Review Article

Review on liver transplant for hepatocellular carcinoma

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Abstract: Orthotopic liver transplant (OLT) is a curative treatment for patients with hepatocellular carcinoma (HCC). It is widely practiced around the world, but there is no specific set of recommendations to guide physicians. Milan criteria (MC) is a starting point in selecting optimal candidates for OLT, but no consensus exists for patients whose tumors exceed beyond MC. This article will review current literature and discuss controversial topics within HCC and OLT.

Keywords: Organ procurement and transplantation network (OPTN); United Network for Organ Sharing (UNOS); hepatocellular carcinoma (HCC); orthotopic liver transplant (OLT); Milan criteria (MC); locoregional therapy (LRT); end stage liver disease (ESLD)

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Introduction

The first solid organ transplant in the modern era was performed in 1883 by Dr. Theodor Kocher, who successfully implanted thyroid tissues in post-thyroidectomy patients (1). The concept of replacing a failed organ through transplant was widely acknowledged soon thereafter. In 1963, Dr. Thomas Starzl performed the first human liver transplant. OLT became the standard of care for end stage liver disease (ESLD) in the 1980s, especially with the invention of various immunosuppressants. Today, the success of OLT is marked by a 1- and 5-yr survival of 85% and 70% (2), in an otherwise terminal condition.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. In some parts of Southeast Asia, it is the most common malignancy, in part due to the endemic spread of Hepatitis B and C viruses. Other common risk factors for developing HCC include cirrhosis, alcohol, and non-alcoholic fatty liver disease. Overall, HCC has become more prevalent globally, causing 250,000 to 1 million deaths annually worldwide (3). Without treatment, HCC has a high mortality rate, with a 5-year survival of 10% (4). OLT offers a potential cure for HCC, especially if the cancer is found in early stages (T1 or T2). Unfortunately, the worldwide shortage of deceased liver donors presents a challenge to justifiably distribute liver grafts among patients in need of OLT.

Epidemiology and overview

In the years prior to 2002, the overall 5-year survival for HCC was merely 11.7% (5). However, it drastically improved over the last decade, due to earlier diagnosis from better cancer screening, and new treatment options, from locoregional therapy (LRT) to OLT.

Liver allocation has come a long way. In the 1980's, distribution of this scarce resource used to be "ad hoc" basis, solely determined by medical providers. In the 1990's, ICU patients and hospital patients had priority over clinic patients, considering that inpatients are likely to have a higher mortality without immediate intervention. In 1998, minimal listing criteria were instituted using the Child-Turcotte-Pugh (CTP) score (6). This scoring system takes into account encephalopathy, ascites, bilirubin, albumin, and pro-thrombin time. A numeric score was then converted to class A, B, or C, with C being on the more severe end of the spectrum. Despite its seemingly comprehensive determinants, this score became quite subjective, requiring physicians to accurately stage hepatic encephalopathy and ascites.

Finally, in 2002, the Model of End Stage Liver Disease (MELD) score was adopted in prioritizing patients for

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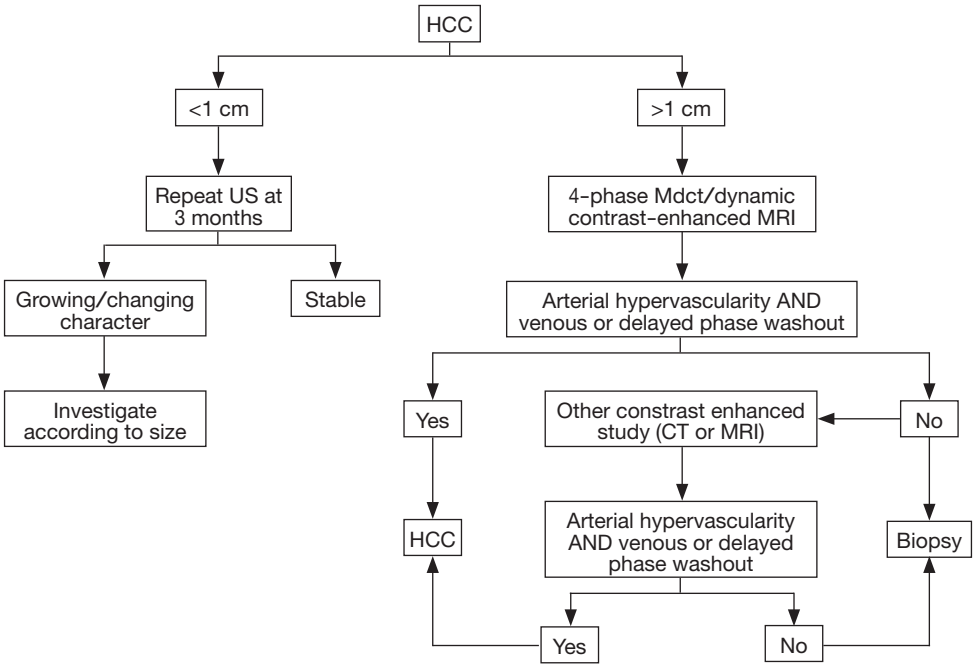

