

Significant symptoms alleviation and tumor volume reduction after combined simultaneously integrated inner-escalated boost and volumetric-modulated arc radiotherapy in a patient with unresectable bulky hepatocellular carcinoma

A care-compliant case report

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Abstract

Background: Clinically, elderly patients with unresectable bulky hepatocellular carcinoma (HCC) are difficult to manage, especially in those with co-infections of hepatitis B and C virus. Herein, we reported such a case treated with radiotherapy (RT) by using combined simultaneously integrated inner-escalated boost and volumetric-modulated arc radiotherapy (SIEB-VMAT). After RT, significant symptoms alleviation and durable tumor control were observed.

Case Summary: At presentation, an 85-year-old male patient complained abdominal distention/pain, poor appetite, and swelling over bilateral lower limbs for 1 month. On physical examination, a jaundice pattern was noted. Laboratory studies showed impaired liver and renal function. Abdominal computed tomography (CT) revealed a 12.5-cm bulky tumor over the caudate lobe of the liver. Biopsy was done, and hepatocellular carcinoma (HCC) was reported histopathologically. As a result, AJCC stage IIIA (cT3aN0M0) and BCLC stage C were classified. Surgery, radiofrequency ablation (RFA), trans-catheter arterial chemoembolization (TACE), and sorafenib were not recommended because of his old age, central bulky tumor, and a bleeding tendency. Thus, RT with SIEB-VMAT technique was given alternatively. RT was delivered in 26 fractions, with dose gradience as follows: 39 Gy on the outer Plan Target Volume (PTV), 52 Gy in the middle PTV, and 57.2 Gy in the inner PTV. Unexpectedly, cyproheptadine (a newly recognized potential anti-HCC agent) was retrospectively found to be prescribed for alleviating skin itching and allergic rhinitis since the last 2 weeks of the RT course (2 mg by mouth Q12h for 24 months).

After RT, significant symptoms alleviation and tumor volume reduction were observed for 32 months till multiple bone metastases. Before and after RT, a large tumor volume reduction rate of 88.7% was observed (from 608.4 c.c. to 68.7 c.c.). No severe treatment toxicity was noted during and after RT. The patient died due to aspiration pneumonia with septic shock at 4 months after bone metastases identified.

Conclusions: SIEB-VMAT physically demonstrated double benefits of intratumor dose escalation and extra-tumor dose attenuation. Significant tumor regression and symptoms alleviation were observed in this elderly patient with unresectable bulky HCC. Further prospective randomized trials are encouraged to demarcate effective size of SIEB-VMAT with or without cyproheptadine.

Abbreviations: AJCC = American Joint Committee on Cancer, BCLC = Barcelona Clinic Liver Cancer, CT = computed tomography, CTCAE = common toxicity criteria of adverse events, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IMRT = intensity-modified radiotherapy, mRECIST = modified Response Evaluation Criteria in Solid Tumors, OR =

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odds ratio, OS = overall survival, PM2.5 = particulate matter $\leq 2.5 \mu\text{m}$, PTV = plan target volume, PVT = portal vein thrombosis, RFA = radiofrequency ablation, RT = radiotherapy, RUQ = right upper quadrant, SBRT = stereotactic body radiotherapy, SIB = simultaneously integrated boost, SIEB = simultaneously integrated inner-escalated boost, TACE = trans-catheter arterial chemoembolization, VAS = visual analog scale, VMAT = volumetric-modulated arc radiotherapy.

Keywords: case report, cyproheptadine, durable response, hepatocellular carcinoma (HCC), radiotherapy (RT), simultaneously integrated inner-escalated boost (SIEB), volumetric-modulated arc radiotherapy (VMAT)

1. Introduction

Hepatocellular carcinoma (HCC) is a major cancer worldwide.^[1–3] In HCC endemic areas (e.g., Taiwan), several risk factors have been identified, such as chronic infections of hepatitis C virus (HCV)^[4–6] and/or hepatitis B virus (HBV),^[7–9] as well as long-term exposure of fine particle pollution (particulate matter $\leq 2.5 \mu\text{m}$ [PM2.5]).^[10] At initial presentation, most HCC patients were diagnosed with locoregionally advanced disease, which prevents from curative managements,^[11] such as surgical resection, percutaneous ethanol injection, and radiofrequency ablation (RFA),^[12] resulting in persistent high death rates.^[2]

For patients with locoregionally advanced disease, several managements may be applied, such as trans-catheter arterial chemoembolization (TACE),^[13,14] targeted therapy (e.g., sorafenib),^[15] and radiotherapy (RT).^[11] In such a condition, RT can be used in conjunction with TACE for patients with^[16] or without portal vein thrombosis (PVT).^[17] Moreover, RT with stereotactic body radiotherapy (SBRT)^[18,19] technique recently showed promising results for managing HCC.^[11,20] Generally, however, though RT is one of treatment modalities for treating HCC,^[11,21,22] the role of RT is mainly limited in palliative managements for symptoms alleviation and possible tumor control.

