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ORIGINAL ARTICLE

Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma: Review of a Local Hospital

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ABSTRACT

Objective: *To review the outcome and safety of stereotactic body radiation therapy (SBRT) for patients with hepatocellular carcinoma (HCC).*

Methods: *Patients who underwent SBRT for HCC between January 2013 and March 2016 at Queen Elizabeth Hospital were reviewed retrospectively. Tumour response and toxicities were evaluated. Local control and overall survival rates were calculated using the Kaplan-Meier method.*

Results: *31 male and 8 female patients aged 54 to 90 (median, 72) years were included. 35 patients had Child-Pugh class A cirrhosis. 35 patients had viral hepatitis, of whom 33 were hepatitis B carriers. One patient was treatment naïve and underwent SBRT as bridging therapy prior to liver transplantation. The remaining 38 patients had received prior loco-regional therapies. The median tumour size was 1.9 cm. 29 patients had only one lesion. The SBRT doses ranged from 30 to 54 Gy in 6 to 7 fractions. After a median follow-up period of 17.8 months, 13 patients had died. The 1- and 2-year overall survival rates were 73.6% and 56.1%, respectively, and the median overall survival was 30.1 months. In 38 patients followed up at 3 months, 28.9%, 23.7%, and 42.1% had a complete response, partial response, and stable disease, respectively. The actuarial local control rate at 1 year was 82.8%. 21 patients had intrahepatic out-of-field recurrence, and four patients had distant metastasis. The 1-year intrahepatic recurrence-free survival was 50.5%, and the median intrahepatic recurrence-free survival was 15.4 months. 13 patients had grade 3 or above toxicity, of whom eight had thrombocytopaenia. One patient had grade 3 hepatic and renal toxicities and died after 2 months due to liver failure and hepatorenal syndrome.*

Conclusion: *SBRT is effective and safe even in previously treated patients. It results in good local control with minimal severe adverse events but a relatively high intrahepatic (out-of-field) recurrence rate.*

Key Words: *Carcinoma, hepatocellular; Radiotherapy*

中文摘要

肝細胞癌的體部立體定向放射治療：一所本地醫院的回顧研究

林河清、鄭海清、顏繼昌

目的：回顧體部立體定向放射治療（SBRT）肝細胞癌（HCC）患者的療效和安全性。

方法：回顧2013年1月至2016年3月在伊利沙伯醫院接受SBRT治療HCC的患者。評估腫瘤反應和放療毒性。使用Kaplan-Meier法計算局部控制率和總生存率。

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結果：共包括31名男性和8名女性患者，年齡介於54至90歲（中位數，72歲）。35名患者有Child-Pugh A型肝硬化。35名患者有病毒性肝炎，其中33名為乙型肝炎帶菌者。一名患者是初次治療，並應用SBRT治療為肝移植創造條件。其餘38名患者曾接受局部治療。中位腫瘤大小為1.9厘米。29名患者為單發腫瘤。SBRT劑量範圍為30至54 Gy分6至7次。中位隨訪17.8個月後，有13名患者死亡。1年和2年總體生存率分別為73.6%和56.1%，中位生存期為30.1個月。38名患者隨訪3個月後，28.9%、23.7%和42.1%分別達到完全緩解、部分緩解和病情穩定。1年精算局部控制率為82.8%。21名患者有肝內放療野外復發，4名患者有遠處轉移。1年肝內無復發生存率為50.5%，中位肝內無復發生存期為15.4個月。13名患者有3級或以上的毒性，其中8例為血小板減少症。一名患者出現三級肝腎毒性在2個月後死於肝功能衰竭和肝腎綜合徵。

