Multicenter Study of Staging and Therapeutic Predictors of Hepatocellular Carcinoma Recurrence Following Transplantation

Theodore H. Welling,[1] Kevin Eddinger,[2] Kristen Carrier,[3] Danting Zhu,[4] Tyler Kleaveland,[5] Derek E. Moore,[6] Douglas E. Schaubel,[4] and Peter L. Abt[2]

[1]Perlmutter Cancer Center and Department of Surgery, NYU Langone Health, New York, NY; [2]Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA; [3]Schools of Pharmacy, University of Michigan, Ann Arbor, MI; [4]School of Public Health, University of Michigan, Ann Arbor, MI; [5]School of Medicine, University of Michigan, Ann Arbor, MI; and [6]St. Thomas Health, Nashville, TN

Orthotopic liver transplantation (OLT) and resection are effective treatments for hepatocellular carcinoma (HCC). However, optimizing OLT and limiting HCC recurrence remains a vexing problem. New HCC Model for End-Stage Liver Disease and allocation algorithms provide greater observation of HCC patients, many while receiving local-regional treatments. Potential benefits of local-regional treatment for limiting HCC recurrence after OLT remain incompletely understood. Therefore, we aimed to define HCC-specific prognostic factors affecting recurrence in a contemporary, multicenter cohort of HCC patients undergoing OLT and specifically whether local-regional therapies limited recurrence. We identified 441 patients undergoing OLT for HCC at 3 major transplant centers from 2008 to 2013. Cox regression was used to analyze covariate-adjusted recurrence and mortality rates after OLT. "Bridging" or "downstaging" therapy was used in 238 (54%) patients with transarterial chemoembolization (TACE) being used in 170 (71%) of treated patients. The survival rate after OLT was 88% and 78% at 1 and 3 years, respectively, with HCC recurrence (28% of deaths) significantly increasing the mortality rate (hazard ratio [HR], 19.87; $P < 0.001$). Tumor size, not tumor number, either at presentation or on explant independently predicted HCC recurrence (HR, 1.36 and 1.73, respectively; $P < 0.05$) with a threshold effect noted at 4.0-cm size. Local-regional therapy (TACE) reduced HCC recurrence by 64% when adjusting for presenting tumor size (HR, 0.36; $P < 0.05$). Explant tumor size and microvascular invasion predicted mortality (HR, 1.19 and 1.51, respectively; $P < 0.05$) and pathologic response to therapy (TACE or radiofrequency ablation) significantly decreased explant tumor size (0.56-1.62 cm diameter reduction; $P < 0.05$). In conclusion, HCC tumor size at presentation or explant is the most important predictor for HCC recurrence after OLT. Local-regional therapy to achieve a pathologic response (decreasing tumor size) can limit HCC recurrences after OLT.

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Hepatocellular carcinoma (HCC) continues to be a significant cause of mortality among all other solid malignancies and is noted to have the fastest rising incidence and mortality in the United States among other cancers.[1] HCC is most commonly associated with chronic liver disease or cirrhosis, with hepatitis C virus (HCV) and increasingly nonalcoholic steatohepatitis (NASH) being common underlying etiologies.[2–4] Therefore, orthotopic liver transplantation (OLT) has been used as a means to effectively treat HCC and underlying liver disease. However, mortality related to HCC recurrence following OLT has continued to remain significant. New HCC allocation policies have recently been implemented to allow for observation time and implementation of local-regional therapies for HCC.[5] Outcomes supporting the rationale for this policy have shown that a greater duration of time following HCC presentation to OLT is protective against mortality following OLT for HCC patients.[6–8]

Although these policies that are predicated on wait time may improve overall survival for HCC patients

Abbreviations: AFP, alpha-fetoprotein; AIH, autoimmune hepatitis; EtOH, ethanol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; OLT, orthotopic liver transplantation; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RFA, radiofrequency ablation; RT, radiation therapy; TACE, transarterial chemoembolization; UNOS, United Network for Organ Sharing; Y90, Yttrium-90.