Herein, we reported an unresectable bulky HCC patient who was treated with RT alone. A combined RT technique of simultaneously integrated inner-escalated boost (SIEB) and volumetric-modulated arc radiotherapy (VMAT) was used, that is, SIEB-VMAT. After RT, significant symptoms alleviation, durable tumor control (37 months), and a high quality of life were observed.

2. Case report

2.1. Oncologic timeline of intervention and outcome

According to the CARE guideline^[23–25] and a previous CARE-compliant report,^[26] we constructed an oncologic timeline to demonstrate cancer diagnosis, staging, intervention, and outcome, chronologically (Fig. 1).

2.2. Patient information

At presentation, an 85-year-old male patient complained of multiple progressive symptoms for 1 month, including upper abdomen distention/pain, bilateral lower limbs swelling, easily fatigue, and poor appetite.

On history review, chronic co-infections of hepatitis B virus (HBV) and hepatitis C virus (HCV) were noted for >30 years. No any therapy was prescribed for HCV and HBV till this presentation. And, he denied any breakout episode of hepatitis.

2.3. Physical exam

On physical examination, consciousness was alert, and JOMAC was intact, in terms of judgment, orientation, memory,

abstraction, and calculation. Significant jaundice was noted over the skin and conjunctiva. Multiple plaques of ecchymosis over the 4 limbs and trunk were also observed. No enlarged nodes were palpated on the neck, supra-clavicle fossa, axillary, and inguinal regions. Clear breathing sounds were auscultated, bilaterally.

On abdominal examination, abdominal distention with significant tympanic sounds was found. Remarkably, dullness sounds on percussion were confirmed over the right upper quadrant (RUQ) of the abdomen. Mild-to-moderate tenderness over epigastric and RUQ regions was palpated. Moderate pitting edema over bilateral lower limbs was identified, which involved legs and feet.

2.4. Diagnostic assessment

For liver function assessment, Child-Pugh B was classified (a total score = 8),^[27,28] in terms of encephalopathy (none, score = 1), ascites (none, score = 1), total bilirubin (1.5 mg/dL, score = 1), albumin (2.6 g/dL, score = 3), and prothrombin time (4 s, score = 2). Note that the level of direct bilirubin was 0.9 mg/dL. In addition, GOT and GPT values were elevated but both within 2-folds of upper limits (76 and 64 IU/L, respectively).

For renal assessment, BUN and creatinine levels were also elevated (28 and 2.2 mg/dL), representing a possibility of mild renal impairment secondary to liver function disturbance.

On images, abdomen computer tomography (CT) showed a bulky liver tumor with size about $12.5 \times 10 \times 8.5$ cm over the caudate lobe of the liver (Fig. 2). Biopsy was done, and pathology reported moderately differentiated hepatocellular carcinoma. After work-up studies, clinical stages were classified as American Joint Committee on Cancer (AJCC)^[29–31] stage IIIA (cT3aN0M0) and Barcelona Clinic Liver Cancer (BCLC)^[32] stage C. Inoperable condition and unresectable status were recognized based on old age, co-infection of chronic hepatitis B and C virus, impaired liver and renal function, bleeding tendency, and central location of the bulky tumor.

2.5. Interventions

As a result, several treatment modalities could not be prescribed safely, including surgical resection, RFA, TACE, and sorafenib. Thereafter, after discussion with the patient and his family, RT alone was given. A combined technique of SIEB-VMAT was applied by using the Varian Eclipse Treatment Planning System (USA; version 11). For SIEB, doses were painting with prescribed gradience, as follows: the outer plan target volume (PTV), 39 Gy (1.5 Gy \times 26 fractions); the middle PTV, 52 Gy (2 Gy \times 26 fractions); and, the inner PTV, 57.2 Gy (2.2 Gy \times 26 fractions; Fig. 3A-C). The whole RT course was smooth (Fig. 1, from October 2012 to November 2012).

Interestingly and unexpectedly, we found cyproheptadine, a recently identified potential anti-HCC agent,^[33–35] was prescribed for alleviating skin itching and allergic rhinitis (2 mg by mouth Q12h; prescribed since the last 2 weeks of the RT course and then persistently used for 24 months).

