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# Risk factors and management of post-liver transplant recurrence of hepatocellular carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) is one of the most common indications for liver transplantation (LT). With expanding criteria and increasing number of transplants, post-transplant recurrence of HCC remains an important cause for concern and portends a poor survival in these patients. Traditionally, HCC recurrence post-LT has been notoriously difficult to manage and their outcomes dismal. A better understanding of the tumour biology and its interplay with the immune system, combined with newer oncological interventions has allowed for improved survivals in these patients. A useful classification of HCC recurrence is where it is divided into oligo-recurrence and disseminated recurrence. This system helps strategize their multi-disciplinary management algorithm and prognosticate outcomes. We provide an overview of the factors which may predict recurrence and summarise the current evidence on the management of post-LT HCC recurrence.

**Keywords:** Hepatocellular carcinoma, post-liver transplantation, recurrence, management

## INTRODUCTION

Hepatocellular carcinoma (HCC) especially in a cirrhotic liver is best treated by liver transplantation (LT) for a myriad of reasons. Apart from providing the widest possible resection margin, LT also treats the underlying liver disease and removes the tumorigenic liver reducing the risk of recurrence. Nevertheless,

despite stringent morphologic selection criteria like the Milan criteria (MC), recurrence is observed in 6%-20% of patients transplanted for HCC[1-3]. Conventionally, post-LT tumour recurrence (TR) has been notoriously difficult to treat and has a universally poor prognosis. It is hence imperative that modifiable risk factors are elucidated. This will help improve patient selection and potentially reduce TR. With no strong consensus or large trials, literature with regards to its management is limited, and often anecdotal. The present narrative review summarizes the current available literature on the risk factors for TR and the management algorithm for HCC recurrence after LT.

## EPIDEMIOLOGY

Despite expanding indications and better elucidation of tumour biology, the incidence of TR has remained remarkably constant over the past two decades at 10%-20%. As demonstrated in a systematic review which included 61 studies, the median time from LT to TR was 13 months (range: 2-132 months) with a recurrence rate of 16%[4]. Even though TR as late as 10 years post-LT has been documented, TR is frequently observed in the first 2 post-LT years. TRs are most commonly observed extrahepatically (as high as 70%); intrahepatic (within the liver graft) recurrence is a rarer phenomenon[1,2,5]. Although post-TR survival show improving trends in recent years, the median survival rates are still under 2 years[1-6].

## RISK FACTORS FOR TUMOR RECURRENCE

Before embarking on the management of post-LT HCC recurrence it is imperative to understand the interplay of tumour, patient, and treatment related factors which may be linked to the increased risk of TR in the post-LT setting.

### Tumour morphology, staging, vascular invasion

The MC set the benchmark for size and number of nodules in predicting the risk of TR and survival in HCC patients undergoing LT[7]. However, it must be borne in mind that the size of the tumour correlate more closely with the risk of TR than the number[8-11]. A meta-analysis of 101 articles by Germani *et al.*[9] showed that the risk of TR had no association with the number of nodules, but was directly proportional to the diameter of the largest nodule. Another cohort study showed 36% increase in the risk of TR for each centimetre increase in the diameter of the largest tumour nodule[11]. The reason postulated in the study was that the size of the tumour directly correlated with the risk of vascular invasion. Hence, size of the tumour is a higher risk factor for HCC recurrence than the number of tumours[3,8,9,11]. Several units have utilised this principle to expand on the MC, demonstrating similar survival figures with their "expanded" criteria. These principles have been succinctly summarised in the "metro-ticket model" for HCC[12].

Macrovascular tumour invasion is considered a contraindication for LT and can be detected on pre-transplant imaging[9-11,13]. Microvascular invasion (mIV) on the other hand can only be identified on explant histopathology. The presence of mIV doubles the risk of death in patients with HCC; it is hence an important factor determining the risk of TR[3,9,10,13]. As also shown by Agopian *et al.*[14] in their series of 865 patients who underwent LT for HCC, the risk of TR was increased by 2-7 times in the presence of vascular invasion. Staging systems act as a surrogate marker for mIV. Tumours within the MC (stage T2 HCC) and beyond MC (up to 7 criteria) were observed to have 16.6% and 50.2% mIV respectively on explant histopathology[3,8,12,14].

