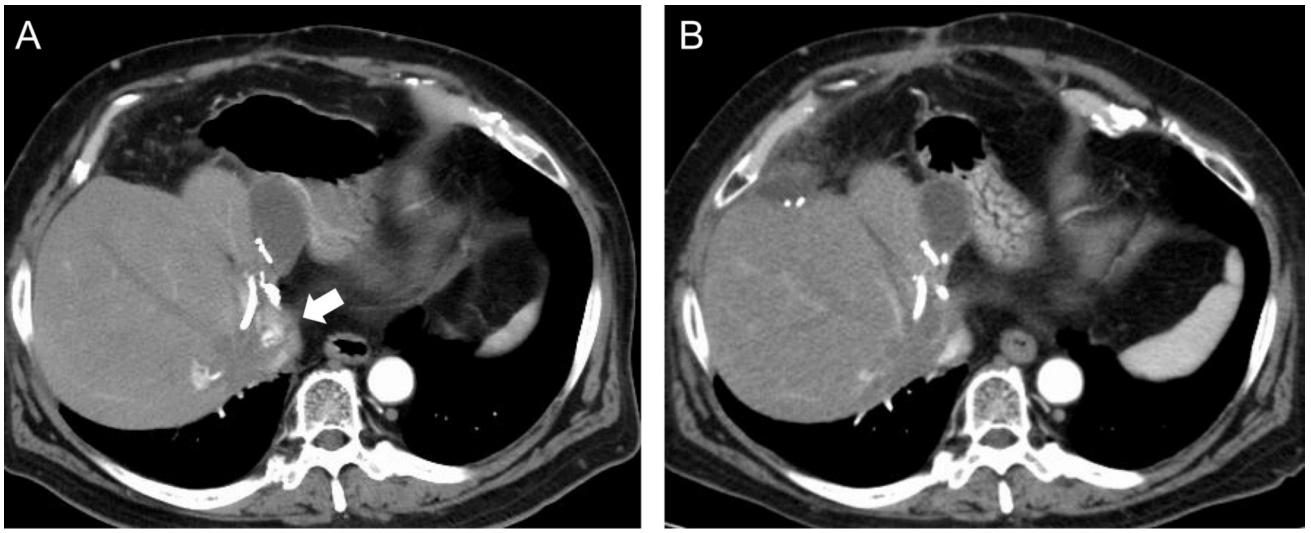

Figure 2. *Contrast-enhanced computed tomography. (A) Pre-treatment contrast-enhanced computed tomography (CT) and (B) post-treatment contrast-enhanced CT images obtained 14 months after the completion of stereotactic body radiotherapy (SBRT) consisting of 40 Gy in 8 fractions. The target volume (arrow) completely disappeared after SBRT.*

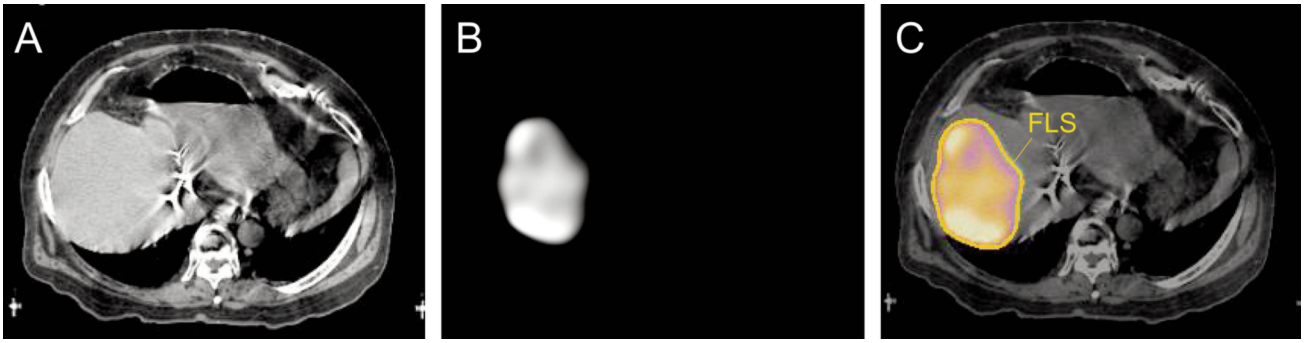

Figure 3. *Images for radiotherapy planning. (A) Planning computed tomography (CT), (B) single-photon emission computed tomography (SPECT) and (C) fused planning CT and SPECT image (planning SPECT/CT). The functional liver structure (FLS) is rendered in orange.*

