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Imaging and Screening of Kidney Cancer

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SYNOPSIS

Renal cell carcinoma (RCC) exhibits a diverse and heterogeneous disease spectrum, but insight into its behavior has provided an improved understanding of potential risk factors, natural history of disease, and imaging features. Appropriately performed, CT and MRI may allow for the identification and accurate preoperative subtyping of RCC and for the assessment of a response to various therapies. Active surveillance is receiving increasing attention as a viable management option in select subgroup of patients and has provided further insight into the natural history of RCC, including the favorable prognosis of cystic renal neoplasms. In this article, we provide a brief review of the epidemiologic, clinical, and imaging features of RCC and the potential role of screening in selected high-risk populations.

Keywords

Kidney Cancer; Magnetic Resonance Imaging; Computed Tomography Imaging; Bosniak Classification; Screening; Active surveillance

Introduction

Renal cell carcinoma (RCC) exhibits a diverse and heterogeneous disease spectrum. Insight into the behavior of RCC has yielded a better understanding of the potential risk factors, natural history of disease, and imaging features. After resection, many patients will do well and may remain disease-free, but in some patients, recurrent/metastatic disease may occur even decades after surgical resection of the primary tumor. Furthermore, patients with a resected RCC are more likely to develop additional renal tumors after resection than the general population. Moreover, tumors being followed with active surveillance may remain

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The Authors have nothing to disclose

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stable for several years, slowly grow, or rapidly enlarge. The radiologist must assume a vital role in the management of patients with RCC, as he/she can be involved in all facets of care including the diagnosis, treatment, and surveillance of RCC. The purpose of this article is to provide the radiologist a brief review of the epidemiologic, clinical, and imaging features of RCC.

Epidemiology

Incidence

Renal cell carcinoma accounts for approximately 90% of all renal malignancies and is the 13th most common malignancy worldwide ¹. The incidence of renal cancer is highest in developed countries with rates generally higher in Europe and North America than in India, Africa, and China ². In the US, the incidence of kidney cancer increased by an average of 1.1% over 2004–2013, and it was estimated that close to 63,000 new cases were diagnosed in 2016 ¹. It is speculated that an increase in cross-section imaging has in part resulted in the increase in incidence with the majority of RCCs being found incidentally, and as a result, tumors are being diagnosed at an earlier stage and smaller size ^{3–6}.

The current treatment model is based on the hypothesis that early intervention should yield better outcomes in survival, as a smaller tumor size at diagnosis has been associated with an improvement in 5-year survival among recently diagnosed patients ⁷. In fact, the 5-year survival rate for kidney cancer was recently reported to be as high as 74% from 2005–2011, increased from 57% between 1987–1989. That being said, interpreting the overall outcomes of patients with RCC has been challenging as population-based mortality data does not support the aforementioned hypothesis. Indeed, although the 5-year survival has improved, the overall mortality rates have shown minimal (if any) change during the same time period (Fig. 1)⁸, suggesting that the higher survival proportion may reflect over-diagnosis rather than a true survival benefit ^{9,10}.

Risk Factors

Multiple factors have been implicated in an increased risk of RCC, such as nutrition and diet, but only a few established risk factors have been confirmed. Age is considered to be a risk factor, as the incidences of RCC in Europe and US increase consistently with age and plateau near 70–75 years of age ¹¹. The estimated risk of RCC for men between the ages of 50 and 59 is around 0.3% compared to 1.3% for individuals 70 years and older ¹. Age-controlled incidences of RCC also indicate a 2:1 predominance of men compared to women ^{2,8}.

Smoking is an established risk factor for RCC with a described dose-response relationship ¹². There is limited data to suggest that cessation may reduce the risk, but only among long-term quitters of ten or more years ¹³. Several case control and prospective studies have shown hypertension and obesity to be risk factors as well ^{11,14}.

The incidence of RCC in patients with acquired renal cystic disease (ARCD) has been reported to be 3–6 times higher than in the general population ^{15,16}, and this risk may not

decrease after renal transplantation¹⁷. RCC in the setting of ARCD tends to be diagnosed at a younger age and exhibit favorable histologic features and prognosis¹⁸.

Several occupational and environmental risk factors have been suggested as well. The most extensively studied is trichloroethylene (TCE), a metal degreaser and chemical additive. There have been an increasing number of studies reporting an increased risk of RCC with increased levels of exposure to this agent but a clear mechanism has not yet been elucidated^{19,20}. A recent meta-analysis also suggested that high cadmium exposure was associated with an increased risk for renal cancer as well²¹.

Genetic predisposition

Numerous familial/hereditary renal cancer syndromes have been described but are overall rare and account for less than 5% of all RCCs²². Patients with hereditary cancer syndromes tend to present at an earlier age and are more likely to have multifocal disease compared to those with non-syndromic RCC. Although a complete discussion of the various syndromes is beyond the scope of this review, the reader should be aware that each of these syndromes tend to be associated with specific histologic subtypes of RCC due to their underlying genetic alterations and that those neoplasms are associated to variable levels of aggressiveness. A few examples are provided in Table 1.

