Current Transplantation Reports (2018) 5:139–144
https://doi.org/10.1007/s40472-018-0191-z

OPTN POLICY (K ANDREONI, SECTION EDITOR)

Liver Transplantation for Hepatoma: Raising the Bar

Mark W. Johnson[1] · Ali Zarrinpar[1] · Elizabeth M. Thomas[1] · Kenneth A. Andreoni[1]

Published online: 29 March 2018

Abstract

Purpose of Review Ever since the birth of liver transplantation, cancer has played a major role in the advances to the field. With improved outcomes came increasing demands on a limited organ supply and the need for policy development to guide organ allocation. This is an attempt to summarize important milestones in the practice and policy developments over the past 50 years with a nod to our collective ability to continue to improve the field of transplantation, care of liver cancer, and value of that gift of life—the donor liver.

Recent Findings The most recent Organ Procurement and Transplantation Network (OPTN) Policy changes further improve liver allocation to cancer candidates with a focus on (1) current hepatocellular cancer (HCC) size and number, (2) downstaging criteria, and (3) AFP limits and will help to better achieve equitable allocation of livers to HCC and non-HCC candidates needing transplantation using objective real-time evidence to base our practice.

Summary We, as a community have and despite our individual needs and patterns, have shown how data collection, review, and discussion can lead to best practice at a grand scale. From its first days as a procedure to our current state of expertise, liver transplantation for HCC remains a classic example of evidence-based practice.

Keywords Liver transplantation · Liver cancer · Hepatoma · UNOS policy

Abbreviations

AASLD	American Association for the Study of Liver Disease
AFP	Alpha-fetoprotein
ALTSG	American Liver Tumor Study Group
AST	American Society of Transplantation
ASTP	American Society of Transplant Physicians
ASTS	American Society of Transplant Surgeons
HALT-C	Hepatitis C Antiviral Long-term Treatment against Cirrhosis
HCC	Hepatocellular cancer
HCV	Hepatitis C virus
HHS/DHHS	Department of Health and Human Services
HRSA	Health Resources and Services Administration
IOM	Institute of Medicine
LRT	Local-regional therapy
MELD	Model of End-Stage Liver Disease
MWA	Microwave ablation
OPTN	Organ Procurement and Transplantation Network
RFA	Radio Frequency Ablation
SRTR	Scientific Registry of Transplant Recipients
TACE	Transarterial chemoembolization
TARE	Transarterial radioembolization
TNM	Tumor, nodes, metastasis classification system
UNOS	United Network of Organ Sharing

Introduction

Ever since the birth of liver transplantation in 1963 under the leadership and vision of Dr. Thomas Starzl [1], cancer has played a major role in the advances to the field [2, 3]. In the 1980s, with the development of novel immunosuppressants and the recognition that long-term outcomes could be achieved in cirrhotics with incidental hepatomas [4], the gap between organ supply and demand began its never-ending widening. As the transplant community became more

This article is part of the Topical Collection on *OPTN Policy*

✉ Mark W. Johnson
Mark.Johnson@surgery.ufl.edu

[1] Division of Transplantation and Hepatobiliary, University of Florida College of Medicine, Gainesville, FL, USA

organized and national with HRSA, Organ Procurement and Transplantation Network (OPTN), United Network of Organ Sharing (UNOS), ASTS, and AST organizations working to develop best practice guidelines and improved organ allocation systems, the policy developments for liver transplantation and hepatocellular cancer (HCC) has become a classic example of longitudinal evidence-based practice. This is an attempt to summarize important milestones in the practice and policy developments over the past 50 years with a nod to our collective ability to continue to improve the field of transplantation, care of liver cancer, and value of that gift of life—the donor liver.

Through the 1980s and 1990s, transplant programs were growing across the world (ref of growth of centers), many within already large, established liver centers where multidisciplinary teams were developing single-center management algorithms for HCC care [5]. During this time period, two influential groups published their results on liver transplantation and HCC that formed the basis of our UNOS policies today. In 1996, the National Cancer Institute, Milan [6], and in 1999 the Barcelona group [7] published their individual center's results of resection versus transplantation for HCC patients and showed with excellent long-term outcomes utilizing an evidence-based algorithm [5, 6]. In 1997, ASTP/AALD had a consensus conference and published their recommendations for minimal listing criteria suggesting "… that the minimal listing criteria for patients with primary liver tumors should admit any patient with tumor confined to the liver, irrespective of size or number of tumors…" [8]. The OPTN/UNOS adopted criteria from these three landmark papers, to implement their first policy on listing for HCC patients, which basically involved using the American Liver Tumor Study Group (ALTSG) modification of the tumor node metastasis (TNM) staging system for HCC when being considered for liver transplantation (T2 lesions) (Table 1) [9].

