ORIGINAL RESEARCH

Extrahepatic metastasis risk of hepatocellular carcinoma based on α-fetoprotein and tumor staging parameters at cross-sectional imaging

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Background: Extrahepatic metastases have important implications in the clinical management of hepatocellular carcinoma (HCC). The purpose of this study was to validate tumor staging parameters and serum AFP as risk factors of HCC metastasis.

Patients and methods: In this retrospective case–control study, patients with a new diagnosis of HCC (N=236), median age 57 years (range 28–89 years), and male-to-female ratio of 183/53 were divided into a "no-met" group (N=101) without extrahepatic metastasis or a "met" group with extrahepatic metastases (N=135). Metastasis risk factors based on tumor staging parameters (size, number, infiltration, and vascular invasion) and serum AFP level were calculated as odds ratio (OR). Sensitivities of the risk factors as metastasis screening tests were also calculated.

Results: AFP >400 µg/mL, index tumor size >5 cm, and vascular invasion individually had strong association with metastasis, with OR (95% confidence interval) of 11.5 (5.9–22.1), 17.7 (9.0–34.8), and 18.9 (8.2–43.9), respectively, but with moderate sensitivities as metastasis screening tests, with 71.9% (65.7–77.3), 75.6% (69.6–80.7), and 58.5% (52.1–64.7), respectively. Composite multiparametric criteria, eg, a logical union of 1) tumor size outside of Milan criteria, 2) AFP threshold >35 µg/mL, and 3) vascular invasion, had excellent OR up to 55.6 (13.0–237.1) with screening sensitivity 98.5% (95.8–99.6).

Conclusion: Serum AFP, tumor size, and vascular invasion are strongly associated with extrahepatic metastasis of HCC, especially when combined into a multiparametric metastasis prediction criterion.

Keywords: hepatocellular carcinoma, risk factor, α-fetoprotein, stage, metastasis

Introduction

Hepatocellular carcinoma (HCC) is currently eighth leading cause of cancer-related deaths in the USA[1] and the fastest growing cancer in mortality.[2] Treatment recommendation depends on the patient's clinical status (eg, liver function and performance status) and tumor stage.[3,4] Patients with advanced-stage HCC, defined by the presence of vascular invasion and/or extrahepatic metastasis, are generally not considered candidates for curative treatment and are usually treated with systemic or palliative therapy. The prognosis of advanced-stage HCC is poor with median survival <1 year, in contrast to the ~70% 5-year survival of early-stage HCC.[5–7]

Extrahepatic metastasis ("metastasis" hereafter) occurs in one-third of patients with HCC,[8,9] with the most common sites being lung, lymph nodes, bone, and adrenal glands.[10,11] Metastases have important management implications, as locoregional therapies (eg, ablation, resection, and liver transplantation) are no longer effective

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controlling extrahepatic disease.[4,5,12,13] Metastasis is also an independent predictor of poor survival.[14–17] Therefore, it is crucial to determine the presence of metastasis at the time of initial HCC diagnosis, as initiation of appropriate therapy will determine survival.[11] However, exhaustive metastasis workup, which may include chest CT and bone scintigraphy, may be costly, time consuming, and unnecessary for those with low risk of metastasis.

Several noninvasive prognostic parameters of HCC have been proposed, including tumor size and serum AFP levels. Tumor size is an independent predictor of HCC progression, metastasis development, and overall survival.[10,18–20] High levels of AFP are independently associated with metastasis risk and poorer prognosis.[21–23] Other parameters, such as vascular invasion and the number of tumors, also have survival implications.[23,24] Accordingly, these parameters are integral part of various HCC staging systems.[12,25–30] To our knowledge, however, no specific criteria have been proposed for HCC metastasis risk stratification.

We hypothesize that the tumor staging parameters (eg, tumor size, number, infiltration, vascular invasion, and AFP) are associated with synchronous or metachronous metastasis in patients with HCC. The purpose of this study was to validate the tumor staging parameters, either as single-parametric criteria or as multi-parametric criteria, as risk factors of HCC metastasis. If validated, such criteria may allow rapid metastasis risk stratification at the time of diagnostic imaging and facilitate timely management decisions including the need for comprehensive metastasis workup.

