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Implications of Discordant Findings Between Hepatic Angiography and Cross-Sectional Imaging in Transplant Candidates With Hepatocellular Carcinoma

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Abstract

The goal of this study was to determine whether the detection of discordant numbers of hypervascular foci at hepatic angiography versus contrast-enhanced (CE) cross-sectional imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] is associated with adverse clinical outcomes in patients with hepatocellular carcinoma (HCC) who are listed for liver transplantation. We retrospectively reviewed the records of 218 consecutive patients with HCC who were listed for a liver transplant and who underwent transarterial chemoembolization at our institution between January 1, 2006 and December 31, 2010. Patients were grouped into 3 categories: (1) the number of nodules at CT/MRI was concordant with the number of hypervascular foci detected at angiography (n = 136), (2) the number of nodules at CT/MRI was greater than the number of hypervascular foci at angiography (n = 45), and (3) the number of nodules at CT/MRI was fewer than the number of hypervascular foci at angiography (n = 37). The study outcomes were liver transplantation and tumor recurrence after transplantation. The detection of at least 3 more hypervascular foci at angiography versus the number of HCC nodules on CT/MRI was associated with a significantly lower rate of transplantation [multivariate subhazard ratio (SHR), 0.39; 95% confidence interval (CI), 0.17–0.92]. The detection of fewer hypervascular foci at angiography versus the number of HCC nodules on CT/MRI was associated with a significantly higher rate of tumor recurrence after transplantation (multivariate SHR, 3.49; 95% CI, 1.27–9.56). In conclusion, liver transplant candidates with HCC who demonstrate discordant findings between angiography and CE CT or MRI may be at a higher risk for dropout from the transplant list and for tumor recurrence after transplantation.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide.[1] Treatment options depend on the tumor stage and liver function.[2] Resection,

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thermal ablation, and liver transplantation are the only potentially curative options.[3] Candidacy for transplantation is based on the Milan criteria [1 lesion ≤5 cm or 2 to 3 lesions ≤3 cm in diameter without macrovascular invasion as determined by multiphase contrast-enhanced (CE) computed tomography (CT) or magnetic resonance imaging (MRI)].[4] Liver-directed therapy, such as transarterial chemoembolization (TACE) and thermal ablation, is offered to patients with unresectable HCC confined to the liver as a bridge to transplantation.[5,6] Local and distal tumor recurrences as well as the presence of a residual disease after liver-directed therapy are common and are among the causes of dropout from the transplant list and high mortality.[7,8] Therefore, identifying and treating recurrent lesions is imperative for maintaining patients' eligibility while they are awaiting transplantation.[5]

The diagnosis of HCC is often based on a characteristic tumor appearance on CE CT or MRI. Tissue diagnosis is usually not required.[3,9] Because CE CT and MRI scans reliably detect only HCC nodules larger than 1 cm and may underestimate the tumor stage,[10,11] an alternative diagnostic imaging tool that can detect additional lesions may improve clinical outcomes.[12] One diagnostic tool that is already employed for some patients with HCC is hepatic digital subtraction angiography (DSA), which is performed in conjunction with arterial therapies used to treat HCC. The sensitivity of DSA for HCC detection has been reported to be in the range of 55% to 77%[13–15] and is better for larger HCC lesions.[16] The sensitivity of CE CT and MRI for HCC detection has been described to be in the 65% to 84%[10,11,14,15] and 62% to 76% ranges,[10,11,14] respectively. In comparison, the sensitivity for the demonstration of ethiodized oil (lipiodol) uptake after TACE in HCC lesions on plain post-TACE radiographs has been reported at 94%,[17] whereas the sensitivity of postlipiodol CT for the detection of hypervascular HCC lesions treated with TACE may approach 100%.[18]

Angiographic images sometimes demonstrate hypervascular foci in the liver that outnumber the lesions detected by CE CT or MRI.[19] Conversely, sometimes there is no angiographic correlate to hypervascular lesions detected on cross-sectional imaging. The clinical significance of these "discordant" findings is unclear. The purpose of this study was to retrospectively review and correlate findings during hepatic DSA obtained at the time of TACE with preceding CE CT and/or MRI in patients with HCC listed for liver transplantation in order to identify patients with discordant lesions and to determine whether the presence of such lesions led to adverse clinical outcomes, such as removal from the transplant list and post-transplant tumor recurrence.

PATIENTS AND METHODS

This retrospective single-center study was approved by the committee on human research of the institutional review board at our institution. The study was deemed compliant with the Health Insurance Portability and Accountability Act. The informed consent requirement was waived.

Patient Population

All patients who were placed on a waiting list for a liver transplant at our institution were identified via access to a prospectively maintained database of liver transplant candidates.

Information included in this database consisted of each subject's name, medical record numbers, listing date, liver disease etiology, birth date, ethnicity, United Network for Organ Sharing (UNOS) tumor-node-metastasis (TNM) HCC tumor stage at listing,[20] Child-Turcotte-Pugh (CTP) score at listing, and Model for End-Stage Liver Disease (MELD) score at listing.

The transplant database was cross-referenced with a list of all patients (age >18 years) who underwent TACE for HCC at our institution between January 1, 2006 and December 31, 2010. The diagnosis of HCC was established by tissue sampling or by multiphase CE CT or MRI in accordance with the American Association for the Study of Liver Diseases (AASLD) imaging guidelines.[3,9] For study purposes, patients with at least 1 hypervascular lesion on the arterial phase measuring at least 1 cm in diameter that demonstrated washout on a delayed phase were included. We adhered to the 2009 AASLD guidelines when cross-sectional studies were interpreted for study purposes. Patients with only hypovascular lesions at CE CT or MRI suspicious for HCC were excluded (not candidates for TACE). In addition, 4 patients with hypervascular lesions were excluded from analysis for the following reasons: 3 patients were transferred to other transplant centers and their clinical outcomes could not be assessed, while 1 patient's angiography data was not available for review and thus agreement between cross-sectional imaging and angiography could not be assessed. A total of 218 patients were included in the study. Demographic data are included in Table 1.

