

Veterans Affairs

**VA Collaborative Consensus on a Pathway for
Imaging of Patients with Suspected or Confirmed
Hepatocellular Carcinoma**

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Introduction:

Hepatocellular carcinoma (HCC) is the 2nd leading cause of cancer death worldwide and the most rapidly growing malignancy in the United States and among Veterans. Due to a high prevalence of chronic liver disease related to viral hepatitis, alcohol use, and obesity, healthcare professionals of the Veterans Administration Healthcare System (VA) diagnose and manage over 2000 incident HCC cases annually. Hepatocellular carcinoma is the sole solid tumor malignancy for which radiologic criteria with or without pathological confirmation can be utilized formally to make a cancer diagnosis. Radiological criteria also dictate patient eligibility for liver transplantation. Therefore, high quality and consistent radiological technique and interpretation are critical aspects of HCC patient care.

Significant heterogeneity exists across the VA nationwide with regard to cross-sectional radiological equipment, cross-sectional radiological protocols, radiologist expertise, case volume and interpretation templates. Policies related to the administration of contrast agents in the setting of renal dysfunction vary widely, and frequently are based upon outdated data. Follow-up protocols after HCC-directed interventions remain non-standardized across the VA system.

The goal of this pathway is to codify best practices for VA radiologists and clinicians who manage hepatocellular carcinoma with regard to:

1. Preferred radiological modalities and imaging sequences (**Section I**)
2. Best practices related to reporting imaging findings in patients with suspected Hepatocellular Carcinoma (HCC) (**Section II**)
3. Best practices related to follow-up imaging after HCC-directed interventions (**Section III**)
4. Best practices related to the use of intravascular contrast agents for the imaging of potential HCC patients in the setting of renal dysfunction (**Section IV**)
5. Guidance related to the interpretation of imaging in the setting of liver transplant candidacy (**Section V**)

This document is not intended to establish guidelines to be enforced at VA medical centers. Rather, it is offered as a pathway to help guide diagnostic imaging of patients who have or are suspected to have HCC. Clinicians and radiologists should always employ their best clinical judgement based on the latest medical evidence and local capabilities to provide care for Veteran patients.

Section I: Preferred Modality and technique/sequences

Recommendation 1.1:

We recommend that MRI be the modality of choice for imaging of patients in whom HCC is suspected or confirmed. Depending on clinical judgment and local practice considerations, multiphasic CT (Rec 1.3 below) is an acceptable alternative.

Type I and type II contrast agents are preferred for routine evaluation; type III (Eovist) for specific indications only.

The following sequences or equivalents are recommended:

1. Axial and coronal T2 single shot breath hold
2. Axial steady state free precession with fat suppression-SSFP (i.e. FIESTA)
3. Axial gradient echo T1 in and out of phase
4. Axial pre and dynamic (4 post contrast phases) T1 with fat suppression (i.e. LAVA, VIBE, THRIVE)
5. Axial and coronal delayed post contrast T1 with fat suppression (about 5 minutes)
6. Type III only: Axial and coronal 20-minute delayed post contrast T1 with fat suppression
7. Local practice preference: Axial diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) map

Recommendation 1.2:

Indications for Eovist (Type III) include:

1. Characterization of focal nodular hyperplasia (FNH) or adenoma
2. Need for high definition evaluation of bile ducts, bile leak or functional evaluation

Recommendation 1.3

For patients imaged with CT

1. Scan with multi-slice scanner (8-slice minimum)
2. Arterial phase, rapid infusion (3-4 cc/second)
3. Portal venous phase
4. Delayed phase

Recommendation 1.4

Basic recommendations for hepatic surveillance ultrasound:

1. Liver cancer surveillance is recommended for all patients with Child-Turcotte-Pugh A and B cirrhosis and patients with Child-Turcotte-Pugh C cirrhosis listed for liver transplant who are eligible for curative or palliative therapies for hepatocellular carcinoma (HCC)
2. Ultrasound surveillance every 6 months is the preferred modality with or without serological testing for alpha-fetoprotein (AFP) for patients with cirrhosis

Special circumstances:

- a. If a quality sonogram cannot be obtained, contrast-enhanced imaging is advised, preferably MRI to limit radiation.
- b. If AFP is checked and elevated, contrast enhanced imaging should be considered.

Section II: Reporting imaging findings in patient s with suspected HCC

Recommendation 2.1:

We recommend implementation of Liver Imaging Reporting and Data System (LI-RADS) 2017 standards (**Appendix A**) into all diagnostic imaging reports for patients with suspected HCC. LI-RADS should be applied in patients at risk for HCC, namely those with cirrhosis, or chronic hepatitis B viral infection, or current or prior HCC, including adult liver transplant candidates and recipients post-transplant. Other conditions or categories are excluded.

