Review Article

Liver transplantation for hepatocellular carcinoma: pre-transplant considerations and post-transplant management

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Abstract: Hepatocellular cancer is the seventh most frequent and third leading cause of cancer death worldwide. At its early stages, it could be amenable to complete cure using surgical resection or ablative therapies. Unfortunately, some patients present with advanced tumor stages or have reduced liver function and locoregional therapies may not be used or effective. Liver transplantation becomes an appealing option as it replaces the ailing liver and offers a chance for complete cure. Outcomes of liver transplantation for hepatocellular cancer have improved with better patient selection and adjuvant therapies allow patients to become eligible for transplantation and minimize dropouts from the waiting list. Post-transplant care, including appropriate surveillance and immunosuppression can also improve long-term outcomes with survival similar to transplantation for non-oncologic indications.

Keywords: Liver transplantation; hepatocellular carcinoma (HCC); liver cancer; chemoembolization; cancer therapy

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Hepatocellular carcinoma (HCC) is the seventh most frequent and third leading cause of cancer death worldwide (1). The incidence of liver cancer increases in patients with cirrhosis and this creates a particular challenge as treatment options need to be adapted to liver function. Surgical resection is a curative option, but among patients with cirrhosis and liver dysfunction this is not always feasible. Locoregional therapies include ablation (ethanol, radiofrequency, microwave), chemoembolization, radioembolization and stereotactic body radiation therapy (SBRT). Ablative techniques are useful for small, single lesions. Embolization modalities are often reserved for multifocal disease, but usually not with a curative intent. Furthermore, in patients with advanced liver disease, locoregional therapies may increase the risk of decompensation and liver failure. In patients with advanced liver disease and limited tumor burden, liver transplantation is an appealing option as it replaces the cirrhotic liver, restoring function as well as reducing the risk of developing new lesions. This review will focus on the use of liver transplantation in the management of hepatocellular cancer.

Transplantation criteria

The initial experience with transplantation for HCC was not encouraging as tumor recurrence occurred in a majority of patients and the 5-year survival rate was as low as 15%, well below the standards of liver transplantation for other diseases (2,3). The principal reason for this poor outcome was the lack of selection of appropriate candidates. This changed with the publication of the work by Mazzaferro *et al.* in 1996 of what is now known as the "Milan criteria" (MC). The criteria are defined as the presence of a single lesion equal or less than 5 cm, or up to 3 lesions, none greater than 3 cm, no evidence of vascular invasion and no regional lymph nodes or distant metastases. MC was associated with a four-year survival rate of 75% (4). It became the reference in the transplant world and is used in the majority of transplant centers. Using the MC, overall survival (OS) for transplantation achieved similar rates than

transplantation for non-malignant indications. A report from the United Network for Organ Sharing (UNOS) that compared three different time periods (1987 to 1991, 1992 to 1995 and 1996 to 2001) showed an increase in 5-year survival for patients undergoing liver transplant for HCC across time periods (25%, 47% and 61% respectively) while the survival rate for non-malignant reasons remained stable at 71% (5). Several studies have validated the performance of these criteria.

However, the MC is criticized as being too restrictive and it is argued that good outcomes can be obtained in patients that are outside its limits. Yao *et al.* from the University of California, San Francisco (UCSF) showed that HCC patients transplanted using an extended criterion beyond Milan, could achieve similar outcomes to those transplanted using the MC (6). The UCSF criteria are defined as a single nodule up to 6.5 cm, or up to three nodules, the largest one not measuring more than 4.5 cm and with a total sum of diameters of less than 8 cm, no evidence of vascular invasion and no regional lymph nodes or distant metastases. A retrospective study by Duffy at al. comparing patients transplanted for HCC under MC and UCSF criteria, based on pre-operative imaging or explant pathology, found similar 5-year post-transplant survival (7). Another study by Muscari *et al.* showed similar 5-year survival and recurrence rates in patients with Milan and UCSF criteria (8). However, in an intention-to-treat analysis using data from the Organ Procurement Transplant Network (OPTN) starting survival assessment at the time of listing rather than at the time of transplant, transplantation outside of MC was associated with worst 1- and 5-year survival (9), likely related to greater incidence of waitlist dropout using extended criteria.

