Lee *et al. Hepatoma Res* 2022;8:20
DOI: 10.20517/2394-5079.2021.139

Hepatoma Research

Original Article

Open Access

Liver cancer understaging in liver transplantation in the current era of radiologic imaging and newer generation locoregional therapies

Hannah M. Lee[1,9], Donna McClish[2,5], Binu V. John[3], Sarah Winks[4], Ryan Clayton[4], Somaya Albhaisi[5], Allawy Allawy[1], Samarth Patel[1,6], Emma C. Fields[7], Scott Matherly[1,9], Brian Strife[8], Chandra Bhati[9], Amit Sharma[9], Richard K. Sterling[1,9]

[1]Division of Gastroenterology, Hepatology, and Nutrition, Department of Medicine, Virginia Commonwealth University, Richmond, VA 23298, USA.
[2]Department of Biostatistics, Virginia Commonwealth University, Richmond, VA 23298, USA.
[3]Division of Digestive Health and Liver Disease, University of Miami, and Division of Gastroenterology and Hepatology, Miami VA Health System, Miami, FL 33125, USA.
[4]Department of Radiology, Virginia Commonwealth University, Richmond, VA 23298, USA.
[5]Department of Internal Medicine, Virginia Commonwealth University, Richmond, VA 23298, USA.
[6]Central Virginia Veterans Health Care System, Richmond, VA 23249, USA.
[7]Department of Radiation Oncology, Virginia Commonwealth University, Richmond, VA 23298, USA.
[8]Division of Interventional Radiology, Department of Radiology, Virginia Commonwealth University, Richmond, VA 23298, USA.
[9]Hume- Lee Transplant Center, Virginia Commonwealth University, Richmond, VA 23298, USA.

Correspondence to: Hannah M. Lee, Virginia Commonwealth University, 1200 E. Broad St., 14th Floor, P.O. Box 980341, Richmond, VA 23298, USA. E-mail: hannah.lee@vcuhealth.org

How to cite this article: Lee HM, McClish D, John BV, Winks S, Clayton R, Albhaisi S, Allawy A, Patel S, Fields EC, Matherly S, Strife B, Bhati C, Sharma A, Sterling RK. Liver cancer understaging in liver transplantation in the current era of radiologic imaging and newer generation locoregional therapies. *Hepatoma Res* 2022;8:20. https://dx.doi.org/10.20517/2394-5079.2021.139

Received: 23 Oct 2021 **First Decision**: 8 Feb 2022 **Revised**: 19 Feb 2022 **Accepted**: 13 Apr 2022 **Published:** 24 Apr 2022

Academic Editors: Roberto Ivan Troisi; James Fung; Allan Tsung **Copy Editor:** Jia-Xin Zhang **Production Editor:** Jia-Xin Zhang

Abstract

Background: Discordance in hepatocellular carcinoma (HCC) staging between pre-transplant imaging and explant pathology is associated with an increased risk of recurrence and death. Our aim was to evaluate variables that predicted concordance/discordance in the era of new generation locoregional therapies (LRT) and improved radiologic technology in diagnosis.

Methods: A single-center retrospective study was performed on patients who received a liver transplant for HCC between 2008-2019. Pre- and post-LT variables, including type of LRT, downstaging (DS), transplant time period, and radiologic response to LRT, were analyzed for concordance/discordance. Kaplan-Meier analysis was used to assess post-LT survival.

Results: Of 146 patients transplanted within Milan Criteria (MC), discordance rates (understaged) were 45%. Discordance was associated with ≥ 3 HCC lesions at diagnosis but not newer generation LRT (transarterial radioembolization/ stereotactic body radiation therapy), traditional LRT or combination. No differences in discordance were seen between transplant periods (2008-2013 *vs.* 2014-2019), but those within MC in the earlier period had higher concordance rates. A trend was observed between DS and discordance.

Conclusion: HCC stage discordance remains common and poorly predictable. Discordance was associated with three or more HCC lesions at the time of diagnosis. Patients within MC transplanted between 2008-2013 was associated with concordance, while a trend was noted between DS and discordance. No other pre- or post- LT variables predicted discordance/ concordance. Discordance was associated with decreased survival.

Keywords: Hepatocellular carcinoma, understaging, liver transplant, radioembolization, stereotactic body radiation therapy (SBRT)

INTRODUCTION

Hepatocellular carcinoma (HCC) is considered curable by liver transplantation (LT) with the optimal outcome when within Milan criteria (MC), defined by one tumor ≤ 5 cm or up to 3 tumors, each ≤ 3 cm without macrovascular spread or metastatic disease[1,2]. HCC within MC has an overall 4-year survival rate of 75%, with a recurrence rate of 8%[1]. To qualify for the Model for End-Stage Liver Disease (MELD) exception points, the United Network for Organ Sharing (UNOS) requires imaging demonstrating T2 HCC[2].

Traditional local regional therapies (LRT), such as transarterial chemoembolization (TACE) and thermal ablation, have been used to treat HCC as a bridge to transplant. However, novel treatment modalities have been added to the LRT armamentarium including transarterial radioembolization (TARE) and stereotactic body radiation therapy (SBRT). These modalities are being used for downstaging (DS) and as a bridge to transplant. Advancements in magnetic resonance imaging (MRI) technology with innovative techniques may have improved sensitivity/ specificity in HCC diagnosis and monitoring of treatment response. Standardization in the classification for HCC reporting on imaging was also developed to decrease variability in interpretation.

Discordance in HCC staging between pre-LT imaging and explant pathology has been reported at 20-30% and is associated with an increased risk of HCC recurrence and death[1,3-5]. Given limited resources in donor allocation, the ability to accurately predict discordance is critical in transplant candidacy selection for HCC. With the advancement in LRT and radiologic technology over the past decade, it is unclear if these factors have reduced the rate of discordance in HCC staging. To address this gap in knowledge, we analyzed patients transplanted for HCC between 2008-2019 and sought to further evaluate pre- and post-LT factors that may predict concordance or discordance.

