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Therapeutic strategies for post-transplant recurrence of hepatocellular carcinoma

Sposito C *et al*. Treatment of post transplant recurrent HCC

Abstract

Despite stringent selection criteria, hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) still occurs in up to 20% of cases, mostly within the first 2-3 years after liver transplant. No adjuvant treatments to prevent such an occurrence have been developed so far. However, a balanced use of immunosuppression with minimal dosage of calcineurin inhibitors and possibly the addition of mammalian target of rapamycin inhibitors is strongly advisable. Moreover, several pre- and post-transplant predictors of recurrence have been identified and may help determining frequency and duration of post-transplant follow up. When recurrence occurs, the outcomes are poor with a median survival of 12 mo according to most retrospective studies: The factor that most impacts survival after recurrence is timing(within 1-2 years from LT according to different authors). Several therapeutic options may be chosen in case of recurrence, according to timing and disease presentation. Surgical treatment seems to provide a survival benefit, especially in case of late recurrence, while the benefit of locoregional treatments has been suggested only in small retrospective studies. When systemic treatment is indicated, sorafenib has been proved safe and effective, while only few data are available for lenvatinib and regorafenib in second line. The use of immune checkpoint inhibitors is controversial in this setting, given the safety warnings for the risk of acute rejection.

Core Tip: Hepatocellular carcinoma (HCC) is becoming the most common indication to liver transplantation (LT). The problem of tumor recurrence after LT, that occurs in up

to 20% of cases, is becoming of increasing interest. In this paper, we performed a review of the available literature on the topic of HCC recurrence after LT. The best preventive measures still rely on pre-transplant selection criteria, since no dedicated follow up guidelines exist and no post-LT adjuvant treatments are available. When recurrence occurs, the prognosis is poor: However, an aggressive surgical treatment, particularly in case of late recurrence, may provide a significant survival benefit.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common liver cancer and the fourth leading cause of cancer-related mortality[1,2]. From the time of its initial developments in the early 60s, liver transplantation (LT) appeared as the ideal cure for HCC on liver cirrhosis because of the perspective to cure at the same time both the tumor and the underlying liver disease. However, the first experiences were disappointing with many authors reporting a 5-year survival of less than 40%, mainly because of recurrences of the primary tumor[3-6]. A retrospective review of these discouraging results progressively led to the observation that survival of patients was directly related to the stage of HCC at the time of LT. This was the basis on which a prospective study was conducted in Milan applying a-priori restrictive criteria for the selection of HCC candidates for LT (namely a single nodule ≤ 5 cm or 2-3 nodules ≤ 3 cm, each with no macrovascular invasion at pre-transplant imaging). The seminal paper published in 1996 demonstrated that LT under such criteria achieved better long term results than any other therapy, with outcomes similar to LT for non-oncologic indications[7]. The so called Milan criteria (MC) were subsequently validated by many other groups reporting 5-year survival rates of 70% or more, and became the benchmark for selecting patients with HCC for LT. Pooled recurrence rates have been reported to be around 8% for patients within MC *vs* 28% for patients beyond these criteria, according to a recent meta-analysis[8]. Thus, HCC recurs in a proportion of recipients who are within MC, while LT may provide cure for some patients who are beyond these criteria. When recurrence occurs, survival is poor and post-LT HCC recurrence is the factor that most

impacts on long term outcomes in this setting. Considering that HCC represents the most common indication for listing in the United States and that since the introduction of direct antiviral agents against hepatitis C virus, the proportion of patients undergoing LT for HCC is increasing worldwide[9,10], the problem of tumor recurrence will probably affect a growing number of patients. However, to date, treatment of HCC recurrence following LT is largely understudied and dedicated guidelines are lacking. The aim of this paper is to provide a review of the current evidence on therapeutic strategies for patients with HCC recurrence after LT.

PREVENTION OF POST TRANSPLANT HCC RECURRENCE
Tumor recurrence may be linked to remaining (previously undetected) extrahepatic HCC at the time of transplantation, or result from the post-transplant engraftment of circulating HCC clones[11]. It is extrahepatic in 50%-60% of cases, with lung, bones and adrenal glands being the most frequently affected sites[12]. Timing of HCC recurrence is variable, but in most cases it occurs within 3 years after LT. Early recurrence (defined as occurring < 1 year after LT) is associated with a significantly worse prognosis, while later recurrence might result in better outcomes and even in cure in selected cases[13].

