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Novel Imaging Methods for Renal Mass Characterization: A Collaborative Review

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Appendix A: Peer Review Summary

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Abstract

Context: The incidental detection of localized renal masses has been rising steadily, but a significant proportion of these tumors are benign or indolent and, in most cases, do not require treatment. At the present time, a majority of patients with an incidentally detected renal tumor undergo treatment for the presumption of cancer, leading to a significant number of unnecessary surgical interventions that can result in complications including loss of renal function. Thus, there exists a clinical need for improved tools to aid in the pretreatment characterization of renal tumors to inform patient management.

Objective: To systematically review the evidence on noninvasive, imaging-based tools for solid renal mass characterization.

Evidence acquisition: The MEDLINE database was systematically searched for relevant studies on novel imaging techniques and interpretative tools for the characterization of solid renal masses, published in the past 10 yr.

Evidence synthesis: Over the past decade, several novel imaging tools have offered promise for the improved characterization of indeterminate renal masses. Technologies of particular note include multiparametric magnetic resonance imaging of the kidney, molecular imaging with targeted radiopharmaceutical agents, and use of radiomics as well as artificial intelligence to enhance the interpretation of imaging studies. Among these, ^{99m}Tc-sestamibi single photon emission computed tomography/computed tomography (CT) for the identification of benign renal oncocytomas and hybrid oncocytic chromophobe tumors, and positron emission tomography/CT imaging with radiolabeled girentuximab for the identification of clear cell renal cell carcinoma, are likely to be closest to implementation in clinical practice.

Conclusions: A number of novel imaging tools stand poised to aid in the noninvasive characterization of indeterminate renal masses. In the future, these tools may aid in patient management by providing a comprehensive virtual biopsy, complete with information on tumor histology, underlying molecular abnormalities, and ultimately disease prognosis.

Patient summary: Not all renal tumors require treatment, as a significant proportion are either benign or have limited metastatic potential. Several innovative imaging tools have shown promise for their ability to improve the characterization of renal tumors and provide guidance in terms of patient management.

Keywords

Renal cell carcinoma; Kidney cancer; Multiparametric magnetic; resonance imaging; Girentuximab; Radiomics; Virtual biopsy; ^{99m}Tc -sestamibi; PET; SPECT; Machine learning; Artificial intelligence

1. Introduction

In recent decades, there has been a steady increase in the incidental detection of small renal masses (SRMs) [1]. With up to 70% of SRMs ultimately being diagnosed as renal cell carcinoma (RCC), this trend has led to an increase in the overall prevalence of this malignancy. Furthermore, because the majority of incidental cases of RCC are localized to the kidney, there has been an overall downward stage migration associated with this disease [2]. Unfortunately, this has not translated to improved rates of cancer-specific survival, suggesting that many newly diagnosed cases of SRMs are benign or of low malignant potential and likely do not require treatment [3].

The increasing detection of SRMs has also led to a rise in unnecessary treatment of benign tumors of the kidney, such as oncocytomas and angiomyolipomas (AMLs). This is because these tumors can be difficult to distinguish from renal cancers on the basis of conventional imaging modalities such as ultrasound, computed tomography (CT), and magnetic imaging resonance (MRI) [4,5]. It is estimated that ~25% of renal masses of <4 cm are preoperatively misclassified as malignant and are needlessly surgically excised [6,7]. A considerable number of patients could therefore be spared from unnecessary interventions and the associated risk of complications or loss of renal function.

Currently, renal mass biopsy (RMB) is considered the gold standard for determining the presurgical histology of an SRM. Adoption of this diagnostic procedure, however, has been hampered by concerns over a high nondiagnostic rate of 10–15% and 10% erroneous diagnoses due to tumor heterogeneity [8–11]. Additionally, RMB is not always feasible due to the anatomic tumor location, and it remains an intrinsically invasive procedure despite a relatively low complication rate [8,9]. Thus, the vast majority of SRMs are removed surgically without prior knowledge of the tumor's underlying histology.

Considering the issues outlined above, there remains a significant need for improvements in the pretreatment characterization of SRMs. Several novel imaging techniques as well as methods of image processing offer promise to noninvasively determine the histology of SRMs—a so-called “virtual biopsy”. Technologies of particular note include multiparametric MRI (mpMRI) of the kidney, molecular imaging with radiopharmaceutical agents, and radiomics as well as artificial intelligence (AI) to enhance image interpretation. In this collaborative review, we provide a summary of these novel and emerging imaging tools for the noninvasive characterization of solid renal masses with an emphasis on topics that are most likely to gain traction in clinical practice.

2. Evidence acquisition

With the consensus of the authors, three main areas of research focusing on improved characterization of solid renal masses were deemed applicable and subsequently explored further: mpMRI of the kidney, molecular imaging with radiopharmaceutical agents, and advanced image processing and interpretation methods (ie, radiomics and AI). A search of the MEDLINE database was conducted to identify original studies related to these three topics. Keywords included “kidney neoplasm”, “renal tumor”, “renal mass”, “magnetic resonance imaging”, “molecular imaging”, “positron emission tomography”, “single photon emission tomography”, “radiomics”, “machine learning”, and “artificial intelligence” along with derivative terms (Supplementary material). Articles were included up to July 1, 2021, and the initial search was limited to studies and investigations published in the past 10 yrs. Articles on the characterization of metastatic disease or response to therapy were excluded as they fall outside of the scope of the current review. The retrieved articles were screened by title and abstract using Rayyan (Rayyan Systems Inc., Cambridge, MA, USA). References cited in the retrieved articles were subsequently searched to identify additional manuscripts of interest that were not included in the initial search to ensure completeness. Figure 1 shows the flowchart of study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria. A total of 149 articles underwent rigorous full-text review by the first author. Articles with the highest level of evidence were evaluated and selected with the consensus of the other authors.

3. Evidence synthesis

3.1. Multiparametric MRI of the kidney

Currently, contrast-enhanced CT (CECT) is the most commonly used imaging modality for assessing renal lesions. Enhancement on CT is indicative of a solid renal mass; however, little else about the lesion can reliably be determined on this basis. Although there are some features on CECT that can be suggestive of a tumor’s histology, these findings typically lack the specificity necessary to make informed clinical decisions. For example, a renal tumor with a central stellate region of relatively low level of enhancement is suggestive of an oncocytoma, but this can easily be confused with central necrosis of an RCC. Similarly, the timing or pattern of contrast enhancement on multiphase CECT has been explored as a means of distinguishing between RCC subtypes, but due the considerable overlap of these features between the various renal tumor histologies this has seen little in the way of clinical adoption [4,5,12–16].