METHODS

A single-center retrospective chart review was performed for all patients who received a LT for HCC between 2008-2019 at Virginia Commonwealth University Medical Center (VCU). This included patients at the Central Virginia Veterans Health Care System Health System (a.k.a VA) affiliated with VCU. All LT recipients met UNOS criteria. Patients were identified through a Redcap database maintained by Hepatology and included if there was at least a 12-month follow-up after LT. The study protocol was approved by the VCU IRB. Pre- and post-LT characteristics, including age, sex, race, etiology of liver disease, initial TNM stage, initial alfa-fetoprotein (AFP) (upper limit of normal 6-9 ng/mL), the number and

type of LRT received, DS, MELD/ MELD-Na, transplant time period, radiologic response to LRT, and explant pathology were analyzed for concordance/discordance. Patients ≥ 18 years who underwent LT for a primary indication of HCC were included. Patients not within MC at the time of LT and who did not have pre- LT imaging within three months of transplant were excluded. Patients overstaged (explant pathology showing lower HCC staging than on pre-LT imaging) and patients found to have incidental HCC on explant were excluded.

Imaging protocols

For HCC diagnosis, we utilized standardized protocols based on imaging criteria following UNOS guidelines. Patients on the transplant list underwent every 3-month imaging. The majority underwent MRI with gadolinium, with most examinations performed on a 1.5T Siemens Avanto MRI scanner. Until 2017, a minority of patients were scanned on a 1.5T GE Signa device. Between 2017-2019, patients were scanned with a 1.5T Siemens Aera or 3.0T Vida device. MRI protocol included multiplanar HASTE, axial fat-saturated T2, axial opposed-phase T1, MRCP, pre- and dynamic post-contrast fat-saturated 3D axial T1 and diffusion weighted images. Four post-contrast images were obtained in the arterial, portal venous, 3-minute and 5-minute delayed phases. Gadolinium contrast agents used over the studied time period included ProHance® (gadoteridol), Magnevist® (gadopentetate dimeglumine), MultiHance® (gadobenate dimeglumine), and occasionally Eovist® (gadoxetate disodium). CT scans used modern equipment. Between 2008- 2014, the CT protocol included unenhanced images followed by post-contrast images obtained in the arterial and portal venous phases. In 2014, an additional delayed venous phase was added to meet American College of Radiology (ACR) Liver Reporting and Data system (Li-RADS) recommendations. The above imaging protocols apply to patients scanned at VCU. Patients scanned within the VA system used different equipment with their own independent protocols.

Variables

Pre-transplant LRT included TACE, thermal ablation, TARE and SBRT. Other treatments included percutaneous ethanol infusion, chemoinfusion (infusion of Adriamycin/cisplatin into the artery feeding the tumor), and proton therapy. On the last pre-LT imaging, we collected data on tumor diameter in cm, the number of lesions, evidence of progression, and the time from imaging to LT in days. Patients were considered DS if initially outside of MC, received LRT, and then documented as within MC before LT. Patients already within MC received LRT only as a bridge therapy. Patients were within UCSF criteria (University of California San Francisco) if: (a) one liver lesion > 5 cm but ≤ 8 cm; (b) 2-3 lesions each less than 5 cm and total diameter of all lesions ≤ 8 cm; or (c) 4-5 lesions each less than 3 cm with total diameter of all lesions ≤ 8 cm. For explant data, tumor number, diameter, differentiation, vascular invasion, LN involvement, and extrahepatic spread were collected and categorized as within or outside MC. Analysis with all variables described above was also performed between the two transplant time periods of 2008-2013 and 2014-2019.

Outcomes

The primary outcome was defined as HCC that was discordant (understaged) based on comparisons of radiologic findings meeting MC on last imaging pre-LT and findings of explant histology. Secondary outcomes were post-LT recurrence of HCC and death.

Statistical analysis

Frequencies and percentages were presented for categorical variables and means (SD) or median (IQR) as appropriate for the full sample and stratified by concordance *vs.* discordance. Serum AFP was analyzed both as a continuous variable and within categories: < 20, 20-99, and >100 ng/mL. Comparisons between frequencies for concordance *vs.* understaged were made using chi-squared tests or exact tests if asymptotic

methods were not appropriate. Similarly, t-tests or Wilcoxon Rank Sum tests were used for the comparison of continuous variables. Survival analysis was used to assess differences in survival or disease-free survival recurrence between those concordant or understaged. Kaplan-Meier curves were produced and a log-rank test compared groups. For an analysis focused on death due to HCC recurrence, other causes of death were considered censored. To determine whether the results were differed by transplant period (i.e., effect modifier for the association between concordance/discordance and variables assessed), the period was divided into two: 2008-2013 and 2014-2019. For binary variables, the Breslow-Day test or Zelen test (an exact test) were used to assess the significance of the transplant period as an effect modifier. For categorical variables with > 2 levels, logistic regression was used with the interaction term evaluated for effect modification, again allowing for an exact test when asymptotic assumptions were not valid. For continuous variables, logistic regression was used to assess for effect modification. Effect modification for survival and disease-free survival was assessed with an interaction term in a model using Cox-proportion hazards regression. For all analyses, when effect modification was detected, the association was assessed and reported separately for the periods 2008-2013 and 2014-2019. Significance was considered for $P < 0.05$. SAS version 9.4 was used for all analyses.

RESULTS

Demographics/ discordance rates

Of the 146 patients transplanted, the mean age was 61 years, with 83% male, 71% white and 14% black [Table 1], the majority (55%) having HCV. Overall, the discordance rate between pre-LT imaging stage and explant was 45%. All cases of discordance involved understaging on imaging. When evaluating sex, race or etiology of liver disease, there was no association between concordance or discordance.

Pre-transplant characteristics

At the time of HCC diagnosis, 85% of patients were within MC [Table 2]. Of the 17% ($n = 25$) who required DS prior to listing, 76% were beyond MC but within UCSF criteria, leaving six beyond both criteria. All patients undergoing LT were downstaged to within MC prior to LT. There was no association between discordance and disease burden within or outside MC ($P = 0.14$) or UCSF criteria ($P = 1.00$). In patients requiring DS, a higher rate of discordance was seen, although not statistically significant ($P = 0.087$). AFP values around the time of HCC diagnosis had no association with concordance/discordance whether considered continuous ($P = 0.7723$) or categorized ($P = 0.1306$). No association with concordance/discordance was found in the number of days from last pre-LT imaging to LT ($P = 0.33$), wait-list time ($P = 0.59$) or mean MELD/MELD Na at time of listing.