TACE Technique

TACE was performed after patients provided written informed consent. A 5-Fr catheter was inserted into the common femoral artery, and an angiographic survey of the celiac and superior mesenteric arteries was performed. DSA was then performed in at least 2 obliquities after catheterization of the common hepatic artery. On the basis of the findings on the common hepatic arteriogram, lobar right and/or left hepatic artery angiography and subselective angiography were then performed in order to identify the arterial supply to hypervascular tumors before TACE was performed. Rates of injection varied from 3 to 5 mL/second in the common hepatic arteries and from 1 to 3 mL/second in lobar hepatic arteries. Each injection was at least 5 seconds in duration. Angiography in the common, proper, and lobar hepatic arteries was performed via a power injector through a power-injectable angiographic catheter. Access to cone-beam CT was not available to the investigators during the study period. All angiographic images were sent to a picture archiving and communication system (PACS). Vessels supplying 1 or 2 hepatic segments were selected with a coaxially placed microcatheter (Renegade HI-FLO; Boston Scientific, Natick, MA). Chemoembolization was performed with an emulsion of 25 mg of doxorubicin hydrochloride, 10 mg of mitomycin C, 50 mg of cisplatin suspended in 10 mL of iodinated contrast (Omnipaque-350; GE Healthcare, Little Chalfont, United Kingdom), and 10 mL of ethiodized oil (Ethiodol; Savage Laboratories, Melville, NY). The administered doses of chemotherapy agents were adjusted in patients with liver or renal dysfunction, leukopenia, and thrombocytopenia. The administration of chemotherapy and Ethiodol emulsion was performed to stasis. If stasis was not achieved, additional embolization with a slurry of gelatin sponge (Gelfoam; Pharmacia-Upjohn, Kalamazoo, MI) until stasis was performed.

CT and MRI Technique

CT examinations were performed with a 16-detector row scanner (LightSpeed LX; GE Medical Systems, Milwaukee, WI). The abdomen was imaged from the dome of the diaphragm to the iliac crests. The contrast used was 150 mL of iohexol (Omnipaque-350; GE Healthcare, Princeton, NJ) injected intravenously through a power injector at a rate of 4 to 5 mL/second. Multiphase CE CT included contiguous unenhanced images with a 5-mm collimation followed by late arterial images with a 35-second delay and 2.5-mm collimation, portal venous phase images with a 70-second delay and 2.5-mm collimation, and delayed images with a 5-minute delay and 2.5-mm collimation.

MRI examinations were performed on 1.5-T magnets (Optima MR360; GE Medical Systems, Milwaukee, WI). Typical imaging sequences covering the abdomen included a 3-plane localizer, axial in- and out-of-phase fast gradient echo T1, coronal single-shot fast spin-echo T2, axial fat-suppressed fast recovery fast spin-echo T2, and axial 3D spoiled gradient echo (3-mm slice thickness, 0-mm space) performed before and after the intravenous administration of gadopentetate dimeglumine at 1 mL/4.5 kg of body weight (Magnevist; Bayer Schering Pharma, Pittsburgh, PA) through a power injector at the rate of 2 mL/second followed by a 30-mL normal saline injection. Dynamic postcontrast axial gradient-echo sequence acquisition was performed 5 times in the arterial, portal venous, and delayed phases of imaging for up to 5 minutes after contrast administration.

Review of Imaging Studies

Electronic medical records (EMRs) of all study subjects were retrospectively reviewed, and the dates of all TACE procedures were determined. Dates of CE cross-sectional imaging studies (CT/MRI) performed before and after each TACE procedure were identified as well. A total of 186 patients were imaged with CT, whereas 32 patients were imaged with MRI. Images and study reports for TACE procedures as well as preceding and subsequent CT/MRI examinations were reviewed by consensus with our institution's PACS by 2 researchers (N.F. and K.Y.) with 9 and 2 years, respectively, of experience with the interpretation of hepatic arteriograms and abdominal CT/MRI studies. Cross-sectional studies and angiograms were reviewed during the same session. A total of 376 CT/MRI and angiogram pairs were reviewed. A median of 1 angiogram and CT/MRI pair was reviewed for each patient (range, 1–4). Patients had a median of 1 TACE procedure after each CT/MRI (range, 1–3). The median total number of TACE procedures per patient was 2 (range, 1–5). The median time interval between cross-sectional imaging and TACE was 31 days (range, 1–63 days), whereas the median time interval between TACE and a subsequent follow-up cross-sectional imaging test was 31 days (range, 21–48 days). Liver lesions that met the following cross-sectional imaging characteristics were considered suspicious for HCC: (1) at least 10 mm in greatest diameter and (2) hypervascular on the arterial phase of cross-sectional imaging and demonstrated washout on the delayed phases of imaging or (3) hypervascular on the arterial phase of cross-sectional imaging and demonstrated interval growth between 2 cross-sectional imaging studies obtained at least 2 months apart. On angiography, only lesions suspicious for HCC (round or ovoid lesions that retained contrast, whereas arterial contrast washed out) were counted. Hypervascular foci with a typical

appearance of an arterial-portal venous shunt (wedge-shaped lesions with portal venous shunting) were not counted.

Findings at angiography and CT/MRI were classified as concordant if the number and location (hepatic lobe or segment) of the lesions seen on angiography and cross-sectional imaging matched between the angiogram and the preceding cross-sectional study. Findings were categorized as discordant if either (1) angiography demonstrated more hypervascular foci than the number of suspicious nodules identified on pre-TACE and post-TACE cross-sectional studies or (2) angiography demonstrated fewer hypervascular foci than the number of suspicious lesions identified on both pre-TACE and post-TACE cross-sectional studies.

For the purpose of statistical analysis, each patient was placed into 1 of 3 categories based on the concordance of angiography and imaging findings: (1) concordant findings at cross-sectional imaging and angiography, (2) discordant findings with more hypervascular suspicious nodules identified at cross-sectional imaging versus angiography, or (3) discordant findings with more hypervascular foci detected by angiography than the corresponding number of hypervascular lesions on CT/MRI. Patients who had more than 1 matched angiogram and cross-sectional study set were placed in the concordant category if none of the matched imaging study sets demonstrated discordance. Conversely, if at least 1 imaging set contained discordant findings, the patient was placed in the corresponding group of patients with discordant findings. None of the patients studied had conflicting discordant findings in the imaging sets (1 set showing more hypervascular foci on angiography versus CT/ MRI and another set showing fewer hypervascular foci on angiography versus CT/MRI for a given patient).

Review of Clinical Information

Clinical information was derived from each patient's EMR. This information included patient demographics (age, sex, and ethnicity), etiology of liver disease, serum alpha-fetoprotein (AFP), and clinical findings regarding ascites and encephalopathy. HCC tumor staging was based on UNOS TNM guidelines. Information on the UNOS TNM stage at the time of listing was obtained from the prospectively maintained database of liver transplant candidates at our institution. Information on the UNOS TNM stage of patients on the transplant list was based on a review of the number and size of lesions present at cross-sectional imaging. Data regarding transplantation outcomes (dates of transplantation or removal from the transplant list, reason for removal from the transplant list, and presence or absence of HCC recurrence after transplant) were derived from the EMRs. Information on patient survival was obtained from EMRs and from the Social Security Death Index. Survival data were collected on the study censor date of July 1, 2014.

