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CASE REPORT

SIRT Combined with Targeted Therapy and Immunotherapy Achieves Sustained Complete Remission in Advanced Hepatocellular Carcinoma: A Case Report

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Background: Sorafenib was the standard systemic therapy for advanced hepatocellular carcinoma (HCC) for over a decade, but has largely been replaced by immunotherapy–based combinations. Current international guidelines recommend atezolizumab plus bevacizumab (A+T) or durvalumab plus tremelimumab (Dur/Tre) as first–line regimens for unresectable HCC. In the 5–year update of IMbrave150, A+T achieved an objective response rate (ORR) of 30% and a 5–year overall survival (OS) rate of 19%. In the Phase III HIMALAYA trial, Dur/Tre produced an ORR of 20%. By contrast, single–agent tyrosine kinase inhibitors (TKIs) such as sorafenib or lenvatinib yield a median OS of only 10–14 months. Median OS with locoregional therapies alone—transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC) and selective internal radiation therapy (SIRT)—range from 8 to 24 months, depending on baseline tumor burden and liver function. Even among responders to immune checkpoint inhibitors (ICIs), only 40–50% maintain durable responses; meanwhile, patients may also experience adverse events of varying severity, highlighting a substantial unmet need. Early–phase studies suggest that combining SIRT with systemic therapy can increase ORR to 40–60% while keeping grade 3–4 toxicities below 15%. Therefore, beyond survival, health–related quality of life (HRQOL) and treatment burden should be incorporated as key endpoints to evaluate the real–world trade–off between disease control and treatment burden.

Conclusion: This case indicates that, even with traditional relative contraindications, such as a high lung–shunt fraction (LSF) and low tumor–absorbed dose (TAD), SIRT may still serve as an "antigen–release platform", providing a foundation for sequential targeted therapy and immunotherapy, enabling deep remission in advanced HCC and creating conditions to maintain or improve HRQOL.

Keywords: health–related quality of life, HRQOL, hepatocellular carcinoma, HCC, immune checkpoint inhibitors, ICIs, immunotherapy

Introduction

Curative-intent therapies for early-stage hepatocellular carcinoma (HCC) include surgical resection, ablation and liver transplantation.[1] For locally advanced disease, intra-arterial approaches—including transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC) and selective internal radiation therapy (SIRT)—are commonly used to improve outcomes.[2,3] Since sorafenib first improved survival in advanced HCC in 2008, it remained the standard systemic therapy for more than a decade but has now largely been replaced by immunotherapy-based combinations.[4] The latest ESMO and ASCO guidelines recommend atezolizumab plus bevacizumab (A+T) or durvalumab plus tremelimumab (Dur/Tre) as preferred first–line systemic combinations, whereas lenvatinib and sorafenib remain alternative first–line tyrosine kinase inhibitors (TKIs) and achieve objective response rates of only 11–18%.[5,6] In IMbrave150, A+T

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achieved an mRECIST objective response rate of 30% and a 12-month overall survival rate of 67.2%.[7] In HIMALAYA, the 5-year overall survival rate was 19.6%.[8] With locoregional therapy alone, including TACE or SIRT, median overall survival ranges from 8 to 24 months depending on baseline characteristics.[9,10] By comparison, lenvatinib plus TACE yielded a median overall survival of 17.8 months in a single study.[11] Even among responders to immune checkpoint inhibitors (ICIs), only 40–50% maintain durable responses, with lower proportions in patients with a high tumour burden.[12] Early-phase studies suggest that SIRT, which can irradiate multiple intrahepatic lesions and may enhance tumour immunogenicity, achieves objective response rates of ≥40% with grade 3–4 toxicities of <15% when combined with ICIs or TKIs.[5,13–15] Nevertheless, a high lung-shunt fraction (LSF) or a low tumour-absorbed dose (TAD) can limit broader use. The present case addresses the evidence gap in patients with LSF ≥20% and low TAD after failure of multiple lines of therapy.

