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In the name of God

Topic:

Contrast Agents in Cancer Imaging and Their Renal Effects

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Contrast Agents in Cancer Imaging and Their Renal Effects

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Contrast Agents in Cancer Imaging and Their Renal Effects

Overview:

Contrast agents are chemical compounds allowing the visualization of specific anatomical structures of the human body in medical imaging and integral part to many imaging methods. *Ref. [1]*

Contrast Agents in Cancer Imaging and Their Renal Effects

Overview:

Contrast agents are chemical compounds allowing the visualization of specific anatomical structures of the human body in medical imaging and integral part to many imaging methods. *Ref. [1]*

Contrast agents are utilized to characterize lesions in solid organs; visualize vascular structures; follow up tumor activity; evaluate infections, abscesses, and other inflammatory diseases; and detect tissue perfusion. In addition, with the use of an appropriate contrast agent, it is possible to visualize any tubular structure, such as the gastrointestinal system, cerebrospinal fluid, salivary glands, breast ducts, and lymphatic vessels. *Ref. [1]*

Contrast Agents in Cancer Imaging and Their Renal Effects

Overview:

Iodine- and barium-containing compounds are frequently used in X-ray-based imaging modalities (radiography, fluoroscopy, computed tomography (CT), angiography), and gadolinium-containing compounds are utilized in magnetic resonance imaging (MRI). *Ref. [1]*

Contrast Agents in Cancer Imaging and Their Renal Effects

Overview:

Iodine- and barium-containing compounds are frequently used in X-ray-based imaging modalities (radiography, fluoroscopy, computed tomography (CT), angiography), and gadolinium-containing compounds are utilized in magnetic resonance imaging (MRI). *Ref. [1]*

Depending upon the anatomical structure to be visualized, contrast agents can be administered in different ways, including intravenous, intra-arterial, intrathecal, oral and rectal routes. *Ref. [1]*

Contrast Agents in Cancer Imaging and Their Renal Effects

Approach to Renal Mass *Ref. [2]*

Contrast Agents in Cancer Imaging and Their Renal Effects

Questions:

The following questions helps in the characterization of a renal lesion:

1

Is Mass Cystic or Solid?

- ✓ Knowing if a mass is cystic or solid is the single most important question for the evaluation of a renal mass. The key imaging feature for the differentiation is the presence of enhancement on **Contrast**-enhanced CT scan or MRI.
- ✓ A cystic mass is a lesion composed of no enhancing fluid. (HU<20)

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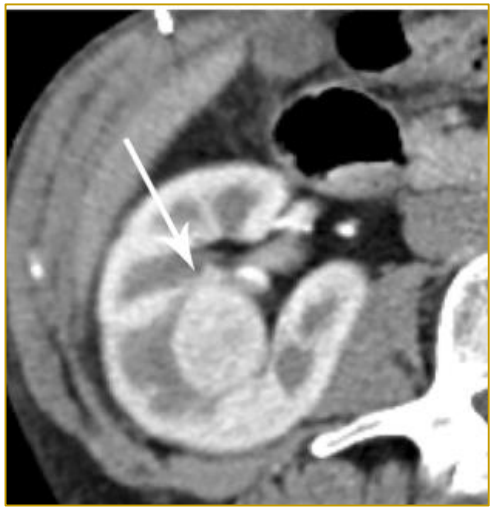
Questions:

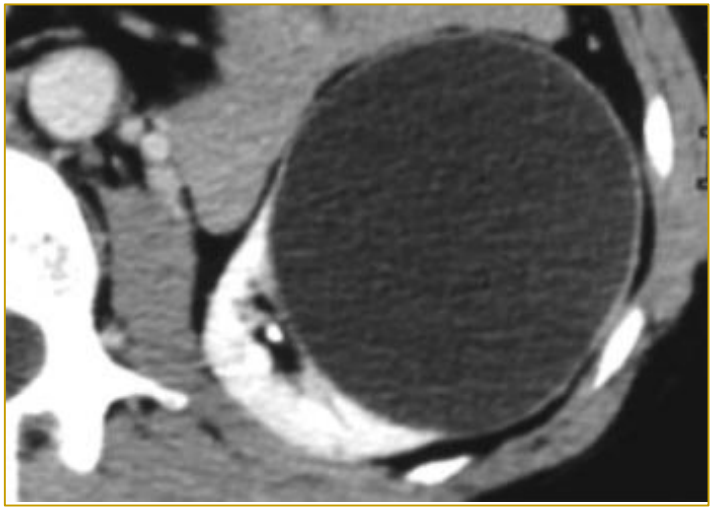
The following questions helps in the characterization of a renal lesion:

1

Is Mass Cystic or Solid?



