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A National Survey of Hepatocellular Carcinoma Surveillance Practices Following Liver Transplantation

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Background. Recurrence of hepatocellular carcinoma (HCC) is an important predictor of survival after liver transplantation (LT). Recent studies show that early diagnosis, aggressive treatment, and surveillance may improve outcomes after HCC recurrence. We sought to determine the current practices and policies regarding surveillance for HCC recurrence after LT. **Methods.** We conducted a web-based national survey of adult liver transplant centers in the United States to capture center-specific details of HCC surveillance post-LT. Responses were analyzed to generate numerical and graphical summaries. **Results.** Of 101 eligible adult liver transplant centers, 48 (48%) centers across the United States responded to the survey. Among the participating centers, 79% stratified transplant recipients for HCC recurrence risk, while 19% did not have any risk stratification protocol. Explant microvascular invasion (mVI) was the most common factor used in risk stratification. Use of pretransplant serum biomarkers such as alpha-fetoprotein (AFP) was variable, with only 48% of the participating centers reporting specific "cutoff" values. While a majority of centers (88%) reported having a routine imaging protocol for HCC recurrence surveillance, there was considerable heterogeneity in terms of frequency and duration of such surveillance. Of the centers that did risk stratify patients to identify those at higher risk of HCC recurrence, about 50% did not change their surveillance protocol. **Conclusions.** Our study affirms significant variability in center practices, and our results reflect the need for high-quality studies to guide risk stratification and surveillance for HCC recurrence.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is an increasingly prevalent indication for liver transplantation (LT), accounting for at least 22% of transplant indications in the United States.[1] Recurrence of HCC has been reported in 6%–18% of recipients transplanted for this indication[2-5] and has been identified as an important predictor of survival.[6] Emerging data and expert consensus support post-LT surveillance for HCC recurrence, as early diagnosis and timely intervention may offer access to curative therapies and improve long-term survival.[3,5-8] Risk factors for HCC recurrence have been clearly identified, and a variety of prediction tools to guide post-LT management are available.[2] Despite this growing body of literature, the use of these predictors have not been widely adopted in post-LT management.[2,9,10] Furthermore, optimal surveillance protocols to detect HCC recurrence early have not been established.[11] We hypothesized that this knowledge gap has led to significant variability in program-level surveillance of post-LT HCC recurrence. Hence, we conducted a national survey to define the spectrum of existing practices for detecting HCC recurrence after LT among the United States liver transplant centers, focusing on surveillance protocols, use of risk stratification methods, and immunosuppression practices.

MATERIALS AND METHODS

Survey Instrument Design

We created an electronic survey (Supplementary Material) on the web-based survey platform, www.surveymonkey.com (SurveyMonkey Inc., San Mateo, CA). The survey included logic-based questions and options for objective as well as descriptive responses. The survey collected data regarding the participating transplant center, including donation service areas (DSA), transplant volume, and data pertaining to HCC surveillance protocols. Data were also collected to capture the following main domains: (1) use of risk stratification methods for patients at risk of HCC recurrence after LT; (2) use of serum biomarkers such as alpha-fetoprotein (AFP), "cutoff" values, and optimal timing of measurement; (3) use of HCC surveillance protocols across centers, including the use of "risk-stratified" protocols; and (4) impact of HCC recurrence risk on immunosuppressant regimen decision. The final survey included 16 questions with branch logic questioning. For this reason, the number of responses for branch logic questions was expected to vary. The survey was reviewed and acknowledged to be exempt by the Indiana University Institutional Review Board. The research was conducted in accordance with 45 CFR 46.101(b) and Indiana University Human Research Protection Program policy.