Figure 1 An algorithm for diagnosis of HCC based on AASLD guideline. Printed with permission from AASLD.

liver transplant (7). This score was initially developed to predict mortality in patients with complications of portal hypertension undergoing transjugular intrahepatic portosystemic shunt placement (TIPS) (8). It is calculated based on three objective variables: international normalized ratio (INR), bilirubin, and serum creatinine. This score was subsequently found to be also useful in predicting three months mortality in patients with liver disease, and thus is currently used to prioritize deceased donor liver allocation. Disadvantage of this scoring system is that it does not take into account quality of life issues, such as when hepatic encephalopathy or ascites can be detrimental to patients' lives. Other than the MELD score along, there are several other factors that go into candidacy for a liver transplant, including BMI, social support, cardiac/pulmonary status, portal vein patency, and other malignancy or co-morbidities.

In regards to allocation, the United States is divided into 11 different regions. Deceased donor livers that become available in a certain region can be shared amongst those living within the region (9) (unos.org). The higher the MELD score, the higher on the list one becomes. However, every region has a different MELD average for receiving a liver, thus making certain regions more favorable in receiving a liver than others. Currently, the national average MELD score for liver transplant is 27 (2). However, the average MELD score in some areas varies from 26-33, depending on blood type. On average, for patients with MELD 21-30, the mean waiting time to OLT is 128 days. For MELD score 31-40, mean time is approximately 29 days. Average wait time can differ drastically by regions, which has resulted in inequity in organ allocation between different areas of the country.

Diagnosis of HCC

In recent years, as a result of better cancer screening, patients with HCC are diagnosed earlier (10). Diagnosis of cancer often requires pathology confirmation; however, HCC is an exception. AASLD published its most recent guideline which states that lesions greater than 1 cm, with triple phase CT or MRI showing arterial enhancement, followed by portal venous phase washout, can confirm the diagnosis of HCC, without a liver biopsy (11). New nodules greater than 1cm in cirrhotic liver showing typical pattern of HCC are nearly 100% specific with high positive predictive power (12-14). If initial imaging does not show typical pattern, then a second imaging modality should be pursued. Atypical imaging pattern on CT or MRI, such as iso- or hypo-vascular enhancing lesion during arterial phase without portal washout should undergo biopsy (*Figure 1*). Major

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complications associated with a biopsy include bleeding and needle tract seeding of tumor, which has been reported in multiple cases (15). A large retrospective study done by Wang *et al.* in China showed a 0.2% risk of implantation of metastases and 0.4% risk of hemorrhage (16).

Molecular markers for detecting HCC

Elevations of alpha-fetoprotein level in the serum is not very sensitive (39-65%) nor specific (76-94%) for the diagnosis of HCC. Most recent AASLD guideline recommends against testing AFP to screen for HCC in cirrhotic patients. On the other hand, AFP has found a role in the monitoring of response and tumor progression after treatments. Diaz *et al.* observed that a reduction in serum AFP level after LRT predicts tumor reduction (17). Also, the pre-operative clinical prognostic factor for mortality and recurrence after treatment was AFP level higher than 300 ng/mL (18). In addition, AFP also has a role in predicting post-transplant outcomes. Several studies showed patients with significantly elevated AFP prior to transplant have poorer outcomes (19). Some experts even feel that AFP >1,000 ng/mL should be the criteria used to delist otherwise eligible patients. However, this is still an area of debate.

