DIAGNOSTIC IMAGING OF SMALL RENAL MASSES

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Intensive use of radiological and diagnostic procedures has led to more frequent detection of small renal masses in the last two decades. The term "small renal mass" refers to renal tumors up to 4 cm, but some authors define them as tumors up to 3 cm in diameter. Diagnostic imaging may play an important role in making a decision about the treatment of these tumors, which involves surgery, ablative treatment or active monitoring. In this article, we described the imaging methods in the diagnosis of small renal tumors, and radiological characteristics of the three most common renal tumor entities (renal cell carcinoma, angiomyolipoma and oncocytoma). Radiological characteristics of benign and malignant tumors of the kidney often overlap, and therefore their adequate radiological differentiation can be very difficult. Computerized tomography, along with magnetic resonance imaging, is still the method of choice, and imaging before and after contrast administration is the gold standard to assess the malignancy of the tumor. An ultrasound examination can be used in a long-term active surveillance protocol, because of the advantages it has such as the safety of the patient and cost effectiveness. The application of newer diagnostic methods such as contrast enhanced ultrasound and "diffusion weighted MR imaging", showed good results, but the diagnostic criteria are still not sufficiently aligned. Recently, attempts have been made to implement different computer, diagnostic algorithms that could improve the diagnosis of small renal masses using a computerized tomography. Acta Medica Medianae 2016;55(3):66-75.

Key words: small renal mass, renal cell carcinoma, angiomyolipoma, oncocytoma, imaging

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Introduction

Diagnosis and treatment of renal tumors has been significantly improved by its early radiologic detection in the last two decades (1). Early radiologic detection of renal masses by using ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI) has also led to smaller average size of the mass at the time of initial detection. The term “small renal mass” (SRM) is used to refer to these tumors, usually defined as less than 4 cm in diameter (2), while some authors consider SRMs as those that are 3 cm or smaller (3). SRMs can be presented as malignant or benign tumors. Although the most of SRMs are malignant, approximately 20 % of incidentally discovered SRMs are benign, especially those with diameter less than 1 cm (4). Management of SRMs may include surgery (radical or partial nephrectomy), ablative therapy or active surveillance, depending on radiologic characteristics of the tumor, patient age and comorbidities. Active surveillance can be indicated when SRM is not radiologically suspected of malignancy, especially in older patients with significant comorbidities. It implies radiological monitoring of size, growth rate and morphological characteristics of the tumor at specific time intervals. In the case that the tumor does not change its size or shows its minimal growth, an active surveillance continues. In the case of significant tumor growth, as well as the appearance of malignant radiological features, the possibility of surgical or ablative treatment is considered. Therefore, it is necessary that the radiologist recognize the imaging features of SRMs, with the purpose of evaluating tumor type and characteristic, so that the patient may undergo appropriate treatment (5).

In this review, we describe the radiological features of SRMs, based on well-known findings in the literature, which are the results of recent studies. We focused on the three most common renal tumor entities (renal cell carcinoma, angio-
myelolipoma and oncocytoma) in terms of their common imaging findings and differential features.

**Measurement of size and growth rate in small renal masses**

Renal mass size and growth rate measurement are usually performed by using CT and MRI, although US can also be useful in a long-term active surveillance of SRMs. The most common and simplest method of reporting renal mass growth is to measure the linear growth. The maximal cross-sectional diameter is measured with the growth rate expressed as the change in diameter per year (cm/year) (6). When measuring in this fashion, care should be taken to measure the mass at the same level within the kidney on both the new and prior study in order to compare the growth interval. By measuring the linear growth of a tumor using axial cross-section images, it is assumed that the tumor is spherical in shape and growing equally in all directions. For that reason, linear growth rate may not fully reflect the change of tumor volume, and therefore volumetric growth rate is more precise to reflect the growth of SRMs (7). Growth can be also expressed as tumor doubling time, which represents the time taken by a tumor to double in volume (8). Many studies have analyzed the growth kinetics of SRMs. A meta-analysis which included 234 SRMs demonstrated that most renal masses grew at a relatively slow rate of 0.28 cm/year (9). In a study of Bahouth et al. from 54 patients with SRMs, in which significant growth rate was recorded, eight masses underwent nephron-sparing surgery, of which two were oncocytomas and six were renal cell carcinoma. Growth rate and mass diameter on diagnosis were significantly greater in the group of patients who underwent a surgery (10). Although most incidental SRMs are slow-growing, it cannot be safely assumed that lack of growth correlates with an absolute indolent clinical course. Kunkle et al. observed 106 renal masses that were grouped together based on growth rates: group 1 consisted of 35 enhancing masses with a zero or negative growth rate, and group 2 included 71 lesions which showed median growth rate of 0.31 cm/year. Extirpation was performed in 17% of lesions in group 1 and in 51% of lesions in group 2. Malignancy rates were similar in the two groups, and these data have been used to support the fact that growth rate does not correlate with malignancy (11).