Recommendation 2.2:

For patients with discrete nodules (five or fewer), each lesion greater than 10 mm diameter should have the following reporting findings specified

1. New or existing lesion
2. Couinaud segment
3. Observation size (in mm)
4. Description of findings to include presence or absence of:
 - a. Arterial phase hyperenhancement (APHE)
 - b. Washout (attenuation of lesion is LESS than that of surrounding parenchyma)
 - c. Enhancing capsule
 - d. Threshold growth defined as: Size increase of a mass by a minimum of 5 mm AND as follows:
 - $\geq 50\%$ increase in size in ≤ 6 months Or
 - $\geq 100\%$ increase in size in > 6 months OR
 - Previously unseen on CT or MRI, now ≥ 10 mm, in ≤ 24 months
 - Measure on same phase, sequence, and plane on serial exams
5. LI-RADS numerical score: For LR-5, we recommend specifying if lesion is LR-5g or LR-5us. (Denoting either threshold growth, or a lesion with washout and visibility at screening ultrasound).

For patients with multiple lesions, or infiltrative disease, radiologists should use their judgement to convey clinically relevant findings in the clearest manner.

Recommendation 2.3:

For patients contemplated for transplant we recommend that each individual lesion greater than 10 mm in diameter should have the following findings specified:

1. New or existing lesion
2. Couinaud segment
3. Observation size (in mm)
4. Description of findings to include presence or absence of:

- a. Arterial phase hyperenhancement (APHE)
 - b. Washout (attenuation of lesion is LESS than that of surrounding parenchyma)
 - c. Enhancing capsule
 - d. Threshold growth
5. OPTN score (see section V)
 6. For radiologists outside of a transplant center, OPTN findings, if reported, should be stated to be “consistent with.....OPTN class”, inasmuch as only transplant centers can supply OPTN classification per United Network of Organ Sharing policy.

SECTION III: FOLLOW-UP IMAGING GUIDELINES POST INTERVENTION

After the surgical, ablative or catheter-based treatment of HCC, we make the following recommendations:

Recommendations:

- 1.1 Follow up imaging should be performed after all the target tumors have been treated.
- 1.2 Multi-phase contrast enhanced MRI is the preferred modality utilizing protocol sequences outlined in **SECTION I** above. Multi-phase contrast enhanced CT is an acceptable alternative. Ultrasound is inadequate.

We offer the following recommendations with respect to imaging interval post treatment, understanding that follow-up may vary depending upon the specific treatment, lesion characteristics, treatment plan and practitioner experience:

- 1.3 **TACE/TAE:** Initial scan at 6-12 weeks. If no residual disease present, follow-up at 3 months
- 1.4 **Ablation:** Initial scan at 6-12 weeks. If no residual disease present, follow-up at 3 months
- 1.5 **Y90:** Initial scan at 12 weeks. If no residual disease present, follow-up at 3 months
- 1.6 **SBRT:** Initial scan at 12 weeks. If no residual disease, follow-up at 3 months
- 1.7 **Resection:** Initial scan at 12 weeks. If no residual disease, follow-up at 3 months
- 1.8 Report residual disease per LI-RADS 2017 guidelines
 - LR-TR Nonviable (treated tumor probably or definitely not viable)
 - LR-TR Equivocal (treated tumor equivocally viable)
 - LR-TR Viable (treated tumor probably or definitely viable)
- 1.9 If no recurrence identified on first post treatment imaging, recommend contrast enhanced MRI-CT every 3 months until patient reaches 2-years recurrence free survival, then every 6-12 months thereafter, unless patient gets transplanted and is HCC-free after appropriate surveillance, or does not want additional surveillance.

Section IV: Consensus Pathway on the Use of Intravascular Contrast Agents for the Imaging of Potential HCC Patients in the Setting of Renal Insufficiency/Common Problems

The consensus panel offers the following observations and recommendations regarding the administration of CT and MR contrast agents:

There is an increasingly well-documented body of evidence that intravenous administration of current generation iodinated contrast agents **DOES NOT** pose a risk of renal injury¹. Notwithstanding the emerging literature, the panel recommends adoption of American College of Radiology (ACR) guidelines as outlined in the ACR Manual on Contrast Media Version 10.3, May 31 2017².

