



Insights into treatment for hepatocellular carcinoma with tumor thrombus in the inferior vena cava or right atrium

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Hepatocellular carcinoma (HCC), one of the most common liver cancers, often has a poor prognosis when it involves macrovascular invasion. Oncological emergencies including pulmonary embolism, heart failure, and even sudden death could happen when it develops a tumor thrombus (TT) in the inferior vena cava (IVC) or right atrium (RA), indicating an exceptionally grim prognosis (1). Although systemic therapy is the only standard treatment recommended by guidelines (2), other treatment modalities are explored including surgery, radiotherapy, etc. in some centers. Surgery, as the only potential curative treatment, has been explored in several selected cases. A case of long-term survival of 15 years and cancer-free survival of 9 years was reported by surgical resection with a heart-first approach under cardiopulmonary bypass (CPB) (3), suggesting that aggressive surgery together with multidisciplinary treatments might achieve long survival. However, due to the aggressiveness and challenge of surgical resection-massive resection area, potential significant blood loss, and bypass needed, surgical resection is applied in very limited centers. Nevertheless, safety, efficacy, and long-term survival benefits for these patients are poorly investigated.

In a substantial effort to shed light on this challenging

scenario, Ichida *et al.* (4) carried out a large-scale nationwide study in 23 institutions in Japan with experience in performing liver resection for HCC patients with TT. A total of 119 HCC patients with TT in the IVC or RA, including 49 with type I TT, 42 with type II TT, and 28 with type III TT, were included in this study. Surgical procedures varied among these subgroups, with a majority of patients undergoing major hepatectomy. In some cases, simultaneous resections of other organs such as the diaphragm, adrenal gland, and lymph nodes were also performed. Nevertheless, due to the complexity of Type III TT removal, CPB was more frequently used during procedures in patients with Type III TT. Importantly, no significant difference in the frequency and severity of surgery-related complications was observed, although one surgery-related death was observed in the type III group, suggesting that it is safe to receive surgery in experienced centers with skillful hands. In terms of survival, the median survival time was 2.47 years in the type I group, 1.77 years in the type II group, and 1.02 years in the type III group, respectively. Although no statistically significant difference was observed, Type III patients had the shortest median survival. The median time to recurrence was similar across

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all three groups. Furthermore, several risk factors for survival were revealed, including an indocyanine green retention rate at 15 minutes (ICG R 15) >15% and the presence of ≥ 3 tumors. CPB use and ≥ 3 tumors were identified as risk factors for recurrence. Interestingly, they also demonstrated that noncurative resection for HCC with TT, followed by further curative therapy in the form of resection, radiofrequency ablation (RFA), or systemic therapy, had extended survival, indicating that noncurative resection with additional therapy might be a viable treatment option for these patients.

This study represents the largest investigation into the postoperative outcomes of HCC with TT in the IVC or RA. Given the rarity of this disease, a multicenter survey, as employed in this study, appears to be the optimal study design for acquiring data relevant to the consideration of surgical indications and treatment strategies. Although previous studies compared outcomes between surgical and nonsurgical treatments for HCC with TT in the IVC or RA (5), the present study specifically focused on surgical outcomes for these patients, taking into account the location of TT, and demonstrated that surgical intervention should be contemplated in Type I and II groups without identified risk factors while the prognosis of Type III with risk factors was notably poorer. Additional investigations, including assessments of the effectiveness of adjuvant therapies utilizing innovative agents, are crucial to enhancing postoperative outcomes for these specific patient populations.

In the real scenario, multidisciplinary treatments, including surgery, transcatheter arterial chemoembolization (TACE), radiotherapy, and systemic therapy are often offered to these patients. TACE is the most commonly used procedure for advanced HCC. Chen *et al.* have compared the efficacy of surgery and TACE and found that the median time in surgery was 6.9 months longer than that in the TACE group (20.9 *vs.* 14.0 months, $P < 0.05$), suggesting that surgery is the better option for HCC patients with TT (6). Moreover, a study also compared the efficacy of surgery and intensity-modulated radiation therapy (IMRT) and revealed that the overall survival and recurrence-free survival rates were significantly higher for patients with TT receiving surgery than those who received IMRT (7). However, when TT develops into IVC, similar survival outcomes were obtained after surgery and IMRT (7), suggesting that radiotherapy could be an efficient treatment for patients with TT in IVC. Considering the long course of IMRT, which usually takes more than 5 weeks,

stereotactic body radiotherapy (SBRT) is now applied in various cancers, which delivers a larger dose of radiation to the target, shortens the treatment course, and finishes in 5 days (8). In 2019, we reported an HCC case with extensive TT in IVC and RA successfully treated by SBRT with no severe adverse effects encountered (9). Contrast-enhanced magnetic resonance imaging one month after SBRT demonstrated no thrombus in IVC and RA, and the huge lesion on the right lobe also shrank. It suggests that SBRT towards TT could successfully control thrombus and prevent oncological emergencies and offers opportunities to receive subsequent treatments. With this successful experience, we carried out a study to further investigate the local efficacy and safety of SBRT in the treatment of TT in the IVC and RA associated with HCC. A total of 43 patients were enrolled, including 12 cases with Type I TT, 14 cases with Type II TT, and 16 cases with Type III TT. Our preliminary analysis showed that 42 patients completed SBRT and one discontinued due to pulmonary embolism. The median overall survival for the entire patient was 9.5 months, with 10.6 months, 22.3 months, and 4.3 months for Type I, Type II, and Type III TT, respectively. Among the 28 patients with complete imaging assessment after 3 months of follow-up, 11 (39.3%) achieved complete remission (CR), 14 (50.0%) showed partial remission (PR), and 3 (10.7%) had stable disease. Our unpublished data suggests that SBRT, as part of comprehensive treatment, could reduce TT size efficiently, thus decreasing the risk of thrombus detachment leading to pulmonary embolism and buying time for subsequent systemic treatment and thereby extending survival. This conclusion was further supported by several studies published by other teams investigating SBRT for HCC with TT in the IVC and RA (10-12). Systemic therapy, as the standard treatment recommended by guideline, Sorafenib is recommended for patients in the late stage. However, the efficacy of sorafenib in HCC patients with TT is controversial. A randomized Phase III trial demonstrated that Lenvatinib is non-inferior to sorafenib for overall survival, though with significantly improved progression-free survival, time to progression, and objective response (13). Novel agents are still urgently needed for HCC patients with TT.

Surgery, as the potentially curative treatment, brings survival benefits to these patients, especially patients with Type I and II TT. Although this study is a multicenter survey, it offers a higher level of evidence for surgery approaches to HCC patients with TT in the IVC and RA. Moreover, it demonstrates the risk factors that may

associated with surgical outcomes and helps to distinguish surgical candidates that may benefit from procedures in the future. Ultimately, adjuvant therapy could also extend survival for these patients. Multidisciplinary treatments are needed for advanced HCC patients, especially HCC with TT in IVC and RA.

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Footnote

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