Imaging of Renal Cell Carcinoma

In the evaluation of renal masses, the radiologist should seek to accomplish two main goals: lesion detection and classification. An optimal imaging protocol facilitates the identification of contrast enhancement, the primary criterion for diagnosing renal cell carcinoma, and in assessing the degree of vascularity, the latter which may be used to suggest a specific subtype of RCC. In addition, the radiologist must provide accurate information about tumor staging and renal vascular anatomy to facilitate a potential surgical and/or ablation intervention.

Imaging Protocols

Computed Tomography (CT)—CT imaging protocols used for the evaluation of renal masses have been described elsewhere^{23–25}. A conventional CT protocol routinely includes pre- and multiphasic post-contrast images. Volumetric datasets provided by modern CT scanners can be reconstructed in multiple planes and be of variable slice thickness preserving excellent image quality.

Pre-contrast images are used to obtain a baseline attenuation value in the lesion of interest and help identify the presence of calcifications, hemorrhage, and/or fat. Thin slices (i.e. 2–3 mm) may facilitate the detection of fat in these images and therefore may help in the characterization of renal masses²⁶. For the purpose of detection of a renal mass and determination of contrast enhancement, post-contrast images should be obtained during the nephrographic phase (60–90 seconds after). During the corticomedullary phase (acquired 20–45 seconds after contrast injection), there is peak enhancement of the renal cortex, readily delineating it from the relatively hypovascular medulla, and these images are helpful in determining the vascularity of the lesion, delineating vascular anatomy, and identifying

hypervascular metastases. However, peripheral hypervascular masses may be of similar attenuation to and obscured by the renal cortex and small central hypovascular lesions may be mistaken for the relatively hypoattenuating medulla^{25,27}. Moreover, the added radiation dose of a routine acquisition during the corticomedullary phase may not be justified. Uniform renal parenchymal enhancement during the nephrographic phase better delineates otherwise subtle lesions which may have been overlooked during the corticomedullary phase and is useful in demonstrating enhancement in hypovascular neoplasms²⁵. Excretory phase images (3–5 minutes post-injection) can be obtained as well and may be helpful in identifying potential pathology in the collecting system and ureter.

With the increasing utilization of dual-energy CT (DECT), the conventional multiphasic CT may soon be modified. Several studies support the use of virtual unenhanced datasets as a surrogate for the standard pre-contrast acquisition, which would result in a decrease in radiation dose^{28–30}. However, small differences in measured quantitative values between virtual and conventional unenhanced images have been reported^{29,30}, and further studies are required before the routine implementation of virtual unenhanced images.

Magnetic Resonance Imaging (MRI)—The standard sequences in a multiparametric magnetic resonance imaging (mpMRI) protocol have been described elsewhere^{31,32}. The ideal mpMRI protocol includes conventional sequences, such as T2-weighted (T2W) and chemical-shift imaging, combined with multiphasic contrast-enhanced images (MCE) to provide a comprehensive evaluation of renal neoplasms. Appropriately performed, mpMRI may be able to provide information beyond what can be achieved with CT alone, but achieving a high-quality exam can be more challenging and depends on factors beyond sequence selection, including adequate patient cooperation.

T2W spin-echo acquisitions can be performed using either multishot or single-shot techniques, with or without fat-suppression. Although multishot sequences provide greater image contrast, signal-to-noise ratio (SNR), and spatial resolution, single-shot fast spin-echo (SSFSE)/half-Fourier single-shot turbo spin-echo (HASTE) sequences are routinely used at the authors' institution when imaging the upper abdomen to help mitigate image degradation caused by respiratory motion.

Gradient-recalled echo (GRE) techniques allow for rapid imaging and adequate SNR and can be used to acquire 2-D T1-weighted in-phase (IP) and opposed-phase (OP) images for detection of intralesional fat³³. 3-D dual-echo Dixon-based acquisitions can also be used to obtain thinner, contiguous slices in a single breath-hold and reconstructed into water, fat, IP, and OP imaging data sets³⁴.

For multiphasic post-contrast imaging, the authors prefer to use 3D fat-suppressed spoiled gradient echo (SPGR) techniques to acquire T1-weighted images in the coronal plane. However, these can be acquired in the axial plane as well. Images are acquired during the corticomedullary phase, which is timed to the arrival of contrast to the kidneys using an MR fluoroscopic technique, in addition to early and late nephrographic phases. A Dixon-based fat saturation technique provides more homogenous fat suppression over a larger field-of-view.