Enhancing Solid Mass



Simple Renal Cyst

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Questions:

The following questions helps in the characterization of a renal lesion:

1

Is Mass Cystic or Solid?

✓ **Cystic lesions:**

- The Bosniak classification groups cystic lesions into 5 categories based on their imaging appearance on **Contrast**-enhanced CT scan or MRI. The classification is used to determine management of cystic lesion.

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Questions:

The following questions helps in the characterization of a renal lesion:

1

Is Mass Cystic or Solid?

✓ **Cystic lesions:**

Bosniak classes I and II: simple or minimally complicated cysts are considered benign and need no treatment or imaging follow-up.
Bosniak classes III and IV: complicated cysts with thick septations or enhancing nodules are usually considered surgical lesions due to the higher risk of malignancy.
Bosniak class IIF category includes complicated cysts requiring imaging follow-up.

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Questions:

The following questions helps in the characterization of a renal lesion:

1

Is Mass Cystic or Solid?

✓ **Solid lesions:**

- An enhancing mass is considered a solid lesion. On CT scan, enhancement is considered present when there is at least a 20-HU increase in attenuation after **contrast** injection. An increment of 10-20 HU is considered indeterminate and requires further evaluation with additional imaging, biopsy, or imaging follow-up.

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Questions:

The following questions helps in the characterization of a renal lesion:

1

Is Mass Cystic or Solid?

✓ **Solid lesions:**

➢ In renal masses, clear cell and chromophobe RCC usually show avid enhancement, papillary RCC is characterized by minimal enhancement. Benign renal lesions, such as oncocytoma and fat-poor AML, may show avid enhancement.

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Questions:

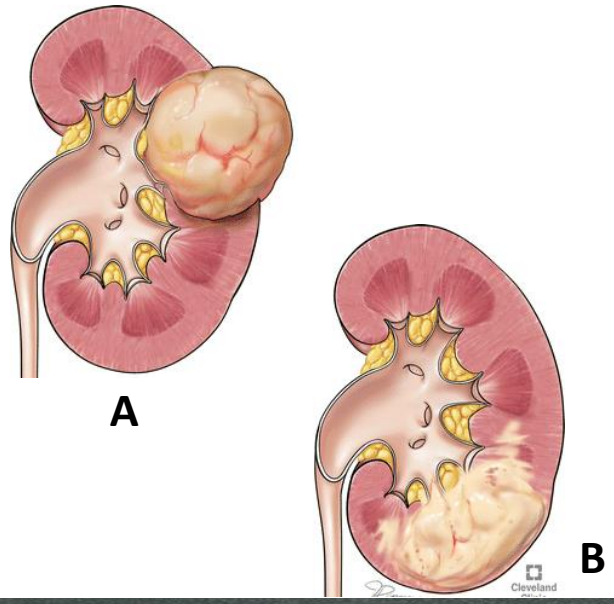
The following questions helps in the characterization of a renal lesion:

2

If a mass is solid, the next step is to evaluate the growth pattern on Contrast-enhanced CT scan or MRI:

A:
Expansile (ball-shaped growth pattern): 90% of RCCs, Oncocytomas and angiommyolipomas (AMLs)

B:
Infiltrative: transitional cell carcinoma, a minority of RCCs, medullary carcinoma and sarcomatoid tumors



A

B

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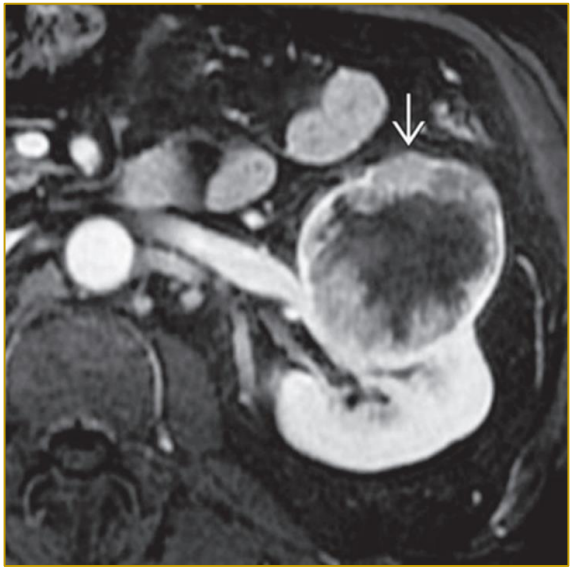
Questions:

The following questions helps in the characterization of a renal lesion:

2

If a mass is solid, the next step is to evaluate the growth pattern on Contrast-enhanced CT scan or MRI:

- ✓ Axial gadolinium enhanced MRI of a 57 year old man with renal cell carcinoma shows a typical expansile growth pattern.
- ✓ The mass has heterogeneous enhancement.