MRI offers several advantages over CT for the characterization of renal masses. First, MRI offers improved contrast resolution and eliminates concerns regarding ionizing radiation. More importantly, however, various MRI sequences can be combined to form a multiparametric study that can more reliably probe the underlying histology of a renal mass [4]. mpMRI combines anatomic information from the T1- and T2-weighted imaging sequences with other MRI sequences, such as chemical-shift imaging to display micro- and macroscopic fat, diffusion-weighted imaging (DWI) to assess tumor cell density, and dynamic contrast enhancement to display tumor vascularity [17]. Limitations of mpMRI include its relatively higher costs than CT and significantly longer examination times [18].

Contemporary mpMRI protocols can offer anatomic insight and provide qualitative, semiquantitative, and fully quantitative imaging biomarkers that correlate with histological subtype, tumor grade, and clinical behavior. In one study, Sasiwimonphan et al [19] reported a sensitivity of 73%, a specificity of 99%, and an accuracy of 96% for the differentiation of fat-poor AMLs (fpAMLs) from RCC using a T2 tumor to renal cortex signal intensity ratio of <0.9 combined with either an arterial-to-delayed enhancement ratio of >1.5 or a signal intensity index of $>20\%$ along with a T1 signal intensity ratio of >1.5 . Similar observations have been made using mpMRI to diagnose fpAMLs, and a recent systematic review reported a sensitivity of 83% and a specificity of 93% for this diagnosis [20].

Kay et al [21] developed and implemented an mpMRI protocol with a predefined diagnostic algorithm in which several imaging sequences were consecutively analyzed to predict RCC histology among SRMs (Fig. 2). In this study, seven reviewers independently reviewed mpMRI images of 109 renal masses using this algorithm as a guideline for the most likely histopathological diagnosis, but were allowed to over-rule the algorithm ad libitum. Using this qualitative diagnostic framework, the authors observed a sensitivity of 85% and a specificity of 76% for the prediction of clear cell RCC (ccRCC). Similarly, the authors reported a sensitivity of 80% and a specificity of 94% for the prediction of papillary RCC (pRCC). Performance of the reviewers was poorest with regard to the diagnosis of benign renal masses and chromophobe RCC (chrRCC). Overall, the average accuracy of the reviewers was 65% when using the algorithm but only 43% when the algorithm was not followed.

Using this same algorithm, Canvasser et al [22] developed a subjective scale, known as the clear cell likelihood score (ccLS), for the prediction of ccRCC histology. This scoring system assigns a given SRM a score of 1 to 5 (very unlikely to very likely) to indicate the reader's level of certainty that the tumor represents a ccRCC. Using this system, the authors found that scores ≥ 4 had a sensitivity of 78% and a specificity of 80%, while scores ≥ 3 had values of 95% and 58%, respectively. Steinberg et al [23] reported similar results after prospectively assigning ccLSs to 454 renal masses. In this study, the authors found a positive predictive value of 91% for ccLS ≥ 4 and a negative predictive value of 94% for ccLS ≤ 2 . Although these results do not provide information on malignant versus nonmalignant tumor histology or tumor aggressiveness, they could inform subsequent SRM management. For example, Canvasser and coworkers [22] found that an approach where ccLS 1–2 SRMs would undergo active surveillance, equivocal ccLS 3 lesions would be biopsied, and ccLS 4–5 tumors would be treated surgically, would decrease the rate of RMB to 20% while limiting the rate of unnecessary treatment of oncocytomas and AMLs to 4.5% and 1.7% of the cohort, respectively.

Quantitative analysis of MRI acquisitions have also shown promise in renal mass characterization. In a recent systematic review, the use of apparent diffusion coefficient values derived from DWI sequences was found to have moderate accuracy for the prediction of malignant versus benign histology with pooled values of sensitivity and specificity of 86% and 78%, respectively [24]. Moreover, DWI can aid in the distinction of high-grade from low-grade ccRCC with moderate test accuracy, but is not able to accurately differentiate between RCC subtypes [24,25]. Similarly, preliminary data in 34 patients using

arterial spin labeled MRI, a technique to quantitatively assess tissue perfusion without the use of an exogenous contrast agent, revealed higher tumor perfusion in oncocytomas than in RCC, and lower perfusion in pRCC than in non-pRCC, which could contribute to the characterization of indeterminate renal masses [26].

3.2. Molecular imaging

Molecular imaging is a branch of radiology that provides for the in vivo visualization and quantification of various normal and diseased processes within the body at the cellular and molecular levels. Most commonly, this involves the use of a radiopharmaceutical agent that binds to or is taken up by a target tissue of interest. This differs from conventional imaging modalities such as CT or ultrasound, which more simply allow for the visualization of physical structures within the body based on size and density. A molecular imaging test designed to target a cellular process specific to a renal tumor subtype (eg, an overexpressed protein or upregulated metabolic pathway) could not only allow for the detection of sites of disease, but, in the case of SRM imaging, possibly also provide critical information on a given tumor's underlying histology. To date, a handful of radiolabeled molecular probes have been studied with this application in mind. Two radiotracers in particular— ^{99m}Tc -sestamibi and radiolabeled girentuximab—stand poised to be incorporated into routine clinical practice for this purpose in the near future.

3.2.1. Single photon emission computed tomography/CT with ^{99m}Tc -sestamibi—A promising approach for the characterization of indeterminate renal masses involves the use of ^{99m}Tc -sestamibi, which is a lipophilic cationic mitochondrial imaging agent that is currently widely used for myocardial and parathyroid imaging [27,28]; ^{99m}Tc -sestamibi accumulates in cells with high mitochondrial content and low multidrug resistance pump (MDR) expression [27]. A significantly increased mitochondrial mass and decreased MDR expression are characteristic of renal oncocytomas. The high mitochondrial content found within oncocytomas is the result of pathogenic mutations leading to the accumulation of respiration defective mitochondria [29]. Conversely, ccRCCs are relatively devoid of mitochondria and have high MDR expression [30]. Other RCC subtypes tend to have varying amounts of mitochondria, but MDR activity outweighs their presence [27]. On this basis, it was first hypothesized that single photon emission computed tomography (SPECT) imaging with ^{99m}Tc -sestamibi can aid in the discernment of benign versus malignant renal tumors (Fig. 3).