結論：即使在曾接受治療的患者中，SBRT是有效和安全的，並具有良好的局部控制和極少的嚴重不良事件，但肝內（野外）復發率相對較高。

INTRODUCTION

According to the Hong Kong Cancer Registry in 2014, hepatocellular carcinoma (HCC) was the fourth most common cancer, with an incidence of 25.5 per 100,000 people, and a mortality rate of 21.9 per 100,000 people. Treatments for HCC include surgical resection, local ablation, and liver transplantation. Nonetheless, patients are often unsuitable for these treatments due to advanced disease, poor functional reserve of liver with underlying cirrhosis, donor shortage, or inaccessible location of tumour. For patients who are not mendable by curative treatment but have no major vascular thrombosis, transarterial chemoembolisation (TACE)[1,2] or radioembolisation using Yttrium-90 microspheres[3,4] have been shown to increase survival. Sorafenib is a multi-targeted receptor tyrosine kinase inhibitor and has been shown to improve overall survival of around 2.5 months.[5,6]

With the advent of new technologies, highly conformal radiation therapy such as stereotactic body radiation therapy (SBRT) can deliver higher doses of radiation to liver tumours in a small number of fractions, with the dose to adjacent normal tissues or organs optimally limited. The steep dose gradient achieved by intensity-modulation leads to delivery of a high dose to the target volume with tight conformity. SBRT can be an alternative to ablation / embolisation when these therapies have failed or are contraindicated.[7-9] This study reviewed the outcome and safety of SBRT for patients with HCC.

METHODS

This study was conducted in compliance with the Declaration of Helsinki. Patients who underwent SBRT for HCC between January 2013 and March 2016 at Queen Elizabeth Hospital were reviewed retrospectively.

Eligibility criteria for SBRT included (1) HCC lesions unsuitable for or failing after resection, local ablation, or TACE after discussion in the multidisciplinary team meeting; (2) relatively good liver reserve with uninvolved liver volume of preferably ≥700 ml; (3) maximal dimension of tumour ≤5 cm and ≤3 tumours; (4) HCC with no invasion to the surrounding structures and no extra-hepatic disease; (5) Eastern Cooperative Oncology Group performance score of 0 to 2; (6) adequate liver function with a Child-Pugh score of 5 to 7, bilirubin of <3x the upper limit of normal, alanine aminotransferase of <6x the upper limit of normal, international normalised ratio of <1.5; (7) adequate renal function with serum creatinine of <200 umol/l; (8) adequate haematological function with haemoglobin of >9 g/dl, neutrophils of >1.0 x 10^9/l, and platelets of >50 x 10^9/l; (9) no gross ascites or recent gastrointestinal bleeding in the preceding 2 months; (10) no prior external radiotherapy to the liver or upper abdomen and no prior radioembolisation; and (11) no active viral hepatitis. The multidisciplinary team comprised hepatic surgeons, interventional radiologists, hepatologists, and clinical oncologists. Patients included were either not suitable for further liver resection (surgical or medical contraindications) or had refused surgery.

Patients were immobilised in a supine position using a customised whole-body Vaclok with the arms raised. Liver motion was assessed using fluoroscopy under

free breathing. An abdominal compression device was applied if the craniocaudal movement of the dome of the diaphragm was ≥1 cm. Three-phase contrast-enhanced computed tomography and free-breathing four-dimensional computed tomography were used for SBRT planning. Diagnostic imaging was co-registered with the best liver-to-liver image registration, focusing on the targeted lesion.

Gross tumour volume was defined as arterial-enhancing lesions with washout on imaging. A margin was generally not added to clinical target volume for subclinical extension unless there was a high risk of microscopic disease (such as post-ablation cavity, post-TACE volume adjacent to gross tumour volume, and non-enhancing vascular thrombus). Internal target volume was determined by breathing motion on four-dimensional computed tomography. Planning target volume was expanded from the internal target volume by 0.5 cm to account for set-up uncertainties.

According to the dose fractionation scheme from Princess Margaret Hospital of University of Toronto,[7] SBRT was given through multiple static conformal beams or volumetric arc therapy at a dose of 30 Gy to 54 Gy in 6 to 7 fractions. In patients with centrally located lesions (i.e. away from luminal structures such as the stomach and bowels), a higher dose of up to 54 Gy in 6 fractions was given provided that the mean liver dose and normal tissue complication probability were within safety limits. In patients with lesions close to luminal structures or when the mean liver dose was above the safety limit (especially for multiple tumours in different liver segments), a lower dose of 30 Gy was given. Patient position at each fraction was confirmed using cone-beam computed tomography only.