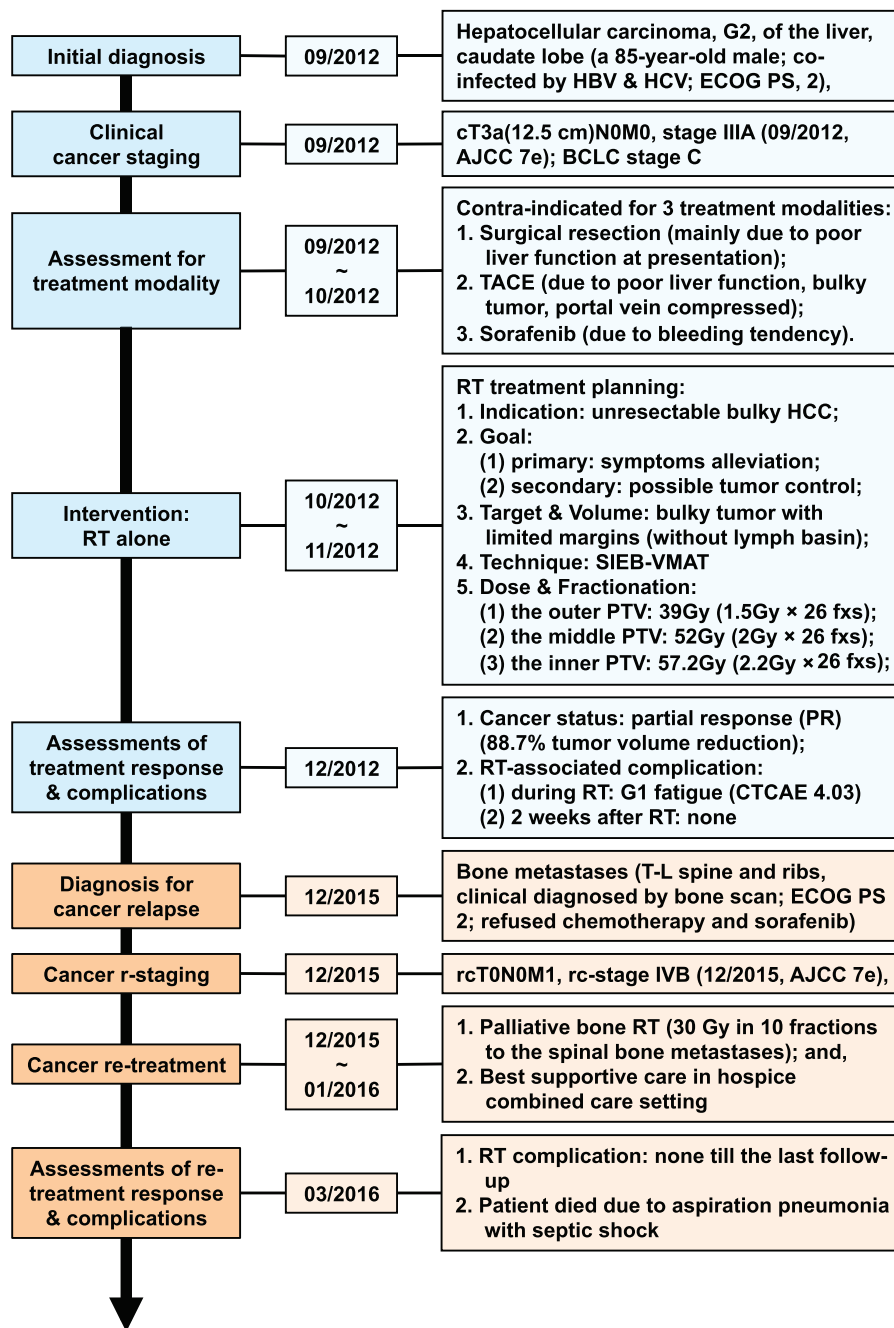


Figure 1. An oncologic timeline representing cancer diagnosis, staging, and treatments. This timeline represents the patient's oncologic diagnosis-staging-treatment history chronologically. As shown, overall survival time of the patient is 3 years and 6 months (from 09/2012 to 03/2016). Note that a relatively long progression-free survival after completion of liver RT is documented (37 months; from 11/2012 to 12/2015). AJCC=American Joint Committee of Cancer, BCLC=Barcelona clinic liver cancer staging, CTCAE=Common Terminology Criteria for Adverse Events, ECOG=Eastern Cooperative Oncology Group, fxs, fractions, G2=grade 2, Gy=Gray, HBV=hepatitis B virus, HCC=hepatocellular carcinoma, HCV=hepatitis C virus, PR=partial response, PS=performance status, PTV=plan target volume, SIEB=simultaneously integrated inner-escalated boost, T-L spine=thoracic and lumbar spine, VMAT=volumetric-modulated arc radiotherapy. Note: For a better visual sensation, the figuring style of our oncological timeline is as follows: blue-color blocks, representing for the cancer initial course; and, orange-color blocks, depicting for cancer recurrent/relapse course.

2.6. Follow-up and outcomes

For HCC-associated symptoms, upper abdominal fullness, poor appetite, and lower limbs edema were improved gradually during and after RT. Remarkably, according to the common toxicity criteria of adverse events (CTCAE) version 4.03,^[36] no significant treatment-associated toxicity was found, except for grade 1

fatigue during RT (i.e., relieved after rest). No late RT sequelae were observed till the last follow-up.