The role of diffusion-weighted imaging (DWI) for the detection and characterization of renal masses continues to evolve. Some investigators have reported some value in the determination of the histologic diagnosis in renal masses^{35,36} and the characterization of high-grade RCC³⁷. However, a recent meta-analysis indicated only moderate diagnostic accuracy in the characterization of renal masses and determination of high-grade clear cell histology³⁸. The lack of standardization of the DWI acquisition protocols across different MRI vendors and different medical centers is likely responsible, at least in part, for the less than optimal diagnostic performance. Breath-hold, single-shot echo-planar imaging (EPI) techniques allow for rapid DWI acquisitions and help limit motion artifact. However, the number of signal averages and/or b-values may be limited by the duration of the breath-hold resulting in poor SNR. Alternatively, free-breathing techniques may be incorporated to provide multiple signal averages, thereby improving SNR and contrast-to-noise ratio, but at the cost of longer acquisition times.

Characterization of Enhancement

The fundamental principle in diagnosing RCC relies on identifying the presence of enhancement within a renal lesion. MRI has a potential advantage over conventional CT because its sensitivity to detect small amounts of gadolinium is higher than that of CT for iodinated contrast. Furthermore, subtraction images, which are created by digitally subtracting the unenhanced image from the corresponding post-contrast image allow for the removal of any native T1 signal intensity from the post-contrast image, thereby displaying signal solely due to enhancement. However, this technique is highly dependent on adequate and reproducible breath-holds for accurate co-registration of images; if this is not fulfilled, mis-registration may occur and thus determination of enhancement on these images is not reliable. Alternatively, if subtraction images are unavailable or of poor quality, determining the percentage change in signal intensity within the lesion is an additional method for determining enhancement; an increase 15% in signal intensity on post-contrast images compared to pre-contrast images is indicative of enhancement on MRI exams³⁹.

Demonstrating enhancement on CT can be complicated by multiple factors. First, the definition of enhancement varies. Traditionally, a change in 10 HU was suggested as a threshold for determining enhancement⁴⁰. Subsequent studies showed that the attenuation in cysts may artificially increase by more than 10 HU between unenhanced and post-contrast images due to beam-hardening effects caused by the marked enhancement of the adjacent renal parenchyma, and the apparent increase in attenuation may be more pronounced in small and completely intrarenal lesions^{41–43}. As such, some have suggested this threshold be increased to 15–20 HU^{42,44}, but others still advocate using 10 HU⁴¹. Because identifying enhancement should be unequivocal due to the significant implications in the management of a renal lesion, some suggest further increase the threshold to > 20 and consider a change between 10–20 HU as equivocal and potentially requiring further imaging with MRI⁴⁵.

DECT may help overcome these limitations of conventional CT. By using the image data acquired at two different energy levels, virtual monochromatic images simulating the attenuation of an ideal monochromatic beam may be reconstructed from the DECT

dataset⁴⁶. There have been an increasing number of studies describing the utility of these virtual monochromatic datasets in mitigating the effect of beam hardening for small, intrarenal lesions^{47–49}. Additionally, DECT image data can be reconstructed to generate material density images. This can be used to produce the previously described virtual unenhanced, water-only image but can also be used to create an iodine-only image (Fig. 2)⁵⁰. This allows for the possibility to obtain a direct quantification of iodine concentration within a renal lesion, thereby allowing for the identification and quantification of otherwise subtle enhancement in a hypovascular or hyperattenuating renal lesion^{51–53}.

Characterization of Cystic Renal Cell Carcinoma

Nomenclature—The definition of “cystic” RCC is highly variable and the term may include a variety of pathologic entities, such as multilocular cystic RCC or one of a more common subtypes of RCC, including clear cell and papillary, with cystic components. This distinction is not solely an academic exercise; as will be discussed in the following sections, there is increasing data to support that cystic renal neoplasms demonstrate a more indolent pattern of behavior and favorable prognosis when compared to solid renal tumors. This is best exemplified by multilocular cystic RCC, a specific subtype now sanctioned by the World Health Organization as a tumor of low malignant potential, more specifically “multilocular cystic renal neoplasm of low malignant potential”⁵⁴. However, this neoplasm is composed entirely of cysts whose walls are lined by a single layer of clear cells and septa may contain groups of clear cells but no expansile growth. Specifically, a solid-mass forming component should be absent (Fig. 3)⁵⁴. Importantly, there is not reported evidence of metastatic disease caused by this tumor in the literature.

Up to 15% of all renal cell carcinomas may contain a cystic component⁵⁵, but there is no uniform agreement as to what amount of cystic and/or solid component should be present to separate a solid mass with cystic change from a complex cystic mass with a solid component by imaging. Prior studies evaluating the prognosis of patients with “cystic” RCC have proposed a variable percentage of cystic components ranging from 75% to 90%^{56–58}.

However, regardless of the threshold chosen, the more fundamental issue of identifying a region of true cystic change on preoperative imaging persists. What may be interpreted as a region of cystic change on imaging may correspond to a variety of lesion characteristics, including necrosis and hemorrhage, on histopathology. A recent retrospective study by Park et al.⁵⁹ evaluating the postoperative outcome of cystic renal neoplasms found a cystic proportion 45% on the pre-operative CT to be an independent prognostic factor for survival, which is a step in the right direction. Future studies looking at defining certain imaging phenotypes and correlating with outcome are needed.