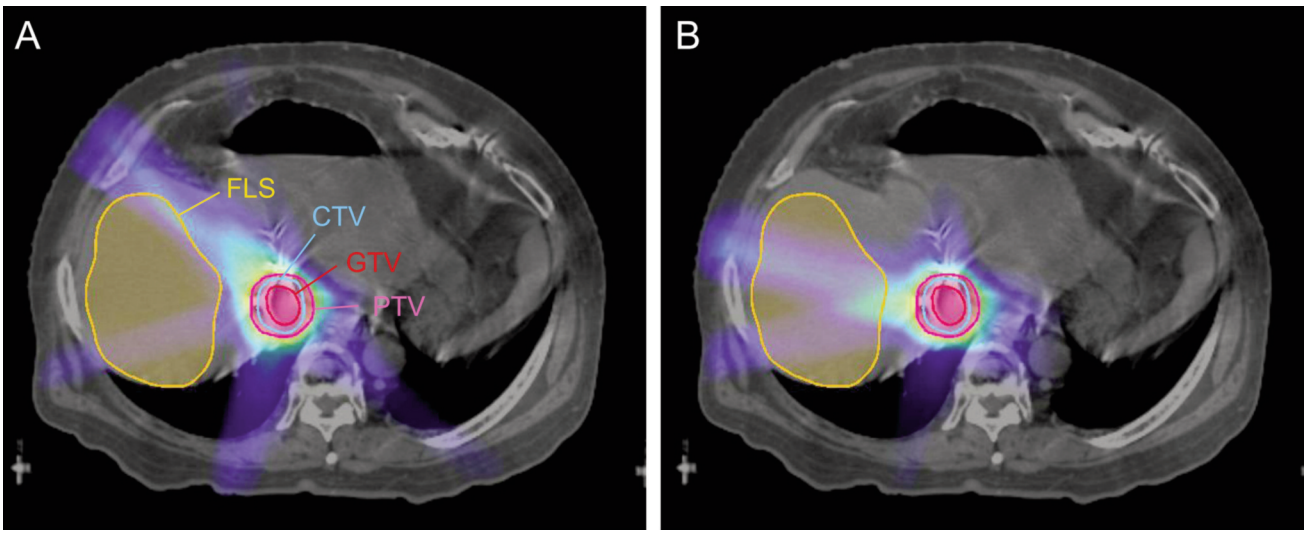

Figure 4. *Dose distributions of plans F (A) and plan C (B). The functional liver structure, gross tumour volume, clinical target volume and planning target volume are rendered in orange, red, blue and pink, respectively. FLS: Functional liver structure; GTV: gross tumour volume; CTV: clinical target volume; PTV: planning target volume.*