Toward the end of the 1990s, the demand for liver organs began to surpass the supply to such an extent, that significant inequalities became apparent in the accessibility of transplantation for candidates with allocation being heavily weighted on wait times rather than severity of liver disease. Furthermore, time on the waiting list did not correlate with the risk of death while waiting (severity of disease) which added to the concerns regarding disparity in liver allocation [10]. Thus, in 1998, Health and Human Services (HHS) issued a mandate that deceased donor livers for transplantation be prioritized in a more equitable manner, emphasizing the concept of transplant the sickest first irrespective of waiting time [11]. This became part of "The Final Rule" [12] and outlined a philosophy of organ allocation (sickest first with less influence of geography or waiting time) that shaped the next 10 years in liver transplantation.

In response to DHHS and IOM Final Rule, the OPTN/UNOS adopted the Model of End-Stage Liver Disease (MELD) scoring system for allocating liver organs to candidates on the waitlist. This removed much of the subjectivity of the previous "status" system and all but eliminated the time-waiting influence. It based allocation of the liver organ objectively on the candidate's severity of illness as defined by their 3-month mortality risk [13–15]. In that allocation system was an exception priority given to candidates with HCC. This exception priority intended to balance the higher dropout rate while awaiting an organ for HCC candidates (waitlist mortality) while maintaining good long-term outcome post-transplantation. The exception points attributed to HCC candidates initially were 24 priority points for T1 lesions and 29 priority points for T2 lesions. This quickly led to recognition of the inequities of waitlist mortality, transplant rates, and outcomes between HCC and non-HCC candidates [16] resulting in several revisions of the HCC exception priority point system between 2002 and 2005 (Table 2) [17].

Although the intention of the exception points for HCC candidates was to accommodate the expected higher risk of dropout caused by the progression of the malignancy, it became clear that practice behaviors changed based upon the policies of the OPTN/UNOS on candidacy and allocation. Thus, in 2008–2009, a national consensus conference convened to develop recommendations on liver allocation for the HCC candidates [18]. This conference submitted several novel and apropos ideas regarding allocation to HCC candidates, including (1) standardization of pathology reporting and radiologic imaging, (2) the use of locoregional therapy (LRT) in HCC candidates, (3) downstaging criteria, and (4) an observational period. The concept of downstaging criteria for listing HCC candidates is logical in that as treatment options for HCC such as TACE, TARE, MWA, and RFA were developed and were refined, post-transplant outcomes for those patients downstaged and maintained within Milan criteria were acceptable and equivalent to candidates within Milan at initial listing [19, 20••]. The introduction of an observation period [21••] and incorporation of AFP limits [21••]

Table 1 American Liver Tumor Study Group—modified TNM Staging Criteria

Stage	T	Description
I	T1	Solitary lesion < 2.0 cm, N0, M0
II	T2	Solitary lesion 2.0–5.0 cm or up to 3 lesions, all < 3.0 cm, N0, M0
III	T3–4	Solitary lesion > 5.0 cm; multiple lesions with any > 3.0 cm, N0, M0
IV	Any T	N1 or any N with M1

Table 2 Timeline of OPTN changes to MELD exception points for patients with HCC

Year	MELD points
2002	29 points for T2 lesions 24 points for T1 lesions
2003	24 points for T2 lesions 20 points for T1 lesions
2004	24 points for T2 lesions Zero points for T1 lesions
2005	22 points for T2 lesions Zero points for T1 lesions
2015	Lab MELD at time of listing for T2 lesions 28 points after 6 months within Milan Additional priority points every 3 months to a maximum MELD of 34 points

appeared to select out those HCC candidates with aggressive tumors—more likely to have early metastatic disease after transplantation—and offered better utilization of a limited resource.

Between 2005 and 2015, two other influences worth mentioning in the maturation in the OPTN/UNOS HCC-transplantation policy were (1) ongoing shortages of livers and geographic disparities [22] and (2) an increasing incidence of HCC in the USA (Fig. 1) [23]. In an effort to improve equity among liver transplant candidates and address the geographic disparities in access, the OPTN implemented a series of changes to organ allocation policies. Thus borne the Regional Share 15 rule (2005), the Regional Share 35/National Share 15 policy (2013), a revised point system for HCC candidates with a mandatory 6-month waiting period, and a "cap" of 34 points allowed HCC candidates (Table 2). These last two changes in HCC policy came about in the belief that it would increase the number of transplants for non-HCC candidates, decrease the number of transplants for HCC candidates, decrease the geographic variability in the transplant rates for HCC, and ensure those candidates with high lab MELDS (share 35) would have access to transplantation due to their high waitlist mortality [24••].

