4,3,2,1...How Many Phases are Needed? Balancing Diagnostic Efficacy and Radiation Modulation for MDCT Imaging of Renal Cell Carcinoma

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Background

- Renal cell carcinoma (RCC) is the 8th most common malignancy in adults, with rising incidence[1].
- Incidentally diagnosed tumors via CT, MRI, and ultrasound are steadily increasing and accounted for 60% of cases in the 1990's compared with 10% in the early 1970's. [2]
- Renal imaging is the only body MDCT protocol where 4 phases of image acquisition may be supported by literature, but 4 phase acquisition can lead to radiation doses of up to 56 mSv.
- MDCT protocol revision to reduce phases must consider the relative diagnostic utility of each phase.

Overview

- This exhibit combines literature and case review to define the relative utility of each MDCT phase in diagnosis, management and follow up imaging.
- Surveillance imaging is performed for small masses, necessitating a determination of optimal protocol for lesion characterization (to triage appropriately) and radiation modulation during serial MDCT exams.
- Specific goals include:
  - ❑ Understanding how each phase contributes to diagnostic efficacy
  - ❑ Balancing diagnostic efficacy with radiation dose modulation
  - ❑ Devising an algorithm for radiation reduction by reducing acquisitions during follow-up based on disease status

RCC Subtypes

- Histologic subtypes of RCC
  - Clear Cell (conventional) ~ 60-65% of cases
  - Papillary ~ 13-15% of cases.
    - More favorable prognosis compared to clear cell.
  - Chromophobe ~5%
    - Best prognosis amongst RCC, rarely metastasizing [4]
- Imaging features reliably distinguish histologic subtypes and guide surgical decision making.
- For small masses (< 4 cm), active surveillance has gained interest as opposed to nephron sparing surgery and ablation, particularly in elderly or patients with significant comorbidities. Noninvasive diagnostic information to characterize RCC subtype can help make an informed treatment decision.

Percutaneous Needle Biopsy

- Renal biopsy for diagnosis of RCC remains controversial
- A recent systematic review with > 3000 biopsies demonstrated:
  - High PPV, indicating strong confidence with positive result
  - High non-diagnostic rate (14%), with the majority of non-diagnostic lesions found to be malignant at surgical pathology.
  - Poor negative predictive value with 36.7% of benign biopsy lesions found to be malignant at surgical pathology. [5]
- NCCN guidelines do not recommend biopsy prior to surgery.
  - Biopsy may be considered in cases of small lesions to establish diagnosis of RCC and active surveillance strategies, cryoablation, radiofrequency ablation strategies.
  - Biopsy should also be considered when attempting to distinguish between urothelial carcinoma or lymphoma.
- Absence of tissue diagnosis necessitates MDCT protocol design and interpretative practice that can provide the most diagnostic information about histologic subtype.

JHH 4 Phase MDCT Protocol

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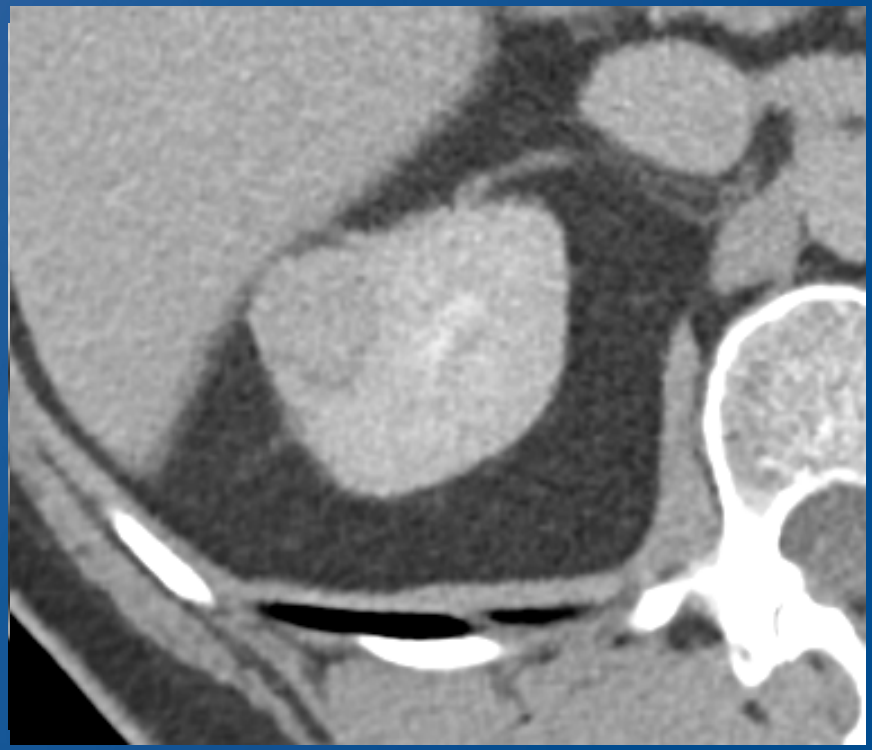
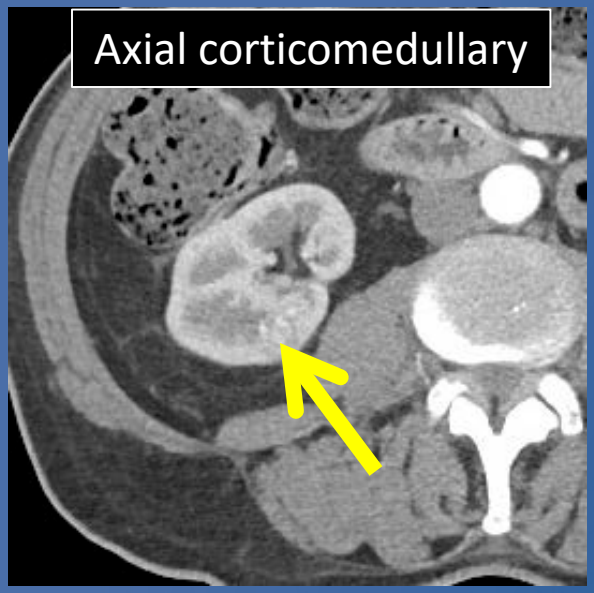
- Noncontrast phase
  - Visualization of fat & calcifications
  - Assess degree of enhancement
  - Using dual energy scanners, a virtual noncontrast dataset can be created to eliminate this acquisition
- Arterial phase (corticomedullary, CM)
  - Obtained at 25-35 seconds to evaluate arterial vasculature for tumor parasitization in additional to renal parenchyma
  - Longer delays often used (35-55 seconds)
- Venous phase (nephrographic)
  - Obtained at 60-70 seconds
  - Longer delays often used (90-120 seconds)
- Delayed phase (excretory)
  - Obtained at 3-5 minutes
  - Longer delay results in beam hardening artifact that can obscure collecting system

