REVIEWS IN UROLOGY

Imaging Techniques in the Diagnosis of Renal Cell Carcinoma: Contemporary Trends and Future Directions

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Abstract

Increasing radiographic detection of incidental small renal masses has led to a growing concern regarding overtreatment of these lesions. Given the limitations of computed tomography and magnetic resonance imaging, there is an unmet need for improved kidney imaging techniques that can provide more accurate assessments of renal lesions. This review provides a summary of established kidney imaging modalities and also those likely to be meaningful in the near future. Kidney imaging has evolved, with several modalities contributing to the overall diagnostic landscape. There is great optimism that a new era of molecular imaging in renal cell carcinoma can vastly improve diagnostic capabilities and limit unnecessary invasive procedures.

Introduction

In recent years, increasing radiographic detection of small renal masses has led to a greater prevalence of incidentally found renal cell carcinoma (RCC).[1] Interestingly, this increased detection has led to downward stage migration of RCC and no subsequent improvement in cancer-specific survival resulting from earlier detection and interventions, leading to the conclusion that many small renal masses carry low malignant potential and are potentially being overtreated.[2] Kidney mass biopsy has been used more commonly over the past decade to reduce unnecessary surgery in patients with an indeterminate mass. Urologists' widespread use of renal mass biopsy has been hampered by several key constraints: potential for a nondiagnostic result (about 10%); undersampling due to tumor heterogeneity; and invasive nature of the biopsy procedure, with occasional clinically significant complications (eg, bleeding, site pain).[3,4] Accordingly, there is a notable unmet need for improved imaging modalities that can provide noninvasive, accurate renal mass characterization, allowing urologic surgeons to better assess and risk-stratify these lesions. This review provides a concise summary of current commonly used imaging modalities and a preview of technologies on the horizon.

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Ultrasonography

As a safe, low-cost, noninvasive examination, ultrasonography is the current screening standard for the evaluation of renal masses, with a sensitivity of 82% to 83% and a specificity of 98% to 99%,[5-7] although the sensitivity is lower for masses smaller than 3 cm in size.[8] Disadvantages of ultrasonography are that cancer staging is not fully possible and that large patients are not ideal candidates because of the technical difficulties in obtaining adequate images. Contrast-enhanced ultrasonography has gained popularity in the past decade because postcontrast ultrasonography increases the sensitivity and specificity of the modality in the characterization of renal masses. Contrast-enhanced ultrasonography can better differentiate small isoechoic or small solid lesions, better characterize complex cystic lesions, and differentiate tumors from pseudotumors. Also, contrast agents are not excreted by the kidneys, so there is no excretory phase, and patients with kidney impairment can be assessed more practically. Further advantages of ultrasonography include the lack of radiation exposure and the utility for patients with allergies to contrast media. Limitations include ultrasonography's operator-dependent nature and interference from bowel gas or nearby bony structures.

Computed Tomography

Currently, computed tomography (CT) scanning with contrast enhancement is the most frequently used imaging modality for assessment of renal masses. Generally, enhancement (>10 Hounsfield units from precontrast to postcontrast imaging) on CT images is concerning for a malignant renal tumor. In addition, a single properly phased scan can be used to detect and stage RCC (locally and distantly) and provide information for surgical planning. Although some features on CT images can suggest tumor histology (eg, timing of enhancement, enhancement degree, central scar), poor specificity in these factors for predicting histology has limited the modality's application.[9,10] Radiation exposure, contrast-related allergic reactions, and kidney impairment are also unique disadvantages of CT. Finally, CT has low diagnostic capability for several types of lesions: cystic renal masses, hypoattenuating lesions, lipid-poor angiomyolipomas, and focal inflammatory or infectious masses. These lesions often necessitate serial scans, other modalities, or renal mass biopsy before surgical or ablative intervention can be confidently carried out. Even with these limitations, high resolution, reproducibility, quick turnover and efficient workflow, and acceptable cost allow CT to remain the primary choice for renal mass imaging.

ABBREVIATIONS

CT, computed tomography

MRI, magnetic resonance imaging

PET, positron emission tomography

RCC, renal cell carcinoma

REDIRECT, Pre-surgical Detection of Clear Cell Carcinoma (ccRCC) Using Radiolabeled G250-Antibody

^{89}Zr, zirconium-89

ZIRCON, 89ZR-TLX250 for PET/CE Imaging of ccRCC—ZIRCON Study

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the abdomen is a suitable substitute when contrast-enhanced CT is contraindicated. Some centers even prefer this approach because of the lower level of radiation compared with CT. If the status of the renal veins and inferior vena cava cannot be determined on CT images, then contrast-enhanced multiphasic 3-dimensional magnetic resonance venography can be performed. The National Comprehensive Cancer Network guideline recommends abdominal MRI to assess suspected tumor involvement in the inferior vena cava or as an alternative to CT for renal mass detection and staging in cases where the use of contrast is contraindicated because of allergy or renal insufficiency. Similar to CT, various MRI sequences and strategies (eg, contrast enhancement patterns, perfusion scores, T1/T2 phase variations) have been used to predict histology, without overwhelming success.

The use of MRI is limited by patient cooperation because MRI is more sensitive to motion artifact than CT. Advances in techniques for limiting motion as well as techniques that allow free breathing may reduce these limitations, but MRI is still more expensive and less readily available than CT. Finally, patients with pacemakers, certain types of medical implants, or severe claustrophobia cannot undergo MRI.