undergoing OLT, it is still unclear which HCC-related factors are most likely to influence HCC-specific outcomes such as HCC recurrence. Specifically, the influence of factors related to initial HCC presentation, final pathology, and benefits of local-regional therapy such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) are incompletely defined. Prior studies are either conflicting, lack specific evaluation of these important variables, or are underpowered to fully evaluate their impact on HCC recurrence following OLT.[9–12] Commonly used databases (eg, United Network for Organ Sharing [UNOS]; Scientific Registry of Transplant Recipients) do not provide detailed data with respect to imaging (before and after therapy), explant pathology with respect to response, or specific follow-up with respect to HCC disease recurrence.[13–15] Other studies represent those of single centers, and although informative, they may not be translatable to other centers or lack untreated controls to specifically evaluate the role of local-regional treatments.[16]

Both RFA and TACE are known to provide a survival benefit in appropriately selected HCC patients on the basis of HCC tumor stage.[17–20] Furthermore, recent technical advances in how TACE is implemented (superselective/selective versus lobar) appear to have improved HCC tumor responses in more contemporary studies.[21] However, the specific effects of these therapies in patients who ultimately undergo OLT for HCC on HCC recurrence remain controversial.

We therefore aimed to better understand and inform future liver allocation policy decisions and treatment strategies for HCC patients who are potential OLT candidates. Thus, we sought to more completely identify the effects of disease presentation, treatments, and response to treatments on HCC recurrence following OLT. A multicenter retrospective cohort of HCC patients who underwent OLT at 3 major transplant centers was examined. We identified HCC disease-related factors at initial presentation of HCC and whether success of local-regional therapies predicted HCC recurrence following OLT in this multicenter cohort.

Address reprint requests to Theodore H. Welling, M.D., Perlmutter Cancer Center and Department of Surgery, NYU Langone Health, Alexandria Center for Life Science West, 430 East 29th, 660B, New York, NY 10016. Telephone: (646) 754-2672, ext. 42672; FAX: (646) 501-4564; E-mail: theodore.welling@nyumc.org

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Patients and Methods

PATIENT DATA EXTRACTION

The study was conducted after institutional review board approval at all study sites. No donor organs were obtained from executed prisoners or other institutionalized persons. Consecutive patients from 2008 to 2013 undergoing OLT from 3 major contemporary transplant centers (University of Pennsylvania, University of Michigan, and Vanderbilt University) were identified with a diagnosis of HCC confirmed on explant pathology. HCC and liver disease characteristics were determined at the time of initial diagnosis of HCC (not formal evaluation of OLT) and at the time of OLT. Patients were required to have at least 2 years of follow-up following OLT. Other diagnoses discovered on explant pathology (eg, cholangiocarcinoma or mixed HCC-cholangiocarcinoma) were not included in the cohort. Patients who underwent local-regional treatment were excluded from the cohort if there was incomplete treatment details, such as those treated at outside centers before presentation. Patients were not included if their follow-up was at a center different from that at which they received the OLT. Patients were listed for OLT at the 3 centers if they met Milan criteria.

The following patient data were recorded: age, sex, liver disease etiology, laboratory Model for End-Stage Liver Disease (MELD) score, MELD exception status at OLT, listing date, and date of OLT. HCC presenting tumor burden or stage was determined by examining computed tomography or magnetic resonance imaging reports and using modified Response Evaluation Criteria in Solid Tumors criteria for diagnosis of HCC according to the American Association for the Study of Liver Diseases guidelines. Subsequent radiographic reports were similarly characterized either following local-regional therapies or at the time

closest to OLT, depending on time elapsed between initial evaluation or treatment and OLT. Serum alpha-fetoprotein (AFP) was also serially determined at presentation and at time of OLT. Explant tumor pathology regarding stage was determined by a review of the pathology reports and recording of maximal tumor size, tumor number, and presence or absence of microvascular invasion. Only viable tumor tissue on explant was used to characterize tumor number and size on final pathology and thus pathologic stage. For example, tumors that were completely necrotic (100% necrotic) were equated to a pathologic complete response for which the viable tumor diameter would be 0 cm. Maximal radiographic and explant pathologic response was recorded if local-regional therapy was used. Responses were characterized as either no response, partial response, or complete response.