HCC characteristics

For patients with solitary lesions at diagnosis, 66% were in the discordant group and 67% in the concordant group [Table 3]. In those with multifocal lesions at diagnosis, patients with ≥ 3 lesions had 36% discordance *vs.* 11% concordance. This was statistically significant ($P = 0.046$). There was no association between concordance/discordance and location of the HCC lesion(s) (unilobar *vs.* bilobar).

Last imaging before transplant

The majority of patients (95%) underwent MRI *vs.* 5% with CT. Overall, 66% had a complete radiologic response to treatment on the last imaging pre-LT, with 68% in the discordant group and 64% in the concordant group. No statistical significance was seen between concordance and treatment response seen on the last pre-LT imaging (partial or complete). No association was seen between discordance and tumor multifocality, new HCC lesion, increase in tumor size or treatment response on last imaging [Table 3].

Table 1. Demographics

	Overall (*n* = 146)	Discordant (Understaged) (*n* = 65)	Concordant (*n* = 81)	*P*-value
Age, mean (SD)	60.6 (5.8)	61.1 (5.3)	60.2 (6.1)	0.3266
Sex				0.9541
Male	121 (82.9)	54 (83.1)	67 (82.7)	
Female	25 (17.1)	11 (16.9)	14 (17.3)	
Race				0.4421
White	104 (71.2)	46 (70.8)	58 (71.6)	
Black	20 (13.7)	7 (10.8)	13 (16.0)	
Other	22 (15.1)	12 (18.5)	10 (12.3)	
Liver Disease*				0.1486
HCV	80 (54.8)	40 (61.5)	40 (49.4)	
HCV+ ETOH	24 (16.4)	10 (15.4)	14 (17.3)	
NAFLD	16 (11.0)	4 (6.1)	12 (14.8)	
ETOH	10 (6.8)	6 (9.2)	4 (4.9)	
Combination**	5 (3.4)	3 (4.6)	2 (2.5)	
Other	11 (7.5)	2 (3.1)	9 (11.1)	
Hospital Center				0.8935
VA	62 (42.5)	28 (43.1)	34 (42.0)	
VCU	84 (57.5)	37 (56.9)	47 (58.0)	

*Exact test or Wilcoxon; **Combinations of diseases: HCV + NAFLD/ ETOH + NAFLD/ HBV + HCV; SD: standard deviation.

Pre-transplant HCC treatment

The majority of patients (97%) were treated with LRT. Most received TACE (71%), followed by thermal ablation at 43%. Only 3% received other traditional treatments including chemoinfusion, percutaneous ethanol injection and proton therapy. For new generation LRT, 17% received TARE and 6% received SBRT. While 75% received only traditional LRT with either TACE, RFA, and PEI, 12% received only new generation pre-LT LRT with either TARE and/or SBRT. Another 10% received a combination of traditional and new generation LRT. No association between concordance/discordance was seen between patients receiving traditional LRT only or new generation LRT only, or a combination of both new and old LRT. No correlation was seen between concordance/discordance and patients receiving multiple *vs.* single LRT [Table 4].

Explant characteristics

In the discordant group, 16% had well-differentiated HCC, 69% had moderately differentiated, and 15% had poorly differentiated. In the concordant group, 14% had well-differentiated, 69% had moderately differentiated, and 10% had poorly differentiated. There was no association between HCC histopathology and discordance. Only a trend was noted towards discordance with microvascular invasion on explant (P = 0.053). Of note, two patients likely had mixed HCC-cholangiocarcinoma (CC) with incidental discovery of CC on explant. One with a combination of HCC was unable to be differentiated. The second only had CC on histopathology with surrounding necrosis. This likely reflected treated HCC as the patient did have significantly high AFP prior to LRT and subsequent normalization of AFP after treatment [Table 5].

There was an association between patients with explant histology outside of MC and discordance (31%) (P < 0.0001). Of the 19 outside MC explant staging, 10 were within UCSF criteria, and all were in the discordant group. With tumor multifocality on explant, 32% had ≥ 2 HCC nodules and was associated with higher discordance rates (51% discordant group *vs.* 18% concordant group); P < 0.0001. The median size of the

Table 2. Pretransplant characteristics

	Overall (*n* = 146)	Discordant (Understaged) (*n* = 65)	Concordant (*n* = 81)	*P*-value
Milan Criteria at diagnosis 2008-2019				0.1357
Yes	124 (84.9)	52 (80.0)	72 (88.9)	
No	22 (15.1)	13 (20.0)	9 (11.1)	
Milan Criteria at diagnosis* 2008-2013				0.0130
Yes	48 (87.3)	16 (72.7)	32 (97.0)	
No	7 (12.7)	6 (27.3)	1 (3.0)	
Milan Criteria at diagnosis 2014-2019				0.5931
Yes	76 (83.5)	36 (83.7)	40 (83.3)	
No	15 (16.5)	7 (16.3)	8 (16.7)	
Downstaged prior to transplant listing				0.0871
Yes	25 (17.1)	15 (23.1)	10 (12.4)	
No	121 (82.9)	50 (76.9)	71 (87.6)	
UCSF Criteria for those downstaged (*n* = 25)				1.000
Yes	19 (76.0)	11 (73.3)	8 (80.0)	
No	6 (24.0)	4 (26.7)	2 (20.0)	
AFP (ng/mL)** (*n* = 109) (Mean SD/median IQR)	162.8 (785.7) 18.7 (62.0)	59.8 (113.3) 20.7 (89.5)	246.9 (1050.6) 14.3 (38.1)	0.7723
AFP(ng/mL)Group*(*n* = 109)				0.1306
<20	58 (53.2)	24 (49.0)	34 (56.7)	
20-99	28 (25.6)	17 (34.7)	11 (18.3)	
≥ 100	23 (21.1)	8 (16.3)	15 (25.0)	
Days Last image to transplant (mean SD/median IQR)**	46.2 (26.4) 43.0 (36)	44.2 (26.7) 39 (35)	47.7 (26.3) 48 (37)	0.3323
Days List to transplant (mean SD/median IQR)**	156.0 (270.6) 106.0 (150)	155.6 (214.8) 101.0 (147)	156.2 (309.6) 121 (158.0)	0.5877
Meld Na** (mean SD/median IQR)	16.0 (7.3) 15.0 (9.0)	16.4 (6.9) 16.0 (8.0)	15.7 (7.6) 13.0 (9.0)	0.3245
Meld** (mean SD/median IQR)	14.0 (7.1) 12.0 (7.0)	14.0 (6.9) 13.0 (5.0)	14.0 (7.3) 12.0 (7.0)	0.6842
Transplant Period				0.2478
2008-2013	55 (37.7)	22 (33.8)	33 (40.7)	
2014-2019	91 (62.3)	43 (66.2)	48 (59.3)	