In a first report on this concept, Gormley et al [28] showed that a single large renal oncocytoma displayed uptake of the ^{99m}Tc -sestamibi radiotracer, whereas five other renal tumors were devoid of radiotracer signal. Next, Rowe et al [30] showed that oncocytomas exhibited ^{99m}Tc -sestamibi uptake on SPECT/CT at or near the renal background level, whereas RCCs appeared as photopenic defects. In a prospective study of ^{99m}Tc -sestamibi SPECT/CT that included 50 patients with a solitary renal mass imaged prior to surgery, Gorin et al [31] reported sensitivity of 87.5% and specificity of 95.2% for the diagnosis of renal oncocytomas and hybrid oncocytic/chromophobe tumors (HOCTs). Two false-positive tumors were identified as eosinophilic variants of chrRCC, which are typically indolent [32]. These findings were subsequently externally validated by Tzortzakakis et al [33] who

studied 27 patients harboring 31 tumors, and found that 11 of 12 (91.6%) oncocytomas and three of three (100%) HOCTs were correctly identified with ^{99m}Tc -sestamibi SPECT/CT. They noted two false positives, one pRCC with slight uptake, and one AML. Additional validation of this imaging modality has recently been performed by Sistani et al [34] and Asi et al [35].

The implementation of ^{99m}Tc -sestamibi SPECT/CT in the diagnostic workup of indeterminate renal tumors could potentially spare a substantial number of patients from unnecessary interventions. A recent decision analysis that simulated lifetime health utilities and direct medical costs from a US health payer perspective suggested that the use of ^{99m}Tc -sestamibi SPECT/CT as the initial diagnostic test for newly diagnosed SRMs followed by RMB to confirm benign or indolent tumors would be a cost-effective approach for the management of these tumors compared with RMB alone or upfront surgery [36]. Moreover, in this modeling study, the combination of ^{99m}Tc -sestamibi SPECT/CT followed by RMB led to the fewest treated benign/indolent tumors with an acceptably low number of untreated malignant SRMs.

The findings presented above, combined with the fact that ^{99m}Tc -sestamibi is already approved worldwide for use in myocardial and parathyroid imaging, make this imaging test poised for widespread clinical adoption in the near term. Moreover, SPECT/CT is a relatively inexpensive imaging modality and access to these scanners is relatively commonplace, making the adoption of this imaging technique quite feasible.

3.2.2. Positron emission tomography/CT with radiolabeled girentuximab—A

second molecular imaging tool of particular promise for the characterization of solid renal masses utilizes one of several radiolabeled forms of the humanized monoclonal antibody girentuximab. Girentuximab, formerly known as the G250 antibody, selectively binds with high affinity to the cell surface zinc metalloenzyme carbonic anhydrase IX (CAIX). Under normal physiological conditions, CAIX is upregulated in response to hypoxic conditions and serves to catalyze the reversible hydration of carbon dioxide. CAIX is overexpressed in approximately 95% of ccRCCs, following the loss or inactivation of the Von Hippel-Lindau (VHL) tumor suppressor gene, which is a hallmark event in the pathogenesis of this tumor [37,38]. Of note, CAIX is also overexpressed in the recently described clear cell papillary RCC, which represents 2–4% of renal cortical tumors and follows a more indolent disease course [39].

Girentuximab can be labeled with a number of different radionuclides and has been studied as both a diagnostic and a therapeutic agent for ccRCC [40]. In 2007, Divgi et al [37] performed a prospective study of ^{124}I -girentuximab positron emission tomography (PET)/CT, in which 26 patients with an indeterminate renal mass were imaged prior to surgery. Remarkably, this imaging test correctly identified 15 of 16 (93.8%) ccRCCs without any false-positive results. Following this successful pilot study, the same group conducted the prospective, multicenter, REDECT trial, comparing the accuracy of ^{124}I -girentuximab PET/CT versus conventional CECT for the diagnosis of ccRCC among 195 patients with an indeterminate renal mass scheduled for surgery [41]. In this positive trial, ^{124}I -girentuximab

PET/CT correctly identified cases of ccRCCs with reported sensitivity and specificity values of 86.2% and 85.9%, as compared to 75.5% and 46.8% for conventional CECT.

Following the results of the REDECT trial, a confirmatory study of PET imaging with girentuximab was requested by the US Food and Drug Administration prior to the regulatory approval of this novel imaging agent [42]. This second multicenter prospective study, known as the ZIRCON trial, is currently underway at 30 sites worldwide ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03849118) identifier [NCT03849118](https://clinicaltrials.gov/ct2/show/study/NCT03849118)). It is worth noting that in this trial, an ^{89}Zr -labeled form of girentuximab is being studied in place of the ^{124}I -labeled antibody (Fig. 4). This is because studies have suggested that labeling girentuximab with ^{89}Zr leads to higher tumor uptake and retention, and perhaps more sensitive detection of ccRCC than the ^{124}I -labeled radiotracer [43,44]. This observed difference stems from the fact that ^{89}Zr becomes “charge trapped” in the cytoplasm of tumor cells after internalization and breakdown of the antibody. In contrast, free ^{124}I is released into circulation. As a result, imaging with ^{89}Zr -girentuximab PET/CT results in a superior signal-to-noise ratio than the ^{124}I -labeled version of the antibody. SPECT/CT in combination with girentuximab has also been investigated. Muselaers et al [45] found a positive predictive value of 94% for the detection of ccRCC with ^{111}In -girentuximab SPECT/CT in a study that included 22 patients. However, PET offers distinct advantages over SPECT in terms of superior image resolution and shorter image acquisition time [46].

Despite these encouraging data, it is worth noting that there are several factors that may present a barrier to the widespread clinical adoption of intact monoclonal antibodies as molecular imaging probes. For example, the long residence of antibodies in the bloodstream is associated with relatively high background levels and requires a several-day interval from the time of injection to image acquisition [47]. In the case of girentuximab, this interval is 5–7 d, which introduces logistical hurdles to test administration. In contrast, $^{99\text{m}}\text{Tc}$ -sestamibi SPECT/CT imaging is performed only ~75 min after the administration of this small molecule radiotracer [30]. The use of low-molecular-weight molecular imaging agents targeting CAIX could overcome this limitation and are currently being investigated [48]. Future endeavors may also focus on the development of dual radiotracers employed in a single imaging acquisition. For instance, a dual-radiotracer SPECT imaging test with $^{99\text{m}}\text{Tc}$ -sestamibi and ^{111}In -girentuximab could potentially classify an indeterminate renal mass as oncocytoma/HOCT, ccRCC, or other tumor histology with a single imaging study.

