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# Liver Transplantation for Hepatocellular Carcinoma: A Time to Push Forward

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Despite improvements in therapeutic modalities over the past decade hepatocellular carcinoma (HCC) remains the second leading cause of cancer related deaths accounting for approximately 700,000 deaths worldwide each year [1]. HCC is frequently multifocal and arises in setting of cirrhosis (>80%) [2], hence surgical resection of HCC with curative intent is only feasible in 20-30% of patients at time of diagnosis [3]. We have known for years that liver transplantation (LT) is the gold standard for HCC therapy in the setting of significant liver disease given its oncologic advantage of replacing the organ harboring malignancy all while reversing the physiologic liver dysfunction. In 1996 Mazzafero et al. demonstrated that by limiting LT to HCC patients with a single tumor of ≤ 5 cm, or up to 3 tumor nodules ≤ 3 cm, excellent outcomes could be achieved giving rise to the influential Milan Criteria [4]. In many parts of the world, great efforts have been made to push the envelope, transplanting patients with tumors well outside Milan; yet in the United States, we remain stagnant in our behavior. Yao et al. created what we now know as the UCSF criteria which includes a single tumor ≤ 6.5 cm, or up to three 3 tumor nodules ≤ 4.5 cm with total tumor diameter ≤ 8 cm [5]. The Toronto group used tumor biology and imaging without any size or number limit for recipient selection with excellent oncologic outcomes [6]. These groups, amongst many others, demonstrated results rivaling the Milan Criteria; however we remain entrenched in the past, relatively unchanged in our behavior in the United States despite these excellent outcomes. Meanwhile, we continue to live in an era where the physiologic MELD at transplant is rising, with patients transplanted from the ICU, on life support and increasingly in need of simultaneous liver kidney transplant. This ultimately depletes another precious organ resource while patients are waiting 6-10 years in some cases on the kidney-alone waitlist.

It remains enigmatic looking at the big picture of liver allocation with regards to HCC. We are granting exception to size and number of tumor alone but in reality we have increasingly more data to go on. Most definitive expression of HCC tumor biology derives from explant pathology, with multiple studies demonstrating that microvascular invasion and dedifferentiated grading are accurate predictors of HCC recurrence [7-9]. We do however recognize these pathologic features are not available to most clinicians. Preoperative biopsy is not necessarily predictive of ultimate explant pathology and thus should be used with caution as recent preliminary data suggests sensitivity and positive predictive values of 40% or less. It has been demonstrated that tumor grade on preoperative needle core biopsy does not often correlate with final explant pathological grade or presence of microvascular invasion [10,11]. Unfortunately pretransplant pathology, at least in its current state, offers us limited ability to remedy our problem of predicting what is most important: tumor biology.

Fortunately there are some trends in biomarkers that might be able to help with the determination of tumor behavior. By no means are they the end all, as many patients with aggressive tumors do not produce markers like serum alpha-fetoprotein (AFP), but they should not be ignored when looking at tumor exception points. Pre-LT serum AFP has been shown to strongly correlate with post-LT survival. Studies have shown 5-year survival of 72% when AFP <200 μg/L as compared to 34% when AFP >1000 μg/L [12], as well as 5-year recurrence free survival of 90% when pre-LT AFP ≤ 200 μg/L versus 40% when pre-LT was AFP >800 μg/L [13]. In fact, it was shown that by combining the UCSF or Metroticket criteria with additional constraint of pre-LT AFP <100 yields an estimated 5-year recurrence free survival of 100% [14]. Moreover, the Alberta group, generated a patient selection score based on total tumor volume (TTV) ≤ 115 $cm^3$ and AFP ≤ 400 μg/L in 2011 [15]. The authors showed the expansion of Milan criteria to the TTV/AFP criteria achieves post-transplant tumor-free survival comparable to Milan criteria while pushing the envelope and allowing a 20% increase in the number of eligible transplant recipients [16].

In addition to AFP, Des-γ carboxyprothrombin (DCP) or protein induced by vitamin K absence or antagonist II (PIVKA-II) is another biomarker that has been studied and has shown strong predictive value for HCC recurrence post-LT [13,17].

Furthermore, neutrophil-to-lymphocyte ratio (NLR) is a unique marker of systemic inflammation that has demonstrated efficacy in prediction of HCC recurrence and outcome post-LT, thought to be related to neutrophil relationship with circulating vascular endothelial growth factor and ultimate tumor angiogenesis. Halazun et al. found that NLR ≥ 5 and preoperative tumor size >3 cm were independent markers of aggressive tumor biology. Based on these findings, they created a scoring scheme that was superior to Milan criteria at prediction of recurrence and overall survival [18]. These results cannot be persistently ignored.

Lastly, one of the most predictive factors for HCC recurrence after transplant is tumor response to locoregional therapy. While we know that complete pathologic response to locoregional therapy portends an excellent oncologic posttransplant prognosis with virtually negligible recurrence risk, we do not have this data pretransplant when selecting candidates [19]. We do however know that HCC tumor response to locoregional therapy has also been evaluated as surrogate for tumor biology. Multiple groups have compared 5-year post transplant recurrence free survival between patients who underwent LT after downstaging compared to those meeting Milan criteria at diagnosis and found similar results [20,21]. Patients within Milan but with tumors that have continued contrast enhancement on axial imaging and rising AFP despite locoregional therapy remain transplantable and are still granted exception points in our current system despite what

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is presumed to be poor tumor biology. We must start looking at the aggregate representation of each patient's tumor. Research is heading this way as demonstrated by the first comprehensive nomogram that takes into account multiple parameters including serum biomarkers (AFP, NLR and cholesterol), as well as tumor response to treatment and macromorphologic variables. This nomogram was shown to be an excellent predictor of tumor recurrence and mortality (C-statistic 0.79) [22]. Although not made up of entirely pretransplant variables it is no question a step in the right direction.