Recommendations:

- 4.1 For complex patients with cirrhosis and potential acute kidney injury, standard estimated glomerular filtration rate (eGFR) calculations are unreliable³. We recommend renal consultation to guide iodinated contrast administration.
- 4.2 Iodinated Contrast: We recommend the following patients be screened with eGFR within 30 days of intravenous administration of iodinated contrast material:
 - a. Age > 60 years
 - b. History of Renal Disease: Dialysis, Renal Transplant, Single Kidney, Renal Cancer, Renal Surgery/Nephrectomy
 - c. History of Hypertension Requiring Medical Therapy
 - d. Use of Metformin or Metformin Containing Medications
 - e. History of Diabetes Mellitus
- 4.2.1 For all screened patients:
 - 4.2.1.1 If $eGFR \geq 30$ mL/min/1.73 m², contrast administration is considered safe
 - 4.2.1.2 If $eGFR < 30$ mL/min/1.73 m², consider indication for test, hydrate according to protocol and obtain informed consent—see **Appendix B**
- 4.2.2 Regarding Metformin
 - 4.2.2.1 If $eGFR \geq 30$ mL/min/1.73 m², no need to modify metformin dosing

¹McDonald RJ et al. Intravenous Contrast Material Exposure is Not an Independent Risk Factor for Dialysis or Mortality. *Radiology* 2014; 273: 714-725.

²Available online at: https://www.acr.org/~media/ACR/Documents/PDF/QualitySafety/Resources/Contrast-Manual/Contrast_Media.pdf?la=en.

³Mindikoglu AL et al. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. *Hepatology*. 2014 Apr;59(4):1532-42.

4.2.2.2 If eGFR < 30 mL/min/1.73 m², withhold at time of study, after determination of renal function stability, re-institute at 48 hours

4.2.3 Patients receiving hemodialysis:

4.2.3.1 Low (Isovue, Omnipaque, Optiray etc) or iso osmolar (Visipaque) contrast recommended.

4.2.3.2 Dialysis suggested immediately after administration for patients with a history of congestive heart failure and/or volume overload

4.3 MR contrast agents:

4.3.1 No renal screening or informed consent required for patient receiving type II contrast agents: [Gadobenate dimeglumine (MultiHance-Bracco), Gadobutrol (Gdavist-Bayer HealthCare Pharmaceuticals), Gadoterate acid (Dotarem-Guerbert), Gadoteridol (ProHance-Bracco Diagnostics)].

4.3.2 Renal screening required for type I agents [Gadodiamide (Omniscan-GE Healthcare), Gadopentetate dimeglumine (Magnevist-Bayer HealthCare Pharmaceuticals), Gadoversetamide (OptiMark- Guerbert)] or type III agents [Gadoxetate disodium (Eovist-Bayer HealthCare pharmaceuticals)] in following patient populations:

- a. History of Renal Disease: Dialysis, Renal Transplant/Single Kidney, Renal Cancer, Renal Surgery
- b. History of Hypertension Requiring Medical Therapy
- c. History of Diabetes Mellitus

4.3.2.1 For screened patients:

- a. Type I agents contra-indicated if eGFR <30 mL/min/1.73 m² unless on chronic hemodialysis
- b. Type I agents acceptable if eGFR ≥ 30 mL/min/1.73 m²
- c. For eGFR < 30 mL/min/1.73 m², Type II agents are acceptable

4.3.3 Gadolinium retention and new class warnings: Recent studies have identified Gadolinium remaining in patient's bodies for months or even years after administration. This retention has not been linked to adverse health effects in patients with normal renal function, and FDA has concluded that the benefit of Gadolinium based contrast agents continues to outweigh potential risks, however, FDA will soon require that every patient read a yet to be released educational brochure prior to receiving GBCAs and to have the opportunity to ask questions prior to their examination.

Section V: Miscellaneous Topics including OPTN staging criteria for transplantation—FOR TRANSPLANT CENTER IMAGERS, SURGEONS AND HEPATOLOGISTS

The Organ Procurement and Transplantation Network (OPTN) is operated under contract with the U.S. Dept. of Health and Human Services by the United Network for Organ Sharing (UNOS).

UNOS/OPTN policy allows some patients with liver cancer and specific imaging as well as clinical criteria to be awarded automatic MELD exception points to increase prioritization for liver transplantation. Without such exception points, under current allocation models, most hepatocellular carcinoma patients would never receive a transplant organ. Therefore, ensuring that a potential transplant candidate obtains adequate imaging and appropriate interpretation is of vital importance to such veterans.

Recommendation 5.1

CT/MRI LI-RADS should be applied to liver transplant candidates meeting LI-RADS eligibility criteria, that is, patients who are candidates for liver transplant (or have been transplanted), cirrhosis, chronic hepatitis B or current/prior HCC, including adult liver transplant candidates and recipients posttransplant.