Correlation With Histopathology

All explanted livers were processed according to routine clinical protocol, with the freshly explanted livers sliced serially at 10-mm intervals. Macroscopically visible neoplastic nodules were evaluated with microscopy after hematoxylin and eosin staining. The percentage of necrosis was defined as the volume of necrotic areas divided by the total tumor volume and was classified into 1 of the following ranges: <30%, 30% to 60%, 61% to

90%, 91% to 99%, and 100%. The longest diameter of viable tumor component was reported as well.

All pathology reports were retrospectively reviewed to extract data on the tumor type [HCC, cholangiocarcinoma (CC) and mixed histology hepatocellular-cholangiocarcinoma (HCC-CC)], the longest diameter of viable and nonviable components, the presence of lymphovascular invasion, extrahepatic metastases (if incidentally detected intraoperatively) or extracapsular extension, tumor location, and Edmondson-Steiner tumor grade.[21] The pathologic stage in explants was reported on the basis of the UNOS TNM staging system.[20]

Study Outcomes and Statistical Analysis

Data were analyzed with respect to the following 2 clinical outcomes: time to transplantation and time to tumor recurrence after transplantation. In addition, the histopathologic outcome of a high viable tumor burden was studied only for patients who received a transplant. A high viable tumor burden was defined as pathologic UNOS T3 or T4 stage[20] or the presence of metastatic disease at explant. The main predictor tested was discordance between angiography and cross-sectional imaging findings with respect to the number of identified suspicious hypervascular lesions at CT/MRI and hypervascular foci at angiography. Groups of patients with either more hypervascular foci detected at angiography or more suspicious lesions seen at CT/MRI were analyzed with reference to patients with concordant findings between angiography and cross-sectional imaging. Groups of patients with discordant imaging findings were further subdivided by the difference in the number of detected lesions (1 or 2 lesions versus 3 or more lesions).

Competing risk regression models were used to evaluate the association of each of the 2 clinical outcomes with respect to the main predictor variables with univariate and multivariate analyses. Logistic regression analysis was used for the histopathologic outcome. The following additional variables were tested in the multivariate analysis: (1) continuous variables [age (in years), CTP score at listing, MELD score at listing, and maximum observed AFP level (ng/mL) on the transplant list], (2) binary variables [sex, presence or absence of hepatitis C virus (HCV) infection, and CTP score <9 versus ≥9], and (3) categorical variables [ethnicity, etiology of liver disease, UNOS TNM stage at listing, highest observed UNOS TNM stage on the list, latest available UNOS TNM stage based on a CE CT or MRI scan before transplantation (for transplant recipients) or the last available scan (for nontransplant patients), Child-Pugh class, MELD score (<10 versus 10–14 versus 15–19 versus ≥20), and maximum serum AFP level on the transplant list (<200 versus 200–500 versus >500 ng/mL).

For the outcome of time to transplantation (n = 152), competing events were defined as removal from the transplant list due to HCC progression (n = 33) and death due to hepatic decompensation on the transplant list (n = 9). Patients who remained active on the wait list (n= 3) and those removed from the transplant list for reasons other than HCC progression and liver function decompensation (n= 21) were censored. For the outcome of tumor recurrence after transplantation (n = 16), the competing event was defined as death due to a cause other than tumor recurrence after transplantation (n= 22). Patients without tumor recurrence who were alive on the censor date of July 1, 2014 (n= 114) were censored.

Competing risk analyses were performed with STATA 13 (StataCorp LP, College Station, TX). Logistic regression analyses were performed with SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Population

Demographic data are summarized in Table 1. A total of 218 adult patients (median age at the time of listing, 57 years; range, 21–77; 172 males and 46 females) with hypervascular lesions diagnosed as HCC on the basis of histopathology (14 patients) or AASLD imaging guidelines (204 patients) were included. Hepatitis C infection was the most common etiology of liver disease. At the time of listing, 85% of the patients had Child-Pugh class A or B cirrhosis. In 16 patients, HCC was diagnosed after listing for transplantation. The remainder of the patients carried the diagnosis of HCC at the time of listing. A total of 11 patients were lost to follow-up after removal from the transplant list.

Imaging Findings

Imaging findings for all 218 patients were evaluated (Fig. 1). The total number of evaluable matched angiography and cross-sectional imaging sets was 376. The median number of evaluable matched imaging study sets per patient was 1 (range, 1–6). The prevalence of discordant findings for patients followed with CT and MRI was similar.

The number and location of the tumor nodules (Table 2) were concordant among all of the available imaging study sets for 136 patients (62%). For all of these patients, the number and approximate location of the hypervascular foci detected at angiography corresponded to the suspected hypervascular lesions detected on cross-sectional imaging.

For 37 patients (17%), more hypervascular foci were detected on at least 1 angiogram than the number of HCC nodules seen on the preceding cross-sectional imaging studies. There was a median of 1 discrepant imaging study set per patient with a discrepancy (range, 1–3). Up to 10 additional hypervascular foci were seen at angiography. The majority of patients (21 patients) had 1 or 2 additional hypervascular foci apparent at angiography.

Conversely, 45 patients (21%) had fewer hypervascular foci detected on at least 1 angiogram than the number of HCC nodules seen on the preceding cross-sectional imaging studies. The median number of discrepant imaging study sets per patient with a discrepancy was 1 (range, 1–4). Cross-sectional imaging studies detected up to 9 more suspected lesions in comparison with angiograms. However, the majority of patients (32 patients) had 1 or 2 suspicious nodules that were not detected at angiography.

Clinical and Pathologic Outcomes

Clinical outcomes for the study population are summarized in Table 3. Graphs for the cumulative incidence functions for transplantation and tumor recurrence outcomes derived from the competing risk analysis are shown in Figs. 2 and 3. The univariate and multivariate subhazard ratios (SHRs) and 95% confidence intervals (CIs), which were calculated in the competing risk regression in order to derive cumulative incidence functions for all outcomes, are summarized in Tables 4 and 5, respectively.

Liver Transplantation—Of the 218 patients included in this study, 152 (70%) received a liver transplant, 3 patients (1%) remained active on the transplant list as of the data censor date of July 1, 2014, and 63 patients (29%) were removed from the waiting list. The most common reasons for removal from the transplant list were radiographic and laboratory evidence of tumor progression based on CE CT or MRI and serum AFP levels (33 patients) and decompensation of liver function leading to multi-organ failure (9 patients). Patients were not removed from the transplant list on the basis of angiographic findings. The lesion size and number for the purposes of listing for transplantation were assessed only on the basis of CE CT or MRI.

The median time interval from listing to liver transplantation for the 152 transplant patients (ie, excluding patients who died or were removed from the list before transplantation) was 13.1 months (range, 0.2–93 months). Deceased donor transplants were used for 148 patients, whereas 4 patients received a living donor transplant. The median time interval from the last TACE procedure to transplantation for transplant patients was 5.2 months (range, 0–28.9 months). The cumulative incidence of transplantation, calculated from competing risk regression, was 34% at 1 year, 56% at 2 years, and 67% at 5 years.