Survey Population and Administration

A national list of 185 adult liver transplant program directors (medical and surgical) was obtained from American Society of Transplantation databases. From this list, a direct email with the web-based survey link was sent to the medical and surgical directors of adult liver transplant programs (Figure S1, SDC, http://links.lww.com/TP/C35). Weekly automated reminders were then sent to centers who did not respond during the initial 8 weeks. We further solicited response through personalized email invitations to nonresponding centers. The survey was open for a total of 7 months (September 2018–April 2019). No incentives or honorarium were provided for completion of the survey. Identification of respective centers was voluntary, but geographic transplant region and a valid contact email from the participants were mandatory for possible future clarification of descriptive responses.

Statistical Analysis

The responses to the survey questions were analyzed to generate numerical and graphical summaries. For categorical variables, frequencies and percentages were used. For descriptive surveillance protocols, descriptive tables were generated from complete protocols to highlight surveillance imaging frequency variation every year post transplant. For any duplicate responses from a single transplant center (n = 3), responses were matched and clarified with the center to include only 1 complete response per center for our final assessment.

RESULTS

Participant Characteristics

Of 101 eligible adult liver transplant centers, there were 48 (48%) unique responses that were included in the analysis. The participating centers were of varied size (Figure S1, SDC, http://links.lww.com/TP/C35) and represented all the Organ Procurement and Transplantation Network (OPTN) designated transplant regions (Figure S2, SDC, http://links.lww. com/TP/C35). The participants included transplant hepatologists (n = 23, 48%), medical directors (n = 14, 29%), surgical directors (n = 5, 10%), and other transplant professionals (n = 6, 12%). The average total adult LTs performed at participating centers was 82 ± 37 cases per year (range, 22–170).

Risk Stratification

The majority of participating centers (38/48, 79%) had a risk stratification strategy to identify patients at higher risk of HCC recurrence. Most centers stratified patients for recurrence into "high risk" versus "low risk" categories (29/35, 83%), while some centers had "high," "intermediate," and "low" risk categories (6/35, 17%) (Table 1).

Variables used to determine the recurrence risk category included pretransplant imaging and biomarker data as well as explant pathology. The presence of microvascular invasion (mVI) (36/37, 97%), differentiation grade of tumor (19/37, 51%), and the discrepancy between pretransplant radiologic tumor size or number and explant pathology (28/37, 76%) were the most common features used for stratification. Three centers (3/37, 8%) reported additional pretransplant and explant risk factors, including tumor growth within 6–9 months before LT and prior downstaging of tumors that were beyond Milan criteria, mixed histology tumors (with features of intrahepatic cholangiocarcinoma) (Figure 1).

Serum AFP measured before LT (11/27, 41%) or at the time of LT (6/27, 22%) was the most commonly used biomarker to determine HCC recurrence risk, although 9 centers did not use serum AFP at all. Thirteen centers (13/27, 48%) reported using specific cutoff values for serum AFP (between 100 and 500 ng/mL), 14 centers did not use a specific cutoff value, and 1 center used serum AFP trend with dynamic slope (Table 1).

Only 4 centers (4/38, 11%) reported the use of validated risk stratification models such as the "RETREAT" score[12,13] (n = 3) and "Metroticket" model[14,15] (n = 1).

Surveillance Protocols

Forty-six centers noted having a surveillance protocol (96%, 46/48), of which 4 centers (8.7%) noted only using a protocol for those deemed high-risk for recurrence. While the majority of centers (32/43, 74%) included chest and abdominal cross-sectional imaging within their surveillance protocol, 9 centers (9/43, 21%) obtained only abdominal cross-sectional imaging, and only 2 (2/43, 3%) centers included the use of a bone scan (Figure 2A). In addition to imaging, AFP was incorporated in the protocol by 65% of respondents (26/40).

Complete detailed protocols, including frequency and duration of surveillance, were available from 27 centers. There was considerable variation in the duration of surveillance. While the majority of centers (13/27, 48%) reported a total duration of 5 years, there were centers (5/27, 18%) that discontinued surveillance after initial 2 years (range 2–5 y) (Figure 2B; Table S1, SDC, http://links.lww.com/TP/C35). The variation in frequency of imaging was noted for every year after transplant in routine protocols (Figure 2C; Table S1, SDC, http://links.lww. com/TP/C35). The most common frequency was imaging every 3–4 months in the first year, followed by every 6 months in the second year, and every 6–12 months at 3 years or beyond.

