

# The Number of Small HCC Nodules in Patients within the Alpha-Fetoprotein Score before Liver Transplantation Is a Prognostic Risk Factor

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## Background and Aims:

In France, the current criteria for liver transplantation (LT) for hepatocellular carcinoma (HCC) require an alpha-fetoprotein (AFP) score  $\leq 2$ . The AFP score takes into account the serum AFP level, the number of HCC nodules and the size of the largest nodule. According to this score, patients with  $> 3$  HCC nodules are eligible for LT, as long as they are small ( $\leq 3$  cm) and the AFP level is  $\leq 100$  ng/mL. This study shows that the number of small HCC nodules in patients within the AFP score before LT has a prognostic value.

## Methods:

We included 143 patients consecutively transplanted for HCC in our center, between 2013 and 2017, with an AFP score  $\leq 2$ . The number and size of HCC nodules, and the AFP level were assessed at listing and at the last evaluation before LT. HCC histological features on native liver were assessed. We compared the overall survival (OS) and disease-free survival (DFS) post-LT of patients with  $\leq 3$  versus  $> 3$  HCC nodules (current criteria) and, respectively,  $< 5$  versus  $\geq 5$  HCC nodules, all within the AFP score. The Mann-Whitney U test for continuous variables and Pearson's chi-square test were used, or Fisher's exact test for categorical variables. Survival rates were calculated using the Kaplan-Meier method, and groups were compared with the log-rank test.

## Results:

Among 196 patients listed for HCC, 36 (18.4%) were not transplanted due to drop-out. 17 patients, still waiting for LT at the end of the study period, were excluded from analysis. The main characteristics of the 143 transplanted patients are summarized in the **Table 1**. Among them, 128 (89.5%) patients had at least one bridging treatment: transarterial chemoembolization  $n = 83$ , radiofrequency  $n = 16$ , surgical resection  $n = 22$ , other treatment  $n = 22$ , without any difference among the subgroups ( $\leq 3$  versus  $> 3$  HCC nodules). The pathological features of native liver are summarized in the **Table 2**. The median follow-up of the whole cohort was of 44 months. The 3-years OS of patients with  $\leq 3$  versus  $> 3$  HCC nodules at listing were of 90.3% versus 67.3%, respectively ( $p = 0.04$ ). The 3- and 5-years OS of patients with  $\leq 3$  versus  $> 3$  HCC nodules at last imaging before LT were of 89% and 77.9% versus 83.6% and 50% ( $p = 0.3$ ), as shown in **Figure 1A**. The DFS at 3 and 5 years for patients with  $\leq 3$  versus  $> 3$  HCC nodules at last imaging before LT were of 80.9% and 73.9% versus 59% and 49% ( $p = 0.09$ ), as shown in **Figure 1B**. At last imaging before LT, 8 patients presented  $\geq 5$  HCC nodules, while still within the AFP score; they had a significantly lower OS than those with  $< 5$  nodules: 5-years OS of 24.4% versus 78.1% ( $p = 0.01$ ), as showed in **Figure 2**.

**Table 1. Characteristics of Transplanted Patients**

	Whole cohort (n=143)	P-value
Median age at LT (SD) - yr	63.3 $\pm$ 7.4	
Sex: M/F - no. (%)	118 (82)/25 (17)	
Etiology of the underlying liver disease (%)		
• Alcohol	41.3	
• HCV infection	27.9	
• HBV infection	11.9	
• NASH	10.5	
• Others*	4.9	
• HCC on normal liver	3.5	
Patients with $> 3$ HCC nodules - no. (%)		
• At listing on the WL	16 (11)	
• At last imaging before LT	17 (12)	
• At pathological analysis	41 (29)	
Bridging therapy - no. (%)	128 (89.5)	
HCC recurrence post LT - no. (%)	25	
• If $> 3$ nodules at last imaging before LT	5/17 (29.4)	$p = 0.13$
• If $\leq 3$ nodules at last imaging before LT	16/126 (15.3)	
• If $\geq 5$ nodules at last imaging before LT	3/8 (37.5)	$p = 0.09$
• If $< 5$ nodules at last imaging before LT	18/135 (13.3)	

