Hepatocellular Carcinoma, Alpha Fetoprotein, and Liver Transplantation

Subjects: Oncology

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Hepatocellular carcinoma (HCC) is one of the leading indications for liver transplantation and has been the treatment of choice due to the oncologic benefit for patients with advanced chronic liver disease (AdvCLD) and small tumors. For HCC patients undergoing liver transplantation, alpha fetoprotein (AFP) has increasingly been applied as an independent predictor for overall survival, disease free recurrence, and waitlist drop out. In addition to static AFP, newer studies evaluating the AFP dynamic response to downstaging therapy show enhanced prognostication compared to static AFP alone.

hepatocellular carcinoma alpha fetoprotein liver transplantation

1. AFP in the Pre-Operative Setting, Allocation and Down-Staging

1.1. Survival and Recurrence

Pre-transplant AFP levels have been shown to be independent predictors of survival and disease recurrence in patients undergoing liver transplantation for HCC. In a 2001 retrospective analysis of 70 patients, Yao et al. found AFP levels > 1000 ng/mL served as an independent predictor of mortality with a hazard ratio of 2.96, independent of whether patients were within Milan Criteria [1]. For the majority of the US, except under certain protocols, the absolute preoperative value of AFP > 1000 ng/mL has been utilized as a red line due to the high risk of recurrence and mortality [2][3][4][5]. Hameed et al. 2014 established that by implementing a cutoff of patients with preoperative AFP > 1000 ng/mL they would exclude only 4.7% of patients from being eligible for transplant, while gaining a 20% reduction in post transplantation HCC recurrence [2]. This preoperative cutoff of AFP > 1000 ng/mL was adopted by the US allocation criteria in 2017, except under region-based protocols, such as the Region 5 down-staging for “all comers” with HCC [6][7].

Although a pre-operative level of 1000 ng/mL appears to be a prohibitive cutoff, there have been multiple studies identifying adverse outcomes associated with lower AFP levels [8][9][10][11][12][13]. In 2009, a large review of more than 6000 patients in the SRTR database confirmed AFP was an independent predictor of survival with a recommended cutoff of 400 ng/mL for access to liver transplant [10]. The Toronto group published a study demonstrating a preoperative AFP > 500 ng/mL as a predictor of poor outcomes with 10 year patient follow-up [11]. A US study, one of the largest United Network for Organ Sharing (UNOS) reviews of over 6000 HCC patients within

Milan Criteria, found that 5-year survival progressively decreased as AFP increased, with a measurable survival discrimination with an AFP nadir of 15 ng/mL for 5-year survival outcomes (5-year survival: AFP < 15 ng/mL 74%, AFP 16–65 ng/mL 66.1%, AFP > 65 ng/mL 57.4%) [14].

Lower AFP has also been correlated with lower rates of post-transplant recurrence and survival, irrespective of Milan criteria. In select patients exceeding Milan criteria, those with AFP < 100 ng/mL could obtain a 5-year risk of recurrence of only 14.4% vs. 47.6%, $p = 0.006$ [4]. While exact AFP cutoff values demonstrating the best post-transplant outcomes are not exact, AFP < 15 ng/mL at transplant had similar outcomes irrespective of whether the tumor burden was within or beyond Milan Criteria [14].

1.2. AFP Dynamics

In addition to the absolute static preoperative value of AFP, there has been evaluation of the dynamic changes of AFP prior to transplantation in response to preoperative therapies and overall post-transplant outcomes. One of the first studies reviewed 153 patients undergoing liver transplantation for HCC (78% underwent locoregional therapy). The first and last AFP points over time were used to generate an AFP slope of progression and found that AFP slope > 15 ng/mL/month had poorer survival (54% vs. 76% $p = 0.02$) at 5 years [15]. Interestingly, in this study, neither static preoperative AFP levels nor Milan criteria reached statistical significance for predicting postoperative recurrence or survival. In a larger review of 336 patients undergoing liver transplantation (98% of whom had preoperative locoregional treatment), Giard et al. established an AFP slope > 7.5 ng/mL/month had a 3-fold higher relative risk of recurrence, which was also strongly associated with microvascular invasion (OR 6.8, $p = 0.008$) [16].