A 59-year-old man with advanced HCC received six cycles of HAIC and two sessions of TACE, alongside systemic A+T. Follow-up imaging showed intrahepatic tumour progression and new bilateral pulmonary metastases. The patient subsequently underwent SIRT and, 5 days later, started durvalumab plus donafenib. Four months after treatment initiation, intrahepatic tumour volume had decreased by 30%, α-fetoprotein (AFP) had fallen from 3839 ng/mL to 3.27 ng/mL, and protein induced by vitamin K absence-II (PIVKA-II) had declined from 5901.21 mAU/mL to 63.78 mAU/mL; pulmonary metastases also regressed. The patient ultimately underwent conversion surgery and has remained in complete remission on durvalumab maintenance therapy.

Case Presentation

A 59-year-old man presented to a local tertiary hospital with a 5-month history of upper abdominal pain. Abdominal MRI revealed a right-lobe hepatic mass measuring approximately 137×96 × 130 mm, highly suggestive of HCC, with invasion of the right anterior branch of the portal vein (Figure 1A–C). An ultrasound-guided percutaneous biopsy confirmed moderately to poorly differentiated HCC on histopathology. Chest MRI showed a small, well-circumscribed nodule in the dorsal segment of the right lower lobe, along with bilateral pulmonary fibrotic foci (Figure 2A). The disease was classified as Barcelona Clinic Liver Cancer stage C (BCLC C). The patient had chronic hepatitis B with cirrhosis and had

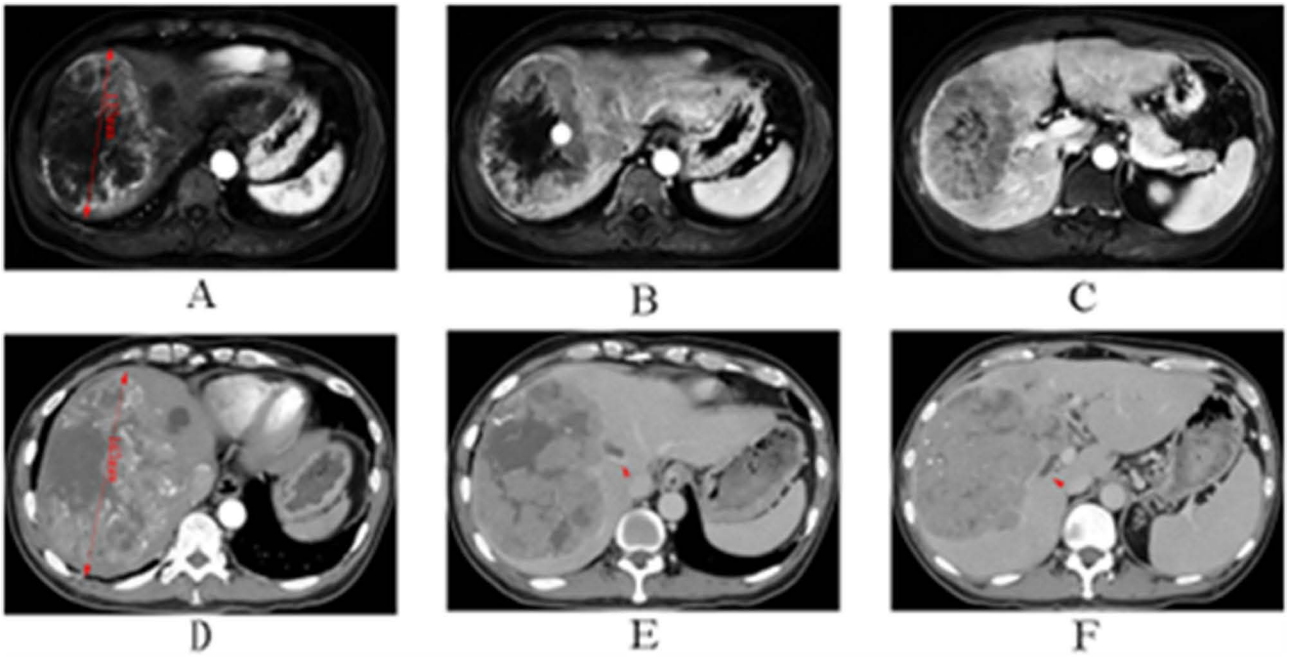

Figure 1 In (**A**), the bidirectional arrow indicates the tumour size at initial presentation, measuring approximately 137 mm. (**B** and **C**) show that neither the middle hepatic vein (MHV) nor the right hepatic vein (RHV) was involved before the initiation of therapy. In (**D**), the bidirectional arrow indicates the tumour size after disease progression following multiple lines of therapy, measuring approximately 165 mm. In (**E**), the arrow indicates MHV invasion after multiple lines of therapy. In (**F**), the arrow indicates RHV invasion after multiple lines of therapy.