Prevention of recurrence through selection criteria
Considering that the risk of post-LT recurrence is strictly related to pre-transplant HCC stage and treatments, recurrence is firstly prevented by the application of pre-LT selection criteria able to identify patients at higher risk. Proposals of expansion of MC have been initially developed using tumor morphology, namely size and number of nodules. In fact, these factors have been demonstrated as surrogate markers of microvascular invasion (MVI) and/or poor tumor differentiation, which are the principal determinants of biological aggressiveness and therefore of the risk of post-LT recurrence[14]. Expanded criteria increased the acceptable size and number of HCC nodules with respect to MC, but the considerable heterogeneity coupled with

differences in accuracy of liver imaging techniques probably represent the greatest limitation of criteria based only on morphology.

To overcome these limits, criteria incorporating serum markers as surrogates of biological tumor features such as α-fetoprotein (AFP) have been proposed. In particular, by combining the morphological characteristics of the tumor and AFP values it was possible to develop selection criteria for LT definitively exceeding MC, while even decreasing the risk of post-LT recurrence[15,16]. A strategy combining tumor burden with the assessment of response to pre-LT locoregional treatments (LRT) as a marker of favorable tumor biology has gained broader acceptance[17]. For patients beyond MC, a common strategy is to downstage patients by means of locoregional or surgical therapies. In fact, patients successfully downstaged within accepted criteria share the same prognosis of patients within the criteria *ab initio* and so far[18], response to therapies appears as one of the best surrogates of favorable tumor biology and thus an optimal selection tool for candidates to LT[17,19,20]. Patients progressing in the pre-LT period despite LRT have in fact significantly worse post-LT outcomes with respect to patients with stable or responding disease. Finally, tumor differentiation, MVI, presence of circulating cancer cells and genomic markers have also been suggested as selection criteria for LT, but these assessments require a biopsy, which might induce tumor seeding. Furthermore, it is well known that tumors are heterogeneous and show areas of varying degrees of differentiation and genomic features.

Post-transplant surveillance

Considering that post-LT recurrence is mostly asymptomatic, and that early detection of recurrence may have a positive impact on long-term outcomes, post-transplant surveillance has an important role in this setting. However, no guidelines from the major HBP societies are available and surveillance protocols are mostly center-specific, often with a high heterogeneity between centers as recently reported[21]. Few retrospective studies on post-LT surveillance have been published to date, and several

questions regarding frequency, duration, and imaging modality for a cost-effective surveillance remain open.

For what regards imaging modality, cross sectional imaging of the abdomen [with either multiphase computed tomography (CT) or magnetic resonance imaging] and non-contrast lung CT scan allow detection of the most frequent sites of recurrent HCC[21,22]. Cross sectional imaging of the brain, bone scintigraphy or positron emission tomography-CT are indicated only in case of clinical suspicion and not on a regular basis, while it seems reasonable to check for AFP levels at each surveillance visit even if no data is available to support this indication.

Given that the majority of recurrences occur within the first three years after LT, there is general agreement to indicate surveillance imaging and visits more frequently in this time frame (*i.e.*, every 4-6 mo) and yearly thereafter[22]. Some authors suggest interrupting surveillance after the fifth year. However, recurrences (either *de novo* tumors or true recurrences) have been repeatedly reported up to 10-15 years after LT[23]; considering that late HCC relapse is associated with a better prognosis with respect to earlier events and that it is sometimes curable, it seems reasonable to prolong yearly surveillance for at least ten years.

Ideally, frequency and duration of surveillance would be based on the assessed risk of post-LT HCC recurrence. Several proposals have been made in this sense, and the RETREAT score[24] (that includes AFP at LT, presence of MVI and sum of maximum size + number of vital nodules) is the most recent and promising predictor in terms of discriminative power and validation on a large scale registry. However, no prospective validation is available to date, and the cost-effectiveness of a surveillance program based on the risk of recurrence has yet to be demonstrated.