In 2014, Zheng et al. published a meta-analysis of observational studies comparing outcomes of HCC patients undergoing either resection or transplantation. He showed that although 1-year survival was similar between the two modalities, 3- and 5-year survivals were better with transplantation over resection and with less recurrences [25••]. This bore out in practice as more patients with HCC were listed for transplantation as physicians and surgeons utilized the current policies to best provide long-term care for their patients. As our treatment modalities improved for HCC, more and more patients were being "bridged" to transplantation through the mandatory waiting period such that a greater percentage of candidates were waiting on the list than predicted.

Case in point: In 2015, HCC was the leading diagnosis among recipients of liver transplants [26]. In the 2011 HALT-C trial, Lok et al. reported the incidence of HCC in HCV patients with fibrosis or cirrhosis to be between 5 and 15% [27]. In the current SRTR database (May 16, 2017), 48% of the listed patients with a MELD 30–34 in the US are HCC exceptions (223 of 468) and 52% of the listed patients with a MELD 25–29 in the US are HCC exceptions (539 of 1029). Overall, 2482 listed patients of 14,448 total listed are HCC exceptions (17%).

Clearly, the criteria for allowing HCC priority points are weighted in favor of HCC candidates and need re-evaluation. Improved bridging and/or non-resection therapeutic modalities (TACE, TARE, ablative techniques) allowed for longer waitlist management without dropout of HCC tumors such that increasing trend of listing patients with low MELDs but with HCC exceptions so that a backlog of 30–34 MELD recipients is overwhelming donor supply and in disfavor to non-HCC candidates. Waiting time, it seems, has again become an influential factor in liver organ allocation.

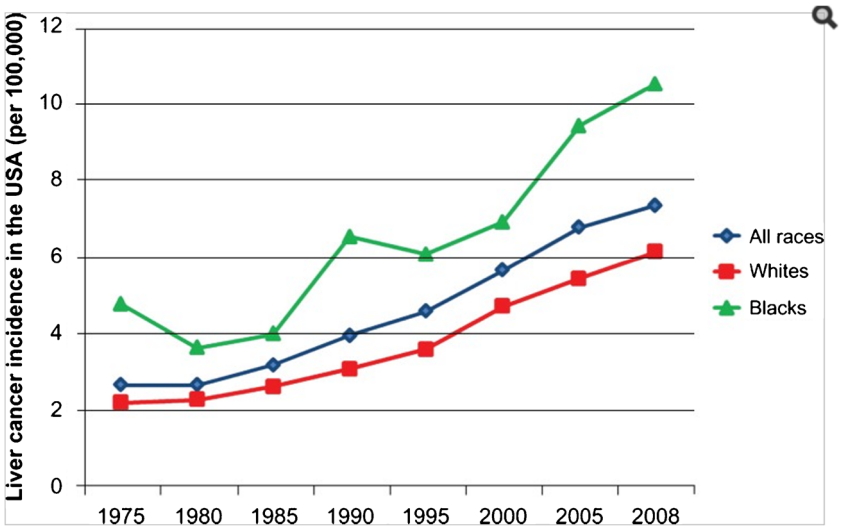

Fig. 1 Age-adjusted incidence rates of liver cancer (per 100,000) in the USA based on the Surveillance, Epidemiology, and End Result database from 1975 to 2008 [23]. This work is published and licensed by Dove Medical Press Limited. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed

This inequity in liver allocation again has led the transplant community, leadership, and the OPTN/UNOS to revisit the HCC priority exception policy. Current policy changes put forth through the committee, modeling algorithms, professional vetting, and public comment are as follows.

Single Small Lesion Criteria

Current policy provides *automatic priority* for candidates that meet T2 criteria, described as:

1. One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size
2. Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size

Changes proposed include:

1. Eliminating automatic MELD exception points for candidates that have had complete response to LRT
2. Candidates with single small lesions (2–3 cm) must be treated with LRT prior to eligibility for automatic MELD exception
3. Candidates will be eligible for HCC exception MELD if the lesions persist after LRT or new lesions develop (but must remain within HCC criteria)

Downstaging

Successful downstaging of an HCC lesion to T2 criteria is associated with a low rate of HCC recurrence and post-transplant outcomes similar to initial T2 HCC Milan Criteria [28].