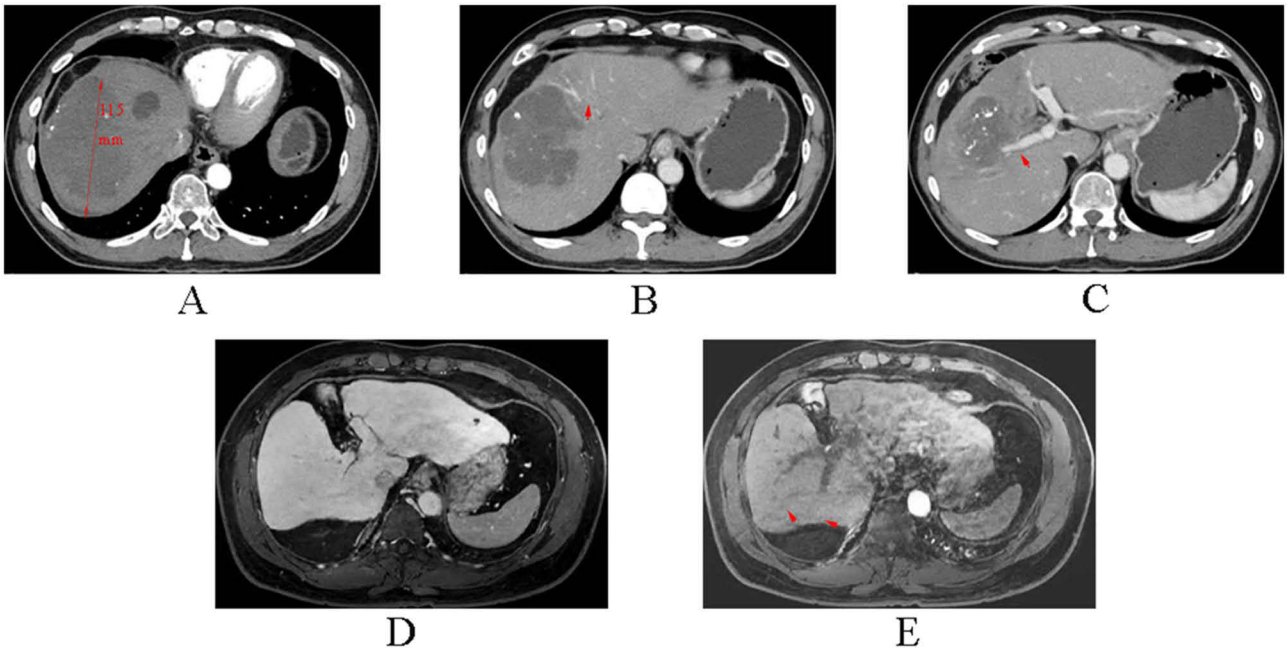

Figure 2 In (**A**), the bidirectional arrow indicates the tumour size after SIRT, measuring approximately 115 mm. In (**B**), the arrow indicates improvement in middle hepatic vein (MHV) involvement after SIRT. In (**C**), the arrow indicates improvement in right hepatic vein (RHV) involvement after SIRT. (**D**) shows the tumour status at follow-up after surgical resection. In (**E**), the arrow indicates improvement in the right hepatic vein branch at postoperative follow-up (the MHV had been resected).

been taking entecavir (0.5 mg once daily) regularly since diagnosis. He also had a 30-year smoking history. No other HCC-related risk factors were identified.

