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MINIREVIEWS

Challenges related to clinical decision-making in hepatocellular carcinoma recurrence post-liver transplantation: Is there a hope?

Nourhan Badwei

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Abstract

Hepatocellular carcinoma (HCC) is a common liver malignancy and represents a serious cause of cancer-related mortality and morbidity. One of the favourable curative surgical therapeutic options for HCC is liver transplantation (LT) in selected patients fulfilling the known standard Milan/University of California San Francisco criteria which have shown better outcomes and longer-term survival. Despite careful adherence to the strict HCC selection criteria for LT in different transplant centres, the recurrence rate still occurs which could negatively affect HCC patients' survival. Hence HCC recurrence post-LT could predict patients' survival and prognosis, depending on the exact timing of recurrence after LT (early or late), and whether intra/extrahepatic HCC recurrence. Several factors may aid in such a complication, particularly tumour-related criteria including larger sizes, higher grades or poor tumour differentiation, microvascular invasion, and elevated serum alpha-fetoprotein. Therefore, managing such cases is challenging, different therapeutic options have been proposed, including curative surgical and ablative treatments that have shown better outcomes, compared to the palliative locoregional and systemic therapies, which may be helpful in those with unresectable tumour burden. To handle all these issues in our review.

Key Words: Hepatocellular carcinoma; Recurrence; Liver transplantation; Prognosis; Clinical decisions; Management

Core Tip: In this review, challenges and debates related to the management of hepatocellular carcinoma recurrence after liver transplantation (LT) were carefully handled, discussing the risk factors, pre/post-LT prediction models of tumour recurrence, and different therapeutic approaches either curative or ablative in the settings of post-LT immunosuppression.

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INTRODUCTION

Hepatocellular carcinoma (HCC) represents the most common form of primary liver malignancy, which mainly occurs in chronic liver disease patients with underlying cirrhosis. Over the last two decades, HCC incidence has been increasing globally, mainly in Africa and Asia, and it's expected to continue rising till 2030, owing to the prevalence of viral aetiology, which causes end-stage liver disease with HCC, also steatotic liver disease is a growing critical issue which is endemic in certain regions including united states and occurs in those with underlying obesity, dyslipidaemia and diabetes[1,2]. Several therapeutic options have been listed in international liver societies' guidelines, including hepatic resection and liver transplantation (LT) which represent the surgical curative therapies in selected patients with HCC. As regards LT, it has been preferred in earlier-stage HCC patients who fulfil the standard Milan/ University of California San Francisco (UCSF) criteria, owing to the removal of both the tumour burden and the rest of the underlying cirrhotic carcinogenic background, hence providing longer survival outcomes of up to 70% over 5 years, also other expanded criteria have been proposed in different transplant centres that yield lower survival rates compared to the standard Milan/UCSF criteria[3-6]. Despite careful adherence to the strict HCC selection criteria for LT in different transplant centres, up to 20% of transplanted HCC patients may develop tumour recurrence which negatively affects up to 25% of cases survival. Therefore, HCC recurrence acts as a prognostic predictor for morbidity and mortality among post-LT HCC patients. The timing of HCC recurrence can be categorised into early and late, the earlier occurs within 24 months post-transplantation and is frequently associated with poor prognosis, it's thought to be a result of HCC micro-metastasis engraftment, as HCC cell clones might circulate before, during or even after the time of surgery from non-detectable-extrahepatic-metastasis. On the contrary late HCC recurrence, occurs beyond two years and is often associated with a better prognosis, it may be related to delayed latent or de novo tumor cell engraftment which usually occurs on chronic liver disease or cirrhotic allograft. Most recipients commonly present with extrahepatic HCC recurrence in the lungs, bone, and adrenals, however, combined intra/extrahepatic recurrence may occur (40%) and the intrahepatic site of tumour recurrence is considered the least one[7-10].