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Questions:

The following questions helps in the characterization of a renal lesion:

3

Does Mass Contain Fat?

- ✓ A renal mass containing macroscopic fat is overwhelmingly likely to be an AML.
- ✓ Although RCC may rarely contain fat. This generally occurs when large tumors have engulfed fat or have undergone osseous metaplasia; the presence of dense calcification with fat within a renal mass is highly suspicious for RCC.

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Questions:

The following questions helps in the characterization of a renal lesion:

4

Is Mass Solitary or Are There Multiple Masses?

When multiple solid renal masses are seen, one should consider syndromes.

- ✓ Multiple RCCs and cysts occur in von Hippel-Lindau disease.
- ✓ Multiple AMLs should raise the index of suspicion for tuberous sclerosis.
- ✓ Lymphoma and metastases can also present with multiple masses.

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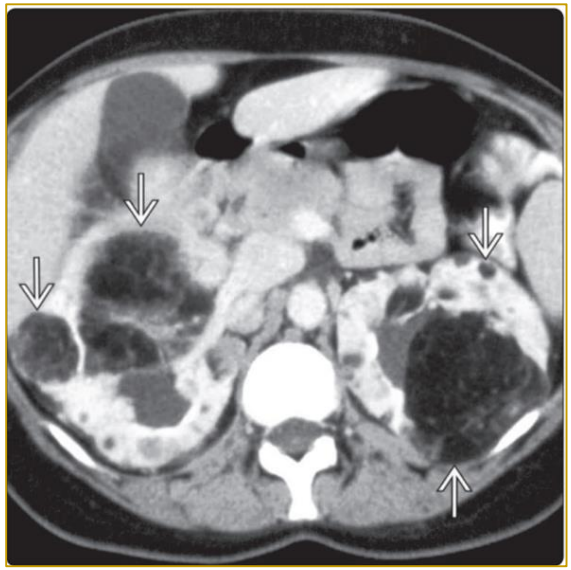
Questions:

The following questions helps in the characterization of a renal lesion:

4

Is Mass Solitary or Are There Multiple Masses?

- ✓ Axial contrast enhanced CT scan shows multiple bilateral renal fat containing masses, consistent with multiple classic AMLs in a patient with tuberous sclerosis.



Classification of Contrast Agents

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Iodine-Based Contrast Agents:

These agents can be divided according to :

1) Osmolarity (high>1500 mOsm/kg, low: 600–1000, or iso: 280–290)

2) Ionicity (ionic or nonionic)

3) Number of benzene rings (monomer or dimer)

Ref. [3] and [4]

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Iodine-Based Contrast Agents:

- ✓ Nonionic contrast agents cause less discomfort and fewer adverse reactions compared with ionic agents.
- ✓ Low-osmolarity and iso-osmolarity contrast agents are associated with significantly lower rates of acute reactions compared with high-osmolar agents.

Ref. [3] and [4]

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Iodine-Based Contrast Agents:

Table summarizes different generations of iodinated contrast media with their corresponding iodine content and osmolality.

Ref. [2]

1st Generation: Ionic High-Osmolar Contrast Media		
Name	Iodine Content	Osmolality
Diatrizoate *(Hypaque 50)*	300 mg/mL	1550 mOsm/kg
Metrizoate *(Isopaque 370)*	370 mg/mL	2100 mOsm/kg
2nd Generation: Nonionic Low-Osmolar Contrast Media		
Name	Iodine Content	Osmolality
Iopamidol *(Isovue 370)*	370 mg/mL	800 mOsm/kg
Iohexol *(Omnipaque 350)*	350 mg/mL	880 mOsm/kg
Iopromide *(Ultravist 370)*	370 mg/mL	770 mOsm/kg
Ioxilan *(Oxilan 350)*	350 mg/mL	700 mOsm/kg
3rd Generation: Nonionic Iso-Osmolar Contrast Media		
Name	Iodine Content	Osmolality
Iodixanol *(Visipaque 320)*	320 mg/mL	290 mOsm/kg