Four days after the biopsy at the outside hospital, the patient was transferred to our centre and started the first cycle of HAIC with oxaliplatin (85 mg/m^2) plus raltitrexed (3 mg/m^2). Six cycles were administered at 3–4-week intervals, and two sessions of TACE were performed approximately 4 weeks apart. The first TACE used drug-eluting microspheres loaded with epirubicin (60 mg), whereas the second used epirubicin (30 mg) combined with 10 mL of iodized oil (Lipiodol). Four weeks after the final TACE, follow-up abdominal CT showed tumour enlargement compared with prior imaging, with a massive right-lobe lesion measuring approximately 165×120 × 151 mm and portal vein tumour thrombus involving the main trunk and right branch (Figure 1A–F). Chest CT revealed newly developed multiple solid nodules in both lungs, consistent with pulmonary metastases (Figure 3A and B). Liver function was Child–Pugh class A, ECOG performance status was 1 and the Model for End-Stage Liver Disease (MELD) score before SIRT was 8. Although the disease was classified as BCLC C, the marked intrahepatic progression and new pulmonary lesions prompted escalation of treatment. Before SIRT, serum AFP was 3839 ng/mL and PIVKA-II was 5901.21 mAU/mL. Planning 99mTc-MAA scintigraphy showed an LSF of 20.1% and tumour-to-normal liver uptake ratios (TNR; expressed as TAD/NLTD) of 11.2, 9.1 and 12.5. Partition-model dosimetry recommended an injected activity of 2.0 GBq, targeting a TAD of 70 Gy. After informed consent, super-selective catheterization of the right superior, right inferior and middle hepatic arteries was performed on 10 April 2024, and 2.3 GBq of resin microspheres (SIR-Spheres®, 20–60 μm) was delivered. No radiation pneumonitis, gastroduodenal reflux or grade ≥2 hepatotoxicity occurred during the procedure or within 30 days. On day 5 after SIRT, systemic therapy with durvalumab (1500 mg every 3 weeks) plus donafenib (0.2 g twice daily) was initiated. Approximately 4 months after SIRT, follow-up abdominal MRI showed that the dominant right-lobe lesion had decreased in maximum diameter from 165 mm to 115 mm (30% reduction), with central necrosis and improved involvement of the middle and right hepatic veins (Figure 2A–C). AFP decreased from 3839 ng/mL to 3.27 ng/mL and PIVKA-II from 5901 mAU/mL to 63.8 mAU/mL. Chest CT showed regression of most pulmonary nodules (Figure 3C). 18F-FDG PET–CT demonstrated mixed-density masses with cystic and necrotic changes in segments VIII and IVa, as well as multiple small lung nodules; none showed increased glucose uptake, indicating no hypermetabolic metastases. The patient subsequently underwent right hepatectomy, portal vein thrombectomy and cholecystectomy. Postoperative pathology showed extensive

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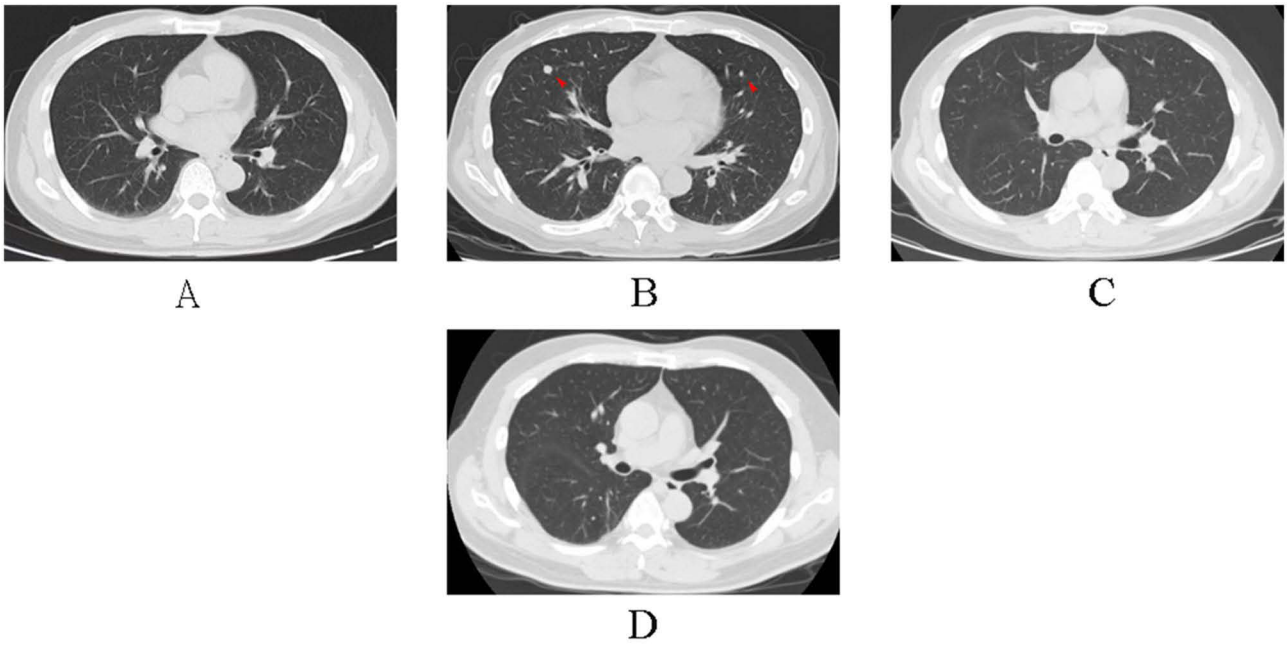