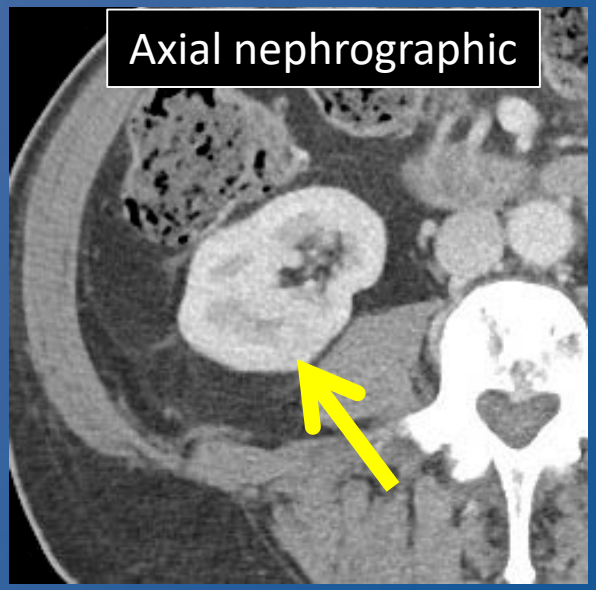


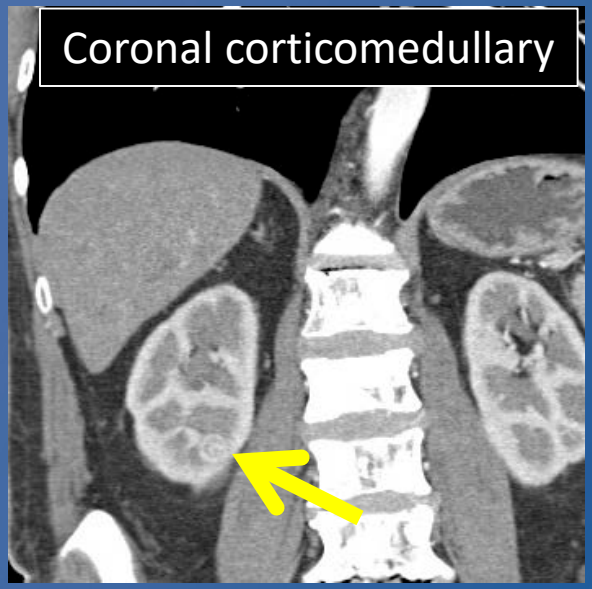
RCC Detection

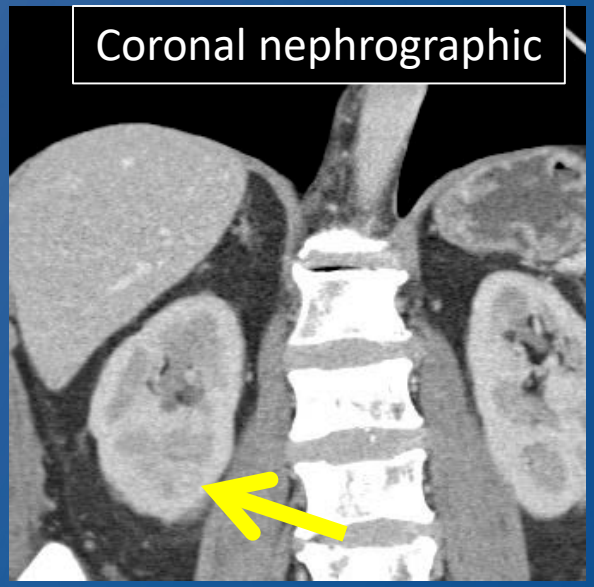
- Corticomedullary phase is critical as clear cell makes up the majority of cases and avidly enhances in the arterial phase.
- Nephrographic phase has been shown to be more sensitive for detecting small renal masses <5 cm.[6]
- Lesion conspicuity depends on location. For example, a small vascular RCC will be better visualized on CM phase if located in the medulla, which is why small cortical masses are missed.
- Multiplanar reconstructions make subtle lesions more apparent.

Multiphase & MPR for Detection









Subtle hypervascular lesion within the posterior right kidney, which is isoattenuating on venous phase and only apparent on the arterial images. The lesion is subtle on the axial image but is more apparent on coronal MPR. Inspection of kidneys with coronal MPRs is critical component of search patterns to ensure diagnostic efficacy.

RCC Characterization

- Size
  - Directly applicable to staging
- Enhancement
  - All lesions will demonstrate some degree of enhancement.
  - Degree of enhancement aids in differentiating between varying subtypes of renal cell carcinoma
- Heterogeneous vs homogeneous
- Distinguishing features
  - Presence of fat
  - Central scarring
  - Necrosis
- Vascular invasion
- Local invasion
- Regional lymph node metastasis
- Metastasis

Clear Cell RCC

- Small masses are more homogeneous, but tumor becomes heterogeneous as it enlarges
  - Intratumoral hemorrhage, necrosis, calcifications
- Hypervascular with avid arterial enhancement
  - Mean corticomedullary phase attenuation of 140 HU in study including 409 patients with clear cell RCC. [8]
  - It is important to note that nephrographic phase clear cell lesions are still more avidly enhancing than the other subtypes.
  - Lesions typically progressively washout from corticomedullary to nephrographic and delayed phase. [9]

Papillary RCC

- Homogeneous
- Hypovascular relative to the renal parenchyma.
- Progressive uptake of contrast from corticomedullary to nephrographic and excretory phases.
  - Highly specific for papillary RCC
- Lower mean attenuation on both corticomedullary and nephrographic phases than clear cell and chromophobe. [10]
  - Corticomedullary phase mean density 50-60 HU and nephrographic phase mean density 65-75 HU [4]

Chromophobe RCC

- Lesions tend to be more homogeneous compared to clear cell lesions.
- Lesions often hypovascular relative to the renal cortex demonstrating moderate contrast uptake.
  - Mean attenuation 80-100 HU in corticomedullary phase, less than clear cell but more avidly enhancing than papillary. [4]
  - There is some overlap and corticomedullary phase enhancement may rival that of clear cell lesions.
- Approximately 1/3 of cases demonstrate central scar similar in appearance to oncocytoma. [11]

Differentiating Clear Cell vs Chromophobe vs Papillary RCC

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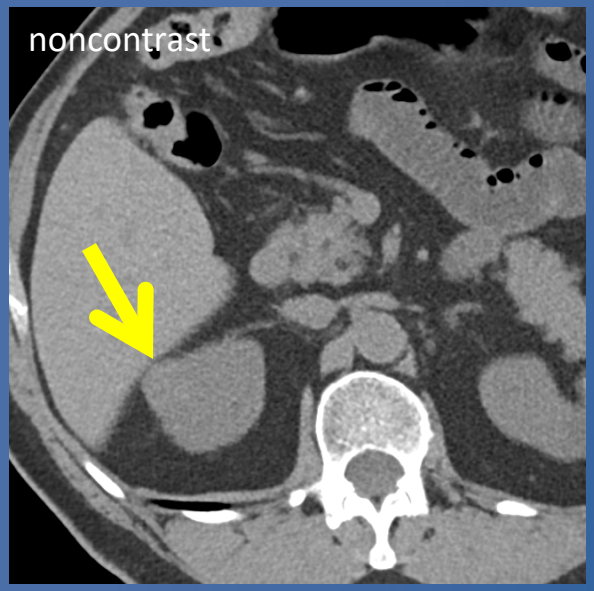
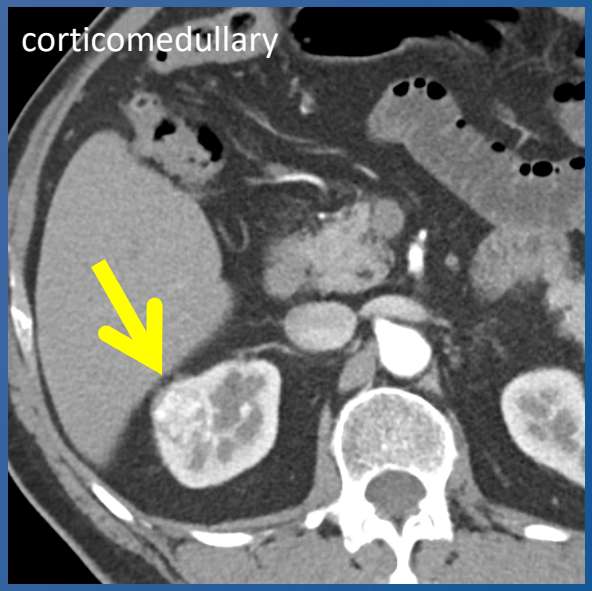
- Clear cell lesions will appear heterogeneous whereas papillary will appear homogeneous.
- A central stellate scar or spoke-wheel enhancement is characteristic of chromophobe RCC or oncocytoma.
- Enhancement pattern across phases provides diagnostic information, supporting use of 4 acquisitions for initial characterization
  - Clear cell RCCs usually enhance most during corticomedullary phase and progressively washout.
  - Absolute attenuation <100 HU highly specific for non-clear cell subtype, with the caveat that high grade clear cell RCC develop regions of necrosis with reduced vascularity. [8]
  - Progressive uptake of contrast from corticomedullary to nephrographic phase characteristic of papillary RCC. [9]

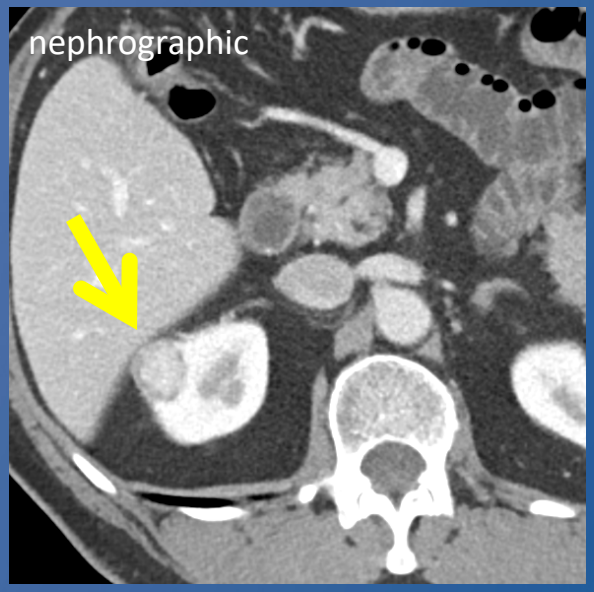
Differentiating Clear Cell vs Chromophobe vs Papillary RCC

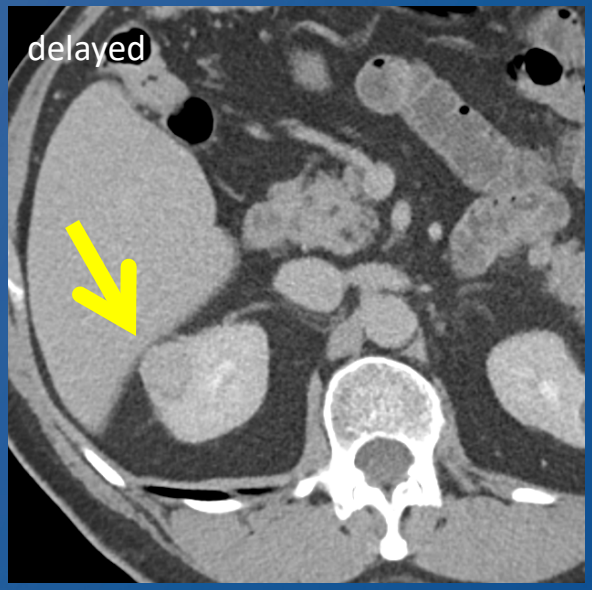
- Enhancement thresholds from baseline
  - Clear cell can be differentiated from papillary with an enhancement threshold from baseline of 55 HU on corticomedullary, 65 HU on nephrographic, and 55 HU on excretory phase with 94% sensitivity.
  - Clear cell can be differentiated from chromophobe with an enhancement threshold of 75 HU from baseline on corticomedullary, 85 HU on nephrographic, and 60 HU on excretory with 92% sensitivity. [12]
- Absolute washout ratio has also been shown to be helpful in distinguishing between clear cell and papillary.
  - Absolute washout ratio = 100 x (Corticomedullary – Excretory)/(Corticomedullary – Unenhanced)
  - Absolute washout ratio threshold of 11.4 highly sensitive and specific for differentiating clear cell from papillary RCC, 88 and 92 % respectively.
  - Chromophobe demonstrates a similar washout pattern to clear cell. [8]
- Both of these metrics demonstrate the utility of including unenhanced and excretory phase imaging at diagnosis.