Initial tumor size (defined as the maximal diameter) was the most common studied baseline characteristic used to predict the growth rate of SRMs. However, the correlation between initial tumor size and growth rate is still unclear. Study of Han et al. reported that many complex cystic renal masses small—er than 2 cm were benign, suggesting that lesion size should be taken into account when formulating treatment plans for complex cystic renal masses along with Bosniak classification (12). Several studies reported that in patients with smaller tumor diameter, the growth rate is much lower and most patients present with less advanced disease (13, 14). One study reported that SRMs, including those pathologically proven to be RCC, also had slow growth rate (15). As for the risk of recurrence after surgery for SRMs, Ito et al. investigated the predictors for recurrence in localized small renal tumors. They found that tumor size and the percentage of tumor necrosis were significant predictors of recurrence (16). On the other hand, Crispen et al. demonstrated that smaller renal tumors had greater volumetric growth rate than larger renal tumors, showing that growth rate of tumors decreases with the increase of tumor size (17). Organ and co-authors reported that maximum diameter of the mass was not a good predictor of growth in T1a renal lesions (18).

**Radiological features of small renal masses**

**Ultrasonography**

SRMs are usually incidentally detected using a routine US examination. Diagnosis of simple cyst can be completely established using an US imaging, with no need for further imaging modalities. Additional CT or MRI is generally recommended for characterizing all non-simple cystic renal masses (19). However, some studies reported that US can be also used for complete evaluation of Bosniak category II cysts (20). Considering that US evaluation depends mainly on the size, location and echogenicity of the tumors, differentiation of SRMs may be quite challenging, especially of small, iso-echoic, intraparenchimal tumors (those that do not deform renal contour) (21). Ultrasonography is helpful in suggesting the fat content in small AMLs, which is highly echogenic relative to the renal cortex. Hyperechogenicity similar to the renal sinus fat has been regarded as the hallmark of AML. However, small AMLs with minimal fat (mFAML) may be presented as homogenously hypoechogenic, isoechoic or slightly hyperechoic masses (22). Small RCCs also show a variable echogenicity on US, from hypoechogetic to most commonly hyperechogenic pattern. Well-defined hyperechoic small renal mass with hypoechogenic rim and intratumoral cystic area may suggest RCC (23). Yang et al. tried to clarify the relationship between the echopatterns and tumor sizes of RCC by grading echogenicity from grade I to V. Small RCCs tended to be relatively homogeneous in echogenicity and ranged from grade II (higher than medulla but not higher than renal cortex) to grade III (higher than cortex but not higher than liver/spleen) echogenicity (24). Lee et al. tried to differentiate small AMLs from RCC by measuring a relative echogenicity. The relative echogenicity of the tumor was calculated by setting the grayscale of the renal cortex as 0% and sinus fat as a 100%. The relative echogenicity of non-fatty AMLs (88%) was significantly lower than fatty AMLs (106.3%)}
%), and higher than any subgroups of RCCs (44.1%) (25). Small sized oncocytoma usually appears as homogeneous renal mass that is isoechoic with the echogenicity of the renal parenchyma with well-demarcated margins. The spoke wheel or stellate scar appearance on US, well-known characteristic findings, are usually difficult to see in small oncocytomas (26). In other words, the echo-pattern and ultrasound characteristics of SRMs often overlap between benign and malignant tumors. For that reason, grayscale US is often considered inferior to CT and MRI in differentiation of SRMs, but it might play a significant role in evaluating renal mass size in patients on an long-term active surveillance protocol, especially having in mind reduction of costs and radiation exposure (27).

