

**Title:**

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**Challenges in metastatic hepatocellular carcinoma: beyond tumor stage in guiding treatment**

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Dear Editor,

Extrahepatic disease in hepatocellular carcinoma (HCC) is a relatively frequent finding (10-15 %). The lungs are the most common metastatic site, followed by bone and adrenal glands (10 %). Despite therapeutic advances, the prognosis remains poor, with a median survival of six months.



## Case report

We present the case of a 71-year-old male with chronic alcoholic liver disease and portal hypertension (PH). In January 2019, a 3.5 cm HCC was detected in segment II and treated with microwave ablation. Follow-up showed normalization of AFP from 59 to 7 ng/mL, and imaging revealed residual necrosis. After 18 months without recurrence, a 4.7 cm HCC was detected in the same liver segment with normal AFP levels. A second microwave ablation was performed, followed by transarterial chemoembolization (TACE). Seven months later, despite radiologic stability and normal AFP, a 14 mm lesion appeared in the left adrenal gland. Close monitoring was initially chosen, but progression prompted a biopsy, confirming HCC metastasis.

The multidisciplinary team (MDT) in collaboration with an external reference center initiated Sorafenib treatment, but no response was observed. With continued progression and the unavailability of Regorafenib due to financial limitations, Nivolumab was administered, completing eight sessions combined with radiotherapy. Other systemic approaches were not yet approved at that time. AFP levels were elevated (29.5 ng/mL) due to extrahepatic disease (adrenal metastasis measuring 12 cm), but no radiological signs of active HCC were observed. With liver remission, no evidence of PH and disease progression limited to the adrenal gland, MDT opted for curative-intent surgery. The procedure involved resection of the pancreatic tail, spleen, kidney, left adrenal gland, and atypical hepatectomy, including treated HCC.

Six months later, a new HCC lesion in segment VII was treated with TACE. Despite a good radiological response and AFP normalization, a second adrenal metastasis appeared in the right adrenal gland, prompting another curative surgery. Intraoperative ultrasound confirmed no additional lesions. Following the diagnosis of the initial metastasis, the patient remained clinically stable and asymptomatic for five years.

## Discussion

Managing advanced HCC is challenging, even with the advent of immunotherapy, the article by De la Torre et al. (2024) highlight advances and limitations in immunotherapy, as well as the potential of dual immunotherapy, with studies such as



CheckMate 459, CheckMate 040, IMbrave150, and Himalaya. However, metastases management remains complex, with traditional staging systems often insufficient. Hong Kong Liver Cancer classification has proven effective in identifying candidates for aggressive therapies, even in advanced stages, which improves outcome.

AFP is limited as an isolated biomarker since 40 % of advanced HCC cases have normal levels. Emerging biomarkers, such as liquid biopsy, offer promising alternatives for disease monitoring. While immunotherapy has advanced, managing metastases remains a challenge. The presented case shows how a multidisciplinary approach can guide successful outcomes, emphasizing the need for ongoing research to optimize treatment strategies.

## References

1. Kwak HV, Hsu DS, Chang CK. Isolated adrenal metastasis for hepatocellular carcinoma: a case report and literature review. *AME Case Rep* 2022;6:18. DOI: 10.21037/acr-21-75
2. Sormaz IC, Yegen G, Akyuz F, et al. Recurrent Hepatocellular Carcinoma in the Right Adrenal Gland 11 Years After Liver Transplantation for Hepatocellular Carcinoma: a Case Report and Literature Review. *Indian J Surg* 2017;79(5):450-4. DOI: 10.1007/s12262-017-1680-5
3. Hanif H, Ali MJ, Susheela AT, et al. Update on the applications and limitations of alpha-fetoprotein for hepatocellular carcinoma. *World J Gastroenterol* 2022;28(2):216-29. DOI: 10.3748/wjg.v28.i2.216
4. Long HY, Huang TY, Xie XY, et al. Treatment strategies for hepatocellular carcinoma with extrahepatic metastasis. *World J Clin Cases* 2021;9(21):5754-68. DOI: 10.12998/wjcc.v9.i21.5754.
5. De la Torre M, Sangro P, D Avola D, et al. Inmunoterapia en carcinoma hepatocelular. *Rev Esp Enferm Dig* 2022;114(11):663-70. DOI: 10.17235/reed.2022.8876/2022



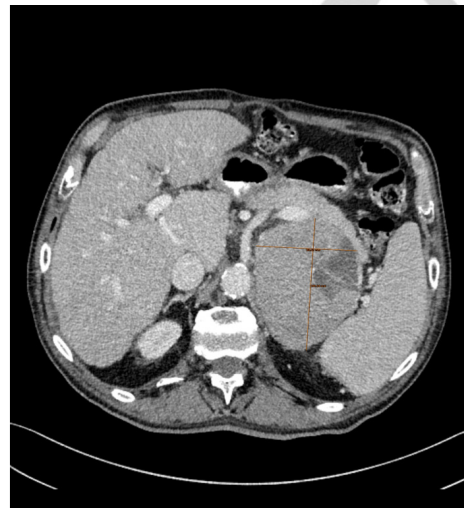
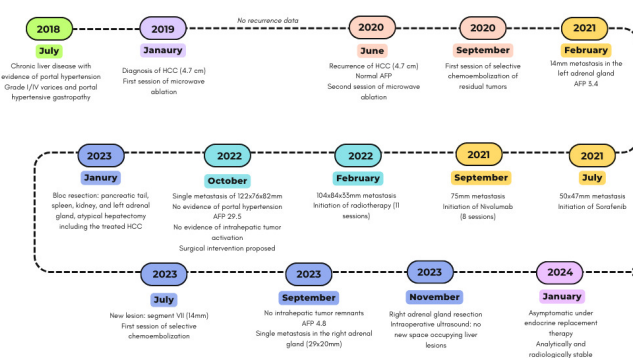


Figure 1. A. Timeline of events for the patient. B. Metastasis in the left adrenal gland (12.2 cm × 7.6 cm × 8.2 cm).