### Degree of differentiation

Differentiation of a tumour is an indication of its biology. On explant histopathology 11%-25% of tumours have been noted to be poorly differentiated[9,15,16]. This frequency increases with progressive expansion of the morphological selection criteria. A significantly higher risk of up to 40% TR has been observed when the

tumour is poorly differentiated[16]. Unfortunately, due to its inherent bias, pre-LT tumour biopsy has a poor sensitivity (29%) and positive predictive value (35%) in identifying these sub-group of tumour; and is not recommended[17].

### Circulating tumour cells and cell-free DNA

The field of biomarkers is an area garnering a lot of interest. These markers are important when the tumour is a non-secretor with regards to conventional tumour markers like alpha-fetoprotein (AFP). Potentially a simple blood test can help in the diagnosis, prognostication, and management of TR, a modality termed as "liquid biopsy"[18-20]. Detecting circulating tumour cells (CTC) is one such tool which enables the assessment of treatment completeness. Epithelial cell adhesion molecule (EpCAM)-positive CTC in the peripheral blood have shown to demonstrate a significant association with advanced disease and shorter overall survival. A study from China which included 193 post-LT for HCC patients demonstrated that the presence of EpCAM-positive CTC was predictive of TR[21,22]. The significant finding in the study was that serial CTC monitoring detected TR even in tumour marker (AFP and PIVKA-II) negative patients. Another series from Germany showed that the positive predictive value of CTC detection for TR was 89%, even when the TR was untraceable by current imaging techniques[23]. The study also showed that CTC could define the burden of micro-metastases and hence was also useful in prognosticating TR.

Circulating cell-free DNA (cfDNA) is a short fragment of double-stranded extracellular DNA that is released into the bloodstream by tumour apoptosis and/or dead cells, and is found in many types of cancers including HCC[24-28]. The development of next generation sequencing has allowed for this modality to mature into one of clinical importance. The levels of cfDNA drop back to normal when a tumour is completely removed. Hence, the levels of postoperative circulating cfDNA correlate with the presence of microscopic residual disease. Therefore, postoperative cfDNA helps identify the high-risk group for TR and has potential to be excellent monitoring tool for TR, especially when traditional methods of cannot provide evidence[24-28].

### Alpha-fetoprotein and response to loco-regional therapy

Sixty percent of patients with HCC have elevated AFP levels. Very high AFP levels (> 1000 ng/mL) are strongly associated with mIV and high TR (47% at 5 years)[1,3,13,29]. Based on this statistic, certain centres exclude patients from the LT waitlist when the AFP levels are higher than 1000 ng/mL. Interestingly, a very low AFP (< 16 ng/mL) also predicts a poor post-LT survival[1,3,11,13,29]. A dramatic reduction in AFP following locoregional therapy (LRT) indicates an absence of extra-hepatic disease, and is a favourable prognostic indicator[3,11]. Response to LRT is also a marker of the biological behaviour of the tumour[30-32]. As shown by Merani *et al.*[33], even patients with an initial AFP above 1000 ng/mL could achieve a good outcome as long as their AFP dropped below 400 ng/mL with LRT. A systemic review and meta-analysis of studies over a 20-year period showed that patients who were initially beyond MC (stage T3 HCC) and received LRT as down-staging therapy had a significantly higher 1-year and 5-year post-LT overall and disease-free survival (DFS) rates[3,32]. Hence, LRT as downstaging or bridging therapy also plays a valuable role in prognostication.

### Neutrophil-lymphocyte ratio

Neutrophil-lymphocyte ratio in the peripheral blood is a marker of inflammatory response. Aggressive tumours are noted to elicit a more exuberant inflammatory response; this phenomenon can be assessed using the neutrophil-lymphocyte ratio[30-32]. It is utilised as an easily accessible tool to prognosticate tumours. Though not widely used, an elevated neutrophil-lymphocyte ratio (> 5), as confirmed by a meta-analysis, has been associated with higher mIV and poorer survival[30-32].