Staging of HCC

Once HCC is diagnosed, staging with either CT or MRI of the chest, abdomen and pelvis is required. The Barcelona Clinic Liver Cancer developed a staging system in 1999 that takes into account the performance status, characteristic of the tumor (single nodule or multi-nodular), vascular invasion, and presence of portal HTN. This BCLC classification system has become a widely accepted algorithm for all HCC patients in earlier disease, linking their current status prognosis with treatment recommendations. The widely accepted TNM staging system of many malignancy, although considered, seems to have inferior prognostic ability of long term survival for HCC, mostly because the severity of liver disease and complications of cirrhosis are not included as part of the staging system (20).

Indications of liver transplant listing: Milan criteria (MC)

When OLT initially became widely practiced, early work on transplanting patients with HCC had high post-OLT recurrence rate and subsequently high mortality. The poor outcome was in part related to the indiscrete selection of patients. Over the last two decades, investigators began to describe and define tumor characteristics that predict chance of recurrence after treatment and those associated with high mortality. In 1993, Bismuth *et al.* showed that those with at most three tumors, each less than 3 cm had a better outcome with OLT compared to surgical resection (21). In 1996, Mazzaferro *et al.* proposed the MC, which showed that patients with solitary HCC <5 cm or up to three lesions each smaller than 3 cm, without macrovascular invasion or extrahepatic spread, had a 5-year survival of 70% after OLT (22). This survival benefit is comparable to OLT in non-HCC population. Given the excellent outcome, MC has been adapted globally (EASL and AASLD guidelines) in selecting HCC patients for liver transplant (23,24). In addition, to acknowledge the high mortality of HCC (25), patients diagnosed with HCC are given priority listing in terms of extra points to match their mortality. Although MELD score is a useful tool to accurately predict high mortality in ESLD patients, it is less powerful for HCC patients (AASLD guideline). Therefore, to give HCC patients equal opportunity for OLT, they are given 22 points for solitary HCC 2-5 cm or three nodules each <3 cm. In addition, 10% point increase every three months due to estimated 15% mortality increase (26).

The adoption of the MC offered a promising 5-year post-OLT survival at 70%, in keeping with the non-HCC transplant group (22). Although Milan criteria is well validated (*Table 1*), the cutoff size and number are rather arbitrary. Thus, many find MC to be overly stringent, limiting a few potentially acceptable candidates from transplant. In addition, some argue that imaging may underestimate tumor size. Freeman *et al.* evaluated the UNOS database and reported that radiologic exams are not very precise, underestimating tumor load in 27% of the patients while overestimating in 30% of the population (30). Imaging technique, protocols, and expert interpretation are also variable among transplant centers. This further leads to questioning of the cutoff tumor number and size dictated by the MC. For these reasons, a number of experts are looking into expanding or modifying the criteria for OLT listing.

Expanding criteria

Although MC (one nodule <5 cm or up to three nodules, each <3 cm) outlines an acceptable risk to justifiably transplant HCC patients, the precise amount of tumor

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Table 1 Outcomes (HCC Recurrence rate, 5-year survival) of HCC patients transplanted under the Milan criteria

Studies	Number of patients	Tumor selection	Selection technique	Recurrence rate	Overall survival (%)
Mazzaferro, *et al*. (NEJM, 1996) (22)	48	Single <5 cm, or up to 3 nodules, none >3 cm	CT angiogram	8% (at 4 years)	75 (at 4 years)
Bismuth, *et al*. (Semin Liver Dis, 1999) (27)	45	Single <3 cm, or up to 3 nodules, none >3 cm	CT	11% (at 5 years)	74 (at 5 years)
Llovet, *et al*. (Hepatology, 1999) (28)	79	Single ≤5 cm	Dynamic CT	4% (at 5.4 years)	74 (at 5 years)
Jonas, *et al*. (Hepatology, 2001) (29)	120	Single <5 cm or up to 3 nodules, none >3 cm	Explant pathology	N/A	71 (at 5 years)

burden to be considered reasonable is not well established.

An attempt to expand beyond MC was done in 2001 by University California at San Francisco (UCSF). They developed the UCSF criteria: *single nodule <6.5 cm; or multiple nodules with the largest <4.5 cm in diameter and the sum of total diameters <8 cm*. Comparing UCSF to MC, the survival rate after transplant appeared to be similar (19). Although the results were exciting for those who do not initially qualify for MC, critics noted that in this study, only 24% of the population fell outside the MC. This may lead to dilution of poorer outcomes in those with larger tumors burden. Furthermore, the UCSF study is a retrospective analysis based on explants pathology, not pre-transplant radiology (31). The study included explant pathology and microvascular invasion (MVI) in the prognostic model, but these information are not usually available until post-OLT. A later paper by University California at Los Angeles (UCLA) with similar design validated the UCSF criteria, where 40% patients were outside MC but within UCSF (32). However, the UCSF criteria will need additional validation.