RECURRENCE RISK FACTORS ASSOCIATED WITH HCC PATIENTS

The concept of hepatocarcinogenesis mainly relies on persistent injury by different risk factors with lipotoxicity-induced oxidative stress of hepatic parenchyma that eventually results in fibrosis with increased risk of genomic instability and tumorigenesis microenvironment development in a cirrhotic background. Genetic studies have correlated the HCC genomic landscape with onco-drivers, such as somatic mutations, copy number variations, and epigenetic modifications. Hence two main HCC groups have been classified in different studies according to the characteristic genomic alterations with subsequent oncogenic pathways of the next-generation sequencing, and so differ in the histopathological features and the prognosis; The proliferative variant is usually characterised by poor histopathological features, presence of vascular invasion, and so elevated tumour biomarkers, hence it's considered an aggressive phenotype with worse outcome and high recurrence rate. On the contrary, the non-proliferative phenotype has been associated with better survival owing to favourable clinicopathological features. Regarding the 2 major HCC subclasses, they have been identified through integrated criteria of histological features, transcriptomic analysis, and genetic aberrations; The proliferative variant is most often poorly differentiated, associated with chromosomal instability/TP53 mutations, and even includes cancer cells with progenitor features. On the contrary, the non-proliferative subgroup mainly displays a well-differentiated phenotype with chromosomal stability and preserved hepatocytic markers expression. The reflection of previous data on clinical practice and management may somehow explain the heterogeneity in tumour behaviour, which could affect the diagnosis and even prognosis of HCC patients[11,12]. Various studies have thoroughly discussed risk factors and predictors for HCC recurrence integrating them into different pre/post-transplant prediction models, which include bio-humoral markers, radiological and pathological features, tumor doubling time progression and post-locoregional therapeutic response; Regarding medical predictors for HCC recurrence that have been reported in several studies, mainly include larger tumor size, advanced histopathological features, presence of vascular invasion (micro/macro), and elevated alpha-fetoprotein (AFP), moreover, the association with AFP-mRNA, AFP-L3, Des-gamma carboxy prothrombin, and inflammatory marker levels (the neutrophils-to-lymphocytes ratio) with tumour recurrence have shown promising results. On the other hand, the response to locoregional therapies as downstaging strategies, as well as ischemia time at transplant surgery have been considered an important parameter of HCC recurrence. In addition, it has

been observed that post-transplant immunosuppression treatment may be related to tumour recurrence, as calcineurin inhibitors (CNIs) may promote cancer progression and spread. At the same time, the mammalian target of rapamycin (mTOR) has shown anticancer and anti-angiogenic effects[13-21]. Recently, the molecular markers may act as red flags and risk predictors for tumor recurrence including genes, proteins and miRNAs as reported by Badwei[22]. Based on the previous findings several pre/post-transplant selection criteria and prediction models for better post-transplant survival in HCC recipients have been proposed (summarized in Table 1), however, an ideal one has not yet been well-defined[13-21].

Pre-transplant selection criteria for HCC patients

In the past, considering the proper selection of HCC candidates for liver transplantation has been a challenging step and a matter of debate to the transplant team among different centres for fear of the associated worse outcome and the risk of tumour recurrence. In 1996, the Milan Criteria (MC) published by Mazzaferro *et al*[13], was adopted globally as a gold standard and most reliable selection criteria for pre-transplant HCC patients, owing to the associated well post-transplant survival exceeding 70% over 5 years. Since then, other criteria related to tumour burden have been developed and validated in different transplant centres such as UCSF and up to 7 criteria, showing acceptable comparable survival results to the standard Milan criteria. Later, several expanding selection models were accepted and widely adopted in various centres, however, widening the boundaries and eligibility criteria to accept more HCC patients on the waiting list for LT came at the expense of post-transplant survival and tumour recurrence (metro ticket). A hint to know, the eligibility criteria of the various selection models for the pretransplant HCC candidates mainly rely on tumour burden features (size and number), which do not necessarily reflect the biological behaviour and the aggressiveness of the tumour as discussed before. However, combining tumour biomarkers with related altered morphological features has proved their efficacy in estimating post-LT survival probability regarding HCC recurrence risk. Most of the studies have reported and correlated the added value of AFP level as a useful predictor of HCC candidates' drop-out and exclusion on the LT waiting list, as well as the risk of tumour recurrence and overall survival, where pre-LT high AFP levels were found to be associated with HCC recurrence and worse survival after transplantation, as seen in the metro ticket 2.0 model which includes AFP variations along with tumour morphology, and so it may be useful in predicting post-transplant tumour-related death, in addition, incorporation of the radiological response of modified response evaluation criteria in solid tumours (mRECIST) to neoadjuvant therapies related data can enhance the predictive accuracy of metro ticket 2.0 model[4,5,14,19-21]. On the other hand, the observed AFP threshold was variable in different studies (> 7.5 ng/mL, > 15 ng/mL or > 50 ng/mL), and several cut-off values have been adopted in the different transplant centres (100 ng/mL, 200 ng/mL, 400 ng/mL, 1000 ng/mL). Still, no threshold value has been universally standardized as an exclusion criterion[23-27].