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Visipaque:

- ✓ Arguably the most advanced CT contrast agent on the market today is iodixanol (Visipaque®), which was first approved in 1996. Iodixanol is a nonionic dimeric agent and is the only CT contrast agent available with osmolarity similar to blood (290 mOsm/kg)

Ref. [5]

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Gadolinium-Based Contrast Agents:

GBCAs are classified according to :

1)Ionicity (ionic or nonionic)

2)The chelating ligand (macrocyclic or linear)

3)Their pharmacokinetics (extracellular or organ specific)

Ref. [3] and [6]

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Gadolinium-Based Contrast Agents:

- ✓ Both ionic and nonionic GBCAs can be used for intravascular injection with relatively little or no difference in acute reactions and discomfort.
- ✓ Macrocyclic and ionic chelates tend to be more stable than other gadolinium compounds, and therefore, have a decreased risk for causing NSF.

Ref. [3]

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Chelating Ligand:

- ✓ Many of the paramagnetic materials used as contrast agents in MRI contain toxic metal ions. Therefore, in order to reduce toxicity, gadolinium is not applied in its natural form but is applied in a chelate form by attaching with a ligand such as DTPA(Diethylenetriamine pentaacetate).

Ref. [7]

Contrast Agents in Cancer Imaging and Their Renal Effects

Chelating Ligand:

- ✓ Gadolinium compounds with long fatty chains such as Gd-EOBDTPA82 and to a lesser degree Gd-BOPTA83 are metabolized by the liver in certain proportions and excreted via the bile ducts. Therefore, these molecules are liver-specific agents and are preferred for contrast enhancement of the liver parenchyma and evaluation of the biliary tract. Therefore, these agents are very suitable for detecting liver lesions such as liver metastasis.

Ref. [1]

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Renal Adverse Effects

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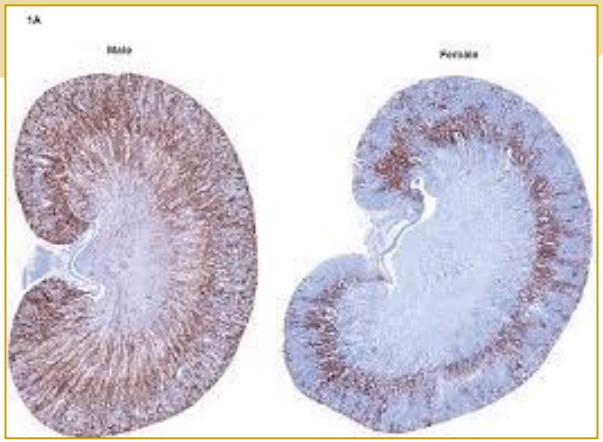
ACR Committee on Drugs and Contrast Media 2023:

- Contrast Material– induced Nephrotoxicity (CIN)
- Nephrogenic Systemic Fibrosis (NSF)



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CIN:

CIN is described as *"a sudden deterioration in renal function (i.e. acute kidney injury) following the recent intravascular administration of contrast media in the absence of another nephrotoxic event. "*

Ref. [3]

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CIN:

The criteria for diagnosing CIN:

1) Absolute serum creatinine increase ≥0.3 mg/dL (>26.4 µmol/L).
2) A percentage increase in serum creatinine ≥ 50% (≥1.5-fold above baseline).
3) Urine output reduced to ≤ 0.5 mL/kg/hour for at least 6 hours

Ref. [8]

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Risk Factors:

The most important risk factor is pre-existing severe renal insufficiency :

Patients with an eGFR <30 mL / min/1.73m^2 to be at significant risk (patients with eGFR 30-44 mL / min/1.73m^2 are at borderline but not statistically significant risk)

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Risk Factors:

Multiple other risk factors have been proposed, including :

Diabetes mellitus, dehydration, cardiovascular disease, diuretic use, advanced age, hypertension, hyperuricemia, and multiple iodinated contrast medium doses in a short time interval (<24 hours)

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Risk Factors:

- Anuric patients with end-stage renal disease who do not have a functioning transplant kidney are not at risk for CIN because their kidneys are nonfunctional; these patients may receive intravascular iodinated contrast material without risk of additional renal injury.

- But, patients undergoing dialysis who make more than 1-2 cups of urine/day (100 mL) should be considered non-anuric and treated as high-risk patients.

