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# Cardiac Metastasis After Curative Treatment of Hepatocellular Carcinoma: Assessment of Risk Factors, Treatment Options, and Prognosis

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## Abstract

Hepatocellular carcinoma (HCC) is primary hepatic malignancy with a high incidence of recurrence. The risk of recurrence directly correlates to patient's overall prognosis. Management of advanced HCC involves a combination of surgical resection, locoregional therapy, and systemic treatment. Distant metastases are rare, and intraventricular cardiac metastases are even more infrequent. This brief review details an illustrative case of cardiac metastasis after curative treatment of primary HCC and then summarizes the literature on risk factors, treatment options, and patient prognosis in the setting of distant metastases from HCC. Prognosis of metastasis to the heart is generally poor, and available evidence emphasizes the importance of maintaining regular posttreatment screening for metastases in patients with HCC. Given the variable presentation and high risk of recurrence, it is critical to have individualized multimodality treatment plans. (*J Patient Cent Res Rev.* 2022;9:181-184.)

## Keywords

hepatocellular carcinoma; cardiac metastases; recurrence; hepatitis; multimodality imaging; dyspnea

**H**epatocellular carcinoma (HCC) is a primary hepatic malignancy associated with a high incidence of recurrence, and the risk of recurrence directly determines long-term prognosis.<sup>1</sup> Incidence of distant metastasis after curative resection is relatively low, and the most common site of recurrence is within the liver. After combined treatment of hepatectomy, a locoregional therapy such as ablation, and systemic therapy of primary tumor, the resulting risk of extrahepatic metastasis is unknown.

Extrahepatic metastases occur primarily in the lung, intra-abdominal lymph nodes, bone, and adrenal glands.<sup>1</sup> Cardiac metastases without local recurrence are extremely rare and present a unique challenge in both diagnosis and determination of the optimal treatment plan. When cardiac metastasis is present, it most often involves the right atrium. Intraventricular septum involvement and isolated intracavitary metastasis of HCC are rare.<sup>2</sup> Standardized treatment of extrahepatic metastasis after curative hepatic resection has not been

established, and the diagnosis of post-HCC cardiac metastasis is associated with a poor prognosis.

## Illustrative Case

A 62-year-old man presented with a medical history of chronic hepatitis B cirrhosis and primary HCC. He was not a transplant candidate as his tumor was outside the Milan criteria due to tumor burden and vascular invasion. On initial presentation, his serum alpha-fetoprotein (AFP) level was 5 ng/mL, Model for End-Stage Liver Disease (MELD) score was 6, and Child-Pugh score placed him in Class A. He underwent transarterial chemoembolization (TACE) with doxorubicin to reduce tumor burden, followed by right portal vein embolization with subsequent right hepatectomy. Surgical pathology showed invasive, moderately differentiated HCC and microvascular intrahepatic venous invasion. Given the microvascular invasion, he received sorafenib for HCC treatment. He followed up with hepatology for surveillance AFP test and computed tomography (CT) scan of chest and abdomen every 6 months.

Six years after hepatectomy, he presented with dyspnea on exertion and chest tightness. Physical examination revealed a new systolic murmur. Transthoracic echocardiogram revealed a 4 × 2.5 cm echogenic mass in the right ventricle causing compression of the intraventricular septum. The mass partially traversed the tricuspid valve annulus, resulting in mild mechanical obstruction. Coronary angiogram

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revealed normal coronary arteries. CT angiography (Figure 1) and cardiac magnetic resonance imaging (MRI) showed a large lobulated mass emanating from the right ventricular free wall, with a portion of the mass extending in the tricuspid valve orifice. It also showed an extensive mass effect on septum and left ventricular cavity, along with partial right ventricular outflow obstruction.

Transesophageal echocardiography (TEE)-guided endomyocardial biopsy was consistent with metastatic HCC. Serum AFP was 11 ng/mL. He was offered palliative surgical debulking to remove the risk of cardiac compromise. Given the metastatic nature of HCC, he was not a candidate for a combined heart and liver transplant. Patient deferred surgical intervention and opted for systemic therapy. Given his advanced tumor, he was started on a combination of vascular endothelial growth factor (VEGF) inhibitor and immune checkpoint inhibitor atezolizumab plus bevacizumab. He tolerated 4 total cycles of treatment, and his follow-up cardiac MRI after treatment showed presence of a 9.5 cm mass. The patient expired shortly after.