The detection of 3 or more hypervascular foci at angiography that were not expected on the basis of the preceding CE CT or MRI (Fig. 2B, Tables 4 and 5) was associated with a significantly lower rate of receiving a liver transplant in both univariate and multivariate analyses (multivariate SHR, 0.39; 95% CI, 0.17–0.92). Conversely, the detection of more hypervascular lesions at CT/MRI, regardless of the magnitude of the discrepancy, was not associated with a lower rate of liver transplantation (Fig. 2C). Multivariate analyses also demonstrated that UNOS HCC tumor stage 3 or 4 by imaging and a lower native MELD score at the time of listing were independently predictive of lower odds of transplantation (Table 5).

Explant Histopathology: Histopathology reports were available for all 152 liver transplant recipients (Table 1). The diagnosis of HCC was confirmed for 142 of the patients; 7 of these patients had evidence of microvascular invasion (MVI), 1 patient (0.7%) with a fibrolamellar variant had gross tumor invasion of the portal vein but no pathologic evidence of extrahepatic disease, 1 patient (0.7%) had concomitant MVI and extracapsular tumor extension, and 2 patients (1.4%) had extrahepatic metastases diagnosed upon pathologic analysis (one patient with lymph node involvement and another patient with a peritoneal implant). No suspicious macronodules were demonstrated in 6 of the transplant recipients (4%), and 1 patient (0.7%) had intrahepatic splenosis but no intrahepatic malignancy. In 1 patient, a solitary 1.3-cm focus of CC (but no HCC) without lymphovascular invasion was discovered; 2 patients had HCC-CC, one with 3 nodules measuring up to 3.3 cm and another with one 2.3-cm nodule. MVI was demonstrated in both patients with HCC-CC.

Of the 142 patients with histopathologically confirmed HCC, 48 patients (34%) had 100% tumor necrosis in the explant, 52 recipients (37%) had a solitary focus of a viable tumor (<2 cm in maximum diameter in 31 patients, 2–5 cm in maximum diameter in 20 patients, and >5 cm in maximum diameter in 1 patient), 27 patients (19%) had 2 or 3 viable tumor foci (18 with lesions up to 3 cm in maximum diameter and 9 with at least 1 lesion >3 cm in

diameter), and 14 patients (10%) had more than 3 viable intrahepatic nodules. Thus, the majority (83%) of the patients with HCC had pathologic UNOS stage T0, T1, or T2. The majority (91%) of the viable HCC lesions were moderately or well differentiated.

There were no statistically significant associations demonstrated between advanced HCC stage upon pathologic analysis (UNOS T3 or T4, or metastatic disease), high tumor grade, or the presence of MVI and the detection of more or fewer hypervascular foci at angiography than expected on cross-sectional imaging. None of the other predictors tested as a part of the univariate or multivariate models were associated with advanced pathologic T stage in explants.

Tumor Recurrence: Tumor recurrence after transplantation was detected in 16 organ recipients (11%). Two of these patients had CC or mixed HCC-CC, whereas another 2 patients had HCC with MVI at explant histopathology. The remaining 12 patients had HCC without MVI. The cumulative incidence of recurrence was 4% at 1 year, 5% at 2 years, and 11% at 5 years. Two patients developed synchronous extrahepatic and intrahepatic recurrence, whereas the remaining 14 patients were found to have extrahepatic metastases without allograft involvement.

Patients who had more hypervascular lesions demonstrated by cross-sectional imaging than detected on a subsequent hepatic angiogram had a significantly higher risk of posttransplant tumor recurrence after transplantation (Fig. 2, Table 5) after adjustments for covariates (multivariate SHR, 3.49; 95% CI, 1.27–9.56). Multivariate analyses also demonstrated that a lower CTP score at listing, a higher maximum observed AFP level, an advanced-stage HCC at explant (UNOS T3, T4, or metastatic disease), and the presence of high-risk histologic features at histopathology (including lymphovascular invasion, extracapsular extension, metastatic disease, CC or mixed HCC-CC histology, and high-grade HCC differentiation based on the Edmondson scale) were independent predictors for higher odds of posttransplant tumor recurrence (Table 5).

Subgroup Analysis for Patients With More Hypervascular Foci at Angiography

—At least 1 more hypervascular focus at angiography than expected on the basis of the preceding CE CT or MRI was detected in 37 patients, whereas 16 patients (7.3% of the study population) had at least 3 more hypervascular foci at angiography. For these patients, imaging findings at angiography were correlated with subsequent CE CT or MRI and pathology reports in order to determine whether discordant lesions represented tumor foci. Pathology follow-up was available for 21 patients who underwent a transplant, 9 of whom were found to have HCC lesions that corresponded to the angiographic findings (Table 6). CE CT or MRI follow-up was available for 12 of the patients who did not undergo transplantation, and 9 of them were found to have lesions that correlated to angiographic findings (Table 6).

Clinical and pathological outcome data for the subgroup of patients who had 3 or more hypervascular foci at angiography that were not expected from the preceding CE CT or MRI are summarized in Table 7. Six patients (37%) underwent transplantation, whereas 10 patients (63%) were removed from the transplant list (7 patients were removed because of

HCC progression). The median number and range of discrepant hypervascular foci were similar between patients who did and did not undergo transplantation ($P = 0.85$). Patients who were removed from transplantation tended to have higher maximum AFP levels ($P = 0.26$) and higher radiographic UNOS T stages ($P = 0.03$) based on the immediate pretransplant or last available cross-sectional imaging study (for patients removed from the transplant list).

Explant tumor histology demonstrated HCC in all 6 transplant recipients (with MVI in 2 patients and without MVI in the remaining 4 patients). Only 1 patient had a pathologic disease beyond UNOS T2. One patient who had 10 more hypervascular foci detected at angiography than expected on the basis of the preceding CE CT developed metastatic HCC to the cervical spine 29.1 months after liver transplantation. All of this patient's hepatic lesions demonstrated complete necrosis at explant.

Pathologic correlates to the discordant angiographic foci were found in 1 of the 6 patients, whereas the remaining 5 patients had no histopathologic correlates to angiographic findings. A match between the number and location of lesions between CE CT or MRI and histopathology was present for 4 patients. For 1 of the patients, CT detected 4 lesions, whereas only 1 was present upon pathologic analysis. For another patient, CT demonstrated 2 lesions, whereas 7 lesions were present upon pathologic analysis.