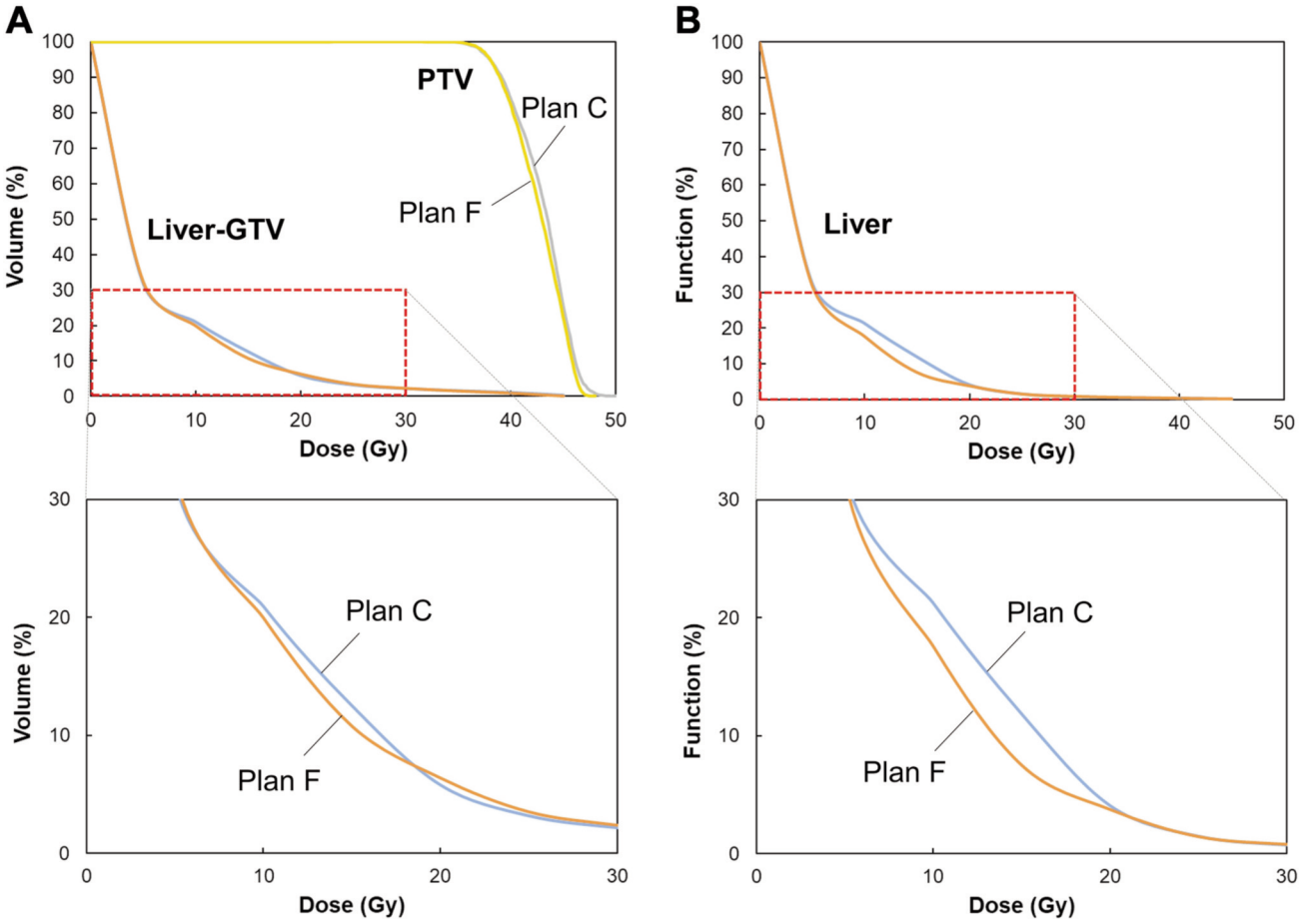

Figure 5. *(A) Dose-volume histogram of the non-cancerous liver parenchyma (liver – GTV) and (B) dose-function histogram of the liver. GTV: Gross tumour volume; PTV: Planning target volume.*

Table I. *Dose parameters of plans F and C.*

	Plan F	Plan C	Plan F – Plan C
DVH parameter			
PTV			
D_{95} (Gy)	38.0	38.0	0.0
D_{98} (Gy)	37.1	37.0	0.1
$CI_{100\%}$	0.81	0.82	–0.01
$CI_{98\%}$	0.85	0.87	–0.02
$CI_{95\%}$	0.88	0.88	0.00
HI	0.22	0.24	–0.02
Spinal cord			
D_{max} (Gy)	7.8	8.0	–0.2
Oesophagus			
D_{max} (Gy)	23.6	24.2	–0.4
Stomach			
D_{max} (Gy)	15.7	16.4	–0.7
Duodenum			
D_{max} (Gy)	10.2	10.8	–0.6
Liver – GTV			
V_5 (%)	32	32	0
V_{10} (%)	20	21	–1
V_{15} (%)	11	13	–2
V_{20} (%)	6	6	0
V_{25} (%)	4	3	1
V_{30} (%)	2	2	0
V_{35} (%)	2	2	0
V_{40} (%)	1	1	0
V_{45} (%)	0	0	0
Mean dose (Gy)	5.4	5.4	0.0
DFH parameter			
Liver			
F_5 (%)	32	32	0
F_{10} (%)	18	21	–3
F_{15} (%)	7	12	–5
F_{20} (%)	4	4	0
F_{25} (%)	1	1	0
F_{30} (%)	1	1	0
F_{35} (%)	0	0	0
F_{40} (%)	0	0	0
F_{45} (%)	0	0	0

DVH: Dose-volume histogram; PTV: planning target volume; CI: conformity index [$CI=V_{Tref}/V_T \times V_{Tref}/V_{ref}$, where V_{Tref} is the volume of the target covered by the reference isodose, V_T is the target volume and V_{ref} is the volume of the reference isodose (10)]; HI: homogeneity index [$HI=(D_{2\%} - D_{98\%})/D_{50\%}$, where $D_{x\%}$ is the absorbed dose received by x% of the planning target volume (10)].

Authors' Contributions

YK and RT conceived and designed the study, analysed and interpreted data and wrote the manuscript. TS, TM, YF, SS, YS and NO designed the study, interpreted data and reviewed the article. All Authors have read and approved the final manuscript.

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