### Aetiology

Post-LT reactivation of hepatitis B virus (HBV) has shown a strong association with TR[30-32]. There is also a direct correlation of the HBV viral load and TR. Those with HBV viral load above 5 log have a 2.5-fold risk of TR[30-32]. Interestingly the opposite is also true, studies have shown a very good temporal relationship between TR and HBV reactivation. TR is associated with an increased risk of HBV recurrence after LT, suggesting that HBV replication in tumour cells may contribute to this viral recurrence[34,35]. Data with regards to hepatitis C virus (HCV) treatment with directly acting antiviral therapy (DAA) and TR has been mixed and needs long-term validation[36-39]. While the sustained virological response (SVR) rates have been very encouraging, the incidence of HCC in HCV patients has remained relatively constant[40-42]. Literature is divided with regards to SVR achieved by DAA and their effect of TR. In the CUPILT cohort, of 313 patients, only 2.2% who achieved SVR had TR[37]. While a smaller series showed a higher TR (28%) in patients treated pre-LT with DAAs[36]. Another study from Milan further muddied the waters by showing no significant difference in TR among patients treated pre-LT with DAAs[42].

Up to a quarter of patients undergoing LT for HCC are obese. Obese patients tend to have a higher frequency of mIV and consequently a higher risk of TR[3,43]. This could be due to an increased expression of vascular endothelial growth factor (VEGF) from their adipose tissue which stimulates angiogenesis. Contrary to this, HCC in non-alcoholic fatty liver disease patients have a more indolent behaviour. Studies including those analysing the UNOS database have shown a 32%-80% lower rate of high-risk characteristic of TR[3,44,45].

### Time to LT and bridging therapy

Time to LT plays a significant part in the outcome. A waiting period enables an assessment of tumour biology[46]. On the other hand, allowing too long a waiting period will lead to tumour progression and a poorer outcome. A multicentre study from North America noted that patients had a significantly higher risk of TR if transplanted before 6 months or after 18 months of diagnosis of HCC[47]. During this waiting period rigorous follow-up is indicated along with bridging therapy to prevent dropouts. A favourable response to bridging therapy in the form of complete necrosis has been associated with a lower risk of TR[48-50]. A partial necrosis on the other hand, is associated with a higher risk of lymph node metastases and consequently a higher TR[48,49].

### Donor age

Evidence in this regards points to a higher risk of TR when older liver grafts are used in the LT. This has been linked to increased preservation injury and susceptibility to cold ischemia[51]. Liver grafts from donors older than 60 years of age have been linked to a 70% higher risk of TR than those patients who received younger liver grafts[52].

### Ischemia time and ischemic/reperfusion injury

Ischemia-reperfusion injury incites an inflammatory reaction which can accelerate tumour growth and promote micrometastases. A significantly higher risk of TR has been observed when the cold and warm ischemia times are over 10 h and 50 min respectively[3,51,53].

### Surgical technique

Minimal manipulation of the tumour-bearing liver during explant hepatectomy remains a crucial aspect of the operation[54,55]. Breach or spillage can lead to dissemination of tumour cells. The piggyback technique of LT involves preserving the native inferior vena cava. This technique could potentially involve a more vigorous manipulation of the liver while mobilising the liver off the inferior vena cava. There are reports of a "no-touch" modification to the explant hepatectomy in living donor LT (LDLT) which enable a complete