Imaging Features

Traditionally, radiologists have used the Bosniak renal cyst classification system when evaluating a cystic-appearing renal mass. Developed in 1986 by Morton Bosniak, the system suggested a standardized nomenclature to classify and guide management of renal cystic lesions based on certain imaging features⁴⁰. The classification system describes 5 different categories of cystic lesions (I, II, IIF, III, and IV) with the increasing number corresponding

to increase in complexity within the lesion and higher likelihood of malignancy. The categories are differentiated based on the presence and morphologic features of calcifications and septations, in addition to the degree of septal enhancement (i.e. perceived versus measurable) and precontrast attenuation.

A Bosniak I cyst corresponds to a simple cyst. These cysts have a thin, smooth wall and fluid attenuation/signal without septa, enhancement, or calcification. Category II cysts are minimally complex cysts. These cysts can have a few and thin (< 3 mm) septations with perceived, but not measurable, enhancement. Small, border-forming calcifications may be present. This category also includes small (< 3 cm) homogeneously hyperattenuating, nonenhancing lesions. Both category I and II cysts are considered benign and require no additional follow-up imaging.

Bosniak IIF includes mildly complex cysts, which require follow-up imaging. These cysts can have multiple, thin or minimally thickened septa with perceived enhancement. Thick/nodular calcifications may also be present. The large (> 3 cm) nonenhancing, hyperattenuating cysts are included in this category as well. The majority Bosniak IIF cysts are benign⁶⁰, but require follow-up imaging. However, the interval and duration of follow-up imaging has not been clearly defined. In a recent meta-analysis up to 7% of these lesions were malignant⁶¹.

Bosniak III lesions include cysts with multiple and thick, enhancing septa and/or thick walls. The incidence of malignancy in resected Bosniak III lesions is overall higher than in Bosniak IIF cysts, but highly variable with rates reported between 30%–100%^{62,63}. Finally, category IV lesions include cystic lesions with enhancing soft-tissue components, which may be adjacent to or separate from the wall or septa (Fig. 4). Lesions included in this category are considered malignant until proven otherwise. Traditionally, surgical resection has been the suggested management of category III and IV lesions, given their increased likelihood of malignancy.

Both clear cell carcinoma (ccRCC) and papillary renal cell carcinoma (pRCC) may present as a predominantly cystic mass. A complex, predominantly cystic mass with avidly-enhancing, irregular and nodular septa is said to be highly specific (94%) for low-grade ccRCC⁶⁴. A characteristic appearance of pRCC is a cystic-appearing hemorrhagic mass with a hypoenhancing mural nodule, which has been described to have a specificity of 94% as well (Fig. 5).

Characterization of Solid RCC

The imaging characteristics of RCC are highly variable, but certain imaging features on CT and MRI may be used to favor a particular subtype. The degree of enhancement has been consistently shown as a means to differentiate certain subtypes of RCC. An advantage of MRI over CT is that tissue signal characteristics on different sequences can be used in conjunction with the degree of enhancement to assist in subtyping.

ccRCC is a hypervascular subtype, and this is reflected in its pattern of enhancement. On multiphasic imaging, the peak enhancement of ccRCC occurs during the corticomedullary

phase, as much as or greater than the renal cortex^{65–68}. pRCC is a hypovascular neoplasm and almost always hypoenhancing during the corticomedullary phase with its peak enhancement occurring during the nephrographic phase. Chromophobe RCC (chrRCC) can demonstrate variable patterns of enhancement, but tends to be less vascular than ccRCC and show an intermediate degree of enhancement (between 50–60% that of the renal cortex) during the corticomedullary phase^{65,68}.

On CT, several methods have been suggested to distinguish pRCC from ccRCC. Using multiphasic threshold levels of 55 Hounsfield units (HU) during the corticomedullary phase, 65 HU during the nephrographic phase, and 55 HU in the excretory phase was reported to have an accuracy of 85%, sensitivity of 94%, a positive predictive value of 86%, and a negative predictive value of 81%⁶⁵. In a separate study, using a threshold of 100 HU on the corticomedullary phase to distinguish ccRCC and pRCC provided an accuracy of 95.7%, sensitivity of 98.3%, and specificity 92%⁶⁹. Iodine quantification with DECT may also play a role in differentiating ccRCC from pRCC. Using a tumor iodine concentration threshold of 0.9 mg/mL yielded a sensitivity of 98.2%, specificity of 86.3%, positive predictive value of 95.8%, and a negative predictive value of 93.7%⁷⁰.

