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Large hepatocellular carcinoma treated with sequential SBRT and immunotherapy with anti-VEGF (Vascular Endothelial Growth Factor) therapy

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SUMMARY

Managing large solitary hepatocellular carcinoma (HCC) remains challenging as guidelines recommend a palliative approach given the general poor prognosis without accounting for variations in the underlying tumour biology. Surgical resection provides significantly better survival than other modalities for HCC, but only a small proportion of patients with large tumours qualify for surgical resection. Recently, with technological advances in radiation therapy, stereotactic body radiation therapy (SBRT) has emerged as an alternative treatment option for HCC . In this paper, we present a patient who was diagnosed with a 13 cm HCC with vascular invasion. SBRT was delivered as a locoregional therapy followed by immunotherapy with the outcome of complete pathological response observed on right hemi-hepatectomy.

BACKGROUND

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer worldwide and the second cause of cancer death after lung cancer in men.[1] In 80%–90% of cases, HCC occurs in patients with underlying liver cirrhosis with hepatitis B and C, the two main risk factors worldwide.[2] Treatment selection depends on characteristics of the tumour, severity of underlying liver dysfunction, age and other medical comorbidities.[3] Liver transplantation and tumour resection are the main curative treatment options. However, only a minority of patients fall into this category.[4] Stereotactic body radiation therapy (SBRT), developed using advances in external beam radiotherapy technology, has become an alternative treatment option for non-resectable HCC. In this case report, we present a case of large HCC with vascular invasion, deemed initially unresectable, which was treated successfully with SBRT and sequential immunotherapy plus anti-VEGF (Vascular Endothelial Growth Factor) therapy followed by surgical resection.

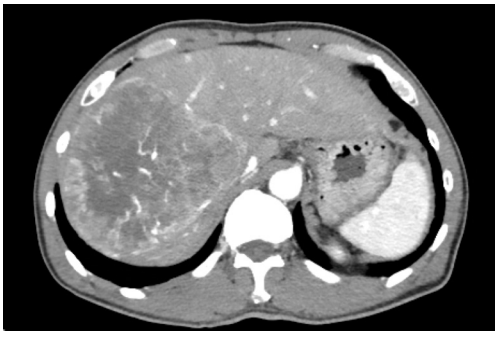

Figure 1 CT triple phase scan showing a large 13 cm hyper vascular mass with arterial enhancement and central necrosis in segment V, VI, VII, VIII.

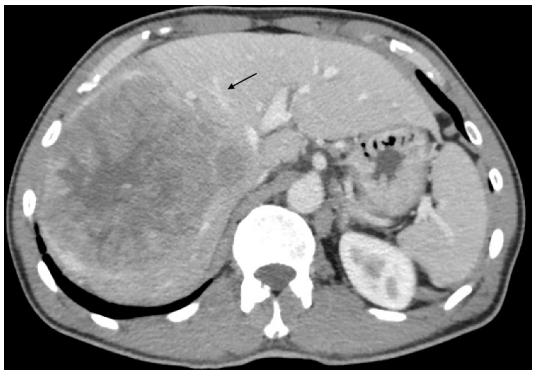

Figure 2 CT scan portal venous phase demonstrating venous invasion of the lesion with tumour thrombus in the middle hepatic vein (arrow).

CASE PRESENTATION

An ECOG 0 man in his 60s was referred to our liver clinic by his general practitioner with abdominal pain, weight loss and fatigue. An ultrasound subsequently demonstrated a large (127×111×99 mm) heterogeneous mass in the right lobe of the liver. The patient had history of untreated chronic hepatitis B and was undergoing annual surveillance overseas for HCC. During initial consultation, there was no evidence of chronic liver disease on examination, but he had a palpable liver.

INVESTIGATIONS

Laboratory tests showed bilirubin <4 μmol/L, ALP 76 unit/L, GGT 88 unit/L, ALT 66 unit/L, AST 142 unit/L, alpha fetoprotein 4.6 ug/L, positive HBsAg and HbeAb and non-reactive HBsAb in keeping with chronic hepatitis B infection.