Cross-sectional imaging may not reliably assess the size of tumors and criteria based only on imaging do not take into account the tumor biology. The Toronto criteria (TC) are based on experience with a more liberal acceptance of patients for transplantation. Patients could become candidates if there was no extra-hepatic disease, no systemic or constitutional symptoms directly related to the HCC, no macrovascular invasion on imaging and the dominant lesion was not poorly differentiated on biopsy, regardless of the number or size of the lesions. When compared to patients transplanted within MC, there was no difference in 5-year OS or disease-free survival (DFS) (10). In addition, within this cohort, they found that imaging understaged 30% or overstaged 23% of the patients within MC or outside of MC respectively. These results were validated in a prospective cohort of patients obtaining similar 1-, 3- and 5-year survival rates in patients transplant within MC or TC. The drop-out rate from the transplant list was higher in patients beyond MC and thus TC had a lower 5- and 10-year survival on an intention-to-treat analysis (11). An alpha-fetoprotein (AFP) above 500 ng/mL was associated with poorer outcomes in both groups.

The total tumor volume (TTV) has also been proposed as a criterion for the selection of candidates for liver transplantation. TTV is calculated by summing up the volume of all lesions that have HCC characteristics. Toso *et al.*, on the basis of receiving operating characteristic curves from a retrospective evaluation of the Alberta Liver Transplant Program, proposed a TTV of 115 cm^3 as a cut-off value. This value was then validated in two different eternal cohorts. Using TTV, there was a better correlation between radiological and pathological assessment compared to UCSF and MC. There was no statistically significant difference between TTV and MC in the cumulative risk of mortality or recurrence of HCC after transplantation (12). As elevated AFP levels are associated with tumor recurrence after transplantation (12,13), their addition improved the TTV model. Patients with either TTV greater than 115 cm^3 or AFP levels greater than 400 ng/mL had a decreased cumulative survival compared to patients that met both criteria (14). The TTV and AFP criteria (which included absence of macrovascular invasion and extra-hepatic disease) were recently prospectively validated. Compared to MC, the TTV and AFP criteria were associated with a greater dropout rate from the waiting list (42.1% *vs.* 25.1%) and consequently a reduced survival from the time of listing (53.8% *vs.* 71.6% at 4 years). However, recurrence (9.4% *vs.* 4.5%) and post-transplant survival (74.6% and 78.7% at 4 years) rates were similar in both groups (15).

There are many other criteria that have been studied and validated and they all share the objective of improving the limitations of the MC (16-20). Expanded criteria will allow for transplantation of patients with advanced disease that would still have an adequate outcome. This has led to the concept of the "Metro ticket", where the "farther the distance, the higher the price". In essence, the criteria can be expanded, but at the cost of a decreased in survival. This concept was created after a study by Mazzaferro *et al.* using a web-based survey that included 1,556 patients transplanted for HCC (1,112 patients had HCC exceeding MC) (21). A prediction calculator is available online that can calculate the expected 5-year survival based on pre-transplant staging and AFP or according to explant

pathology (22). These extended criteria have not been widely accepted and MC remains the standard of care in the majority of transplant centers. However, the guidelines form the 2010 International Consensus Conference on liver transplantation for HCC have stated that patients could be considered for liver transplantation beyond MC based on the dynamics of local waiting lists (23). The American Association for the Study of Liver Disease (AASLD) guidelines acknowledge that liver transplantation is an effective therapy for HCC within the MC and that it may be an option in patients beyond it in combination with tumor downstaging (24).

Organ allocation

In the United States and in Canada, organ allocation of deceased donor livers is based upon the Model for End stage Liver Disease (MELD) score. This score uses laboratory values [international normalized ratio (INR), total bilirubin and creatinine] to predict survival in patients with liver disease. Patients with higher scores are at greater risk of mortality and are given priority on the transplant list. However, the MELD criterion is not useful in predicting mortality in patients that have HCC as a competing risk. Patients with HCC may not show significant liver dysfunction until late in the disease and could have progression of their tumor burden beyond transplant criteria resulting in waitlist dropout.

In the United States, patients with American Liver Tumor Study Group (ALTSG) stage II HCC (single HCC between 2 and 5 cm , or 2 or 3 lesions, none greater than 3 cm) (25) who are potential liver transplant candidates are granted "exceptional" points. Patients listed with smaller or larger tumors will not receive exception points (26). Since October 2015, patients that qualify for exceptional points are registered at their calculated MELD HCC for the first 6 months. If patients are still within criteria after 6 months, they are granted a MELD score of 28, which will increase every 3 months to a maximum of 34 points (27,28). The cap was set at a MELD of 34 to avoid patients with HCC to be included in the Regional Share 35 policy.

