Transplant International

INVITED COMMENTARY

Remnant vital tissue following locoregional therapy for hepatocellular carcinoma: another player in the game

Angel Rubin[1,2] & Marina Berenguer[1,2,3]

1 Hepatology and Liver Transplantation Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain
2 CIBERehd, Instituto Carlos III, Madrid, Spain
3 Faculty of Medicine, University of Valencia, Valencia, Spain

Correspondence
Marina Berenguer MD, Hospital Universitario La Fe, Avda Fernando Abril Martorell n° 106, Valencia 46026, Spain.
Tel.: +34 659072301;
fax: +34 961246257;
e-mail: marina.berenguer@uv.es

Transplant International 2018; 31: 972–974

Received: 18 April 2018; Accepted: 19 April 2018

LT is considered the best curative treatment for patients with cirrhosis and HCC within Milan criteria (MC) [1], but its applicability is limited by the shortage of liver grafts. In addition to tumor size and number, other variables, particularly those that are surrogates of tumor biology, should be identified, validated, and incorporated into the HCC allocation policy to improve the current suboptimal estimation of post-LT benefit. LRT are typically used to bridge the patient to LT and are recommended if the expected waiting time for LT is longer than 6 months [2]. Alternatively, HCC downstaging through LRT may result in transplant eligibility in a proportion of out-of-MC patients [3]. Interestingly, in clinical practice there is a widespread attitude to treat most wait-listed patients [4]. One advantage of LRT is the potential to identify patients with different probabilities of cancer progression; partial or no response to LRT has been shown to be associated with a higher recurrence rate after LT [5]. In that sense, it has been suggested that response to pre-LT LRT, assessed through radiological mRECIST criteria, represents a surrogate marker of tumor biology [6,7]. Hence, for patients with high tumor load or poor radiological response, the test of time (3 months of observation after LRT and subsequent restaging) – "ablate and wait" [8] – can be helpful in selecting the adequate HCC candidate to LT by excluding those with rapidly progressive lesions. In recent years, there has been an accrued interest on assessing the impact of LRT on long-term outcome post-transplantation. A recent systematic review and meta-analysis concluded that the use of LRTs is associated with a nonsignificant trend toward improved wait-list and post-transplant outcomes, although the authors also highlighted the high risk of selection bias in the available evidence [9]. Importantly, the effectiveness of bridging LRT on reducing HCC recurrence and improving post-LT survival

doi:10.1111/tri.13274

appears to be limited to patients who achieve a complete pathologic response evaluated on explant pathology [10]. In this issue of *Transplant International*, Manzia *et al.* [11] analyze the role of remnant vital tissue (RVT) of the target lesion after LRT in predicting post-LT HCC recurrence. The study is based on a multicenter cohort of 276 patients undergoing LRT (with a median of two procedures per patient) followed by LT (with a median waiting time of 4 months). At referral 79.3% of patients were radiologically classified as MC-IN with 20.7% MC-OUT but up-to-7-IN [12]. Of the latter, 75.4% were successfully downstaged to MC-IN. HCC was solitary in 68% cases, and in 93% of the cases, the target lesion was ≤5 cm (median target lesion size of 2.6 cm). The most common LRT applied was transarterial chemoembolization. Pre-LT mRECIST response was considered complete in 53%, partial in 24%, stable disease in 10%, and with disease progression in 12%. Median necrosis of the target nodule was 70%, and median RVT was 0.7 cm. The authors found that the size of de RVT in the target HCC at pathologic examination is a strong independent determinant of HCC recurrence, so that only 5% of patients (either within or beyond MC) with no RVT showed a 5-year HCC recurrence compared to 40% in patients having a RVT ≥ 2 cm. To date, this is the first study evaluating in detail the specific magnitude of the pathological RVT in the target nodule and suggesting that a cutoff value of RVT >2 cm (n = 65) is an important predictor of post-LT disease-free survival and recurrence. As expected, this group of patients had higher alpha-fetoprotein (AFP) levels, lower rates of complete response and higher rates of partial response along with worse tumor grade, higher microvascular invasion, and more frequent MC-OUT, all known risk factors associated with HCC recurrence. In addition, when only pathological aspects were investigated, RVT ≥2 cm was a strong predictor of recurrence, similar to microvascular invasion and superior to poor grading or histological MC-OUT status. The study had some limitations such as its retrospective design, the relative small sample size and particularly the low number of recurrences (n = 30), and a short median follow-up (slightly > 2 years). Another caveat is the definition of RVT, calculated at the target nodule without consideration of additional treated lesions in cases with multiple lesions and multiple treatments. The cumulative tumor diameters (sum of the maximal tumor diameters) were not analyzed either nor the presence of microsatellite lesions. Finally, the authors did not analyze the dynamic evolution of AFP in response to LRT or the possible correlation with the amount of RVT. A major advantage of the study though is that response to LRT was evaluated through mRECIST criteria, considering intratumoral necrotic areas when estimating the decrease in tumor load, and not just a reduction in overall tumor size. The study findings are consistent with previous studies that report lower HCC recurrence rates in patients with complete pathological response after LRT [10,13]. In summary, RVT could be useful in the future development of new prognostic scores similar to the RETREAT score [13] to estimate the risk of HCC recurrence. However, the applicability of the findings raised by Manzia *et al.* in optimizing allocation in HCC patients is still unclear given that pre-LT radiological findings did not predict accurately the extent of RVT and that RVT can only be determined in the explant. The main benefit derived from this study is possibly to consider patients with RVT ≥ 2 cm in the explanted liver at high risk of HCC recurrence and include them in specific immunosuppression and surveillance protocols. In addition, given that RVT was also associated with HCC recurrence in MC-IN patients, the authors proposed a more liberal use of LRT in this group of patients. However, one should also weight in the potential side effects associated with LRT, particularly TACE [14] and the fact that improved outcome is possibly limited to those with adequate response to LRT, as suggested by a recent large study [5]. In conclusion, this is the first, large-scale study to show a significant relationship between RVT size and post-LT outcome, with worse disease-free survival observed in those with remnant HCC tissue size >2 cm. Another player in the game to predict outcome for HCC patients!

Funding

The authors of this study have not been funded.

Conflict of interest

The authors have declared no conflicts of interest.

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