Patients and methods
Study design and patient population

This retrospective case–control study at a tertiary-care public hospital was approved by the University of Texas Southwestern Medical Center's Investigational Review Board. Data were de-identified in compliance with Health Insurance Portability and Accountability Act. The need to obtain informed consent was waived. A review of an HCC clinic database was conducted to identify 457 consecutive patients with a new diagnosis of HCC between January 2005 and December 2011. HCC diagnosis was made either by direct tissue sampling or dynamic contrast-enhanced cross-sectional imaging (CT or MRI) per routine clinical care, interpreted by staff pathologists and radiologists, respectively. Two authors (AGS and ACY) adjudicated each case to confirm that it met diagnostic criteria by histology or the American Association for the Study of Liver Disease.[31] Routine evaluation of metastatic disease included chest X-ray and abdominal-pelvic

CT (if not already performed). Additional imaging, such as chest CT and bone scan, was performed at the discretion of the treating physician.

By chart review, patients were divided into the following two cohorts: 1) "no-met" cohort comprised patients without documented metastasis at the time of HCC diagnosis and during the first 12-month follow-up period from the initial diagnosis and 2) "met" cohort with documented metastasis at the time of initial diagnosis or detected during the first 12-month follow-up. A single index imaging study (CT or MRI) was selected for each patient. For those in the no-met group, the index study was the initial imaging examination leading to the HCC diagnosis. For those in the met group, the index imaging study was the pretreatment imaging examination closest to the time of metastasis diagnosis. Patients were excluded from the study if the image/clinical data were incomplete, or determination of the HCC metastasis status was compromised: 1) no documented metastasis but follow-up period <12 months; 2) no available pretreatment CT or MRI; 3) systemic HCC treatment during the follow-up period; 4) index CT/MRI images not available; 5) no contemporaneous pretreatment serum AFP, defined as <3 months of the index CT/MRI; and 6) history of any other cancers. The inclusion–exclusion criteria and the number of patients are graphically summarized in Figure 1.

Data collection

For each patient, the index study's images and its radiology report were reviewed. An axial image series that best depicted the tumor boundary was selected. The size of the dominant (index) tumor, either meeting the AASLD imaging criteria or biopsy proven, was measured as maximum axial diameter. Other nonindex tumors were measured, if they met the imaging criteria or had similar imaging features as the biopsy-proven index tumor. For diffuse infiltrative HCC, its size was coded as 99 cm due to difficulty in delineating the tumor boundary. Presence of vascular invasion (ie, involving either portal vein or hepatic vein) and infiltrative morphology were determined based on the official radiology report, in order to maintain consistency with the patient's clinical management decisions.