Characteristics regarding presence or absence of local-regional therapies were also recorded, as were type of therapy used (eg, TACE, RFA, radiation), individual characteristics of TACE (such as selective versus nonselective and type of agent used). Decisions regarding the use of local-regional therapies were made at the discretion of individual centers and incorporated down-staging or bridging intent as recommended by guidelines using Barcelona Clinic Liver Cancer criteria.[18]

STATISTICAL ANALYSIS

For descriptive analysis of the study cohort, numeric variables were summarized by the sample mean, whereas percentages were used for categorical covariates. Cox regression was used to analyze covariate-adjusted recurrence rates. Death was treated as a competing risk, in the sense that the hazard rate for recurrence applied to patients actually at risk for recurrence (ie, alive with no previous recurrence), known as the cause-specific hazard in the competing risks literature.[22]

Five different HCC recurrence rate models were fitted. These were designed to specifically isolate whether particular covariates might influence HCC recurrence. All 5 models adjusted for age, sex, etiology, AFP at OLT, laboratory MELD at OLT, difference between HCC exception MELD score and laboratory MELD score, and time between initial HCC presentation and OLT. The individual models were characterized by which of the remaining additional covariates were included, and these depended on the particular goal or hypothesis each model was designed to test for with the focus on an effect of a particular covariate on HCC recurrence. Specifically, model 1 focused on initial presentation of tumor characteristics (tumor number, size of largest tumor) based on radiography. Model 2 instead focused on the same tumor characteristics, but it was based on information available on explant pathology; the model also included an indicator for microvascular invasion (1 = yes; 0 = no) and calendar year of diagnosis. Model 3 evaluated initial tumor characteristics (size, number) and also the rate of change of such characteristics, as well as calendar year. Model 4 sought to describe the effect of calendar year as a means of describing recurrence trends over time. Because of the lack of adjustment for tumor characteristics or treatment type, the calendar year of diagnosis effect estimated through model 4 is expected to represent the aggregate effects of potential changing trends in HCC diagnosis and treatment over time. Finally, model 5 contained covariates for initial tumor size and number, as well as local-regional treatment category (RFA, TACE, RFA and TACE, or no treatment).

Additional, separate proportional hazards models (models 1-3, Table 3) were also fitted to the outcome of death. Note that death was not considered censored for patients who experienced recurrence. Death was censored as a separate outcome following OLT because patient deaths were due to either HCC recurrence or other non-HCC related causes. Similar to HCC recurrence as an outcome, a set of mortality outcome models was fitted with the same covariates for models 1-3 in Table 3. Separate models for calendar year of diagnosis or treatments with mortality as the outcome were not created for mortality analysis.

We then fitted an additional separate Cox model for death, which included a time-dependent binary (0,1) covariate for HCC recurrence. At OLT, all patients had the recurrence covariate set to 0; for patients who experienced recurrence, the covariate switched to 1 at the time of recurrence and remained at 1 thereafter. The purpose of this model was to quantify the covariate-adjusted effect of HCC recurrence on subsequent mortality.

Additionally, we designed linear regression models (models 1 and 2, Table 4) to specifically analyze the effect of covariates to determine the final tumor size on explant pathology. Covariates were those noted at the time of OLT or initial presentation (model 1). Model 2 includes the same covariates but also types of local-regional treatments (versus no treatment) to the linear regression analysis.

Results

BASELINE CLINICAL CHARACTERISTICS

A total of 441 transplant patients were identified with a diagnosis of HCC during the interval of 2008-2013 that met the defined inclusion and exclusion criteria. Their baseline clinical characteristics are presented in Table 1. As expected, the majority of patients were male by nearly a 4:1 ratio and HCV was the most common underlying liver disease etiology (69.0%) with NASH/cryptogenic and alcohol making up the next most common etiologies, 10.4% and 8.8%, respectively. The median follow-up for the entire cohort was 47.3 months following transplant. Median AFP at initial presentation was 15.5 ng/mL. Patients who initially presented outside of Milan criteria were 11.4% of the entire cohort. The median number of tumors at presentation was 1.0, and the median size at presentation was 2.0 cm. "Bridging" or "downstaging" local-regional TACE or RFA therapy for HCC was used in 238 (54%) of HCC patients and TACE was the most common local-regional therapy used, being used in 170 (71%) of the patients treated. RFA was the next most common modality, used for 51 (21%) of treated patients, and combined TACE and RFA was used for 17 (7%) of treated patients. Other treatments were used rarely in this cohort and included radiation therapy (RT) (2 patients), Yttrium-90 (Y90) (1 patient), resection (1 patient), and ethanol (EtOH) ablation (2 patients). Fifteen patients not treated with local-regional therapy had incidentally discovered HCC on explant of which 11 (73.3%) were within Milan criteria. The mean time following initial HCC presentation to OLT was 11.4 months. The survival rate following OLT was 88% and 78% at 1 and 3 years after OLT, respectively (Fig. 1). There was an overall 30% mortality rate for the cohort due to all causes (133 patients) of which HCC recurrence accounted for 37 of these deaths. Thus, HCC recurrence was the cause for mortality in 28% of patient deaths after transplant.