Post-transplant surveillance and prediction models in HCC patients

Despite no definite clear surveillance protocols for HCC recipients that could be universally standardized in different transplant centres and even documented in international liver societies, it's widely accepted to strictly keep surveillance after transplantation at regular intervals commonly during the first two/three years, owing to the high incidence of HCC recurrence risk, however, it may be prolonged up to 5-10 years for fear of late tumour recurrence probability. Different diagnostic imaging [contrast-enhanced computed tomography (CT)/magnetic resonance imaging (MRI)] has been considered as the modality of choice and standard of care for the evaluation of HCC recipients, which could differ regarding frequency, duration and even the modality of imaging among different transplant centres; Abdominal imaging (CT/MRI) and non-contrast CT chest represents the most frequently used diagnostic surveillance tools for the detection of common sites of recurrent HCC, while indications of positron emission tomography–CT and bone scan are limited to clinical suspicion cases. A hint to know, gadoxetate-enhanced MRI imaging modality has shown promising results in differentiating HCC phenotypes (proliferative and non-proliferative) where the aggressive proliferative variant showed the characteristic rim-like peripheral arterial enhancement with large central hypo-enhancing component (necrotic areas), which could be useful in predicting poor overall survival and intra-/extra-hepatic metastases risk associated with proliferative HCC phenotype[28-30]. On the other hand, serial checking of post-transplant AFP levels has been routinely done during surveillance of HCC recipients among various transplant centres, as it has proved its efficacy in different studies as a valuable prognostic marker for the prediction of tumour recurrence in post-transplant HCC cases. Hence, AFP has been incorporated into various predictive models, including risk estimation of tumour recurrence after transplantation (RETREAT) score which was recommended by the American Association for the Study of Liver Diseases (AASLD) guidelines as a promising prognostic score in evaluating patients' 5-year recurrence risk with proper guidance of optimal screening intervals, as higher scores associated with decreased post-LT survival at 3 years[31,32].

MANAGEMENT OF POST-TRANSPLANT HCC RECURRENCE

Despite no clear universal consensus documented regarding the management of post-transplantation HCC recurrence in international liver societies and guidelines, the decision-making in the treatment approach is often accomplished by the multidisciplinary transplant team which is tailored according to each case scenario, owing to the associated heterogeneous data related to presentation and available therapeutic options for those presented with tumour recurrence. Potential therapeutic options mainly include curative treatment (surgical resection and ablation) and palliative strategies (chemo-/radio-embolization and systemic chemotherapy), their indications mainly rely on the various stages of tumour recurrence. HCC recipients who presented with an oligo-recurrence stage (intra-/extra-hepatic) have been usually treated

Table 1 List of common pre/post-transplant predicting models and scores used in practice

Criteria name	Characteristics	Biomarkers
Milan criteria	Single tumor > 5 cm or ≤ 3 tumors ≤ 3 cm, with no vascular invasion	
UCSF criteria	Single nodule ≤ 6.5 cm or 2-3 nodules ≤ 4.5 cm and total tumor diameter ≤ 8 cm, with no vascular invasion	
Seoul criteria	Tumor size (≤ 3, 3.1-5, 5.1-6.5, > 6.5 cm) and number (1, 2-3, 4-5, > 5)	AFP (≤ 20, 20.1-200, 200.1-1000, > 1000 ng/mL)
Up-to-7 criteria	Sum of the largest tumour size and number of lesions < 7	
AFP-French model	Tumor size (≤ 3, 3-6, > 6 cm) and tumour number (1-3, ≥ 4)	log^{10} (AFP) simplified version: AFP level (≤ 100, 100-1000, > 1000 ng/mL)
AFP/TTD criteria	Total tumor diameter ≤ 8 cm	AFP ≤ 400 ng/mL
TTV/AFP model	Total tumor volume < 115 cm^3, and no macrovascular invasion or extra-hepatic spread	AFP < 400 ng/mL
Extended Toronto criteria	Any size or number of tumours, and no vascular invasion or extra-hepatic spread; No poorly differentiated grades; No symptoms related to cancer (weight loss >10 kg and/ ECOG ≥ 1 in 3 months)	
Pre-MORAL score	Largest tumor size > 3 cm	Maximum AFP > 200 ng/mL, preoperative NLR ≥ 5
Metro ticket 2.0 model	Tumor number and size of the largest tumor	AFP (< 200, 200-400, 400-1000, > 1000 ng/mL)
Metro ticket 2.0 + mRECIST criteria	Tumor number and size of the largest tumor; Radiological response to neoadjuvant therapies (mRECIST criteria)	AFP (< 200, 200-400, 400-1000, > 1000 ng/mL)
Metro ticket 2.0 with LI-RADS criteria	Tumor number and size of the largest tumor (Tumor burden evaluated according to LI-RADS criteria)	log^{10} (AFP)
RETREAT score	Tumor number and size (explant); Presence of vascular invasion	AFP level at transplant
AFP score	Largest tumor size and number	AFP level
TRAIN score	Response to LRT (mRECIST); NLR ratio waiting time till LT	AFP level
MORAL score	Largest tumor size and number explant tumor pathology (differentiation grade) NLR ratio	AFP level