### **Incidence of Cardiac Metastasis Post-HCC Treatment**

The incidence of secondary tumor metastasis to the heart is reported to be 1.5%–21%, and approximately 5%–10% of patients with HCC may develop cardiac metastasis.<sup>2</sup> Most cardiac metastases are continuous extensions of intrahepatic HCC. Isolated cardiac metastases that are discontinuous with intrahepatic HCC are exceedingly rare.<sup>3</sup> Cardiac invasion is seeded through the vascular system or by infiltration from neighboring organs. A few cases reported the hematogenous route as a cause of HCC, with right ventricular metastasis without inferior vena cava and right atrium metastasis.<sup>4</sup> Zhang et al published a report in 2019 of all patients with the diagnosis of isolated right ventricular metastasis with myocardial infiltration<sup>2</sup> — a scenario unlike the patient described in our illustrative case.

### **Cardiac Testing and Diagnosis**

The diagnosis of metastatic HCC into the cardiac cavity is often overlooked because symptoms are either not present or are nonspecific. Most patients have nonspecific symptoms at the early stages and present with chest pain or dyspnea at advanced stages when the tumor burden compromises cardiac function. As previously described, our patient presented with dyspnea on exertion and chest tightness, and an acute coronary event was initially suspected. Further workup was done only after left heart catheterization was negative for coronary artery disease.

Due to rarity, there are no standardized screening recommendations for cardiac metastasis in patients who



**Figure 1.** Computed tomography angiography showing a cardiac mass.

survive HCC. Tameda et al reported a case of cardiac metastasis presenting with abnormal electrocardiogram (negative T-wave at V1-V4) that prompted further cardiac testing.<sup>5</sup> The authors recommended detailed cardiac testing in all patients with electrocardiographic abnormality in patients with HCC, even in the absence of symptoms, to rule out cardiac metastases. Multimodality imaging may be required to detect cardiac metastases from HCC,<sup>2</sup> and TEE-guided endomyocardial biopsy is usually required for definitive diagnosis and differentiation of recurrent metastatic HCC from de novo malignancy. Of note, these tumors commonly cause right ventricular outflow obstruction; isolated inflow obstruction is rare.<sup>2</sup>

### **Treatment Options and Associated Risk Factors**

The treatment for cardiac metastatic HCC is not well established. Surgical debulking may be necessary to prevent hemodynamic compromise.<sup>2</sup> Transcatheter chemoembolization has been reported as a potential treatment option; however, its efficacy is currently unknown.<sup>6</sup> Prognosis remains very poor,<sup>4</sup> and the longest reported survival time was 9 months.<sup>2</sup> Multidisciplinary combined treatment with chemotherapy, radiotherapy, and surgery may decrease symptoms, but this approach is still considered palliative.<sup>2</sup>

Our patient had several features that can add a unique perspective to HCC. For one, isolated extrahepatic recurrence after 6 years is uncommon. In their retrospective study, Portolani et al reported 4 out of

145 patients to have extrahepatic recurrence.<sup>7</sup> Taketomi et al reported extrahepatic recurrence after 1.8 years of presentation with primary tumor.<sup>8</sup> Given the variable clinical presentation, Yan et al classified patients with extrahepatic recurrence into three categories.<sup>9</sup> Pattern I includes patients with the first recurrence in the liver and late-onset metastasis after repetitive locoregional treatment. Pattern II has a simultaneous intrahepatic and extrahepatic recurrence. Pattern III consists of those patients with only extrahepatic recurrence. In pattern I, portal vein invasion predominated, whereas in pattern III, hepatic vein invasion was more prominent. Extrahepatic recurrences are more common in patients with liver tumors invading the tumor capsule macro- or microscopically, tumors in the hepatic vein, a high serum AFP concentration, and more advanced stage per TNM classification.<sup>3</sup> Natsuizaka et al reported that patients with advanced HCC develop extrahepatic metastases significantly more frequently than those with early HCC.<sup>10</sup> In a population-based study, Yan et al showed that a primary tumor size of >5.8 cm is an independent risk predictor for distant metastases in the wake of HCC; they recommended those patients undergo regular follow-up.<sup>11</sup> Our patient was characterized as pattern III, and his risk factors included TNA stage of IIA, initial tumor size of 10.5 cm, and vascular invasion.