The impact of surveillance programs on post-recurrence survival has been scarcely studied. Interestingly, a recent multicentric study on 232 patients who experienced HCC recurrence found that increasing number of post-LT surveillance scans (with cut-off at 3 surveillance scans within the first 2 years) was associated with improved survival and possibility of undergoing potentially curative treatments[25].

Role of immunosuppression

Improvements in the management of immunosuppression reduced rejection episodes favouring long-term graft survival; calcineurin inhibitors (CNIs) tacrolimus and cyclosporine played a fundamental role in this improvement. However, several studies demonstrated that CNI exposure is associated with an increased risk of tumor recurrence with a dose-dependent effect[26]. It is likely that the immunosuppression induced by CNIs prevents the immune system from detecting and destroying circulating or dormant HCC cells and therefore, dosage of CNIs should be maintained with the aim of balancing this risk without increasing the risk of rejection episodes.

Mammalian target of rapamycin inhibitors (mTORi) sirolimus and everolimus are another class of immunosuppressants targeting some HCC pathways, which showed antiangiogenic and antiproliferative effects in experimental models[27]. Data from retrospective studies and meta-analyses suggest that, compared to CNIs, the use of mTORi reduces the risk of post-LT HCC recurrence and increases long-term survival. In the most recent meta-analysis including 23 comparative studies [17 observational and 6 randomised controlled trial (RCT)] with 6495 patients, recurrence free survival (RFS) was significantly increased with mTORi - based therapy at 1 and 3 years with a non-significant increase at 5 years[28]. Overall survival (OS) was also significantly improved, as well as recurrence rate being lower in the mTORi arm without differences based on the type of mTORi. However, there is only one RCT that compared post-LT immunosuppression containing mTORi (sirolimus) *vs* non-containing mTORi[29]. In this international trial randomizing 525 patients appeared to be an advantage in the sirolimus group regarding RFS in the first 3-5 years. However, this benefit was subsequently lost with further follow-up and the trial failed to meet the primary endpoint of demonstrating a significant reduction of recurrences in the mTORi-containing immunosuppression group.

Adjuvant treatments after LT

Several attempts had been performed with chemotherapy as an adjuvant treatment to prevent HCC recurrence after LT[30,31]. Being HCC a chemo-resistant tumor, cytotoxic systemic therapies failed to provide any consistent benefit in this setting and have been abandoned in the last decade[32]. Sorafenib, an oral multikinase inhibitor that showed significant improvements in survival of patients with advanced HCC, has been tested in small studies in the setting of adjuvant treatment for HCC after LT. Despite some initial signs of efficacy, with one phase I study showing a significant reduction in the risk of HCC recurrence with a maximum tolerable dose of sorafenib 200 mg twice a day[33], other single-center case series failed to confirm these data and to date no RCTs are available. Lenvatinib, a more recent targeted therapy for advanced HCC, has not been prospectively tested in the adjuvant setting; a small retrospective case series confirmed an acceptable drug safety and patient tolerance but did not show any significant reduction in terms of HCC recurrence[34]. Immune checkpoints inhibitors (ICIs) have emerged as a treatment option for advanced-stage HCC. No studies are available on ICIs as an adjuvant post-LT treatment. A recent systematic review and pooled analysis reviewed 14 patients receiving ICIs for recurrent disease after LT for HCC: 11 of them (78.6%) died, and graft rejection was the cause of death in 5 cases (45.4%). The high rejection rate raises the question of safety of ICIs in transplanted patients, even in the setting of overt recurrence[35]. Thus, to date, no anticancer treatments can be recommended to prevent HCC recurrence after LT, and it is unlikely that they will become available in the near future.

TREATMENT OF POST-TRANSPLANT HCC RECURRENCE

Literature concerning the efficacy of each treatment modality is scarce, with the many limitations related to the small number of patients included, the frequent use of combined treatment and the different patterns of recurrence, all acting as confounding factors. In the majority of cases (50%-60%) recurrence is extrahepatic and affects the following sites: Lungs (40%-60%), bones (25%-30%), adrenal glands (10%), lymph nodes (10%) and peritoneum (10%)[12]. Liver-only recurrence occurs in 15%-40% of patients

while combined liver and extrahepatic recurrence accounts for 30%-40% of cases. The therapeutic options clearly depend on location, multifocality and clinical presentation of recurrence (Figure 1).