TABLE 1. Descriptive Statistics on Study Cohort

Characteristic	Value (n = 441)
Age, years	56 (44, 68)
Sex, female	20.9%
AFP initial presentation, ng/mL	15.5 (2, 569)
AFP at OLT, ng/mL	19 (2, 437)
Laboratory MELD at OLT	13 (7, 27)
MELD difference (HCC exception – laboratory)	9.4 (0, 20)
Initial presentation	
Tumor size, cm	2.5 (1, 4.9)
Tumor number	1 (0.8)
Explant pathology	
Tumor size, cm	2.0 (0, 5)
Tumor number	1 (1.7)
Time from initial presentation to OLT, months	6.5 (1.4, 39.1)
Etiology	
Cryptogenic	5.0%
EtOH	8.8%
HBV	7.7%
HCV	69.0%
NASH	5.4%
PSC/PBC/AIH	2.3%
Other	1.3%
Local-regional treatment, n (%)	238 (54)
TACE	170 (71)
RFA	51 (21)
TACE and RFA	17 (7)
Death	30.0%
HCC recurrence	7.9%

NOTE: Data are given as median (5th and 95th percentile) or n (%), unless otherwise noted.

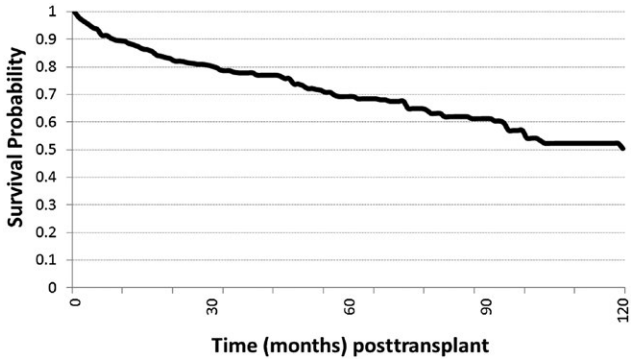

FIG. 1. Survival rate (event = death) by time (in months) following OLT for HCC.

PREDICTORS OF HCC RECURRENCE FOLLOWING TRANSPLANT

Results of the Cox regression models for HCC recurrence rate are in Table 2. Initial modeling (Table 2, model 1) showed that baseline etiology of liver disease, age, and sex had no apparent effect on HCC recurrence following OLT. Incidentally discovered HCC patients (n = 15) had an HCC recurrence rate of 13.3% (n = 2 patients). The difference between laboratory MELD score and MELD HCC exception score at OLT was a significant predictor of HCC recurrence, such that

there was a 7% decrease in recurrence risk for every laboratory MELD unit decrease in score. Maximum initial tumor size also predicted recurrence, with a calculated 36% increase in the HCC recurrence risk for every 1.0-cm increase in tumor size at presentation. The number of HCC tumors at presentation did not significantly predict recurrence. When explant pathology characteristics were substituted into the model for initial tumor presentation (Table 2, model 2), maximum tumor size had an even greater effect on the recurrence risk, with a 73% increase for every 1.0-cm increase in tumor size. The number of tumors found on explant pathology likewise had no association with recurrence. Microvascular invasion identified on explant pathology had a significant, 4.54-fold increased risk for HCC recurrence rate following OLT, similar to previous studies. When maximum tumor sizes were taken into account both at initial presentation and at the time of OLT (Table 2, model 3), evidence of progression (increasing tumor size) had the most profound effect such that there was a >6-fold increase in HCC recurrence risk for every 1.0 cm of maximum tumor size progression.