For laboratory tests—before, during, and after RT—weekly follow-up GOT/GPT profiles (IU/L) were as follows: 76/64 (before), 74/87 (2nd week), 88/96 (3rd week), 101/118 (4th week), 104/124 (5th week), 47/40 (6th week; the end of RT), and

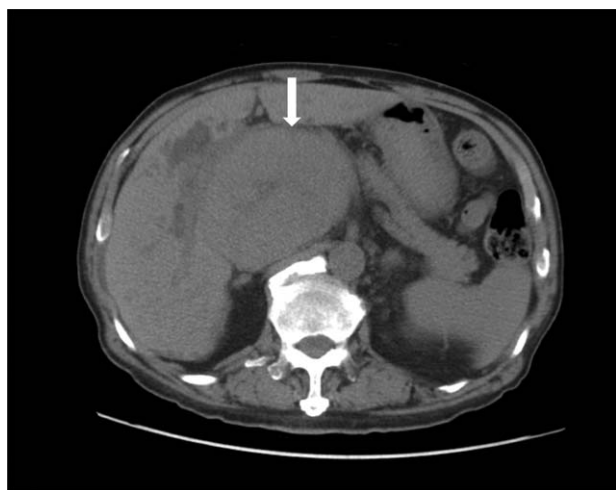


Figure 2. Pre-RT bulky tumor over the caudate lobe of the liver. The arrow indicates the bulky liver tumor with a size of 12.5 × 10 × 8.5 cm (estimated tumor volume by RT planning system, 608.5 c.c.). Note that intravenous contrast cannot be given safely due to an elevated level of serum creatinine of 2.2 mg/dL. The AFP level is 16,580 U/L at this timing (09/2012). AFP=alpha-fetoprotein, RT=radiotherapy.

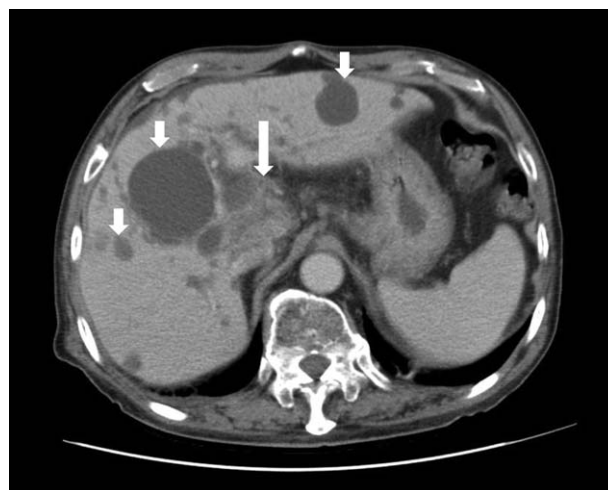


Figure 4. Abdominal CT at 1 month after RT: significant tumor shrinkage. A significant regression of the irradiated liver tumor was observed (as the long white arrow; residual size, 4.9 × 4.2 × 3.1 cm; estimated volume, 68.7 c.c.). Partial response (PR) was noticed (a volume reduction rate of 88.7% when compared with pre-RT bulky tumor [608.5 c.c.]). Multiple liver cysts are also noted (as the short white arrows). Note that mild regeneration of the normal liver is evident. Also note that intravenous contrast can be prescribed while CT imaging due to an improved creatinine level of 1.4 mg/dL. An AFP level was 48 U/L at this timing (12/2012). AFP=alpha-fetoprotein, CT=computed tomography, PR=partial response, RT=radiotherapy.

37/27 (1 month after RT). Follow-up total bilirubin levels were decreased from 1.5 (before) to 0.5 mg/dL (1 month after RT). Creatinine levels were also attenuated from 2.2 (before) to 1.4 mg/dL (1 month after RT). Remarkably, the albumin level was increased from 2.6 g/dL (before) to 3.1 g/dL (1 month after RT). Taken together, these laboratory profiles supported remission of HCC-associated symptoms after RT.

For tumor control, the largest diameter of the viable tumor part was recorded for estimating tumor response according to modified Response Evaluation Criteria in Solid Tumors (mRECIST).^[37] Simultaneously, auto-calculated tumor volume (c.c.) by the RT planning system (Eclipse Version 11) was also reported in the following CT images.

First, on pre-RT CT, the largest diameter of viable HCC was 12.5 cm (September 2012; size, 12.5 × 10 × 8.5 cm; volume, 608.5 c.c.; Fig. 2). Second, on post-RT CT, the largest diameter of the irradiated viable HCC was 4.9 cm (December 2012; 1 month after RT; size, 4.9 × 4.2 × 3.1 cm; volume, 68.7 c.c.; Fig. 4). As a result, a significant tumor response

(partial response [PR]) was noted, with a post-RT volume reduction rate of 88.7%.

More notably, the last follow-up abdominal CT (July 2015, 32 months after RT; tumor volume, 5.8 c.c.; Fig. 5) showed a persistent tumor regression (near-complete response [near CR], with a large volume reduction rate of >99% when compared with the pre-RT bulky tumor).

As a result, after RT with combined SIEB-VMAT technique, a relatively durable progression-free survival with a high quality of life was noted (37 months; from November 2012 to December 2015; Fig. 1 and Fig. 6).

Note that a gradual regeneration of the normal liver is noted after persistent tumor burden reduction (Fig. 4 and Fig. 5, when compared with Fig. 2), supporting that restoration of liver function and alleviation of malignant symptoms are possible after effective anti-HCC treatments.

