Introduction: Patients with hepatocellular cancer (HCC) within Milan Criteria (MC) waiting for liver transplantation (LT) are approached in two different ways: direct LT vs. first treating the tumor using LRT. In these patients, the usefulness of LRT is still questioned.

Aim: To investigate the role of LRT in patients with MC-IN HCC waiting for LT in terms of risk of de-listing, intention-to-treat (ITT) survival and post-LT recurrence.

Material and Methods: the EurHeCaLT database allowed to identify 1177 MC-IN HCC patients listed for possible LT. Using propensity score matching, two homogeneous groups of directly transplanted (n = 205) vs. firstly LRT treated patients (n = 205) were studied.

Results: Median follow-up period was 3.6 years (IQR: 1.5–7.5). Comparing the groups, only two differences were observed, namely a longer median waiting time in the LRT-first group (5 vs. 4 months; p = 0.04) and a greater median dimension of the target lesion at the moment of LT or de-listing in the direct-LT group (2.0 vs. 1.7 cm; p < 0.0001). At multivariate Cox regression analysis, three indepen- dent risk factors for ITT-death were identified: MELD (HR=1.04; p = 0.005), radiological progression beyond MC (HR = 2.04; p = 0.03) and alpha-fetoprotein slope >15 ng/mL/month (HR = 1.75; p = 0.03). At multivariate analysis, multimodal LRT approach (HR=3.18; p = 0.01) and maximal diameter of the main HCC lesion (HR = 1.53; p = 0.045) were independent risk factors for post-LT recurrence. Repetitive LRT was not a significant risk factor in both the analyses. Survival over one year in de-listed patients was more common in LRT-first cases (5.9 vs. 1.0%; p = 0.01).

Conclusions: The use of (repetitive) LRT has no detrimental effect in MC-IN patients waiting for LT. LRT represents a tool allow- ing to further optimize the liver allocation process by selecting patients presenting a high-risk for drop-out (avoiding thereby futile liver transplants). The biological tumor response to the LRT is more than the LRT itself the strongest predictor of intention-to-treat sur- vival and recurrence.