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Research Article

Advanced Imaging Modalities for Hepatocellular Carcinoma: Is MRI with EOVIST Really Better?

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Abstract

Background: Hepatocellular cancer (HCC) is the third leading cause of cancer-related death worldwide and the third most common indication for liver transplantation in the United States. Efforts toward perfecting imaging-based diagnosis have increased to avoid the need for liver biopsy. Eovist (gadolinium-EOB-DTPA), compared to conventional gadolinium-enhanced MRI (MRI-Gd) or triple-phase contrast-enhanced computed tomography (CT), is considered a superior method for detection of hepatocellular cancer (HCC). In patients with cirrhosis, Eovist enhances lesion-to-liver contrast and differentiates vascular shunts and dysplastic nodules from HCC, an important distinction as outcomes of transplantation depend on the degree of cancer burden. We investigate whether MRI with Eovist (MRI-E) is more accurate for evaluation of HCC than MRI-Gd or CT.

Methods: Retrospective analysis of all patients with HCC undergoing liver transplantation at Cedars-Sinai Medical Center from 2009-2014 was conducted. Multicentric tumors were included if they could be uniquely identified across modalities based on anatomic location. Number and size of lesions measured by MRI-E, MRI-Gd, or CT were compared to explant pathology using repeated measures ANOVA and linear regression analysis. Viability on imaging *vs.* pathology was compared using chi-squared tests.

Results: Sixty-four patients with 137 HCC tumors were imaged with MRI-E (n=96), MRI-Gd (n=63), and/or CT (n=53); 33 tumors were measured with all 3 modalities. The number of lesions identified by MRI-E was highly concordant with pathology and higher than the number detected by MRI-Gd or CT ($p<0.05$). All three imaging modalities underestimated maximum tumor diameter relative to pathology ($p=.0003$). Maximum tumor diameter by MRI-Gd had stronger correlation with pathology than MRI-E or CT ($p=0.008$). MRI-E ($\chi^2=3.52$, $p=0.061$) and CT ($\chi^2=3.57$, $p=0.059$) were better at assessing viability than MRI-Gd ($\chi^2=1.22$, $p=0.268$).

Conclusions: This is the first study to compare imaging of HCC using MRI-E, MRI-Gd, or CT to explant pathology. MRI with Eovist is a useful adjunct for liver transplant candidacy evaluation with superior assessment of the number of HCC lesions, but it may have limited precision when assessing lesion size.

Keywords: Hepatocellular cancer; Cirrhosis; Liver transplant; Eovist

Introduction

Hepatocellular carcinoma (HCC) is the most common primary hepatic malignancy and accounts for nearly 50% of deaths for patients with cirrhosis [1]. The standard of care since the incorporation of Milan criteria for the treatment of HCC in patients with cirrhosis and HCC is liver transplantation in those with early stage but unresectable lesions [2]. Transplantation for cirrhosis and hepatocellular carcinoma has the highest success for potential cure by eliminating both the cancer and the cirrhotic liver, which is the biggest risk factor for development of HCC. One year and five year survival after liver transplant for HCC is approximately 92% and 80% [3] and has been largely dependent upon early detection and staging [4]. Even with careful patient selection and adjunct therapies while waiting on the transplant list, HCC still recurs post-transplant at a rate of 3.5-21%, and is associated with increased mortality compared to recipients without recurrence [5]. HCC is unique in that the positive predictive value of imagining findings nears 100%; hence, tissue diagnosis, with its associated complications including post-procedural pain, bleeding, risk of tumor seeding, and difficulties in evaluating multiple lesions over long periods of time in patients with cirrhosis, has become increasingly unpopular [6,7]. Advanced imaging modalities, in lieu of tissue diagnosis, are used to discriminate HCC from other types of liver lesions and to reliably characterize the number, size, and viability of HCC lesions and to determine candidacy for transplantation.