Since the introduction of the Milan Criteria, a rich body of evidence has emerged to support the notion that tumor biology can be predicted to a degree using variety of clinical parameters that maybe available to clinicians when evaluating potential liver transplant recipients. Although patients now must wait 6 months before being upgraded to 28 MELD exception points, tumor biology is not adequately elucidated during this time period. Patients remain stuck in an epoch that rewards small size and less tumors yet takes into account minimal tumor behavior. In an era of individualized medicine, we must embrace transformation as the literature is amassing. Comprehensive evaluation of each recipient and tumor should be mandated to push the transplant envelope while maintaining excellent oncologic outcomes. With more tools in our repertoire, we must make changes. We need to do better.

## References

1. Ferlay JSI, Ervik M, Dikshit R, Eser S, Mathers C, et al. (2012) F.GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet], Lyon.
2. Marsh JW, Geller DA, Finkelstein SD, Donaldson JB, Dvorchik I (2004) Role of liver transplantation for hepatobiliary malignant disorders. Lancet Oncol 5: 480-488.
3. Schwartz M, Roayaie S, Konstadoulakis M (2007) Strategies for the management of hepatocellular carcinoma. Nat Clin Pract Oncol 4: 424-432.
4. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, et al. (1996) Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 334: 693-699.
5. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, et al. (2001) Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 33: 1394-1403.
6. DuBay D, Sandroussi C, Sandhu L, Cleary S, Guba M, et al (2011) Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. Ann Surg 253: 166-172.
7. Margarit C, Charco R, Hidalgo E, Allende H, Castells L, et al. (2002) Liver transplantation for malignant diseases: selection and pattern of recurrence. World J Surg 26: 257-263.
8. Iwatsuki S, Dvorchik I, Marsh JW, Madariaga JR, Carr B, et al. (2000) Liver transplantation for hepatocellular carcinoma: a proposal of a prognostic scoring system. J Am Coll Surg 191: 389-394.
9. Llovet JM, Brú C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 19: 329-338.
10. Pawlik TM, Gleisner AL, Anders RA, Assumpcao L, Maley W, et al. (2007) Preoperative assessment of hepatocellular carcinoma tumor grade using needle biopsy: implications for transplant eligibility. Ann Surg 245: 435-442.
11. Young RS, Aldiwani M, Hakeem AR, Nair A, Guthrie A, et al. (2013) Pre-liver transplant biopsy in hepatocellular carcinoma: a potential criterion for exclusion from transplantation? HPB (Oxford) 15: 418-427.
12. Todo S, Furukawa H, Tada M (2007) Japanese Liver Transplantation Study G. Extending indication: role of living donor liver transplantation for hepatocellular carcinoma. Liver Transpl 13: S48-S54.
13. Fujiki M, Takada Y, Ogura Y, Oike F, Kaido T, et al. (2009) Significance of des-gamma-carboxy prothrombin in selection criteria for living donor liver transplantation for hepatocellular carcinoma. Am J Transplant 9: 2362-2371.
14. Grat M, Kornasiewicz O, Lewandowski Z, Holowko W, Grat K, et al. (2014) Combination of morphologic criteria and alpha-fetoprotein in selection of patients with hepatocellular carcinoma for liver transplantation minimizes the problem of posttransplant tumor recurrence. World J Surg 38: 2698-2707.
15. Toso C, Asthana S, Bigam DL, Shapiro AM, Kneteman NM (2009) Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. Hepatology 49: 832-838.
16. Toso C, Meeberg G, Hernandez-Alejandro R, Dufour JF, Marotta P, et al. (2015) Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. Hepatology 62: 158-165.
17. Chaiteerakij R, Zhang X, Addissie BD, Mohamed EA, Harmsen WS, et al. (2015) Combinations of biomarkers and Milan criteria for predicting hepatocellular carcinoma recurrence after liver transplantation. Liver Transpl 21: 599-606.
18. Halazun KJ, Hardy MA, Rana AA, Woodland DCT, Luyten EJ, et al. (2009) Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. Ann Surg 250: 141-151.
19. Agopian VG, Morshedi MM, McWilliams J, Harlander-Locke MP, Markovic D, et al. (2015) Complete pathologic response to pretransplant locoregional therapy for hepatocellular carcinoma defines cancer cure after liver transplantation: analysis of 501 consecutively treated patients. Ann Surg 262: 536-545.
20. Cucchetti A, Cescon M, Bigonzi E, Piscaglia F, Golfieri R, et al. (2011) Priority of candidates with hepatocellular carcinoma awaiting liver transplantation can be reduced after successful bridge therapy. Liver Transpl 17: 1344-1654.
21. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, et al. (2015) Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology 61: 1968-1977.
22. Agopian VG, Harlander-Locke M, Zarrinpar A, Kaldas FM, Farmer DG, et al. (2015) A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. J Am Coll Surg 220: 416-427.

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