Staging for the lesion included a contrast-enhanced CT scan of the liver, which demonstrated early features of liver cirrhosis and a 13 cm hypervascular mass with arterial enhancement and early venous washout (LIRAD-5). The lesion occupied segments V, VI, VII, VIII with evidence of tumour thrombus invading the middle hepatic vein. There were innumerable (>20) small hepatic arterioportal shunts (HAPS) in almost all segments of the liver (figures 1 and 2). A chest CT and bone scan showed no evidence of distant metastasis.

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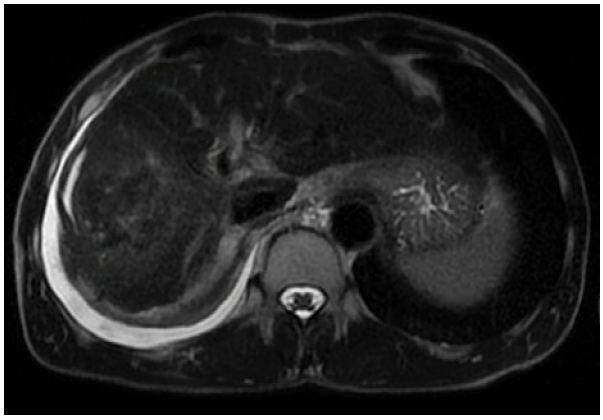

Figure 3 MRI liver (T2) demonstrating no enhancement of the lesion post-SBRT and immunotherapy. SBRT, stereotactic body radiation therapy.

TREATMENT

The case was discussed in the HCC multidisciplinary team meeting and due to the size and invasion to the main vascular structure, the lesion was deemed unresectable. The decision was made to treat the dominant lesion with SBRT followed by systemic treatment. The patient was also commenced on antiviral treatment with entecavir 0.5 mg/day. He received SBRT of 30 Gy in five fractions to the dominant lesion in segment VII and the nearby HAPS. On completion of SBRT, he was commenced on 9 cycles of atezolizumab (1200 mg/day intravenous infusion) and bevacizumab (15 mg/kg/day intravenous infusion). The patient tolerated the whole treatment plan and did not experience any complications from it.

One month after finishing SBRT and immunotherapy, MRI liver with contrast using primovist demonstrated a significant reduction of the size of the HCC from 13 cm to 7cm and no venous invasion (figure 3).

The case was further discussed in the HCC meeting and given the significant response of the disease, including resolution of tumour thrombus in the middle hepatic vein, the patient was deemed surgically resectable.

At laparotomy, the tumour in segment VII and VIII was densely adherent to the diaphragm with significant surrounding inflammation due to SBRT. Due to the size and position of the lesion, local resection was not possible; therefore, a right hemihepatectomy with resection of middle hepatic vein and the adherent diaphragm was performed. The surgery took 4 hours to complete with an estimated blood loss of 400 mL.

OUTCOME AND FOLLOW-UP

Day 2 following resection, the patient developed postoperative bleeding requiring an exploratory laparotomy where active bleeding from the stapler line on the right portal vein was identified and controlled. Subsequently, the postoperative recovery was uneventful, and the patient was discharged on day 8 post primary surgery.

Histopathology remarkably confirmed a completely resected 70 mm necrotic mass with no residual hepatocellular cancer and no evidence of vascular invasion. At 1-year follow-up, the patient remains clinically well with no evidence of disease recurrence on contrast-enhanced CT of the chest, abdomen and pelvis.