On MRI, ccRCC can demonstrate variable signal intensity on T1- and T2-weighted images, but commonly demonstrates hyperintense signal on the latter, in addition to avid enhancement during the corticomedullary phase⁶⁸. Intracytoplasmic deposition of lipids in ccRCC results in a characteristic appearance on chemical shift imaging with areas of the intravoxel fat appearing hypointense on the OP images relative to the IP images⁷¹. pRCC most often shows a lower signal intensity relative to the renal cortex on T2-weighted images in the vascularized portions of the tumor. On T1-weighted images, pRCC commonly exhibits non-enhancing areas of hyperintense signal due to intralesional hemorrhage. chrRCC can show variable patterns of signal intensity and can appear hypo- to hyperintense relative to renal cortex on T2-weighted imaging. Papillary tumors frequently demonstrate marked restriction on DWI compared to ccRCCs³⁶.

Several imaging features have been described that suggest a higher-grade of tumor. The presence of a central area of non-enhancement, retroperitoneal collateral vessels, and venous invasion are associated with high-grade ccRCC⁶⁴. Irregularity or interruption of the tumor pseudocapsule, a rim of normal renal parenchyma surrounding the tumor, suggests locally advanced disease and a high nuclear grade⁷². On DECT, a significant correlation between iodine concentration and Fuhrman tumor grade for both ccRCC and pRCC has been described⁷⁰. Focal areas of marked restricted diffusion have been correlated to high grade ccRCC³⁷.

Natural History and Active Surveillance

The greatest increase in incidentally detected renal masses has been in the small and localized tumors (< 4 cm), which now account for greater than 50% of all renal masses identified¹¹. Approximately 20%–30% of these small renal masses (SRMs) are benign and the majority demonstrate an indolent growth pattern^{73–75}. This has resulted in a growing body of literature evaluating active surveillance for the management of SRMs and where

insight into the natural history of RCC is being derived. However, near 20% of SRMs show an aggressive, malignant behavior^{75,76}. Patients older than 70 years of age have been found to be at an increased risk for high-stage and high-grade disease. Similarly, is this population in which most SRMs are now being diagnosed and who are more likely to have comorbidities and increased surgical risk^{77,78}. Therefore, there is a need to develop biomarkers that inform on the biology of SRM and predict their natural history.

Active surveillance (AS) is preferentially reserved for patients who are unable to undergo surgery due to competing risks from comorbidities or are unwilling⁷⁹. For those placed on AS, the American Urological Association (AUA) and National Comprehensive Cancer Network (NCCN) guidelines recommend abdominal imaging with CT or MRI within 6 months from initiation of AS and subsequent imaging (CT, MRI, or ultrasound) performed annually thereafter for as long as the patient is on active surveillance^{80,81}. During this time, the size of the lesion should be closely monitored, as growth kinetics is a commonly cited surrogate for metastatic potential and potential indication for further intervention. Although the growth rates for SRMs may be highly variable, several studies have reported a mean growth rate varying between 0.3 cm/year to 0.4 cm/year^{77,82,83}. One systematic review showed lesions on AS that progressed to metastatic disease demonstrated a significantly higher growth rate (0.8 cm/year) compared to those with favorable outcomes (0.3 cm/year)⁸⁴.

Outside of growth rate and size, imaging features to predict outcome are limited, but there are increasing number of studies suggesting that “cystic” RCC may follow a more favorable course of disease. Multiple studies have reported an excellent prognosis in patients with cystic RCC after surgery, regardless of size, with an exceedingly rare incidence of metastases^{57,58,85–87}.

Follow-up After Therapy

Patterns of Recurrence

Local or systemic recurrence occurs in approximately 30% of patients who undergo surgical resection for localized RCC⁸⁸. The most common sites of metastases are lung (45%), bone (30%), lymph node (22%), liver (20%), adrenal (9%) and brain (8%)⁸⁹. As with most malignancies, the greatest risk of recurrence is early in the post-treatment setting with the majority of recurrences occurring less than 3 years after surgery^{90,91}. The timing of recurrence is related to the tumor stage with reported median times to recurrence for T1, T2, and T3 tumors of 38, 32, and 17 months, respectively⁹². The risk is affected by several factors, including tumor grade and stage, presence of nodal metastases, and RCC subtypes. For tumor stages I to IV, the reported 5-year cancer specific survival rates are 91, 74, 67, and 32%, respectively⁹³. Tumors with sarcomatoid differentiation, medullary carcinoma, and collecting duct carcinoma all exhibit a higher risk for metastatic disease⁹⁴. Late recurrences (i.e. >5 years after surgery) occur in patients with smaller masses, lower stage, and lower nuclear grade than those with earlier recurrence/metastatic disease⁹⁵.

For SRMs, partial and radical nephrectomies show similar risks for progression and renal cancer-related deaths, with the former's risks estimated to be 4.5% and 3%, respectively⁹⁶.