Changes proposed include:

1. Candidates outside Milan criteria, who have undergone successful downstaging (to be within T2 criteria), will be allowed the same 6-month window before granting exception points as candidates with initial T2 presentation and listing.
2. Candidates that meet one of the following criteria are eligible for inclusion in a downstaging protocol:

(a) One lesion greater than 5 cm and less than or equal to 8 cm
(b) Two or three lesions each less than 5 cm and total diameter of all lesions less than or equal to 8 cm
(c) Four or five lesions each less than 3 cm and total diameter of all lesions less than or equal to 8 cm

3. Candidates who are eligible and then complete local-regional therapy must be successfully downstaged into T2 criteria to receive a MELD exception.

High Alpha-fetoprotein Threshold

There is growing evidence that factors other than just size and number of HCC lesions are associated with increased risk of recurrence and poor outcomes post-transplantation. AFP level is a recognized predictor of poor outcomes and increased recurrence of HCC [21]. The OPTN/UNOS liver subcommittee reviewed data looking at AFP levels and post-transplant outcomes and concluded that an AFP > 1000 ng/ml had a 245% increased risk of mortality post-transplant and should not receive automatic priority [29].

Changes proposed include:

1. Candidates with lesions meeting T2 criteria but with an AFP greater than 1000 are not eligible for a standardized MELD exception.

(a) If these lesions fall below 500 after local-regional therapy, the candidate is eligible for a standardized MELD exception.

2. Candidates with an AFP level greater than or equal to 500 at any time point following local-regional therapy will be referred to the review board.

A new proposal being considered that will dramatically effect current listing patterns and organ allocation is the elimination of automatic exception points allotted to extensions for HCC exception [30••]. Current policy does not require a candidate meet T2 criteria and this has led to higher percentage of candidates with MELD scores between 28 and 34 that have no evidence of HCC (or less than T2 lesions) and low MELD scores (< 15). Current proposed policy change would require programs to submit updated exception requests at the time of extension that show a candidate remains within initial HCC criteria (T2 or recurrence/persistence after LRT). Overall, it is estimated that these current HCC exception proposals will affect almost 1000 patients currently listed for HCC exception priorities and increase the equity in access to liver organs between HCC and non-HCC candidates.

These policies will also help us as a transplant community better serve our patient population—treating accurately and successfully those patients with HCC and stable liver disease—and re-distributing the limited organ supply to those recipients with severe liver disease who need transplantation most urgently.

We, as a community and despite our individual needs and patterns, have shown how data collection, review, and

