HCC with PVT. Complete pathologic response following transarterial radioembolization: A case report

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide and management of this disease remains challenging in many cases. For patients with Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) disease, systemic therapy with Sorafenib has been the standard of care with median overall survival (OS) rates of less than one year. Patients presenting with portal vein tumour thrombosis (PVT) are considered to have a particularly dismal survival. For select patients, various loco-regional therapies may improve outcomes and even aid in downstaging to surgical resection or liver transplant. We present a case report of an adult male patient with a unilobar HCC with lobar portal vein invasion who underwent transarterial radioembolization (TARE) as a downstaging procedure. The patient had complete radiological response and then underwent a liver transplant. Complete pathological response was confirmed in the liver explant. At time of writing, almost 4 years following diagnosis, this patient was still alive with no evidence of recurrence. Patient selection is key when deciding on the optimal management of HCC and multidisciplinary team (MDT) involvement is encouraged.

Introduction

HCC is predicted to be the third to fourth most common cause of cancer-related mortality in the world[1,2]. The main risk factors for this disease are related to chronic inflammatory conditions of the liver, most commonly hepatitis B, hepatitis C, excessive alcoholic use, non-alcoholic fatty liver disease and aflatoxin exposure[3]. Successful management of this disease is challenging with many patients succumbing to their disease within months to years of diagnosis.

For patients with very early (0) or early (A) stage disease according to the BCLC guidelines[1], the disease is potentially curable by surgical resection or transplantation. Patients who are non-surgical candidates may be cured by various ablative procedures – thermal (radiofrequency and microwave), chemical (acetic acid or percutaneous ethanol injection) or cryoablation.[4] However, these stages represent the minority of cases of patients diagnosed with HCC. Furthermore, some patients who are potentially transplantable at diagnosis will upstage due to waiting times on transplant lists.

Unfortunately, most patients present with intermediate stage (B) or advanced stage (C) disease. The standard of care for these patients according to the BCLC treatment algorithm are transarterial chemoembolization (TACE) and systemic therapy, respectively.[1,5]

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Across the stages and in well-selected patients, loco-regional therapies may aid in downstaging disease to surgery or as a bridging therapy while awaiting transplant. These include the ablative procedures listed above, transarterial approaches including TACE, transarterial embolisation (TAE), drug-eluting bead chemoembolization (DEB-TACE) and TARE as well as contemporary external beam radiotherapy techniques such as volumetric modulated radiotherapy (VMAT) and stereotactic body radiotherapy (SBRT).[1,4,21,26]

For appropriate disease stages the therapies which have demonstrated a survival benefit include surgery (resection and transplant), ablation, TACE, sorafenib, lenvatinib and regorafenib and more recently the combination of atezolizumab with bevacizumab.[22]

Other ablative procedures, embolisation without chemotherapy and radiotherapy have shown tumouricidal effects but no proven survival benefit. Hence, selection of the most appropriate modality should be individualized, and given the plethora of treatment options available as well as the variable and often controversial benefits of the available modalities, discussion and management within a multidisciplinary team is advised.[1]

We present a case of a male patient with advanced stage (C) disease at presentation (with portal invasion) who underwent TARE as a downstaging procedure to liver transplant.

