

Resection or transplantation for hepatocellular carcinoma: is the decision clear for patients beyond Milan criteria?

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Hepatocellular carcinoma (HCC) is the second leading cause of cancer related mortality worldwide, and in western countries, its incidence is on the rise (1,2). The majority of these patients have underlying liver disease and cirrhosis from hepatitis B (HBV) and/or hepatitis C (HCV), alcoholism, and non-alcoholic steatohepatitis (NASH). The standard surgical therapies, which provide the greatest hope for a cure are resection and transplantation (3,4). Unfortunately, these therapies are not without their shortcomings. Intrinsic liver dysfunction is usually present, limiting the extent of resection, a shortage of available organs limits transplantation, and frequent late detection of disease limits both (5).

It has yet to be determined which therapy confers the best results. Several meta-analyses have shown resection is associated with superior 1-year survival than transplantation, but transplantation demonstrated a better late survival (6-8). A multi-institutional study from the HCC East-West study group showed suboptimal outcomes for overall survival (OS) and disease-free survival (DFS) for resection in patients beyond the Milan criteria (9). Applying the UCSF criteria, which includes patients that are beyond the Milan criteria, has demonstrated survival outcomes equivalent to that of the Milan criteria (10). However, resection has been shown to be equivalent to transplantation in patients beyond Milan criteria with preserved liver function (8).

The recent study published by Zaydfudin *et al.* is the

largest comparison of resection versus transplantation for HCC beyond Milan Criteria to date (11). In this retrospective, multi-institutional study that spanned 21 years, 608 patients with HCC without vascular invasion underwent either resection or transplantation. At the time of diagnosis, all patients met one of the following criteria: (I) a single tumor >5 cm; (II) 2 or 3 tumors with at least one tumor exceeding 3 cm; or (III) more than 3 tumors of any size. Any patient with major vascular invasion was excluded. Primary outcomes measured were DFS and OS.

Total 608 patients were included with 480 (79%) in the resection group compared to 128 (21%) in the transplantation group. DFS and 1-, 5-, and 10-year OS was significantly greater for the transplantation group ($P<0.001$ and $P<0.001$). Models controlling for age and tumor size showed transplantation was associated with greater OS, and models controlling for age, presence of multiple tumors, and tumor size showed transplantation was associated with greater DFS ($P<0.001$ and $P<0.001$).

A major difference between the two groups was the rate of pre-operative down-staging. Pre-operative down-staging therapy was utilized in 83.1% of transplantation patients compared to 5.4% of resection patients ($P<0.001$). This resulted in 53% of patients in the transplant group being down-staged to within the Milan criteria. One-year and 5-year OS was not significantly different between transplantation patients who were not pre-treated or did not downstage to within Milan criteria compared to all patients

undergoing resection ($P=0.509$); however, DFS was greater in the transplantation group ($P=0.017$). When comparing the patient who were down-staged and then proceeded to resection versus the patients who were down-staged and then proceeded to transplantation, there was a significant advantage in favor of transplantation for both DFS and OS (both $P\leq 0.012$).

What are the major conclusions that we can draw from this study by Zaydfudin *et al.*? First, it reaffirms that expanding beyond the Milan criteria can provide significant DFS and OS in select patients with HCC. Based on the results presented, a patient that presents beyond Milan Criteria that can be down-staged with pre-operative therapy to within the criteria will have significantly improved DFS and OS from transplantation versus resection. Additionally, the study argues for pre-operative treatment, as response appears to be the best indicator of tumor biology.

Despite the results of this study, questions still remain. Was the improved survival a function of transplantation or of tumor biology? If tumor biology is responsible then it will be crucial to identify the biologic differences within these tumors. Additionally, there are several patient demographic and clinical characteristic discrepancies between the resection and transplantation groups. Are these results a product of any of these differences?

Organ allocation is always a major concern when discussing expanding the indications for transplantation. According to the United Network for Organ Sharing (UNOS), in the United States there are currently 14,385 patients awaiting liver transplantation, and in 2016, only 7,841 liver transplantations were performed (12). This represents a major deficiency, and it is of the utmost importance to allocate the organs available to those who receive the maximum benefit or for those with no other option. Living donor liver transplantation (LDLT) has been utilized to try to bridge this gap; however, results from LDLT have been inferior to cadaveric orthotopic liver transplantation and put the donor at risk. Xenotransplantation has been described in the literature and represents a promising solution to organ shortage, but this option is not yet ready for practice (13,14).

In conclusion, there is still much work to be done to establish the best operation for patients with HCC that is beyond Milan criteria. The study performed by the Zaydfudin *et al.* has demonstrated a select group that will benefit from transplantation over resection. The authors should be congratulated on their work.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No.11 Lyon, France: International Agency for Research on Cancer; 2012 1.0. Available online: <http://globocon.iarc.fr>
2. Center MM, Jemal A. International trends in liver cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2011;20:2362-8.
3. Koniaris LG, McKillop IH, Schwartz SI, et al. Liver regeneration. *J Am Coll Surg* 2003;197:634-59.
4. McKillop IH, Moran DM, Jin X, et al. Molecular pathogenesis of hepatocellular carcinoma. *J Surg Res* 2006;136:125-35.
5. Milgrom DP, Maluccio MA, Koniaris LG. Management of Hepatocellular Carcinoma (HCC). *Curr Surg Rep* 2016;4:20.
6. Rahman A, Assifi MM, Pedroso FE, et al. Is resection equivalent to transplantation for early cirrhotic patients with hepatocellular carcinoma? A meta-analysis. *J Gastrointest Surg* 2012;16:1897-909.
7. Zheng Z, Liang W, Milgrom DP, et al. Liver transplantation versus liver resection in the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. *Transplantation* 2014;97:227-34.
8. Koniaris LG, Levi DM, Pedroso FE, et al. Is surgical resection superior to transplantation in the treatment of hepatocellular carcinoma? *Ann Surg* 2011;254:527-37; discussion 537-8.
9. Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg* 2013;257:929-37.
10. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh

- modified TNM criteria. *Liver Transpl* 2002;8:765-74.
11. Zaydfudim VM, Vachharajani N, Klintmalm GB, et al. Liver Resection and Transplantation for Patients With Hepatocellular Carcinoma Beyond Milan Criteria. *Ann Surg* 2016;264:650-8.
 12. UNOS. Transplant Trends [Internet]. Richmond, VA, USA: United Network for Organ Sharing; 2017. Available online: https://www.unos.org/data/transplant-trends/-transplants_by_organ_type+year+2016
 13. Butler JR, Paris LL, Blankenship RL, et al. Silencing Porcine CMAH and GGTA1 Genes Significantly Reduces Xenogeneic Consumption of Human Platelets by Porcine Livers. *Transplantation* 2016;100:571-6.
 14. Butler JR, Martens GR, Estrada JL, et al. Silencing porcine genes significantly reduces human-anti-pig cytotoxicity profiles: an alternative to direct complement regulation. *Transgenic Res* 2016;25:751-9.

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