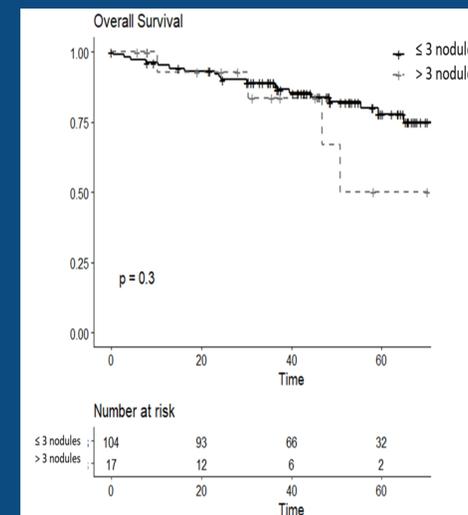
**Table 2. Pathological Features**

	121 (85)
Fibrosis F3/F4*	121 (85)
Mean diameter of the largest nodule (mm) <sup>b</sup>	17.4 $\pm$ 12.88
Macroscopic vascular invasion*	3 (2)
Microscopic vascular invasion*	42 (29)
Histological Grading (Edmondson - Steiner)*	
• No viable lesion	31 (21.7)
• E1	32 (22.4)
• E2	53 (37)
• E3	26 (18.1)
• E4	1 (0.7)

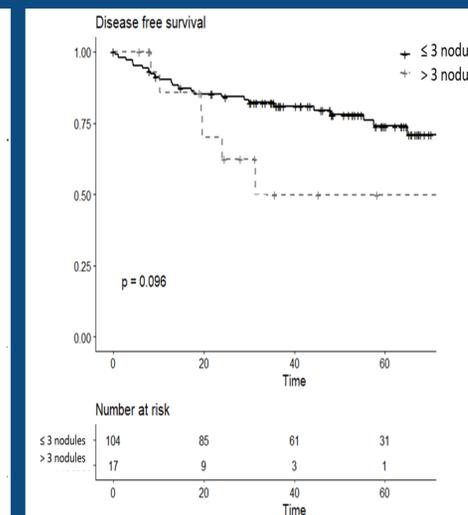
M/F: Male/Female; NASH: Non-Alcoholic Steatohepatitis; WL: Waiting List; \* Budd-Chiari disease; Wilson disease; autoimmune hepatitis; hemochromatosis.

E: Edmondson - Steiner grading; F: fibrosis. <sup>a</sup> Values are given as no. (%); <sup>b</sup> Values are given as mean  $\pm$  SD.

**Figure 1A.**



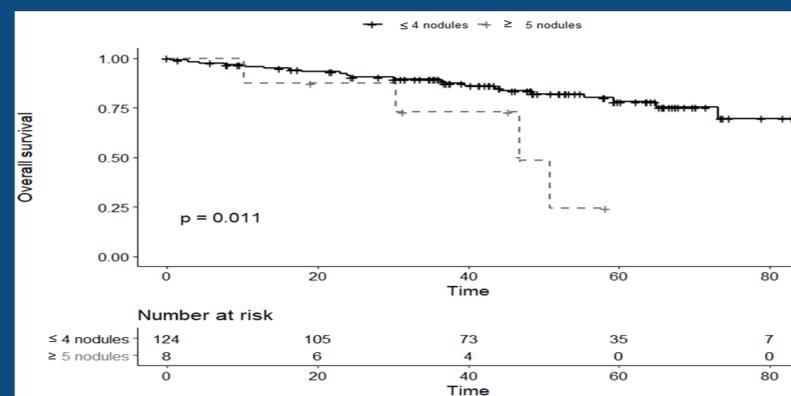
**Figure 1B.**



**Figure 1A. OS and 1B. DFS for patients with  $\leq 3$  HCC nodules (bold line) vs  $> 3$  HCC nodules (dashed line) at last imaging before LT.**

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**Figure 2. OS for patients with  $< 5$  HCC nodules (bold line) versus  $\geq 5$  HCC nodules (dashed line) at last imaging before LT.**

## Conclusions:

Although the current AFP score provides satisfactory outcomes post-LT for HCC, we highlight here the poorer outcomes of patients presenting five or more HCC nodules at last imaging assessment before LT, despite bridging therapy. These results need to be confirmed by a larger validation cohort. In this case, a modification of the AFP score, by adding an upper threshold of five HCC nodules could be considered, to exclude progressive HCC after listing, as they show shorter survival rates.