3.2.3. Other radiotracers

3.2.3.1. PET/CT with ^{18}F -FDG.: The most widely used PET radiotracer in the field of oncology is 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F -FDG), which targets malignant cells exhibiting cytosolic aerobic glycolysis. However, this radiotracer has only a limited role in the evaluation of primary renal masses due to its physiological renal excretion and high background activity in the kidney. For example, a meta-analysis by Wang et al [49] reported pooled sensitivity of only 62% for ^{18}F -FDG PET for renal lesion detection. Furthermore, this sensitivity does not seem to improve significantly with the use of modern PET/CT [49–51]. In addition, ^{18}F -FDG is largely unable to aid in distinguishing between the various renal tumor histologies due to the fact that this radiotracer is nonspecifically taken up by any

tumor displaying an increase in aerobic glycolysis. However, some studies have shown that semiquantitative and quantitative analyses of ^{18}F -FDG PET uptake are associated with the presence of higher nuclear grade or sarcomatoid features, and thus prognosis [51–57].

3.2.3.2. Prostate-specific membrane antigen–targeted PET/CT.: Despite the specificity implied by its name, the cell surface protein prostate-specific membrane antigen (PSMA) is expressed in the neovasculature of a number of solid tumors, including RCC. Although a majority of studies evaluating PSMA-targeted imaging of RCC have focused on patients with metastatic disease [58–62], some have investigated the clinical utility of this class of imaging agents for the noninvasive characterization of solid renal masses [63,64]. For example, using quantitative ^{68}Ga -PSMA-11 PET/CT kinetics, Golan et al [63] demonstrated increased radiotracer uptake and slower washout in malignant versus benign renal tumors. Moreover, Gao et al [64] found that increased ^{68}Ga -PSMA-11 uptake was associated with the presence of higher nuclear grade and adverse pathological features, including tumor necrosis and sarcomatoid or rhabdoid features. However, the diagnostic performance of this imaging test for the evaluation of primary renal masses remains limited due to poor tumor-to-background ratios and is likely more applicable for imaging of metastatic lesions or evaluation of response to systemic therapy.

3.2.3.3. PET/CT with ^{11}C -acetate.: PET/CT with ^{11}C -labeled acetate targets rapidly dividing cancer cells due to its incorporation into cell membrane precursors [65]. It has been found to be potentially useful for the differentiation of AMLs from RCC when ^{11}C -acetate PET/CT is combined with a separately performed ^{18}F -FDG PET/CT study, with sensitivity of 94% and specificity of 98% [66]. Markedly increased ^{11}C -acetate uptake was observed in the AMLs, whereas all were ^{18}F -FDG negative. In the same study, the authors found that all chrRCC showed ^{11}C -acetate uptake but no ^{18}F -FDG uptake, whereas the inverse pattern was observed in pRCC [66]. However, the need for two separate PET studies and the short half-life of ^{11}C limit the clinical applicability of this imaging test.

A summary of novel imaging tests for renal mass characterization is provided in Table 1. Multiple other radiotracers and ligands are under preclinical investigation, but have been studied only in a few patients and are far from translation into clinical practice.

3.3. Radiomics and AI

Analytic methods for more in-depth analysis of medical images have been a topic of increasing interest. As a broad concept, radiomics involves high-throughput extraction of quantitative information from medical images. Briefly, after imaging processing and standardization, a region or volume of interest is identified and subsequently segmented either manually or semiautomatically [67]. Radiomic features are then generated from the pixel/voxel data within these segmented volumes. While many radiomic features have been described, the Image Biomarker Standardization Initiative recently standardized a set of 169 radiomic features, including morphological characteristics, features related to intensity, and texture features derived from gray-level and neighborhood gray tone/level matrixes [67]. Although these radiomic features were not specifically developed for renal tumors,

standardization of radiomic features might enable verification of radiomic software and improve the reproducibility of these studies.

Predefined quantitative radiomic features can be used to predict histological tumor characteristics. Alternatively, these can be fed into machine learning algorithms, a type of AI that can parse data, learn from data, and make decisions based on what has been learned. Machine learning models can combine radiomic features with demographic, histological, genomic, or transcriptomic features to predict patient outcomes. In turn, deep learning can be regarded as a subcategory of machine learning, in which a layered structure of algorithms, a so-called artificial neural network, is used. Deep learning algorithms extract information directly from raw images without the need of segmentation and generate features adaptive to a certain problem to capture the full range of information provided by the images [68,69]. These analytic methods can be used for renal mass subtyping, nuclear grade prediction, and prediction of molecular features. Moreover, these data can be combined in integrative multi-omics biomarker models to further increase their predictive accuracy. Figure 5 shows a schematic representation of a typical radiomic workflow.

3.3.1. Renal mass sub typing—Radiomic models based on CT texture analysis, as well as AI-derived deep learning classifiers based on routine CT or MRI images, have shown a fair degree of diagnostic accuracy for the differentiation of benign versus malignant renal masses [70–76]. In one example, Xi et al [76] developed a residual convolutional neural network (ResNet)-based deep learning model for this clinical application that incorporated data from clinical variables and conventional MRI sequences (T2 weighted and T1 postcontrast). Their model was developed using data from 1162 renal masses (655 malignant and 507 benign) from a multicenter cohort divided into training, validation, and test sets. An analysis of clinical data alone by the deep learning model resulted in an area under the curve (AUC) of 0.54 for discerning benign from malignant renal tumors. The individual analyses of T1-postcontrast and T2-weighted sequences yielded AUCs of 0.59 and 0.70, respectively. Incorporation of all three data inputs resulted in superior performance by the deep learning model as compared to a radiomics-based classifier (AUC of 0.76 vs 0.54). Additionally, the model outperformed expert radiologists in terms of sensitivity (92% vs 80%), specificity (41% vs 35%), and overall accuracy (70% vs 60%).