UCSF: University of California San Francisco; AFP: Alpha-fetoprotein; TTD: Total tumor diameter; TTV: Total tumor volume; ECOG: Eastern cooperative oncology group; MORAL: Model of recurrence after liver transplant; NLR: Neutrophil to lymphocyte ratio; mRECIST: Modified response evaluation criteria in solid tumors; LI-RADS: Liver imaging reporting and data system; RETREAT: Risk estimation of tumor recurrence after transplant; TRAIN: Time–radiological-response–alpha-fetoprotein–inflammation.

with curative options, which have shown acceptable responses with good prognosis and survival, compared to the worse outcome associated with palliative and best supportive strategies used in the stage of disseminated HCC recurrence. Although an aggressive approach to treating post-transplant tumour recurrence has been adopted in selected centres by combining surgical and non-surgical therapies for better long-term survival rates[10,33].

Surgical resection

Liver resection is considered the treatment of choice in cases diagnosed with oligo recurrence form of intra-hepatic origin, where it has been usually associated with good survival results over 3-5 years, also a median survival of around two years has been reported in various studies for those who were treated surgically, compared to non-surgical therapies which have shown lower results, moreover, there was an added value in survival benefit in selected cases with post-transplant HCC regarding the aggressive modality approach. Hence, to achieve optimum overall and free recurrence survival post hepatic resection, the transplant board should carefully address and properly handle important parameters including the tumour features, disease burden severity, operative-related considerations such as the possibility of extensive hilar adhesions sequelae post-LT and postoperative morbidity (60%-80%) with a high risk of infections owing to immunosuppression intake, functioning and tumour free residual hepatic reserve, and the recipient performance status. However, it was observed that only 30% of HCC cases presented with oligo-recurrence to fit such treatment modality, so further prospective studies on larger scales are needed to evaluate surgical resection-related challenges and limitations in the management of oligo-recurrences. On the other hand, surgical resection can be indicated in extrahepatic sites including lung, vertebra, adrenals, lymph node, and peritoneum, as reported in various case studies with post-transplant HCC oligo-recurrences with favourable outcomes, and also retrospective cohort studies reported mastectomy procedure as an effective surgical modality in post-transplant pulmonary HCC recurrence with acceptable 2-5 year survival rates[34-38].

Thermal ablative therapy

Despite liver resection being considered the favourable curative approach in HCC oligo recurrence, HCC recipients who are not deemed suitable for such treatment may receive ablative therapies (radiofrequency ablation, microwave ablation) in particular, for tumours distant from viscera and major vessels to avoid the heat sink related side effect. Moreover, it's preferred over surgical resection in deep-seated tumours which would require a major hepatectomy with the associated risk of postoperative morbidity, however, the lower tumour size (< 3 cm) and number with limited extrahepatic spread are considered important predicting parameters for treatment efficacy with an associated low incidence of related morbidity/mortality. Hence ablative therapy represents an alternative curative option with acceptable survival results compared to surgical resection, as reported by Huang *et al*[39] who compared two groups of HCC recipients with tumour recurrence treated surgically and radiofrequency ablation, showing no differences in the 5-year overall survival, however, limited by the small sample size for further clinical trials evaluation on larger scales[40-42].