Recommendation 5.2

The minimum information that should be provided in the report so a provider can determine if the lesion could meet criteria for liver transplant (“OPTN Class 5 lesions”, namely, 5A, 5 A-g, 5B and 5T) include:

1. Number of lesions whose diameter exceeds 10mm
2. Maximum diameter of lesions with at least 10 mm diameter
3. Presence of enhancement, delayed wash-out, and/or peripheral rim
4. If comparison with another study of at least 6 months apart, whether there has been an increase in 50% in size.
5. Although not meeting OPTN 5A or 5B criteria, LR-M and LR-TIV should be reported, as they may affect pretransplant workup and/or transplant eligibility

Recommendation 5.3

To obtain HCC MELD score exception points the OPTN/UNOS policy states that “*must be interpreted by a radiologist at a transplant hospital*”, therefore, OPTN scores are not required to be reported but sufficient data for a Transplant Physician Reviewer to assess whether the patient would meet OPTN criteria should be provided.

Recommendation 5.4

If the CT or MRI scan is technically or inadequate or incomplete, any lesion should be classified as OPTN Class 0 and imaging must be repeated or completed to receive an HCC MELD exception.

UNOS/OPTN policies regarding HCC MELD exception points are constantly in evolution. Please refer to UNOS/OPTN Liver Allocation Policy Section 3.6.4 for current policies. See **Appendix C** for current OPTN criteria for Class 5 “definite HCC.”

Recommendation 5.5

All candidates meeting LI-RADS 5 criteria should have in the dynamic contrast-enhanced CT or MRI report both the number and size of lesions BEFORE locoregional therapy is administered.

Recommendation 5.6

If not performed within previous 6 months, a non-contrast CT chest to rule out metastatic disease should be recommended. Bone scan is recommended in patients with high alpha-fetoprotein (AFP > 1,000 ng/dL), or with bone symptoms.

Recommendation 5.7

For single liver cancers between 10 and 19 mm, the decision on treatment prior to automatic T2 exception points, depends on the center and patient’s preference and clinical parameters. The presence of 2-3 OPTN 5A cancers between 10 and 19 mm qualifies a patient for automatic T2 exception points. Treatment of a **solitary** 10 to 19 mm HCC before development of a 2nd precludes qualification for automatic MELD exception points.

Recommendation 5.8

MRI/CT of the liver needs to be done in transplant candidates on a transplant waitlist every 3 months to maintain UNOS/OPTN status.

Recommendation 5.9

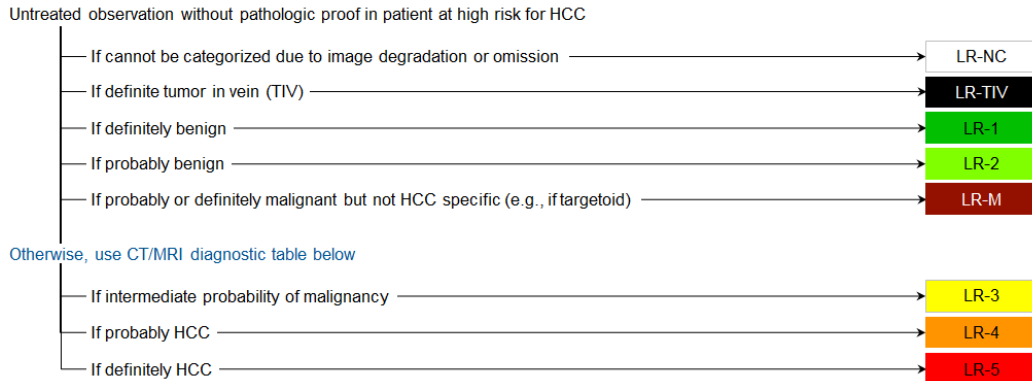
A diagnosis of “small HCC” can be considered in lesions less than 10 mm diameter since those with “at least” 10 mm can meet criteria for transplant. Small HCC may be considered when the lesion has arterial hyperenhancement, a defined capsule or washout. Accuracy of imaging studies for lesions < 10 mm are provided in Appendix C Table 2. CT and MRI are superior compared to ultrasound for HCC; we recommend following small lesions with the index modality in which they are first identified. While follow-up guidelines for small HCC do not exist, we recommend 3 month interval follow-up based on NCCN 2017 and LI-RADS guidelines for small lesion follow-up.

Recommendation 5.10

We recommend CT or MRI surveillance for non-HCC cirrhotic patients waitlisted for transplantation.