Several radiomic models based on quantitative CT texture features have been found to be helpful in the differentiation of fpAML from RCC, which currently represents a common imaging dilemma [77–83]. In a study of 41 fpAMLs and 130 RCCs, a CT texture analysis machine learning classifier outperformed expert radiologists in the differentiation of fpAML from RCC, ccRCC, and non-ccRCC, with AUCs of 0.96, 0.97, and 0.89 versus 0.67, 0.68, and 0.64, respectively [81]. Similarly, MRI texture features may be useful for the differentiation of fpAML from ccRCC [84]. Interestingly, Lee et al [85] showed that a deep learning approach outperformed conventional machine learning in the differentiation of fpAML from ccRCC, improving the sensitivity from 69% to 77% and specificity from 71% to 76%. Deep learning models were also able to distinguish oncocytomas from chrRCC in a small study on 20 renal masses, with reported sensitivity of 100% and specificity of 89% [86].

Typically, ccRCC has a more heterogeneous radiological appearance than other renal tumors [87,88]. Therefore, radiomic models based on CT and MRI texture analysis may be able to distinguish ccRCC from non-ccRCC subtypes [87–89]. Moreover, these texture features could also be useful in the differentiation of type I from the more aggressive type II pRCC [90,91]. Duan et al [90] studied 62 pRCCs, and reported sensitivity and specificity of 89% and 80%, respectively, for the differentiation of type I from type II pRCC using a CT texture analysis model. Vendrami et al [91] found that type I and type II pRCCs had significantly different MRI texture features, but this did not translate into an improved discriminative ability when added to a model using only qualitative MRI features. Interestingly, Schieda et al [92] also found that increased heterogeneity on CT texture analysis correlated with the presence of sarcomatoid features in ccRCC, which, in turn, correlates with worse prognosis.

3.3.2. Nuclear grade prediction—Multiple radiomic studies have focused on the evaluation of tumor aggressiveness through the prediction of nuclear grade. Both CT- and MRI-based radiomic approaches have been shown to accurately predict the presence of high-versus low-grade ccRCC, often through the use of texture analysis [93–100]. Cui et al [97] studied 460 patients with pathologically proven ccRCC, and developed and externally validated mpMRI- and multiphase CT-based machine learning models that could reliably distinguish high- from low-grade ccRCC, resulting in test accuracies of 73% and 79%, respectively. A deep learning approach based on conventional MRI was able to accurately distinguish high- from low-grade RCC in a multi-institutional cohort of 376 patients harboring 430 RCCs, with a test accuracy of 88% [101]. Notably, these advanced radiomic pipelines were developed based on resected nephrectomy specimens, which may introduce selection bias thereby limiting applicability in the setting of indeterminate renal masses.

3.3.3. Radiogenomics—The search for prognostic and predictive biomarkers to individualize and guide treatment approaches has been an area of great research interest in recent years [102–104]. The emerging field of radiogenomics investigates the association of quantitative and radiomic features with gene mutations and gene expression–based molecular signatures. These surrogate imaging biomarkers could tackle the issues of tumor heterogeneity and sampling bias that are associated with tissue-based biomarkers [11].

An example of the application of radiogenomics for renal mass characterization can be found in a recent report by Udayakumar and coworkers [105]. In this study, the authors investigated the correlation between contrast enhancement pattern on MRI with gene expression profiles in cases of localized ccRCC. Interestingly, they found that areas of high enhancement correlated with higher angiogenic gene expression in corresponding tissue samples acquired by multiregion tumor sampling. Conversely, areas of low enhancement seemed to be enriched in immune-related gene expression signatures. In a separate cohort of patients with metastatic ccRCC, higher enhancement scores, reflecting increased angiogenesis, were associated with better outcomes with antiangiogenic therapy.

In another study, Jamshidi et al [106] showed the feasibility of developing a noninvasive image-based surrogate of a prognostic molecular assay for renal tumors. More specifically, the authors developed a radiomic tool based on single CT images of patients with ccRCC

that achieved 70% agreement with the results of a previously validated prognostic gene expression assay. The surrogate radiomic tool was able to predict disease-specific survival in this cohort of patients allowing for it to serve in place of the invasive tissue-based assay. Similarly, Yin et al [107] studied whether ^{18}F -FDG PET/MRI could serve as a surrogate biomarker for ccRCC molecular tumor subtype, as defined by the 34-gene ClearCode34 classifier. The authors' radiomic model achieved a correct classification rate of 87% for distinguishing between the two prognostically distinct molecular subtypes of ccRCC (ie, ccA vs ccB).

In addition to correlation with gene expression signatures, radiogenomics can be used to predict the presence of somatic gene mutation status. In one example, The Cancer Genome Atlas—Renal Cell Carcinoma Imaging Research Group conducted a multi-institutional, multireader, study that found a significant association between imaging features on CT and/or MRI with BAP1 and MUC4 mutational status in cases of ccRCC [108]. In their study, ill-defined tumor margins and presence of calcifications were associated with BAP1 mutations, which are strongly correlated with unfavorable outcomes [102,108,109]. Additionally, exophytic growth pattern was associated with MUC4 mutations, which is potentially correlated with improved survival [108,109]. Radiogenomics models that implement machine learning have also been shown to predict VHL, BAP1, and PBRM1 mutational status in several studies using publicly available datasets [110–113]. VHL mutation and inactivation, which are associated with higher angiogenic gene expression, is characteristic of ccRCC, and the loss of PBRM1 is associated with improved survival [102,109]. Using quantitative CT features in a radiogenomics model, Chen et al [113] reported an AUC of >0.85 for the prediction of all three gene mutations. In turn, Marigliano et al [114] found a significant association between one CT texture analysis feature and the tumoral expression of miRNA 21–5p, which is involved in RCC tumorigenesis and is associated with poor prognosis [109,115,116].

Despite the encouraging data presented above, it is worth noting that the low prevalence of many of these molecular abnormalities limits the utility of radiogenomics in clinical practice at the present time. Moreover, gene-based changes in several radiomic features might not be consistent across imaging phases, and the clinical relevance of the radiogenomics models in these studies is rarely tested directly. Regardless, with the vast amount of genomic and transcriptomic data rapidly becoming available, this field is likely to evolve in the near future.

3.3.4. Current limitations and future directions in radiomics—Although the field of radiomics is currently moving at an unprecedented pace, and the potential of radiomic and AI applications seems limitless, there are several key challenges to overcome prior to the more widespread study and clinical adoption of radiomic and AI-based tools for renal mass characterization. For example, development of radiomic applications is inherently dependent on the provided datasets, which often suffer from a significant selection bias since these do not include all histological subtypes. Moreover, imaging data are often collected from surgically treated tumors in a retrospective fashion, which might lead to an over-representation of more aggressive tumors selected for surgical treatment. Pooling of

multiple large datasets might overcome some of these limitations and allow for an adequate representation of rarer histological subtypes.