To further delineate the effect of explant pathology maximum tumor size on overall HCC recurrence rate, we grouped explant maximal tumor sizes into quintiles in order to nonparametrically assess the effect of tumor size on HCC recurrence rate (Fig. 2). Indeed, the effect of maximum tumor size appeared to be nonlinear with an apparent threshold effect at a 4.0-cm tumor size to predict recurrence following OLT. Note that, on the basis of radiographic images at initial presentation, the functional relationship between maximum tumor size and HCC recurrence rate was less clear and demonstrated no threshold effect (data not shown).

The year of HCC diagnosis at initial presentation appeared to affect overall HCC recurrence rate following OLT (Table 2, model 4) when initial presenting tumor characteristics and explant findings were removed from the model. Therefore, HCC recurrence rate decreased by 19% for every yearly increment in calendar year of diagnosis. Thus, improving aggregate trends in HCC diagnosis and treatment were observed over time for this cohort because this model was not adjusted for tumor characteristics and local-regional treatments.

Factors that predicted a lower HCC recurrence rate, other than smaller tumor size on initial presentation or on final pathology and independent of wait time showed that local-regional treatment for HCC had a lower predicted HCC recurrence rate (Table 2, Model 5). Specifically, the use of TACE reduced HCC recurrence by 64% when adjusting for initial tumor size at presentation. Thus, when controlled for initial tumor size, the rate of HCC recurrences per 100 patient years was reduced from 2.26 recurrences down to 1.72 recurrences with local-regional treatment. Use of RFA did not appear to predict a lower recurrence rate except when accounting for radiographic response such that complete absence of a radiographic response predicted as much as a 15-fold increase in recurrence risk. Notably, for patients receiving RFA, 11.5% had tumors over 3.5 cm and 17% had tumors over 3.0 cm in size. Combined use of RFA and TACE did not reach statistical significance toward reducing HCC recurrence risk following OLT. Other treatment modalities, such as radiation therapy or Y90, were used in too small of a sample size to permit analysis.

FACTORS ASSOCIATED WITH MORTALITY IN HCC PATIENTS FOLLOWING OLT

Because mortality following OLT can occur due to non-HCC-related complications of OLT, we sought to identify whether any of the HCC-related patient factors were predictive of overall mortality. This is important from the perspective that HCC recurrence accounted for the cause of death in 28% of all patient deaths after OLT. In this multivariate analysis, with death as the endpoint, patient factors such as sex and etiology were not predictive for mortality (Table 3). However, more advanced age incrementally increased mortality by 16%-20% for every 5-year increment (Table 3, models 1-3). With respect to HCC-related factors, tumor number at initial presentation or on pathology, not tumor size at initial presentation, predicted mortality with a 26%-28% increase in death rate per tumor (Table 3, models 1 and 3). However, on the basis of information available at explant pathology (Table 3, model 2), the number of tumors was no longer associated with mortality, whereas maximum tumor size did exhibit a significant association (19% increase in mortality rate per cm). Microvascular invasion was associated with a 51% increase in mortality rate, a result which approached but did not attain statistical significance (P = 0.07). Elevated AFP, particularly >1000 ng/mL, predicted a higher mortality rate following OLT consistent with prior reports showing an effect on HCC recurrence and survival (Table 3,

TABLE 2. Cox Regression Analysis for HCC Recurrence Rate Following OLT

Characteristic	Model 1	Model 2	Model 3	Model 4	Model 5
Age (per 5 years)	0.97	1.01	1.00	0.97	0.98
AFP at OLT (per 1000 ng/mL)	1.00	1.00	1.00	1.00	1.00
AFP: rate of increase	—	0.99	0.99	0.99	—
Sex, female	1.34	2.12	1.80	1.24	1.33
MELD at OLT	0.98	1.01	0.98	1.00	0.97
MELD difference (exception – laboratory)	0.93*	1.01	0.95	0.95	0.95
Initial presentation					
Tumor size	1.36*	—	1.53*	—	1.45*
Tumor number	0.99	—	1.06	—	1.08
Explant pathology					
Tumor size	—	1.73*	—	—	—
Tumor number	—	1.08	—	—	—
Progression (tumor size increase)	—	—	6.32*	—	—
Progression (tumor number increase)	—	—	1.11	—	—
Time from initial presentation to OLT	1.01	1.00	1.00	1.00	1.01
Treatment (versus no treatment)					
RFA	—	—	—	—	0.85
TACE	—	—	—	—	0.36*
RFA and TACE	—	—	—	—	0.87
Calendar year of diagnosis (per year)	—	0.80*	0.87	0.81*	—
Microvascular invasion	—	4.54*	—	—	—