*Exact test; **Wilcoxon test; *P* = 0.0294 for effect modification; IQR: interquartile range; SD: standard deviation.

largest tumor diameter on explant was 2.0 cm, with no association between discordance. Single lesions on explant whether < 3 cm, 3-5 cm or > 5 cm had no correlation with concordance/discordance. There was an association between pathologic response to treatment on explant (partial, complete, progression) and concordance/discordance ($P < 0.0001$). While 74% of discordant patients and 27% of concordant patients had a partial response, no discordant patients had a complete response. Pathologic progression on explant was seen in 25% in the discordant group *vs.* 6% in the concordant group ($P < 0.0001$).

Transplant time periods

Concordance/discordance was compared between the two periods of transplantation: 2008-2013 *vs.* 2014-2019, to determine the impact of improved imaging modalities and newer generation LRT. During the period of 2008-2013, 38% of patients were transplanted, with 34% in the discordant group. In the period of

Table 3. HCC characteristics

	Overall (*n* = 146)	Discordant (Understaged) (*n*=65)	Concordant (*n* = 81)	*P*-value
Multifocal tumor at diagnosis				0.9480
Yes	49 (33.6)	22 (33.8)	27 (33.3)	
No	97 (66.4)	43 (66.2)	54 (66.7)	
# Nodules if multifocal at diagnosis *(*n* = 49)				0.0455
2	38 (77.5)	14 (63.6)	24 (88.9)	
3 or more	11 (22.5)	8 (36.4)	3 (11.1)	
Tumor location at diagnosis (*n* = 144)				0.7169
Unilobar	122 (84.7)	55 (85.9)	67 (83.7)	
Bilobar	22 (15.3)	9 (14.1)	13 (16.3)	
Imaging modality*				1.000
MRI	138 (94.5)	61 (93.8)	77 (95.1)	
CT	8 (5.5)	4 (6.2)	4 (4.9)	
Multifocal tumor at transplant*				1.000
Yes	5 (3.4)	2 (3.1)	3 (3.7)	
No	141 (96.6)	63 (96.9)	78 (96.3)	
Tumor size on last imaging before transplant (cm) (*n* = 49) Median (IQR)*	2.0 (0.8)	1.65 (0.95)	2.2 (0.6)	0.0669
New lesions on last imaging before transplant*				0.6290
Yes	4 (2.7)	1 (1.5)	3 (3.7)	
No	142 (97.3)	64 (98.5)	78 (96.3)	
Size increase last imaging before transplant*				1.000
Yes	9 (6.2)	4 (6.1)	5 (6.2)	
No	137 (93.8)	61 (93.9)	76 (93.8)	
Response to treatment on last imaging before transplant*				0.7939
Complete	96(65.7)	44 (67.7)	52 (64.2)	
Partial	6 (4.1)	2 (3.1)	4 (4.9)	
Other/none	44 (30.1)	19 (29.2)	25 (30.9)	

*Exact test; HCC: hepatocellular carcinoma; IQR: interquartile range; SD: standard deviation; CT: computed tomography; MRI: magnetic resonance imaging.

2014-2019, 62% were transplanted, with 66% cases of discordance. No statistically significant differences were seen between these two periods (P = 0.25). Further analysis was performed to assess any modifying effect on the association of concordance/discordance and pre- and post-transplant variables during these two time periods. None of such modifying effects was seen for any of these variables except MC at diagnosis (P = 0.0294) and microvascular invasion (P = 0.0270). Patients outside of MC at diagnosis during the transplant period of 2008-2013 were noted to have higher discordance rates (27% *vs.* 3%, P = 0.013). No significant differences in concordance/discordance were seen for those within MC transplanted between 2014 - 2019 (P = 0.59) [Table 2]. Microvascular invasion during the transplant period of 2014-2019 was associated with discordance (26%) *vs.* concordance (4%) (P = 0.0055) [Table 5].

Post-transplant survival and recurrence

Median follow-up after transplant was 1507 days [min = 0 and max = 4622 (IQR: 822-2688)]. Among the 21% (n = 30) of patients who died, 13 % were in the discordant group and 8% were in the concordant group. Discordance was associated with an increased risk of death (P = 0.0136) [Figure 1]. While 10% (n = 14) had recurrence with 6% from the discordant group and 3% from the concordant group, no statistical

Table 4. Pre-transplant treatments

	Overall (*n* = 146)	Discordant (Understaged) (*n* = 65)	Concordant (*n* = 81)	*P*-value
Resection*				0.7550
Yes	11 (7.5)	4 (6.1)	7 (8.6)	
No	135 (92.5)	61 (93.9)	74 (91.4)	
RFA				0.8391
Yes	62 (42.5)	27 (41.5)	35 (43.2)	
No	84 (57.5)	38 (58.5)	47 (56.8)	
TACE				0.1589
Yes	103 (70.5)	42 (64.6)	60 (75.3)	
No	43 (29.5)	23 (35.4)	20 (24.7)	
TARE				0.2046
Yes	25 (17.1)	14 (21.5)	11 (13.6)	
No	121 (82.9)	51 (78.5)	70 (86.4)	
SBRT				0.7314
Yes	9 (6.2)	3 (4.6)	6 (7.4)	
No	137 (93.8)	62 (95.4)	75 (92.6)	
Other treatments*				0.3816
Yes	5 (3.4)	1 (1.5)	4 (4.9)	
No	141 (96.6)	64 (98.5)	77 (95.6)	
Locoregional therapy*				0.8523
None	4 (2.7)	2 (3.1)	2 (2.5)	
Unimodal	88 (60.3)	41 (63.1)	47 (58.0)	
Multimodal	54 (37.0)	22 (33.8)	32 (39.5)	
Traditional/New generation locoregional therapy *(*n* = 142)				0.9386
No Treatment	4 (2.7)	2 (3.1)	2 (2.5)	
Traditional only	110 (75.3)	48 (73.8)	62 (76.5)	
New generation only	17 (11.6)	7 (10.8)	10 (12.3)	
Combined	15 (10.3)	8 (12.3)	7 (8.6)	

*Exact test; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; SBRT: stereotactic body radiation therapy.

significance was seen between recurrence-free survival and discordance ($P = 0.07$) [Figure 2]. Not all causes of death were HCC-related. Of the 30 deaths, 10 died from HCC recurrence, 4 from non-HCC, liver-related complications, and 16 from non-HCC, non-liver-related complications [Table 6]. A survival analysis considering only death as defined as HCC death (other causes of death and no death as censored) was performed, showing differences between the discordant and concordant groups [$P = 0.0491$] [Figure 3].