Currently, the American Association for the Study of Liver Disease (AASLD) published guidelines for surveillance and diagnosis of HCC includes screening ultrasound (US) every 6 months until there is evidence of a lesion, at which point computed tomography and/or magnetic resonance imaging become the more appropriate method used for staging [8] (Figure 1). The Organ Procurement

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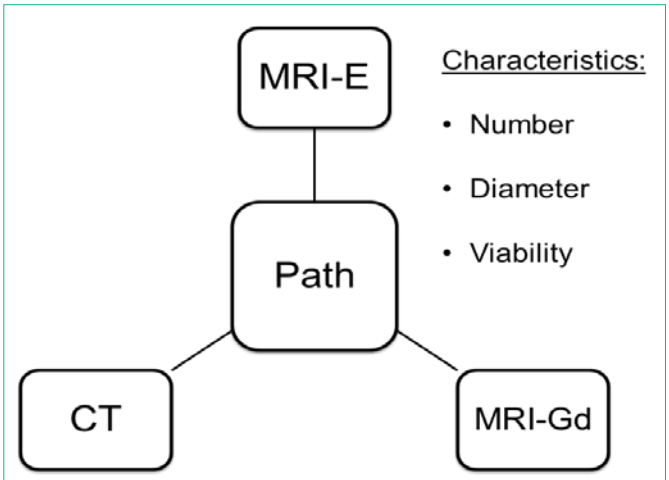

Figure 1: Tumor characteristics assessed by advanced imaging modalities relative to pathologic correlation.

Transplant Network (OPTN) and United Network for Organ Sharing (UNOS) has also recently published its minimum accepted criteria for the evaluation and classification of HCC if to be considered for transplantation exception listing, and includes: liver imaging with multiphase contrast enhanced radiography (CT or MRI) performed or interpreted at a transplant center, single lesion ≥2 cm and ≤5 cm, or 2 or 3 lesions ≥1 cm and ≤3 cm in size, and meet specific imaging characteristics [9] (Table 1). Lesions which have characteristics that are beyond these criteria have a significantly worse prognosis with transplantation.

The current clinical standard is to obtain contrast enhanced multiphasic CT or MRI to evaluate hepatic lesions that include arterial, portal venous, and delayed phase images [8,10,11]. The per-lesion sensitivity of MR imaging of all sizes is 77-100% and for CT it is 68-91% [12,13-16]. Either CT or MRI equally identify lesions >2 cm (100%), while lesions 1-2 cm in size have a sensitivity of being detected on MRI 44-47% and on CT 40-44%, and lesions <1 cm are poorly detected by both methods [12,13-16].

In recent years, several liver-specific contrast media have been developed to enhance the ability of MRI to detect and characterize hepatic lesions [17]. The goals of imaging livers that are cirrhotic are to differentiate malignant (HCC, cholangiocarcinoma, metastases) from non-malignant related nodules (ie. regenerative, dysplastic, or benign). MRI contrast agents are broadly categorized as either non-specific agents, such as conventional gadolinium (Gd), that distribute into the vascular and extravascular spaces, or hepatocyte/biliary specific agents, such as gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA or Eovist in the USA) which distribute in the arterial, venous, and delayed hepatobiliary phases 20-60 minutes after intravenous (IV) injection [18]. Functionally, in the late phases after Eovist injection, the contrast in taken up by functional hepatocytes and increases the lesion-to-liver contrast enabling tumor identification. Theoretically, this may also be beneficial in identifying early stage, low grade HCC.

Table 1: OPT classification system for nodules seen on imaging of cirrhotic livers (adapted from OPTN published policy).