hepatectomy without manipulating the tumour-bearing liver[56,57]. Herein, a veno-venous bypass is created, and the native inferior vena cava is excised and replaced with a prosthetic graft. Literature evidence is sparse in this regard, and a study by Mangus *et al.*[54] found no difference in the rates of TR irrespective of the technique of outflow reconstruction[1,3,55]. Early studies including a meta-analysis comparing LDLT and deceased donor LT (DDLT) for HCC reported 60% greater DFS in patients who underwent DDLT than those who underwent LDLT[3,13,58,59]. The possible explanations for poorer outcomes in the LDLT arm included a shorter waiting time to LT, which did not allow for an assessment of the tumour biology and identification of more aggressive tumours. Another reason suggested was the greater surgical manipulation in LDLT which could potentially contribute to the spread of neoplastic cells. Finally, it was suggested that rapid liver graft regeneration along with release of growth factor and cytokines could promote tumour growth and lead to TR. However, more recent and larger series including those from the A2ALL cohort have shown similar TR and DFS for LDLT and DDLT and that the previously presented results were skewed due to a staging bias[13,58-62].

### Immunosuppression

It has indubitably been shown that the native immune system is a key player in cancer control and that a subdued immune defence combined with tumour induced inflammation are responsible for TR[2-4,63]. A 2.8-fold higher risk of TR has been observed in patients who had high calcineurin inhibitor (CNI), specifically tacrolimus levels (above 10 ng/mL) in the first month post-LT[1,3,64,65]. mTOR inhibitors are a class of immunosuppressants which inhibit angiogenesis and cell proliferation. This purported anti-tumour effect is a property which is being explored to expand its applicability in transplant oncology two meta-analyses of 5 and 42 studies respectively noted a significantly lower risk of TR when mTOR inhibitors were used as immunosuppressants in conjunction with CNIs[66,67]. The multicentre randomised SILVER trial aimed at assessing the efficacy of mTOR inhibitors (sirolimus) in LT for HCC. The mTOR inhibitor group had a 50% lower risk of TR at one year and a higher DFS at 4 years post LT[68]. This benefit was observed in the younger population and in tumours within MC. There was also a gain of 6.4 months of DFS in the mTOR inhibitor group. The role of other immunosuppressants like antimetabolites, corticosteroids, or monoclonal antibodies have not been adequately assessed to make for a meaningful conclusion[3,5,13,63]. Nonetheless, reports suggest a generally increased risk of post-LT malignancy with their use. To summarise, minimising immunosuppression is a prudent approach. A higher dose of CNIs, especially in early post-LT period is associated with a higher risk of TR, while mTOR inhibitors reduce the risk of TR.

## POST-LT SURVEILLANCE

There is no firm consensus on the protocol, frequency or duration of monitoring TR after LT[50,69,70]. Most centres follow a similar protocol of thoraco-abdominal CT and AFP levels at 3- to 6-months intervals during the first 2 or 3 years. The interval between the tests is increased after 2 years. A bone scintigraphy and/or PET Scan is reserved for patients who present with symptoms or suspicion of TR. In an attempt to stratify the risk of TR, studies have proposed objective scoring systems on the basis of AFP, histopathological characteristics like mIV, and tumour morphology[69,71,72]. These have, however, not found widespread acceptance and remain sporadically used.

## STAGING

TR is essentially a metastatic disease and its management can only be guided by a comprehensive staging process; the essence of which is to delineate the extent of disease. PET-CT scans help in functional and anatomical assessment of the disease burden. Two radio isotopes are routinely used for HCC[73,74]. C11-acetate PET better defines well-differentiated HCC, while the more unfavourable biology tumours tend to be FDG avid. PET-CT are very sensitive in picking up bone metastases[75,76]. When PET-CT is unavailable, a

contrast CT should be combined with Tc-bone scan to complete a skeletal survey[2,4,70].

## MANAGEMENT OF TR

The patient should be jointly managed by the transplant surgeon, physician, oncologist, and radiologist as a multidisciplinary approach.