CT/MRI LI-RADS® v2017 ESSENTIALS



CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		APHE (not rim)		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count major features: • "Washout" (not peripheral) • Enhancing "capsule" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 LR-5

Observations in this cell are categorized LR-4, except:

- LR-5g, if ≥ 50% diameter increase in < 6 months (equivalent to OPTN 5A-g)
- LR-5us, if "washout" and visibility at screening ultrasound (per AASLD HCC criteria)

If unsure about the presence of any major feature: characterize that feature as absent

Appendix B: CONTRAST AGENTS AND RENAL IMPAIRMENT IN HCC PATIENTS

*all numeric reference from ACR Manual on Contrast Media –Version 10.3/May 31, 2017, chapters 9-15

SEE ALSO, VA POLICY _____ ON CONTRAST MEDIA

Intravascular Iodinated Contrast Agents

Calculated estimated glomerular filtration rate (eGFR) is more accurate than is serum creatinine at predicting true GFR [1]. There is no agreed-upon threshold of serum creatinine elevation or eGFR declination beyond which the risk of contrast induced nephropathy (CIN) is considered so great that intravascular iodinated contrast medium should never be administered. Each contrast medium administration always implies a risk-benefit analysis for the patient, contrast medium administration for all patients should always be taken in the clinical context, considering all risks, benefits and alternatives [2,3]. At the current time, there is very little evidence that IV iodinated contrast material is an independent risk factor for acute kidney injury (AKI) in patients with $eGFR \geq 30$ mL/min/1.73 m². Therefore, if a threshold for CIN risk is used, 30mL/min/1.73 m² seems to be the one with the greatest level of evidence [4]. No serum creatinine or eGFR threshold is adequate to stratify risk for patients with AKI because serum creatinine in this setting is unreliable. However, in patients with AKI, the administration of iodinated contrast medium should only be undertaken with appropriate caution, and only if the benefit to the patient outweighs the risk.

- **Suggested List of Indications for Renal Function Testing Prior to the Intravascular Administration of Iodinated Contrast Administration:** this list encompasses most patients and is consistent with ACR guidelines
- Age > 60
- History of Renal Disease: Dialysis, Renal Transplant/Single Kidney, Renal Cancer, Renal Surgery
- History of Hypertension Requiring Medical Therapy
- Use of Metformin or Metformin Containing Medications
- History of Diabetes Mellitus

A baseline serum eGFR should be obtained prior to the intravascular injection of contrast medium in all patients at risk for CIN. There is no agreed upon acceptable maximum interval between obtaining renal function labs and the administration of intravascular iodinated contrast in patients at risk for CIN. Many practices have established a thirty-day maximum for outpatients with shorter although variable recommendations for inpatients. Patients who are scheduled for a routine intravascular study that do not have any of the above risk factors do not require baseline serum eGFR determination prior to iodinated contrast administration.

A) **Metformin**

Iodinated contrast in patients taking metformin is a potential concern for furthering renal damage in patients with acute kidney injury, and in patients with severe chronic kidney disease (stage IV or stage V). The ACR recommends

that patients taking metformin be classified into one of two categories based on the patient's renal function (as measured by eGFR).

Category I

In patients with no evidence of AKI and with $eGFR \geq 30$ mL / min/1.73m², there is no need to discontinue metformin either prior to or following the intravenous administration of iodinated contrast media, nor is there an obligatory need to reassess the patient's renal function following the test or procedure.

Category II

In patients taking metformin who are known to have acute kidney injury or severe chronic kidney disease (stage IV or stage V; i.e., $eGFR < 30$ mL / min/1.73m²), or are undergoing arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries, metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours after the procedure and reinstated only after renal function has been re-evaluated and found to be normal. *FDA has more stringent recommendation:* April 2017 Update- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an estimated eGFR between 30 and 60 mL / min/1.73m², in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

B) Prevention of CIN/Hydration

The major preventive action to mitigate against CIN in patients at risk is to provide intravenous volume expansion prior to contrast medium administration [5-11]. The ideal infusion rate and volume is unknown, but isotonic fluids are preferred (Lactated Ringer's or 0.9% normal saline). One acceptable protocol is 0.9% saline at 100 mL/hr, beginning 6 to 12 hours before and continuing 4 to 12 hours after. There is no compelling evidence for the use of Sodium bicarbonate, N-acetylcysteine or Mannitol and Furosemide

C) Choice of Iodinated Contrast Media

A reported meta-analysis from the literature concerning the relative nephrotoxicity of high osmolality contrast media (HOCM) and low osmolality contrast media (LOCM) concluded that LOCM are less nephrotoxic than HOCM in patients with underlying renal insufficiency. [12] There is no definitive evidence that iso-osmolar iodinated contrast has any benefit over LOCM.