Class	Description	Comments
0	Incomplete or technically inadequate study	Repeat study required for adequate assessment; automatic priority MELD points cannot be assigned based on a OPTN 0 classified imaging study
1	No evidence of HCC on good quality, appropriate surveillance exam	Typically, surveillance would continue according to routine practice at the respective transplant center
2	Benign lesion(s) or diffuse parenchymal abnormality with no dominant focal lesion	Typically, need for any further imaging would be determined on a clinical basis according to routine practice at the respective transplant center
3	Abnormal scan, indeterminate focal lesion(s), not currently meeting radiologic criteria for HCC	Typically, follow-up imaging would be performed in 6-12 months
4	Abnormal scan, intermediate suspicion for HCC (meets some radiologic criteria for HCC-could represent HCC)	Consider short term F/U in 3 months (lesions ≥ 2 cm maximum diameter) to 6 months (lesions < 2 cm maximum diameter). Imaging follow-up should be considered if biopsy is negative or not possible.
5	Meets radiologic criteria for HCC	May qualify for automatic exception depending on stage
	5A: ≥ 1 cm and < 2 cm measured on late arterial or portal phase images	Increased contrast enhancement on late hepatic arterial phase AND washout during later contrast phases AND peripheral rim enhancement (capsule/pseudocapsule).
	5A-g: same size as 5A	Increased contrast enhancement on late hepatic arterial phase AND growth by 50% or more documented on serial CT/MRI obtained ≤6 months apart.
	5B: maximum diameter ≥ 2 cm and ≤ 5 cm	Increased contrast enhancement on late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule/pseudocapsule) OR growth by 50% or more documented on serial CT/MRI obtained ≤ 6 months apart.
	5T: prior local regional treatment for HCC	Describes any residual lesion or perfusion defect at site of prior UNOS class 5 lesion.
	5X: maximum diameter ≥ 5 cm	Increased contrast enhancement on late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule/pseudocapsule) OR growth by 50% or more documented on serial CT/MRI obtained ≤ 6 months apart.

Multiple studies suggest that MRI with hepatobiliary contrast agents is the most sensitive method for detecting small HCC, those less than 2 cm, which traditional non-specific contrast imaging has proven to poorly diagnose [19-25]. Previous studies comparing Eovist MRI (MRI-E), Gd MRI, and CT have reported mixed results, showing higher per-lesion sensitivity with Eovist, while other studies have shown no difference between MRI-E and CT [19,26,27]. In order to determine the true accuracy of diagnostic imaging, it is imperative to correlate such findings with the histopathology of the explanted whole liver. Few studies, of small sample size, have compared MRI-E or Primovist with explant pathology and have concluded varying sensitivities from 60-85% [28,29,30]. The purpose of our study was to determine if MRI-E more accurately characterized HCC compared to MRI-Gd or contrast CT by comparing to whole liver explant pathology.

Methods

Study population

This study was reviewed and approved by the Cedars-Sinai Institutional Review Board. Two hundred seventy-eight orthotopic liver transplants (OLT) for cirrhosis were performed between 2009 and 2014, which included 64 patients with a pretransplant diagnosis of hepatocellular carcinoma, all of whom were within Milan criteria at the time of OLT. Patient demographics, imaging modalities used to evaluate liver lesions, pathology results of the explant specimen, and clinical outcomes were retrospectively gathered. All participants had undergone at least one of the following imaging studies within 3 months of transplant: CT, MRI-Gd, or MRI-E. Our transplant center is located in Region 5 of UNOS, where patients generally experience an extended period of time on the wait list before liver transplantation (median wait time for a candidate with a MELD of 15 is 2277 days, compared to median 639 days nationally according to most recent OPTN data). For patients undergoing down staging procedures including ethanol ablation, hepatic artery chemoembolization (TACE), or radiofrequency ablation (RFA) prior to OLT, only imaging performed after the final intervention was included for analysis.

CT technique

All CT scans of the abdomen and pelvis were obtained using a GE 64-detector Light Speed VCT instrument with slice thickness of 5 mm. Iodinated contrast was injected at a dose of 1.5 mL/kg body weight at a rate of 4-6 mL/s for a total of 30 s. Three contrast-enhanced dynamic phases were obtained to include: arterial (18 s), portal venous (45 s), and equilibrium (150 s).