Figure 3 (**A**) illustrates the absence of pulmonary involvement at baseline (initial presentation). In (**B**), the arrow indicates multiple solid pulmonary nodules that developed after several lines of systemic therapy, which were considered metastatic lesions. (**C**) demonstrates multiple solid nodules in both lungs after SIRT, most of which have decreased in size or number compared with the previous scan. (**D**) shows follow–up findings after surgical resection: multiple solid and ground–glass nodules in both lungs, fewer than on the prior examination.

tumour necrosis with fibrous hyperplasia and chronic inflammatory infiltration; the tumour necrosis rate exceeded 90%, and necrotic tissue within the vascular thrombi was densely infiltrated by histiocytes without viable tumour cells, consistent with a pathological complete response after SIRT (Figure 4A). Postoperatively, durvalumab maintenance (1500 mg every 3 weeks) was continued and donafenib was discontinued. During maintenance, no grade ≥3 treatment-related adverse events occurred; only grade 1 fatigue was reported and resolved with rest.

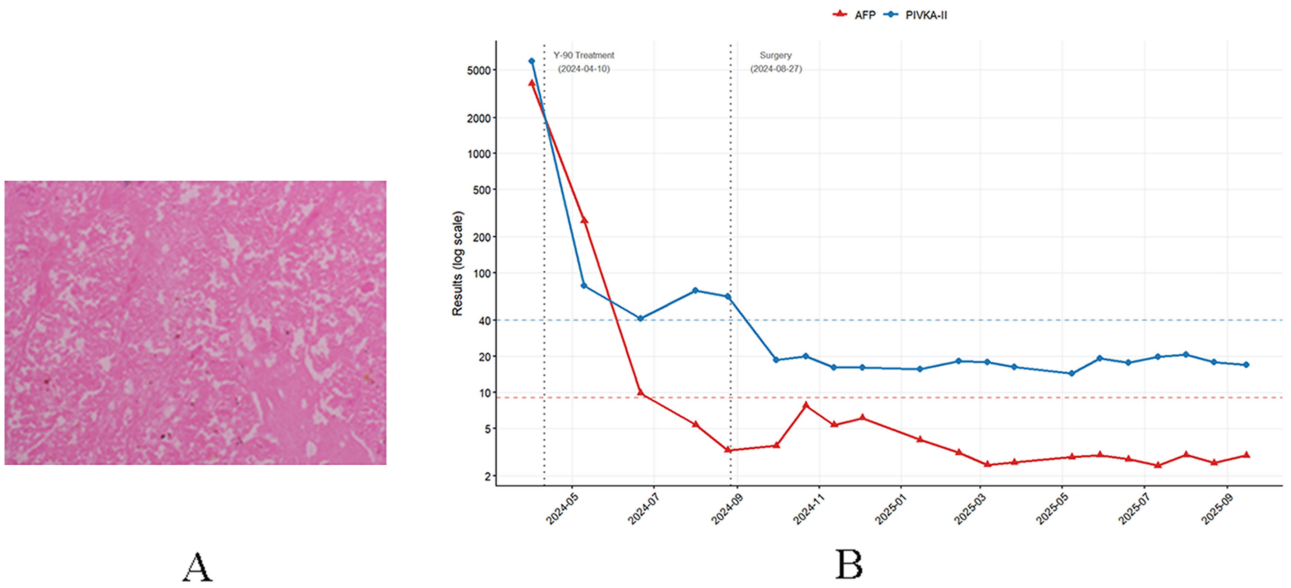

Figure 4 (**A**) shows that approximately four months after SIRT, no definite viable tumour cells were observed microscopically, which is consistent with a pathological complete response following Y–90 therapy. (**B**) shows the dynamic changes in tumour markers before SIRT and during postoperative follow–up. Dashed lines indicate reference ranges: AFP (normal: 0–9 ng/mL); PIVKA–II (normal: 0–40 mAU/mL) Vertical dotted lines Indicate treatment time points.

Seventeen months after SIRT, follow-up abdominal MRI showed postoperative changes consistent with partial right hepatectomy. A patchy, well-demarcated low-signal area measuring 58×34 × 35 mm was noted in the resection bed (Figure 2A–E) and was interpreted as postoperative change. Chest CT showed multiple solid and ground-glass nodules in both lungs, fewer than on the previous examination (Figure 3A–D). Postoperatively, serum biochemical parameters remained within normal limits, and histopathological examination of the tumor confirmed a pCR. (Figure 4A and B).

Discussion

Current international guidelines recommend an LSF of <20% and a TAD of ≥100–120 Gy during pre-procedural planning for SIRT to balance efficacy and safety.[16,17] In this patient, the LSF was 20.1% and the estimated TAD was ~70 Gy, which would be considered suboptimal. However, given concomitant pulmonary metastases and failure of multiple lines of systemic therapy, SIRT was performed after thorough counselling. No radiation pneumonitis or grade ≥3 adverse events were observed. β-particles emitted by yttrium-90 not only exert direct cytotoxicity against tumour cells but may also induce immunogenic cell death, thereby activating the dendritic cell–T cell axis and potentially eliciting abscopal effects.[18]

