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Title: The radiological response and inflammation scores predict tumour recurrence in patients treated with transarterial chemoembolization before liver transplantation

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1 What did this study explore? The aim of this study was to investigate the prognostic value of the radiological response after transarterial chemoembolization (TACE) and inflammatory markers in patients affected by hepatocellular carcinoma (HCC) awaiting liver transplantation (LT).

2 How did the authors perform all experiments? The study population was retrieved from the institutional, prospectively entered database of the Hepatobiliary and Transplant Unit of Polytechnic University of Marche, Ancona. Between August 2005 and December 2014, 70 consecutive patients who exclusively underwent one or more TACE sessions prior to LT were enrolled. The patient demographics, aetiology of cirrhosis, Child-Pugh and Model for End-Stage Liver Disease (MELD) scores, and imaging and pathological records were collected for each patient. Laboratory factors related to tumour biology such as serum AFP and inflammation-based scores were recorded at two different well-defined

time points: the day of admission to perform the first TACE and immediately before surgery. Two radiologists evaluated the baseline contrast-enhanced imaging (dynamic MRI or CT) and last available imaging before LT to define the tumour response according to mRECIST and EASL guidelines. A dedicated liver pathologist performed the analysis of all explanted livers that were serially cut into sections of approximately 0.5-cm thick; in order to explore the accuracy of radiological criteria in predicting the histological outcome, the percentage of necrosis of the cumulative tumour area was calculated and compared with the preoperative radiological findings.

3 How did the authors process all experimental data? Categorical variables of the study population were reported as numbers and percentages and were compared with Fisher's exact test. Continuous variables were reported as medians and interquartile ranges (IQRs); the Mann-Whitney U test was applied to compare continuous variables in different subgroups of patients, whereas any difference in laboratory values before and after TACE therapy was investigated using the Wilcoxon test. The rank correlation test for nonparametric continuous variables (Kendall's tau) was applied to investigate the relationship between the amount of necrosis and different categories of the radiological response. The agreement in defining the radiological response between mRECIST and EASL criteria was explored by the k-cohen test. The impact of each individual variable in determining HCC recurrence-free survival (RFS) was assessed by the Kaplan-Meier method and was compared by the log-rank test. A multivariate Cox proportional regression model (stepwise method) was designed to investigate risk factors independently related to HCC recurrence, considering only preoperative variables that proved to be significant (p -value<0.05) after univariate analysis.

4 How did the authors deal with the pre-study hypothesis? The results of our study demonstrated that a lack of response to TACE and a high platelet-to-lymphocyte ratio before surgery are strongly predictive of tumor recurrence, independently of the Milan criteria status at referral. The overall diagnostic accuracy of radiological criteria in predicting histological necrosis was 72.9% and 68.6% for mRECIST and EASL criteria, respectively.

5 What are the novel findings of this study? When assessed preoperatively, radiological criteria are useful to predict histological necrosis of the TACE-treated HCC nodules. Our data suggest that patients who experience an objective response to TACE according to mRECIST criteria or not exceeding a pre-LT PLR value of 150 can achieve optimal results in terms of tumour-free survival, independently of their Milan criteria status at the initial evaluation. Consequently, these 'biological' and 'dynamic' tumor parameters should be integrated in the selection algorithm to increase the number of transplantable patients and to improve the recurrence-free survival rates in TACE-treated candidates for LT.