US Doppler imaging (color or power) can be utilized to study the presence and distribution of the vessels inside SRMs. According to study of Jinzaki et al., vascular distribution seen on power Doppler US can provide useful additional information in differentiation between benign and malignant renal tumors. The classification reported in this work categorizes tumor vascular architecture on power Doppler US into five patterns: pattern 0 -no signal; pattern 1 -intratumoral and focal signals; pattern 2 -penetrating vessels; pattern 3 -peripheral vascular distribution; and pattern 4 -mixed, penetrating and peripheral vessels. Among the 64 small renal neoplasms in the study, no RCC exhibited patterns 0, 1, or 2. All of the 26 RCC, but only 20 % of AML, were associated with patterns 3 or 4 (28). On the other hand, Pallwein et al. noticed that unenhanced color Doppler US had sensitivity and specificity in differentiation from benign and malignant SRMs 46%, respectively (29). Gerst et al. showed no significant correlation between lesion vascular patterns on color and power Doppler imaging among different RCC subtypes (30). However, power Doppler can be used to differentiate pseudotumoral lesions located at the level of the renal cortex (31).

Contrast-enhanced ultrasonography (CEUS) is an imaging technique that allows a real-time evaluation of microvasculature after intravenous administration of special microbubble contrast agents (32). US contrast agents are very safe, with a very low rate of anaphylactic reactions. Since they are not excreted by the kidneys, they do not affect renal function, and therefore can be safely administered to patients with renal insufficiency (33). On CEUS, renal perfusion is shown in the following phases: early arterial, late arterial or cortical, and medullary phase. Regardless of enhancement (hypo or hyper), the vascularity of renal tumors on CEUS is different from normal parenchyma, at least in one vascular phase (34). Hyperenhancement in the late arterial phase was the most important finding for predicting small renal parenchymal lesions (<5cm) to be RCCs in a study of Fan L. and co-workers (35). On the other hand, Atri M et al. reported that lesion hypovascularity relative to the adjacent cortex in the arterial phase was seen in only malignant SRMs, dominantly in papillary RCC (36). In a study of Lu et al, one of characteristics typical for mFAML in differentiation from clear cell RCC (ccRCC) was centripetal, homogeneous enhancement (37). Characterization of complex renal cysts that are indeterminate on CT has been improved with additional CEUS imaging, due to its high sensitivity in detecting microbubbles in the peripheral wall or intracystic septa of the lesion. CEUS may be also useful in monitoring the patients with SRM after ablative treatment, due to avoidance of nephrotoxicity and radiation (38).

Magnetic resonance imaging

MRI of renal masses may be reserved for the clinical settings of renal insufficiency, allergy to intravenous contrast, or as a problem-solving modality when the CT findings are non-diagnostic (39). Renal mass evaluation may be conducted by using conventional MRI techniques: T2-weighted (T2W), fat-suppression, and chemical shift imaging. Imaging is mostly performed before and after gadolinium-based contrast administration (40).

A homogeneous hyperintense lesion with a thin wall on T2W images can be accurately characterized as a simple cyst. Presence of septa or other hypointense (hemorrhagic or proteinaceous) content on T2W images may suggest complicated renal cyst (41). The presence of enhancement within a renal lesion after the administration of gadolinium-based contrast material is the most reliable criterion for distinguishing solid masses from cysts with MRI. Simple renal cyst do not present enhancement after gadolinium administration, while enhancement within renal mass indicate potential malignancy (42). However, recent studies have raised concern about the routine use of MRI contrast agents, especially in patients with advanced renal insufficiency, as there has been shown a potential link between nephrogenic systemic fibrosis (NSF) and gadolinium exposure in this kind of patients (43).

Solid renal mass that is heterogeneously hyperintense to the renal cortex on T2W imaging may suggest a RCC. ccRCC most frequently demonstrates a signal intensity similar to that of the renal parenchyma on T1-weighted images and increased signal intensity on T2-weighted images (44). However, MRI appearance of ccRCC may vary depending on the presence of hemorrhage and necrosis. Central necrosis is important MRI feature, which may be in correlation with aggressive histology and disease progression of the tumor (45). It can be seen as a homogeneous hypointense area in the center of the mass on T1-weighted images or moderate to high signal intensity area on T2-weighted images. Post-contrast images demonstrate the lack of enhancement in areas of necrosis and marked enhancement in the viable components of the tumor.
Intratumoral hemorrhage has a variable appearance depending on the stage of degradation of the component blood products. Subacute to chronic hemorrhage generally demonstrates high signal intensity on both T1- and T2-weighted images, as long-standing hemorrhage is typically hypointense on both T1- and T2-weighted images (46). In a study group of 92 SRMs less than 2 cm, higher frequency of necrotic areas and lower frequency of hemorrhage were reported in ccRCC in comparison to other lesions (47). A hypointense rim or pseudocapsule may be seen on both T1- and T2-weighted images and is thought to be related to compression of the adjacent renal parenchyma by the expanding tumor (53). Although not specific (also seen in some oncocytomas) presence of pseudocapsule in SRMs has been related to RCCs, usually of low histologic grade, slow growing, and less likely to metastasize (48).