Another large meta-analysis was done by Mazzaferro *et al*. (33) in 2009 to study those individuals who do not fit into MC. The study included 1,556 patients transplanted from 36 centers. Their concept of expansion was termed "up to seven criteria"—number of tumors is up to seven, and the sum of tumor diameters up to 7 cm. The 5-year overall survival of this population after OLT is approximately 71.2%. They also initiated the "Metroticket concept"—the further one expands beyond MC, the more one pays in terms of higher recurrence and poorer post-OLT survival.

Currently, expansion beyond MC still requires more validation. Tumor recurrence may be under reported in OPTN database, thus no national data is available to support criteria for expansion (34). Many opponents of expansion criteria have shown that tumors exceeding the MC may have increased risk of MVI, microsatellites, and poorly differentiated tumor type (29,31,35-39)—all of which are associated with poorer outcomes. Therefore, the decision of expansion still falls on the individual centers to define the maximum cutoff size and number of HCC lesion at which the risk of recurrence may be considered acceptable. Another point of consideration is distributive justice. Due to the shortage in donor livers, this resource should be shared fairly among HCC and non-HCC patients. The post-OLT outcome of the expansion group must be similar or only slightly worse than the MC group to justify fair allocation. Volk *et al*. showed that a liberal approach to transplant selection would lead to a 44% increase in risk of death for all patients on the waitlist (40). He estimated that the 5-year post-OLT survival for HCC group needs to be at least 61%, to not have harmful effect on non-HCC group. To add to the complexity of this issue, there is regional variation in post-OLT success which muddies the nation-wide policy (34).

Downstaging to meet MC for transplant

The MC (single tumor <5 cm, or up to three tumors each <3 cm) is currently used for eligibility to OLT. For tumor burden beyond Milan, there are two ways to achieve a potential transplant. One is by expanding the criteria as explained above, and the other option is to undergo local regional therapy (LRT). LRT allows for shrinkage of tumor burden to meet MC, so one can be listed for OLT. This method is termed downstaging. There are several studies validating downstaging, and they are outlined in *Table 2*.

The technique of choice for downstaging is institution dependent. There is very limited head-to-head comparison

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Table 2 studies for down-staging prior to orthotopic liver transplant (OLT) in patients with cirrhosis and hepatocellular carcinoma (HCC)

Studies	Tumor selection	Selection technique	Number of patients		5-year survival	
			Within MC	Beyond MC	Within MC	Beyond MC
Yao, *et al*. (Hepatology, 2001) (19)	1 nodule ≤6.5 cm; up to 3 nodules, none >4.5 cm, total tumor burden ≤8 cm (UCSF)	Explant pathology	46	14	72%	N/A
Roayaie, *et al*. (Ann Surg., 2002) (41)	Not defined	Radiology	None	43	None	44%
Yao, *et al*. (Am. J. Transplant, 2007) (31)	UCSF criteria	Radiology	130	38	80.7% (Combined)	
Cillo, *et al*. (Am J. Transplant, 2007) (36)	N/A	Radiology	37	31	75% (at 3 yrs)	90%
Ravaioli, *et al*. (Am. J. Transplant, 2008) (38)	1 nodule 5-6 cm; 2 nodules ≤ 5 cm; up to 5 nodules ≤4 cm with total tumor burden ≤12 cm	Radiology	88	32	71% (3 yrs)	71% (3 yrs)
Herrero, *et al*. (Liver Transpl, 2008) (37)	1 nodule ≤6 cm; 2-3 nodules ≤ 5 cm (Navarra criteria)	Radiology	47	24	70%	73%
Silva, *et al*. (Liver Transpl, 2008) (42)	1 nodule ≤5 cm; 2-3 nodules ≤ 5 cm; total tumor burden ≤10 cm	pathology	231	26	62%	69%
Mazzaferro, *et al*. (Lancet Oncol, 2009) (33)	Total tumor burden ≤7 cm AND number nodules ≤7 (Metroticket)	Pathology	444	283	73%	71%