### Immunosuppression

Irrespective of the type of recurrence, type and dose of immunosuppression should be titrated. The aim is to allow the body's immune system to act against the tumour, while protecting the graft from rejection. Although it is intuitive to reduce CNIs to a sub-therapeutic level, there are no recommendations on the optimum levels which should be maintained in this scenario[2,63,68,69]. Apart from an active dose reduction and immune-modulation, a switch in the immunosuppressants should also be considered. As described previously, while the data on reducing TR is relatively robust for mTOR inhibitors, there is sparse literature on their role in treatment of established TR after LT[66-68]. mTOR inhibitors as monotherapy are poor immunosuppressants and have a higher risk of rejection. It is, therefore, a common practice to incorporate an mTOR inhibitor with a low dose CNI upon the diagnosis of TR. Overall, immunosuppression should be individualized and tapered to permit an anti-tumour immune response.

### Oligo-recurrence

Historically, all post-LT TR were considered terminal events, and were managed with palliation. Classification of recurrence into two categories has allowed for a better definition, delineation of extent of disease, management, and prognostication of the disease load. Broadly, TR can be classified into oligo-recurrence (OR) and disseminated recurrence (DR). The term OR was first introduced in 1995 to described TR that was amenable to surgery or LRT with an aim to achieve either R0 resection or tumour control[77,78]. This classification led to a conceptual shift from a palliative intent to one of cure[1,2,6,77,78]. An objective definition for OR by size, number, or location has not been proposed and may be impractical due to the heterogeneity of TR. Instead, it provides a conceptual viewpoint in the management of TR with a limited tumour burden.

### Extra-hepatic oligo-recurrence

Extra-hepatic TR constitute over 70% of the recurrences[2,4,5]. They are most commonly seen in the lungs followed by the bones. A series from Korea showed a significantly higher 5-year survival rate (44.7% *vs.* 12.8%) when pulmonary OR (defined in the study as up to 3 tumours) were resected[79]. Residual pulmonary reserve and function remained an important consideration in such resections[2,70,79,80]. Stereotactic body radiotherapy (SBRT) is an option for patients where inadequate lung function precludes resection. Experience from a European multicentre series of 637 patients treated with SBRT showed that in well selected candidates the 3-year overall survival was 39.2%. SBRT has also been successfully used to treat OR in the bones (local control of 79%-88%)[6,81,82]. Orthopaedic stabilisation of the affected bone may be needed before or during the course of SBRT to avoid pathological fractures. TR can also occur in the lymph nodes. This when picked up on imaging can be resected in the form of a formal lymph node dissection and clearance. Other extrahepatic sites include the adrenal glands. Options include a surgical excision of the recurrence. Trans-arterial chemoembolization (TACE) has also been shown to be effective in the managing adrenal metastases of HCC[83-85]. Achieving R0 margins has been shown to provide a survival benefit and hence, when feasible, resection should be offered for OR[1,2,6,69].

### Hepatic oligo-recurrence

TR in the liver graft should be differentiated from post-LT *de novo* HCC. Most TR occur early (within 2 years) in the post-LT period, and the characteristics are likely to be similar to that of the primary disease.

On the other hand, *de novo* HCC occur years after LT, and more so in a diseased liver-graft (fibrosis, cirrhosis, chronic rejection, *etc.*). The key consideration between the two lies in its prognostication, *de novo* HCC are more likely to be limited to the liver, and hence amenable to cure when detected early[86].

### Surgery

Resection for liver based OR has been shown to be beneficial. Consideration for surgery may vary depending on the unit's policy and hinges on the tumour burden, location, and post-resection functional liver remnant. Since TR is usually early, liver function itself may not preclude surgery. Several series have shown increased median survival with surgery as compared to systemic therapy (28-65 months *vs.* 5-15 months)[2,4-6,87,88]. It must however be acknowledged that only 25%-50% of patients with OR eventually undergo an operation. This could lead to a selection bias, and the true benefit of surgery may never be elucidated. The presence of adhesions in the hepatic hilum and immunosuppression may explain the higher early postoperative morbidity. Nonetheless, long term survival (up to 70% 3-year survival) has been demonstrated with R0 resection and should be considered when practicable[2,4-6,87,88].