The primary criterion for the SBRT plan was whether the 30 Gy isodose line could adequately cover the planning target volume, while conforming to the prescribed doses based on the Radiation Therapy Oncology Group 0915 protocol.[10] The prescribed isodose line should encompass at least 95% of planning target volume and 100% of the clinical target volume. Maximum dose should be ≤130% of the prescribed dose and located inside the planning target volume. The mean dose to the liver minus gross tumour volume should preferably be <14 Gy. Stringent dose constraints were followed to reduce the normal tissue complication probability to <5% (Table 1).

Patients were followed up at least once during SBRT for acute toxicities and then after 1 month and every 3 months for the first year, with physical examination, blood tests, liver and renal function tests, alpha-fetoprotein level, and imaging.

Tumour response was assessed using the modified Response Evaluation Criteria in Solid Tumours.[11]

Table 1. Normal tissue constraints in six fractions for plan acceptance.

Organ	Maximum dose (Gy)
Kidney	Mean <12
Spinal cord	<27
Stomach (0.5 ml per dose)	<32
Duodenum (0.5 ml per dose)	<33
Small bowel (0.5 ml per dose)	<34
Large bowel (0.5 ml per dose)	<36

Table 2. Patient and treatment characteristics (n = 39).

Characteristic	Value*
No. of males : females	31 : 8
Age (years)	72 (54-90)
Underlying liver disease	
Hepatitis B	33 (84.6)
Hepatitis C	2 (5.1)
Child-Pugh score	
A5	27 (69.2)
A6	8 (20.5)
B7	3 (7.7)
B8	1 (2.6)
Eastern Cooperative Oncology Group performance status	
0-1	38 (97.4)
2	1 (2.6)
Barcelona Clinic Liver Cancer stage	
A / B	35 (89.7)
C	4 (10.3)
Previous treatment	
Any	38 (97.4)
Resection	10 (25.6)
Transarterial chemoembolisation	33 (84.6)
Radiofrequency ablation	24 (61.5)
Percutaneous ethanol injection	11 (28.2)
Baseline alpha-fetoprotein (IU/ml)	19 (<2-7045)
No. of lesions treated	
1	29 (74.4)
2	5 (12.8)
3	5 (12.8)
Size of liver lesions (cm)	1.9 (0.6-5)
Gross tumour volume (cm^3)	12.2 (0.5-171.9)
Planning target volume (cm^3)	76.6 (11.6-428.7)
Uninvolved liver volume (cm^3)	978.3 (493.9-1752.8)
Mean liver dose (cGy)	1329.8 (332.5-1872.3)
Prescription dose (Gy)	54 (30-54)
Median biologically effective dose (Gy)	102.6

* Data are presented as median (range) or No. (%) of patients unless otherwise stated.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 4.02. Recurrence-free and overall survival rates were calculated using the Kaplan-Meier method.

RESULTS

31 male and 8 female patients aged 54 to 90 (median, 72) years were included (Table 2). 35 patients (89.7%) had Child-Pugh class A cirrhosis. 35 patients (89.7%) had viral hepatitis, of whom 33 were hepatitis B carriers (84.6%). One patient was treatment naïve and underwent SBRT as bridging therapy prior to liver transplantation. The remaining 38 patients (97.4%) had received prior loco-regional therapies including surgical resection, TACE, radiofrequency ablation (RFA), or percutaneous ethanol injection. The median tumour size was 1.9 (range, 0.6-5) cm. 29 patients (77.4%) had only one lesion.

After a median follow-up period of 17.8 (range, 2.6-35.1) months, 13 patients (33.3%) had died, including one patient who died after 2 months due to atypical radiation-induced liver disease (RILD). The 1- and 2-year overall survival rates were 73.6% and 56.1%, respectively, and the median overall survival was 30.1 months (Figure 1).