Molecular Imaging

TECHNETIUM-99M SESTAMIBI

The newest and most exciting development in kidney imaging is the emergence of molecular imaging techniques. These techniques use nuclear tracers that are more specific to cellular elements contained within RCCs. Technetium-99m sestamibi was the first modality to show promise in this area, featuring a mitochondrial-avid tracer that accumulates preferentially within oncocytic neoplasms as opposed to kidney cancers, which tend to have less mitochondrial mass.[11] Subsequent clinical series evaluating this phenomenon in more detail have reported impressive sensitivity (>85%) and specificity (>90%) for technetium-99m sestamibi in the prediction of benign vs malignant pathology upon resection.[12,13] Although technetium-99m sestamibi is already approved by the US Food and Drug Administration for use in myocardial and parathyroid imaging and is inexpensive, uptake of this modality has not been robust over the past decade. Reader learning curve, scan time, poor accuracy in small lesions, and a limited number of imaging centers offering single-photon emission CT are likely contributory.

GIRENTUXIMAB POSITRON EMISSION TOMOGRAPHY

The newest molecular tool for RCC is girentuximab, a monoclonal antibody that selectively binds to carbonic anhydrase IX, overexpressed in 95% of clear cell RCCs. Given this specificity, there is tremendous interest, as in prostate-specific membrane antigen–based applications in prostate cancer, in using this antibody for diagnostic imaging and as a therapeutic target down the road. Importantly, girentuximab has hepatic excretion, optimizing kidney visualization. The Pre-surgical Detection of Clear Cell Renal Cell Carcinoma (ccRCC) Using Radiolabeled G250-Antibody (REDECT) trial compared girentuximab positron emission tomography (PET) with traditional CT for accurately assessing indeterminate renal masses. The investigators found that girentuximab PET strongly outperformed CT for prediction of clear cell kidney cancer, with 86% specificity vs 47% specificity for CT.[14] This finding set the stage for the 89Zr-TLX250 for PET/CT Imaging of ccRCC—ZIRCON Study (ClinicalTrials.gov identifier NCT03849118), an international multicenter prospective trial conducted at 36 sites between 2019 and 2022. This study used a zirconium-89 (^{89}Zr)–labeled form of girentuximab, thought to have greater intracellular retention than the iodine-based tracer used in REDECT.[15,16] ZIRCON included 300 patients with a single indeterminate renal mass measuring 7 cm or less on CT or MRI scans that was concerning for clear cell RCC. Patients underwent imaging with ^{89}Zr-girentuximab PET/CT, and then underwent surgical removal as the reference histologic standard. Among patients who underwent surgical resection following a suspicious CT/MRI finding, 67% had clear cell cancer, and 145 of 284 (51%) had T1a disease (≤4 cm). Investigators found that ^{89}Zr-girentuximab PET/CT had a sensitivity of 86% and a specificity of 87%, with a positive predictive value of 93%. Notably, this high degree of accuracy remained in T1a lesions and in very small lesions (>95% positive predictive value in tumors ≤2 cm). Importantly, internal validation among readers in the study was more than 91%, suggesting reproducible assessment of the scans among radiologists. Optional whole-body imaging was performed at investigator discretion. In an exploratory analysis, preliminary evidence demonstrated the utility and feasibility of ^{89}Zr-girentuximab PET/CT to detect metastatic lesions. No concerning safety issues were identified with the tracer agent.

Based on the results of the ZIRCON[15,16] trial, early access programs are underway. When approved, ^{89}Zr-girentuximab PET/CT will likely change the

imaging landscape in RCC. As previously mentioned, sestamibi single-photon emission CT is limited by access, especially at community and smaller centers; PET/CT is a more recognized and widely used modality (especially at community sites), given familiarity with cancer indications and other well-established tracers (fluorodeoxyglucose, prostate-specific membrane antigen). ^{89}Zr-Girentuximab PET can provide superior RCC local disease staging and may also lead to better assessment of distant metastatic lesions. Computed tomography imaging has provided historical comfort and familiarity for urologists regarding surgical planning because it often delineates the surgical capsule of the tumor and nearby critical renal structures (hilum, renal sinus, collecting system). Early evidence supports the role of ^{89}Zr-girentuximab in improving imaging for surgical decision-making,[17] and further data supporting the technique's use is expected from the ongoing early access program.[18]

Some potential limitations of ^{89}Zr-girentuximab exist. Carbonic anhydrase IX is not ubiquitous on all clear cell tumors, and it has been shown that decreased expression of carbonic anhydrase IX is associated with poor survival in advanced RCC.[19] Economics will also need to be a consideration, because the main driver of cost for PET is in the tracer, which usually runs about 5 to 6 times the total cost of contrast-enhanced CT and 2 to 3 times the cost of abdominal MRI. The success of PET adoption in RCC will also depend on facility factors, such as distribution networks, tracer storage and handling requirements and capabilities, and staff and credentialing barriers for radiopharmaceutical administration.

Conclusion

Kidney imaging has evolved, with several modalities contributing to the overall diagnostic landscape. Although contrast-enhanced CT and MRI remain the most useful and popular examinations, a new era of molecular imaging is emerging that has the potential to vastly improve diagnostic capabilities and limit unnecessary invasive procedures. The arrival of these modalities is expected to have profound impacts on the noninvasive diagnosis of RCC, tumor staging, and posttreatment surveillance.

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