The overall failure rate for ablative therapies, including radiofrequency ablation and cryoablation, has been reported to range from 2%–10%⁹⁷. However, assessing the overall risk for local recurrence, development of metastatic disease, and death from T1a RCC after ablation is confounded by the different techniques available for ablation, lack of pretreatment biopsy confirmation of tumor, lack of uniform definition of a local recurrence, and difficult in assessing recurrent/residual tumor on biopsy or radiographic imaging.

Surveillance Strategies After Therapy

Presently, there are no universally accepted guidelines for follow-up imaging after therapy, and there have been no prospective or randomized controlled trials to clarify what imaging surveillance protocol is the most efficacious. Most guidelines, including the AUA and NCCN, suggest surveillance strategies based on risk-adapted protocols, which stratify patients into groups based on TNM staging.

For T1a and T1b tumors with negative lymph nodes, several guidelines suggest less frequent follow-up imaging due to the low-risk for recurrence. Typically, a chest radiograph may be obtained every 6 to 12 months for 3 years and then annually until year 5. Baseline abdominal imaging is recommended within 3 to 12 months following a partial or radical nephrectomy. Subsequent imaging varies depending on individual risk factors and type of surgery. For partial nephrectomy, if the initial baseline imaging was negative, abdominal surveillance imaging may be performed at yearly intervals for 3 years. After radical nephrectomy, subsequent imaging after a negative baseline study is considered optional⁸¹. For T2 through T4 tumors, or any T stage with positive lymph nodes, AUA and NCCN suggest baseline chest and abdominal imaging within 3 to 6 months following surgery. Continued follow-up imaging is suggested every 3 to 6 months for at least 3 years, and then annually thereafter for up to 5 years^{80,81}.

After ablative therapies, the AUA and NCCN recommend cross-sectional imaging at 3 and 6 months after therapy. If treatment success is documented by imaging, abdominal and chest radiographs are then recommended annually for 5 years with further imaging considered optional.

Imaging Appearance

Assessing for recurrence on imaging requires evaluation with at least dual-phase (arterial and portal venous) post-contrast imaging, as metastatic lesions tend to show enhancement characteristics similar to those of the primary tumor. One study reported 9% ccRCC metastases in the liver or pancreas were seen only on arterial phase images⁹⁸. If ablative therapies were used for the primary lesion, pre-contrast imaging should be included to provide baseline attenuation values.

On CT imaging, evaluating the ablation zone requires careful review of pre- and post-contrast phases. After a successful ablation, the zone of ablation should appear as a region of increased attenuation (> 40 HU) on the unenhanced studies surrounded by a rim of fat attenuation⁹⁹. On MRI, the ablation zone often shows heterogeneous hyperintense signal on T1-weighted and hypointense signal on T2-weighted images¹⁰⁰. A thin, smooth rim of enhancement surrounding the ablation should be considered a benign finding that may be

encountered. After radiofrequency ablation, a characteristic thin rim of soft tissue is present around the area of preserved fat that surrounds the ablation zone, which has been described as the “halo sign” – which can be confused with the appearance of an angiomyolipoma (Fig. 6) ¹⁰¹. An enlarging nodular or crescentic area of enhancement should be considered recurrent disease until proven otherwise ^{99,100}.

RCC can metastasize to virtually any part of the human body with case reports documenting recurrence in the subcutaneous tissues, oral cavity, and testicle ^{102–104}. However, the lungs are the most common site of metastatic disease in RCC ¹⁰⁵. The appearance of RCC metastases in the lung can manifest in a variety of manners, from a small and well-defined nodule to an irregularly shaped mass, and can enhance avidly ¹⁰⁶. It is important to recognize that patients with RCC may develop primary lung tumors given the known association of smoking to both neoplasms. This possibility should be considered in the presence of a single pulmonary nodule and in those patients where a single pulmonary nodule exhibits progression in the setting of stable disease/response elsewhere ¹⁰⁷. Furthermore, primary lung neoplasms tend to demonstrate a spiculated appearance compared to the more common smooth rounded appearance of lung RCC metastases.

Bones metastases are common affecting up to 32% of patients with metastatic disease ¹⁰⁸. Most often they present as a lytic lesion with a soft tissue component. Detection of lytic bone metastases is challenging given the frequent negative results with both CT and ^{99m}Tc-labeled bone scintigraphy ¹⁰⁹. Similarly, ¹⁸F-labeled fluorodeoxyglucose (FDG) positron emission tomography (PET) has limited value due to inconsistent tumor uptake in RCC. ¹⁸F-labeled sodium fluoride PET/CT is highly sensitive although it is not widely available and/or reimbursed.

Solid organ metastases in the abdomen and pelvis otherwise lack a specific imaging characteristics and can have a variety of appearances, including a uniformly-enhancing, hypervascular mass or a rim-enhancing and centrally necrotic lesion. Of note, the different RCC histologic subtypes exhibit predilection for different organs ¹¹⁰, including solid organs. For example, clear cell carcinoma metastases to the pancreas are not uncommon whereas chromophobe RCC has a predilection to metastasize to the liver ¹¹⁰. Adrenal metastases are common in RCC and may become evident years after resection of the primary tumor ⁹⁵.