Clear Cell RCC Case



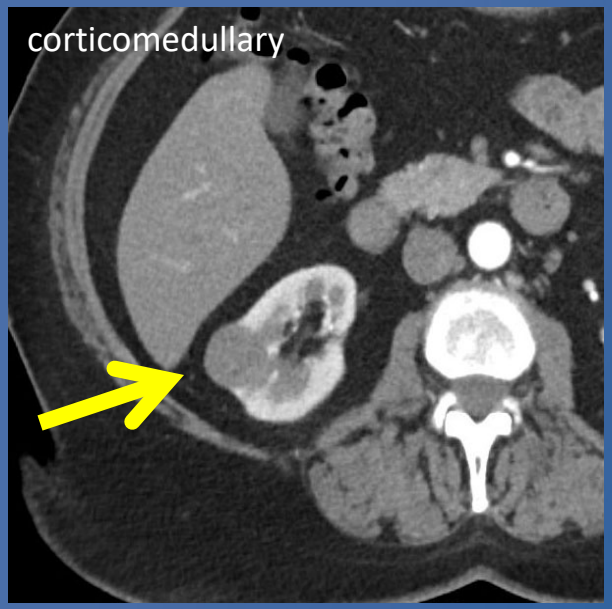


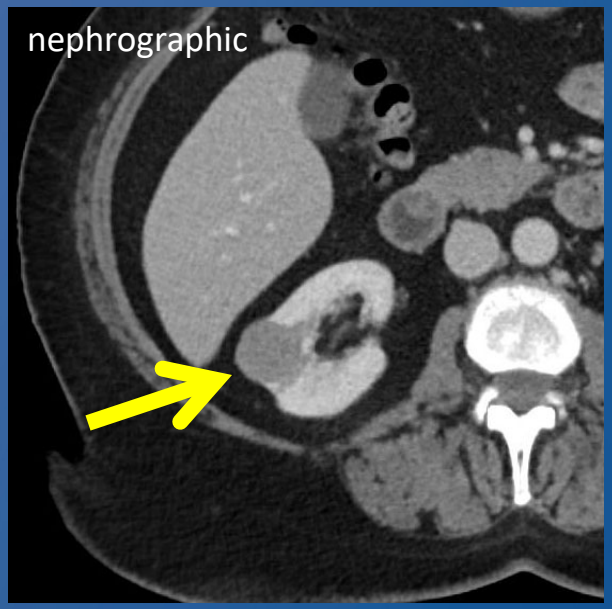


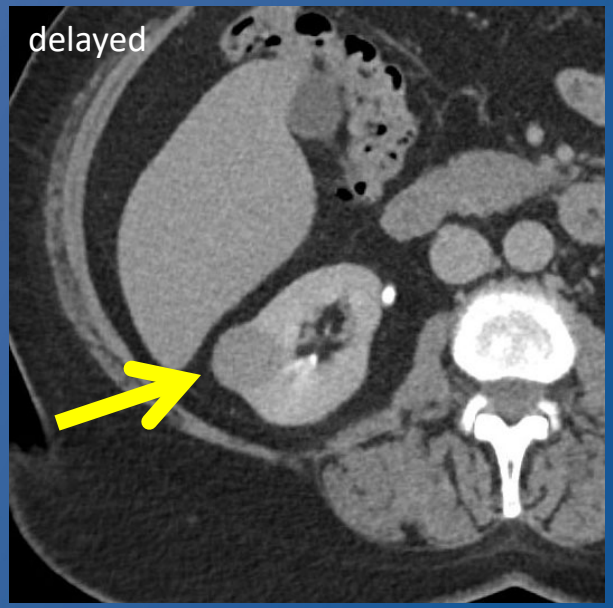


Classic imaging features in 71 year old female with pathologically proven clear cell RCC (arrow) of the right kidney. Heterogeneous avidly enhancing lesion that is highest attenuation on arterial phase and progressively washes out measuring 160 HU on corticomedullary phase, 155 HU on nephrographic phase, and 86 HU on delayed phase.

Papillary RCC Case







Homogeneous mildly enhancing lesion within the right kidney reaching 49 HU on corticomedullary phase and 66 HU on venous and delayed phases resected and found to be a papillary RCC. Progressive enhancement as seen in this case characteristic of papillary lesions and not a feature of clear cell lesions.

Mimicking Lesions

- Oncocytoma
  - A heterogeneous moderately or avidly enhancing mass that can mimic clear cell or chromophobe. Central hypoattenuating stellate scar seen in approximately 1/3-1/2 of cases but can also be seen in necrotic RCC and is commonly seen in chromophobe.
  - CT criteria for differentiating oncocytoma such as segmental enhancement inversion and washout characteristics in the literature ultimately have limited clinical application.
  - Promising molecular imaging studies are ongoing using ^{99m}Tc-Sestamibi to differentiate oncocytoma from renal cell carcinoma.
    - Oncocytomas are mitochondria rich masses and thus demonstrate a high avidity for Sestamibi.
    - Importantly, clear cell and papillary renal cell carcinoma do not take up Sestamibi.
    - Chromophobe RCC is a source for potential false positive.
- Lipid poor angiomyolipoma
  - Approximately 5% of angiomyolipomas have minimal or no visible fat on imaging.
  - Homogeneous enhancement pattern and prolonged enhancement are valuable findings to differentiate lipid poor angiomyolipoma from RCC. These two findings demonstrated a positive predictive value of 91% and a negative predictive value of 87% in one study. [13]
  - Homogeneous hyperdensity relative to renal parenchyma on unenhanced CT. This finding is not specific but may make further diagnostic studies worthwhile.

Enhancement & Grade

- Multiple studies have shown an inverse relationship between the degree of enhancement in clear cell lesions and Fuhrman grade.
- In 255 patients with pathologic proven clear cell lesions and age > 58 years: irregular tumor margins and low degree of corticomedullary phase enhancement (less than 0.65 lesion to cortex relative enhancement) were independent risk factors for high grade malignancies. [3]
- One possible explanation is that the degree of necrosis in higher grade lesions contributes to the decreased attenuation.

Preoperative Staging Treatment Planning

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- Multi-phase CT critical for treatment planning.
- CT can accurately characterize size, local spread, extension into the renal vein and IVC, lymph node and distant metastatic disease.
- Utility of each phase for treatment planning.
  - Corticomedullary demonstrates the vascular supply to the kidney, identifies arterial parasitization, important for operative approach and identifies clear cell metastases.
  - Nephrographic phase shows IVC extension, important for staging.
  - Excretory phase shows tumor extension into the collecting system, important for selecting nephron sparing procedure vs nephrectomy[14]

