Conflict of interest

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Quentin M. Anstee
The Liver Unit, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK
Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK

Bryan Jaques
Hepatopancreatobiliary Team, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK

Mark Hudson
The Liver Unit, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK

Helen L. Reeves*
The Liver Unit, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK
Hepatopancreatobiliary Team, Freeman Hospital, Newcastle-upon-Tyne Hospitals NHS Foundation Trust, UK
Northern Institute for Cancer Research, Newcastle University, Newcastle-upon-Tyne, UK
*Corresponding author.
E-mail address: H.L.Reeves@ncl.ac.uk

Response to locoregional treatment and alpha-fetoprotein trend in liver transplant candidates for HCC: *Dwarfs standing on the shoulders of giants*

To the Editor:

We read with great interest the correspondence on the paper published by Otto *et al.*, [1] on the response to repeated trans-arterial chemo-embolization (TACE) as a discriminating tool for selection of liver transplant (LT) candidates with hepatocellular carcinoma (HCC). Paul *et al.* [2] evidenced the relative small sample size and the lack of information on the role of TACE on waiting-list dropout. Our aim is to support the results obtained by Otto *et al.* with the strength and the statistical power of a new recently published European study.

Using prospectively recorded data from 6 Centers with different allocation systems, we have confirmed the role of the response to locoregional treatments (LRT) as predictor of survival and HCC recurrence [3]. mRECIST progression after LRT and alpha-fetoprotein (AFP) slope >15 ng/ml/month resulted independent predictors not only in 116 Milan-criteria (MC)-OUT, but also in 306 MC-IN patients. Moreover, no TACE alone but also different LRTs were performed in the routine pre-LT workout, demonstrating that response to LRT works well independently from the stage.

We agree on the Zurich Conference recommendations [4]: The preoperative assessment of the size of largest tumor or total diameter remains crucial. However, pre-operative radiological staging for MC-IN and MC-OUT patients may differ in both directions in up to 25% of cases when compared to post-transplant histopathology [5]. Although response to LRTs has already been shown in the beginning of the nineties as a useful tool for the selection of HCC patients as the seminal paper by Majno *et al.* clearly shows [6], the delayed introduction in clinical practice of standardized and effective LRT techniques (TACE, radiofrequency ablation, radio-embolization) has hampered their routine use in the pre-LT management of HCC. As a consequence, the evaluation of the prognostic role of response after LRT has only recently been implemented.

Mehta and Yao synthesized that there is "growing evidence that size and number tell only a partial tale of the tumor charac-

teristics that predict post-transplant recurrence" [7]. It is not known yet if LRTs represent *per se* a surrogate of tumor biology or if LRT works only through the proof of time. On this scope, we recently demonstrated that "fast track" LT does not allow to time the selection patients according to tumor aggressiveness [8].

We recognize some limitations. Both the studies by Otto *et al.* and Lai *et al.* did not investigate the effect of LRT on the dropout during waiting-time. However, an ongoing analysis performed on 821 patients coming from the EurHeCaLT study group further confirmed the role of radiological progression as selection tool in terms of drop-out rate [9].

Secondarily, CT scans older than 5 years are not always well evaluated by mRECIST criteria.

In conclusion, waiting for reliable preoperative predictive markers of both adverse outcome and response to pretransplant treatment [10], morphologic criteria remain the giants in the evaluation of LT candidates. Biological criteria still are the dwarfs. However, when dwarfs climb the shoulders of giants, they have the chance to see far, allowing longer survivals.

Conflict of interest

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Quirino Lai*
Starzl Unit of Abdominal Transplantation, St. Luc University Hospital, Catholic University of Louvain, Brussels, Belgium
Department of General Surgery and Organ Transplantation, Umberto I Hospital, Sapienza University, Rome, Italy
*Corresponding author.
E-mail address: lai.quirino@libero.it

Alfonso W. Avolio
Liver Unit, Department of Surgery, Agostino Gemelli Hospital, Catholic University, Rome, Italy

Ivo Graziadei
Gastroenterology and Hepatology, Department of Internal Medicine II, Innsbruck Medical University, Innsbruck, Austria

Jan Lerut*
Starzl Unit of Abdominal Transplantation, St. Luc University Hospital, Catholic University of Louvain, Brussels, Belgium
*Corresponding author.
E-mail address: Jan.lerut@uclouvain.be

For the European Hepatocellular Cancer Liver Transplant (EurHeCaLT) Study Group

Reply to "Response to locoregional treatment and alpha-fetoprotein trend in liver transplant candidates for HCC: *Dwarfs standing on the shoulders of giants*"

To the Editor:

I thank Dr. Lai for his letter stressing some important issues of our recent publication [1]. With great interest I have recognized that Dr. Lai's analysis of the EurHeCaLT data endorse the principles of our statements in a much greater cohort of patients [2]. We have focussed on response of hepatocellular carcinomas