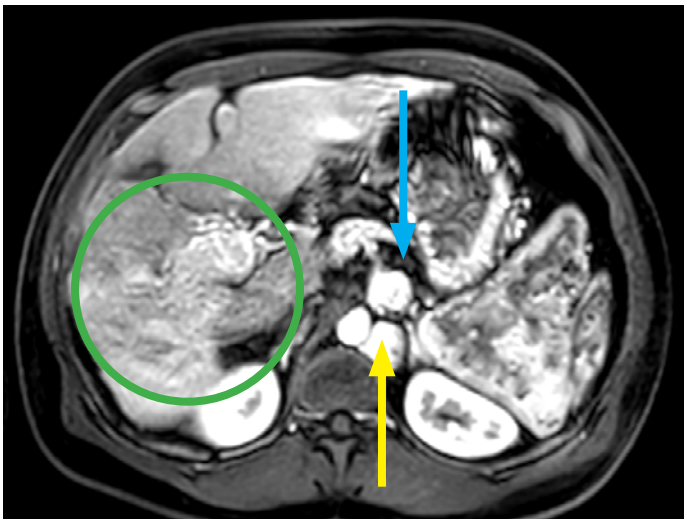
Case Description

Mr. PC was a 43-year-old male, PS 0, who presented in early 2017 with abdominal pain and bleeding oesophageal varices.

He had a history of long-standing hepatitis C which had been diagnosed in the early 1990s and was virally suppressed on serum HCV RNA quantitation PCR. He had showed sustained viral suppression post treatment with direct acting antivirals. Following work-up the patient was diagnosed with an advanced stage HCC with portal vein involvement. A liver biopsy in January 2017 revealed features of chronic active hepatitis with features suggestive of autoimmune hepatitis (AIH) and incipient cirrhosis. The AIH was considered to be related to his Hepatitis C.

An MRI study using liver specific contrast (Gadoxetate disodium, Primovist®, Bayer) was performed. The MRI of the liver revealed an infiltrative hypervascular tumour within the atrophic right lobe with invasion into the right portal vein (figure 1). The restricted diffusion signal of the infiltrative lobar tumour and the right portal vein tumour thrombus is shown in figure 2. The right portal vein tumour thrombus did not extend into the left portal vein or main portal vein (figure 3). A staging CT scan also done in January 2017 did not reveal any extrahepatic metastases. The MRI (figure 1) and CT scan showed an incidental 2.3cm splenic artery aneurysm and a left sided IVC. The patient's Child-Pugh score was A6 and the ALBI score was -1.89 (Grade 2). His AFP was elevated at 31.4µg/L (normal range 0-7). Of note his platelet count was low (83 x 10^9/L) due to hypersplenism because of portal hypertension. Liver and renal function laboratory studies were within normal limits.

Figure 1. Arterial phase T1 MRI study showing hypervascular infiltrative tumour of the atrophic right lobe with right portal vein invasion (green circle). Incidental splenic artery aneurysm noted (blue arrow) and left side IVC (yellow arrow) noted.



The patient was considered irresectable and was outside criteria for liver transplant. Following a multidisciplinary team discussion, it was decided to offer him an attempt at downstaging of the disease by TARE.

A planning hepatic arteriogram for the TARE demonstrated the tumour supply to be predominantly from the right hepatic artery with minimal supply from the segment 4 artery (fig 4). Coil embolization of the segment 4 artery was performed to promote redistribution of flow into the tumour to be entirely from the right hepatic artery (fig 5). The gastroduodenal artery was not embolised. A splenic artery angiogram confirmed the splenic artery aneurysm (fig 6). Technetium-99 labelled MacroAggregated Albumin (MAA) was injected into the right hepatic artery and a whole-body planar isotope study

Figure 2. DWI MRI showing restricted diffusion in the right lobe and right portal vein tumour (circle).

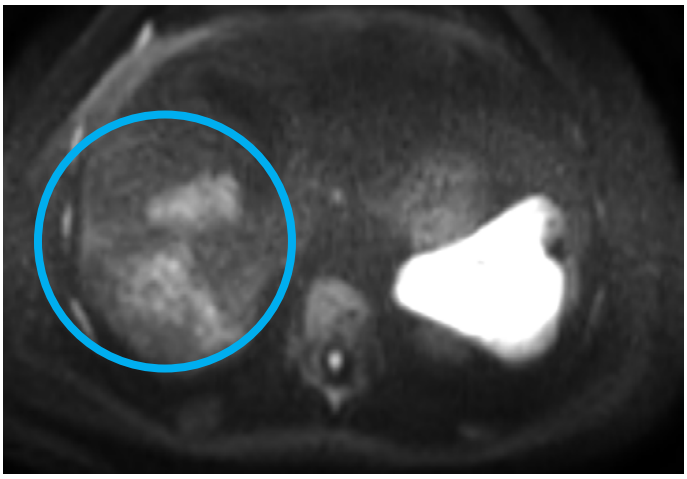


Figure 3. Venous phase T1 MRI showing normal enhancement of uninvolved left portal vein (arrow).