NOTE: Values presented for each model are HRs.
*Significant at $P < 0.05$.

model 1).[23,24] Likewise, when AFP increased between initial presentation and time of OLT (Table 3, model 2), this had a more profound association with mortality with over a 3-fold effect. The model with HCC recurrence as a time-dependent predictor estimated that HCC recurrence increases mortality almost 20-fold (hazard ratio [HR], 19.87; $P < 0.001$).

PREDICTORS OF HCC EXPLANT PATHOLOGY

Because HCC explant pathology, particularly final tumor size, had the most profound effect on HCC recurrence rate and is the most potentially modifiable HCC-related factor, we sought to isolate which factors might overall influence this effect using explant pathology as the endpoint. In Table 4, 2 linear regression models were designed to evaluate factors affecting size of the largest tumor (cm diameter) at explant. Both models evaluate characteristics at the time of OLT. However, model 2 also includes HCC treatment categories. On the basis of model 1, the significant predictors of tumor size at explant are initial presenting tumor size (positive sign = increasing tumor size) and calendar year of diagnosis (negative sign = decreasing tumor size). Model 2, which included treatments, showed increased initial tumor size still significantly increases explant size, whereas explant size still decreased significantly with increasing calendar year of diagnosis. In addition, model 2 reveals that, relative to no HCC treatment, RFA treatment, TACE treatment, or combined RFA and TACE treatment was significantly associated with decreased maximal tumor size at explant. The effect of receiving both RFA and TACE was greater than the sum of RFA-alone and TACE-alone, indicating a potential synergistic effect on decreasing tumor size at explant.

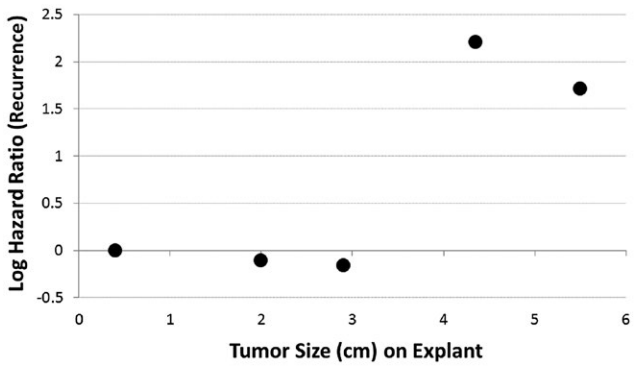

FIG. 2. Relationship between maximum tumor size on explant pathology and log HR for HCC recurrence. Results were obtained through a Cox regression model (containing all adjustment covariates) and 5 categories for tumor size (cm). Each log HR is plotted against its respective tumor size.

TABLE 3. Cox Regression Analysis for Mortality Rate Following OLT

Characteristic	Model 1	Model 2	Model 3
Age (per 5 years)	1.16*	1.16*	1.19*
AFP at OLT (per 1000 ng/mL)	1.12*	1.00	1.11
AFP: rate of increase	—	3.42†	1.19
Sex, female	1.45	1.59*	1.51†
MELD at OLT	1.03†	1.03	1.02
Difference in MELD (exception – laboratory)	0.97	0.99†	0.96†
Tumor size: initial presentation	1.07	—	1.06
Tumor number: initial presentation	1.26*	—	1.28*
Tumor size: explant pathology	—	1.19*	—
Tumor number: explant pathology	—	1.09	1.28*
Progression (tumor size increase)	1.47	—	1.47
Progression (tumor number increase)	1.41*	—	1.41*
Time from initial presentation to OLT	1.01	1.01	1.01
Treatment (versus no treatment)			
RFA	—	—	—
TACE	—	—	—
RFA and TACE	—	—	—
Calendar year of diagnosis (per year)	—	1.01	1.05
Microvascular invasion	—	1.51†	—

NOTE: Values presented for each model are HRs.
*Significant at $P < 0.05$.
†Near significant at $0.05 < P < 0.10$.