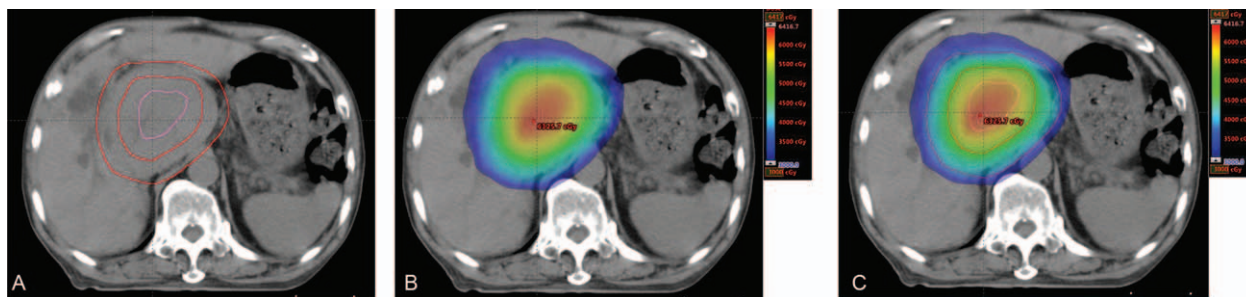


Figure 3. Target delineation and dose painting of SIEB-VMAT to the bulky liver tumor. Panel A, target delineation for the 3 levels of PTV. Dose prescriptions were as follows: the outer PTV, 39 Gy; the middle PTV, 52 Gy; and the inner PTV, 57.2 Gy. All doses were simultaneously prescribed in 26 fractions. Panel B, dose painting according to panel A. Panel C, a combined image of Panels A and B. PTV=plan target volume, SIEB=simultaneously integrated inner-escalated boost, VMAT=volumetric-modulated arc radiotherapy. Note 1: For Panels B and C, the margin of the dose painting (blue color) reveals a total dose of 30 Gy that delivered in 26 fractions. Note 2: The highest dose of the whole RT treatment planning is 64.167 Gy (delivered in 26 fractions). In this cut of axial image, the highest dose is 63.257 Gy (also delivered in 26 fractions; Panels B and C).



Figure 5. Abdominal CT at 32 months after RT: further tumor shrinkage. The residual tumor showed persistent and further shrinkage (as the long white arrow; estimated tumor volume, 5.8 c.c.). A good tumor control of near-complete response was noticed (a volume reduction rate of >99%, when compared with the pre-RT bulky tumor [608.5 c.c.]). Note that margins of the residual tumor cannot be well defined due to its spilling-like morphological pattern. Multiple liver cysts are also noted (as the short white arrows). Remarkably, moderate liver regeneration is observed (more evident than that of Fig. 4). The AFP level was 32 U/L at this timing (07/2015). AFP=alpha-fetoprotein, CT=computed tomography, RT=radiotherapy.

3. Discussion

The main finding: RT with SIEB-VMAT technique was useful in this elderly patient with unresectable bulky HCC; significant tumor volume reduction and durable treatment response resulted in a high quality of life.

Elderly patients with unresectable bulky HCC are still difficult to manage. Many treatment modalities cannot be conducted safely, such as RFA, TACE, and targeted therapy (e.g., sorafenib).^[11] As a result, most (if not all) of these patients were excluded from clinical trial candidates, and few items were known about them.

Herein, we reported such an elderly patient with an unresectable bulky HCC. RT with combined SIEB-VMAT technique was given. Surprisingly, significant symptoms alleviation and effective tumor control were noted, resulting in a relatively durable disease-free time interval. Further prospectively clinical trials are encouraged.

Clinical reasoning for applying SIEB-VMAT in this elderly patient with unresectable bulky HCC: maximizing therapeutic gains for double benefits of better tumor control and fewer treatment toxicities.

Simultaneously integrated boost (SIB)^[38–40] technique is a well-known modern RT-prescribing technique; it can be used in combination with several RT-irradiating techniques, such as intensity-modified radiotherapy (IMRT)^[41–43] and VMAT.^[44–46] In the literature, several types of bulky tumors have been