Antiangiogenic agents, such as tyrosine kinase inhibitors (TKIs), are being increasingly used in the treatment of metastatic RCC ¹¹¹. Tumor response with these agents may present with changes in perfusion with or without changes in size ¹¹². This may be reflected by qualitative and semi-quantitative decreases in enhancement on conventional post-contrast imaging, though more novel quantitative techniques to assess tissue perfusion have been described. On MRI, a decrease in tumor blood flow on arterial spin labeling (ASL), as soon as 1 month after therapy, and enhancement on dynamic-contrast enhanced MRI (DCE-MRI) may predict a favorable outcome ^{113,114}. A recent study evaluating the use of DECT in patients on antiangiogenic therapy suggested iodine maps may be more sensitive in the detection of an early response when compared to traditional measurements of attenuation ¹¹⁵. The use of automated segmentation algorithms to identify the amount of viable, enhancing tumor burden may facilitate the assessment of RCC response to TKIs ¹¹⁶.

Role of Imaging in Screening

General Population

There are no established guidelines for RCC screening in the general population. As with ovarian cancer, RCC is neither a common nor a rare disease, so screening the general population with CT or MRI would be unlikely to show a positive impact on tumor-specific mortality. This is highlighted by the fact that the increase in incidentally detected RCC has had a small effect on overall mortality with metastatic disease identified in up to 30% of newly diagnosed cases. Moreover, an imaging screening protocol based on CT and/or MRI would be financially prohibiting whereas ultrasound is likely to not achieve enough sensitivity to serve in that role. As non-syndromic risk factors for RCC are further elucidated, a targeted approach in screening may one day be established, but currently, a large randomized controlled trial of renal cancer screening has yet to be performed.

Genetic Predisposition

The management of patients with an inherited predisposition to RCC requires a multidisciplinary approach and some form of routine imaging for lifelong surveillance of renal tumors. Annual screening with CT or MRI is recommended for most patients with a genetic predisposition, though the interval and age at which surveillance imaging begins varies.

For patients with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome, screening begins at an early age, as tumors can be detected as early as 11 years of age and are often aggressive with distant metastases even when small^{117,118}. As such, tumors identified in patients with HLRCC are resected with wide margins and not placed on active surveillance or ablated. The management for patients with succinate dehydrogenase-deficient kidney cancer (SDH-RCC) is very similar given its early age onset (younger than 30 year of age) and association with aggressive renal tumors¹¹⁹.

In contradistinction, annual or biannual surveillance imaging in patients with Birt-Hogg-Dube (BHD) syndrome is recommended starting at the age of 20, and tumors are managed with active surveillance until 3 cm in size, similar to the management of individuals with Von Hippel-Lindau syndrome¹²⁰. In hereditary papillary renal cell carcinoma (HPRC) syndrome, tumors develop most often in the 6th and 7th decade of life, though early onset families have been described (Fig. 7)¹²¹. Tumors in HPRC are more often slow growing and managed with active surveillance. To our knowledge, a screening protocol for HPRC has not been proposed.

Conclusion

Further insight into RCC has provided an improved understanding of its complex epidemiological, clinical, and imaging features. As our knowledge of RCC continues to advance, screening protocols may one day be established in selected populations to help decrease the current mortality rate. Imaging biomarkers and further refinement of classification schema may help identify tumors with low likelihood of progressive disease that may benefit from active surveillance.

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KEY POINTS

- Renal cell carcinoma (RCC) represents a heterogeneous disease spectrum with broad clinical outcomes and various appearances on imaging.
- CT and MR allow for detailed pre- and post-treatment assessment of RCC.
- Current classification system of cystic-appearing renal masses attempts to provides uniform terminology and guidance for management.
- Increasing data supports active surveillance in a select subgroup of patients and has provided further insight into the natural history of RCC.

Fig. 1. Incidence in Kidney Cancer in the U.S

A sustained increased in the incidence of kidney cancer has not translated into a decreased mortality. Data from the “Surveillance, epidemiology, and End Results” [SEER] Database from the National Cancer Institute [NCI]) (<http://seer.cancer.gov/>).

Fig. 2. Solid renal mass identified on a single phase dual-energy CT scan obtained after the patient presented to the emergency room with abdominal pain

(A) Post-contrast coronal CT image of the upper abdomen, obtained during the portal venous phase, shows a partially exophytic mass (white arrow) arising from the upper-mid right kidney, which appears hypoattenuating relative to the renal parenchyma, but demonstrated an attenuation near 80 Hounsfield units (HU). (B) Reconstructed iodine-only image clearly demonstrates iodine accumulation within the lesion (1.8 mg/mL), consistent with a solid renal neoplasm (white arrow). On the (c) reconstructed water-only image, the mass (white arrow) appears iso- to hyperattenuating (near 40 HU). The attenuation difference between the reconstructed water-only and the post-contrast images also confirms the lesion corresponds to a solid, enhancing mass. (D) Post-contrast subtraction MR image

from a subsequently performed MR confirms enhancement within the mass. The patient is scheduled to undergo a percutaneous biopsy and radiofrequency ablation in the near future.