D) Dialysis and Iodinated Contrast Administration

Patients with anuric end-stage chronic kidney disease who do not have a functioning transplant can receive intravascular iodinated contrast medium without the risk of further renal damage. Patients receiving dialysis are at a theoretical risk of pulmonary edema and anasarca from the osmotic load imposed by intravascular iodinated contrast medium because they cannot readily clear the excess intravascular volume. Complications were not observed in one study of patients on dialysis who received intravascular nonionic iodinated contrast medium. In patients at risk for fluid overload, low osmolality or iso-osmolality contrast media should be employed with dosing as low as necessary to achieve a diagnostic result. Unless an unusually large volume of contrast medium is administered, or there is substantial underlying cardiac dysfunction, there is no need for urgent dialysis after intravascular iodinated contrast medium administration [13].

1) Intravenous Gadolinium Based Contrast Agents (GBCAs)

Based on current knowledge, it is estimated that patients with end-stage CKD (CKD5, eGFR<15 mL / min/1.73m²) and severe CKD (CKD4 eGFR 15-29 mL / min/1.73m²) have a 1% to 7% chance of developing NSF (nephrogenic systemic sclerosis) after one or more exposures to group 1 GBCAs (see chart below)[14-20]. However, most patients who developed NSF had end-stage kidney disease and were on dialysis at the time of exposure. Between 12% and 20% of confirmed cases of NSF have occurred in patients with AKI, often superimposed upon CKD [21,22]. Some cases of NSF have developed in patients with AKI without underlying CKD [23]. Hence, AKI alone is also a risk factor for NSF.

TABLE 1. ACR Manual Classification of Gadolinium-Based agents Relative to Nephrogenic Systemic Fibrosis

<p>Group I: Agents associated with the greatest number of NSF cases: Gadodiamide (Omniscan-GE Healthcare), Gadopentetate dimeglumine (Magnevist-Bayer HealthCare Pharmaceuticals), Gadoversetamide (OptiMark- Guerbert)</p> <p>Group II: Agents associated with few, if any, unconfounded cases of NSF: Gadobenate dimeglumine (MultiHance-Bracco), Gadobutrol (Gadavist-Bayer HealthCare Pharmaceuticals), Gadoterate acid (Dotarem-Guerbert), Gadoteridol (ProHance-Bracco Diagnostics)</p> <p>Group III: Agents for which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported: Gadoxetate disodium (Eovist-Bayer HealthCare pharmaceuticals)</p>
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A) ACR Guidelines for the Administration of Intravenous Gadolinium Contrast

- Based on the most recent scientific and clinical evidence [23-31] the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional prior to intravenous administration.
- Outpatients who may be receiving group I or group III agents should be screened for conditions and other factors that may be associated with renal function impairment:

Suggested List of Indications for Renal Function Testing in Outpatients Prior to the Intravenous Administration of Class I or III Gadolinium Contrast Agents

- 1) History of Renal Disease: Dialysis, Renal Transplant/Single Kidney, Renal Cancer, Renal Surgery
- 2) History of Hypertension requiring Medical Therapy
- 3) History of Diabetes Mellitus

For those outpatients identified by screening to have risk factors for impaired renal function and in whom administration of a group I or group III agent is planned, an eGFR determination prior to GBCA administration

should be obtained (See below for recommendations based on lab findings). There is no consensus on the timing of labs prior to exam, we usually perform them within 30 days.

- For all inpatients, an eGFR level should be obtained within 2 days prior to planned administration of a group I or group III GBCA. In addition, ordering health professionals should assess inpatients for the possibility of AKI, as eGFR calculation alone has limited accuracy for the detection of AKI.
- For patients with chronic kidney disease, stage 4 or 5 (eGFR <30 mL / min/1.73m²) not on chronic dialysis group I GBCAs are contraindicated.
- Due to the temporal lag between eGFR (which is calculated using serum creatinine values) and actual glomerular filtration rates, it is not possible to determine whether a given patient has AKI based on a single eGFR determination. Accordingly, group I agents should be avoided in patients with known or suspected AKI. If GBCA is to be administered in this setting, a group II agent is preferred.