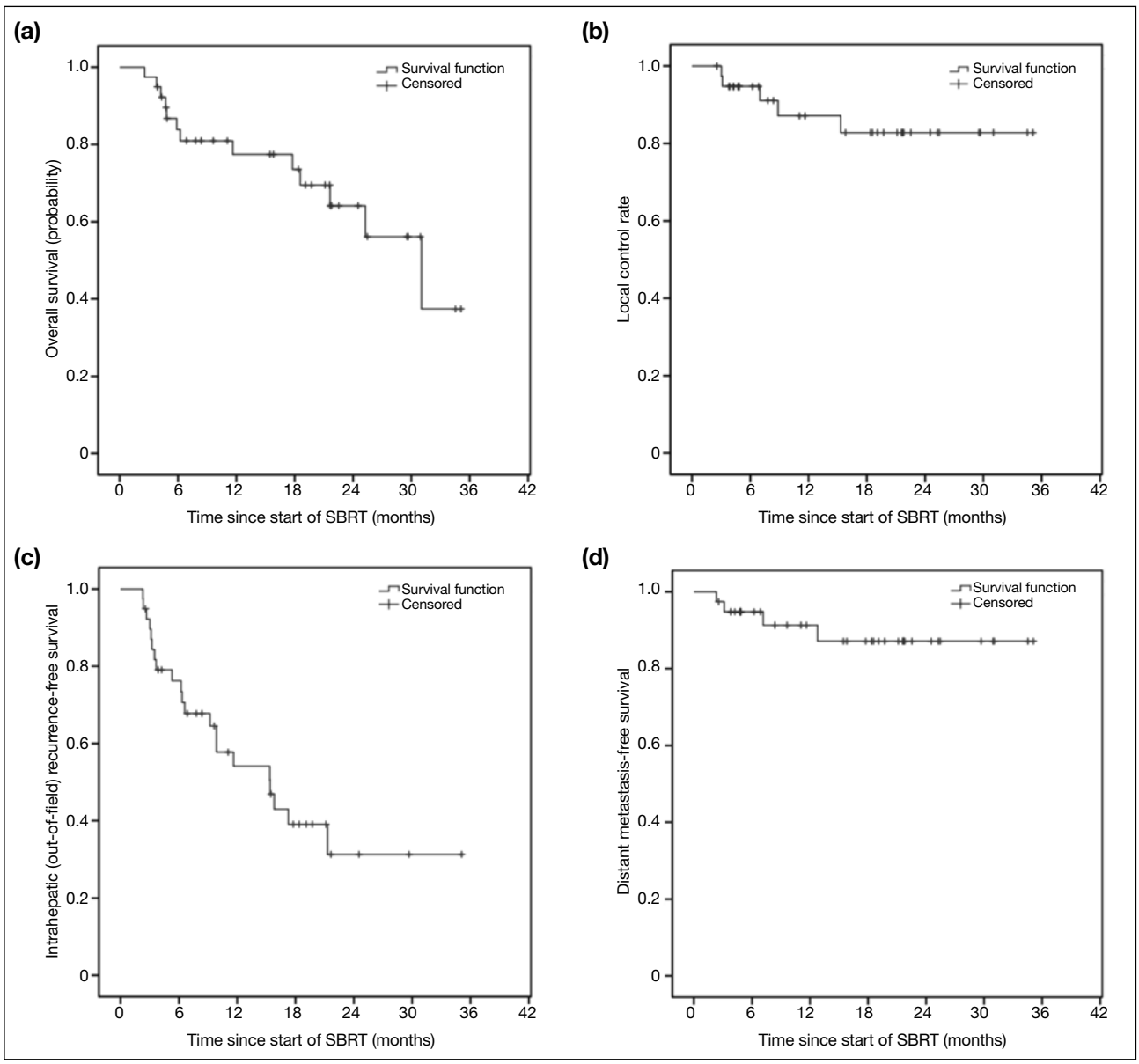

Figure 1. Kaplan-Meier curves showing (a) overall survival, (b) local control, (c) intrahepatic out-of-field recurrence-free survival, and (d) distant metastasis-free survival after stereotactic body radiation therapy (SBRT).