Subgroup Analysis for Patients With More Hypervascular Lesions at CT/MRI— The types of liver-directed therapy used to treat discordant lesions are summarized in Table 8. Pathologic correlation was available for 32 patients who underwent a liver transplant (Tables 6 and 9). Nineteen of these patients (59%) were found to have HCC nodules in the explants that corresponded to the discordant lesions at CE CT or MRI. All patients with more lesions at cross-sectional imaging than detected by angiography were treated with TACE. Empiric TACE to the expected target vessel based on CT/MRI imaging was employed in 21 patients, and 1 of them was treated with subsequent radiofrequency ablation (RFA). For 4 patients with 2 or 3 lesions detected by cross-sectional imaging in the same liver lobe but only 1 hypervascular focus seen at angiography, all lesions appeared to be treated (contained ethiodized oil) on the basis of CT scans obtained approximately 1 month after TACE. Four patients underwent RFA for lesions that were not detected angiographically.

No additional therapy to angiographically occult lesions was employed in 14 patients. All lesions left untreated were smaller than 2 cm in diameter at the time of detection and on follow-up. For 6 patients, angiographically occult lesions remained stable until transplantation 3 to 14 months (median, 3 months) after angiography with discrepant findings. Pathology reports for these 6 patients showed no correlates for any of the discordant nodules except in 1 patient with 3 viable discordant HCC lesions (largest, 2.3 cm). For 5 patients, discordant lesion(s) became undetectable on follow-up imaging. Pathologic correlates were available for 4 of these patients. Three patients had viable HCC nodules up to 2.5 cm in diameter corresponding to a CT abnormality seen 3 months earlier, whereas the fourth patient had no pathologic correlate to CT findings.

Patients who received any treatment for discordant lesions (TACE or RFA) were significantly more likely to have no viable tumor in the explant (UNOS T0 disease) in comparison with patients whose discordant lesions were not treated ($P = 0.03$). There was also a trend toward a lower likelihood of UNOS T3 disease in explants for patients who received TACE or RFA for discordant lesions ($P = 0.07$).

DISCUSSION

The number of hypervascular foci detected angiographically does not always correlate with the number of suspicious hypervascular nodules detected by the preceding CE multiphase cross-sectional imaging study. If a suspicious lesion is angiographically occult, effective treatment by arterial methods may not be effective. Conversely, the detection of more hypervascular foci at angiography than expected on the basis of the preceding CE CT or MRI might imply that either (1) some of the HCC lesions were missed by the cross-sectional study, (2) the disease progressed between the cross-sectional study and the angiogram, or (3) the additional hypervascular foci detected at the time of the angiography are due to a nonneoplastic process, such as an arterioportal shunt. Because of this diagnostic uncertainty, current practice guidelines do not recommend changing the treatment plan (or transplant listing status) on the basis of the angiography findings alone.[3,9,22]

In this study of 218 patients with HCC who were listed for liver transplantation, 45 patients (21%) were found to have at least 1 angiogram that demonstrated fewer hypervascular foci than expected on the basis of the number of suspicious nodules seen on the preceding cross-sectional study. This observation was not associated with a higher risk of tumor recurrence in a univariate analysis. However, multivariate analysis demonstrated that the detection of more nodules on CT/MRI versus angiography was independently predictive of a 3.5-fold-higher risk of tumor recurrence after transplantation in multivariate models, which included other previously validated clinical and pathologic predictors of posttransplant tumor recurrence such as CC[23] or mixed HCC-CC histology[24] and the presence of MVI in tumor explants.[25] Thus, the demonstration of more nodules by CT/MRI may indeed be predictive of a higher risk of posttransplant tumor recurrence. Alternatively, the risk may have been falsely elevated because of the large difference between sample sizes (99 versus 32 patients) and missing data, which are limitations of this retrospective study.[26]

When a lesion does not demonstrate hypervascularity at angiography, arterial therapy is less likely to be effective. Because lesions that are occult at angiography may nevertheless harbor an untreated tumor, empiric TACE with or without thermal or chemical ablative therapy for the treatment of such lesions should be considered before transplantation. Ineffective therapy before transplantation may lead to reduced survival after liver transplantation.[5]

Another 37 patients (17%) had at least 1 angiogram that demonstrated more hypervascular foci than expected on the basis of the preceding CE CT or MRI. The demonstration of at least 3 more hypervascular foci at the time of the angiography than expected on the basis of the preceding CE CT or MRI was independently predictive of a more than 2.5-fold-lower chance of receiving a liver transplant according to the multivariate models. Other variables

tested in this model have been associated with dropout from the transplant list in patients with HCC.[5,27] A majority of the patients in this subgroup (10 patients, 63%) developed radiographic and biochemical evidence of HCC progression some time after angiography and were ultimately removed from the waiting list 0.8 to 19.4 months (median, 6.5 months) after the angiogram that documented the discrepant findings. This observation suggests that discrepant hypervascular foci could have been related to previously unsuspected additional HCC foci that were not detected by cross-sectional imaging. None of the patients were removed from the transplant list solely on the basis of discrepant angiographic findings.

Conversely, 6 patients (37%) with at least 3 or more hypervascular foci not seen on cross-sectional imaging received a liver transplant. Interestingly, only 1 patient had disease beyond the Milan criteria at explant, whereas 3 patients had no detectable viable HCC in explants. All of these patients received liver-directed therapy 0.1 to 12.9 months (median, 2.7 months) between the time of the angiogram that documented the discrepant findings and the liver transplant. The additional hypervascular foci likely represented additional HCC lesions in the patient with a high disease burden at explant and may have been neoplastic in the other patients as well, but they responded to the subsequent liver-directed therapy. Alternatively, some of these hypervascular foci may have been due to a nonneoplastic process, such as arteriovenous shunts.

This study was limited by its retrospective design, which included the associated limitations of missing clinical data. The median time interval between angiography and preceding cross-sectional imaging in the study was 31 days (range, 1–63 days), and this introduced the possibility of disease progression in the time period between CT/MRI and DSA. However, in clinical practice, arterial therapy is frequently delayed by at least a month after HCC diagnosis to allow for clinical consultations and procedure scheduling. It is possible that part of the reason for the observed discrepancies between the number of nodules at CT/MRI and hypervascular foci at angiography was the inability of DSA to discern between individual lesions appreciated on CT/MRI. However, the extent of the contribution of this limitation to our results could not be evaluated without the availability of cone-beam CT.

Cone-beam CT allows for the acquisition of CT images during conventional angiography. Images are acquired during the rotation of the angiographic C-arm around the patient while a prolonged injection of iodinated contrast medium through an intra-arterial catheter is performed. The rotational angiographic images can then be processed and viewed as multiplanar reformations as well as a 3-dimensional angiogram. This technology can be used for confirmation of adequate lesion targeting during arterial therapy planning for HCC and may demonstrate lesions that are occult by either DSA or multiphase CE CT.[28,29] In cases where there is a discrepancy between angiographic and preprocedural cross-sectional imaging findings, cone-beam CT can be helpful in providing an intraprocedural cross-sectional imaging that correlates to findings at DSA.