The AFP level (μg/mL) and other demographic and clinical data including the age, sex, and Child-Turcotte-Pugh stage were recorded. Etiology of liver disease, including hepatitis C (positive serum antibody or RNA), hepatitis B (positive surface antigen), alcohol-related liver disease (alcohol intake >40 g/day for ≥10 years), nonalcoholic steatohepatitis (negative work-up for other etiologies in the presence of the metabolic syndrome), and others/unknown, was noted.
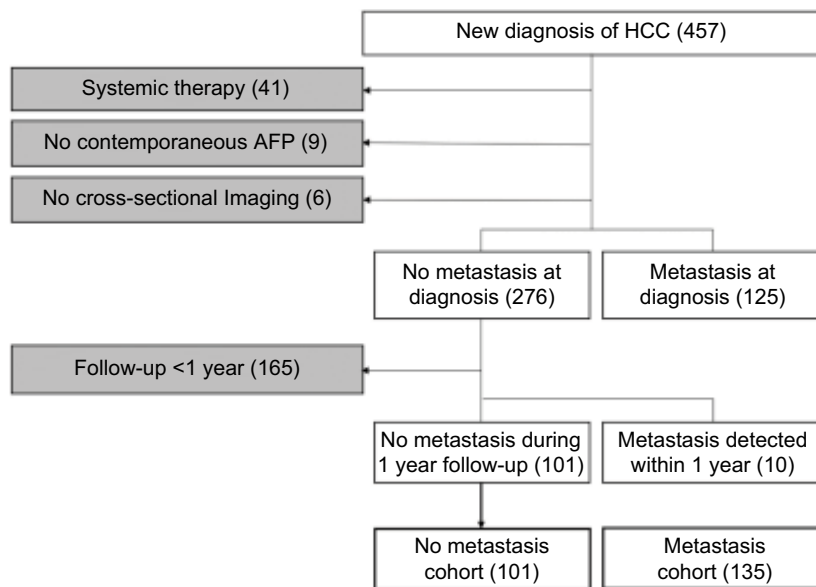
Figure 1 Flowchart of inclusion and exclusion criteria (white and gray, respectively) with the number of subjects meeting each criterion in parentheses.
Abbreviation: HCC, hepatocellular carcinoma.

A database was constructed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), which recorded tumor size, number, AFP, infiltration, and vascular invasion status, as well as the metastasis status (met vs no-met).

Metastasis risk criteria

Various staging parameters were considered as candidate metastasis risk factors and included AFP, tumor size, number, vascular invasion, and infiltrative morphology. These parameters were primarily derived from the following HCC staging systems: American Joint Commission on Cancer TNM system,[25] Barcelona Clinic Liver Cancer system,[26] Cancer of the Liver Italian Program score,[27] and Chinese University Prognostic Index.[28] Although not strictly a staging system, the Milan criteria for liver transplant eligibility[12] was also considered. Okuda et al[29] and Japan integrated staging score[30] were not considered separately, as the former did not include absolute size threshold and the latter used the TNM system for local staging. Although infiltrative morphology is not a part of any existing staging system, its metastasis risk was evaluated as it is associated with poor prognosis.[32,33] The continuous variables (ie, AFP, index tumor size, and number of tumors) were stratified into discrete intervals (ie, interval data) according to the threshold values used in different staging systems as follows: AFP intervals 0–35, 35–400, and >400 µg/mL; index tumor size 0–3, 3–5, and >5 cm; and number of tumors 1, 2–3, and >3. Bivariate variables (vascular invasion and infiltrative morphology) were treated as categorical data.

Statistical analysis

Statistical analyses were performed using R Version 3.3.1.[34] Summary statistics was calculated for demographic and clinical data, and the differences between the no-met and met cohorts were assessed using Mann–Whitney U test for continuous data and chi-square test for categorical data. Multivariate logistic regression was performed to identify statistically significant independent risk factors of metastasis. Rather than constructing a computationally demanding regression model, however, we considered a series of simple single- or multiparametric criteria based on previously proposed threshold values. This approach is conceptually analogous to the Milan criteria,[12] which incorporates several parameters (tumor size, number, vascular invasion, and extrahepatic metastasis) into a single decision-rule using logical (union or intersection) operations. For each single- and multiparametric risk criteria, the association with metastasis was assessed by constructing the standard 2×2 contingency table and calculating the odds ratio (OR) with 95% confidence intervals (CIs). Treating the risk criteria as a diagnostic test, the sensitivity, specificity, accuracy, and positive and negative predictive values were also calculated with their respective 95% CIs. The metastasis sensitivity between the single- and multiparametric criteria was compared using exact binomial test using R's Diagnostic Test Comparison for Paired Study Design package (DTComPair). P-values <0.05 were considered statistically significant, after Benjamini–Hotchberg adjustment for multiple testing when appropriate.[35]

Results

Patient population

The summary statistics of the study population (n=236) is summarized in Table 1, including the demographics, clinical data, and the tumor staging parameters. There was no significant difference in the patient age, sex, race, or liver disease etiology between the met and no-met cohorts. Patients with metastases tended to have more advanced cirrhosis (CPT stage B or C). All tumor staging parameters were significantly worse in the met cohort than in the no-met cohort, with greater AFP values and index tumor size, as well as multifocal disease, vascular invasion, and infiltrative tumor being more frequent. As expected, liver-directed HCC treatment was more common in the no-met cohort.