In 38 patients followed up at 3 months, 28.9%, 23.7%, and 42.1% had a complete response, partial response, and stable disease, respectively. The actuarial local control rate at 1 year was 82.8% (Figure 1). 21 patients had intrahepatic out-of-field recurrence, and four patients had distant metastasis. The 1-year intrahepatic recurrence-free survival was 50.5%, and the median intrahepatic recurrence-free survival was 15.4 months (Figure 1).

All patients completed the whole course of SBRT without interruption. No patient had major gastrointestinal toxicities (including bleeding and perforation) or typical RILD. 13 patients had grade 3 or above toxicity, of whom eight had thrombocytopaenia (Table 3). One patient had grade 3 hepatic and renal toxicities and died after 2 months due to liver failure and hepatorenal syndrome. The patient had hepatitis B virus cirrhosis and a history of right nephrectomy due to obstructive nephropathy secondary to renal stones. He also had a history of biliary stone at the proximal common bile duct complicated by obstruction and hilar stricture that required stenting. His baseline liver function was Child-Pugh class of A6 and baseline serum creatinine was 122 μmol/l, with estimated creatinine clearance of 71 ml/min by the Cockcroft and Gault formula. He presented with increasing malaise and jaundice 7 weeks after completion of SBRT. Biliary stent blockage was suspected in view of the elevated bilirubin level without parenchymal enzyme derangement. Endoscopic retrograde cholangiopancreatography revealed only a small amount of sludge passing, and the stent was revised with good drainage. Nonetheless, liver and kidney functions progressively deteriorated with increasing ascites, and atypical RILD was suspected. He was put on supportive care and died at 2 months.

DISCUSSION

Surgical resection is the standard of care for HCC. For patients in whom surgery is not appropriate, non-surgical loco-regional interventions such as regional arterial therapies (TACE or selective internal radiation therapy) or local ablative therapies (RFA, percutaneous ethanol injection, microwave ablation, cryoablation, or SBRT) are suggested.

The local control rate in our patients was comparable with that in other studies. One study reported 1- and 2-year local control rates of 87% and 74%, respectively.[7] Two studies from Korea and Japan also reported similar control rates.[8,9] In studies of RFA, the local control rate was 70% to 90% for small tumours[12-14] and significantly lower for tumours >3 cm.[15,16] In a study of RFA and SBRT, patients with tumours ≥2 cm treated with RFA had a lower rate of freedom from local progression.[17] Increasing tumour size predicted failure after RFA but not after SBRT.[17] The reduced efficacy of RFA for larger lesions is likely due to increasing distance from the heat source and incomplete coagulative necrosis, but the efficacy of SBRT is not tumour size dependent.[7,17] Efficacy of RFA is reduced when the tumour is close to major vessels due to the heat sink effect, but this does not occur in SBRT.

There is no consensus on the role of SBRT in the management algorithm for HCC. No randomised, phase III study has compared SBRT with other standard therapies. SBRT is indicated for tumours up to 10 cm in patients with early-stage HCC without vascular invasion or extrahepatic disease in whom liver transplantation and resection are contraindicated.[18] For tumours <2 cm, both SBRT and RFA achieve similar outcomes in local control and overall survival. Nonetheless, SBRT may be a better option for tumours >2 cm.[17] TACE is indicated

Table 3. Biochemical and haematological toxicities within first 3 months of treatment.

Toxicities	No. (%) of patients			
	All grades	Grade 3	Grade 4	Grade 5
Biochemical				
Creatinine	6 (15.4)	1 (2.6)	0	0
Albumin	10 (25.6)	1 (2.6)	0	0
Aspartate aminotransferase / alanine aminotransferase	12 (30.8)	1 (2.6)	0	0
Bilirubin	14 (35.9)	0	1 (2.6)	0
International normalised ratio	7 (17.9)	0	0	0
Haematological				
Haemoglobin	29 (74.4)	0	0	0
Leukocytes	26 (66.7)	1 (2.6)	0	0
Platelets	33 (84.6)	8 (20.5)	0	0

when RFA is not suitable or in patients with ≥5 tumours without invasion to major branches of vessels.