References—Adapted from ACR Manual on Contrast Media – Version 10.3 / May 31, 2017

1. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130(6):461-470.
2. Davenport MS, Cohan RH, Khalatbari S, Ellis JH. The challenges in assessing contrast-induced nephropathy: where are we now? *AJR Am J Roentgenol.* 2014;202(4):784-789.
3. Katzberg RW, Newhouse JH. Intravenous contrast medium-induced nephrotoxicity: is the medical risk really as great as we have come to believe? *Radiology.* 2010;256(1):21-28.
4. Davenport MS, Khalatbari S, Cohan RH, Dillman JR, Myles JD, Ellis JH. Contrast material-induced nephrotoxicity and intravenous low-osmolality iodinated contrast material: risk stratification by using estimated glomerular filtration rate. *Radiology.* 2013;268(3):719-728.
5. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. *N Engl J Med.* 2006;354(4):379-386.
6. Weisbord SD, Palevsky PM. Prevention of contrast-induced nephropathy with volume expansion. *Clin J Am Soc Nephrol.* 2008;3(1):273-280.
7. Merten GJ, Burgess WP, Gray LV, et al. Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA.* 2004;291(19):2328-2334.
8. Navaneethan SD, Singh S, Appasamy S, Wing RE, Sehgal AR. Sodium bicarbonate therapy for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Am J Kidney Dis.* 2009;53(4):617-627.
9. Taylor AJ, Hotchkiss D, Morse RW, McCabe J. PREPARED: Preparation for Angiography in Renal Dysfunction: a randomized trial of inpatient vs. outpatient hydration protocols for cardiac catheterization in mild-to-moderate renal dysfunction. *Chest.* 1998;114(6):1570-1574.
10. Zoungas S, Ninomiya T, Huxley R, et al. Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med.* 2009;151(9):631-638.
11. Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomized controlled trial. *Lancet.* 2014;383(9931):1814-1823.

12. Heinrich MC, Haberle L, Muller V, Bautz W, Uder M. Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low- osmolar contrast media: meta-analysis of randomized controlled trials. *Radiology*. 2009;250(1):68-86.
13. Younathan CM, Kaude JV, Cook MD, Shaw GS, Peterson JC. Dialysis is not indicated immediately after administration of nonionic contrast agents in patients with end-stage renal disease treated by maintenance dialysis. *AJR Am J Roentgenol*. 1994;163(4):969-971.
14. Grobner T. Gadolinium--a specific trigger for the development of nephrogenic fibro sing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant*. 2006;21(4):1104-1108.
15. Marckmann P, Skov L, Rossen K, et al. Nephrogenic systemic fibrosis: suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. *J Am Soc Nephrol*. 2006;17(9):2359-2362.
16. Broome DR, Girguis MS, Baron PW, Cottrell AC, Kjellin I, Kirk GA. Gadodiamide-associated nephrogenic systemic fibrosis: why radiologists should be concerned. *AJR Am J Roentgenol* 2007;188(2):586-592.
17. Sadowski EA, Bennett LK, Chan MR, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology* 2007;243(1):148-157.
18. Shabana WM, Cohan RH, Ellis JH, et al. Nephrogenic systemic fibrosis: a report of 29 cases. *AJR Am J Roentgenol* 2008;190(3):736-741.
19. Wertman R, Altun E, Martin DR, et al. Risk of nephrogenic systemic fibrosis: evaluation of gadolinium chelate contrast agents at four American universities. *Radiology* 2008;248(3):799-806.
20. Collidge TA, Thomson PC, Mark PB, et al. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort. *Radiology* 2007;245(1):168-175.
21. Abu-Alfa AK. Nephrogenic systemic fibrosis and gadolinium-based contrast agents. *Adv Chronic Kidney Dis* 2011;18(3):188-198.
22. Prince MR, Zhang H, Morris M, et al. Incidence of nephrogenic systemic fibrosis at two large medical centers. *Radiology* 2008;248(3):807-816.
23. Kalb RE, Helm TN, Sperry H, Thakral C, Abraham JL, Kanal E. Gadolinium-induced nephrogenic systemic fibrosis in a patient with an acute and transient kidney injury. *Br J Dermatol* 2008;158(3):607-610.
24. Amet S, Launay-Vacher V, Clement O, et al. Incidence of nephrogenic systemic fibrosis in patients undergoing dialysis after contrast-enhanced magnetic resonance imaging with gadolinium-based contrast agents: the Prospective Fibrose Nephrogenique Systemique study. *Invest Radiol*. 2014;49(2):109-115.
25. Bruce R, Wentland AL, Haemel AK, et al. Incidence of Nephrogenic Systemic Fibrosis Using Gadobenate Dimeglumine in 1423 Patients With Renal Insufficiency Compared With Gadodiamide. *Invest Radiol*. 2016;51(11):701-705.
26. Martin DR, Krishnamoorthy SK, Kalb B, et al. Decreased incidence of NSF in patients on dialysis after changing gadolinium contrast-enhanced MRI protocols. *J Magn Reson Imaging*. 2010;31(2):440-446.
27. Michaely HJ, Aschauer M, Deutschmann H, et al. Gadobutrol in Renally Impaired Patients: Results of the GRIP Study. *Invest Radiol*. 2017;52(1):55-60.
28. Nandwana SB, Moreno CC, Osipow MT, Sekhar A, Cox KL. Gadobenate Dimeglumine Administration and Nephrogenic Systemic Fibrosis: Is There a Real Risk in Patients with Impaired Renal Function? *Radiology*. 2015;276(3):741-747.
29. Reilly RF. Risk for nephrogenic systemic fibrosis with gadoteridol (ProHance) in patients who are on long-term hemodialysis. *Clin J Am Soc Nephrol*. 2008;3(3):747-751.
30. Soulez G, Bloomgarden DC, Rofsky NM, et al. Prospective Cohort Study of Nephrogenic Systemic Fibrosis in Patients With Stage 3-5 Chronic Kidney Disease Undergoing MRI With Injected Gadobenate Dimeglumine or Gadoteridol. *AJR Am J Roentgenol*. 2015;205(3):469-478.
31. Wang Y, Alkasab TK, Narin O, et al. Incidence of nephrogenic systemic fibrosis after adoption of restrictive gadolinium- based contrast agent guidelines. *Radiology*. 2011;260(1):105-111.