Of 38 centers that stratified HCC recurrence risk, 21 centers (55%) had a more intense "high risk" surveillance protocol for patients deemed at higher risk for HCC recurrence. Similar to routine surveillance protocols, there was a wide variation in frequency of abdominal imaging in such high-risk protocols

TABLE 1.
Questionnaire responses

Questionnaire responses			
Question	Response	N	%
1. For patients transplanted due to HCC or found to have HCC on explant (incidental), does your center have a risk stratification method for recurrence post-LT (n = 48)	Yes	38	79
	No	9	19
	Skipped	1	3
2. If yes, then please list the risk categories patients are assigned to (n = 35)	High vs low risk	29	83
	High vs intermediate vs low	6	17
3. If "Risk stratification Models" are used, please list the ones used at your program (n = 38)	Yes	4	11
	No	12	32
4. If AFP levels used, then describe "cut off" values used to define different risk categories (please include the timing of these values in relation to the time of transplant, eg, Pre, At, or Post LT)			
4A. Timing of AFP (n = 27)	Pre-LT	11	41
	At LT	6	22
	Not used or applicable	9	33
	Trend/slope	1	4
4B. AFP "cutoff" values (n = 27)	Yes	13	48
	No	11	41
	"Model" based	2	7
	Trend	1	4
5. Do you have any standard surveillance protocol in practice for HCC patients post LT (n = 48)	Yes	42	87.5
	None or unless "high risk"	4	8
	Skipped	2	4
6. Do you have any different (more intense) surveillance protocol for HCC in patients stratified as high risk for recurrence (n = 48)	Yes	21	44
	No	24	50
	Maybe	3	6
7. In patients transplanted for HCC, is an effort made to use mTOR as part of the immunosuppression regimen when possible (n = 46)	Yes	18	39
	Always	1	2
	Only those deemed higher risk	17	37
	No	10	22

AFP, alpha-fetoprotein; HCC, Hepatocellular carcinoma; LT, liver transplantation; mTOR, mammalian target of rapamycin.

