

Locoregional therapy response in patients with hepatocellular cancer waiting for liver transplantation: Only selection or biological effect?

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Abstract

Locoregional treatments (LRT) represent a broad strategy used for reducing the risk of drop-off and contextually improving the survivals in patients with hepatocellular cancer receiving a liver transplantation (LT). However, it is not sufficiently clear if LRT are only a surrogate of tumor aggressiveness or if they consent a real benefit in terms of tumor stabilization. A recent study by Pommergaard *et al* reported the results from the European Liver Transplant Registry. Patients receiving LRT before LT had better 5-year survival rates respect to no-LRT cases (69.7% vs 65.8%; $P < 0.001$). When the number of LRT was tested, one-to-two treatments were connected with improved survivals respect to no treatment [hazard ratio (HR) = 0.85 and 0.71, respectively]. The efficacy of LRT was also reported in the presence of larger tumors (HR = 0.78) and micro-macrovascular invasion (HR = 0.71). The results observed in the present study are partially in discordance with other analyses showing a detrimental effect of LRT. The main problem in the interpretation of these results is connected with the possible initial selection biases present in the studies. The most recent guidelines suggest to perform LRT before the transplant, but the level of evidence is typically low due to the absence of prospectively designed studies.

Key words: Allocation; Recurrence; Trans-arterial chemo-embolization; Radiofrequency ablation; Model for end-stage liver disease

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Core tip: The role of locoregional treatments in the setting of hepatocellular cancer and liver transplantation is controversial. On one side, neoadjuvant approaches should consent a selection of tumor aggressiveness. On the other side, a real survival improvement thanks to the tumor ablation should be achieved. Recent evidences report an effective beneficial role of locoregional strategies in terms of survival and recurrence. However, several biases must be taken into account in these studies, due to the heterogeneous characteristics of treated *vs* untreated subjects. Further studies are need with the intent to clarify this important topic.

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INTRODUCTION

Liver transplantation (LT) represents the gold-standard treatment in patients with unresectable hepatocellular cancer (HCC) developed on underlying cirrhosis^[1]. Unfortunately, LT represents a scarce resource, mainly due to the limited number of available donors^[2]. Thus, in patients awaiting LT, disease burden may progress beyond the conventional LT criteria while on the waiting list^[3]. Several strategies have been adopted with the intent to alleviate the risk of drop-out due to tumor progression: for example, Model for End-Stage Liver Disease (MELD) exception points are routinely used in several regions in the presence of T2 HCCs^[4]. Another widespread strategy is the use of locoregional treatments (LRTs) as a neo-adjuvant strategy with the intent to bridge patients to LT^[5] or downstage patients initially outside transplantation criteria^[6].

Response to LRT has been correlated with improved post-LT survival rates in several studies^[7,8]. However, it is not sufficiently clear if LRTs are only a surrogate of tumor aggressiveness, efficaciously selecting patients with favorable tumor biology, or if they are beneficial concerning tumor stabilization, mainly in case of complete or partial response.

STUDY ANALYSIS

In a recent Issue on Transplant International, Pommergaard *et al*^[9] reported the results of a multicentric study based on the European Liver Transplant Registry (ELTR) and focused on the use of LRT in HCC patients undergoing LT. A total of 4978 patients (no LRT = 1406, 28.2%; LRT = 3572, 71.8%) were enrolled. As expected, the median waiting time was longer in the LRT group

(4 mo *vs* 1.7 mo; $P < 0.001$) and the median MELD score was higher in the directly transplanted subjects (12 *vs* 10; $P < 0.001$). Overall, patients receiving LRT before LT had better 5-year survival rates respect to no-LRT cases (69.7% *vs* 65.8%; $P < 0.001$). When the different treatment types were investigated, the use of radiofrequency ablation (RFA) had the strongest association with an improved overall survival [hazard ratio (HR) = 0.51]. The beneficial effect was also observed in case of the combination of RFA and trans-arterial chemo-embolization (TACE) (HR = 0.74). Several sub-analyses were also done. As for the number of LRT performed, one-two treatments were connected with improved survivals respect to no treatment (HR = 0.85 and 0.71, respectively). On the opposite, three or more treatments showed no association (HR = 1.11).

When a subclass of HCCs being larger (> 3 cm) or with more nodules (> 5 lesions) was examined, LRT maintained their protective role for the risk of death (HR = 0.78). In this context, RFA, TACE or combined RFA + TACE all were significantly associated with improved survival (HR = 0.54, 0.81, and 0.60, respectively).

Stratifying the entire population according to the underlying liver status (cirrhosis *vs* non-cirrhotic liver), in case of HCC on cirrhosis LRT were also protective (HR = 0.86).

In the presence of pathological micro-macrovascular invasion, the effect of LRT was strong (HR = 0.71). Both RFA and TACE (HR = 0.54 and 0.69, respectively) were associated with improved survival.

PERSPECTIVE

The role of LRT in the setting of HCC and LT has not been fully clarified, mainly in light of the potential detrimental effects of repetitive treatments. For example, a recent meta-analysis performed on 1122 TACE patients showed an increased risk of post-LT hepatic artery complications (odds ratio = 1.57; $P = 0.02$)^[10]. Another study from the US performed on 3601 patients all meeting the Milan Criteria, showed that the increasing number of LRT significantly predicted post-LT recurrence (3 LRTs: HR = 2.1; $P < 0.001$; 4 + LRTs: HR = 2.5; $P < 0.001$)^[5]. Interestingly, LRT patients achieving complete response had superior 5-year recurrence-free survivals when compared with untreated cases or LRT subjects not achieving complete response (72% *vs* 69% *vs* 67%; respectively)^[5]. The here described study performed on a large population of European HCC cases showed the beneficial role of LRT, mainly in case of RFA use. Moreover, the repetitive number of treatments was not connected with worse results. LRT maintained their protective role for the risk of death even when larger tumors or harmful clinical conditions like vascular invasion were investigated. It is difficult to definitively clarify if the LRT only select low-risk HCC, or if their ability of tumor burden zeroing should also have some impact regarding survival improvement. It is clear that

the response after LRT is a robust predictor of post-LT course. A recent large multicentric European study based on 2103 HCC patients identified the poor radiological response after LRT as one of the most important predictors for the risk of low intention-to-treat benefit after transplant^[11]. Another multicentric European study performed on 276 cases all treated with LRT showed that an HCC-related remaining vital tissue in the main lesion ≥ 2 cm at pathological assessment after LT was a strong independent risk factor for post-LT recurrence (HR = 5.6; $P < 0.001$)^[12]. All of these results have been positively recognized by the recent European Association for the Study of the Liver (EASL) guidelines, in which it is stated that "in LT candidates with HCC, the use of pre-transplant (neoadjuvant) loco-regional therapies is recommended if feasible, as it reduces the risk of pre-LT drop-out and aims at lowering post-LT recurrence - particularly when complete or partial tumour response are achieved"^[13]. Unfortunately, although the strength of recommendation for this statement is strong, the scientific evidence is low, clearly underlining the lack of prospectively designed studies. More researchers are needed, with the intent to better explore the role of LRT concerning intention-to-treat survivals.

Moreover, we should remember the critical impact that local allocation rules and waiting time duration may play on the role and the effect of LRT. As an example, in the United States most HCC patients wait for at least six months from the diagnosis before having the opportunity to be transplanted. More studies also focused on these aspects are surely needed.

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