A complicating issue in studies of AFP dynamics and determination of AFP slope over time is reliability of AFP measures in the setting of variable locoregional therapies, a lack of accounting for viral hepatitis status, and other issues [17]. It is unclear what threshold of AFP slope is definitively associated with poor outcomes, and wide ranges of positive AFP slopes have been associated with poor outcomes [16][18][19]. It is clear from a clinical standpoint, that tumors that continue to express high levels of AFP despite locoregional therapy have concerning tumor biology, which may warrant more aggressive locoregional therapy, consideration of systemic therapies, as well as avoidance of liver transplantation. There are no uniform practice guidelines related to how to utilize AFP dynamics. Clinicians do not have reliable indicators of ideal AFP slope that correlated with post-transplant outcomes. AFP slope can range widely, with regard to method of calculation as well as final values, which leads to uncertain clinical correlations [16][18][19]. Like the static preoperative AFP, the exact AFP slope values that are relevant is subject of debate.

1.3. Down-staging and Allocation

Down-staging is the application of pre-transplant therapies, typically locoregional liver-directed therapy, to decrease the size and number of liver lesions to meet acceptable criteria for transplantation [20]. In 2017, the UCSF downstaging criteria were adopted by UNOS as the upper tumor burden limit for patients eligible for down-staging, with the exception of patients falling under regional protocol variances. Patients meeting the down-staging UCSF

criteria (single tumor > 5 and ≤ 8 cm in diameter, 2–3 tumors each ≤ 5 cm in diameter with a sum of all tumors ≤ 8 cm, or 4–5 lesions each < 3 cm sum of all tumors ≤ 8 cm and no evidence of vascular invasion) have been established to achieve similar post-transplant outcomes once down staged to within Milan as compared to patients always within Milan criteria [21].

These criteria were supported by a recent UNOS database review (n = 3819), comparing groups always within Milan, with those down-staged per UNOS / UCSF down-staging criteria (UNOS-DS), and those with initial tumor burden beyond UNOS criteria [22]. Although the post-transplant 3-year survival was comparable between the Milan and UNOS-DS groups (83.2% vs. 79.1% $p = 0.17$), within the downstaging groups, AFP ≥ 100 ng/mL at the time of transplant (HR 2.4, $p = 0.009$) and short wait-list region (HR 3.1, $p = 0.005$) were associated with increased risk of post-transplant death. Only AFP ≥ 100 ng/mL proved to be an independent predictor of HCC recurrence [22]. This study supported the current placement of upper limits on tumor burden amenable to downsizing but perhaps more importantly also suggested further evaluation of AFP's role in prognosticating post-transplant outcomes in down staged patients.

An SRTR database investigation of 6817 patients with a diagnosis of HCC followed the trend of AFP after downstaging treatment. They found that patients with AFP levels originally > 400 ng/mL (even as high as > 1000) who had sufficient treatment response to reduce AFP ≤ 400 ng/mL had similar intention-to-treat and post-transplant survival to patients with AFP always ≤ 400 ng/mL (81% vs. 74% at 3 years, $p = 0.14$ and 89% vs. 78% at 3 years, $p = 0.11$, respectively) [8].

In a similar vein, Grat et al. found that patients with AFP persistently < 100ng/mL (97.3%) and those whose AFP dropped below 100 ng/mL (100%) after locoregional treatment, had significantly better 5-year recurrence-free survival compared to those whose AFP rose from <100 ng/mL (75%) or was always >100 ng/mL (38.4%) ($p < 0.001$) [23]. These studies suggested a link between AFP response to downstaging and post-transplant recurrence-free survival.

In 2017, the US Allocation system formally adopted an AFP cutoff of 1000 ng/mL to qualify for HCC exception points. If AFP > 1000 ng/mL, the patient would be required to downstage to an AFP < 500 ng/mL and stay <500 ng/mL for 3 months prior to qualification for exception points [20]. The AFP response to therapy, as a result of this policy, would provide a more precise measurement of tumor biology over time as compared to the initial fears of recurrence from the static initial AFP value of 1000 ng/mL, as previously discussed [2].

