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Role Of Protein Induced By Vitamin-K Absence-II In Hepatocellular Cancers That Do Not Produce Alpha-fetoprotein

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Background : The elevation of Protein Induced by Vitamin-K Absence-II (PIVKA-II) is an adverse prognostic factor in patients with hepatocellular cancer (HCC) undergoing liver transplantation (LT). No definitive answer exists on the impact of PIVKA-II in terms of post-LT HCC recurrence in patients that did not produce (≤20 ng/mL) or produce (>20 ng/mL) alpha-fetoprotein (AFP).

Methods : We report an observational retrospective study based on an international collaborative registry on LT and HCC recurrence. Between 2000 and 2019, 639 patients transplanted with the primary diagnosis of HCC were enrolled in five collaborative centers (Kyoto, Japan; UCL-Brussels, Belgium; Fukuoka, Japan; Ancona, Italy; Rome Sapienza, Italy). With the intent to minimize the initial selection bias, an inverse probability therapy weighting (IPTW) method was adopted.

Results : In the post-IPTW population, PIVKA-II (HR=2.00; 95%CI=1.52-2.64; P <0.0001) and AFP (HR=1.82; 95%CI=1.48-2.24; P <0.0001) emerged as the most relevant independent risk factors for recurrence. Also the diameter of the target lesion (HR=1.18, 95%CI=1.12-1.23; P <0.0001), the number of nodules (HR=1.08, 95%CI=1.06-1.10; P <0.0001), and the necessity to perform a salvage transplant (HR=2.49, 95%CI=1.38-4.50; P=0.003) were independent risk factors for recurrence. When a sub-analysis focused only on patients not secreting AFP was performed, PIVKA-II confirmed its independent relevance, with an HR=2.06 (95%CI=1.26-3.35; P=0.004). PIVKA-II was an independent risk factor for recurrence in the subgroup of patients secreting AFP, with an HR=2.84 (95%CI=1.96-4.12; P <0.0001). When the entire population was categorized into four subclasses according to the value of AFP (≤ or >20 ng/mL) and PIVKA (≤ or >300 mUA/mL) at the time of LT, the lowest recurrence rates were observed in the subclass with low AFP-low PIVKA-II (5-year recurrence rate=8.0%). Patients with high AFP-low PIVKA-II (5-year recurrence rate=15.9%) and low AFP-high PIVKA-II (5-year recurrence rate=23.4%) showed intermediate results. Finally, the subclass composed of high AFP-high PIVKA-II cases had the worst results, with a 5-year recurrence rate of 35.1%.

Conclusions : PIVKA-II is a relevant risk factor for post-LT HCC recurrence. The role of this marker is independent respect to the modifications of AFP. In many cases, AFP not secreting patients present high PIVKA-II values. Combining the two markers adds relevant information for predicting the post-LT risk of tumor recurrence.

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