Single-parametric criteria

The metastasis risk of each staging parameter is summarized in Table 2. All staging parameters were associated with metastasis with variable strength, with ORs ranging 2.9–18.9. Multifocality had the weakest and vascular invasion had the strongest association with metastasis. The criteria with greatest sensitivity for extrahepatic metastasis were index tumor size >3 cm (91.9%), Milan size criteria (85.9%), and AFP >35 µg/mL (82.2%). Criteria with greatest specificities were infiltrative tumor (98.0%), number of tumors >3 (95.0%), and vascular invasion (93.1%).

Logistic regression

Multivariate logistic regression results are summarized in Table 3. Milan size criteria were excluded from this analysis

Table 1 Demographic and clinical data

Patient characteristics	Total	No met	Met	P
Demographics				
Number of patients	236 (100%)	101 (42.8%)	135 (57.2%)	
Median age (range) (years)	57 (28–89)	55 (37–79)	58 (28–89)	0.084
Sex (male/female)	183/53	76/25	107/28	0.500
Race				
Caucasian	61	27	34	0.645
Black	89	34	55	
Hispanic	69	31	38	
Others	17	9	8	
Etiology of liver disease				
HCV	163	71	92	0.678
HBV	25	8	17	
Alcohol	28	12	16	
NASH	13	7	6	
Others/cryptogenic	13	4	9	
Child-Turcotte-Pugh stage				
A	99	56	43	0.001
B	93	32	61	
C	43	12	31	
Unknown	1	1	0	
Tumor staging parameters				
AFP median (IQR)	148 (12–4116)	14 (5–81)	1,725 (113–18,104)	<0.001
Index tumor size (IQR) (cm)	5.0 (2.9–10.0)	2.9 (2.0–4.2)	8.7 (5.4–14.0)	<0.001
Single/multiple	140/96	74/27	66/69	<0.001
Vascular invasion (–/+)	150/86	94/7	56/79	<0.001
Infiltrative tumor (–/+)	208/28	99/2	109/26	<0.001
Loco-regional therapy				
Treatment (yes/no)	104/132	78/23	26/109	<0.001
Liver transplantation	4	4	0	
Chemoembolization	66	56	10	
Thermal ablation	13	12	1	
Surgical resection	22	20	2	
Radioembolization	6	1	5	

Notes: No met, patients with no documented metastasis within 12 months of follow-up; Met, patients with synchronous or metachronous metastasis within 12 months of follow-up. Etiology – others, cryptogenic cirrhosis (N=8) and Wilson's disease (N=1). (–/+) indicates feature absent/present.
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NASH, nonalcoholic steatohepatitis