Intra-arterial loco-regional therapies

Intra-arterial therapies with trans-arterial chemoembolization (TACE) or radioembolization with yttrium-90 (Y90) may be offered for cases with multi-focal intra-hepatic HCC recurrence, as reported in a prospective study regarding management for non-resectable intra-hepatic tumour recurrence which has shown a survival benefit of TACE compared to systemic therapy. However, there were TACE-related concerns that have been raised which include the possibility of anatomical technical challenges in hepatic vasculatures (arterial stenosis or kinking) and extensive hilar adhesions in the post-transplant setting, moreover, the biliary ischemia risk (lobar section treatment owing to adopting less selective embolization manoeuvres), with the absence of vascular collaterals, no serious complication rates regarding TACE procedure safety have been documented in a systematic review related to post-transplant HCC recurrence. On the other hand, radioembolization with Y90 has shown promising results in treating recurrent HCC cases, without significant side effects. In addition, no significant difference has been reported in a systematic review and meta-analysis regarding treatment with radioembolization-Y90 compared to systemic targeted therapies. However further data are needed to universally standardize such locoregional modalities of treatment instead of individual and sporadic evaluation by the transplant multidisciplinary board in various centres[10,43-45].

Radiation and systemic chemotherapy

Stereotactic body radiation therapy (SBRT) can be considered a potential therapeutic option for local HCC recurrence with promising results, as it mainly relies on an image-guided focused radiation technique, also it may aid in the modulation of tumour immunity response through upregulated tumour-specific cytotoxic T cells. Various prospective studies reported the efficacy of SBRT in larger tumours (2–7 cm) with around 90% response over 2 years post-treatment in a primary HCC setting. Similarly, a retrospective study by Au *et al*[46], reported that six HCC cases of post-transplant recurrence were treated with SBRT with an acceptable response over a year median follow-up, however later local and distant recurrence occurred. A hint to know, SBRT has been evaluated as a potential therapy for pulmonary, skeletal and lymph node oligo-recurrence control, however in sporadic case reports. On the contrary, the use of systemic chemotherapy including doxorubicin, 5-Fluorouracil and platinum-based agents has shown little benefit in those presented with disseminated tumour recurrence, owing to being a chemotherapy-insensitive tumour[47-51].

Systemic-targeted therapy

The definite impact of systemic therapy on post-transplant HCC recurrence is still lacking for further clinical trial evaluation. Sorafenib was the first approved oral tyrosine kinase inhibitor (TKI) to be used as first-line chemotherapy in advanced HCC stages and disseminated recurrence cases and has shown better outcomes (7–20 months) compared to the best supportive treatment. Hence, TKIs have been combined with other therapeutic options for disseminated HCC recurrence, as reported in various retrospective studies that showed tumour regression (complete/partial) after receiving combined treatment of sorafenib with mTORi in post-transplant HCC recurrence particularly in earlier stages, however, hand-foot syndrome and diarrhoea have been reported as a common adverse effect of sorafenib therapy, also significant drug toxicity particularly if combined with mTORi and often leading to dose reduction and non-compliance. Since then, new systemic drugs have been developed to be used as alternative options to sorafenib, where Regorafenib and Lenvatinib were approved in 2017/2018 randomised phase 3 trials to be used as second-line options following failure or non-tolerance to sorafenib in advanced primary HCC cases. Additionally, Yang *et al*[52], and Iavarone *et al*[53], reported the efficacy and safety profile of regorafenib use in post-transplant HCC recurrence cases who were non-responders and non-compliant to sorafenib, with median overall survival of around 1.5 years[54-58], moreover, recently Cabozantinib (TKI) and monoclonal antibodies (ramucirumab) have shown promising results in the treatment of post-LT HCC recurrence. However, the definite indications of various systemic therapies in the presence of immunosuppressants in post-transplant patients with tumour recurrence are still complex and need further evaluation of their efficacy and related toxicity[59,60]. A hint to know, systemic therapies combined with loco-regional therapies (surgical resection, ablation, SBRT) have been adopted as clinical trials in selected centres for the treatment of post-transplant HCC oligo-recurrence, as reported by Yang *et al*[52], who showed an added survival benefit in patients with HCC oligo-recurrence, who received surgical resection and followed by radiotherapy for skeletal spread, TKIs, and mTORi[52,54].

