

PREDICTING SURVIVAL AFTER LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CARCINOMA BEYOND THE MILAN CRITERIA: A RETROSPECTIVE, EXPLORATORY ANALYSIS

Vincenzo Mazzaferro¹, Josep M Llovet^{2,7}, Rosalba Miceli¹, Sherrie Bhoori¹, Marcello Schiavo¹, Luigi Mariani¹, Tiziana Camerini¹, Sasan Roayaie², Myron E Schwartz², Gian Luca Grazi³, René Adam⁴, Peter Neuhaus⁵, Mauro Salizzoni⁶, Jordi Bruix⁷, Alejandro Forner⁷, Luciano De Carlis⁸, Umberto Cillo⁹, Andrew K Burroughs¹⁰, Roberto Troisi¹¹, Massimo Rossi¹², Giorgio E Gerunda¹³, Jan Lerut¹⁴, Jacques Belghiti¹⁵, Ilka Boin¹⁶, Jean Gugenheim¹⁷, Fedja Rochling¹⁸, Bart Van Hoek¹⁹, **Pietro Majno**²⁰, on behalf of the Metroticket Investigator Study Group

¹National Cancer Institute, Milan, Italy, ²Mount Sinai School of Medicine, New York, NY, USA, ³S Orsola Malpighi Hospital, Bologna, Italy, ⁴Hôpital Paul Brousse, Villejuif, Paris, France, ⁵Charité University and School of Medicine, Berlin, Germany, ⁶Molinette Hospital, Turin, Italy, ⁷Liver Cancer Group, Hospital Clinic, Barcelona, Spain, ⁸Niguarda Hospital, Milan, Italy, ⁹Padova University Hospital Medical School, Padova, Italy, ¹⁰Royal Free Hospital, London, UK, ¹¹Ghent University Hospital Medical School, Ghent, Belgium, ¹²La Sapienza University—Umberto I Hospital, Rome, Italy, ¹³University Hospital Modena, Modena, Italy, ¹⁴University Hospital St Luc, Brussels, Belgium, ¹⁵Hopital Beaujon, Paris, France, ¹⁶University Hospital of Campinas, São Paulo, Brazil, ¹⁷Hôpital Archet-2, Nice, France, ¹⁸Nebraska Medical Center, Omaha, NE, USA, ¹⁹Leiden University Medical Centre, Leiden, Netherlands, ²⁰Hôpitaux Universitaires de Genève, Geneva, Switzerland.

Introduction: Patients undergoing liver transplantation for hepatocellular carcinoma within the Milan criteria (single tumour ≤ 5 cm in size or ≤ 3 tumours each ≤ 3 cm in size, and no macrovascular invasion) have an excellent outcome. However, survival for patients with cancers that exceed these criteria remains unpredictable and access to transplantation is a balance of maximising patients' chances of cure and organ availability. The aim of this study was to explore the survival of patients with tumours that exceed the Milan criteria, to assess whether the criteria could be less restrictive, enabling more patients to qualify as transplant candidates, and to derive a prognostic model based on objective tumour characteristics, to see whether the Milan criteria could be expanded.

Méthode: Data on patients who underwent transplantation for hepatocellular carcinoma despite exceeding Milan criteria at different centres were recorded via a web-based survey completed by specialists from each centre. The survival of these patients was correlated retrospectively with the size of the largest tumour nodule, number of nodules, and presence or absence of microvascular invasion detected at pathology. Contoured multivariable regression Cox models produced survival estimates by means of different combinations of the covariates. The primary aim of this study was to derive a prognostic model of overall survival based on tumour characteristics, according to the main parameters used in the Tumour Node Metastasis classification. The secondary aim was the identification of a subgroup of patients with hepatocellular carcinoma exceeding the Milan criteria, who achieved a 5-year overall survival of at least 70%—ie, similar to the outcome expected for patients who meet the Milan criteria.

Résultats: Over a 10-month period, between June 25, 2006, and April 3, 2007, data for 1556 patients who underwent transplantation for hepatocellular carcinoma were entered on the database by 36 centres. 1112 patients had hepatocellular carcinoma exceeding Milan criteria and 444 patients had hepatocellular carcinoma shown not to exceed Milan criteria at post-transplant pathology review. In the group of patients with hepatocellular carcinomas exceeding the criteria, the median size of the largest nodule was 40 mm (range 4–200) and the median number of nodules was four (1–20). 454 of 1112 patients (41%) had microvascular invasion and, for those transplanted outside the Milan criteria, 5-year overall survival was 53.6% (95% CI 50.1–57.0), compared with 73.3% (68.2–77.7) for those that met the criteria. Hazard ratios (HR) associated with increasing values of size and number were 1.34 (1.25–1.44) and 1.51 (1.21–1.88), respectively. The effect was linear for size, whereas for number of tumours, the effect tended to plateau above three tumours. The effect of tumour size and number on survival was mediated by recurrence ($b=0.08$, $SE=0.12$, $p=0.476$). The presence of microvascular invasion doubled HRs in all scenarios. The 283 patients without microvascular invasion, but who fell within the Up-to-seven criteria (hepatocellular carcinomas with seven as the sum of the size of the largest tumour [in cm] and the number of tumours) achieved a 5-year overall survival of 71.2% (64.3–77.0).

Conclusion: More patients with hepatocellular carcinoma could be candidates for transplantation if the current dual (yes/no) approach to candidacy, based on the strict Milan criteria, were replaced with a more precise estimation of survival contouring individual tumour characteristics and use of the up-to-seven criteria.