### Radiofrequency ablation/microwave ablation

Concerns of surgical morbidity have prompted an increasing interest in other LRTs like radiofrequency ablation (RFA) and microwave ablation (MWA). However, unfavourable tumour location (proximity to other viscera and blood vessels, superficial lesions, *etc.*) and tumour burden are limiting factors in its application. Survival benefit has been demonstrated for small lesions (< 3 cm in size); the evidence however, is sparse in this regard[2,4,89].

### Trans-arterial chemoembolization

As compared to RFA, TACE allows for a wider area of regional control[90,91]. When anatomically localised, limitations of tumour burden may not apply in this case. Three-year survival of 6%-48% has been achieved with TACE, and disease progression or breakthrough is usually observed in the form of extra-hepatic disease[92-96]. Due to concerns of biliary ischemia related complications, the role of TACE has remained undefined for TR. There are, however, reports of TR control with this modality[94-96].

### Trans-arterial radioembolization

Intra-parenchymal administration of Yttrium-90 microspheres enables a higher intensity to be localised onto the tumour bearing liver. Despite issues like cost and availability, trans-arterial radioembolization (TARE) has gained acceptance in the management of unresectable HCC. The main reason being that tumour or bland portal vein thrombus, is not a contraindication for its application[92,93]. Isolated reports have demonstrated a good response in the management of TR[94-97].

### Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) allows for a focused external beam of RT to ablate the tumour while sparing the adjacent liver. In addition to minimising damage to the normal liver, SBRT also stimulates the immunity and has shown to work synergistically with systemic therapy which modulate the immune system (e.g., anti-PD1 therapy)[2,4,98]. Apart from anecdotal reports of its efficacy in TR, there are no formal studies in this regard. Moreover, the role of immunotherapy is highly controversial in the post-LT setting (discussed below).

### Disseminated recurrence

When the TR is disseminated and not amenable to LRT, the management changes from an intention to cure to one of prolonging survival.

### Chemotherapy

HCCs are notoriously chemo-resistant tumours, and chemotherapy has limited role in its management. Several small series analysing the role of chemotherapy in TR post-LT have shown no objective response[1,2,4,94,99-101]. Numerous chemotherapeutic agents have been used, and this heterogeneity attests to the fact that no one particular regimen is effective. Adverse effect profile in these patients remain another limiting factor in the use of chemotherapeutic agents. A meta-analysis found up to 86% incidence of adverse effects when adjuvant chemotherapy was used in the post-LT setting[94]. The meta-analysis also noted that there was no evidence to demonstrate whether the use of chemotherapy affected TR rates.

### Targeted therapy

Sorafenib is a multi-kinase inhibitor proven to have anti-HCC action. The SHARP trial was the first of its kind to show that sorafenib provided a 3-month survival advantage in patients with advanced HCC[102]. Interestingly, in mice, Sorafenib and mTOR inhibitors have a synergistic effect on inhibiting tumour growth. A study of 15 patients showed a similar survival advantage when the two drugs were combined[101,103,104]. This, however, came at the expense of higher drug toxicity and bleeding complications.

The RESORCE trial was a phase 3 multicentre randomized controlled trial which showed regorafenib to improve survival in patients with advanced HCC which had progressed despite sorafenib therapy[105-108]. It is noteworthy that post-LT TR was an exclusion criterion for the study, as it was in all other phase III studies on systemic therapies. The only study to date to evaluate the role of systemic sorafenib-regorafenib in TR was a retrospective, observational, multicentre, international study involving 14 centres across Europe and Argentina[109]. Despite a near universal occurrence of adverse events, the trial showed a median survival after regorafenib therapy and sorafenib-regorafenib sequential treatment to be 12.9 months and 38.4 months, respectively. Nonetheless, the median time to recurrence in the study was 26.4 months, indicating a bias towards selecting outpatients with a better prognosis. An interesting finding noted in the study was that regorafenib which is a competitive inhibitor of cytochromes led to a significant increase in the levels of CNIs and mTOR inhibitors.