This study suggests that a demonstration of 3 or more hypervascular foci at angiography that are not expected on the basis of the preceding cross-sectional imaging study correlates with a significantly decreased likelihood of receiving a transplant. Conversely, a demonstration of fewer hypervascular foci at angiography than expected on the basis of the preprocedural CE

CT or MRI correlated with a higher risk of HCC recurrence after transplantation. In these patients, discordant lesions should be treated aggressively by locoregional techniques (particularly ablation) before transplant. Our findings do not support the use of angiography in determining liver transplantation candidacy. However, the detection of an unexpectedly high or low number of lesions by hepatic artery DSA warrants further intraprocedural evaluation by cone-beam CT (if available) and close subsequent follow-up with CE CT or MRI. Patients with discordant imaging findings also require close follow-up with multiphase CE CT or MRI after transplantation in order to monitor for tumor recurrence. Further prospective study using cone-beam CT technology is needed to understand what the cross-sectional correlates to the unexpected additional hypervascular foci at angiography may represent.

Acknowledgments

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Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
CC	cholangiocarcinoma
CE	contrast-enhanced
CI	confidence interval
CT	computed tomography
CTP	Child-Turcotte-Pugh
DSA	digital subtraction angiography
EMR	electronic medical record
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCC-CC	mixed histology hepatocellular-cholangiocarcinoma
HCV	hepatitis C virus
MELD	Model for End-Stage Liver Disease
MRI	magnetic resonance imaging
MVI	microvascular invasion
NC	unable to calculate
NS	not statistically significant
NT	not tested
PACS	picture archiving and communication systems

RFA	radiofrequency ablation
SHR	subhazard ratio
TACE	transarterial chemoembolization
TNM	tumor-node-metastasis
UNOS	United Network for Organ Sharing

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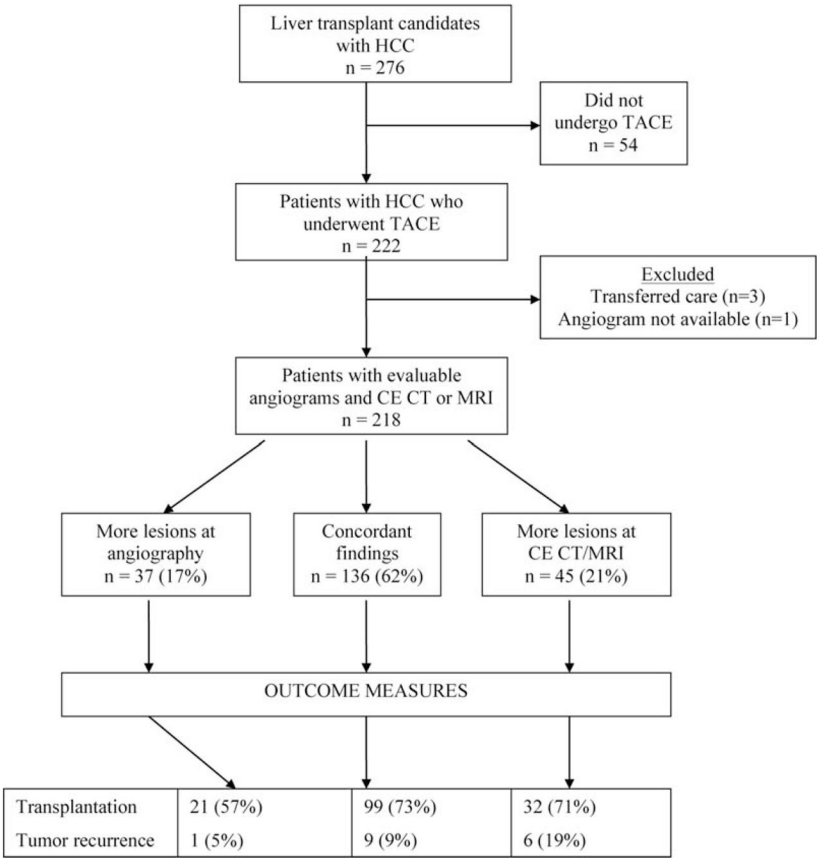

Figure 1.
Flow diagram summarizing the patient selection and the main study outcomes.

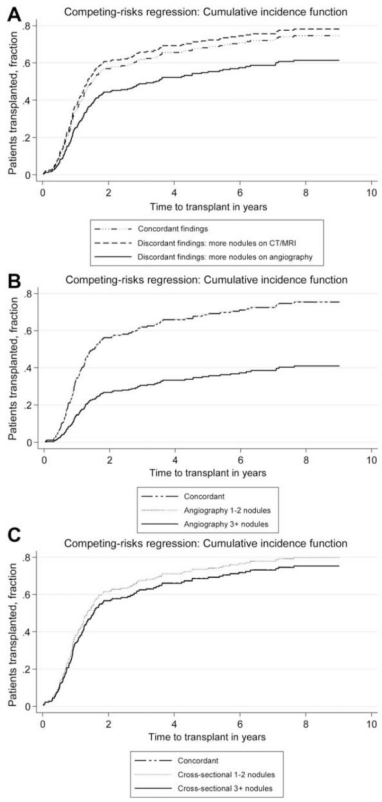

Figure 2.

Competing risk regression analysis of the cumulative incidence of transplantation in patients with concordant findings between angiography and cross-sectional imaging versus (A) patients with more or fewer hypervascular foci at angiography than expected on the basis of preceding cross-sectional imaging, (B) patients with 1 or 2 or at least 3 more hypervascular foci at angiography than expected on the basis of preceding cross-sectional imaging, and (C) patients with 1 or 2 or at least 3 fewer hypervascular foci at angiography than expected on the basis of preceding cross-sectional imaging.

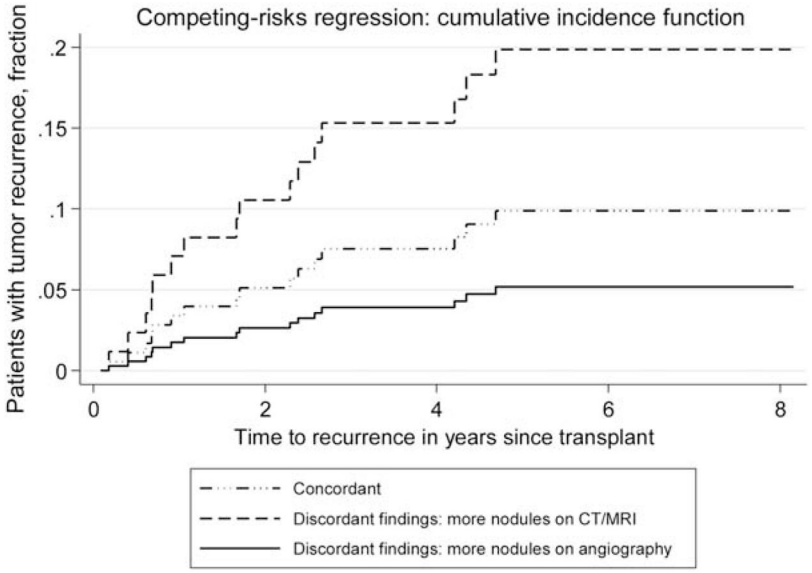

Figure 3.