Preoperative Staging Treatment Planning

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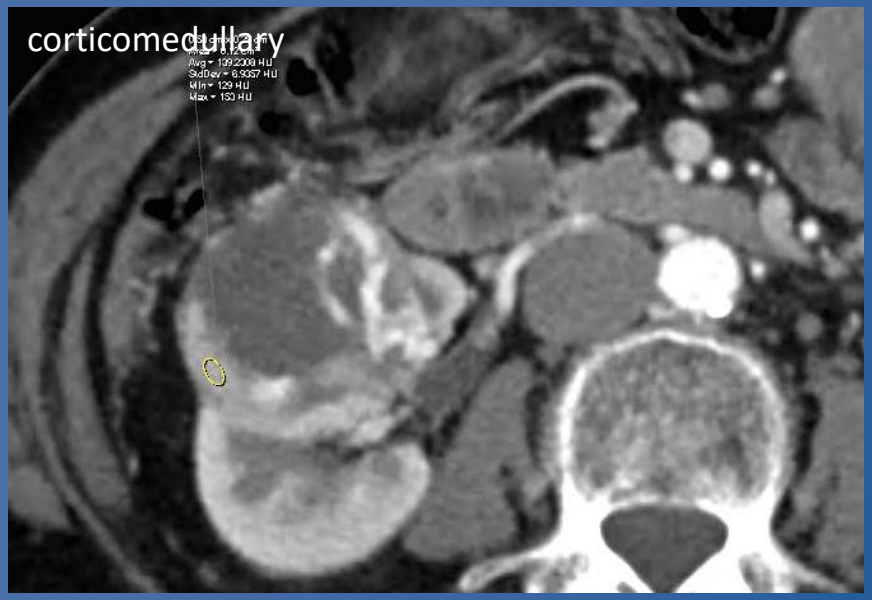
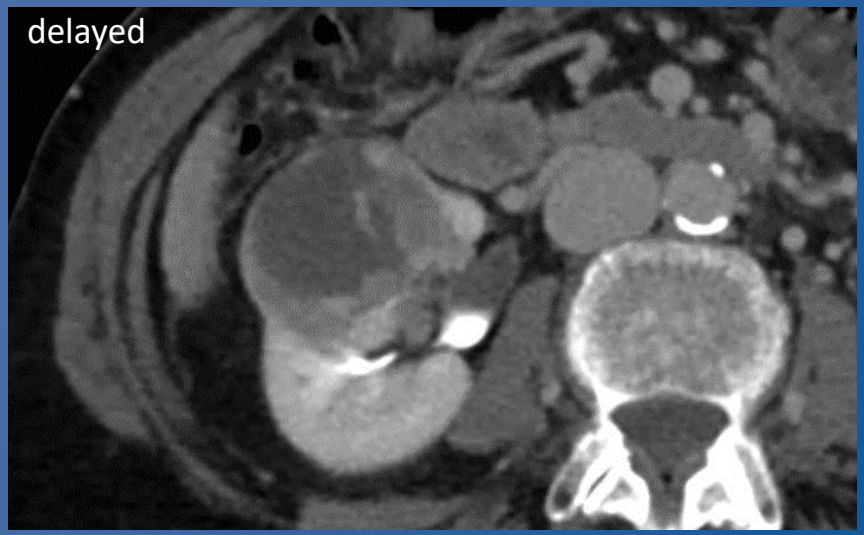
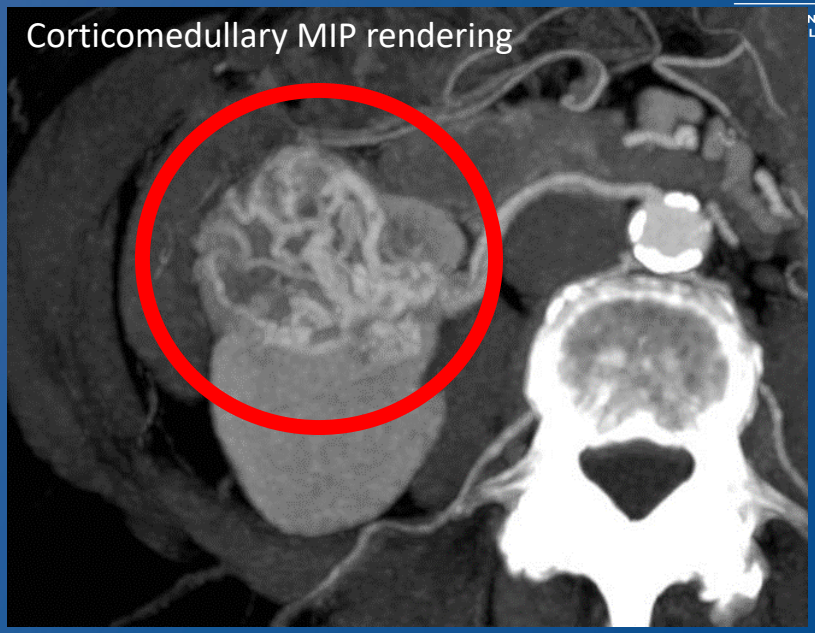
- In addition to basic staging and delineating surgical anatomy, multiphase CT can provide further diagnostic information to help guide management.
- Imaging findings suggestive of chromophobe or papillary subtypes, which carry a better prognosis than clear cell, can better inform a patient considering conservative treatment options such as active surveillance or nephron sparing therapy.
- Conversely, imaging features suggestive of clear cell RCC, which carries a worse prognosis, enable patients and clinicians to recognize lesions likely to behave more aggressively.
- If pathologically proven to be clear cell, the degree of enhancement has been shown to be inversely correlated with tumor grade.

CT Findings Aiding in Surgical Planning







79 year old woman with newly diagnosed highly vascular clear cell carcinoma in the right kidney. Multiphase imaging enables reliable distinction of clear cell from papillary and chromophobe variants by demonstrating CM phase hypervascularity and progressive washout on nephrographic and delayed phases. Large feeding arteries (circle), demonstrated by arterial phase MIP rendering, may result in conversion from a laparoscopic to an open procedure and are important to report to the urologist.

Surveillance After Nephrectomy

- Total nephrectomy
  - Surgical material, calcifications, and bowel or pancreas occupying the surgical site can create diagnostic challenges.
  - Unenhanced phase on 1st post-operative scan can distinguish surgical material, calcification, or dense ingested material within bowel. These lesions will not enhance on subsequent phases.
- Partial nephrectomy
  - Arterial phase is critical to distinguishing hypervascular residual or recurrent tumor from postsurgical change, even tiny lesions. [15]
  - Recurrent neoplasms likely to demonstrate a strongly enhancing mass that progressively washes out on later phases as opposed to mildly enhancing ill defined desmoplastic reaction which shows persistent mild enhancement. [16]
  - Delayed phase important to identify collecting system leak.

Partial Nephrectomy: Surgical Material vs Tumor

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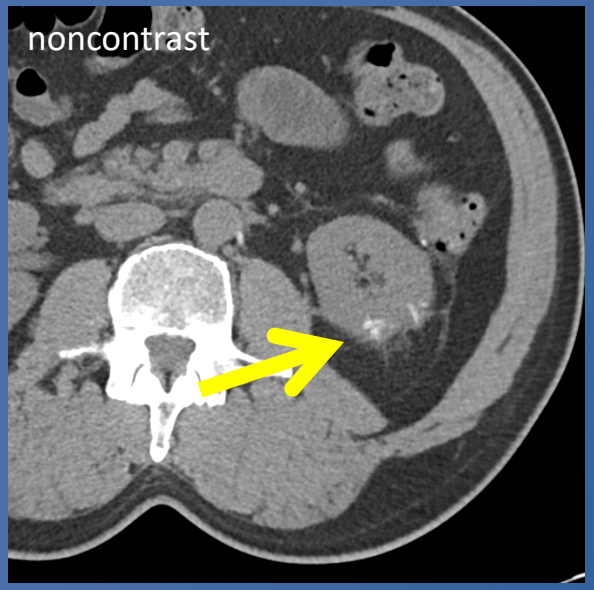
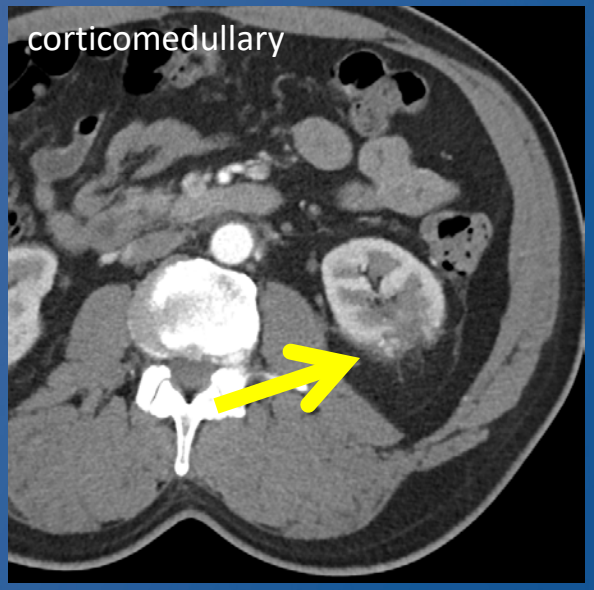
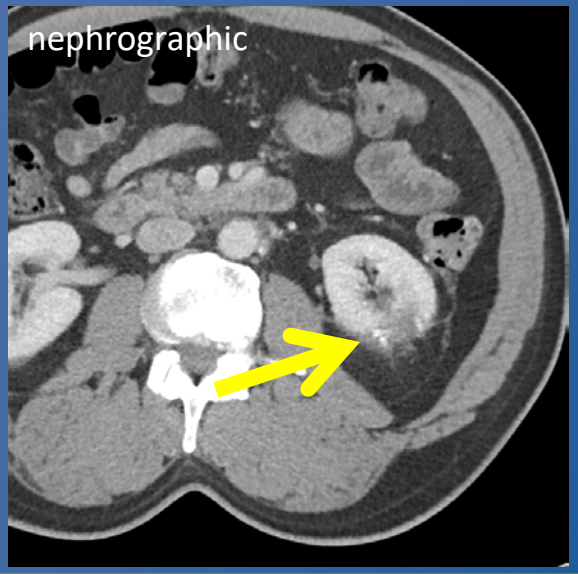
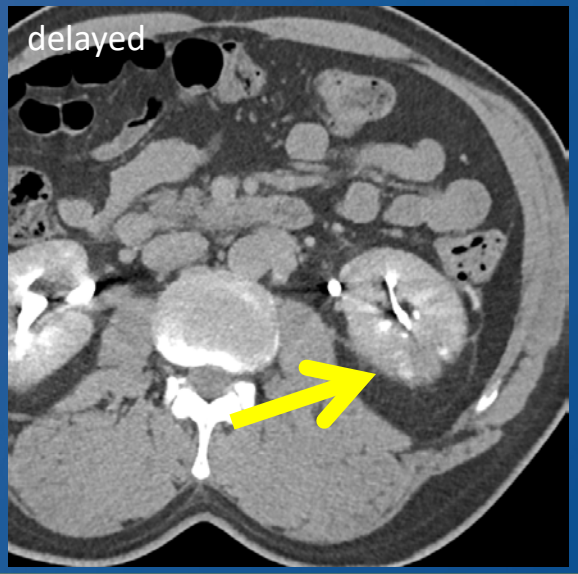