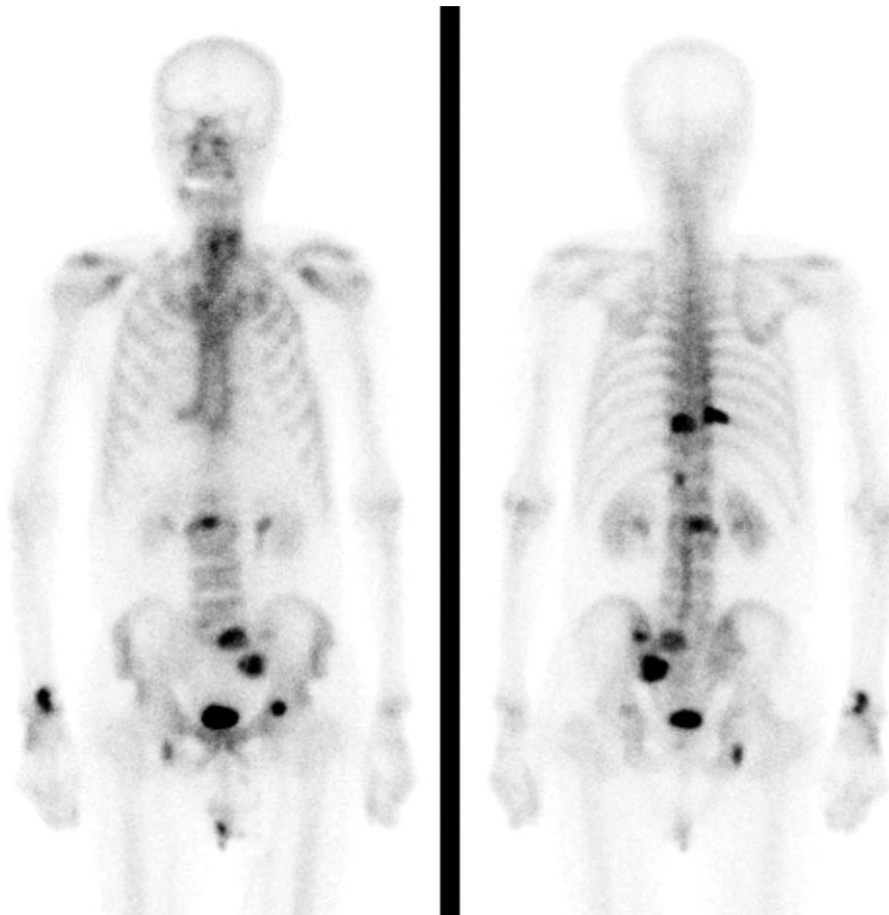


Figure 6. Bone scan at 37 months after RT. At 37 months after RT (12/2015), the patient complained of persistent lower back pain for 2 weeks. Bone scan showed multiple increased uptakes over the T-L-S spine and pelvic bone, being compatible with multiple bone metastases. An elevated AFP level (78,650 U/L) was noted. AFP=alpha-fetoprotein, RT=radiotherapy, T-L-S spine=thoracic-lumbar-sacral spine.

irradiated by integrating SIB, such as lung cancer,^[47] esophagus cancer,^[48] and soft tissue sarcoma.^[49] In general, significant tumor volume reduction with a prolong progression-free survival is frequently observed.^[49]

Recently, a modified-SIB technique—focusing on intratumor dose escalation—has been reported to induce more significant tumor regression in several unresectable bulky tumors, such as huge pelvic mass,^[50] retroperitoneal mass,^[51] breast masses,^[52] and liver tumors.^[53] In the present case, we used a similar modified SIB by incorporating VMAT, i.e., SIEB-VMAT. When compared with the published modified-SIB,^[50–52] a similar point was that a larger fraction size is delivered to the geometrically central region of a bulky tumor (in the same treatment fractions), intending to gain a better tumor control.

But differently, we used a smaller fraction size (1.5 Gy; not the conventional 1.8–2.0 Gy per fraction) to the peripheral zone of the irradiating tumor, intending to minimize RT-associated treatment toxicities. In our near 5-year experience, this peribulky-tumor dose-attenuation strategy was particularly useful in elderly patients. As shown in the present case, this strategy gained an effective tumor control with a cost of negligible toxicities. We named this modified technique (i.e., combined intratumor dose escalation and extra-tumor dose attenuation) as simultaneously integrated inner-escalated boost (SIEB). This manipulation achieved double benefits in treating elderly patients with bulky tumor: a higher intratumor dose gained a higher tumor control; on the contrary, a lower peripheral tumor dose achieved lower treatment toxicities. As a result, therapeutic gain was largely increased.

The present case showed us that this strategy works well. Further prospective studies are encouraged to explore the actual effective size of this modification, especially in elderly patients or those patients with multimorbidities.

An incidental finding arising both biology and clinical interesting: whether combined RT with cyproheptadine is able to increase tumor control in HCC is not clear.

The present case harbors an interesting point. That is, though we used SIEB-VMAT to escalate intratumor dose for increasing tumor control, the prescribed inner dose of 57.2 Gy in 26 fractions was not extremely high as that of previous studies (i.e., the inner highest dose of around 90 Gy).^[50–52] Thus, whether our observed effective and durable tumor control results from RT itself, a purely intrinsic high radiosensitivity of the irradiated HCC, or a combined effect of other factors is not clear.