(Figure 2D; Table S1, SDC, http://links.lww.com/TP/C35). Most common frequency reported ranged from imaging every 3–6 months for the majority of the initial 5 years after transplant. Total surveillance duration was not specified in 43% (9/21 centers) of the protocols; however, discontinuation of surveillance after 2 years was lower (14%) compared with standard surveillance (22%). Overall, most of these protocols included more frequent abdominal and chest imaging studies as compared to standard surveillance protocols. Forty-two (87%) LT centers used a routine surveillance protocol for their patients who had nonhigh risk HCC or were found to have incidental HCC on explant, while 4 centers (8%) did not do surveillance unless HCC recurrence risk was deemed to be high.
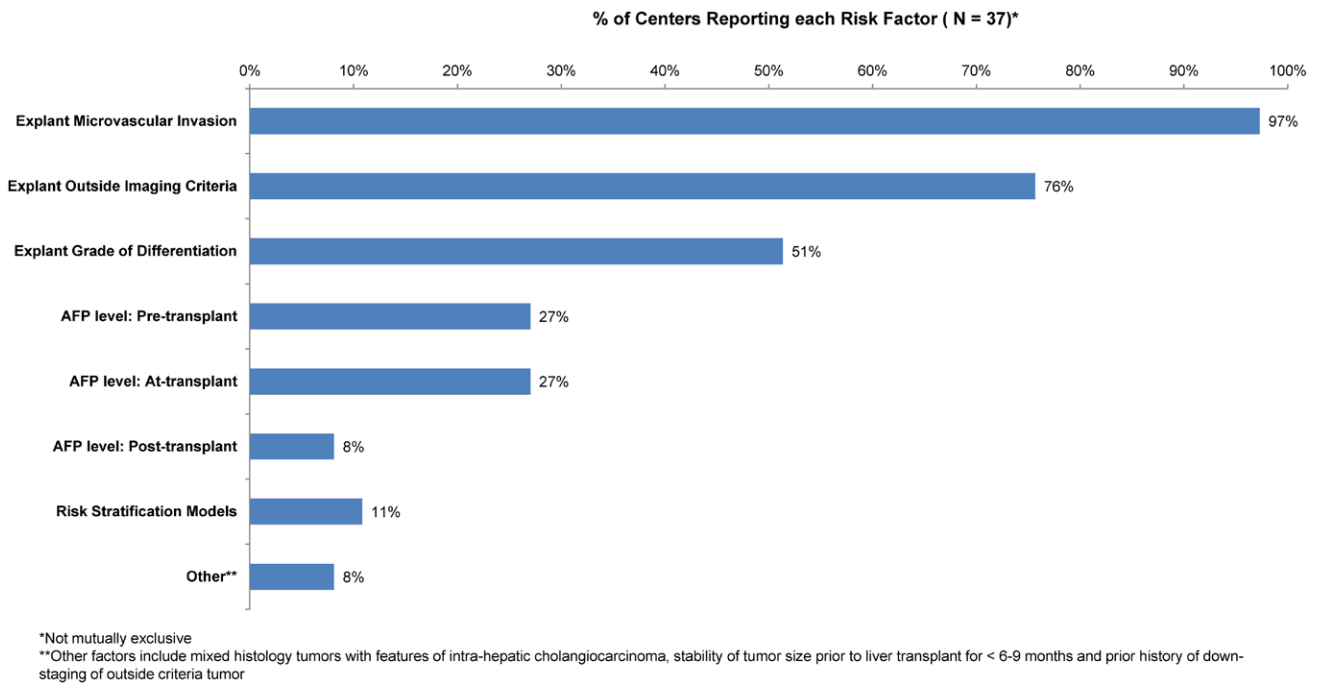
Immunosuppression Therapy

For the majority of centers (78%), HCC recurrence risk influenced post-LT immunosuppression therapy choice. The most common (19/46, 41%) approach was the preferential use of mammalian target of rapamycin (mTOR) inhibitors in all HCC patients when able, while 17 centers (17/46, 37%) reported use in only those deemed at higher risk for recurrence and 10 centers (10/46, 28%) reported no influence of HCC recurrence risk on immunosuppression regimen decision (Table 1).

DISCUSSION

HCC has become a leading indication of LT;[1] however, tumor recurrence can occur in up to 16% of patients and negatively impacts survival after LT.[9] Early detection of tumor recurrence may identify patients who are amenable to treatments with curative intent and may improve long-term survival.[3,5-8] With this growing body of literature, it is important to understand the current state of HCC recurrence surveillance practices in the United States with the goal of identifying opportunities to improve healthcare delivery for HCC-related transplant recipients. Herein, we report the results of the first national survey on center-specific practices for post-LT HCC risk stratification and surveillance. Cumulatively, our findings show that there is significant variability in surveillance practices and protocols amongst LT centers from all UNOS regions in the United States. Based on our findings, we have identified several areas of practice advancement and key research initiatives the LT community needs to embrace to improve outcomes for the growing population of LT recipients with HCC.

Center-level variability in HCC surveillance may be key source of inequality in post-LT outcomes. Quality improvement projects at the regional and national level need to emphasize the use of evidence-based risk prediction, which is typically based on characteristics such as mVI, histological differentiation grade, radiographic understaging with explant tumor burden being beyond the Milan criteria, serum biomarker (ie, AFP) level, and response to locoregional therapies.[2] Following these data, 79% of centers in our study reported using risk stratification clinically to identify patients at higher risk of HCC recurrence and most commonly

% of Centers Reporting each Risk Factor (N = 37)*

*Not mutually exclusive
**Other factors include mixed histology tumors with features of intra-hepatic cholangiocarcinoma, stability of tumor size prior to liver transplant for < 6-9 months and prior history of down-staging of outside criteria tumor