DISCUSSION

In the era of new generation therapeutics for HCC as a bridge to LT with improved imaging technology and standardized classification in imaging reporting, our study is the first to evaluate pre- and post-LT variables that may predict concordance/discordance in patients transplanted for HCC during both older and newer era of transplantation between 2008-2019. We observed a 45% discordance rate between the pre-LT imaging stage and explant, much higher than the 22%-27% seen in studies[1,3,5]. Consistent with previous studies, we also confirmed higher rates of death in the discordant group. What is novel in our study is the comparison between the older and newer era of LT, including improved imaging modalities, and patients who received

Table 5. Post-transplant/Explant characteristics

	Overall (*n* = 146)	Discordant (Understaged) (*n* = 65)	Concordant (*n* = 81)	*P*-value
Max nodule size- explant med (IQR) (*n* = 87)*	2.0 (1.5)	1.8 (1.9)	2.0 (0.8)	0.7256
Multifocal-explant (*n* = 145)				< 0.0001
Yes	47 (32.4)	33 (50.8)	14 (17.5)	
No	98 (67.6)	32 (49.2)	66 (82.5)	
Single lesion size (*n* = 41)*				0.8478
< 3 cm	30 (73.2)	20 (69.0)	10 (83.3)	
3-5 cm	9 (21.9)	7 (24.1)	2 (16.7)	
>5 cm	2 (4.9)	2 (6.9)	0 (0.0)	
Cancer on explant				< 0.0001
No	53 (37.7)	1 (1.6)	52 (64.2)	
Yes	91 (62.3)	62 (98.4)	29 (35.8)	
Histology (if cancer found) *				0.2252
Well differentiated	14 (15.4)	10 (16.1)	4 (13.8)	
Moderately differentiated	63 (69.2)	43 (69.3)	20 (69.0)	
Poorly differentiated	12 (13.2)	9 (14.5)	3 (10.3)	
Mixed HCC-cholangiocarcinoma	2 (2.2)	0 (0.0)	2 (6.9)	
Microvascular invasion (2008-2019)				0.0525
Yes	24 (16.4)	15 (23.1)	9 (11.1)	
No	122 (83.6)	50 (76.9)	72 (88.9)	
Microvascular invasion*(2008-2013)				1.00
Yes	11 (20.0)	4 (18.2)	7 (21.2)	
No	44 (80.0)	18 (71.8)	26 (88.1)	
Microvascular invasion (2014-2019)				0.0055
Yes	13 (14.3)	11 (25.6)	2 (4.2)	
No	78 (85.7)	32 (74.4)	46 (95.8)	
Macrovascular invasion*				0.4452
Yes	1 (0.7)	1 (1.5)	0 (0.0)	
No	145 (99.3)	64 (98.5)	81 (100)	
Path Response*				< 0.0001
Partial	70 (47.9)	48 (73.8)	22 (27.2)	
Complete	53 (36.3)	0 (0.0)	53 (65.4)	
No response	2 (1.4)	1 (1.5)	1 (1.2)	
Progression	21 (14.4)	16 (24.6)	5 (6.2)	
Outside of milan criteria- explant (*n* = 144)				< 0.0001
Yes	21 (14.6)	20 (31.2)	1 (1.2)	
No	123 (85.4)	44 (68.8)	79 (98.8)	
Within UCSF criteria -explant (*n* = 19)*				0.4737
Yes	10 (52.6)	10 (55.6)	0 (0.0)	
No	9 (47.4)	8 (44.4)	1 (100.0)	

*Exact test or Wilcoxon test; HCC: hepatocellular carcinoma; IQR: interquartile range.

traditional LRT *vs.* newer generation LRT, combination or multiple modalities *vs.* single modality. Despite these differences, no association between concordance and discordance was found.

Table 6. Causes of death

	Overall	Discordant (Understaged)	Concordant
Deaths	30	19	11
Causes of death			
HCC recurrence	10	7	3
Non- HCC, liver-related complications	4	4	0
Non- HCC, non- liver related complications	16	8	8
(a) Infection/sepsis	4	0	4
(b) Renal failure	0	0	0
(c) Other	12	8	4

HCC: hepatocellular carcinoma.

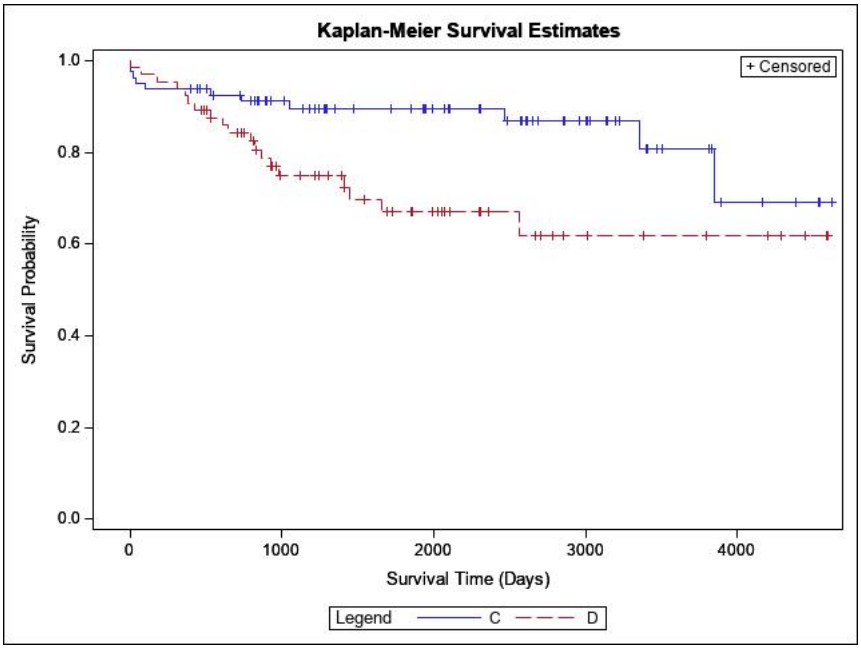

Figure 1. Comparison of survival distributions. Discordant (D): 19 deaths; Concordant (C): 11 deaths; $P = 0.0136$.