Indeed, generalizability and reproducibility remain a key issue among radiomic studies and need to be addressed prior to possible widespread clinical implementation [117]. Kocak et al [118] assessed 30 studies involving AI in renal mass characterization and found that only 10% of studies performed a generalizability assessment using independent or external validation. The same was concluded by Ursprung et al [119], who assessed the methodological quality of 57 radiomic studies. Of these, only three used external validation sets and one used a publicly available validation dataset. None of the studies shared code, regions of interest, or images. Moreover, scanner models as well as acquisition and reconstruction protocols are highly variable between and within institutions and impede generalizability. Manual segmentation of a region of interest is labor intensive, and successful automated segmentation methods, preferably three dimensional, are currently lacking. Highly reproducible segmentation techniques would be needed for widespread adoption of radiomic applications. While deep learning models do not require this guided segmentation of a region or volume of interest, these unsupervised approaches sacrifice critical clinical knowledge, which might lead to overfitting of these predictive models and indicates the need for structured quality assessment. Overall, this means that while the feasibility of radiomic and AI applications seems apparent, the reproducibility is seriously lacking and may halt the integration of radiomics into routine clinical practice. AI methods may be less dependent on variations among scanners and protocols, although such algorithms can function as “black boxes” in which the output is not explainable in human terms, which may also slow adoption.

4. Conclusions

A number of novel imaging tools are currently under investigation to improve the noninvasive characterization of solid renal masses. Several of these tools are poised for widespread clinical adoption and will likely serve to augment or possibly replace RMB in the workup of solid renal masses, thus providing a comprehensive virtual biopsy. Among these tools, ^{99m}Tc -sestamibi SPECT/CT for the identification of renal oncocytomas/HOCTs and PET/CT with radiolabeled girentuximab for the identification of ccRCC are, by far, closest to implementation in routine clinical practice. Ultimately, it is likely that regardless of the imaging techniques used, radiomics and AI-powered interpretative tools will be required to maximize the diagnostic accuracy and utility of these tests. Furthermore, these advanced interpretative tools stand to possibly allow for more in-depth characterization of solid renal masses in terms of tumor grade, underlying genomic abnormalities, and clinical behavior.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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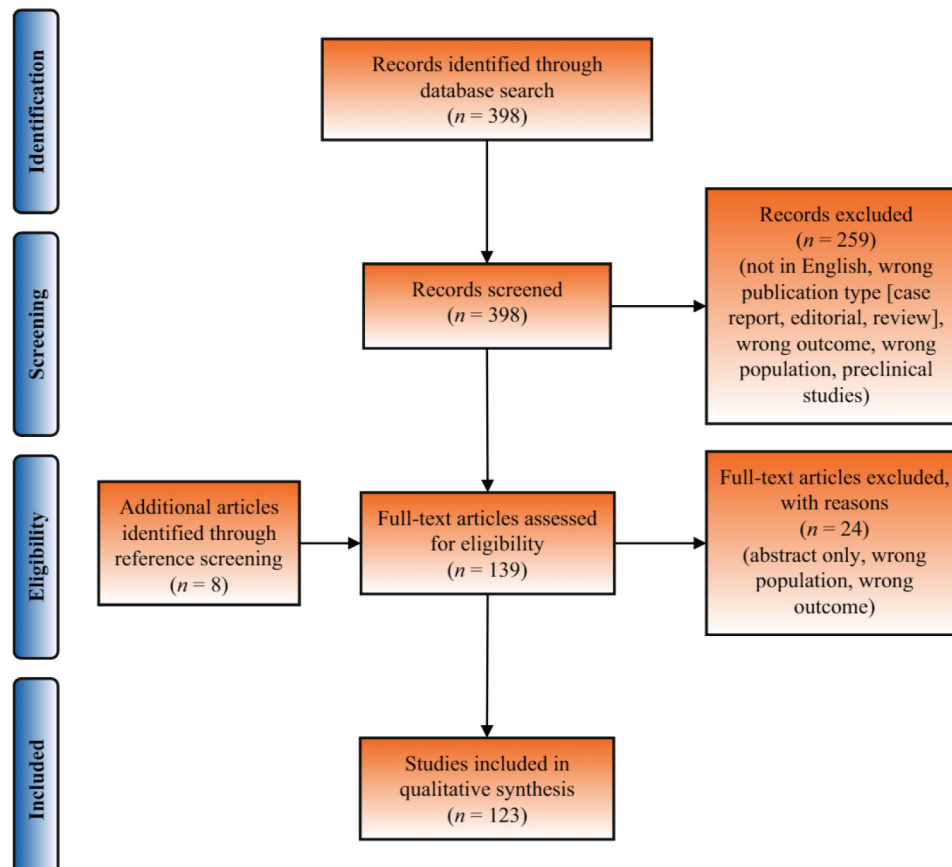


Fig. 1 –.
PRISMA flowchart showing study selection. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