FIGURE 1. Frequency of risk factors used for stratification reported by US liver transplant centers. AFP, alpha-fetoprotein.
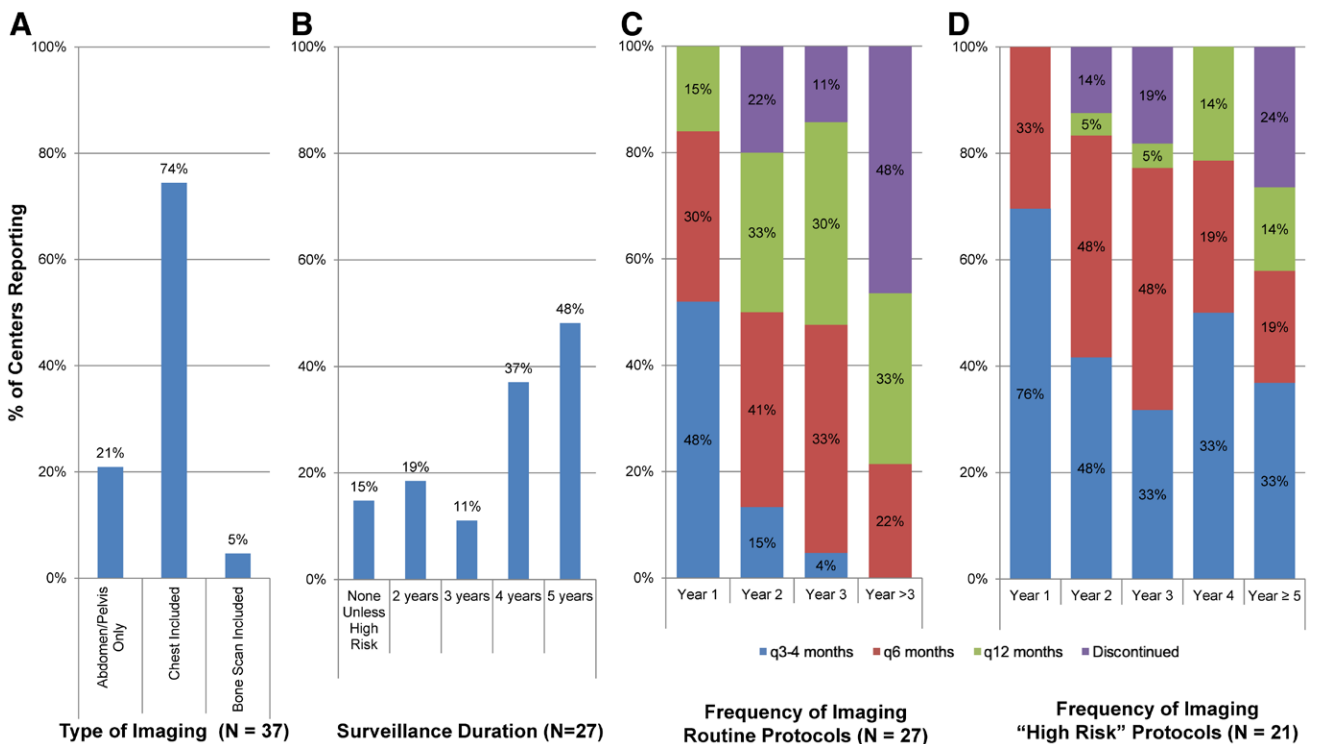
FIGURE 2. Features of surveillance protocols at US liver transplant centers by (A) imaging location; (B) duration of surveillance; (C) imaging frequency in routine protocols; and (D) imaging frequency in "high risk" protocols.

identified using explant mVI as a risk factor for HCC recurrence, followed by radiographic understaging and histological grade of the tumor. More recently, prognostic and predictive models have also been developed to either risk stratify individuals before LT (for better selection) or after LT (for recurrence prediction). These models include the RETREAT score,[12,13,16] MetroTicket model,[14,15] MORAL score,[17] and