Table 1. Imaging Requirements for Class 5 Lesions

Class	Description
0	Incomplete or technically inadequate study
5A	<p>Must meet <u>ALL</u> the following:</p> <ol style="list-style-type: none"> 1. Maximum diameter of at least 1 cm and less than 2 cm as measured on the late arterial or portal phase images 2. Increased contrast enhancement, relative to hepatic parenchyma on late arterial phase 3. Either of the following: <ul style="list-style-type: none"> • Washout during the later contrast AND peripheral rim on delayed phase • Biopsy
5 A-g	<p>Must meet <u>ALL</u> the following:</p> <ol style="list-style-type: none"> 1. Maximum diameter of at least 1 cm and less than 2 cm as measure on late arterial or portal phases images 2. Increased contrast enhancement, relative to hepatic parenchyma, on late arterial phase 3. Maximum diameter increase of at least 50% documented on serial MRI or CT obtained at least 6 months apart
5B	<p>Must meet <u>ALL</u> of the following:</p> <ol style="list-style-type: none"> 1. Maximum diameter of at least 2 cm and less than or equal to (\leq) 5cm, as measured on late arterial or portal phase images. 2. Increased contrast enhancement, relative to hepatic parenchyma, on late hepatic arterial images 3. <i>One</i> of the following: <ul style="list-style-type: none"> • Washout on portal venous/delayed phase. • Peripheral rim enhancement. • Maximum diameter increase, in the absence of ablation, by 50% or more and documented on serial MRI or CT obtained at least 6 months apart. Serial imaging and measurements must be performed on corresponding contrast phases. • Biopsy
5T	Any OPTN Class 5 5A, 5A-g, 5B lesion that was automatically approved upon initial request or extension and has subsequently been ablated

Available at https://optn.transplant.hrsa.gov/media/1922/liver_hcc_criteria_for_auto_approval_20160815.pdf

[accessed on 7/28/2017]

UNOS T2 criteria are described as:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size.
- Two or three lesions each greater than or equal to 1 cm and less than or equal to 3 cm in size

T2 HCC lesions are eligible for a standardized MELD exception if they have an AFP less than 1000 ng/mL and EITHER of the following:

- One lesion greater than or equal to 2 cm and less than or equal to 5 cm in size.
- Candidates with a single lesion between 2 and 3 cm are subject to additional requirements
- If lesion is treated and has a complete response, the candidate is not eligible for standardized MELD exception points
- If lesion meets OPTN class 5 criteria and PERSISTS after 1 or more episodes of LR therapy, OR a new lesion OPTN class 5 appears, then the patient will be eligible for MELD exception points

Table 2. Summary of Diagnostic Accuracy of Imaging for Hepatocellular Carcinoma for lesions less than 10 mm (adapted from Chou et al. PMID: 25984845)

Imaging modality	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR	Negative LR
Ultrasound without contrast	0.09 (0.02-0.29)	0.93 (0.79-1.0)	1.3	0.98
CT	0.32 (0.25-0.41)	0.69 (0.52-0.82)	1.0 (0.59-1.8)	0.99 (0.77-1.3)
MRI	0.51 (0.41-0.62)	0.89 (0.56-0.98)	4.6 (0.92-23)	0.55 (0.42-0.72)