Table 2 Single-parametric criteria for metastasis

Criteria	Threshold	Odds ratio	Sensitivity	Specificity	Accuracy	PPV	NPV
AFP (µg/mL)	>35	8.0 (4.4–14.5)	82.2 (76.8–86.6)	63.4 (57.0–69.3)	74.2 (68.2–79.4)	75.0 (69.0–80.2)	72.7 (66.7–78.1)
	>400	11.5 (5.9–22.1)	66.7 (60.4–72.4)	85.1 (78.0–89.2)	74.6 (68.6–79.8)	85.7 (80.6–89.7)	65.6 (59.3–71.5)
Index tumor size (cm)	>3	15.8 (7.6–32.9)	91.9 (87.6–94.8)	58.4 (52.0–64.6)	77.5 (71.7–82.5)	74.7 (68.7–79.9)	84.3 (79.0–88.4)
	>5	17.7 (9.0–34.8)	75.6 (69.6–80.7)	85.1 (78.0–89.2)	79.7 (74.0–84.4)	87.2 (82.2–90.9)	72.3 (66.2–77.6)
Number of tumors	>1	2.9 (1.6–5.0)	51.1 (44.7–57.5)	73.3 (67.2–78.6)	60.6 (54.2–66.7)	71.9 (65.8–77.3)	52.9 (46.4–59.2)
	>3	12.0 (4.6–31.5)	38.5 (32.5–44.9)	95.0 (91.4–97.3)	62.7 (56.3–68.7)	91.2 (86.8–94.3)	53.6 (47.2–59.9)
Milan size criteria	a	16.7 (8.7–32.2)	85.9 (80.8–89.9)	73.3 (67.2–78.6)	80.5 (74.9–85.1)	81.1 (75.6–85.7)	79.6 (73.9–84.3)
Vascular invasion	–	18.9 (8.2–43.9)	58.5 (52.1–64.7)	93.1 (89.0–95.8)	73.3 (67.3–78.6)	91.9 (87.6–94.8)	62.7 (56.3–68.7)
Infiltrative tumor	–	11.8 (2.7–51.0)	19.3 (14.7–24.8)	98.0 (95.2–99.3)	53.0 (46.6–59.3)	92.9 (88.7–95.6)	47.6 (41.3–54.0)

Notes: Data in parentheses are Wilson's 95% confidence interval. [a]Milan size criteria: one tumor <5 cm or up to three tumors <3 cm with no extrahepatic disease or vascular invasion.
Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

Table 3 Tumor staging parameters and multivariate logistic regression

Risk factor	Categories	# patients	Odds ratio (95% CI)	Unadj P-value	Adj P-value
α-Fetoprotein (µg/mL)	<35	88 (37.3%)	2.41 (1.52–3.80)	0.0002	0.0008
	35–400	43 (18.2%)			
	>400	105 (44.5%)			
Index tumor size (cm)	<3	70 (29.7%)	4.11 (2.54–6.65)	<0.0001	<0.0001
	3–5	49 (20.8%)			
	>5	117 (49.6%)			
Number of tumors	1	140 (59.3%)	1.82 (1.03–2.98)	0.0378	0.1111
	2–3	39 (16.5%)			
	>3	57 (24.1%)			
Vascular invasion	Absent	150 (63.6%)	5.90 (2.04–17.04)	0.0011	0.0039
	Present	86 (36.4%)			
Infiltrative morphology[a]	Absent	208 (88.1%)	3.56 (0.36–17.31)	0.3529	0.8646
	Present	28 (11.9%)			

Notes: [a]Although infiltrative morphology is not a part of existing staging system, its metastasis risk was evaluated as it is a marker of poor prognosis. The P-values were adjusted using the Benjamini–Hochberg method for multiple comparisons.
Abbreviations: CI, confidence interval; Unadj, unadjusted; Adj, adjusted.

for its obvious correlation (by design) with tumor size and number. After correction for covariates, the following risk factors were independently associated with metastasis: AFP level, index tumor size, and presence of vascular invasion, all with adjusted *P*-values <0.05. No significance was detected for the number of tumor nodules and infiltrative morphology, after correcting for effects of AFP, tumor size, and vascular invasion.

Multiparametric criteria

Of all possible logical combination of the independent risk factors (AFP, tumor size, and vascular invasion), only those that would improve sensitivity by "union" operations (to be used as metastasis screening test) were analyzed and results are shown in Table 4. Other logical combinations of risk factors, or other choices of threshold values and ranges, were not exhaustively considered to control the total number of simultaneous tests and associated penalty on the adjusted *P*-values. All combination criteria of AFP, size, and vascular

invasion performed well with high sensitivities ranging from 86.7 to 98.5% for the detection of extrahepatic metastasis, with variable specificities and ORs. Multiparametric criteria including "Milan size or vascular invasion or AFP >35 µg/ mL" had the highest sensitivity and OR of 98.5% and 55.6, respectively. The sensitivity of this multiparametric criteria was significantly better (*P*<0.001) than those of Milan size criteria, vascular invasion, or AFP >35 µg/mL alone as single-parametric criteria. Therefore, for patients determined to be within the Milan criteria based on imaging, the presence of extrahepatic metastatic disease is virtually excluded if AFP is also <35 µg/mL.