Competing risk regression analysis of the cumulative incidence of tumor recurrence after liver transplantation in patients with concordant findings between angiography and cross-sectional imaging versus patients with more or fewer hypervascular foci at angiography than expected on the basis of preceding cross-sectional imaging.

TABLE 1

Patient Demographics, Liver Disease Severity, and Tumor Burden (n = 218)

Demographics	
Age, median (range), years	57 (21–77)
Sex	
Male	172 (79%)
Female	46 (21%)
Ethnicity	
African American	7 (3%)
Asian/Pacific Islander	73 (33%)
Caucasian	96 (44%)
Hispanic	34 (16%)
Other	8 (4%)
Etiology of liver disease	
HCV	106 (49%)
HBV	41 (19%)
Alcohol	12 (5%)
Other	59 (27%)
Severity of liver disease	
Child-Pugh-Turcotte score at time of listing, median (range)	7 (4–13)
Child-Pugh Class at time of listing	
A	106 (49%)
B	79 (36%)
C	33 (15%)
MELD score at time of listing, median (range)	11 (6–37)
MELD score at time of listing by range	
<10	89 (41%)
10–14	78 (36%)
15–19	36 (17%)
≥20	15 (7%)
Tumor burden	
UNOS TNM stage at listing	
No HCC present at listing	16 (7%)
T1	57 (26%)
T2	145 (67%)
Maximum observed UNOS TNM stage	
T1	27 (12%)
T2	116 (53%)
T3	72 (33%)
T4	3 (1%)
Extent of viable HCC in explants (pathologic UNOS TNM)	
T0	48 (34%)

Demographics	
T1	31 (22%)
T2	38 (27%)
T3	22 (15%)
T4	1 (1%)
Metastatic disease	2 (1%)
Histopathologic findings	
HCC without MVI	134 (88%)
HCC with MVI	7 (5%)
Fibrolamellar HCC with macrovascular invasion	1 (1%)
CC	1 (1%)
HCC-CC with MVI	2 (1%)
No atypical macronodules	6 (4%)
Intrahepatic splenosis	1 (1%)
HCC tumor differentiation [Edmondson and Steiner[21] (1954)]	
Well	35 (38%)
Moderate	49 (53%)
Poor	8 (9%)
Maximum observed AFP level, median (range), ng/mL	32.9 (1.0–331,000)
Maximum observed AFP level by range	
<200 ng/mL	157 (72%)
200–500 ng/mL	19 (9%)
>500 ng/mL	42 (19%)

TABLE 2

Imaging Findings

Finding Category	n (%)	Lesion Diameter (cm): Median (Range)
Concordant findings	136 (62)	2.9 (1.1–8.2)
More hypervascular foci detected at angiography	37 (17)	Unable to calculate
Magnitude of discrepancy		
1 focus	13	
2 foci	8	
3 foci	4	
4 foci	4	
5 foci	2	
6 foci	1	
9 foci	1	
10 foci	4	
More nodules detected on cross-sectional imaging	45 (21)	1.5 (1.1–3.5)
Magnitude of discrepancy		
1 nodule	19	2.0 (1.1–3.5)
2 nodules	13	1.9 (1.1–2.9)
3 nodules	7	1.5 (1.1–2.8)
4 nodules	3	1.3 (1.1–2.2)
5 nodules	1	1.2 (1.1–1.4)
9 nodules	2	1.5 (1.1–2.2)

TABLE 3

Clinical and Histopathologic Outcomes

			More Foci at Angiography			More Lesions at CT/MRI		
	All Patients (n = 218)	Concordant Findings (n = 136)	Any Number (n = 37)	1 or 2 Lesions (n = 21)	3+ Lesions (n = 16)	Any Number (n = 45)	1 or 2 Lesions (n = 13)	3+ Lesions (n = 32)
Outcome Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Transplantation								
Received a transplant	152 (70)	99 (73)	21 (57)	15 (71)	6 (37)	32 (71)	23 (72)	9 (69)
Removed from transplant list	66 (30)	37 (27)	16 (43)	6 (29)	10 (62)	13 (29)	9 (28)	4 (31)
Due to HCC progression	33 (50)	19 (51)	10 (63)	3 (50)	7 (70)	4 (31)	3 (33)	1 (25)
Due to liver decompensation	9 (14)	5 (14)	2 (12)	1 (17)	1 (10)	2 (15)	1 (11)	1 (25)
Due to another reason	24 (36)	13 (35)	4 (25)	2 (33)	2 (20)	7 (54)	5 (56)	2 (50)
Tumor recurrence*								
Number of recurrences	16 (11)	9 (9)	1 (5)	0 (0)	1 (17)	6 (19)	5 (22)	1 (11)
High viable tumor burden at explant†								
Number of observations	27 (18)	15 (15)	6 (29)	5 (33)	1 (17)	6 (19)	5 (22)	1 (11)

*As of the data censor date of July 1, 2014.

†A high viable tumor burden is defined as pathologic UNOS T3 or T4 or the presence of metastatic disease. The analysis was limited to 152 patients who received a liver transplant before the data censor date of July 1, 2014.

TABLE 4

Summary of Univariate Analyses for Clinical and Histopathologic Outcomes With Respect to Discrepant Findings Between Angiography and Cross-Sectional Imaging

	Number of Discordant Hypervascular Foci		
Clinical Outcome	**Any**	**1 or 2**	**3+**
Transplanted			
More foci at angiography	0.69 (0.43–1.13)	1.00 (0.58–1.74)	0.38 (0.16–0.90)
More nodules on CT/MRI	1.11 (0.74–1.66)	1.14 (0.72–1.82)	0.99 (0.48–2.08)
Tumor recurrence after transplant			
More foci at angiography	0.51 (0.07–3.95)	NC*	1.69 (0.22–13.25)
More nodules on CT/MRI	2.12 (0.74–6.08)	2.48 (0.81–7.62)	1.21 (0.16–9.19)
High viable tumor burden at explant†			
More foci at angiography	2.21 (0.75–6.73)	2.83 (0.84–9.43)	1.14 (0.12–10.32)
More nodules on CT/MRI	1.3 (0.46–3.72)	1.61 (0.50–4.82)	0.70 (0.08–6.03)

NOTE: SHRs and 95% CIs are given with respect to the group of patients with concordant findings between angiography and cross-sectional imaging.