between different procedures. While some studies follow RECIST (Response Evaluation Criteria in Solid Tumors) as down-staging measure, most use MC as an endpoint. Once the tumor burden is managed within an acceptable range, patients will be monitored closely for at least three months prior to listing (34,43,44). This process allows time to observe the behavior of the tumor. A period of waiting time prior to listing is not without benefit. It allows physician to select out those with aggressive tumors, therefore high risk for transplant. A study from Northwestern University, using living donor model, has hypothesized that fast track transplant for HCC has higher rate of recurrence post-OLT (45).

Currently, no clear guideline exists to exclude anyone from undergoing downstaging (41,46-48). However, distant metastasis or macrovascular invasion usually precludes patients from undergoing the procedure, given the high risk of recurrence. In the United States, only several regions have a clear down-staging protocol in place (43,47). Pomfret *et al*. proposed a limit on downstaging: single tumor <8 cm, or 2-3 tumors each <5 cm, with sum of tumor diameters <8 cm, exclude vascular invasion or number lesions >3. This proposal was raised in the 2010 report of national conference on liver allocation in patients with HCC. However, this proposal will need to be further validated (34).

LRT

Many techniques are available for LRT: transarterial chemoembolization (TACE), radiofrequency thermal ablation (RFA), radioembolization, resection, conformal-radiotherapy (CRT) and tyrosine kinase inhibitor sorafenib. The choice of technique is determined by location, size and number of lesions. It is also dependent on the expertise of the institution. The goal of LRT is two folds: one is to downstage the tumor, and the other is to help patient maintain on the transplant list during the waiting period if their tumor grew in size.

TACE utilizes intra-arterial injections of chemotherapeutic drug into the hepatic artery followed by Iodized oil (lipiodol) injection (49). It has been shown to decrease dropout rate (9-14%) (50,51), improve survival (52,53), and allows for longer wait time on the transplant list (211-274 days) (50,51). The term "drop-out" refers to delisting of patients due to tumor progression or complications of HCC that prohibits OLT. Moreover, some showed that TACE prior to transplant may even result in decreased post-transplant recurrence rate (17%

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vs. 36% non-treatment) (54-56). However, additional data and validation would be needed to prove that LRT in fact lower HCC recurrence or improve survival after transplant.

RFA employs electrical conduction and heat generated to ablate the HCC lesion. It is done under imaging guidance. This technique requires careful selection of patient to prevent tumor seeding (subcapsular tumors and direct nodule puncture) (57). One study done by Ng *et al*. showed complete tumor ablation in 92.7% of 192 patients. With a median follow-up of 26 months, local recurrence occurred in 28 patients (14.5%) (58).

Resection is rarely used in cirrhosis related HCC, but is the primary mode in non-cirrhotic HCC (59). CRT is an option for patients who failed other LRT or not eligible for other LRT due to the tumor anatomy (60). Sorafenib has been proven effective as well, but has high complication and is associated with high dropout rate (61).

LRT allows patients to stay on the list for a longer period of time and therefore decreasing overall dropout rate (33,62). Several studies showed a dropout rate of only 0-10% at 12 months for low grade tumor (T1 or T2 patients) treated with LRT (50,54,57,63). Another study reports dropout rate being as high as 30% without bridging therapy for those meeting MC. LRT is now widely accepted and practiced, with OPTN data showing that 65% of HCC patients received LRT prior to transplant (34). University of California in San Francisco (UCSF) conducted a review on patients undergoing LRT. They found that those who successfully underwent tumor reduction and subsequently transplant, the 5-year survival is approximately 84% (44). This high survival rate suggests LRT may benefit patients who initially do not meet MC.

Multi-phase CT or MRI should be performed 4-6 weeks after each LRT (34), to measure residual tumor burden. One can also monitor for serum level of AFP. Those with AFP <500 ng/mL have better response than those with AFP >1,000 ng/mL at initiation of down-staging (18,31). AFP in this scenario can be monitored for signs of recurrence in those patients whose AFP returns to normal after treatments.

Drop-outs and wait-list monitoring

Depending on different regions of the country, average wait time to liver transplant varies. However, the limited donor pool often leads to an inevitably long wait time. Longer wait time is associated with more drop-outs from the waitlist. For each month on the list without a liver transplant, the rate of drop-out is estimated to increase by 4.0% (28).