Responses to treatment were classified as either none, partial, or complete. For the 238 patients treated with either RFA or TACE, 50% had a pathologic response at least as favorable as the radiographic response. The proportion was slightly higher for patients treated with TACE (at 52%) compared with those receiving RFA (44%).

Discussion

Recent studies have led to a change in HCC OLT allocation policy such that an observation period is beneficial before OLT once a radiographic diagnosis of HCC is established.[5–8] This presumably offers time for the following:

1. The individual HCC biology to declare itself.
2. The radiographic stage to be secured.
3. Perhaps allow local-regional therapies to identify patients who may or may not benefit from OLT.
4. Control HCC tumor burden while other workup and listing proceeds for OLT.

Indeed, local-regional therapies such as RFA and TACE are well established to create a pathologic and radiographic response in many patients, translating into a survival benefit when properly deployed.[17,18,20] However, the benefit of local-regional therapy during this observation period toward limiting HCC recurrences and thus HCC-related mortality is not completely defined, particularly in the context of other known prognostic predictors for HCC recurrence.

The present study identified that HCC tumor stage, particularly tumor size was 1 of the most important predictors for both HCC recurrence and mortality. HCC recurrence was overall the most significant predictor for mortality for all patients undergoing OLT for HCC. We have shown, similar to prior studies, that microvascular invasion was 1 of the most significant predictors of HCC recurrence, independent of tumor size.[24] AFP elevation, either at the time of transplant or the rate of AFP increase, had no independent effect on HCC recurrence when tumor size was included in the multivariate models. Later calendar year of diagnosis had an independent effect of lowering the risk of HCC recurrence. This is likely related to either improved diagnostics over time or the increasing use of local-regional therapies over time in this multicenter cohort. Indeed, inclusion of TACE treatment to the models showed a reduction of HCC recurrence when compared with no local-regional treatment and also when initial presenting tumor size was included in the model. This effect of TACE was independent of time from initial presentation to the time of OLT (total wait time; Table 2, model 5). Indeed, time from presentation of HCC to the time of OLT was not independently predictive in the models for HCC recurrence (Table 2), whereas treatment, initial tumor size, tumor progression, and pathologic characteristics were independently predictive, suggesting that factors other than "wait time" were important for predicting HCC recurrence, particularly tumor stage and treatment.

Use of local-regional therapies increased over time, likely initially affected by lower transplant waiting times in the included eras for participating centers during the early part of this cohort. Thus, the total proportion of patients receiving local-regional treatment was less than a recent UNOS database study.[25] However, the present study had a much longer median follow-up of 47.3 months and takes into account initial HCC presentation stage and subsequent management. Prior studies, such as the UNOS study, assess the stage from the time of transplant listing filing which is often dependent on many other medical and social factors. The inclusion of a nontreated HCC group also serves as an additional control allowing the current study to isolate potential separate effects of local-regional treatment on HCC-related outcomes.

TABLE 4. Linear Regression Analysis for Predictors of Tumor Size at OLT Explant Pathology

Characteristic	Model 1	Model 2
Age (per 5 years)	0.005	0.006
AFP at OLT (per 1000 ng/mL)	0.019	0.075
Sex, female	–0.16	–0.13
MELD at OLT	0.026†	0.014
Difference in MELD (exception – laboratory)	–0.024	–0.024†
Tumor size: initial presentation	0.27*	0.31*
Time from initial presentation to OLT	–0.004	–0.000
Treatment (versus none)		
RFA	—	–0.56*
TACE	—	–0.63*
RFA and TACE	—	–1.62*
Calendar year of diagnosis (per year)	–0.13*	–0.084*

NOTE: Values presented for each model represent estimated increase (>0) or decrease (<0) in maximum tumor size (cm) per unit increase in the covariate as indicated, covariate-adjusted.
*Significant at $P < 0.05$.
†Near significant at $0.05 < P < 0.10$.