Yttrium-90 is an almost pure β-emitter. Resin microspheres used in clinical practice (for example, SIR-Spheres®, 20–60 μm in diameter) are delivered via the hepatic artery and preferentially lodge within tumour microvasculature. The emitted β-particles (mean tissue penetration, 2.5 mm; maximum, 10.3 mm) can directly kill tumour cells and may also trigger immunomodulatory effects.[18] Combining locoregional treatment with systemic immune-based therapies has emerged as a key strategy to improve outcomes in advanced HCC. SIRT can induce immunogenic cell death through β-irradiation, leading to the release of damage-associated molecular patterns such as ATP and HMGB1. SIRT has also been reported to increase the proportion of PD-1-positive CD8+ T cells and the density of intratumoural CD8+ T-cell infiltration, which may contribute to an abscopal effect (regression of distant, non-irradiated metastases).[19] ICIs block PD-1–PD-L1 signalling, reverse T-cell exhaustion and can amplify the antitumour immune response initiated by SIRT, thereby improving control of both intrahepatic disease and extrahepatic metastases.[20–22] This rationale supports deep responses and, in selected patients, subsequent conversion surgery.[15,23] However, SIRT-induced immunogenic cell death may be attenuated by intratumoural hypoxia. Hypoxia reduces ATP release and calreticulin exposure—key steps in immunogenic cell death—thereby limiting dendritic cell antigen uptake; in parallel, hypoxia upregulates hypoxia-inducible factor 1α, promotes PD-L1 expression on tumour cells and tumour-associated macrophages, and suppresses CD8+ T-cell activation.[24] Preclinical evidence suggests that donafenib may alleviate hypoxia through two complementary mechanisms: inhibition of VEGF signalling to reduce abnormal, leaky tumour vessels and promote vascular normalization; and inhibition of PDGFR signalling to suppress cancer-associated fibroblast activation and fibrosis. These effects may relieve hypoxia-mediated suppression of SIRT-induced immunogenic cell death and synergistically enhance dendritic cell maturation and CD8+ T-cell infiltration.[24,25] Previous reports showing no significant benefit of Y-90 plus TKI therapy may reflect the limited ability of VEGFR-dominant TKIs (for example, sorafenib) to reverse cancer-associated fibroblast-driven stromal fibrosis and hypoxia, as well as reduced adherence due to hand–foot skin reaction, diarrhoea and other adverse effects in 30–40% of patients.[26,27] By contrast, the triple combination of SIRT, donafenib and ICIs may establish a synergistic cascade of antigen release, immune activation and immune maintenance: Y-90 promotes antigen release and dendritic cell priming; donafenib alleviates hypoxia and reinforces immunogenic cell death; and ICIs sustain CD8+ T-cell cytotoxicity by relieving PD-1-mediated inhibition. Together, these modalities may act synergistically to achieve deep remission in advanced HCC.[28–30]

