

# Pre-treatment MR lesions in HCV patients diagnosed with hepatocellular carcinoma after initiating Direct Acting Antiviral therapy

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**Conflict of interest**

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

**Authors' contributions**

RS (Acquisition, analysis and interpretation of data, statistical analysis, drafting of the manuscript); GPA, SF and WI (Study concept and design, interpretation of data, drafting and critical revision of the manuscript).

Dear editors:

Although attainment of sustained virological response (SVR) reduces the incidence of hepatocellular carcinoma (HCC) in patients with chronic hepatitis C virus (HCV) infection, increased risk of HCC remains [1]. In the largest series to date, risk factors associated with persistent HCC risk after SVR achievement included increasing age, presence of cirrhosis and diabetes [2]. It is striking, however, that 35% of HCC cases in that cohort arose within the first year following SVR attainment and the overall median time between SVR and HCC detection was 1.66 years [2]. This observation raises the possibility that HCC was present prior to SVR attainment.

We have been conducting a prospective observational study designed to investigate the effect of Direct Acting Anti-viral (DAA) therapy on the liver of HCV patients using a published non-contrast MRI protocol [3]. Seven (of 41) patients in our study were diagnosed with HCC subsequent to onset of DAA therapy (6 de novo and 1 recurrence). In each case there was, serendipitously obtained, radiological evidence of the presence of HCC before onset of DAA therapy. Here we describe these cases of HCC, 6 of which would have fulfilled criteria for development after SVR according to classification criteria [4, 5].

Six (of seven) patients were male, median age 55 (range 50 – 69), BMI 25.9 (23.4 - 32), MELD 9 (7-15). Six (of seven) had decompensated cirrhosis, 5 had HCV genotype 3, 2 genotype 1a. All patients had a normal pre-treatment  $\alpha$ -fetoprotein, median 9 ng/mL (7 – 15). 4/7 achieved SVR, one died during treatment and two underwent transplant. Post-hoc processing of pre-treatment research MRI scans showed 6/7 lesions were detectable 36 - 511 days before clinical diagnosis of HCC (Figure 1). No pre-treatment lesion was identified in Patient 7, but a lesion was detectable on the post-treatment research scan 106 days before clinical diagnosis.

Only one patient (Patient 3) had recurrent HCC, with radio-frequency ablation 3 years prior to this study. The other six were de novo HCC. 4 HCCs were detected by routine abdominal ultrasound surveillance 14 days following initiation of DAA treatment (Patient 6), or 199 - 389 days post completion of DAA treatment (patients 2, 5 and 7). Of the remaining three patients Patient 1 presented with a raised screening alpha-fetoprotein (49 days post DAA treatment completion), Patient 3 presented with acute decompensation (ascites) 50 days after starting DAAs, and the HCC in Patient 4 was detected on routine imaging at transplant work-up (34 days post DAA treatment completion).

Radiological reports and multi-disciplinary team notes were retrieved. 5/7 patients had clinical MRI scans to confirm the diagnosis of HCC. These clinical scans were anonymised, randomised and the DICOM files exported. Clinical MR images then underwent identical post-hoc processing to the research scans and were reconstructed into 3D images by researchers blinded to the patients' identity. An independent researcher was tasked with matching the clinical and research scans – and succeeded in doing so for all 5 patients (Figure 1). All lesions identified on the DIXON scans were in the same

segment as the HCCs that were subsequently diagnosed. The matching of HCC lesions between the clinical “diagnostic” scans and preceding research DIXON MRI scans, both in terms of anatomical location and similarity in size, is highly suggestive that the HCCs were present but not clinically evident.

Three patients had a screening ultrasound that was reported as normal (9-367 days) after the research MRI scan, analysed post hoc, had a demonstrated a lesion. 5/7 cases of HCC had a normal surveillance ultrasound in the six month period prior to DAA therapy (median interval 36 days). This is consistent with the known relative insensitivity of ultrasound in the detection of tumours [6, 7].