Immunotherapy

Currently, immunotherapy has made a revolution in HCC treatment by changing the overall landscape of systemic therapies' indications in advanced HCC with better outcomes by directing the host's immune response to prompt an immune reaction against the tumour antigens; Programmed cell death protein inhibitors (PD-1) which includes

nivolumab and pembrolizumab have been validated in two large phase trials and approved to be used in primary unresectable HCC. Additionally, significant overall and disease-free survival have been shown in the known open-label phase three trial (IMbrave150 trial) with PD-1 inhibitors atezolizumab plus bevacizumab treatment compared to sorafenib. However, concerns related to their safety profile have been raised, particularly in the transplanted cases, as immune checkpoint inhibitors (ICIs) may cause allograft rejection and liver injury, owing to their role in cell-mediated immunity modulation interfering with post-transplant immune tolerance and may aid in immunosuppression resistance, hence, AASLD advises against the use of ICIs in posttransplant patients given the associated graft loss and mortality high risk[61-67].

ROLE OF IMMUNOSUPPRESSION IN POST-TRANSPLANT HCC RECURRENCE

The definite indication of immunosuppression in HCC recipients with tumour recurrence represents a matter of debate; It is known that adaptive immunity acts against cancerous cells, together with concomitant immunity in case of tumour recurrence and metastasis, through induction of anti-tumour immune response and cellular immunosuppressive pathways, hence, tumour state may be aggravated in the post-transplant settings compared to post-resection, as both adaptive and concomitant immunity are suppressed under the coverage of post-transplant immunosuppression which is essential in preventing graft rejection and loss. This necessitates carefully considering achieving the challenging goal of preventing graft rejection effectively with the lowest dose of immunosuppression, to minimise the possibility of tumour spread once post-transplant HCC recurrence occurs; Various studies supported the association of CNIs (cyclosporine and tacrolimus) with the high risk of tumour recurrence, as a dose-dependent relationship, owing to the immune system inability in case of CNIs intake to detect and destroy circulating/latent tumour cells and therefore, a dosage of CNIs should be modulated to balance this risk without increasing graft rejection risk. On the other hand, mTORis (sirolimus and everolimus) have shown an antiangiogenic and antiproliferative effect in invitro studies, moreover, retrospective studies and meta-analyses observed the associated reduced risk of tumour recurrence and the added longer survival benefit with mTORis-based therapy compared to CNIs treatment, similarly, a large meta-analysis reported a significant recurrence-free survival with mTORi therapy (1-3) years, however with there was a nonsignificant increase at 5 years. The combined sorafenib and sirolimus regimen has been adopted in selected transplant centres for the treatment of recurrent HCC, owing to their synergistic effect as mentioned before (systemic targeted therapies section), however, there is currently insufficient evidence to recommend this broadly[39,68-70].

FUTURE PERSPECTIVES AND LIMITATIONS

Patients with post-transplant HCC recurrence have been considered a mysterious special population for a long time, as being excluded in various clinical trials, therefore there is still scarce data and insufficient evidence-based literature regarding the management strategy for this category of patients; First, the lack of standard screening program including tools and duration for HCC recipients post-liver transplantation, which are individualized according to the transplant board of various centres. Second, the proper selection of immunosuppression protocols in the setting of HCC recipients before and after tumour recurrence represents a challenge to hepatologists, to maintain a balanced state of minimising both graft rejection and tumour recurrence. Third, the management strategy once HCC recurrence is diagnosed needs to be thoroughly evaluated in larger phase trials, including a complete tumour staging and the suitable therapeutic option in the settings of immunosuppression intake, till being universally standardized as guidelines in the international liver societies. Lastly, systemic targeted therapies and immunotherapy proved their efficacy in unresectable HCC and have shown promising results in the post-transplant setting with tumour recurrence but have yet to be further studied on a larger scale with careful consideration of the related side effects[71-73].

CONCLUSION

Post-liver transplantation HCC recurrence represents a serious complication with poor survival. Despite the adherence to the standard selection criteria, there is still an increasing number of detected cases, hence a careful selection of HCC candidates before transplantation is considered a point of concern, as reported in several studies that evaluated various pre/post-transplant prediction models and observed tumour recurrence related risk factors. HCC recurrence has shown unpredictable behaviour, because of the heterogeneous nature associated with the tumour microenvironment. It can present as oligo intra/extra-hepatic spread to widely disseminated form, the adopted management strategy includes curative treatment which has shown acceptable responses with good prognosis, compared to the worse outcomes associated with palliative strategy, however, systemic and immunotherapies have shown promising results, but their related serious adverse effects should be carefully handled under the umbrella of immunosuppression.

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