HALTHCC,[18] among others. Interestingly, only 11% of centers reported using 1 of these more comprehensive models for risk stratification. As current data show these models have an excellent ability to predict recurrence,[11] centers should move to protocolized HCC risk-stratification incorporating the use of a validated prediction model. It is possible the low rate of model-based risk prediction is due to the lack of studies

documenting the efficacy and safety of post-LT surveillance based upon these risk models.[11] Future studies are needed to discern if risk models have the ability to stratify LT recipients by recurrence risk as well as those who may be at such low risk as to not need surveillance.

Serum AFP is the most commonly used serum biomarker to represent the tumor's biological nature and determine prognosis,[19-21] and UNOS implemented a requirement for the serum AFP level to decrease to <500 ng/mL in patients with a baseline serum AFP >1000 ng/mL before MELD exception points could be granted.[22] Despite these data, our study shows that the use of serum AFP to determine the risk of recurrence as reported by participating centers in the real world had different "cutoff" values with only 48% of centers using a specific cutoff value and only 30% of centers using a cutoff value of <500 ng/mL before LT. Newer studies have proposed using an AFP trend or "dynamic" slope rather than a "cutoff" value.[23] Other biomarkers like AFP-L3%,[24] des-gamma-carboxyprothrombin,[25] and neutrophil-lymphocyte ratio[26] were not included in the survey as these markers still lack universal availability and validation. Overall, our results show the majority of centers consider AFP to identify individuals at risk for recurrence; however, considerable variability exists among centers. To close the gap with currently available evidence, efforts are needed now to harmonize how centers use AFP in HCC recurrence risk prediction, possibly through the use of a risk prediction model, as discussed above. In addition, further studies are needed to measure the impact of center variability on post-LT outcomes at the individual, regional level, and national levels to guide equitable healthcare delivery for this high-risk population.

Another focus of our survey was to identify the imaging-based surveillance practices among the US transplant centers. Recurrence patterns are now well-recognized, with about two-thirds of recurrences occurring 12 months after transplant. Hepatic recurrences are noted in around 35%–45% of cases, with lungs and bones being the most common sites for extrahepatic recurrence.[3,8,16] Late recurrence within 2–5 years does occur, while recurrence beyond 5 years is infrequent.[27,28] In line with these data, most participating centers (87%) reported having a protocol in place, which included abdominal ± chest imaging. While 74% of centers included chest imaging, a bone scan was reported only by 5%. Therefore, our study shows that most centers follow protocols that are not incorporating the current knowledge of post-LT HCC recurrence patterns. It is possible more recurrences may be identified earlier if bony imaging is included in surveillance protocols, but such an approach to surveillance needs to be further studied as it is not yet recommended by any consensus guidelines.[2,11]

In addition, future studies are needed to elucidate the length and frequency of screening. In our survey respondents, the total surveillance duration varied from 2 years to 5 years, with nearly half of centers continuing imaging studies until 5 years after LT. Frequency of imaging tended to be quarterly in the first year after transplant to biannual to annual imaging from year 2 and beyond. Collectively, our results show there were significant differences among the LT centers, which may be due to the absence of any established or validated surveillance strategy.[11] In 2017, Mehta et al did propose a posttransplant HCC surveillance regimen stratified by the recipient's RETREAT score, where

low-risk patients do not need surveillance, while moderate and high-risk patients require 3- to 6-month surveillance for 2–5 years, depending on the risk level.[12] However, this approach has not been prospectively validated. While awaiting confirmation, the International Liver Transplant Society Oncology working group conditionally recommended that abdominal and chest CT imaging be performed every 6 months for 3 years after LT combined by serial AFP measurement, albeit citing a low level of evidence.[2] The majority of our survey respondents are applying a more frequent and a longer duration of surveillance imaging in these recipients. Therefore, future studies are needed to assess if a specific surveillance strategy can indeed be cost-effective while improving outcomes for individuals who experience HCC recurrence. These key data would allow clinicians to better balance the risk of radiation exposure and the cost of screening with the benefit of early tumor detection through a scheduled surveillance program.