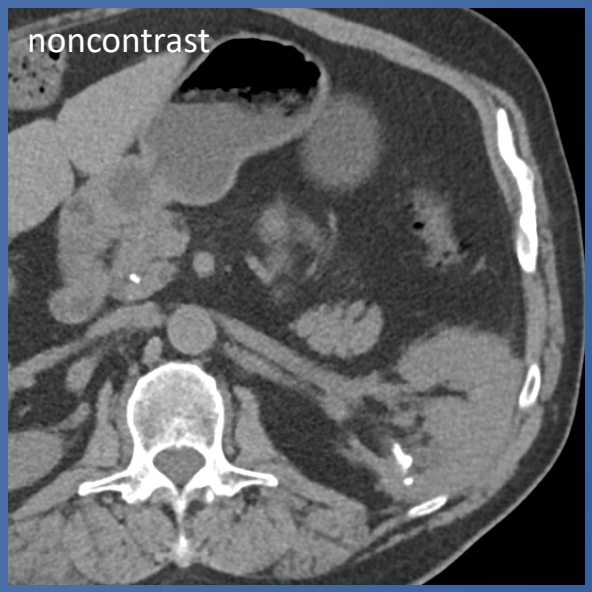


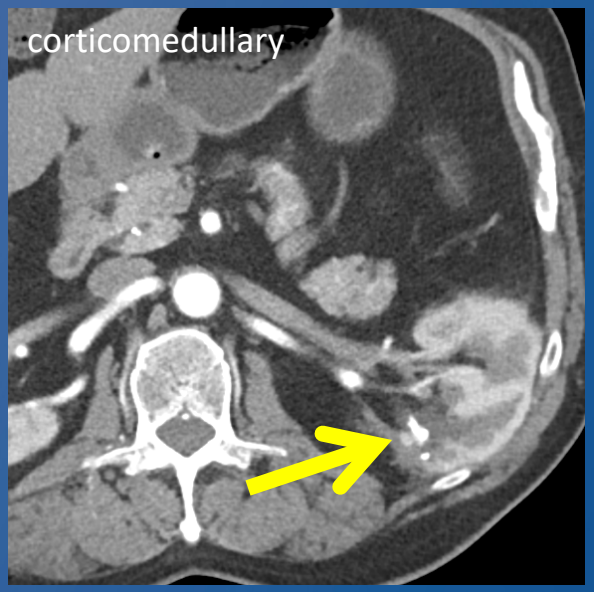


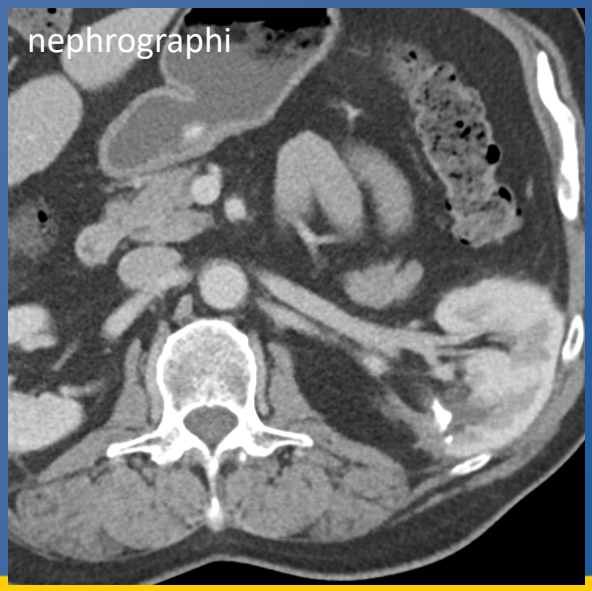


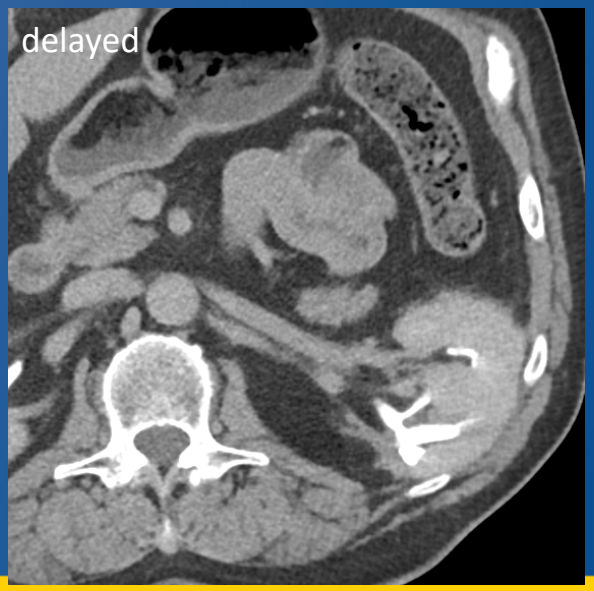
Noncontrast images are essential in the postoperative patient to distinguish surgical material from enhancing tumor recurrence. These images demonstrate surgical material (arrow) at the nephrectomy site that mimics enhancement on postcontrast images.

Partial Nephrectomy: Surgical Material vs Tumor







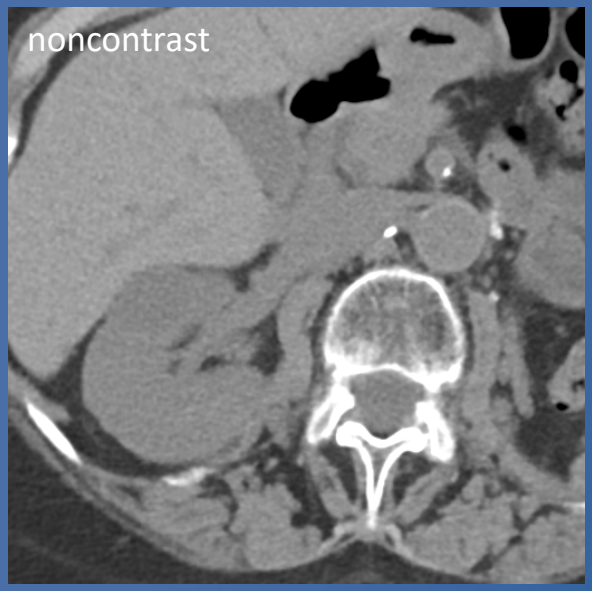


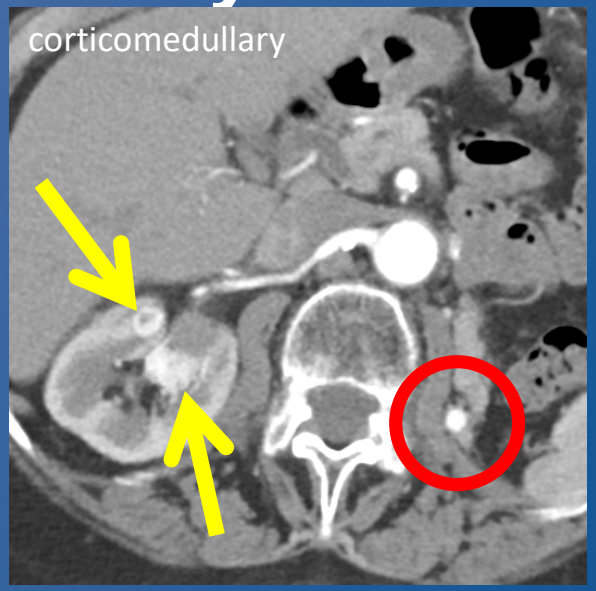
Status post partial nephrectomy with a focus of enhancement (arrow) on corticomedullary phase representing local recurrence. Noncontrast images enable the distinction between surgical material and enhancing lesion. The recurrent lesion is isodense on venous and delayed phase, underscoring the importance of the arterial acquisition