Major risk factors for tumor progression while on the waiting list include: length of wait time and tumor characteristics. UCSF reports a series of dropout rates for patients within MC: 0% dropout at 3 months, 11.0% at 6 months, 57.4% at 12 months, and 68.7% at 18 months (64). The total dropout rate for a median waiting time of 330 days was 22%. Large tumor size and multi-focality of the lesions also correlate to higher risk of tumor progression, thus higher dropout rates. Other factors associated with high dropout rate include resistance to LRT, and AFP >200 ng/mL. OPTN data shows that AFP <500 correlates with a 7.4% dropout, while AFP >1,000 is associated with 24.9% of dropout rate.

Tumor progression monitoring relies on imaging and serum biomarkers. The standard imaging used in most centers is contrast-enhanced CT or MRI (33). Although the interval to repeat imaging is unclear, AASLD recommends every 3-4 months after initial management. A technique under investigation is dual contrast MRI, which is thought to be more sensitive in detecting small HCC lesions than triple phase CT or MRI. Limited information is available on the use of AFP to follow patients on the waitlist. However, in patients whose serum AFP level was initially elevated, and returned to normal after treatment, a subsequent rise in AFP may suggest HCC recurrence.

If tumor progressed past MC on imaging, patient would be deactivated to undergo downstaging, or delisted for palliative treatment if distant metastasis or vascular invasion is found.

Post-transplant monitoring

Roayaie *et al*. reported that HCC patients post-OLT have 18.3% chance of eventual tumor recurrence (65). This group of patients received OLT from 1988-2002; and the median time to tumor recurrence was 12.3 months. Interestingly, the rate of tumor recurrence dropped from 25.5% down to 8-11% after the MC adoption. Tumor recurrence marked a poor prognosis, with median survival <12 months. The 5-year survival is 22% for the recurrent cohort comparing to 64% for its counterpart. Sites of recurrence include liver alone (16%), both intra and extra hepatic (31%), or extrahepatic alone (53%). Liver, lungs and bones are most frequent metastatic organs. The risk factors of tumor reappearance include tumor size, number of lesions, tumor differentiation, MVI and regional lymph node involvement (66). There is a positive

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correlation between the tumor burden prior to transplant and the cancer recurrence rate post-OLT. Similar to waitlist monitoring, post-OLT patients need routine imaging and biomarker surveillance. To detect HCC recurrence early, contrast CT, MR or PET/CT should be done every 6 months to yearly, for the first 3-5 years post OLT (67). Regular ultrasound and AFP are less accurate but also less expensive, may be applied every 3-6 months, up to five years post-OLT. Rise in AFP above 20 ng/mL in patients who had normal AFP should raise the suspicion of recurrence, and one should obtain imaging.

Treatment of HCC recurrence after orthotopic liver transplant (OLT)

Surgical resection is the best option for local HCC recurrence post-OLT. In one study, series of nine patients who underwent resection for HCC recurrence experienced survival rate similar to those who did not have recurrence (68). This surprising results, however, is subject to selection bias and small sample size. If patient is not eligible for resection due to size, location, or multiplicity, radiofrequency ablation or chemoembolization may be next best options. For extrahepatic recurrence post-OLT, surgical management requires those with good functional status, single lesion, and long interval from transplant to recurrence. Bone metastasis survival is especially poor, and most aim to palliate pain with external beam radiation and zoledronate (69).

The SHARP trial published in 2008 showed some benefit with sorafenib to treat unresectable advanced stage HCC (70). Teng *et al*. from Taiwan recently reported sorafenib improves overall survival in HCC post-OLT patients as well (71). The studied patients had pre-transplant tumor beyond MC. Using sorafenib as an adjuvant therapy, there was no tumor recurrence at two years in five studied patients. Using it as palliative therapy after recurrence, there is a trend for survival benefit (50% *vs*. 20% at 18 months) although not statistically significant (P=0.17).

Conclusions

The selection of HCC patients for liver transplant is not a trivial task. It requires a balance between maximizing benefit in HCC patients and minimizing harm to non-HCC patients due to the scarce resource. After this review, there is an obvious need to further validate the criteria that is currently being used. In addition, future research is required to unifying a set of guidelines in LRT and downstaging protocol.

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