In the literature review, we incidentally found a potential anti-HCC agent, that is, cyproheptadine.^[33–35] Clinically, cyproheptadine is an antihistamine agent that can be used for managing skin itching, rhinitis, and allergic reaction. It can also be used for increasing appetite in children. Recently, unexpected significant tumor regressions were observed in 2 HCC patients with lung metastasis who were treated with a combination of thalidomide and cyproheptadine.^[35] Moreover, in vitro experiments showed a cytotoxic effect of cyproheptadine in 2 HCC cell lines.^[35] Further mechanism-exploring experiments demonstrated that cyproheptadine inhibits proliferation of HCC cells via activating P38 kinase to block cell cycle progression.^[33] Finally, a small case series reported additional benefits of cyproheptadine in prolonging overall and progression-free survival in advanced HCC patients treated with sorafenib.^[34]

In the present case, no thalidomide and sorafenib was used. But, cyproheptadine was retrospectively found to be used in conjunction with RT for covering skin itching and allergic rhinitis (2 mg by mouth Q12h for 2 years; prescribed since the last

2 weeks of RT course). But, mainly due to our relatively lower prescribed dose of cyproheptadine than that of prior reports,^[33–35] whether cyproheptadine benefits the present case in terms of tumor control is largely unclear.

However, further prospective studies to test the effect of combined cyproheptadine and RT, particularly SIEB-VMAT, still raise large interests in both biological and clinical aspects.

Gradual normal liver regeneration occurred after durable tumor control of irradiated HCC: restoring liver function and alleviating HCC-associated symptoms

Clinically, liver regeneration is a good sign in treated HCC patients; it may restore, at least partly, impaired liver function and then alleviate malignant symptoms. More notably, liver regeneration may switch an inoperable medical status to an operable condition. In the literature, liver regeneration has been observed after effective treatments of SBRT.^[54] The present case confirmed this observation (Figs. 4 and 5, when compared with Fig. 2), reminding us that significant liver regeneration and symptom alleviation are possible if tumor burden of HCC persistently reduced after effective anticancer treatments.

Unresectable bulky HCC patients: survival and outcome comparison among varied available treatments, for example, TACE, targeted therapy, RT, or their combinations.

Till now, managing unresectable HCC patients are still difficult.^[11] Several modalities are available, including TACE,^[13,14] targeted therapy (e.g., sorafenib),^[15] radiotherapy, and most commonly, their combinations.^[11,20–22] For example, if medical fit, most of these patients were treated with combined TACE and sorafenib, with a median overall survival ranged from 12 to 27 months.^[55] With a cost of frequent adverse events (85.3% [2,732/3,202]), a large observation study recently reported a favored overall survival for patients treated with concomitant-TACE/sorafenib (21.6 months) when compared with those patients treated with nonconcomitant-TACE/sorafenib (9.7 months).^[56]

Similar unsatisfied results have also been reported in patients treated with combined TACE and RT. For instance, unresectable HCC patients treated with this combination have been reported to demonstrate a median overall survival of 20.2 months (95% CI, 8.6–31.9 months).^[57] When compared with TACE alone, better clinical outcomes of combined TACE and RT are also confirmed in a large meta-analysis,^[17] in terms of 1-year survival (odds ratio [OR], 1.36; 95% CI, 1.19–1.54) and complete tumor response (OR, 2.73; 95% CI, 1.95–3.81). More notably, the observed survival benefit is gradually increased from 2 years (OR, 1.55; 95% CI, 1.31–1.85) to 5 years (OR, 3.98; 95% CI, 1.86–8.51).^[17]

Although comparing overall survival is largely beyond the scope of a single case report, the present SIEB-VMAT-irradiated patient seemingly had a relatively longer survival (42 months; from September 2012 to March 2016) when compared with the other HCC patients who were treated at our institute in the similar period. From 2010 to 2013, our unpublished data showed 3-year overall survival rates of 43.1% for all HCC patients (n = 240; any stage) and 13.7% for patients with AJCC stage III and BCLC stage C (n = 19; these data were externally audited by the National Cancer Center Accreditation and the Taiwan Health Promotion Administration).^[58,59] Of the 19 stage-C patients, only 4 patients were treated with a component of RT to their bulky liver tumors. Of the 4 irradiated patients, 2 cases were treated with SIEB-VMAT. One was the present patient who gained relatively good clinical outcomes. But, the other one was immaturely died at the 4th RT fraction due to a lethal bleeding

Table 1**Hypotheses and elements of study PICO.**

Two testable hypotheses in managing unresectable bulky HCC		
	Hypothesis 1	Hypothesis 2
Question	Is SIEB-VMAT able to gain better tumor control with lower (or similar) RT-associated toxicities than that of conventional VMAT?	Is SIEB-VMAT in conjunction with cyproheptadine able to prolong progression-free survival and even overall survival?
Hypothesis	SIEB-VMAT is able to gain double benefits of higher tumor control and lower (or similar) RT-associated treatment toxicities than that of conventional VMAT.	SIEB-VMAT in conjunction with cyproheptadine is able to prolong progression-free survival and even overall survival.
P	Unresectable bulky HCC patients	Unresectable bulky HCC patients
I	SIEB-VMAT	SIEB-VMAT plus cyproheptadine
C	Conventional VMAT	SIEB-VMAT
O	Tumor control; treatment toxicities	Progression-free and overall survival

Note: Though it may be less recommended, for the best hypothesis testing for a potential synergic effect between 2 interventions, it might be considered to test a third hypothesis: "Cyproheptadine is able to improve clinical outcomes."