TACE and local ablative techniques (such as RFA, percutaneous ethanol injection, and microwave ablation) are commonly used as bridging therapies; the evidence to support SBRT as a bridging therapy remains limited. In our study, a 64-year-old man underwent SBRT as bridging therapy prior to liver transplantation. He had cryptogenic cirrhosis secondary to non-alcoholic steatohepatitis (Figure 2). He had no prior loco-regional therapy or resection. SBRT of 54 Gy was delivered in 6 daily fractions. He achieved a complete response and subsequently underwent transplantation with a cadaveric liver 15 months later. The resected liver showed cirrhosis only, with no residual malignancy. Local treatment is commonly used to minimise tumour progression while awaiting liver transplant, and to reduce potential post-transplant recurrence.[19] In a study comparing different loco-regional therapies as bridging treatments, SBRT, RFA, and TACE were comparable in terms of the drop-out rates of transplantation and postoperative complications, HCC recurrence after liver transplantation, and post-transplant survival.[20] Patients were treated with SBRT if they were ineligible for or had disease progression after TACE or RFA. Patients treated with SBRT had worse baseline liver function and a higher Model for End-stage Liver Disease score. SBRT can be a safe alternative bridging therapy to liver transplantation when TACE or RFA is not applicable or have failed in initial tumour control, or in patients with borderline liver function.[20]