The characteristic appearances of AML include variable areas of high signal intensity within the tumor on both T1-weighted and T2-weighted images, mainly due to presence of fat (22). MRI is excellent in evaluating fat content of AML, where two MRI techniques can be used. Firstly, fat-suppression technique generally indicates the presence of macroscopic fat, therefore is useful in differentiating AML with predominantly fatty component. It demonstrates high signal intensity on non-fat saturated sequences, and suppression of signal intensity on sequences following fat saturation (49). The second method is chemical shift imaging which can be used for detection of small amounts of fat. This technique relates to the fact that signal suppression occurs between the fat and non-fat containing components. When the signal loss appears between the border of the mass and the renal parenchyma, it has been called an "india ink artifact" and is indicative of an AML (50). It is essential to have in mind that rarely RCC may have fat component. Therefore, the presence of fat may be strongly indicative, but it is not pathognomonic for AML. Since macroscopic fat in RCC almost always occurs in the presence of ossification or calcification, the absence of these features on imaging will suggest AML (51). Cases of AML with calcifications are rare (52). When it comes to oncocytomas, their MRI appearance is variable and nonspecific. Oncocytomas are typically spheric and well-defined masses showing lower signal intensity on T1-weighted images and higher signal intensity on T2-weighted images in most cases. A well-defined hypointense capsule can be seen surrounding the tumor, but it is not specific (53).

Diffusion-weighted magnetic resonance imaging (DWMRI) measures the random (Brownian) motion of water molecules in a specific tissue, without the need for administration of contrast agents (54). DWMRI provides information on biophysical properties of tissues, such as cell organization, cell density, microstructure and microcirculation. Motion of water molecules in tissue has been shown to be inversely proportional to cellular density (55). The extent of tissue cellularity and the presence of intact cell membranes help determine the impedance of water molecule diffusion. Cancer tissue has also been reported to be associated with impeded water diffusion (56). It is presented by a reduction in signal intensity on DWMRI and expressed with a quantitative parameter called apparent diffusion coefficient (ADC) (57). In a study of Agnello et al. mean ADC values were significantly different between small RCCs, AMLs, oncocytomas and metastatic renal tumors. ccRCCs had significantly lower mean ADC value in comparison with non-ccRCC. On the other hand, no significant difference was found between fat containing AML and mfAMLs (58). Zhang et al. had similar results, showing that DWMRI in combination with non-enhanced MRI features can distinguish ccRCC from other small solid renal tumors with high sensitivity and specificity (59). In a study of Rozenkrantz et al, lower ADC values have also been described in higher grade cc-RCC compared to lower grade cc-RCC (60).

Computerized tomography

CT imaging is most frequently used for characterization of SRMs. The Bosniak classification system is used for the assessment of malignancy in cystic renal masses. In some equivocal cases it may be difficult to declare if a certain cyst should be categorized as a Bosniak II or III cyst, therefore additional MRI may be necessary (61). According to Silverman and co-authors, renal masses can be divided into those for which additional imaging is probably not necessary and those that may warrant additional imaging. Tumor with size <1 cm, with homogeneously attenuation ≤20 HU, is probably benign and additional imaging is not necessary. On the other hand, heterogeneous tumor with attenuation <-10 HU or >20 HU, with the presence of calcifications, may indicate malignancy and needs additional imaging (62). Study results of Connor et al. suggest that most of renal masses (≥1 cm in size) can be evaluated using only an unenhanced CT, reporting that non-calcified renal masses with attenuation <20 HU can be considered benign (63). However, evidence of vascularization with enhanced CT is the key to defining a SRM. A change of 15 or more HU demonstrates significant enhancement. It may be also useful to perform a CT in a delayed phase (at least 15 minutes after contrast administration) to search for the diminution of attenuation measurements over time ("deenhancement"). Deenhancement by ≥15 HU indicates that the mass is suspicious of malignancy (64).