Concordant to previous studies, high AFP levels (>1000 ng/mL), along with rate of AFP increase, were independently associated with a higher mortality rate.[23,24,26] As to the reason why lower AFP levels do not independently correlate, this is likely due to the concept that AFP (in AFP producing HCCs) corresponds to HCC tumor burdens[23] and not necessarily to a more aggressive HCC. This has been demonstrated in the resection literature with respect to tumor stage, not AFP, to independently predict worse prognoses.[27] A similar relationship of microvascular invasion to tumor size has also been noted,[23] but presence of microvascular invasion in the current study and others was a strong independent risk factor. Indeed, there was a threshold effect (Fig. 2) for tumor size diameter of 4.0 cm to increase the risk of HCC recurrence. Thus, tumor size, either radiographically or on final pathology, appears to be the best measurable and perhaps most modifiable factor toward limiting HCC recurrences with respect to the role of local-regional therapies. This suggests that the greatest benefits for local-regional therapy may be derived when tumors ≥4.0 cm are treated such that at least a partial response may be generated to reduce tumors to <4.0 cm in size.

TACE showed a benefit with respect to limiting HCC recurrence on the Cox modeling analysis. RFA did not independently predict a decrease in HCC recurrence except in cases where there was a complete absence of a response in which these patients carried a 15-fold increase in recurrence risk. The lack of significance for RFA to independently decrease HCC recurrence is unclear because RFA has a known, potentially curative, therapeutic benefit when properly applied to tumors <3.5 cm in size.[19,20] Because this study is retrospective, possibilities may include the following:

1. RFA may have been applied to tumors at the borderline of this threshold in that 11.5% of RFA patients had tumors >3.5 cm and 17% had tumors >3.0 cm, or
2. The number of patients receiving RFA alone may have been underpowered to detect a statistical difference.

Indeed, we did note 12 patients who had RFA alone and had a complete pathologic response and no HCC recurrences with 4 patients dying due to non-HCC-related causes (data not shown). However, the number was small and failed to be statistically significant when accounting for other factors.

Tumor size on explant was the most significant, objectively measured, tumor-related factor predicting mortality. Microvascular invasion approached, but did not quite achieve, statistical significance when adjusting for other factors and when tumor size at explant was maintained in the model. This could be due to the known correlation between increasing tumor burden (size) and vascular invasion.[23,27] Given the importance of explant pathology tumor size to predict both HCC recurrence and overall mortality, we used this endpoint to assess the pathologic response of the local-regional therapies. In this analysis, RFA, TACE, or combination (TACE and RFA) versus no treatment had a benefit to reducing tumor burden. This was independent of both calendar year of diagnosis and initial tumor size, suggesting an important effect of local-regional therapy alone. In at least 50% of patients where a pathologic response was noted, the radiographic response was at least as favorable, suggesting that the radiographic response may serve as a useful correlate in future studies when trying to evaluate the success of local-regional therapies and ultimately aiding in determining OLT liver allocation algorithms. However, these correlations would need to be validated in a prospectively designed study. These findings in our present study are in concordance with a recent single-center study evaluating the importance of pathologic response (versus lack of a response) to predict less HCC recurrence.[16] However, the previously referenced study did not contain an untreated group to serve as a control, whereas our present study had the advantage of containing an untreated group for comparison.

The present study is retrospective and does not allow for independent, prospective review of radiographic response; indeed in some patients, it was not able to be performed in time before patients underwent OLT shortly following local-regional therapy. Likewise, independent, prospective pathology review was not possible given the retrospective nature and thus assessments of presence or absence of microvascular invasion could be discordant.[28] Tumor size, either on pathology or on radiographic evaluation, is accepted to be a relatively objective measurement in oncologic studies. Additionally, treatment bias may be present given the retrospective nature of this study cohort. However, the current study does represent contemporary practice among 3 high-volume liver transplant centers, and detailed data regarding tumor characteristics—particularly size, HCC recurrence, and HCC-specific factors—were able to be reliably obtained with adequate follow-up. Although the findings are compelling regarding the possible benefits of local-regional therapies to limit HCC recurrence and mortality following OLT, prospective studies using consistent treatment algorithms and therapeutic endpoints to validate these findings are warranted. Additionally, future prospective studies with perhaps centralized radiographic review would allow study of whether radiographic response could predict overall pathologic response and thus potentially improve stratification of patients for OLT and liver allocation. Thus, clear radiographic predictors of pathologic response in prospective studies may allow for allocation of livers to patients with active, viable tumor burdens, whereas patients who exhibit a complete radiographic response may not require additional treatments.

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