Surgery

Liver resection is safe and provides a survival benefit in case of intrahepatic oligorecurrence[36,37], with a median survival of 28-65 mo observed for patients receiving surgery, compared to 5-15 mo in those receiving systemic treatment only[38-41]. Surgical treatment is feasible in 25%-50% of cases with higher morbidity rate (60%-80%) with respect to primary liver resections[42-44], mainly because of the risk of infections in the context of immunosuppression.

Sapisochin et al[39] retrospectively analyzed 121 patients with HCC recurrence after LT, finding that not being amenable to resection or ablation was an independent predictor of poor prognosis [hazard ratio (HR) = 4.7, 95% confidence interval (CI): 2.7-8.3). An Italian multicentric study analyzed 21 patients with recurrence and reported a significantly better 4-year survival rate in patients treated with surgical resection for intra- and extra-hepatic recurrence compared to those with unresectable disease (57% vs 14%, P = 0.02)[45]. In another series of 106 patients, treatment for recurrent HCC most commonly included chemotherapy (73.5%), surgical resection (23.3%), external beam radiation (13.6%), and ablation (3.9%), with the majority of patients receiving non-surgical therapies (59.2%). The highest survival rates at 3 years were observed in patients receiving surgical therapy alone (60%), followed by patients receiving both surgical and nonsurgical therapy (37%), patients receiving only non-surgical therapy (11%), and patients receiving no treatment (0%)[40]. Time from LT to recurrence is one of the most important prognostic factors, and patients with late recurrence show more favorable 5-year outcomes survival with resection compared to those of patients who recur earlier[46].

Surgery may enhance long-term survival also in patients with pulmonary recurrences amenable to resection, with 5 year survival rates ranging from 34% to 44% in those

undergoing metastasectomy[47-52]. A benefit from surgical treatment is also reported for other sites of recurrence in smaller case series, including vertebrae[53], adrenal glands[54,55], lymph nodes[56], peritoneum[57] and pharynx[58]. In patients with multiple recurrences, some benefits have also been gained from repeated resections, probably reflecting less aggressive tumor biology[41].

Locoregional therapies

Radiofrequency ablation (RFA) for liver recurrences may be proposed with a curative intent for small lesions, with the advantages of a percutaneous approach. In a retrospective single-center series, Huang *et al*[44] compared 15 patients with post-LT HCC recurrence treated surgically with 11 patients treated with RFA. This study demonstrated similar 5-year OS (35% for surgery *vs* 28% for RFA) but a tendency to a worse 5-year disease-free survival in the RFA group (16% *vs* 0%). Another study evaluating safety and efficacy of microwave ablation on a series of 11 patients found this technique safe and tolerable, with a 15.8% rate of local tumor progression after treatment and 15.3% survival at 2 years[59].

Multifocal intrahepatic recurrences may be amenable to trans-arterial chemoembolization (TACE). The largest series collected 28 patients treated by conventional TACE[60]. There were no significant post-treatment complications and the targeted tumor reduced in size by 25% or more in 19 patients (67.9%). However, intrahepatic recurrence or extrahepatic metastases occurred in 26 patients (92.9%) within 6 mo. The 3- and 5-year survival rates following TACE were 6% and 0%, respectively, with a mean survival time of 9 mo. A single-center retrospective investigation compared 14 patients treated with TACE with 14 matched controls who did not receive TACE but chemotherapy, radiation therapy or supportive care. Eight of the 14 patients treated with TACE (57%) showed partial tumor response and had a significantly longer survival compared to those who did not[61].

