

# Hepatic immune-related adverse events during immunotherapy: a comparison between HCC and liver metastases from other solid tumors

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## 1 Introduction

Around 9-20% of patients with unresectable/advanced hepatocellular carcinoma (HCC) receiving immune checkpoint inhibitors (ICI) will develop hepatic immune-related adverse events (HIRAEs). Since liver tumor infiltration could be per se a risk factor for the onset of HIRAEs, we aimed to compare the incidence of HIRAEs in patients with HCC and patients with liver metastases from other cancers. Moreover, we investigated a possible relation between HIRAEs and hepatic tumor burden.

## 2 Method

We selected **76 consecutive patients** treated with ICI at our center between August 2015 and May 2019. 36 patients had unresectable/advanced **HCC**, 40 patients had **liver metastases from other tumors** (4 renal cancer, 25 non-small-cell lung cancer, 11 melanoma). 56 patients received a monoclonal antibody (mAb) targeting PD-1/PD-L1 as a single agent, while 20 patients received a combination therapy with the addition of a mAb against CTLA-4. HIRAEs were categorized according to CTCAE v. 5.0.

Study Population N=76		
	HCC=36	Non HCC=40
<b>Diagnosis</b>	36 HCC	4 mRCC 11 melanoma 25 NSCLC
<b>Gender</b>	24 males (67%) 12 females (33%)	24 males (60%) 16 females (40%)
<b>Median Age</b>	66 years (44-77)	66 years (41-81)
<b>Immunotherapy</b>	16 Ab anti-PD1/PD-L1 (44%) 20 Ab anti-PD1/PD-L1 + Ab anti-CTLA4 (56%)	1 anti-CTLA4 (2%) 39 anti-PD1/PD-L1 (98%)

## 3 Results

**Any grade HIRAEs** were significantly **more frequent in the HCC group** compared to the non-HCC group (50% vs 27%,  $p=0.04$ ), while the frequency of **G3-G4 HIRAEs was comparable** in the two groups (14% vs 5%,  $p=0.41$ ). HIRAEs led to similar rates of temporary treatment interruptions (11% vs 7.5%,  $p=0.70$ ) and permanent discontinuations (0% vs 7.5%,  $p=0.24$ ) in the two groups. **Any grade HIRAEs** were significantly **more frequent** in patients with **three or more HCC liver nodules** ( $p=0.035$ ), while this association was marginally significant in the non-HCC group ( $p=0.055$ ).

HIRAEs in study population			
	HCC	Non-HCC	
<b>Any grade HIRAEs</b>	18 (50%)	11 (27%)	<b><math>p=0.04</math></b>
<b>G3-G4 HIRAEs</b>	5 (14%)	2 (5%)	$p=0.41$
<b>Temporary interruption due to HIRAEs</b>	4 (11%)	3 (7.5%)	$p=0.70$
<b>Permanent discontinuation due to HIRAEs</b>	0	3 (7.5%)	$p=0.24$

Hepatotoxicity according to tumor burden		
	HCC	Non-HCC
<b>Any grade HIRAEs</b>	More than 3 hepatic nodules: 52% ( <b><math>p=0.035</math></b> )	More than 3 hepatic metastases: 82% ( <b><math>p=0.055</math></b> )

## 4 Conclusion

In our retrospective analysis of patients receiving immunotherapy, **HCC patients** suffered from **more frequent HIRAEs** compared to patients with other malignancies metastatic to the liver. On the other hand, we did not observe any significant difference regarding G3-G4 HIRAEs and the rates of treatment discontinuations.

Furthermore, we found that the presence of **three or more liver nodules** was a **predisposing factor for the development of HIRAEs**, suggesting a possible role of hepatic tumor burden as a risk factor for HIRAEs.

## 5 References

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