Few studies have evaluated pre- and post-LT characteristics that may predict discordance. Ecker BL *et al.*[3] evaluated over 300 patients at a single center between the period of 2003-2013 using TACE or ablation for bridging/ DS. Mahmud N *et al.*[5] evaluated regional and center-level variations in 5424 patients from the UNOS database transplanted for HCC between 2012-2016. Mahmud found 25% were understaged but with significant variation between UNOS regions and among transplant centers ranging between 14.8% to 38.1%. They hypothesized that some UNOS regions with a high proportion of understaging rates are due to areas with higher competition for donor organs and higher median MELD scores at LT. They noted that behavioral bias may influence understaging by centers listing patients who have borderline cases. The higher rates of discordance seen in our institution may be explained by differences in imaging protocols, radiologic expertise, reporting conventions, and HCC diagnostic criteria. This may also contribute to the variations and differences seen. Similarly, there may be interobserver variation between radiologists who reviewed imaging at different centers. Our liver transplant program includes patients from the VA health system along the east coast referred to our VA medical center.

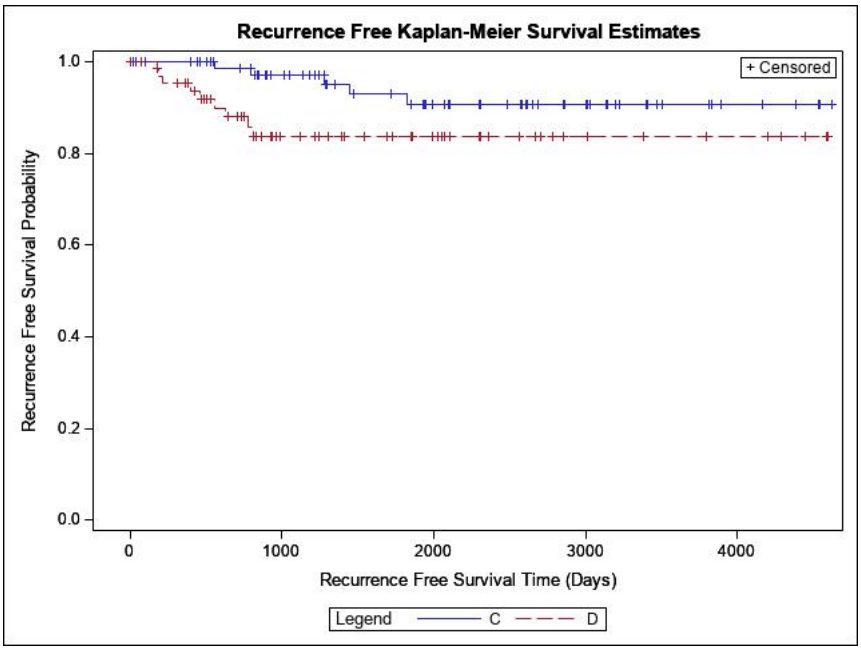

Figure 2. Comparison of recurrence-free survival distributions. Discordant (D): 9 recurrences; Concordant (C): 5 recurrences; *P* = 0.07.

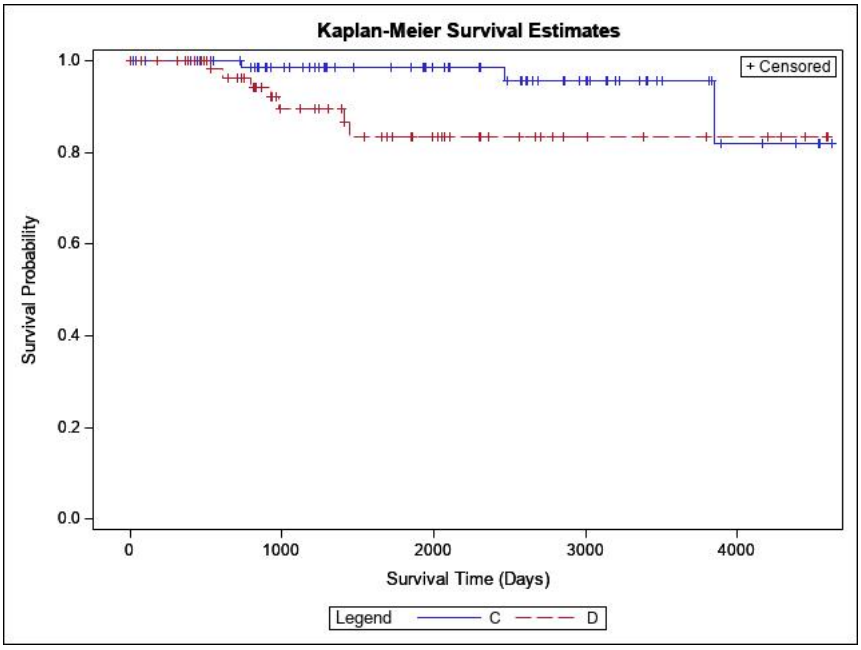

Figure 3. Comparison of survival distributions -deaths due to HCC recurrence. Discordant (D): 7 deaths; Concordant (C): 3 deaths; *P* = 0.0491. HCC: hepatocellular carcinoma.