The sequence and timing of drug administration are likely to be critical determinants of efficacy in SIRT-based regimens that combine targeted therapy and immunotherapy. Studies have reported that an "ICIs-first" strategy achieved an objective response rate of 68%, substantially higher than the 21% reported with a "SIRT-first" approach.[13,31,32] However, other studies using a "SIRT-first" sequence still reported clinical benefit, suggesting that treatment order may be an important source of heterogeneity in outcomes.[23,33,34] With respect to timing, most studies initiated ICIs 1–6 weeks after SIRT, with the longest interval reported being 90 days. Rivoltini et al used T cell kinetic monitoring and found that starting ICIs within 1 month after SIRT could reverse exhaustion of PD-1-positive T cells and prolong the immune

response from 2 weeks to 8 weeks.[28] In the present case, durvalumab was initiated 5 days after SIRT, which falls within this early post-SIRT window and may have contributed to the deep remission observed.

In addition to survival benefit, the impact of treatment on health-related quality of life (HRQOL) and treatment burden is of substantial real-world importance. Previous studies suggest that, among patients with HBV-related HCC, HRQOL deteriorates most markedly as the disease progresses to the end stage, and the overall health utility in the HCC stage is approximately 0.749 (95% CI, 0.678–0.819).[35] From the perspective of the trade-off between treatment outcomes and quality of life, whether a therapy can delay disease progression and reduce the burden of decompensation-related symptoms (for example, recurrent hospitalizations and declining physical function) directly influences the extent to which patients can maintain function and well-being. Conversely, treatment-related deterioration in liver function or worsening symptoms may offset the benefits gained from tumour control.[36] Therefore, when comparing SIRT, TACE and systemic therapy, HRQOL should be considered alongside survival outcomes as a key endpoint and evaluated within a standardized framework of tumour stage and liver function stratification, to more accurately capture the real-world trade-off between disease control and treatment burden.[37–39]

The clinical development of SIRT combined with targeted therapy and immunotherapy for HCC remains at an early stage. Although prospective trials and real-world data support its feasibility, there is still no international consensus on several key issues, including: (1) the optimal systemic regimen (for example, selection of PD-1 versus PD-L1 blockade within ICIs); (2) radiological and pathological criteria for conversion surgery (such as thresholds for tumour necrosis); (3) sequencing strategies in patients with different hepatic functional reserve (Child–Pugh A versus B); and (4) practical cut-offs for treatment planning, such as LSF >20% and TAD <100 Gy. In the present case, the triple regimen of SIRT, donafenib and durvalumab achieved durable complete remission in a patient with high LSF and low TAD, offering clinical insights into these unresolved questions; however, large prospective studies are needed for validation.

Ethics Approval and Consent to Participate

Ethics approval for publication of the case details was granted by the Ethics Committee of The First Affiliated Hospital of Jinan University. Written informed consent was obtained from the patient described in this report.

Consent for Publication

Written informed consent for publication of this case report and accompanying images was obtained from the patient. The consent form was provided in the patient's native language (Chinese) and translated into English for editorial review. The patient understood that direct identifiers would be removed, but complete anonymity could not be guaranteed due to the unique nature of the case.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest related to this work.

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