discussion can lead to best practice at a grand scale. From its first days as a procedure to our current state of expertise, liver transplantation for HCC remains a classic example of evidence-based practice.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, et al. Orthotopic homotransplantation of the human liver. Ann Surg. 1968;168(3):392.
2. Starzl TE, Porter KA, Brettschneider L, Penn I, Bell P, Putnam CW, et al. Clinical and pathologic observations after orthotopic transplantation of the human liver. Surg Gynecol Obstet. 1969;128(2):327.
3. Starzl TE, Giles G, Lilly JR, Takagi H, Martineau G, Schroter G, et al. Indications for orthotopic liver transplantation: with particular reference to hepatomas, biliary atresia, cirrhosis, Wilson's disease and serum hepatitis. Transplant Proc. 1971;3(1):308–12.
4. Iwatsuki S, Gordon RD, Shaw BW, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg. 1985;202(4):401–7.
5. Wall WJ, Marotta PJ. Surgery and transplantation for hepatocellular cancer. Liver Transpl, 2000;6(6 Suppl 2):S16–22.
6. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–700.
7. Llovet JM, Brú C, Bruix, J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. In: Seminars in liver disease (Vol. 19, No. 03, pp. 329–338). © 1999 by Thieme Medical Publishers, Inc..; 1999. pp. 329–338. Semin Liver Dis. 1999;19(3):329–38
8. Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. Liver Transpl Surg. 1997;3(6):628–37.
9. 2017 UpToDate. https://www.uptodate.com/contents/image?imageKey=GAST%2F53242&topicKey=ONC%2F2490&rank=2~150&source=see_link&search=hcc%20transplantata
10. Freeman RB, Edwards EB. Liver transplant waiting time does not correlate with waiting list mortality: implications for liver allocation policy. Liver Transpl. 2000;6(5):543–52.
11. Organ Procurement and Transplantation Network–HRSA. Final rule with comment period. Fed Regist. 1998;63:16296.
12. Organ Procurement and Transplantation: assessing current policies and the potential impact of the DHHS Final Rule. Institute of Medicine; Committee on Organ Procurement and Transplantation Policy. 1999. https://doi.org/10.17226/9628. (https://www.gao.gov/special.pubs/organ/organ.htm) (BOOK = Organ Procurement and Transplantation Assessing Current Policies and the Potential Impact of the DHHS Final Rule Institute of Medicine (US) Committee on Organ Procurement and Transplantation Policy. Washington (DC): National Academies Press (US); 1999).
13. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003;124:91–6.
14. Freeman RB Jr, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002;8:851–8.
15. OPTN/UNOS Liver and Intestinal Organ Transplantation Committee Meeting. Modifications to the policy 3.6.4.4 (liver candidates with hepatocellular carcinoma [HCC]). (HRSA/OPTN. Policy 3.6 organ distribution: allocation of livers. http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp. Accessed 7 July 2012).
16. Sharma P, Balan V, Hernandez JL, Harper AM, Edwards EB, Rodriguez-Luna H, et al. Liver transplantation for hepatocellular carcinoma: the MELD impact. Transplantation. 2004;10(1):36–41.
17. Parikh ND, Singal AG. Model for end-stage liver disease exception points for treatment-responsive hepatocellular carcinoma. Clin Liver Dis. 2016;7:97–100. https://doi.org/10.1002/cld.545.
18. Pomfret EA, Washburn K, Wald C, Nalesnik MA, Douglas D, Russo M, et al. *Report of a national conference on liver allocation in patients with hepatocellular carcinoma in the United States*. Liver Transpl. 2010;16(3):262–78.
19. Ravaioli M, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, et al. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. Am J Transplant. 2008;8:2547–57.
20.•• Mehta N, Heimbach J, Harnois DM, Dodge JL, Burns JM, Lee D, et al. Short waiting time predicts early recurrence of hepatocellular carcinoma after liver transplantation: a multicenter study supporting the "Ablate and Wait" principle. Hepatology. 2014;60:446A. **This paper opened up transplant options for patients outside Milan by utilizing ablative therapies for downsizing HCC.**
21.•• Duvoux C, et al. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. Gastroenterology. 2012;143(4):986–994.e3. **This article was important in showing how selective dropout could further improve outcomes after transplantation for HCC patients and better utilize a limited resource.**
22. A shortage of livers and geographic disparities in access to liver transplantation continue in the United StatesYeh H, Smoot E, Schoenfeld DA, Markmann JF. Geographic inequity in access to livers for transplantation. Transplantation. 2011;91(4):479–86.
23. Dhanasekaran R, Limaye A, Cabrera R. Hepatocellular carcinoma: urrent trends in worldwide epidemiology, risk factors, diagnosis, and therapeutics. Hepatic Medicine : Evidence and Research. 2012;4:19–37.
24.•• Heimbach JK, Hirose R, Stock PG, Schladt DP, Xiong H, Liu J, et al. Delayed hepatocellular carcinoma model for end-stage liver disease exception score improves disparity in access to liver transplant in the United States. Hepatology. 2015;**61**:1643–50. **This paper showed how changes to policy narrowed disparities across the country and assured access to the higher MELD non-HCC candidates.**
25.•• Zheng Z, Liang W, Milgrom DP, Zheng Z, Schroder PM, Kong NS, et al. Liver transplantation versus liver resection in the treatment of hepatocellular carcinoma: a meta-analysis of observational studies. Transplantation. 2014;97(2):227–34. **A meta-analysis showing how liver transplantation offers better long-term outcomes than resection for all child's classifications.**
26. Yang JD, Larson JJ, Watt KD, Allen AM, Wiesner RH, Gores GJ, et al. Hepatocellular carcinoma is the most common indication for

liver transplantation and placement on the waitlist in the United States. Clin Gastroenterol Hepatol. 2017;15(5):767–75.

27. Lok AS, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, et al. Associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology. 2011;140(3):840.
28. Yao FY, Mehta N, Flemming J, Dodge J, Hameed B, Fix O, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. Hepatology (Baltimore, Md). 2015;*61*(6):1968–77. https://doi.org/10.1002/hep.27752.
29. Hameed, et al. Alpha-fetoprotein level > 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. Liver Transpl. 2014;20:945–51.
30.•• OPTN/UNOS Public comment Proposal. Changes to HCC Criteria for Auto Approval. *OPTN/UNOS Liver and Intestinal Organ Transplantation Committee*. 2016. https://optn.transplant.hrsa.gov/media/1922/liver_hcc_criteria_for_auto_approval_20160815.pdf. **Most recent OPTN/UNOS policy proposal and implementation that will help to better distribute a limited resource to those patients who need transplantation in timely fashion.**