Pre-transplant characteristics

In our study, we found no association between concordance/discordance and those within or outside MC at diagnosis. Due to the small sample size, our study likely was underpowered to detect such differences. However, a sub-analysis between transplant periods revealed concordance was associated with MC in patients transplanted in the earlier era (2008-2013). We found no association between

concordance/discordance for patients within UCSF criteria prior to listing, but a trend was noted between discordance and DS. While Mahmud found an association between DS and discordance, Ecker[3] did not. One recent retrospective analysis of the UNOS database evaluated 3819 patients transplanted from 2012-2015[6], and were classified as always within MC, meeting UNOS-DS inclusion criteria (within UCSF criteria) or "all-comers" (AC-DS) with initial HCC beyond UNOS-DS inclusion criteria. While 1/3 meeting UNOS- DS were found to be understaged with explant tumor beyond MC compared with < 15% within MC, HCC understaging increased by 10% for each 1- cm increase in total tumor diameter on last pre-LT imaging. The AC-DS group had inferior survival rates post- LT compared with UNOS-DS group and those within MC. Therefore, DS within MC should be the minimal requirement for LT.

We also evaluated baseline AFP at the time of HCC diagnosis and found no association between concordance/discordance when stratified according to increasing levels. However, it should be noted that AFP values for 37 patients were not available. We did not evaluate serial AFP values up to LT.

HCC characteristics

A novel finding in our study was the association of discordance with three or more HCC lesions at the time of diagnosis which was statistically significant. Multifocal HCC likely reflects aggressive disease, thus suggesting more aggressive tumor biology. These findings may impact clinical management in how these patients are approached when considering LT. Such considerations include more aggressive LRT with complete obliteration of tumor burden prior to LT and counseling patients on the high risk for understaging and recurrence after transplant. At the author's institution, even if progression was seen on the last imaging before transplant, patients could still receive a transplant if the tumor remained within MC. This could be a factor contributing to higher rates of discordance. We found no association between concordance/discordance and location of the HCC lesion(s), tumor multifocality, new HCC lesion or increase in tumor size at last pre-LT imaging. The majority of our patients underwent MRI for HCC monitoring with no correlation between concordance and treatment response, whether partial or complete.

Pre-transplant treatments

TARE and SBRT have emerged as relatively newer LRT in HCC and may be effective in improving tumor control as a bridge to transplant, in DS and reducing post-LT recurrence compared to TACE[6-13]. The use of TARE compared to TACE does have advantages including less abdominal pain, nausea, vomiting, elevated liver tests and fatigue. The advantage of SBRT includes very limited radiation doses to adjacent organs at risk, thus the ability to maintain liver function. Used both in combination with other LRT and as a single modality, SBRT is emerging as the therapeutic tool for small HCC lesions in "difficult to reach" locations or for "difficult to treat" lesions when TACE or TARE have failed. One study evaluated post-transplant outcomes in patients undergoing bridging LRT with TARE *vs.* TACE[8]. A trend toward improved 3-year survival was seen in the TARE group. Microvascular invasion was seen in 3.6% of explants of the TARE group *vs.* 27% in the TACE group. Another study evaluated liver transplant outcomes over a 15-year period between 2004-2018 who received TARE as a bridge or DS[9]. No differences in OS/recurrence-free survival were seen in those bridged or DS. These studies support the effectiveness of TARE for HCC in the setting of bridging and DS prior to LT.

Unlike Ecker and Mahmoud, we compared pre-LT LRT between newer generation TARE and/or SBRT *vs.* traditional TACE/ thermal ablation/ other. We evaluated combination *vs.* single LRT. Ecker evaluated only TACE or ablation[3]. In Mahmoud's study, patients received a single type of LRT prior to LT, with TACE being the most frequent at 63.5%, ablation at 33.3% and TARE at 2.7%[5]. In our study, 17% received TARE, 6% received SBRT, 43% received ablation, and 71% received TACE. Under our "other" category, one received PEI, another proton therapy, and 3 received chemoinfusion. Ecker found no association between

concordance/discordance with their LRT. Mahmud found LRT bridging/ DS status to be a predictor of understaging[5]. In our study, no association between discordance was found between traditional LRT, newer generation LRT, a combination of both or multiple *vs.* single LRT. This lack of association may be attributed to smaller numbers in our study.

Explant characteristics

Similar to Ecker's study, discordance was found in those with explant histology outside of MC, microvascular invasion, tumor multifocality, and pathologic response to LRT. The data on explant pathology will unlikely provide additional guidance pre-transplant in identifying high-risk understaged patients without reliable pre-transplant surrogates that can accurately predict histologic findings.

Transplant time periods

Our study is the first to evaluate concordance/discordance between two different time periods of transplantation: 2008-2013 *vs.* 2014-2019. Although we found no statistically significant differences, further analysis of any modifying effect on pre-transplant variables showed that MC at diagnosis during the transplant period of 2008-2013 had higher concordance rates compared to the period of 2014-2019. This could be explained by differences in practice patterns between these two time periods. In the earlier era, perhaps a more "conservative" approach to HCC diagnosis with strict adherence to MC criteria was followed, given the scarcity of donors.

Despite the newer generation LRT introduced over a decade ago, the advancement of radiologic technology including the advancement of MRI technology and the development of LI-RADS, based on our study, we have not yet improved our ability to predict discordance[14,15]. To standardize the reporting and data collection of CT/ MRI imaging for HCC diagnosis, LI-RADS was first released by the ACR in 2011[16]. The utility of LI-RADS has allowed the application of consistent terminology, reduction of imaging interpretation variability/errors, and has facilitated quality assurance and research.

Despite comparisons between the older and newer era of LT, advancement in our MRI technology appears not to have improved the ability to predict discordance. Variability in the interpretation of imaging results could be attributed to differences in imaging protocols, the level of radiologic expertise and HCC diagnostic criteria used. Another factor to consider is the criteria used to evaluate treatment response to newer LRT which are radiation-based. These differ from conventional LRT. Lesions may undergo coagulative necrosis or internal hemorrhage after TARE, making them more hyperintense on T1-weighted imaging or hyperdense on non-contrast CT. This makes interpretation of the response more challenging.