A debate exists as to the optimal way to allocate organs in patients with HCC. It is disputed that patients with HCC are disproportionately favored over patients with liver dysfunction and that they have a shorter wait time, higher transplantation rates, lower dropout rates and wait list mortality (29). It was in response to these observations that UNOS/OPTN made their modifications to the exceptional point system in 2015. A model based on tumor characteristics and dynamics was recently proposed by a group in Canada (Transplant Quebec). In this model patients who are within MC receive exception points that are based on the number and size of the lesions. Patients that are closer to the limits of MC receive that maximum number of points (25) as they are at the highest risk of waitlist dropout (30). After implementation of their model, HCC patients were not more likely to be transplanted than patients with liver failure without creating differences in graft or patient survival.

There is probably not a uniform organ allocation model that will be identified. Each region has to adapt to their own reality including incidence of HCC, prevalence of other liver diseases, waiting times and dropout rates. However, the selected model has to be fair allowing patient that are at greater risk of death to be prioritized.

Locoregional therapies as a bridge to liver transplantation

Tumor progression while on the transplant list is a source of major concern. Dropout rates as high as 30% to 40% per year have been reported due to shortage of organ donors and increasing waiting times (31). Locoregional therapies are used before transplantation to treat active HCC and prevent tumor extension beyond transplant criteria.

In radiofrequency ablation (RFA), a probe is percutaneously placed into the tumor and thermal energy is produced by an alternating current at high frequency. It was shown to be effective in the treatment of small liver tumors (less than 3 cm) in patients awaiting liver transplant (32). Lu *et al.* reported 1- and 3-year post-OLT survival rates of 85% and 76%, respectively, in 52 patients treated with RFA. Three patients (5.8%) dropped out because of tumor progression (33). Lu *et al.* recently published long-term data (10 years) in 121 patients that received RFA as a stand-alone bridge therapy to liver transplantation. Intention-to-treat OS, recurrence free survival and disease specific survival rates at 5- and 10-year were 63.5% and 41.2%, 60.8% and 37.7%, and 89.5% and 89.5%, respectively. Dropout from the waiting list occurred in 7.4% of patients (34). The retrospective design of the studies and lack of comparison groups limit the interpretability of these results. However, RFA seems to be a safe and effective modality for bridging.

Transarterial chemoembolization (TACE) consists of direct delivery of a chemotherapy agent followed by embolization of the feeding arterial blood vessel to induce

ischemia. The use of TACE for bridging has yielded inconsistent results. Oldhafer *et al.* compared 21 patients who received pre-transplant TACE to 21 controls who did not and found no difference in the survival rate between the two groups (35). Similarly, Pérez Saborido *et al.* compared 18 patients who received TACE prior to liver transplant to 28 patients who did not. They did not find a statistical difference in OS between the two groups, although it is possible that the conclusions were limited by the small sample size, particularly for the 5-year survival (60.5% for TACE *vs.* 38.1% for controls) (36). A multicenter French case-control study found no difference in the 5-year survival in 100 patients treated with TACE compared to 100 controls (59.4% *vs.* 59.3%, respectively) (37). In a retrospective study of 43 patients who underwent TACE compared to 22 controls who did not, Frangakis *et al.* showed a lower dropout rate in the TACE group (3% *vs.* 15%). The 2-year survival rate was also superior in the TACE group (76% *vs.* 57%) but did not reach statistical significance. In this study, patients pre-treated with TACE had in average larger tumors and serum AFP (38). TACE may be more effective in combination with other locoregional therapies. Yao *et al.* found that locoregional therapy with either TACE, RFA or both was associated with an improved 5-year recurrence free survival compared to no therapy (93.8% *vs.* 80.6%). The benefit was greater in patients with T3 disease, but who were still within UCSF criteria (85.9% *vs.* 51.4%) (39).

Radioembolization with Yttrium-90 (Y-90) has also been studied as a potential bridging therapy. Analogously to TACE, Y-90 therapy consists of infusion of radioactive microspheres into the tumor. Tohme *et al.* conducted a retrospective single center review of 20 patients who were treated with Y-90 as the sole modality for bridging. All patients (14/20) that were within MC remained within the criteria before liver transplant and five of them had complete necrosis of tumors on pathological examination (40). Another trial comparing different locoregional therapies used for bridging showed that Y-90 was more frequently associated with complete pathological response on explant examination (41). More trials are needed to support the use of Y-90 as bridging therapy, however, it seems to be an effective option, particularly when TACE can't be used (presence of portal vein thrombosis).