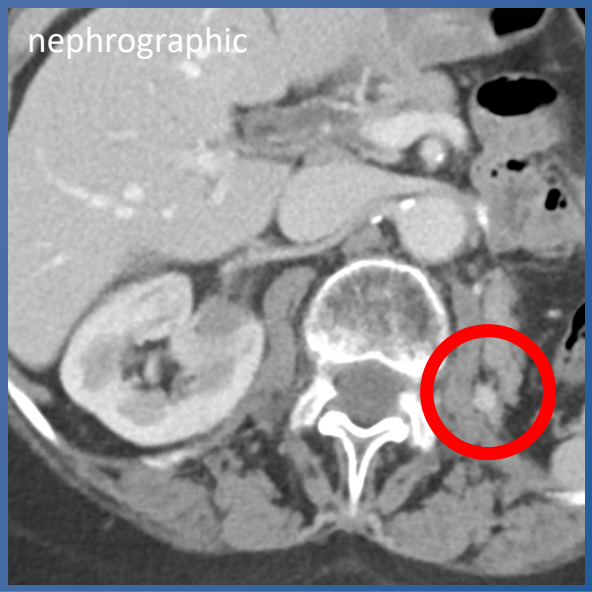
Metastatic Surveillance

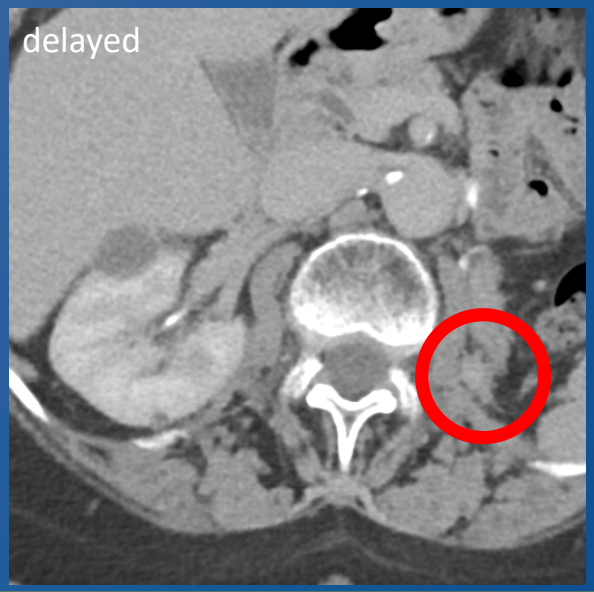
- Arterial phase has been shown to be most sensitive in detection of clear cell metastatic lesions.[15]
- Metastatic lesions may undergo significant washout by venous phase and can become isodense to surrounding tissues.
  - Study with 25 metastatic pancreatic lesions identifiable on arterial phase
  - 20/25 lesions were identified on venous phase imaging
  - 13/25 could be identified on unenhanced scans. [18]
- While arterial phase is typically most sensitive, dual phase acquisition with venous phase has greater sensitivity.
  - Study including patients with hepatic, pancreas, and contralateral kidneys demonstrated multiple lesions for each organ system that were only detected on one phase. [17]
- Risk of metachronous tumor in contralateral kidney is 0.3% and is higher in younger patients[19].
  - Low incidence does not justify precontrast acquisition in all patients.
  - Accurate HU measurements of new small lesion in remaining kidney limited due to size. Noncontrast can be included on follow up scan.

Pancreatic and Contralateral Kidney Metastases



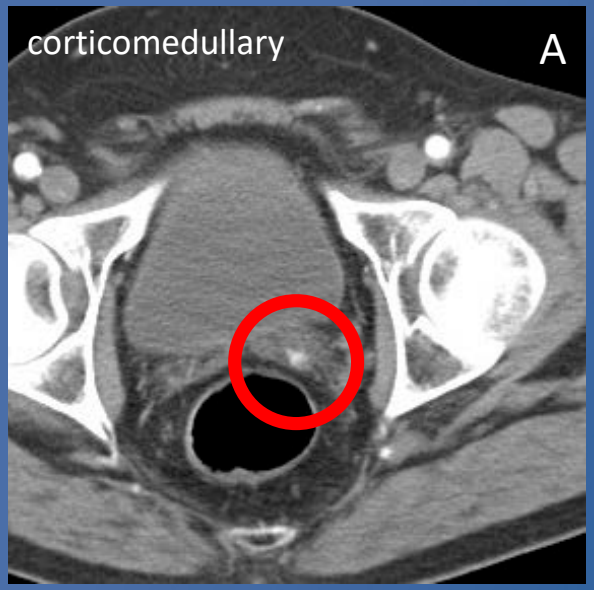


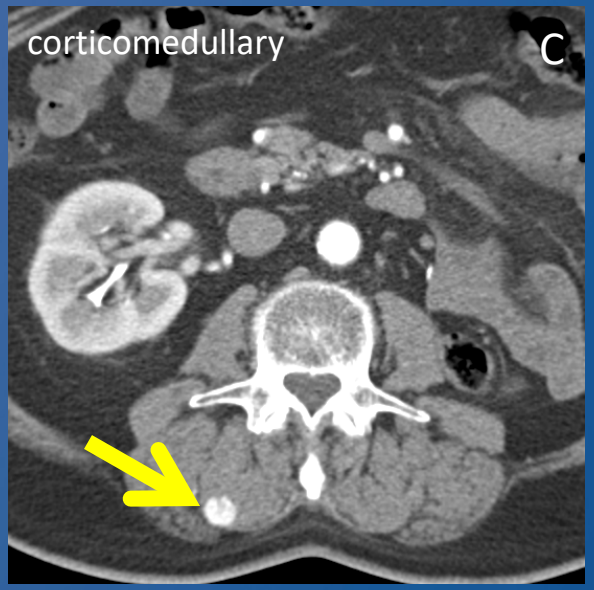


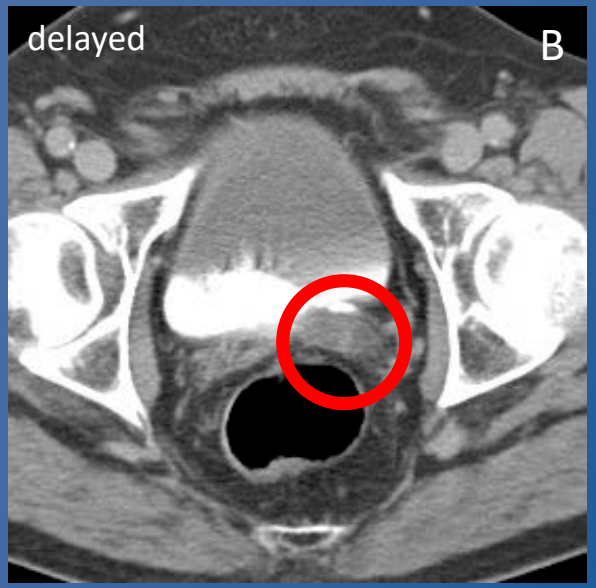


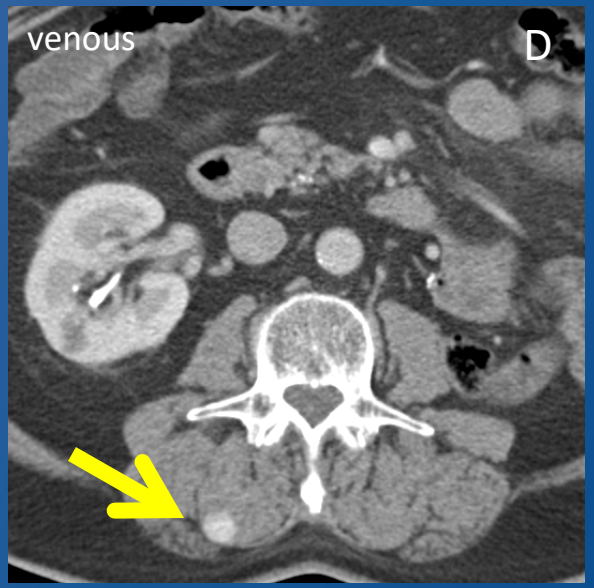
Patient with left clear cell RCC status post nephrectomy, metastases to the contralateral kidney (arrows) and pancreatic tail (circle). The lesions avidly enhance on arterial phase. The renal lesion is nearly isodense on each of the additional phases while the pancreatic lesion remains mildly hyperdense relative to parenchyma on the venous phase. Noncontrast is noncontributory.