Comparison of criteria

The exact binomial test *P*-values for the differences in diagnostic sensitivity between the single-, two-, and three-parametric criteria are shown in Table 5. Depending on the tumor size parameter (>3 cm, >5 cm, or Milan size criteria), two-parametric criteria with combination of size parameter

Table 4 Multiparametric criteria for metastasis

Criteria	Threshold	Odds ratio	Sensitivity	Specificity	Accuracy	PPV	NPV
Index tumor >3 cm or VI	–	23.7 (10.1–55.8)	94.8 (91.1–97.1)	56.4 (50.0–62.7)	78.4 (72.6–83.2)	74.4 (68.4–79.6)	89.1 (84.4–92.5)
Index tumor >5 cm or VI	–	26.3 (13.1–52.9)	86.7 (81.7–90.5)	80.2 (74.6–84.8)	83.9 (78.6–88.1)	85.4 (80.3–89.4)	81.8 (76.3–86.3)
Milan size criteria[a] or VI	–	25.5 (12.1–53.8)	91.9 (87.6–94.8)	69.3 (63.1–74.9)	82.2 (76.8–86.6)	80.0 (74.4–84.7))	86.4 (81.4–90.3)
Index tumor >3 cm or AFP	>35	19.8 (6.8–57.8)	97.0 (93.9–98.7)	37.6 (31.6–44.0)	71.6 (65.5–77.0)	67.5 (61.3–73.2)	90.5 (86.0–93.7)
	>400	23.7 (9.5–58.8)	95.6 (92.0–97.7)	52.5 (46.1–58.8)	77.1 (71.3–82.1)	72.9 (66.8–78.2)	89.8 (85.2–93.2)
Index tumor >5 cm or AFP	>35	19.8 (8.7–44.6)	94.1 (90.2–96.5)	55.4 (49.2–61.7)	77.5 (71.7–82.5)	73.8 (67.8–79.1)	87.5 (82.6–91.2)
	>400	26.3 (12.9–53.7)	89.6 (85.0–93.0)	75.3 (69.3–80.4)	83.5 (78.1–87.7)	82.9 (77.5–87.2)	84.4 (79.2–88.6)
Milan size criteria[a] or AFP	>35	41.5 (12.4–138.9)	97.8 (94.8–99.2)	48.5 (42.3–54.9)	76.7 (70.8–81.7)	71.7 (65.6–77.2)	94.2 (90.4–96.7)
	>400	25.3 (11.5–55.7)	93.3 (89.3–96.0)	64.4 (58.0–70.2)	80.9 (75.4–85.5)	77.8 (72.0–82.7)	87.8 (88.0–91.5)
Index tumor >3 cm or VI or AFP	>35	24.4 (7.2–82.1)	97.8 (94.8–99.2)	35.6 (29.8–42.0)	71.2 (65.0–76.6)	67.0 (60.7–72.7)	92.3 (88.1–95.2)
	>400	33.4 (11.5–97.2)	97.0 (93.9–98.7)	50.5 (44.1–56.9)	77.1 (71.3–82.1)	72.4 (66.3–77.7)	92.7 (88.6–95.5)
Index tumor >5 cm or VI or AFP	>35	27.6 (10.4–73.1)	96.3 (92.9–98.2)	51.5 (45.1–57.8)	77.1 (71.3–82.1)	72.6 (66.6–78.0)	91.2 (86.8–94.3)
	>400	34.8 (15.6–77.5)	93.3 (89.3–96.0)	71.3 (65.2–76.7)	83.9 (78.6–88.1)	81.3 (75.8–85.8)	88.9 (84.2–92.4)
Milan size criteria[a] or VI or AFP	>35	55.6 (13.0–237.1)	98.5 (95.8–99.6)	45.5 (39.3–52.0)	75.8 (69.9–80.9)	70.7 (64.6–76.2)	95.8 (92.3–97.9)
	>400	34.2 (13.7–85.0)	95.6 (92.0–97.7)	61.4 (55.0–67.4)	80.9 (75.4–85.5)	76.8 (70.9–81.8)	91.2 (86.8–94.3)