Management of patients who are deemed at higher risk for recurrence also showed significant variation. Surveillance strategy based on individual recurrence risk may be a more cost-effective approach. Risk stratification models could be considered for such a risk-based strategy; however, the current models have been validated only to predict HCC recurrence and have not been studied prospectively to inform surveillance strategies.[12-15,17,18] Additionally, the impact of risk-based strategies on overall post-LT survival are currently are still being studied. Given this lack of data, about 50% of centers did not have a "high-risk" or more intense surveillance protocol for individuals they identified as having a high risk of recurrence. In centers reporting a "high-risk" protocol, higher risk patients were generally imaged more frequently and for a longer duration after LT.

Mammalian target of rapamycin (mTOR) inhibitors class of immune-suppressive agents has shown to have antiproliferative properties against HCC.[29] A randomized, prospective, multicenter trial (SILVER study) showed a 50% lower risk of tumor recurrence at 1-year post-LT and a higher recurrence-free survival in the first 4 years for those treated with sirolimus as compared to those treated with other immunosuppression; however, the seemed benefit was subsequently lost upon long-term follow-up.[4,30] Despite these results, our results indicate a widely held belief in the potential benefit of mTOR inhibitors as with 78% of centers preferentially using mTOR inhibitors as a part of immunosuppressive regimen in HCC patients. The optimal immunosuppressive strategy has yet to be identified, and it remains to be seen if there exists a selected subset of high risk HCC patients who would benefit from second generation of mTOR inhibitors. This uncertainty and theoretical benefit may be guiding transplant providers to continue to preferentially use mTOR inhibitors.

There are several limitations to this study. We were only able to achieve a response rate of approximately 50% despite multipronged efforts to solicit responses. It is possible that our results are affected by nonresponse bias. Nonresponse may have occurred due to centers not wishing to share management protocols thus skewing our results to show more variation than what truly exists. Conversely, it is also possible centers that do not have specific management practices chose not to respond leading to an underestimation of the current variability in post-LT HCC surveillance practices. The validity

of our results is supported by the diverse nature of participating centers with regard to transplant volume and geographic location. Finally, our conclusions assume respondents provided an accurate representation of center practices. Despite these limitations of sample size, our study identifies an important gap in our current practice of post-LT HCC surveillance.

Taken together, our study represents the most comprehensive assessment of center practices regarding HCC recurrence risk assessment and surveillance to date. We show the wide variation in current practices and reflects the lack of data to guide appropriate surveillance methods beyond the consensus of expert opinions.[2,9,10] Implementation of appropriate surveillance programs may result in earlier detection and possible curative therapy that can lead to improved survival. In addition, harmonizing surveillance protocols between centers and with currently existing evidence will be key to ensuring equitable and high-quality post-LT management to all HCC-related LT recipients. To this end, we recommend that clinicians managing the post-LT care of HCC patients use 1 of multiple prognostic tools to objectively assess HCC risk recurrence after OLT such as RETREAT, US HCC Consortium model, post-moral, the model of Decaens et al, etc.[2,11] While it remains to be determined if a patient's individualized risk of recurrence should dictate the nature of the surveillance program, we recommend that individuals undergoing LT for HCC should be followed for HCC recurrence via a surveillance protocol, which includes chest and abdominal imaging combined with AFP monitoring every 6 months for at least the first 3 years.[2,11] There is not yet clear data guiding immunosuppression management for these patients; however, it is reasonable to consider strategies that allow minimization of calcineurin inhibitor use.[2,11]

In conclusion, in an era with expanding options for HCC treatment, this study highlights the critical need for prospective studies aimed at developing well-defined surveillance protocols for the identification of early recurrence in at-risk individuals. With a rising number of HCC related liver transplants, the need for these evidence-based guidelines is even more urgent.

ACKNOWLEDGMENTS

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