Clear Cell RCC Metastasis



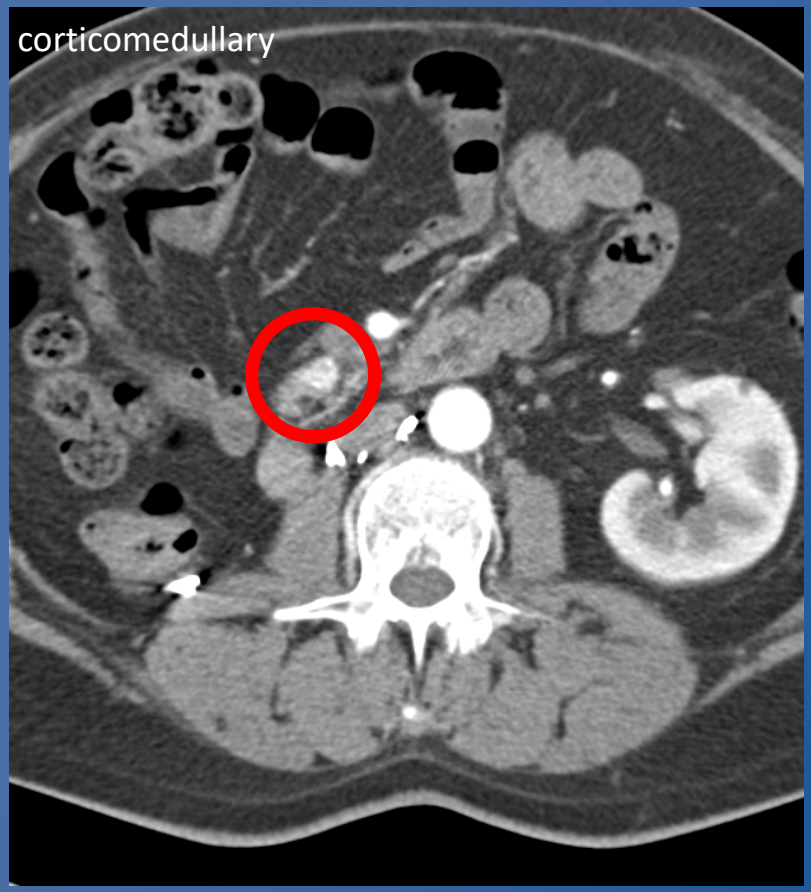


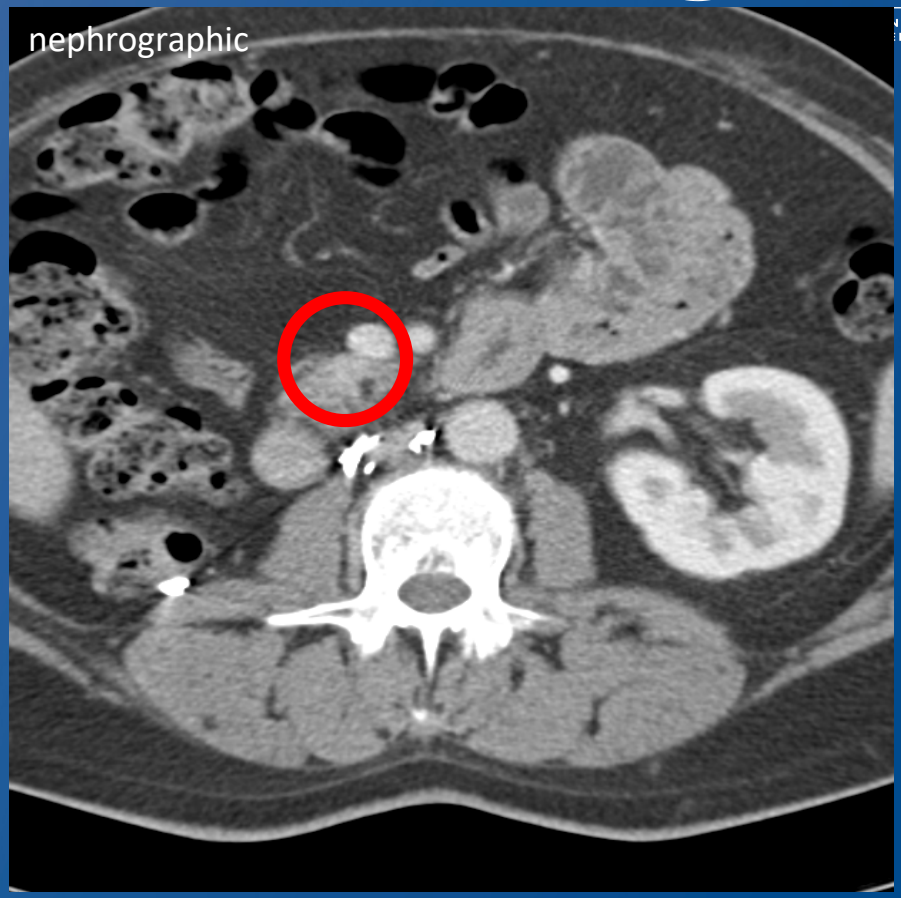




Two different patients are shown. On the left (A,B), arterial and delayed phase images in a patient with clear cell RCC show an arterial phase avidly enhancing metastatic lesion in the left seminal vesicle (circle),which would have been missed on the delayed phase.
On the right (C,D), patient with clear cell status post left nephrectomy has a right paraspinal enhancing metastatic lesion (arrow) more conspicuous on arterial phase.

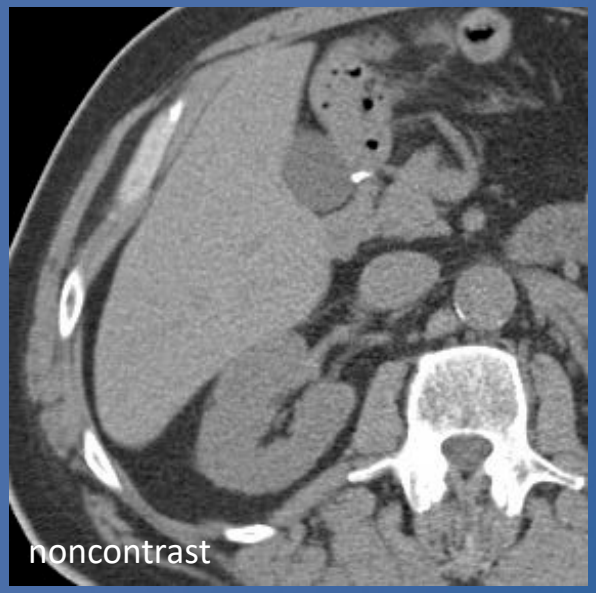
Pancreatic Uncinate Metastasis

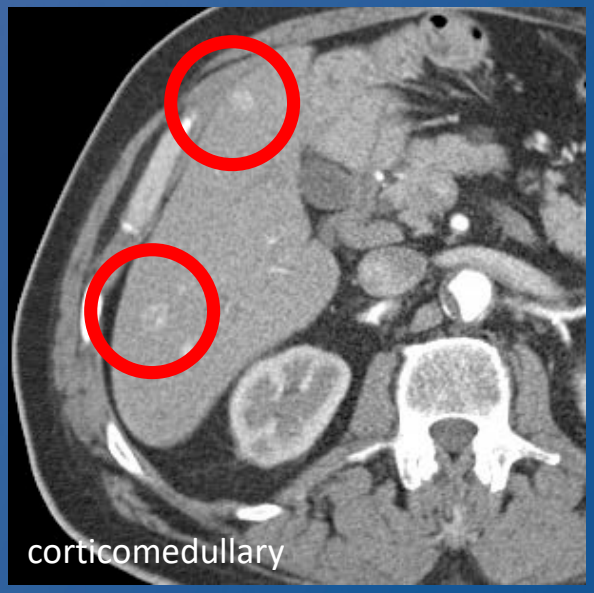


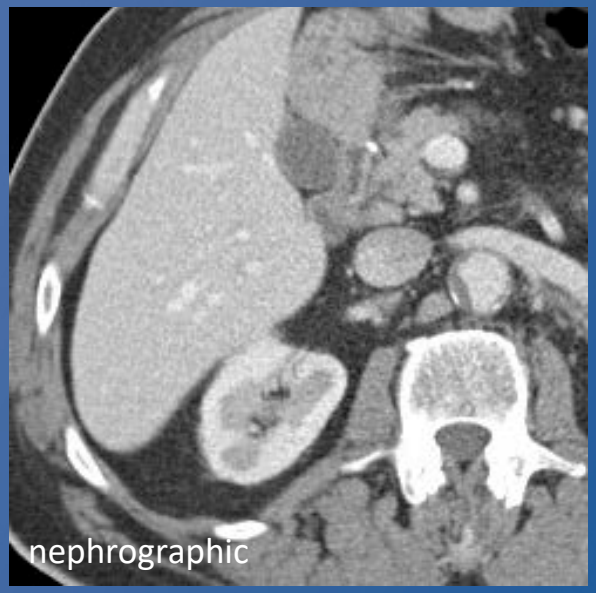


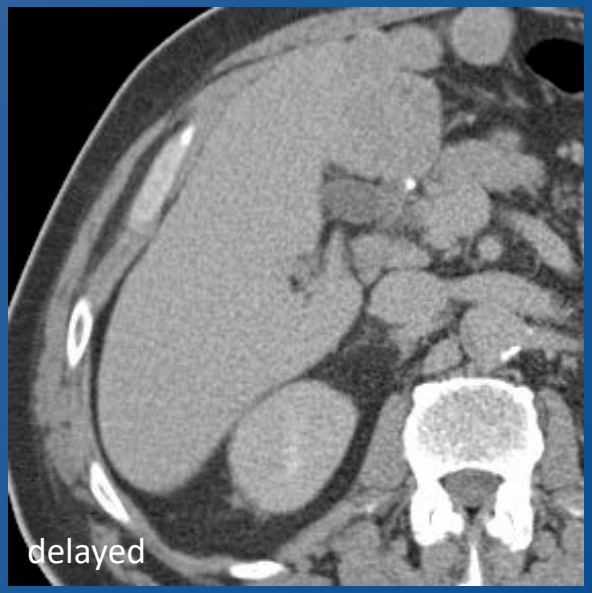
Status post right nephrectomy for clear cell RCC with avidly enhancing metastasis (circle) in the pancreatic uncinate only discernible on arterial phase. The lesion becomes isodense to pancreatic parenchyma on venous phase, again demonstrating the diagnostic importance of arterial phase imaging in RCC surveillance.