Stereotactic body radiotherapy (SBRT) is a technique that delivers high doses of radiation to its target using multiple, non-parallel radiation beams. It has the advantage of minimizing injury to adjacent organs. Previously, conventional external beam radiation therapy could not be used due to the high sensitivity of the liver to radiation injury. Early reports showed a possible role of SBRT as a bridge to transplant (42-44). Recently, Moore *et al.* published their experience of SBRT as a bridge to transplant in 16 patients in which 11 were transplanted. Of these, 3 (27.3%) achieved pathological complete response, 6 (54.5%) achieved pathological partial response, and 2 (18.2%) achieved pathological stable disease. Local control was achieved in all patients. Five other patients were still waiting for transplant at the time of publication and none were removed from the list for tumor progression (45). Further studies are necessary to clarify the future role of SBRT as an option for bridging.

Sorafenib is an orally active multi-kinase inhibitor that is used in the treatment of advanced HCC (46,47). Its side-effects limit use in patients with advanced liver disease. Its potential use as bridging therapy is still being explored. A randomized control trial comparing TACE and sorafenib against TACE with placebo found no difference in time-to-progression, progression-free survival or time-to-liver transplant (48). At this time, its use for bridging therapy can't be recommended.

Locoregional therapies for downstaging to liver transplantation

Unfortunately, many patients present with locally advanced HCC that exceeds criteria for transplant. Downstaging refers to the use of treatment therapies to reduce the tumor load and bring the patient within transplant criteria. There is no established consensus in the optimal therapy, the maximum tumor size or the waiting time after successful downstaging before listing. This explains, in part, the variability in the results from studies. The majority of studies have used TACE as a treatment modality.

Chapman *et al.* published a retrospective study of their cohort transplanted for HCC. There were no size or number limit of lesions and patients could have segmental portal vein involvement. Seventy-six patients had stage III/IV disease and were candidate for downstaging. It was successful in eighteen (23.6%) bringing them within MC and 17 underwent transplantation. There were no significant differences in the DFS or disease-specific survival at 5-years in stage III/IV downstaged and stage II patients (49). In contrast, Ravaioli *et al.* reported a 90% success rate of downstaging (20). They pre-defined the maximum tumor size and number for which downstaging

would have been attempted and all patients had to be within MC for transplantation. Many modalities (RFA, Ethanol ablation, TACE) could have been used for adjuvant therapy. The rate of LT was the similar in patients with MC (67%) and downstaged patients (68%) and both groups had similar 3-year RFS and DFS. However, more patients in the downstaged group dropped out from the list prior to LT because of tumor progression beyond MC (27.1% *vs.* 11.6% in the MC group) (20). A study conducted at UCSF, also using predefined maximum tumor size and number and treated using multiple locoregional therapies showed successful downstaging (within MC) in 43 of 61 patients (70.5%). Thirty-five underwent transplantation and none had a recurrence at 4 years. Intention-to-treat survival was 69% (50). A few studies have evaluated TACE before transplant compared to no treatment in patients exceeding MC. Yu *et al.* using UCSF criteria, showed similar survival and tumor-free rates at 5 years in patients that received downstage therapy compared to those that did not (51).

Adjuvant therapies play a role in allowing patients that are initially not candidates for liver transplantation to become eligible after successfully reducing the tumor burden. While TACE is the favoured modality of treatment, Y-90 radioembolization may become a leading option as well (52,53). The use of these therapies, as well as RFA and SBRT will minimize wait list dropouts due to tumor progression without impacting on long-term outcomes after transplant.

Post-transplant care

The post-operative care of the patient after liver transplantation for HCC is similar than for other liver diseases and they are at the same risk of infectious, renal and metabolic complications. Recurrence of HCC after transplant remains a source of preoccupation and strategies are developed to predict, detect and minimize recurrence. The most valuable action probably occurs before transplantation by selecting patients at lowest risk using customary criteria (21,22,54).

There is no established guideline for post-transplant surveillance in patients transplanted with known HCC or incidentally found in the explant. The AASLD and AST guidelines recommend a CT scan of the abdomen and chest every 6 months for 3 years with serial measurement of the AFP (55). Guidelines from the 2010 International Consensus Conference recommended a CT or MRI of the abdomen every 6 to 12 months (23). The National Comprehensive Cancer Network (NCCN) suggested imaging every 3 to 6 months for 2 years, then annually with AFP levels every 3 months for 2 years and then every 6 months (56).