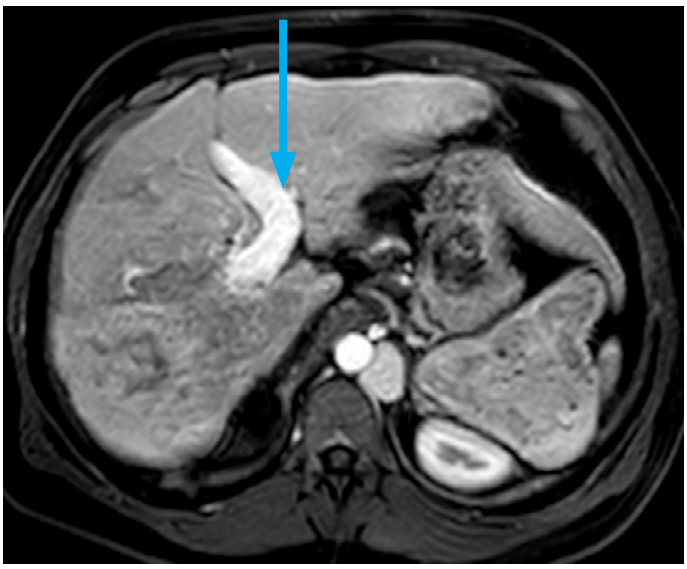


Figure 4. Common hepatic arteriogram showing anomalous branching pattern of the common hepatic artery and most tumour supply from the right hepatic artery with minimal contribution from a segment 4 artery.

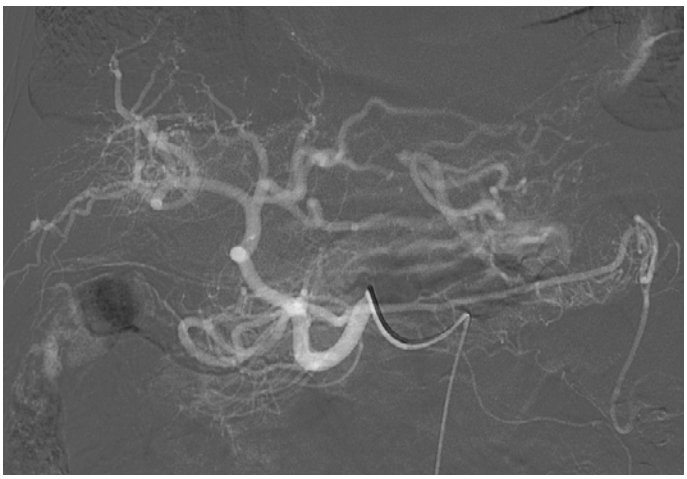


Figure 5a. Right hepatic arteriogram (early phase) showing coil in segment 4 artery (arrow) and the tumour vessels from right hepatic artery.

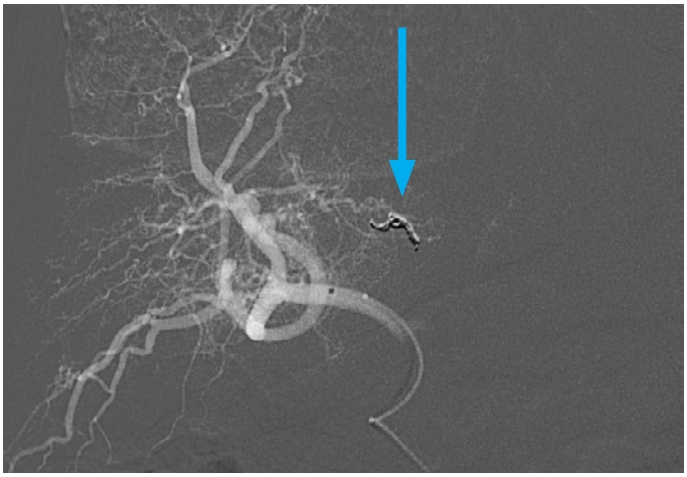


Figure 5b. Right hepatic arteriogram (late phase) showing tumour 'blush' in the right lobe and right portal vein tumour (circle).