*Unable to be calculated because of a lack of events.

†A high viable tumor burden is defined as pathologic UNOS T3 or T4 or the presence of metastatic disease. The analysis was limited to 152 patients (n = 21 for patients with discordant findings) who received a liver transplant.

TABLE 5

Results of Multivariate Analyses With Respect to Selected Predictors and Adverse Clinical and Histopathologic Outcomes

Predictors	Transplant	HCC UNOS Stage 3 or 4 at Explant	Posttransplant Tumor Recurrence
Discordant: more by DSA, 3+ foci	0.39 (0.17–0.92)	NS	NS
Discordant: more by CT/MRI	NS	NS	3.49 (1.27–9.56)
Age, continuous (per year)	NS	NS	NS
Female sex	NS	NS	NS
Ethnicity	NS	NS	NS
Non-HCV liver disease etiology	NS	NS	NS
Median CTP score	NS	NS	0.64 (0.46–0.89)
CTP ≥9	NS	NS	NS
Child-Pugh class	NS	NS	NS
MELD score	1.06 (1.01–1.12)	NS	NS
UNOS TNM stage at listing	NS	NS	NS
Maximum observed UNOS stage	NS	NS	NS
Latest UNOS stage 3 or 4*	0.37 (0.20–0.68)	NS	NS
Maximum AFP level			
201–500 ng/mL	NS	NS	NS
>500 ng/mL	NS	NS	NS
Continuous per 100 ng/mL	NS	NS	1.009 (1.005–1.014)
High viable tumor burden at explant†	NT	NT	4.81 (1.52–15.28)
High-risk histology features‡	NT	NT	5.61 (1.52–20.81)

NOTE: The values given are SHRs and 95% CIs.

*The UNOS stage was based on CE CT or MRI scans taken before transplantation (for transplant recipients) or the last available (for nontransplant patients).

†A high viable tumor burden is defined as pathologic UNOS T3 or T4 or the presence of metastatic disease.

‡High-risk histology features are defined as the presence of 1 or more of the following at histopathology: lymphovascular invasion, extracapsular extension, metastatic disease, CC or HCC-CC histology, and high-grade HCC differentiation based on the Edmondson scale.

TABLE 6

Correlation of Discordant Angiographic Findings With Subsequent Cross-Sectional Imaging and Pathologic Findings

Number of Discordant Lesions	More Hypervascular Foci at Angiography (Correlate Present? Yes/No/Unknown)*	More Lesions at CT/MRI (Correlate Present? Yes/No)†
1	7/3/3	10/5
2	3/5/0	6/2
3	3/1/0	3/2
>3	5/6/1	0/4

*Correlation was performed with explant pathology reports or with follow-up CE CT or MRI (if patients did not undergo transplantation).

†Correlation was performed with explant pathology reports only for liver transplant recipients.

TABLE 7

Subgroup Analysis for Patients With >3 Hypervascular Foci at Angiography Than Expected on the Basis of the Preceding Cross-Sectional Imaging Study

Clinical or Pathologic Parameters	n = 16
Removed from transplant list	10 (63%)
Number of discrepant hypervascular foci, median (range)	4 (3–10)
Highest observed radiographic UNOS stage (T0/T1/T2/T3)*	0/0/4/6
Highest AFP level while on waiting list, mean (standard deviation), ng/mL	87 (9–31, 341)
Time from angiography to delisting, median (range), months	6.5 (0.8–19.4)
Transplanted	6 (37%)
Number of discrepant hypervascular foci, median (range)	5 (3–10)
Highest observed radiographic UNOS stage (T0/T1/T2/T3)*	0/0/5/1
Highest AFP level while on waiting list, median (range), ng/mL	303 (44–775)
Time from angiography to transplantation, median (range), months	2.7 (0.1–12.9)
Recurrence	1 (17%)
Histopathology	
HCC without MVI	4 (67%)
HCC with MVI	2 (33%)
Number of viable tumor nodules, median (range)	1 (0–7)
Longest diameter of largest nodule, median (range), cm	2 (0.2–7.0)
Pathologic UNOS stage (T0/T1/T2/T3)	3/1/1/1

*While on transplant list (before transplantation or delisting).

TABLE 8

Summary of Liver-Directed Therapy for Patients With Fewer Hypervascular Foci Detected at Angiography Than Expected by CT/MRI

Magnitude of Discrepancy and Therapy to Discordant Lesions	n
1 (n = 19)	
Empiric TACE only	8
Empiric TACE +RFA	1
Angiographically occult lesion targeted by TACE for angiographically visible lesion	3
RFA	1
Resection	1
No additional antitumor therapy	5
Angiographically occult lesion <2 cm and not seen on subsequent CT/MRI	1
Angiographically occult lesion <2 cm and stable on subsequent CT/MRI	4
2 (n = 13)	
Empiric TACE only	4
RFA	3
No additional antitumor therapy	6
Angiographically occult lesions <2 cm and not seen on subsequent CT/MRI	4
Angiographically occult lesions <2 cm and stable on subsequent CT/MRI	1
Angiographically occult lesions <2 cm and transplantation <1 month after TACE	1
3 (n = 7)	
Empiric TACE only	4
Angiographically occult lesions targeted by TACE for angiographically visible lesion	1
No additional antitumor therapy	2
Angiographically occult lesion <2 cm and stable on subsequent CT/MRI	1
Permanent hepatic decompensation as a result of TACE	1
>3 (n = 6)	
Empiric TACE only	5
No additional antitumor therapy; angiographically occult lesions <2 cm and transplantation <1 month after TACE	1

TABLE 9

Summary of Histopathologic Findings for Patients With Fewer Hypervascular Foci Detected at Angiography Than Expected by CT/MRI Who Underwent Liver Transplantation

Liver-Directed Treatment (n)	Histology (n)	Number of Viable Tumors: Median (Range)	Longest Tumor Diameter (cm): Median (Range)	UNOS T Stage (T0/T1/T2/T3)
Empiric TACE (n = 17)	HCC without MVI (14)	0 (0–12)	1.9 (1.2–3.5)	9/0/5/3
	HCC with MVI (1)			
	No nodules (2)			
RFA (n = 3)	HCC without MVI (3)	1 (1–4)	3.5 (1.4–4.1)	0/1/1/1
No additional treatment (n = 12)	HCC without MVI (11)	1 (0–3)	2.7 (1.8–5)	3/2/6/1
	HCC with MVI (1)			