MRI technique

All MRI-Gd and MRI-E of the abdomen and pelvis were performed on a 1.5T MR Siemens Magnetom (MR A30) with a phased-array torso coil. Pre-contrast, fat saturation T1-weighted volumetric interpolated breath-hold (VIBE), T1-weigted gradient-echo in-phase and out-of-phase, and fat-suppressed T2-weighted spin-echo single breath-hold were performed in the transverse plane with 5 mm slices.

Dynamic imaging of liver was obtained before (pre-enhanced) and after (enhanced) IV bolus of either gadolinium or Eovist with multiple phases of enhancement captured. In those who received gadolinium, at a dose of at a dose of 0.1 mL/kg body weight at 2-2.5 mL/s, three phases of imaging were obtained: arterial (30 s), portal venous (50 s), and delayed (2 min). In those with who received Eovist, at a dose of 0.1 mL/kg body weight at 2-2.5 mL/s, four phases of imaging were obtained: arterial (30 s), portal venous (50 s), equilibrium (2 min), and delayed (20 min).

Imaging analysis

CT and MRI scans were reviewed and interpreted by two dedicated hepatic specialized radiologists each with more than 10 years' experience. All written radiology reports that were reviewed were documented prior to the time of transplant and hence were unaware of final histopathology. Radiological criteria for the diagnosis of HCC were based upon UNOS guidelines and were strictly adhered to for interpretation of hepatic tumors (Table 1). Lesions <1 cm are indeterminate and cannot be considered as HCC, 1-2 cm lesions must be hypervascular on arterial phase and demonstrate portal venous phase washout and peripheral enhancement or show growth on serial imaging, and 2-5 cm lesions must to be hypervascular on arterial phase and demonstrate portal venous phase washout or peripheral enhancement or show growth on serial imaging. For each patient, the number of lesions, the size of each lesion, and viability was recorded.

Histologic analysis

Explant pathology was reviewed by three hepatic-specialized pathologists, each with more than 10 years' experience, without referring to pretransplant imaging studies for comparison. The explanted livers were sectioned to 5 mm thickness in the sagittal plane and when any type of lesion was identified it was further examined, in direct comparison to its expected location based upon imaging, to determine exact tumor size, extent of viability and necrosis, differentiation, and vascular invasion.

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation (SD). Number and size of lesions measured by CT, MRI-Gd, or MRI-E were compared to explant pathology using repeated measures ANOVA and linear regression analysis. Viability on imaging *vs.* pathology was compared using χ^2 tests. Statistical analyses were performed using Prism 5 (Graph Pad Software, La Jolla, CA). Two-tailed p-values <0.05 were considered significant.

Results

Of the sixty-four patients who underwent OLT with a preoperative diagnosis of HCC, five did not have evidence of viable HCC on final pathology. Each of those 5 participants received at least one down staging intervention including TACE, RFA, and ablation. Demographic characteristics in our patient population are similar to those described in national recipients transplanted for HCC (found in the OPTN database) and are listed in Table 2. Based upon imaging results confirming HCC, many participants underwent a variety of downsizing therapies prior to transplant during the waitlist period. No downsizing treatment was performed between their last reviewed imaging and date of transplant, nor between imaging studies that we compared between each other for the purposes of this study. The median (IQR) time between imaging and OLT was 42 (24-58) days. A total of 100 down staging procedures were performed (75 chemo embolizations, 10 radio embolizations, 7 percutaneous ablations, 8

Table 2: Patient demographics.

Variable	All patients (n = 64)
Age, mean±SD	60±15
Male (n)	45
Cause of liver disease (n)	
Hepatitis B Virus	15
Hepatitis C Virus	41
Alcohol	4
Other	4
Tumor differentiation (n)	
Well	34
Moderate	100
Poor	11
Down staging therapies (n)	
Chemoembolization	75
Radioembolization	10
Percutaneous ablation	7
Other	8

unknown [performed at outside facilities]), with an average of 1.56 per patient.