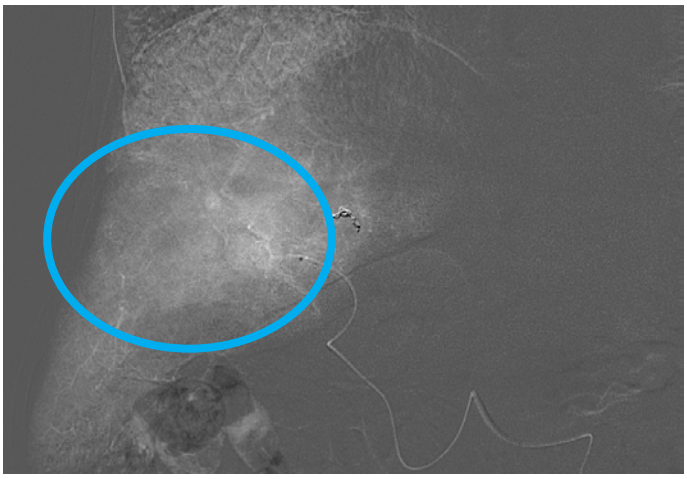
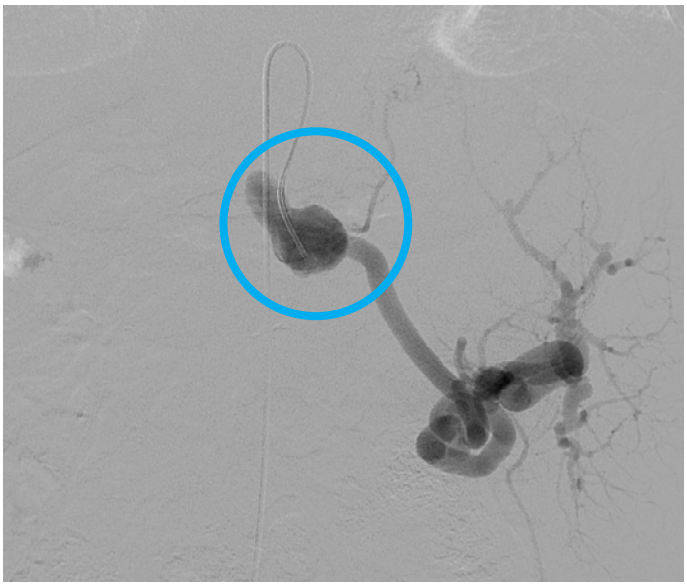


Figure 6: Splenic arteriogram showing the splenic artery aneurysm (circle)



performed. The lung shunt study from the isotope imaging revealed minimal shunting – percent shunt index of 3.2%. There was no evidence of extrahepatic (eg gastro-intestinal) isotope uptake.

The SIR-Spheres® radiation dose required was calculated by the Body Surface Area method based on the patient and tumour volume characteristics. The calculated activity for infusion was 1.80GBq. The patient underwent the TARE procedure in early March 2017. The interventional radiologist placed the infusion catheter in the right hepatic artery and the radiation dose was delivered by the radiation oncologist. The patient developed an access-site groin haematoma which was managed conservatively. The patient had no other procedure-related adverse effects.

A follow up MRI study was performed three months after the TARE which demonstrated a complete radiological response according to the EASL and mRECIST criteria. (figure 7).

Figure 7a. T1 late arterial phase MRI showing wedge shaped enhancement due to radiation induced parenchymal changes, tumour necrosis centrally (blue arrow) lobe and recanalised right portal vein (yellow arrow).