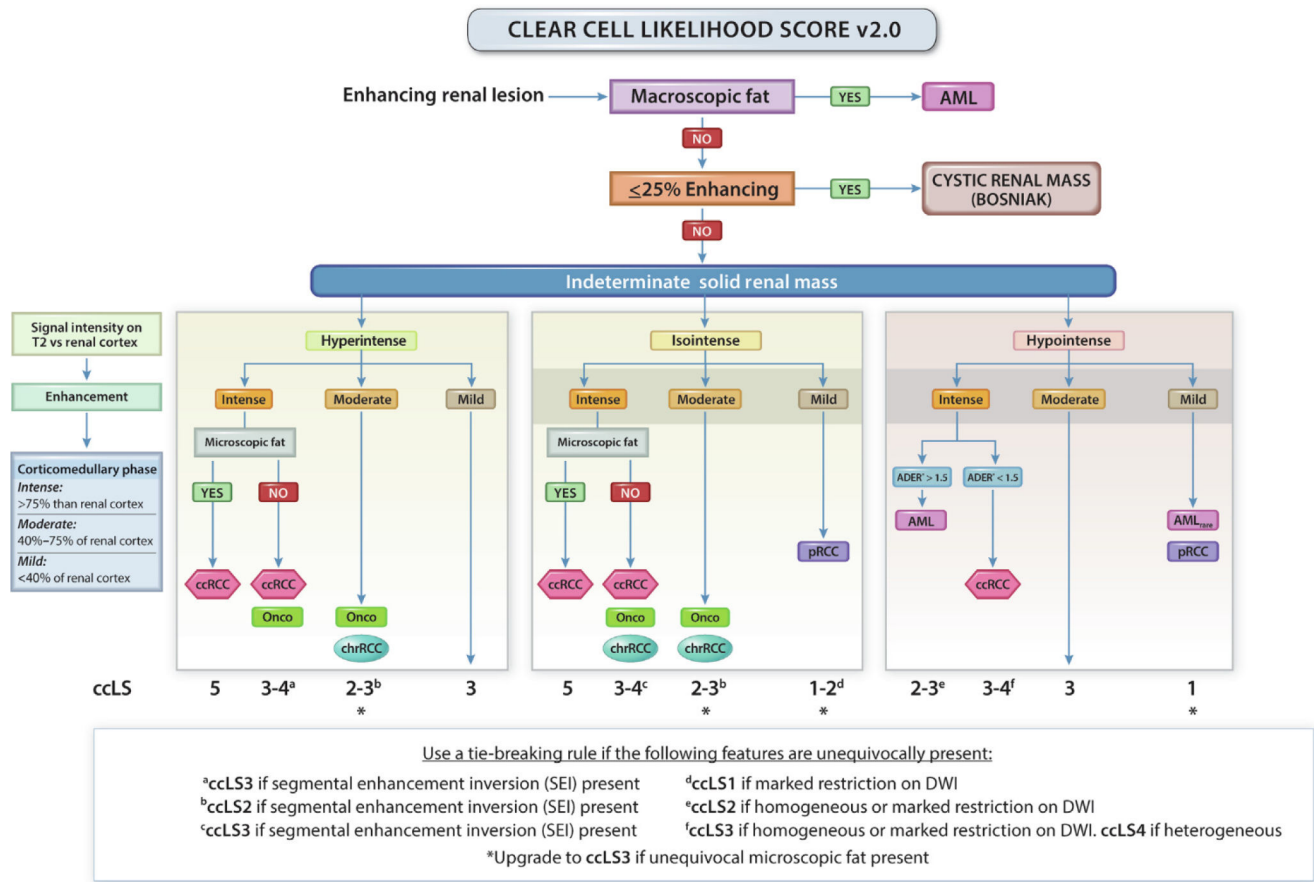


Fig. 2 –
Clear cell likelihood score (ccLS) algorithm version 2.0. Presence of enhancement in $\geq 25\%$ of the mass volume and absence of macroscopic fat represent eligibility criteria for the use of the ccLS algorithm. Signal intensity on T2-weighted single-shot fast/turbo spin echo imaging (T2) relative to renal cortex, enhancement during the corticomedullary phase relative to renal cortex, and presence of microscopic fat are the major criteria evaluated in every mass. Restriction in DWI, segmental enhancement inversion, and arterial-to-delayed enhancement ratio (ADER) are ancillary findings, which are assessed when indicated in the algorithm. AML = angiomyolipoma; ccRCC = clear cell renal cell carcinoma; chrRCC = chromophobe renal cell carcinoma; DWI = diffusion weighted imaging; Onco = oncocyoma; pRCC = papillary renal cell carcinoma. (Figure was reproduced with permission from Pedrosa and Cadeddu [120].)

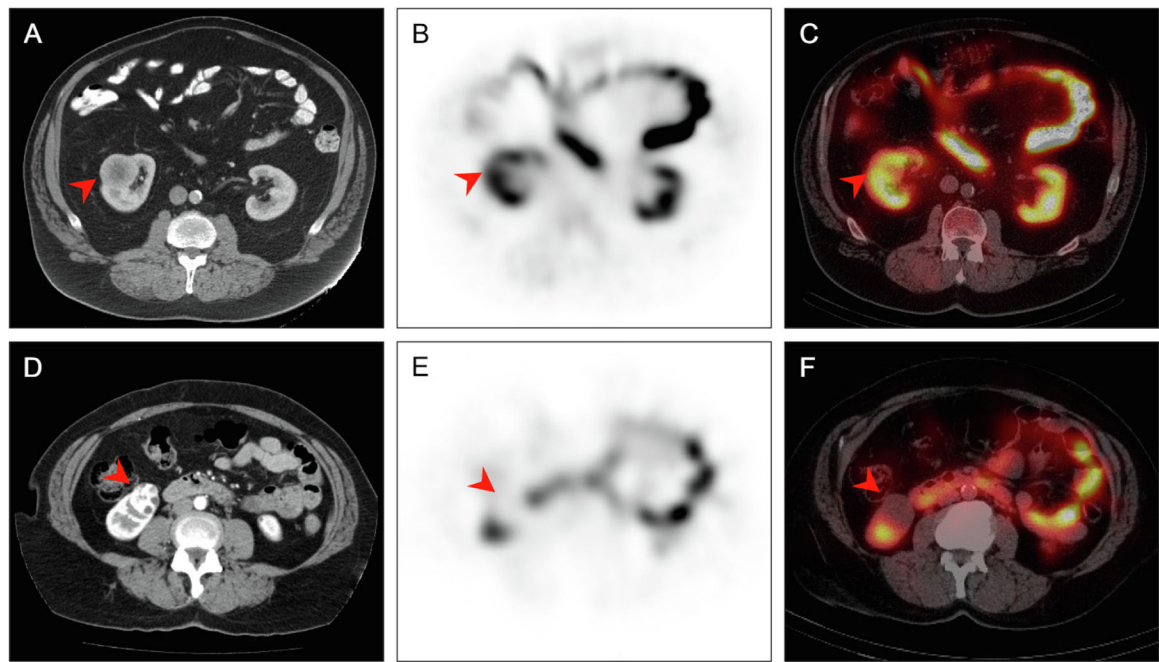


Fig. 3 –.