In 59 participants we identified 137 tumors in the explant specimens, of which 53were seen on CT, 63 on MRI-Gd, and/or 96 on MRI-E. Thirty-three tumors were measured by all three modalities, 45 by CT and MRI-Gd, 36 by CT and MRI-E, and 36 by MRI-E and MRI-Gd. We performed "side by side" comparisons of the explant to imaging for each 137 lesions (Figure 1).

The mean ± SD number of lesions per liver identified on explant pathology was 2.6±1.9, as compared to. 1.2±0.9 lesions detected by CT, 1.5±1.0 on MRI-Gd, and 1.6±1.0 on MRI-E. In side-by-side comparisons of each imaging modality *vs.* pathology, there was a difference between number of lesions on explant *vs.* lesions detected by CT (paired students t-test $p<0.05$), and for lesions on explant *vs.* lesions by MRI-Gd ($p<0.05$), but there was no significant difference between lesions found on explant *vs.* MRI-E. Essentially, the number of lesions identified was equivalent by pathology or MRI-E, which were significantly higher than the number detected by MRI-Gd or CT ($p<0.05$) (Table 3).

All three imaging modalities significantly underestimated maximum tumor diameter relative to pathology (repeated measures ANOVA p=0.0003). Maximum tumor diameter by MRI-Gd had significantly stronger correlation with pathology than MRI-E or CT (p=0.008). The mean ± SD diameter of lesions on final pathology was 1.8±1.5 cm, compared against 0.92±1.3 cm on CT, 1.2±1.3 cm on MRI-Gd, and 0.92±0.9 cm on MRI-E (repeated measures ANOVA $p< 0.05$); and remained statistically significant on side-by-side comparisons.

Given the indeterminate nature of sub-centimeter lesions on pre-transplant imaging and the effect of those data points on overall results, we performed subgroup analyses stratifying by lesion size (<1 cm, 1-2 cm, >2 cm). For lesions <1 cm in diameter, there was no statistically significant difference in size by imaging compared to size by pathology for CT, MRI-Gd, or MRI-E (p=0.16, p=0.37, p=0.08, respectively). For lesions between 1 and 2 cm, there was no significant difference in size measured by CT (p=0.10), but both MRI-Gd and MRI-E significantly overestimated tumor size (p=0.01 for each) relative to size by pathology. For larger lesions >2 cm in diameter, measurements taken by CT and MRI-E did not significantly differ from size by pathology (p=0.19 and p=0.30, respectively). MRI-Gd significantly underestimated the size of larger tumors (p=0.003).

Table 3: Tumor characteristics on imaging *vs.* explant.

	CT	MRI-Gd	MRI-E	Explant	p value
Lesions (n)	1.2±0.9	1.5±1.0	1.6 ±1.0	2.6 ±1.9	<0.05
Size (cm)	0.92±1.3	1.2±1.3	0.9±0.9	1.8 ±1.5	<0.05
Viable tumor	77%	62%	35%	75%	

Data are presented as mean±SD

Seventy-five percent (103 total) of the 137 lesions identified on pathology were found to be viable. Viability on CT, MRI-Gd, and MRI-E was 77% (41 of 53); 62% (39 of 63); and 35% (34 of 96), respectively. MRI-E (χ^2=3.52, p=0.061) and CT (χ^2=3.57, p=0.059) were better at assessing viability than MRI-Gd (χ^2=1.22, p=0.268).

Discussion

The most accurate modality for assessing tumor burden in patients with HCC has yet to be established, but there is growing optimism that liver-specific agents such as Gd-EOB-DTPA enhance sensitivity in determining number, size, and viability of lesions when compared to conventional CT or MRI-Gd. Early studies compared imaging to pathology specimens obtained from biopsy or partial liver resections, but testing against whole liver explant has become the internationally-accepted standard [31]. To our knowledge, this is the largest study comparing explant to CT, MRI-Gd, and MRI-E. In our analysis we found no significant difference in detecting number of HCC lesions between pathology and MRI-E across all tumors studied, and MRI-E was superior when compared to CT and MRI-Gd, supporting our theory that Gd-EOB-DTPA improves pre-transplant HCC detection.