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Prevention:

Suggested Indications for Renal Function Assessment Before The Intravascular Administration

Personal history of renal disease, including:

- Known chronic kidney disease (CKD)
- Remote history of AKI
- Dialysis
- Kidney surgery
- Kidney ablation
- Albuminuria
- History of diabetes mellitus (optional)
- Metformin or metformin-containing drug combination

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Prevention:

- ✓ Prior to contrast medium administration, adequate patient assessment and communication between radiologist and referring clinician are important. Consideration of alternative imaging strategies and an individualized risk-benefit assessment are fundamental.

- ✓ It is not recommended to reduce doses to attempt to mitigate the risk of CIN as this may result in suboptimal or nondiagnostic images. Instead, standard contrast dosing is recommended.

Contrast Agents in Cancer Imaging and Their Renal Effects

Recommendations:

- Dosing intervals shorter than 24 hours be avoided except in urgent situations.
- Low or iso-osmolality contrast agents are less nephrotoxic.
- Intravenous volume expansion prior to contrast medium administration is indicated for patients who have AKI, severe CKD with an eGFR less than 30 mL/min/1.73m^2 or in patients with high-risk circumstances (e.g. numerous risk factors, recent AKI and borderline eGFR:30-44 mL/min./1.73 m^2)

Contrast Agents in Cancer Imaging and Their Renal Effects

Volume Expansion:

- Isotonic fluid such as 0.9% normal saline (NS) is preferred.
- Typical prophylaxis regiments begin 1 hour prior to the exam and continue 3-12 hours after.
- Typical doses may be fixed volume (e.g., 500 mL NS) before and after or weight based volumes (1-3mL/kg per hour).
- Oral hydration has not been well studied for patients with eGFR less than 30 mL/min/1.73 m^2 or in patients with AKI.

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Volume Expansion:

- The use of sodium bicarbonate is challenging and has not yet been confirmed.
- Other theoretical renal-protective medications such as N-acetylcysteine, mannitol ,furosemide ,theophylline, endothelin-1, and fenoldopam are also not recommended for CIN reduction.

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Metformin:

If acute kidney injury were to be caused by the iodinated contrast media, an accumulation of metformin could occur, with resultant lactate accumulation.

Contrast Agents in Cancer Imaging and Their Renal Effects

Metformin:

If acute kidney injury were to be caused by the iodinated contrast media, an accumulation of metformin could occur, with resultant lactate accumulation.

In patients who are known to have acute kidney injury or severe chronic kidney disease (eGFR< 30), or are undergoing arterial catheter studies that might result in emboli to the renal arteries, metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

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NSF:

NSF is a rare but serious systemic disease characterized by fibrosis of the skin and other tissues throughout the body in renally impaired individuals.

❑ Patients should be considered at risk of developing NSF if any of the following conditions apply to the patient:

- **On dialysis (of any form)**
- **Severe or end-stage CKD (eGFR<30 mL/min/1.73 m^2) without dialysis**
- **AKI**

Contrast Agents in Cancer Imaging and Their Renal Effects

Recommendations:

- The lowest dose of GBCA required to obtain the needed clinical information should be used in at-risk patients (0.1 nmol/kg).
- Macrocyclic and ionic chelates have a decreased risk for causing NSF so group II agents are strongly preferred in patients at risk for NSF.
- If a contrast-enhanced cross-sectional imaging study is required in an anuric patient, it would be reasonable to consider administering iodinated contrast media and performing a CT scan rather than an MRI.

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Recommendations:

- In patients who are already receiving dialysis, if feasible, elective GBCA-enhanced MRI examinations be performed before regularly scheduled dialysis.
- One recommended protocol is performing 3-hour dialysis sessions, three times daily for 3 consecutive days. *Ref. [3]*
- Initiating dialysis in those who are not already receiving it is not recommended.

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GBCAs Classification:

Not recommended:

Group I: Agents associated with the greatest number of NSF cases
Gadodiamide (Omniscan® – GE Healthcare)
Gadopentetate dimeglumine (Magnevist® – Bayer HealthCare Pharmaceuticals)
Gadoversetamide (OptiMARK® – Guerbet)

Contrast Agents in Cancer Imaging and Their Renal Effects

GBCAs Classification:

Recommended:

Group II: Agents associated with few, if any, unconfounded cases of NSF
Gadobenate dimeglumine (MultiHance® – Bracco Diagnostics)
Gadobutrol (Gadavist® – Bayer HealthCare Pharmaceuticals)
Gadoteric acid (Dotarem® – Guerbet, Clariscan – GE Healthcare)
Gadoteridol (ProHance® – Bracco Diagnostics)
Gadopiclenol (Elucirem® – Guerbet, Vueway® – Bracco Diagnostics)

Contrast Agents in Cancer Imaging and Their Renal Effects

GBCAs Classification:

Recommendation???