Limitations and strengths

Limitations to our study include the small number of patients and its retrospective nature. Small sample size could have contributed to type II error (i.e., low power). Although a single-center study, patients were referred from various VA hospitals along the east coast to our VA health system. This could contribute to radiologic interobserver variability in evaluating HCC treatment response and progression, as well as variability in imaging protocols and HCC diagnostic criteria. Additional limitations include the use of MRI as our center's primary imaging modality in our HCC protocol, and multimodal treatments not evenly distributed. These could have impacted our results. Strengths of our study include evaluating patients under real-world conditions transplanted up to 2019 who underwent treatment with newer LRT with TARE and SBRT. We were able to evaluate two transplant time periods to further elucidate whether the improvement of our imaging technology, radiologic diagnostic criteria and newer treatment modalities would affect concordance/discordance.

In conclusion, our study supports the ongoing challenges of HCC stage discordance between pre-LT imaging and explant pathology. Despite the advent of more sophisticated radiologic technology, standardized LI-RADS, and novel LRT as a bridge to LT, discordance remains difficult to predict. In our study, the only variable associated with discordance was three or more HCC lesions detected at diagnosis. The only variable associated with concordance was those diagnosed within MC in the earlier era of LT. No other pre- or post-LT variables predicted discordance/concordance, including newer generation or older generation, single or combined LRT. Although we saw only a trend between DS and discordance, growing data supports this association. We also observed decreased survival with discordance. Emphasis on UNOS-mandated uniformity in selection criteria with adherence to UNOS-DS criteria in order to minimize center/regional variations, behavioral bias, and improve survival will likely play a critical role in selecting the ideal transplant candidate. Larger prospective studies incorporating newer LRT for HCC are needed to further elucidate the predictability of discordance to achieve optimal post-transplant outcomes.

DECLARATIONS

Acknowledgment

Services and products in support of the research project were generated by the VCU Massey Cancer Center Biostatistics Shared Resource, supported, in part, with funding from NIH-NCI Cancer Center Support Grant P30 CA016059.

Authors' contributions

Conception and design: Lee HM, Sterling RK
Administrative support: Lee HM, John BV, Sterling RK
Provision of study material or patients: Lee HM, John BV, Winks S, Clayton R, Matherly S, Sterling RK, Bhati C, Sharma A, Strife B
Collection and assembly of data: Lee HM, D McClish, John BV, Albhaisi S, Allawy A, Patel S
Data analysis and interpretation: Lee HM, Sterling RK, McClish D
Manuscript writing: Lee HM, McClish D, John BV, Winks S, Clayton R, Albhaisi S, Allawy A, Patel S, Fields EC, Matherly S, Strife B, Bhati C, Sharma A, Sterling RK
Final approval of manuscript: Lee HM, McClish D, John BV, Winks S, Clayton R, Albhaisi S, Allawy A, Patel S, Fields EC, Matherly S, Strife B, Bhati C, Sharma A, Sterling RK

Availability of data and materials

Not applicable.

Financial support and sponsorship

No financial support disclosures

Conflicts of interest

Authors have no conflict of interest/ no disclosures

Ethical approval and consent to participate

The study "Liver cancer understaging in liver transplantation in the current era of radiologic imaging and newer generation locoregional therapies" published in *Hepatoma Research* was approved by the Virginia Commonwealth University Institutional Review Board. Ethics committee approval was not required for this study as this was a study approved under IRB HM20007405 CR3 Expedited Category 5.

Consent for publication

Written informed consent for this study was not required as this was a retrospective study approved under IRB HM20007405 CR3 Expedited Category 5. Patient consent in this study category has been waived.

REFERENCES

1. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;334:693-9. DOI PubMed
2. Freeman RB, Edwards EB, Harper AM. Waiting list removal rates among patients with chronic and malignant liver diseases. *Am J Transplant* 2006;6:1416-21. DOI PubMed
3. Ecker BL, Hoteit MA, Forde KA, et al. Patterns of discordance between pretransplant imaging stage of hepatocellular carcinoma and posttransplant pathologic stage: a contemporary appraisal of the milan criteria. *Transplantation* 2018;102:648-55. DOI PubMed
4. Duffy JP, Vardanian A, Benjamin E, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 2007;246:502-9;discussion 509. DOI PubMed PMC
5. Mahmud N, Hoteit MA, Goldberg DS. Risk factors and center-level variation in hepatocellular carcinoma under-staging for liver transplantation. *Liver Transpl* 2020;26:977-88. DOI PubMed PMC
6. Mehta N, Dodge JL, Grab JD, Yao FY. National experience on down-staging of hepatocellular carcinoma before liver transplant: influence of tumor burden, alpha-fetoprotein, and wait time. *Hepatology* 2020;71:943-54. DOI PubMed PMC
7. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010;138:52-64. DOI PubMed
8. Zori AG, Ismael MN, Limaye AR, et al. Locoregional therapy protocols with and without radioembolization for hepatocellular carcinoma as bridge to liver transplantation. *Am J Clin Oncol* 2020;43:325-33. DOI PubMed
9. Gabr A, Kulik L, Mouli S, et al. Liver Transplantation following yttrium-90 radioembolization: 15-year experience in 207-patient cohort. *Hepatology* 2021;73:998-1010. DOI PubMed
10. Katz AW, Chawla S, Qu Z, Kashyap R, Milano MT, Hezel AF. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. *Int J Radiat Oncol Biol Phys* 2012;83:895-900. DOI PubMed
11. O'Connor JK, Trotter J, Davis GL, Dempster J, Klintmalm GB, Goldstein RM. Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl* 2012;18:949-54. DOI PubMed
12. Mohamed M, Katz AW, Tejani MA, et al. Comparison of outcomes between SBRT, yttrium-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. *Adv Radiat Oncol* 2016;1:35-42. DOI PubMed PMC
13. Murray LJ, Dawson LA. Advances in stereotactic body radiation therapy for hepatocellular carcinoma. *Semin Radiat Oncol* 2017;27:247-55. DOI PubMed
14. Bharwani N, Koh DM. Diffusion-weighted imaging of the liver: an update. *Cancer Imaging* 2013;13:171-85. DOI PubMed PMC
15. Yuan Z, Zhang J, Yang H, Ye XD, Xu LC, Li WT. Diffusion-weighted MR imaging of hepatocellular carcinoma: current value in clinical evaluation of tumor response to locoregional treatment. *J Vasc Interv Radiol* 2016;27:20-30;quiz 31. DOI PubMed
16. Liver Reporting & Data System (LI-RADS). Available from: https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/LI-RADS [Last accessed on 18 Apr 2022].