Another aspect we investigated was ability to measure size of individual lesions. Earlier data published by Kim, et al. was promising, finding no significant difference between CT and MRI-E, however partial liver resections comprised almost the entirety of their pathology specimens and may have missed HCC present in other areas of the liver that were also not seen on imaging [19]. In addition, only 48% of the patients in their study had underlying cirrhosis, and hence the ability of imaging to detect and differentiate between <1 cm sized lesions in a non-cirrhotic liver is easier. Among the explants included in our study, which were all cirrhotic, we found overall tumor burden, including size, number, and viability were significantly underestimated across all three modalities (p=0.003). In sub-group analysis, all modalities were equivalent to pathology for sub-centimeter tumors, though MRI-E trended toward underestimating size. MRI-Gd and MRI-E both tended to overestimate intermediate-sized lesions (1-2 cm) while MRI-Gd underestimated those that were >2 cm in size. Our results are consistent with smaller studies, finding a decrease in sensitivity in MRI-E in detecting smaller and better-differentiated tumors [29,30]. This has been attributed to the belief that smaller lesions have less arterial neovascularization when

compared to their larger and less well-differentiated counter parts. The decreased enhancement of liver parenchyma was attributed to presence of cirrhosis, resultant hepatocyte dysfunction, and poor contrast uptake.

Given the long waiting period for patients with HCC listed for transplant, novel therapies have been employed to induce tumor necrosis and halt disease progression. After undergoing TACE, RFA, ablation; follow-up imaging can estimate remaining viable tumor and ensure that patients are within Milan criteria. Prior studies have found a 40-44% sensitivity for detecting viable tumor within treatment cavity when comparing MRI-Gd to resection or explant pathology specimens [32,33]. To our knowledge, this is the first study to evaluate whether liver-specific contrast agents may have more sensitivity in detecting viable tumor after down-staging procedures.

Liver transplant waitlist eligibility for patients with hepatocellular carcinoma requires their tumors to be within Milan criteria [single tumor <5 cm or up to 3 tumors all ≤3 cm without extra-hepatic or vascular involvement] if they are prioritized based upon their tumor MELD rather than native MELD [3]. Patients with tumor size and number beyond these criteria whom undergo transplant have a poor prognosis [2], and in almost all cases we base this decision of their extent of disease on our multiphasic contrast enhanced imaging modalities. In addition to the number and size of lesions, the complexity of tumor characterization has become even more complex with addition of downsizing therapies. After such procedures, often there remains evidence of a treated, or non-viable, tumor and in some cases the tumor is only partially treated with some remaining viability. The characterization of treated lesions becomes very complex and hence likely significantly impacts our interpretation of tumor extent and transplant listing eligibility. Our results suggest that CT and MRI-E are more accurate with respect to determination of residual tumor viability.

Our study is subject to the inherent limitations present in retrospective reviews. While this is the largest series to our knowledge comparing imaging to whole liver pathology, the sample size of 64 participants and 137 tumors may be insufficient to draw conclusions regarding the validity of CT, MRI-Gd, and MRI-E. Another limitation is the difference in time between evaluation of HCC by each of the imaging modalities and by pathology. That is to say: for each participant, CT, MRI-Gd, or MRI-E was measured at different time points prior to transplantation. This precludes our ability to capture changes in tumor characteristics that occur between each imaging study, which may account for some of the measurement error. Further, we did not determine which specific tumors underwent downsizing treatments and perform a subgroup analysis. This would be an important next step in determining if the inaccuracies in imaging findings are secondary to a treatment effect.

Conclusion

Our results, similar to those obtained from other studies, suggest that the superior imaging modality for characterization of HCC remains unclear. Rather than attempting to find the single most effective technique, it may be more appropriate to decide which imaging modalities are best suited to characterize each specific factor: size of tumor, number of lesions, tumor viability, and lesions downsized.

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