Differentiation of renal tumors on the basis of ^{99m}Tc -sestamibi uptake. (A) Axial contrast-enhanced CT, (B) axial ^{99m}Tc -sestamibi SPECT, and (C) axial ^{99m}Tc -sestamibi SPECT/CT images of a patient with a right renal mass (red arrow heads). Uptake in the mass is heterogeneous but overall similar to kidney background. There is relative photopenia in the less enhancing central portion of the tumor. The patient underwent percutaneous biopsy that demonstrated an oncocytic neoplasm and was then enrolled in active surveillance. (D) Axial contrast-enhanced CT, (E) axial ^{99m}Tc -sestamibi SPECT, and (F) axial ^{99m}Tc -sestamibi SPECT/CT images of a patient with a right renal mass (red arrow heads). There is no appreciable radiotracer uptake in the tumor. The patient underwent a partial nephrectomy with surgical pathology revealing a clear cell renal cell carcinoma. CT = computed tomography; SPECT = single photon emission computed tomography.

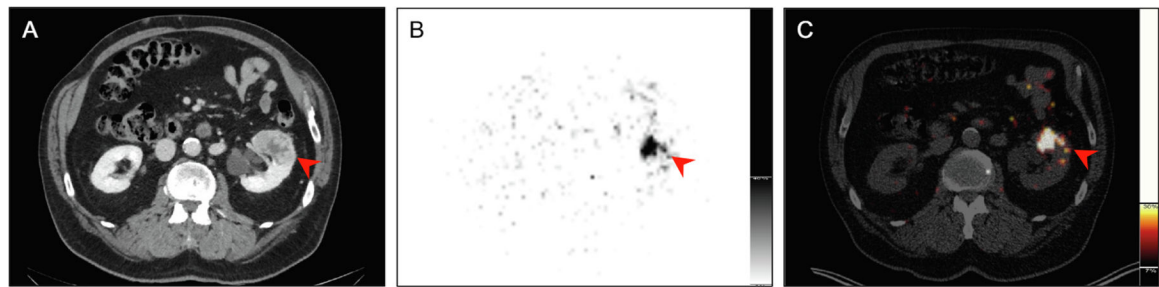


Fig. 4 –.

Differentiation of a renal tumor on the basis of ^{89}Zr -girentuximab uptake. (A) Axial contrast-enhanced CT, (B) axial ^{89}Zr -girentuximab PET, and (C) axial fused ^{89}Zr -girentuximab PET/CT images in a patient with a left renal mass (red arrow heads). There is clear uptake in the mass, with very little background uptake. The patient underwent a partial nephrectomy with surgical pathology revealing a clear cell renal cell carcinoma. CT = computed tomography; PET = positron emission tomography.

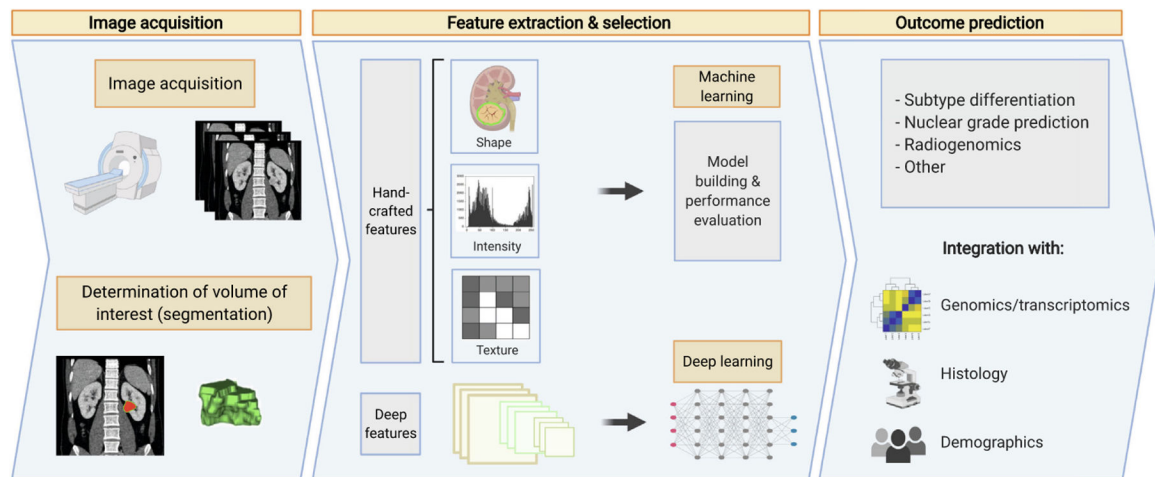


Fig. 5 –.
Schematic representation of a radiomic workflow.

Table 1 –

Summary of novel imaging tests for renal mass characterization.

Imaging method	Potential use	Key features	Limitations
Multiparametric MRI	Differentiation of tumor histology	Improved contrast resolution compared with contrast-enhanced CT No concern for ionizing radiation Use with the clear cell likelihood score (ccLS) predicts the likelihood of clear cell RCC histology Accumulates in cells with high mitochondrial content and low multidrug resistance pump expression	Longer examination times compared with contrast-enhanced CT High cost Low spatial resolution makes it difficult to image small and entirely intrarenal tumors
^{99m} Tc-sestamibi SPECT/CT	Diagnosis of oncocytomas and hybrid oncocytic/chromophobe tumors	Readily available and inexpensive Targets carbonic anhydrase IX, which is a sensitive and specific marker for clear cell RCC Better contrast and spatial resolution than SPECT/CT	Long interval between radiotracer administration and PET/CT scan (3–7 d) Lacks regulatory approval High cost
¹²⁴ I or ⁸⁹ Zr girentuximab PET/CT	Diagnosis of clear cell RCC	Targets malignant cells exhibiting aerobic glycolysis Readily available PSMA is expressed in the neovasculature of most solid malignant tumors	High background activity in the kidney limits the potential for primary renal mass characterization
¹⁸ F-FDG PET/CT	Nuclear grade prediction	PSMA-targeted PET is readily available in most countries	High background activity in the kidney limits the potential for primary renal mass characterization
PSMA-targeted ⁶⁸ Ga-PSMA-11 and ¹⁸ F-DCFPyL PET/CT	Differentiation of benign from malignant histology Prediction of adverse pathological features	Targets rapidly dividing cancer cells due to its incorporation into cell membrane precursors	Need for use in combination with a separately performed ¹⁸ F-FDG PET limits clinical implementation
¹¹ C-acetate PET/CT	Differentiation of AML vs RCC		

AML = angiomylipoma; CT = computed tomography; FDG = 2-deoxy-2-fluoro-D-glucose; MRI = magnetic resonance imaging; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; RCC = renal cell carcinoma; SPECT = single photon emission computed tomography.

Imaging methods are listed in the order of mention in the article's main text.