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; Primovist in many countries)

New Contrast Agents

Contrast Agents in Cancer Imaging and Their Renal Effects

Overview:

Current agents are effective but come with a number of risks. Nephrotoxicity remains the most serious flaw of the currently available agents and the development of kidney-safe radiocontrast agents is sorely needed.

Contrast Agents in Cancer Imaging and Their Renal Effects

Overview:

Current agents are effective but come with a number of risks. Nephrotoxicity remains the most serious flaw of the currently available agents and the development of kidney-safe radiocontrast agents is sorely needed.

In addition, current radiocontrast agents are cleared from the blood pool quickly, require large dosage volumes, may impact thyroid dysfunction, and occasionally cause severe immune responses.

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Nanoparticle Contrast Agents:

- It is likely that nanoparticle contrast agents will make up a large share of the next generation of CT contrast agents
- Because nanoparticles generally have intrinsically low osmolarity, a high concentration of X-ray attenuating elements can be used without increasing the osmolarity of the media above that of blood.
- Nanoparticles of any type can be made large enough to evade glomerular filtration at the kidneys which allow for longer imaging times as well as a decrease or elimination in nephrotoxicity.

Ref. [5]

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Nanoparticle Contrast Agents:

- Nanoparticle contrast agents are capable of cell tracking and targeted imaging.
- Nanoparticle contrast agents may be modified to exhibit therapeutic functions, such as anti-tumor effects. Micellar and liposomal nanoparticles may even be co-loaded with chemotherapy agents.
- Nanoparticles can also be designed so that they do not cross the placental barrier or be transferred into breast milk, a serious practical improvement over current agents.

Ref. [5]

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Nanoparticle Contrast Agents:

- Metallic nanoparticles(such as gold nanoparticle), Micellar nanoparticles, liposomal nanoparticles, Polymeric nanoparticles and lipid nanoemulsions are different types of nanoparticles.
- Micellar, liposomal, and metallic nanoparticles have each shown acceptable safety profiles in murine models on at least one occasion.

Ref. [5]

Contrast Agents in Cancer Imaging and Their Renal Effects

Other Contrast Agents of MRI:

- Currently, numerous nanoparticles conjugated with paramagnetic ions such as iron and manganese with different shapes, sizes, and compositions are being developed.
- The common goal is to produce molecules that are tissue or organ specific and thus provide high contrast resolution for particular indications and have fewer side effects.

Ref. [1]

Contrast Agents in Cancer Imaging and Their Renal Effects

Iron Oxide Nanoparticles:

- These agents include superparamagnetic iron oxides (SPIOs) and ultra-small superparamagnetic iron oxides (USPIOs).
- After intravenous administration, the clinically approved SPIO particles are cleared from the blood by phagocytosis provided by the reticuloendothelial system (RES), so that the uptake of the particles in the liver, spleen, bone marrow and lymph nodes is observed.
- Feridex has been approved by the Food and Drug Administration.

Ref. [7]

Contrast Agents in Cancer Imaging and Their Renal Effects

Manganese Chelates:

- Manganese chelates such as Teslascan (Opacim) and manganese dipyridoxyl diphosphate (MnDPDP) have clinical use for hepatocytes.
- In liver imaging, manganese chelates increase the signaling of hepatocytes in T1-weighted series. Tumor containing tissues do not hold manganese chelates due to not containing hepatocyte and cause the contrast to be apparent between lesion and liver tissue.

Ref. [7]

Contrast Agents in Cancer Imaging and Their Renal Effects

New MRI Methods:

- **Arterial spin labeled (ASL) MRI** provides measures of tissue perfusion without the need of an exogenous contrast agent. Therefore ASL MRI can be used for renal function and detecting renal mass that perfusion in clear cell RCC, chromophobe RCC and oncocytomas is higher than normal renal tissue. *Ref. [9]*

- **Blood oxygen level dependent (BOLD) MRI** is a method that evaluate tissue oxygen levels and renal function. Decreased oxygen levels is visible in both acute and chronic kidney injury. *Ref. [10]*

Contrast Agents in Cancer Imaging and Their Renal Effects

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