Lenvatinib is a tyrosine kinase inhibitor which blocks VEGF as well as fibroblast growth factor (FGF) and platelet derived growth factor (PDGF) pathways. In the non-LT population, a phase 3 randomised control trial (REFLECT trial) showed non-inferior survival with lenvatinib *vs.* sorafenib (13.6 months *vs.* 12.3 months)[110-112]. The adverse event profile was, however, more severe in the lenvatinib arm. Again, there is no strong data regarding lenvatinib in TR. Anecdotal reports demonstrated an extended time to tumour recurrence when lenvatinib was used as systemic therapy for TR. The patient in an Argentinian case report had over 15 months of disease progression-free survival[113]. Although in that report, the authors conceded that there was lack of clarity on the real benefit of lenvatinib on TR survival. Nonetheless, trials (ClinicalTrials.gov Identifier: NCT04168944) are underway to elucidate its role in TR[114].

Cabozantinib inhibits tyrosine kinases, including VEGF receptors 1, 2, and 3, MET, AXL, and the angiopoietin receptors TIE-2, RET, c-Kit, and FLT-3, which are implicated in the progression of HCC and the development of resistance to sorafenib[115-117]. The CELESTIAL trial was a randomized, double-blind, phase 3 trial which evaluated cabozantinib as compared with placebo in previously treated patients with advanced HCC[115]. Here again LT recipients were excluded from the study. The trials showed an additional 2 months' survival benefit as compared to the placebo group. The drug is however not cost effective and is associated with high-grade adverse events. There hence remains a paucity of data on utilizing cabozantinib as the second-line agent[116,117]. Trials including a phase 2 trial (ClinicalTrials.gov Identifier: NCT04204850) assessing the role of cabozantinib in TR are underway, and are likely to complete accruing patients in the next couple of years[118]. Data in the post-LT population could potentially help cabozantinib be part of the

systemic therapy algorithm of TR.

### Immunotherapy

HCCs are a heterogeneous group of tumours driven by inflammation, and hence the rationale to evaluate immunotherapy[119-121]. The immune response is regulated by immune checkpoints. Inhibiting these checkpoints prompt the native immune system to react against the tumour antigen[119,122]. One such immune checkpoint protein is the programmed death receptor 1 (PD-1)[123]. It is an inhibitory molecule expressed on the surface of multiple tissue types and keeps the T cells from attacking tumour cells. Pembrolizumab and nivolumab are monoclonal immunoglobulins against PD-1 that block the signalling of PD-1[119,122]. Encouraging results have been demonstrated in patients with advanced HCC who previously failed sorafenib treatment[124-127]. Their role however in the post-LT remains undefined, especially since boosting the immune system is likely to increase the risk of rejection[128-130]. Case reports and small series of post-LT patients with TR treated anti-PD1 agents have shown a higher incidence of rejection and graft loss. There have, however, been instances where a total remission of TR has been observed[124,125]. Based on these reports, it can be deduced that younger patients in the early post-LT period on an aggressive immunosuppression regimen were at a significantly higher risk of losing their liver graft. Another molecule which follows a different pathway to modulate the immune system is the CTLA-4. Blockade of CTLA-4 by Ipilimumab may in theory allow for anti-tumour response without affecting graft tolerance[119,121,122]. It can hence be concluded that the place of immunotherapy in managing post-LT TR remains to be defined. Their anti-tumour benefit needs to be balanced against the risk of graft rejection and loss. Further studies in large patient cohorts will help elucidate this conundrum.

## CONCLUSION

There is paucity of high-level evidence and a limited experience in the management of post-LT TR. A multi-disciplinary management provides the best possible outcome for these patients who would otherwise have a dismal outcome. Striking a fine balance between tapering immunosuppression to allow for the native immune action against HCC while protecting against rejection is the first step in the management of these patients. Stratifying TR into oligo- or disseminated recurrence enables better prognostication and application of more aggressive therapeutic strategies in selected patients.

## DECLARATIONS

### Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Rammohan A, Rela M

Performed data acquisition, as well as provided administrative, technical, and material support: Rammohan A, Rela M

Final approval of the article: Rela M

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

Both authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

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