1.4. Waitlist Mortality and Dropout

Waitlist mortality and dropout have been a long subject of concern given the historical difficulty of adopting an equitable allocation system. More recent alterations to the US allocation system included a 6-month waitlist period and exception point cap in 2015 to address discrepancies on a national level, and to encourage selection of transplant candidates with favorable tumor biology [24]. Median MELD at Transplant of the transplant center minus three points (MMAT-3) was selected as the exception point score for HCC patients in 2019. Although enacted only

recently, a large UNOS database review of dropout since the MMAT-3 policy has found dropout for both non-HCC (from 12.9% to 11.1%) and HCC (from 14% to 10.7%) patients have begun to normalize, suggesting a more equitable allocation model compared to prior [24]. In 2022, this policy was recently modified so that MMAT would be calculated around the donor hospital rather than the transplant hospital in order to provide relative equal access to transplant for patients in geographically contiguous areas at centers with vastly different median MELDs at transplant. The results of this model of allocation for HCC yields a dynamic MELD score for exception patients based on different match runs from different donors. The same patient may receive a transplant with different exception MELD scores at transplant depending on the origin of the donor organ. The results of this policy are maturing, but they hold significant promise in equitably allocating livers with HCC across the country.

While this is encouraging, there is continued concern that certain HCC patients are being inappropriately prioritized. All HCC patients are currently given the same allocation priority irrespective of their liver dysfunction or tumor biology; therefore, patients at a low risk for dropout are given the same priority as those with high risk. Precision in identifying higher dropout risk patients remains lacking in the current allocation scheme.

Current studies have identified risk factors for dropout, but these studies lack uniformity in access to donor organs. Known risk factors for patient dropout while on the waitlist include a high AFP at time of listing, rapid rise in AFP, lack of response to locoregional therapy and synthetic liver dysfunction [8][21][25][26]. The exact value of static listing AFP level associated with dropout varies widely per study, with ranges from 20 to 400 ng/mL quoted [8][27]. Pre-treatment AFP of >500 ng/mL has also been found to predict dropout, independent of Milan status [11].

AFP has evolved in the downstaging space. In addition to serial evaluation by MRI to look for imaging characteristics consistent with tumor viability, AFP trajectory has been used to evaluate response to therapy. For patients undergoing down-staging with locoregional therapy, in the setting of originally high AFP, dropout risk may be reduced with therapy to the level of those patients whose original AFP was lower and persisted. Merani et al. found a similar dropout rate of 10% in patients with AFP either always <400 ng/mL or who fell below <400 ng/mL following locoregional therapy. Those who were either always over 400 or who rose to > 400 ng/mL had a significantly increased risk of dropout at 25% and 44%, respectively, ($p < 0.001$) [8].

A more recent, large-scale analysis found factors predicting dropout following downstaging pretreatment AFP ≥ 1000 ng/mL (multivariate hazard ratio [HR]: 2.42; $p = 0.02$) and Child's B versus Child's A cirrhosis (multivariate HR: 2.19; $p = 0.04$) [21]. Mehta et al. identified the following factors predicting low dropout rates: AFP < 20 ng/mL, MELD < 15, child's class A, and single 2–3 cm lesions [27]. This was further validated into a risk score in 2021, with static AFP being the most heavily weighted [24].

2. Utilization of AFP following Liver Transplantation

Despite optimization and Milan criteria, HCC recurrence post-transplant still occurs in 10–20% of cases [28]. Most recurrences present with extrahepatic disease (78.1%) and are associated with a median survival of 10 months despite treatment (95% CI, 6.5–15.7 months) [28].

Patients with recurrence have better survival when the disease is amenable to resection, locoregional therapy, and more recently immunotherapy [28][29][30]. As such, early detection of recurrence is imperative to optimize available therapy. Although some centers have post-transplant surveillance protocols, there is no universal post-transplant protocol for screening patients, how to use AFP as a biomarker, or to determine which patients need more intensive surveillance [31].

As previously discussed, preoperative AFP and AFP slope have been shown to be independent predictors of post-transplant HCC recurrence. A large UNOS database review of patients with post-transplant recurrence found a preoperative AFP > 500 ng/mL was also linked to lower recurrence-free survival. Preoperative elevated AFP also proved to be an independent risk factor for survival among recurrent HCC patients, with a 1.6-fold increased risk of death when compared to those with preoperative AFP < 20 ng/mL [32].

In addition to the preoperative AFP, the post-transplant AFP trend can serve as an indicator of recurrence risk. In a retrospective review of 125 patients with elevated preoperative AFP (>20 ng/mL) undergoing liver transplant, patients who had rapid AFP normalization within one-month post-transplant had less tumor recurrence. Non-rapid normalization served as a risk factor, independent of Milan criteria status, for recurrence with a hazard ratio of 4.41, $p < 0.001$ [33]. Utilization of the pre- and post-AFP trends could be useful in developing protocols for recurrence risk and postoperative monitoring.

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