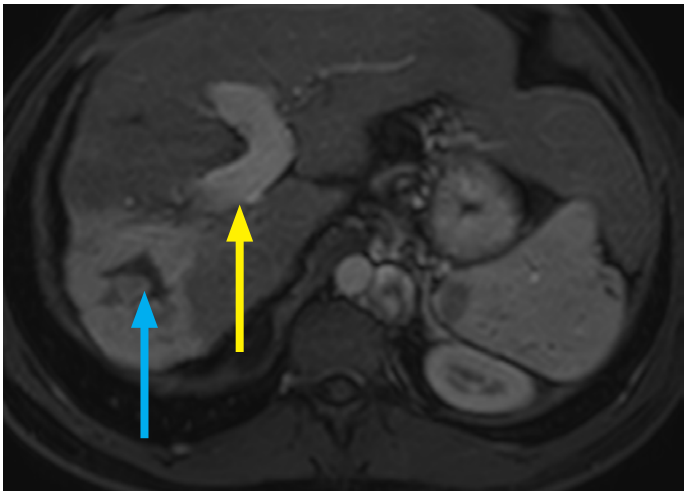
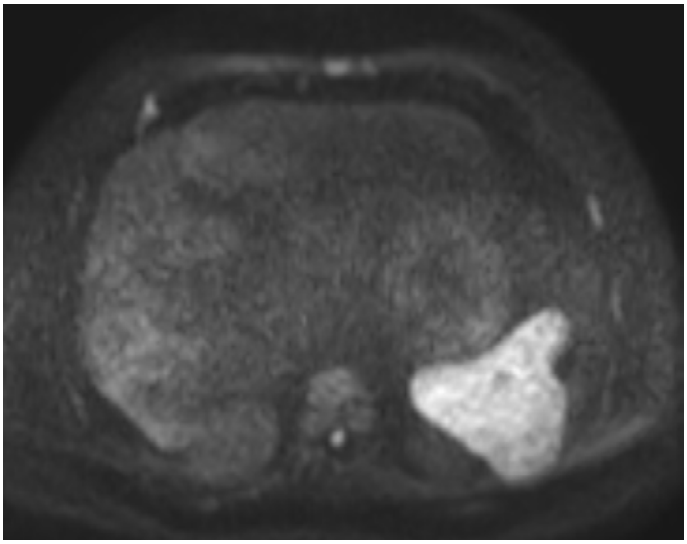


Figure 7b. DWI post TARE showing no restricted diffusion. Minimal signal, somewhat wedge shaped, is from T2 signal "shine through" of radiation induced changes



The patient was then was worked up for liver transplant. Transarterial coil embolisation of the splenic artery aneurysm was performed about two weeks before the liver transplant. In August 2017, a repeat AFP was 5.1kU/L. Mr. PC underwent liver transplant in September 2017 (about six months after the TARE) and histology revealed a complete pathological response and there was no evidence of HCC.

At time of writing the patient remained disease free with no evidence of liver or distal recurrence, almost 4 years following diagnosis.

Discussion

Transarterial radioembolization is a procedure whereby radioactive Yttrium-90 (^{90}Y) -labelled microspheres are injected directly into the feeding arteries of liver tumours.[5] This is possible due to a vascular anatomical advantage whereby liver tumours derive the majority (approximately 80%) of their blood supply from the hepatic arterial system whereas normal liver parenchyma receives most of their bloody supply by the portal system and about 20 – 30% from the arterial system.[6]

^{90}Y is a high-energy, β-emitting isotope with a half-life of 64.1 hours. It decays to stable Zirconium-90. Following administration about 95% of the dose is delivered in 11 days. The average energy of the particles is 0.9367MeV. The microspheres lodge preferentially in the microvasculature surrounding the tumour and induces tumour necrosis. The average tissue penetration is 2.5mm with a maximum range of 11mm.[7,8]