Hepatic Metastasis





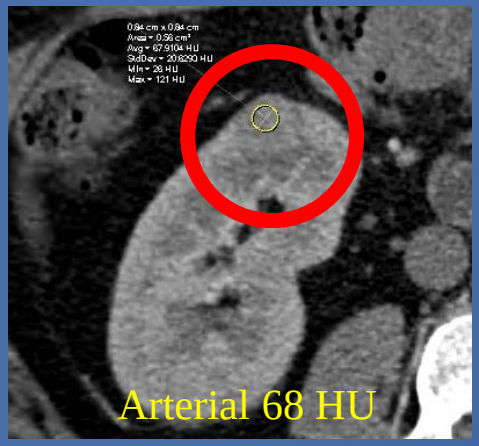


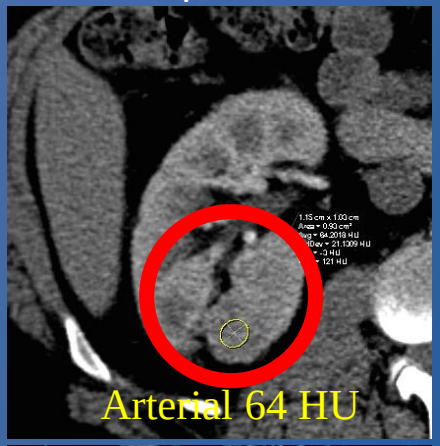


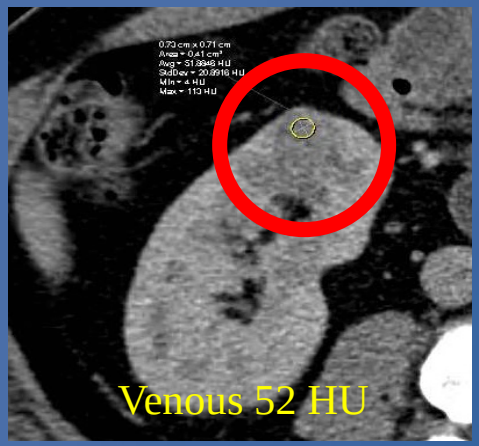
Patient with clear cell RCC status post partial left nephrectomy with avidly enhancing metastatic liver lesions (circles) seen only on arterial phase. The lesions are isodense on all other phases. This case demonstrates the importance of arterial phase imaging in renal cell carcinoma follow-up. Noncontrast is noncontributory.

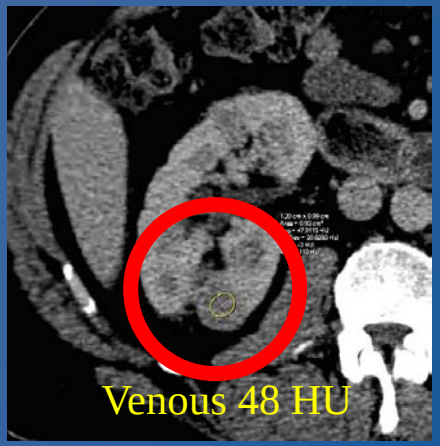
Upper pole mass

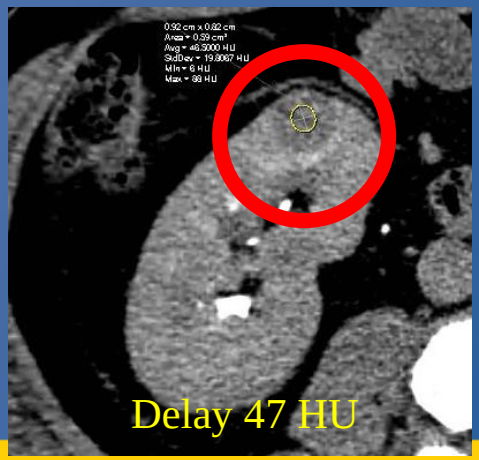
Lower pole mass

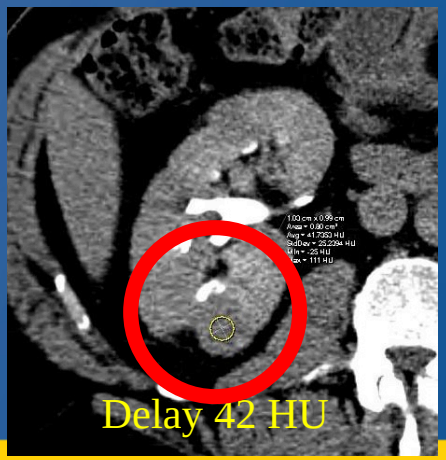












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Contralateral Kidney Metastases

59 year old man status post left nephrectomy for renal cell carcinoma with clear cell and papillary features in remission who developed metastatic disease in the contralateral kidney. Multiple enlarging masses(circles) in the right kidney showed little difference in attenuation between corticomedullary and nephrographic or nephrographic and delayed acquisitions. Comparison across > 2 phases is required for high diagnostic confidence regarding whether the new lesion is a complex cyst or solid mass. Either precontrast or delayed should be performed in addition to corticomedullary and nephrographic.

Arterial Phase for Patients Receiving Antiangiogenesis Agents

- Antiangiogenesis agents have revolutionized metastatic RCC treatment.
  - They are considered cytostatic as opposed to cytotoxic inducing tumor stabilization rather than shrinkage.
  - RECIST criteria is based on tumor size and is still the standard of care for longitudinal tumor response assessment in metastatic RCC. [20]
  - Choi and revised Choi criteria based on size and mean attenuation. Revised Choi exclusively measures in the arterial phase.
- Multiple studies have shown reduction in tumor size and attenuation to be associated with favorable outcomes.
  - Some studies have shown response according to revised Choi criteria to have better correlation with clinical outcomes than RECIST. [21]
  - Multiple studies have shown tumor enhancement on arterial phase to be associated with size reduction and progression free survival.

Proposed MDCT Protocols for RCC tailored to specific clinical scenario

Clinical scenario	Precontrast	CM	Nephrog.	Delayed
Diagnosis- all phases warranted for detection, characterization, staging, preoperative planning • Cyst vs solid mass • Small RCC may be more conspicuous on CM or nephrographic • Distinguish clear cell vs papillary vs chromophobe • Identify metastastic disease • Partial vs full nephrectomy • Laparoscopic vs open surgery	Yes	Yes	Yes	Yes
Status post partial nephrectomy • Operative material vs tumor (noncon & CM) • Identify recurrence in operative bed (multiphase) • Exclude collecting system leak (delay)	1st postop scan only	Yes	Yes	Yes
S/P nephrectomy for clear cell RCC in remission • CM is mandatory for detecting hypervascular recurrent and metastatic disease • Add noncontrast if new mass in contralateral kidney	For new or enlarging contralateral renal mass.	Yes	Yes	No
Metastatic clear cell RCC • CM for best visualizing metastases from clear cell • Decreased arterial phase enhancement indicates treatment response for patients receiving antiangiogenesis agents • Nephrographic for venous involvement	No	Yes	Yes	No
Metastatic papillary RCC	No	No	Yes	No
Resected papillary or chromophobe surveillance	No	Yes	Yes	No
Surveillance of small tumors	No	Yes	Yes	No

Limiting anatomic coverage to reduce radiation exposure

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Quadruple phase protocols	**mSv**
Characterize renal lesion as cyst vs solid: Precontrast, CM, nephrographic and delayed *(abdomen only*)	32
Renal cell carcinoma staging at diagnosis: precontrast and venous (*abdomen only*) arterial and delayed (*abdomen and pelvis*)	44
Status post partial nephrectomy (after 1st scan): corticomedullary and delayed (*abdomen and pelvis*) venous (*abdomen only*)	36
Dual phase follow up for metastatic clear cell RCC: Corticomedullary (*abdomen and pelvis)* Venous (*abdomen only)*	22
No indication: Abdomen and pelvis for 3 of 4 phases Abdomen and pelvis for all 4 phases	 50 56

Johnson PT, Mahesh M, Fishman EK. Image Wisely and Choosing Wisely: Importance of Adult Body CT Protocol Design for Patient Safety, Exam Quality and Diagnostic Efficacy. *JACR* 2015 ; 12: 1185-1190
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Conclusion

- Multiphase abdominal CT plays a critical role in the diagnosis and management of renal cell carcinoma.
- At diagnosis, unenhanced and 3 post contrast phases are necessary for lesion detection and to accurately differentiate pathologic subtypes, offering useful information to guide optimal treatment strategy.
- A 4 phase acquisition can result in radiation dose as high as 56 mSv. Anatomic coverage and number of acquisitions should be tailored to limit radiation exposure for each indication, in an effort to balance diagnostic efficacy with radiation dose modulation.
- Arterial phase imaging is critical in monitoring for local recurrence, metastatic disease, and treatment response in patients with clear cell renal cell carcinoma.

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