The PICO could be as follows: P, unresectable bulky HCC patients; I, Cyproheptadine use; C, Cyproheptadine not use; and O, tumor control, progression-free and overall survival.

C=control/compare, HCC=hepatocellular carcinoma, I=intervention, O=outcomes, P=patient/population, RT=radiotherapy, SIEB=simultaneously integrated inner-escalated boost, VMAT=volumetric-modulated radiotherapy.

event of rupture of esophagus varices secondary to severe liver cirrhosis.

3.1. Strength

Strength 1: As mentioned above, in conducting SIB technique, several RT techniques may be used, such as IMRT^[41–43] and VMAT.^[44–46] In general, when compared with IMRT, VMAT demonstrates a similar target coverage^[60] but with a better radiation dosimetric profile.^[61] The present case used VMAT to conduct a modified-SIB (i.e., SIEB-VMAT), focusing on both intratumor dose escalation and extra-tumor dose attenuation, achieving a good tumor control with minimized treatment toxicities.

Strength 2: As mentioned above, being different from the prior published modified-SIB,^[50–52] our SIEB-VMAT not only focused on simultaneous intratumor dose escalation (from conventional daily dose of 1.8–2.0 Gy up to 2.2–3.0 Gy), but also prescribed extra-tumor dose attenuation (from conventional daily dose of 1.8–2.0 Gy down to 1.2–1.5 Gy, depending on individual conditions).

To our best knowledge, this type of modified SIB has not yet been reported. In our experience, this modification is particularly useful in the following conditions: (1) for bulky tumors that are closely adjacent to critical normal organs, such as lung or small intestine; (2) for recurrent tumors that are largely limited by prior dose–volume constraints, that is, for patients who were treated with reirradiation or even re-reirradiation; or, (3) highly vulnerable cancer patients, such as elderly patients, those with multiple comorbidities, or those with poor performance status.

The present case supported the usefulness of SIEB-VMAT in an elderly patient with unresectable bulky HCC with associated impairments of liver and renal function.

3.2. Limitations

Even the present case was reported in accordance with the CARE guideline,^[23–25] an intrinsic limitation is inevitably existed. That is, the present study just reported treatment experience and clinical outcomes from a single patient. The real effective size of SIEB-VMAT and incidence of its treatment toxicities are largely unknown. Thus, interpreting our data should be cautioned. Further prospective studies are recommended, especially randomized trials to compare SIEB-VMAT with conventional

VMAT (i.e., no simultaneous intratumor dose escalation). The interaction between RT and cyproheptadine also requires further investigation.

3.3. Generated testable hypotheses

The present case generated 2 testable hypotheses in patients with unresectable bulky HCC, as follows (Table 1).

Hypothesis 1: SIEB-VMAT is able to gain double benefits of higher tumor control and lower (or similar) RT-associated treatment toxicities than that of conventional VMAT.

Hypothesis 2: SIEB-VMAT in conjunction with cyproheptadine is able to prolong progression-free survival and even overall survival.

4. Conclusion

For managing locally advanced, unresectable, and inoperable HCC, this case shed us a light that RT with SIEB-VMAT technique may be useful. Treatment goals could be achieved in not only alleviating malignant symptoms, but also generating a durable progression-free time interval. Quality of life of the irradiated patient is able to be improved, especially when liver regeneration is observed. Further randomized clinical trials are encouraged to demarcate the real effective size of SIEB-VMAT. The role of cyproheptadine in irradiating HCC patients arises both biological and clinical interests, suggesting further investigation.

4.1. Patient perspective

Before RT, the patient and his families are very anxious for RT due to a deep fear of RT toxicities, especially concerning patient's old age, impaired liver function, and co-infections of HBV & HCV. After our detailed explanation and ensuring, their anxiety decreased thereafter. Thus, after 2 sessions of physician–patient–family conference, the patient and his families agreed RT to the bulky liver tumor, with 2 treatment goals of symptom alleviation (primary goal) and possible tumor control (secondary goal).

During RT, their anxiety further decreased gradually because near no additional toxicities were found after initiation of RT—only mild fatigue that could be relieved after rest was observed. More notably, malignant symptoms that associated with HCC were decreased gradually, such as lower limbs edema and

abdominal distension/pain. The visual analog scale (VAS) of pain was decreased with time elapsed: 8 (1st week), 8 (2nd week), 7 (3rd week), 6 (4th week), 3 (5th week), and 1 (6th week; the end of RT). Note that this bulky tumor patient presented right upper abdominal pain, which is an unusual symptom of HCC.

After completion of RT, the patient felt much better than before RT status. Near no more abdominal fullness, pain, and lower limbs edema were found. The patient and his families were satisfied with treatment results of RT.

4.2. Informed consent, ethic statement, and guideline compliant

The present case report was written after both an acquisition of patient's informed consent and an approval of our institute of review board (IRB; approved number: B10204018). The reported process, analysis, and interpretation were also in accordance with the Helsinki Declaration (initially written in 1975 and then revised in 1983) and compliant with the CARE guideline.^[23–25]

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