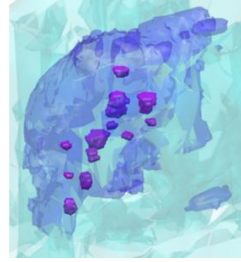
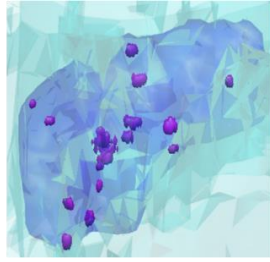
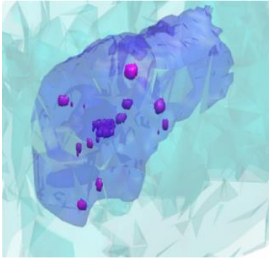
Our data unequivocally demonstrate that lesions which ultimately co-localise with subsequently formally diagnosed HCCs exist *before* DAA therapy is started, and support the argument that the increased prevalence of HCC following DAA treatment is because DAA-treated patients have more advanced liver disease [1, 2] rather than the risk attributable to DAA therapy [8].

Pre-treatment MRI

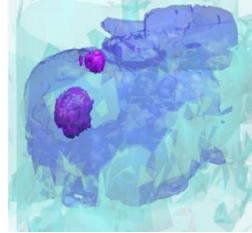
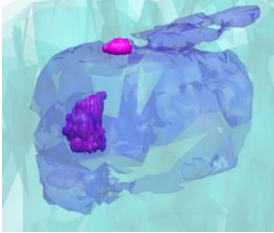
Post-treatment MRI

Clinical Diagnostic MRI

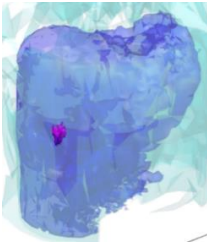
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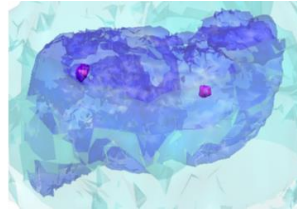
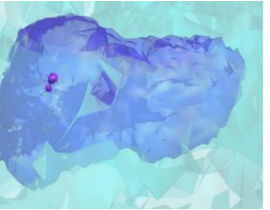
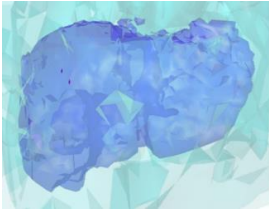
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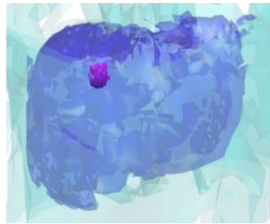
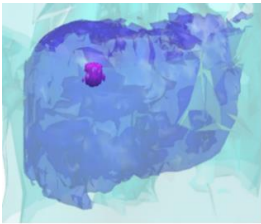
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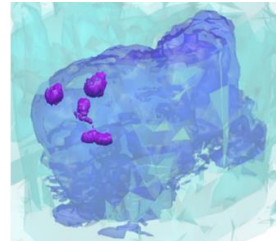
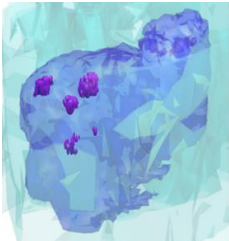
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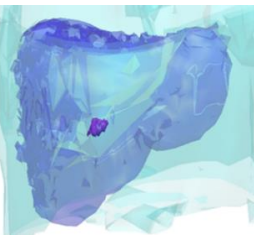
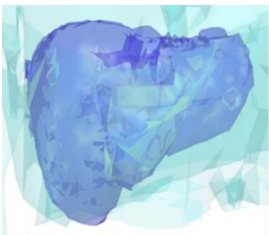


Figure 1: Post-hoc image analysis could retrospectively identify lesions (coloured pink) within the liver (blue) on the water-only DIXON MRI scans of all 7 patients (1-7) who developed HCC before the clinical diagnosis was made. Using in-house software (MATLAB, The Mathworks Inc., Natick, MA), the DIXON water-only images of the pre- and post-MRI scan sessions were thresholded at 80% of the mean liver intensity to automatically segment the lesions from the liver tissue. These images were then 3D rendered.

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