Several studies have attempted to identify predictors of recurrence after transplantation. Agopian *et al.* conducted a retrospective review of 865 patients transplanted for HCC between 1984 and 2013 in a single institution. A nomogram was developed that included the grade of differentiation, presence of vascular invasion (macrovascular or microvascular), downstaging, radiological maximum tumor diameter, AFP, neutrophil/lymphocyte ratio and total cholesterol. This nomogram could predict recurrence and mortality post-transplant with moderate accuracy (c-statistic 0.79 and 0.61, respectively) (57). The Risk Estimation of Tumor Recurrence After Transplant (RETREAT) score has been recently developed from a retrospective cohort of patients transplanted at three academic centers and validated in a cohort of patients within MC who underwent liver transplant at a different institution. Three predictors were identified that included the AFP at the time of transplantation, presence of microvascular invasion and the sum of the largest viable tumor diameter (in centimeter) plus the number of viable tumors. RETREAT was able to stratify 5-year post-transplant risk with good model discrimination and better than MC (58). The Model of Recurrence After Liver Transplant (MORAL) for HCC was developed using pre- and post-transplant variables. The Pre-Moral model included the neutrophil/lymphocyte ratio >5, the AFP >200 ng/mL and largest tumor size >3 cm. The Post-Moral model included grade 4 tumors, presence of vascular invasion, largest tumor size on pathology of >3 cm and the total tumor number on explant >3. Combining both scores provided the Combo-Moral score. All three scores were able to predict with high discrimination (c-statistic 0.82, 0.88 and 0.91, respectively) recurrence free survival and were also superior to MC (59). These models and others (60) show the limitation of pre-transplant imaging in predicting recurrence after liver transplantation and support the use of laboratory data and explant analysis in adjusting risk assessment. However, whether surveillance strategy should be adapted based on these scores has not been proven and at this moment cannot be recommended.

Sirolimus is an immunosuppressive medication that inhibits the activation of mammalian target of rapamycin (mTOR), therefore inhibiting the cytokine driven proliferation of T- and B-lymphocytes. Although devoid of nephrotoxicity which is common with calcineurin inhibitors (tacrolimus ore cyclosporine), sirolimus is associated with

significant side effects (mucositis, oral ulcers, bone marrow suppression, albuminuria, delayed wound healing) that limit its use as a first line agent. Several reports suggested an antiproliferative activity that can be advantageous in patients with hepatocellular cancer (61-63). Clinical evidence came initially from retrospective studies. Zimmerman *et al.* reported a higher disease-free and OS with sirolimus and CNI based immunotherapy when compared to CNI, mycophenolate mofetil and steroids at 1 (93% *vs.* 75%, 96% *vs.* 83%, respectively) and 5 years (79% *vs.* 54%, 79% *vs.* 62%, respectively) (64). Another study showed acceptable rates of recurrence and survival using a *de novo* sirolimus based immunosuppression regimen, even in patients that were beyond MC. One- and four-year tumor-free survivals were 85% and 73% when MC were fulfilled and 82% and 75% when they were not. Similarly, 1- and 4-year tumor-free survivals were 84% and 77% when UCSF criteria were fulfilled and 84% and 72% when they were not (65). Using data from the Scientific Registry of Transplant recipients (SRTR) that included 2,491 patients transplanted with HCC, Toso *et al.* showed a survival benefit of maintenance treatment with sirolimus (hazard rate 0.53, 0.31–0.92) (66). A meta-analysis of these retrospective studies showed the benefits of sirolimus in lowering recurrence rate and improving recurrence-free and recurrence related survival compared to calcineurin inhibitors (67). In a randomized, open-label trial comparing mTOR-free immunosuppression versus a group incorporating sirolimus, the later was associated with a better RFS in the first 3 years and OS in the first 5 years after transplantation. Interestingly, the benefits of sirolimus were more obvious in patients at lower risk of recurrence (transplanted within MC) (68). In summary, the accumulated evidence suggests a possible role for maintenance therapy with sirolimus, but the benefits on RFS may not extend beyond the first three years after transplant and five years for the OS.

Conclusions

Liver transplant is a definitive therapy for HCC in patients that are not good candidates for locoregional therapy due to poor liver function or who have moderately advanced disease. Adjuvant therapies are efficacious in minimizing disease progression and waitlist dropouts, particularly in areas where waiting times are lengthy. While many questions still remain unanswered, notably optimal transplant criteria, with proper patient selection and post-transplant care, it is possible to achieve survival rates that are comparable to other indications for transplantation.

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Footnote

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