Notes: [a]Milan size criteria: one tumor <5 cm or up to three tumors <3 cm with no extrahepatic disease or vascular invasion. Data in parentheses are 95% CIs.
Abbreviations: NPV, negative predictive value; PPV, positive predictive value; VI, vascular invasion.

and either AFP >35 µg/mL or vascular invasion performed significantly better, and three-parametric criteria with combination of all size parameter, AFP >35 µg/mL, and vascular invasion performed significantly better than two-parametric criteria.

Discussion

In patients with new diagnosis of HCC, extrahepatic metastasis can profoundly impact treatment options and prognosis. Determination of metastasis risk using readily available imaging and serum AFP data may facilitate timely management decision-making, including the need for exhaustive metastasis workup. Furthermore, correct risk stratification of these patients may help avoid unnecessary morbidity and cost associated to loco-regional therapy. The purpose of this retrospective study in patients with new diagnosis of HCC was to validate the association between tumor staging parameters and synchronous/metachronous metastases, ultimately to enable rapid metastasis risk stratification based on imaging findings in conjunction with AFP.

Among the staging parameters in existing HCC staging systems, we found that index tumor size, vascular invasion, and AFP are independently associated with metastasis. Logical combinations of these parameters tended to be more strongly associated with metastases, often with significantly higher sensitivity for metastasis detection. In particular, the combination of Milan size criteria, vascular invasion, and AFP >35 µg/ml had the highest OR, sensitivity, and negative predictive values; in those patients in whom these criteria were simultaneously negative, metastasis was exceedingly rare.

The current National Comprehensive Cancer Network (NCCN, Version 2.2016) recommendation for confirmed HCC cases includes a chest CT and optional whole-body bone scintigraphy for metastatic workup.[36] Utility of whole-body PET imaging has been investigated,[37,38] but its use as routine metastasis workup tool remains controversial. Up to 26/109 (24%) of our patients in the met cohort received loco-regional therapy, illustrating the difficulty of predicting extrahepatic metastasis at initial diagnosis with current staging approaches. Our study suggests that only a subset of patients with HCC is higher risk for metastasis who may require formal metastasis workup. Metastasis risk may be easily assessed based multiphasic liver CT or MRI findings in conjunction with serum AFP. In low-risk patients, it may be reasonable to refer immediately to liver-directed therapy, thereby shortening time to therapy and saving cost of additional imaging studies. In our study population, for

Table 5 Pairwise sensitivity comparison *P*-values between single-, two-, and three-parametric criteria

Metastasis prediction criteria	Index tumor >3 cm or VI	Index tumor >3 cm or AFP >35 μg/mL	Index tumor >3 cm or VI or AFP >35 μg/mL
Index tumor >3 cm	0.1250 (0.1500)	0.0156 (0.0312)	0.0078 (0.0234)
Index tumor >3 cm or VI	–	0.3750 (0.3750)	0.1250 (0.1500)
Index tumor >3 cm or AFP >35 mg/mL	–	–	0.0074 (0.0234)
	Index tumor >5 cm or VI	Index tumor >5 cm or AFP >35 μg/mL	Index tumor >5 cm or VI or AFP >35 μg/mL
Index tumor >5 cm	<0.0001 (<0.0001)	<0.0001 (<0.0001)	<0.0001 (<0.0001)
Index tumor >5 cm or VI	–	0.0210 (0.0252)	0.0002 (0.0003)
Index tumor >5 cm or AFP >35 mg/mL	–	–	0.2500 (0.2500)
	Milan size criteria or VI	Milan size criteria or AFP >35 μg/mL	Milan size criteria or VI or AFP >35 μg/mL
Milan size criteria	0.0078 (0.0094)	<0.0001 (<0.0001)	<0.0001 (<0.0001)
Milan size criteria or VI	–	0.0215 (0.0215)	0.0039 (0.0078)
Milan size criteria or AFP >35 mg/mL	–	–	0.0074 (0.0095)