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Fig. 3. Multilocular cystic neoplasm of low malignant potential

Coronal (a) T2-weighted and (b) post-contrast images of the right kidney demonstrate a complex cystic mass in the medial lower pole containing several thickened, enhancing septations without a discrete nodular component. The mass was resected and confirmed to represent a multilocular cystic neoplasm of low malignant potential (ISUP grade 1).

Fig. 4. Bosniak IV cyst in the left kidney

Coronal (a) T2-weighted (b) post-contrast images demonstrate a complex cystic lesion in the lower pole of the left kidney containing multiple thickened septations, in addition to several more discrete-appearing nodule within one of the septa (arrowhead), consistent with a Bosniak IV cyst. The lesion was resected and found to represent a clear cell renal cell carcinoma (ISUP grade 2). Note a few additional simple, Bosniak I cysts in the left kidney.

Fig. 5. Papillary renal cell carcinoma

(A) Coronal T2-weighted image shows a complex cystic-appearing mass in the upper pole of the right kidney (white arrow) with thickened walls, septa, and an possible mural nodule along its inferior wall (white arrowhead). Coronal (b) pre-contrast fat saturated gradient echo image shows areas of high signal intensity in the lesion related to the kidney (asterisk) suggestive of hemorrhagic contents. (C) post-contrast subtraction image demonstrates an irregular-appearing and enhancing mural nodule along its inferior wall (white arrowhead). The mass was subsequently resected and confirmed to represent a papillary renal cell carcinoma (with features of type 1 and type 2; ISUP grade 3).

Fig. 6. Expected imaging appearance after radiofrequency ablation (i.e. the “halo” sign) of a papillary renal cell carcinoma

(A) Coronal post-contrast CT image acquired during the nephrographic phase shows a hypoenhancing mass (white arrow) compared to the pre-contrast image (not shown) arising from the lower pole of the kidney, proven to be a papillary renal cell carcinoma (type 1; ISUP grade 3) on biopsy performed immediately before radiofrequency ablation (RFA). On the MRI performed 3 months after ablation, (b) coronal T2-, (c) coronal pre-contrast T1-, and (d) and coronal post-contrast subtraction images show the treated tumor as a mass-like, non-enhancing region of coagulative necrosis (hypointense on T2- and hyperintense on T1-weighted images) surrounded by fat (white asterisk). Note the overlying thin, subtle rim of enhancement (white arrowhead) representing fibrous tissue and defining the region of the ablation zone.

Fig. 7. Hereditary papillary renal cell carcinoma follow-up imaging

(A) Axial post-contrast CT image demonstrates multiple hypoattenuating lesions which demonstrated subtle hypoenhancement when compared to the pre-contrast image (not shown). A total of 7 lesions were resected, two of which are shown on the image (dashed arrows), and found to represent papillary renal cell carcinomas (type 1; ISUP grade 2). Two additional subcentimeter lesions (solid arrow and arrowhead) were described as too small to further characterize on this CT exam. Axial (b) T2-weighted and (c) post-contrast subtraction images obtained 6 months after the CT and surgical resection shows interval enlargement of the more central lesion (solid arrow), which also shows unequivocal enhancement on the subtraction post-contrast image. Additionally, the more posterior cystic-

appearing lesion seen on prior CT (arrowhead) has also enlarged and now demonstrates multiple thickened septa.

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Table 1

Hereditary renal cell carcinoma syndromes.

Syndrome	Gene	Renal cell carcinoma subtype
Von Hippel-Lindau	<i>VHL</i>	Clear cell RCC
Birt-Hogg-Dube	<i>FLCN</i>	Chromophobe, oncocytoma, hybrid RCC with features of both chromophobe and oncocytoma, clear cell RCC
Hereditary Papillary Renal Cell Carcinoma	<i>MET</i>	Type 1 papillary RCC
Hereditary Leiomyomatosis and Renal Cell Carcinoma	<i>FH</i>	Type 2 papillary RCC
Succinate dehydrogenase-deficient renal cancer	<i>SDHB</i> <i>SDHD</i> <i>SDHC</i>	Clear cell RCC, oncocytic neoplasm, chromophobe RCC

VHL, von Hippel-Lindau tumor suppressor; *FLCN*, folliculin; *MET*, MET proto-oncogene; *FH*, fumarate hydratase; *SDHB*, succinate dehydrogenase complex iron sulfur subunit B; *SDHD*, succinate dehydrogenase complex subunit D; *SDHC*, succinate dehydrogenase complex subunit C