DISCUSSION

HCC is often diagnosed in intermediate or advanced tumour stages. Especially in advanced tumour stages, treatment options are limited, and there is no consensus concerning the best treatment option.[5] Tumour size is one of the main factors to determine the choice of treatment for HCC.[6] Large HCC is defined as tumour size >10 cm and there are limited data and little consensus on treatment strategies for such lesions.[6 7] As large HCCs are more prone to invade into local vasculature, they have higher possibility of metastasis and satellite foci are commonly found on diagnosis.[8] Surgery is the gold standard treatment for large HCCs, however, due to underlying liver cirrhosis and poor hepatic function reserve, the majority of the patients are ineligible for resection on diagnosis.[9]

It is in this challenging therapeutic landscape that SBRT has dramatically come to the fore as a groundbreaking neoadjuvant alternative for those deemed non-candidates for surgical intervention. Harnessing this technique, potent tumoricidal radiation doses are administered over a minimal number of sessions, precipitating targeted cell death.[10 11] Beyond its efficacy, SBRT stands out for its minimal toxicity footprint in HCC management,[12] showcasing outcomes that rival, if not surpass, other local treatment modalities or select (non-transplantation) surgical techniques.[13] The medical community has taken note, with an array of retrospective and prospective research underscoring the commendable local control rates associated with SBRT (table 1).[14–20] Reinforcing this, a 2020 study by Liu *et al* shed light on the impressive 94% freedom from local progression rate in patients classified under Barcelona Clinic Liver

Table 1 Prospective and retrospective studies showing outcome of SBRT

Study	Year	Patient number	Type of study	BCLC stage	Dose and fractionation	Follow-up	Outcome	Toxicity	Level of evidence
Kim *et al*[15]	2021	72	Randomised trial	0-C	66 Gy/10Fr (Proton)	51.6 m	2y LC: 92.8% 2y OS: 91.7%	None	II
Yoon *et al*[16]	2020	50	Prospective	0-A	45 Gy	47.8 m	5y LC: 97.1% 5y OS: 77.6%	4%	IV
Labrunie *et al*[17]	2020	43	Prospective	A-C	45 Gy	4y	2y LC: 94% 2y OS: 69%	5%	IV
Jang *et al*[18]	2020	65	Prospective	0-C	60 Gy	41 m	2y LC: 97% 2y OS: 84%	2%	IV
Park *et al*[19]	2020	290	Prospective	0-A	30–60 Gy	38.2 m	5y LC: 91.3% 5y OS: 44.9%	8.8%	IV
Mathew *et al*[20]	2020	297	Retrospective	0-D	27–60 Gy	19.9 m	3y LC: 91.3% 3y OS: 39%	16%	VI
Liu *et al*[21]	2019	32	Prospective	A-B	30–60 Gy	27 m	2y LC: 87% 27 OS: 81.3%	None	IV

BCLC, Barcelona Clinic Liver Cancer; LC, local control; OS, overall survival; SBRT, stereotactic body radiation therapy.

Cancer (BCLC) stage 0/A, and a notable 74% for those in BCLC B/C stages, all of whom underwent SBRT.[21] The exceptional efficacy of SBRT in this neoadjuvant setting can not be understated, offering newfound hope for patients once considered beyond surgical intervention.

Despite the advanced, poor prognostic presentation, locoregional therapy using SBRT followed by immunotherapy and anti-VEGF therapy achieved effective treatment of the large-volume disease in this patient. Following the liver resection with curative intent, the patient remains disease free after 12 months.

Following several preclinical studies indicating synergistic effect of radiotherapy and immunotherapy, clinical trials designed to further explore this question are currently under development worldwide.[22 23]

Learning points

- There are limited data and little consensus on treatment strategies of large hepatocellular carcinoma.
- Surgical resection provides better outcome in management of hepatocellular carcinoma (HCC)s, but large tumours are frequently non-resectable on diagnosis.
- The utilisation of stereotactic body radiation therapy (SBRT) in the neoadjuvant setting has demonstrated transformative outcomes to our patient with advanced HCC. As both a viable and efficacious alternative, SBRT not only expands the therapeutic arsenal against advanced hepatocellular carcinoma but also potentially paves the way for surgical intervention in cases once deemed insurmountable.
- SBRT followed by Immunotherapy plus anti-VEGF therapy appears safe and effective treatment combination with promising prospect in the neoadjuvant setting to improve resectability in large and locally advanced HCC.

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