Note: Values within parentheses indicate Benjamini–Hochberg adjusted *P*-values for multiple comparisons.
Abbreviation: VI, vascular invasion.

example, the total cost saving would have been $21,000 in MEDICARE US dollars (or ~$90/patient), assuming the standard metastasis workup consisting of chest CT without contrast and whole body bone scan. Patients otherwise not meeting the low-risk criteria may benefit from comprehensive metastasis workup, and any extrahepatic abnormality found on imaging should be scrutinized with high suspicion of metastatic disease, especially those with high AFP >400 μg/mL, vascular invasion, multifocal, or infiltrative tumor(s), due to their moderate to high specificity for metastases.

Due to retrospective design, this study has several limitations. First, patient assignment into the no-met cohort was based on 12-month metastasis-free survival. This requirement was necessary because patients did not undergo uniform metastasis workup; the decision to obtain chest CT, bone scintigraphy, or PET in addition to routine chest radiograph was made at the discretion of the treatment provider, as per NCCN guideline at the time of their clinical care.[39] As this may have led to under-detection of subclinical metastases at initial diagnosis (ie, verification bias), we extended 12 months of clinical and/or imaging observation to allow initially undetected metastasis to declare itself over time. However, this requirement resulted in exclusion of ~1/3 of the potentially eligible patients who were lost during follow-up. Therefore, patients with very aggressive tumors or decompensated cirrhosis may have been underrepresented, as they were not likely to have survived long enough to meet the inclusion/exclusion criteria. Second, the potential therapy effect on metastasis development and detection could not be completely addressed. Patients already receiving systemic therapy at the time of diagnosis were excluded to prevent the confounding effect of systemic therapy on metastases. Majority of the no-met cohort and minority of the met cohort underwent liver-directed therapy. While complete response after such loco-regional therapy likely would not affect the evolution of extrahepatic metastases, partial, stable, or progressive disease could potentially pose additional risk of subsequent metastasis development. However, we believe that this was only a minor concern, since the majority of the met cohort had metastatic disease before initiation of therapy (125 out of 135 in met cohorts), and the possible confounding effect by treatment outcome is expected to be small. This study did not investigate cirrhosis as a risk factor of metastasis. The data on cirrhosis were incomplete, because determination of the cirrhosis status using a reference standard method (random liver biopsy; no serum markers or elastography techniques were available at the time of this study) was often not needed for clinical care. The HCC patient population at this public safety-net hospital has been overwhelmingly (>95%) those with known or suspected cirrhosis, and therefore, this population would not have allowed meaningful sub-analysis, even if the cirrhosis data were available. Finally, this study was conducted in a public safety-net hospital in a large metropolitan area, where patients could present with more advanced HCC in theory compared to insured population undergoing routine HCC surveillance.[40,41] The rate of metastatic disease in this population, however, was similar to previous reports.[8,9] Also, estimates of the OR, sensitivity, and specificity are independent of disease prevalence and hence our results may be generalizable to other patient populations. Our population was composed entirely of cirrhotic patients, most due to chronic hepatitis C infection; this may influence

the frequency of metastasis and AFP threshold level.[42–45] Due to these limitations, the metastasis screening criteria need to be further validated prospectively in an independently sampled population.

Conclusion

This retrospective study validated that tumor staging parameters are associated with metastasis risk in patients with new diagnosis of HCC. Patients with low metastasis risk may be identified based on AFP, tumor size, and absence of vascular invasion. In these patients, comprehensive metastasis workup may not be needed, thereby facilitating timely delivery of treatment and eliminating cost for further diagnostic imaging studies.

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Disclosure

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