There are two commercially available microsphere devices, namely resin SIR-Spheres® (Sirtex Medical) and glass TheraSpheres™ (Boston Scientific). Resin SIR-Spheres® have an average size of 35-micron (range 20 – 60 micron) and in each 5ml vial there are 40-80 million spheres with a specific activity of 50Bq and these spheres are moderately embolic. Each vial contains 3GBq ^{90}Y at the time of calibration. Glass TheraSpheres™ are 20-30-micron particles with a specific activity of 2500Bq, there are 1.2 to 8 million microspheres per dose and they are minimally embolic.[7,8,9]

The study of ^{90}Y radioembolization for hepatic tumours started in the 1960s.[5] Over the decades TARE has been compared to various other locoregional and systemic therapies. It was found to demonstrate tumoricidal activity while being considered safe in well-selected patients for HCC across various disease stages, however, its use has also been controversial given the failure to demonstrate an overall survival benefit in several phase III studies comparing TARE to other therapies.[1,5,14,19,20] Despite this, and given the favourable safety profile, it is used in various instances across clinical stages for indications ranging from best local tumour control, to downstaging or bridging to surgery, to palliation.[5,27]

Efficacy and toxicity data

In 2008, a phase II study reported on by Kulik et al, 108 patients with unresectable HCC with and without PVT treated by TARE were evaluated.[10] The partial response (PR) was 42.2% using WHO criteria and 70% using EASL (European Association for the Study of Liver Cancer) criteria. Stable disease (SD) was present in 34.7% and 23.1% of patients had progressive disease (PD). There were no cases of radiation pneumonitis or radiation-induced gastritis.

In 2009, Salem et al analysed 291 HCC patients who underwent TARE and measured response rate, time to progression (TTP), survival and toxicity. Objective response rates (ORR) were 42% by WHO criteria and 57% by EASL criteria. TTP was 7.9 months for the entire study population (95% CI, 6-10.3). Survival was found to differ based on Child-Pugh status with Child-Pugh A having the longest survival compared to Child-Pugh B patients (17.2 vs 7.2 months; p=0.002). Patients with Child-Pugh B disease who also have PVT had the worst survival (5.6 months). Grade 1-2 toxicities included fatigue in 57%, abdominal pain in 23%, nausea and vomiting in 20% and anorexia in 15%. Grade 3-4 biochemical bilirubin toxicity occurred in 19%. The mortality rate at 1 month was 3% (n=9) and all the patients who died had PVT.

In 2013, Mazzaferro et al reported on a phase II study in HCC patients with intermediate and advanced disease.[12] In 52 patients the ORR was 40.4%. TPP was 11 months and OS was 15 months. The most common grade 3-4 toxicities included bilirubin toxicity of 16.9%, anorexia of 15.4% and nausea and vomiting at 9.6%. There was no pulmonary toxicity or gastroduodenal ulcers reported.

A 2016 meta-analysis of 17 studies reviewed 722 patients with HCC and PVT treated by TARE.[13] Complete response (CR) was 3.2%, PR was 16.5%, SD was 31.3%, PD was 28%. TTP was 5.6 months and OS was 9.7 months. The most common toxicities were fatigue (2.9-67%), abdominal pain (2.9-57%) and nausea and vomiting (5.7-28%) but in most cases these were mild.

In summary regarding safety, potential toxicities include a post-embolic syndrome which is usually mild, with fatigue, abdominal pain, nausea and fever. Biochemical toxicity with elevations of bilirubin and liver enzymes are mostly grade 1-2. Gastrointestinal ulceration, radiation-induced liver disease (RILD), cholecystitis and abscess formation are rare.

TARE compared to TACE

For BCLC B intermediate stage patients, TACE is currently the standard of care. Several studies comparing the two failed to demonstrate a survival benefit for TARE. In 2016, a meta-analysis by Lobo et al including over 550 patients from 5 studies comparing TARE to TACE[14] and found that although there was no survival benefit, when comparing the two modalities in terms of side effect profiles, TARE compared favourably with lower rates of post-embolisation pain.