Tanaka et al showed that extrahepatic recurrence was more common when inflow vein occlusion was not used during hepatectomy.<sup>3</sup> Tumor invasion of the hepatic vein may lead to inadvertent tumor spread during operative manipulation of the hepatic vein; a similar observation was noted in portal vein invasion. The route of extrahepatic metastasis appears to be via the hepatic vein. The vascular occlusion method is used to reduce the risk of hematogenous dissemination. Therefore, inflow occlusion during hepatectomy is advised by Tanaka et al irrespective of the clamping method used. Metastasis through the hepatic vein more commonly occurs at advanced stages than metastasis through the portal vein. Interestingly, a previous study showed blood loss or blood transfusion is associated with higher extrahepatic recurrence.<sup>12</sup> As noted in our case and reported by Taketomi et al,<sup>8</sup> the presence of microscopic hepatic vein invasion and blood loss during surgery are both independent risk factors for increased extrahepatic recurrence after hepatectomy for HCC.

The effect of combined TACE, hepatectomy, and sorafenib on risk of extrahepatic metastasis in the future is unknown, as most patients receive these modalities in different combinations. The increased recurrence in patients receiving TACE with subsequent hepatectomy is likely related to high overall tumor burden, as noted by

Tanaka et al.<sup>3</sup> These patients would be at higher risk for recurrence independent of treatment modality.

Another interesting aspect of our illustrative case is that this patient had normal AFP throughout his clinical course. This is contrary to the report by Kanda et al, which noted at least 1 of 3 tumor biomarkers (AFP, DCP, AFP-L3) is positive in 92.7% of cases with extrahepatic recurrence.<sup>13</sup> Elevation of tumor markers despite well-controlled or reduction of hepatic tumor burden may indicate extrahepatic metastasis. High serum AFP concentrations (>1000 ng/mL in some series) showed a positive correlation to increased prevalence of HCC recurrence.<sup>14</sup> Serum AFP concentration also was reported to be an independent factor for poor prognosis in patients with extrahepatic metastases of HCC.<sup>15</sup> Significantly, our patient had chronic hepatitis B, which has been shown to be associated with extrahepatic metastasis in HCC.<sup>13</sup> After liver resection, adjuvant chemotherapy is generally administered to patients with pathologically confirmed satellite nodules, vascular invasion, or hepatic duct invasion.<sup>12</sup> Our patient received sorafenib for 6 years until his presentation with extrahepatic metastases.

### Unfavorable Prognosis

Patients tend to have poor survival when HCC has spread beyond the liver after hepatectomy. Some studies have reported survival up to 19.2 months.<sup>8</sup> Extrahepatic metastasis could be considered as an independent prognostic factor for patients with liver cancer.<sup>16</sup> Primary tumor status is an essential factor for survival, even in HCC patients with extrahepatic metastases.<sup>3</sup> The metastatic site and treatment for extrahepatic metastasis foci are also crucial in the prognosis of HCC. Disease-free interval after initial hepatic resection seems associated with improved survival in patients with extrahepatic metastasis. Combined chemotherapy, radiotherapy, and surgical approaches on both primary and metastatic lesions may be required to improve a rather poor prognosis of cardiac metastatic HCC.

### Summary

Extrahepatic recurrence, including in the heart, can occur after hepatectomy for hepatocellular carcinoma despite adequate control of primary HCC and strict follow-up surveillance. Cardiac metastases are rare and can be difficult to diagnose and treat. The management of extrahepatic metastases needs to be individualized to the patient in a multidisciplinary fashion, potentially including surgery, radiotherapy, and chemotherapy. Unfortunately, regardless of approach, prognosis for these patients remains poor.

## Patient-Friendly Recap

- Despite successful resection of a common liver cancer called hepatocellular carcinoma, related metastatic tumors may arise in the heart years after surgery.
- While rare, these cardiac metastases are difficult to diagnose and treat. Regular surveillance may be warranted to improve early identification.
- Treatment often involves a multipronged approach of surgery, radiation, and chemotherapy and should be tailored to each individual based on risk factors.

## Author Contributions

Study design: Jain, Sahajpal. Data acquisition or analysis: Jain, Otto, Mohammed Abdul. Manuscript drafting: Jain, Otto, Mohammed Abdul. Critical revision: Chadha, Sahajpal.

## Conflicts of Interest

None.

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