Systemic therapies

The effectiveness of systemic therapies for HCC recurrence following LT is largely unstudied because these patients have been routinely excluded from clinical trials. Sorafenib has been increasingly administered for treatment of post LT recurrences, and a certain amount of data has been collected in the literature regarding its safety and efficacy in this setting. In a case-control study from Sposito et al[62], sorafenib provided improved median survival after HCC recurrence untreatable by surgery or LRTs with respect to best supportive care (10.6 vs 2.2 mo). A meta-analysis published two year later reported a pooled 1-year survival of 36% (range 18%-90%)[63]. The main limitation of sorafenib in transplanted patients is toxicity, often leading to dose reduction, as reported by several studies[62,64]. Close monitoring is warranted for these patients, particularly in case of immunosuppression with mTOR inhibitors, since this association may lead to severe adverse events[65-70]. Regorafenib may be proposed as a second-line treatment in case of progression under sorafenib[71]. In a recent multicenter study, regorafenib provided a median survival of 13.1 mo after sorafenib discontinuation with respect to 5.5 mo of best supportive care in post-LT HCC relapse[72]. Recently approved tyrosine kinase inhibitors (lenvatinib[73] and cabozantinib[74]) and monoclonal antibodies (ramucirumab[75]) will soon be introduced in clinical practice also for the treatment of post-LT recurrence, giving us the opportunity to collect data about their efficacy and toxicity in this setting[76]. Currently, immunotherapy is changing the landscape of systemic therapies for HCC[77-79], but its safety after LT represents a point of concern, since immune checkpoint inhibitors may cause allograft rejection and other serious adverse events[80-85].

FACTORS IMPACTING SURVIVAL AFTER HCC RECURRENCE

Studies evaluating the outcome of patients with post-LT HCC recurrence mostly consist of small and heterogeneous series burdened by significant biases in terms of transplant criteria, availability of different treatments and patients' selection to curative and palliative options[86]. Survival of post-LT HCC recurrence is dismal and significantly worse than relapse after resection (median OS around 12 mo vs nearly 2 years in

transplanted and resected patients, respectively), being immunosuppression a potential driver of such difference[87,88]. A number of factors highly impact on survival, and there is a small subset of patients with more favorable prognosis in whom curative treatments may be undertaken. Table 1 summarizes the results of studies evaluating the prognostic factors and outcome of treatment for HCC relapse after LT.

Time to recurrence and primary tumor features
Several studies showed that time from LT to recurrence has a primary role on outcomes, with early relapse being associated to extremely poor prognosis[37-40,45,89-95] either when defined as occurring within 6 mo[93], 1 year[39,96] or 2 years[97]. Many factors related to the primary tumor biology and aggressiveness affect time to recurrence and/or post-relapse survival: Size (with cutoffs > 30 or > 50 mm)[45,94], staging outside MC[45], bilobar spread[94], absence of peritumoral capsule[45], poorly differentiated tumors[91,95,96], total tumor volume[92], presence of micro- or macrovascular invasion and pre-LT lymphocyte to neutrophil ratio[39,40,91,92]. The use of mTORi in the post-LT setting seems to be related to better post-recurrence outcomes, as shown both in Eastern and Western series[93,96]. Moreover, a history of graft rejection has also been associated with improved outcomes, possibly due to more active anti-cancer immunity[92].

It has been suggested that the observed difference in outcomes between early and late recurrences lies in different underlying biological mechanisms. However, this doesn't turn into a difference in the site of recurrence. In fact, occurrence of extrahepatic, combined intra- and extrahepatic or intrahepatic relapses do not seem to be different in early *vs* late recurrences[94]. While early relapses may be due to undetected extrahepatic metastases or circulating HCC clones implanting in a target organ during or soon after LT, late recurrences are possibly related to a second hit leading to late engrafting of HCC cells remaining latent during the initial post-LT period. In the latter, immunosuppression may also play a role[23]. As for intrahepatic late relapses, a further mechanism to be considered is *de novo* occurrence of HCC, usually arising in the context of chronic liver disease or cirrhosis due to recurrence of primary hepatitis, ischemic

biliary injury or chronic rejection, several years after LT[98]. In such instances, results are expected to parallel those of non-transplant recipients with localized HCC, in which surgery or LRTs are effective in controlling the disease.