A 2009 study by Lewandowski et al compared TARE to TACE in 86 patients for downstaging to transplant eligibility.[15] TARE resulted in significantly higher PR rates (61% vs 37%) as well as improved downstaging from United Network for Organ Sharing (UNOS) T3 to T2 (58% vs 31%). Furthermore, despite the absence of an OS benefit, in the phase II PREMIERE study, Salem et al in 2016 demonstrated a significantly longer median TTP of 26 months for TARE vs. 6.8 months for TACE (p=0.0012) in early-intermediate stage HCC and the authors concluded that TARE could hence potentially decrease transplant list dropout rates.[16]

Another advantage to TARE over TACE is in the setting of PVT. PVT has been considered a relative contra-indication to TACE due to an increased risk of liver toxicity whereas TARE has been shown to be well tolerated even in the setting of PVT. However, as noted before, the presence of PVT does influence prognosis and outcome in patients treated by TARE.[11,17,18]

TARE vs Sorafenib

Two phase III studies recently reported compared TARE to sorafenib. Both the SARAH study[19] (Vilgrain et al) and the SIRveNIB study[20] (Chow et al) failed to show an overall survival benefit for TARE, however, toxicity in the sorafenib arms in both studies were worse – most notably fatigue, abdominal pain, diarrhoea, skin reactions and haematologic effects – compared to TARE.

Evolving concepts and future directions

Current work in the field of radioembolization for HCC includes radiation segmentectomy in carefully selected patients as a method to safely allow for dose escalation to improve response rates and possibly outcomes. One study of 102 patients reported on by Vouche et al for solitary HCC lesions less than or equal to

5cm in size, radiation segmentectomy resulted in CR in 47%, PR in 39% and SD in 12% by mRECIST criteria, with a TTP of 33.1 months. In this study, a third of the patients proceeded to liver transplant and were found to have 90-100% necrosis, especially where the dose exceeded 190Gy.[23]

An interesting retrospective paper by Gordon et al in 2018 described the interesting concept of "Super Survivors" – patients who remain alive more than 3 years after treatment with TARE.[28] In this review, the authors identified 67 patients from their database of 1000 patients who underwent TARE between 2000-2017. Interestingly, the patients spanned BCLC stages A to D and Child-Pugh A to C. Multifocal disease was present in 40% of patients. Median overall survival was 67.5 months and the common variable the patients shared was an imaging response after TARE, suggesting that this might be a prognostic factor. Another notable finding was that patients who underwent segmental TARE were found to have longer OS compared to those undergoing lobar treatment – 80.2 vs 46.7 months (p=0.0024). These are interesting concepts which require further study.

Radioembolisation dosimetry is also an area of active interest given what is known about the tumoricidal effects of radiotherapy based on a dose-response curve noted in many tumour types. With technological advancements in recent years, there is an interest in measuring the radiation dose delivered to the tumour rather than the injected dose.[5] Technetium-99m Macroaggregated Albumin Single Positron Emission Computed Tomography (MAA SPECT/CT) is being used to calculate absorbed tumour dose, health injected liver dose and total injected liver dose. Some studies have shown differences in TTP and OS based on calculated tumour doses.[24,25] Radioembolisation dosimetry is an exciting area of investigation and may lead to further improvements in patient selection and precision medicine.

Conclusions

HCC has a poor prognosis for most patients diagnosed with this disease. Advanced stage disease (C) with PVT has a particularly dismal survival. Across the spectrum of disease stages, various surgical, loco-regional and systemic therapies may be appropriate. Careful patient selection within a multidisciplinary team is paramount to ensuring that the selected therapy results in increase in survival while maintaining the best possible quality of life for the patient. We present the case of a patient with advanced HCC and PVT who responded well to TARE and was able to undergo successful liver transplant. He was still alive at time of writing, almost 4 years following treatment.

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