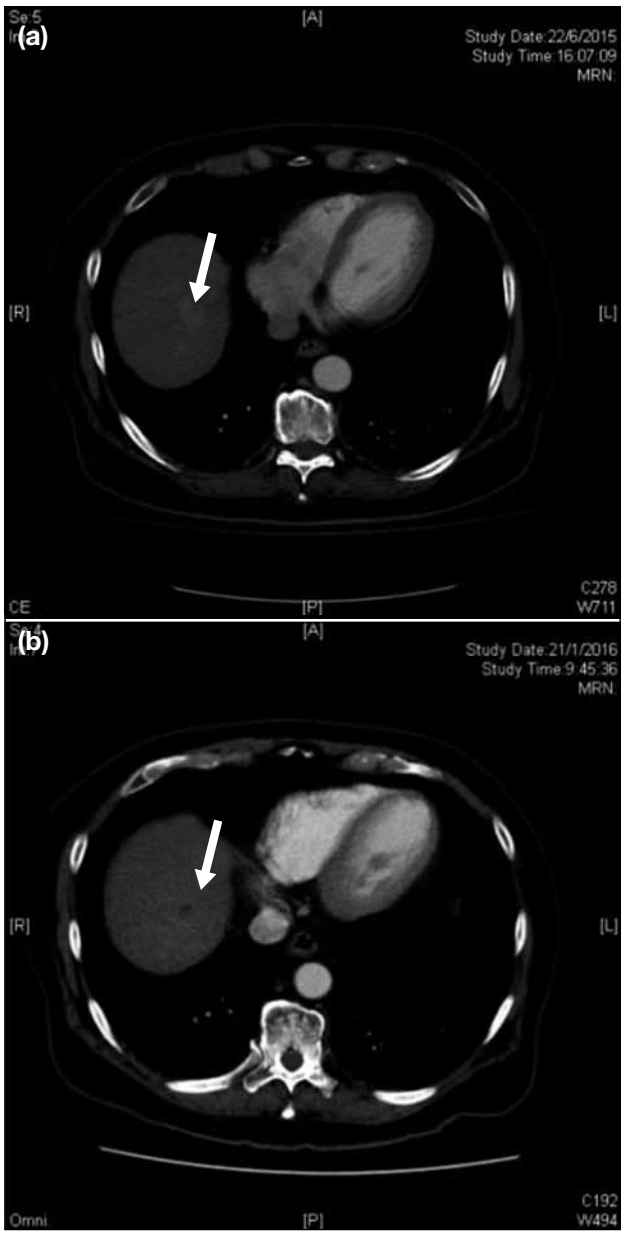

Figure 2. In a 65-year-old man with cryptogenic cirrhosis secondary to non-alcoholic steatohepatitis who underwent stereotactic body radiation therapy (SBRT) before liver transplantation, computed tomography showing (a) an arterially enhancing nodule (measuring 2.1 x 1.5 x 1.7 cm) with contrast washout in segment VIII of the liver near the dome (arrow) before SBRT, and (b) a hypodense lesion of 1 cm (arrow) that is hypo-enhancing in all dynamic phases 3 months after SBRT.

In our study, one patient died at 2 months from atypical RILD. RILD typically occurs at 4 to 8 weeks, but can occur as early as 2 weeks and as late as 7 months after radiotherapy.[21] Its clinical manifestations can be non-specific. Typical RILD usually occurs at 2 weeks to 3 months in patients with no underlying liver disease, with presentation of fatigue, abdominal pain, increased abdominal girth, hepatomegaly, anicteric ascites, and isolated elevated alkaline phosphatase disproportional to other liver enzymes. Pathologically, there is occlusion and obliteration of the central veins of the hepatic lobules, retrograde congestion, and secondary hepatocyte necrosis.[22] In contrast, atypical RILD typically occurs at 1 week to 3 months in patients with underlying liver disease, with presentation of jaundice and markedly elevated liver transaminases >5 times the upper limit of normal (levels commensurate with Common Terminology Criteria for Adverse Events grade 4) in the absence of typical RILD.[22] The underlying pathology of atypical RILD is unclear. Diagnosing RILD is by exclusion and non-invasive imaging findings are non-specific. A high index of suspension is needed to make the diagnosis. One confounder of RILD, especially in patients with underlying liver disease, is the occurrence of morbid events associated with the pre-existing

liver disease. It may be difficult to differentiate RILD from progression of cirrhosis or HCC. Moreover, hepatitis B reactivation can also lead to liver function derangement. Prophylactic antiviral therapy during SBRT is recommended to reduce the rate of post-radiotherapy reactivation or exacerbation of hepatitis B virus. As there is no effective treatment for RILD apart from supportive care, preventive strategies are crucial. Pre-existing liver dysfunction often predisposes patients to the development of RILD, as cirrhosis prevents the repair of radiation injury as well as cellular proliferation. Patients with Child-Pugh class B or C have a higher risk of RILD than those with Child-Pugh class A.[23-25] Other factors associated with a higher risk of RILD include hepatitis B status,[26] prior TACE,[24] concurrent chemotherapy,[27] portovenous tumour thrombosis,[24,28,29] tumour stage,[24] and male gender.[27] Increased mean liver dose is also associated with RILD. In a Korean study, a whole liver dose of >18 Gy was associated with significant progression of Child-Pugh class.[30] When a total liver volume was <800 cm^3 receiving <18 Gy, the probability of Child-Pugh class progression was abruptly increased. An uninvolved liver of >700 ml is a pre-requisite for SBRT. We had treated patients with uninvolved liver volume as low as 493 ml as long as the mean liver dose was within safety limits, and normal tissue complication probability of liver was estimated to be <5%. Low normal liver volume was not associated with increased risk of RILD.[25]

Future study should focus on the optimal dose fractionation and dose constraints to organs at risk. With the high incidence of intrahepatic out-of-field recurrence, SBRT may be combined with other regional or systemic therapies. The Radiation Therapy Oncology Group is conducting a phase III randomised trial of sorafenib versus SBRT followed by sorafenib for patients with liver cancer not suitable for transplant or other loco-regional therapies to determine any survival benefit of SBRT in addition of sorafenib.

CONCLUSION

SBRT is effective and safe even in previously treated patients. It results in good local control with minimal severe adverse events but a relatively high intrahepatic (out-of-field) recurrence rate.

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