Pattern, features and resectability of recurrence
Aside from primary disease features, other studies focused on the pattern of recurrence as a relevant prognostic factor for post-recurrence survival. As expected, limited disease spread with localized nodules (oligo-recurrence), either hepatic or extra-hepatic, has been associated to better outcomes than disseminated multifocal recurrence in several series[36-38,41,45,90]. In addition, a different prognostic impact of hepatic *vs* extrahepatic localization has been repeatedly reported. Hong *et al*'s study showed that liver involvement as the first recurrence site was associated to worse survival, with fewer patients amenable to resection among intrahepatic rather than extrahepatic localizations[93]. A mono-centric French series on 70 HCC recurrences also identified intrahepatic location as an unfavorable prognostic factor and such finding was confirmed in a Latin American series on 105 post-LT recurrences showing a lower probability of treatment in patients with hepatic relapses[41,95]. It may be speculated that this is related to the biological mechanism underlying tumor relapse, with recurrences due to undetected metastases at the time of LT more likely to occur at extrahepatic sites and associated with decreased burden as compared to circulating HCC clones, biologically more aggressive and more likely to implant in the new liver. Of note, peritoneal and bone localizations were also reported as a poor prognostic factors[37,91,96]. Nevertheless, evidence deriving from several studies shows that the best outcomes are observed in patients with unifocal, often extrahepatic disease, easily amenable to surgical resection[36-38,41,45]. In the large series by Sapisochin *et al*[39] cited above, not being amenable to curative-intent treatment (resection or ablation) was an independent indicator of poor survival, together with an AFP ≥ 100 ng/mL at the time of relapse. In another United States single-center study by Bodzin *et al*[40] on 106 recurrences, a prominent prognostic role of recurrence-related factors (AFP at relapse, > 3 nodules,

maximum size of recurrence and bone spread) rather than primary disease features was shown. By combining such factors, a risk score model was built, with accurate stratification of recurrent patients into low-risk (median survival of 70.6 mo), medium risk (12.2 mo) and low risk (3.4 mo) subgroups.

Due to selection bias of surgical patients towards later recurrences, more favorable localizations, less aggressive disease and better performance status, the independent prognostic role of either recurrence pattern or resectability is questionable. The limited disease spread may make patients more likely to undergo surgical excision on one hand, or simply reflect a different tumor biology, etiology, and stage of recurrence on the other hand, as compared to more advanced cases of multifocal recurrence. Even when radical resection cannot be undertaken, it is widely accepted that any kind of treatment of recurrence has a positive prognostic impact. In the multicenter Latin American study, propensity score matching was used in order to evaluate the adjusted treatment effect considering selection bias: Patients treated with both sorafenib and surgery/TACE had better survival compared to the best supportive care regardless of time to recurrence[95]. Although randomized data are unlikely to be available in this context and retrospective comparisons are impaired by intrinsic differences between single site/oligometastatic and disseminated recurrence, surgical treatment remains an independent predictor of improved outcome following post-LT recurrence[37-39,41].

Serum markers

As for primary disease and post-LT outcome, AFP at recurrence as an indicator of disease spread, MVI and biologic aggressiveness was frequently reported as a strong predictor of prognosis, with cutoffs varying from 100 to 1000 ng/mL[39-41,96]. Interestingly, the difference in survival for patients with high AFP was evident regardless of curative-intent treatment, confirming its value as a marker of unfavorable biologic feature, able to guide the clinical management of patients affected by HCC recurrence. Finally, other biochemical markers at recurrence were associated with shorter survival: High bilirubin, possibly as a reflection of graft dysfunction, and low

albumin, related to poor nutritional status as a general prognostic factor outlined in several series[96,99].

CONCLUSION

HCC recurrence after LT is still a dreadful event, occurring in up to 20% of cases. It might be prevented by stringent pre-transplant selection criteria incorporating biological markers of aggressiveness (such as response to therapy, serum markers, histological factors) in addition to size and number of tumors. Several advances in this sense have been made in the last decade, allowing patients with HCC a broader access to LT with more precise prediction of outcomes. In the post-LT period surveillance should be driven by post-LT risk stratification, and the MORAL score seems to be the best cost-effective approach. No adjuvant treatments after LT have been validated to prevent HCC recurrence; however, a balanced use of immunosuppression with minimal dosage of CNIs and possibly the addition of mTORi is strongly advisable. Median post-recurrence survival is 12 mo: The interplay between time-to-recurrence (with a negative impact of earlier events) and the possibility of a radical treatment is the strongest determinant of survival.

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