The typical CT appearance of small RCC is a isodense or hypodense mass, with an attenuation value ≥20 HU, that enhance significantly after administration of contrast medium. However, a small proportion of RCC are hypovascular, and the amount of enhancement may be minimal. Characterization of RCC subtypes using a CT has
proven to be difficult. In a study of Zhang et al. ccRCCs were hypervascular in majority of cases, and necrosis was far more common than in other RCC subtypes. Homogeneous and peripheral enhancing patterns were more predictive of papillary and chromophobe RCCs (65). In a study of Jung et al., heterogeneous enhancement in corticomedullary phase was typical for ccRCC (66). On the other hand, Mancini et al. reported that contrast-enhanced CT features were not significant for differentiating RCC subtypes (67). Differentiation of RCC from benign SRMs has also been very difficult, with the exception of classic, fat rich AML. AML is typically a solid lesion that exhibits fat density (≤-10 HU) on CT scans. However, mfAML still remains a diagnostic challenge, as it can be often identified as RCC. One of the most common findings of mfAML on unenhanced CT is the extent of hyperattenuation compared with the renal parenchyma, although some of these AMLs can be isoattenuated (22). Few studies found CT to be a useful tool in differentiating mfAML from RCC. Yang et al. revealed significant parameters for differentiating RCC from mfAML: hypodense rim, homogeneity and unenhanced attenuation >38.5 HU (68).

On CT, small oncocytomas typically appear as solitary, well-demarcated, homogeneously enhancing renal cortical tumors, with unspecific CT characteristics (69). During a last few years, radiologist have been trying to improve detection and characterization of small oncocytomas by using a CT. It was noticed that a small renal oncocytomas had two distinct segments on corticomedullary phase images, one highly enhanced and the other less enhanced. Furthermore, the highly enhanced segment on corticomedullary phase becomes less enhanced on early excretory phase and the less-enhanced segment on corticomedullary phase images becomes highly enhanced on excretory phase images. This feature was named as segmental enhancement inversion (70). Several studies found this feature to be a characteristic finding of small oncocytomas in comparison to other SRMs (71-3).

Using conventional imaging methods, renal tumor diagnosis is performed by manual quantifications of tumor size and enhancement. It mostly depends on radiologist skills and experience, which may have its negative side, such as high intra and inter-observer variability and more time consuming. For that reason, radiologist have been trying to implement a computer-aided (assisted) diagnostic algorithms in order to better assess renal tumors. The concept of “computer-aided diagnosis” refers to software that analyzes a radiographic finding and estimates the possibility that it may represent a specific disease process (e.g. benign or malignant) (74, 75). There are few studies that proposed this computer-assisted clinical tool to assess and classify renal tumors on contrast-enhanced CT. Linguraru et al. analyzed CT enhancement and morphology of renal lesions via specific statistical descriptors (histograms of curvature-related features) and showed significant separation between benign and malignant tumors (76). In a recently published study, Coy et al. quantified relative enhancement on four-phase MSCT using volumetric 3D computer aided diagnostic algorithm. They reported that ccRCC had significantly higher relative enhancement compared to oncocytoma, AML and other RCC subtypes in the corticomedullary, nephrographic and excretory phase (77).

**Potential pitfalls in characterization of small renal masses**

Pseudoenhancement (defined as an artificial increase of attenuation on CT) can be seen in small, simple renal cysts, which in that way can be mischaracterized as a solid mass suspected of malignancy. It is believed that this finding is a consequence of increased attenuation of the surrounding renal parenchyma on post-contrast images (78). Some authors showed that pseudoenhancement decreases with the distance from enhancing renal tissue, and therefore is rarely seen in exophytic tumors (79). Pseudoenhancement is relatively easy to suspect when a mass appears as a simple cyst and measures ±10 HU on the unenhanced CT scan. However, when a mass measures ≥10 HU on an unenhanced CT scan and “enhances” approximately 10–15 HU after contrast material administration, it is difficult to know if this represents pseudoenhancement of a benign cyst or true enhancement within a renal neoplasm. In those cases, MR imaging or ultrasonography (US) can be used to help establish the true diagnosis (80).

Pseudotumors are benign, radiologic variants consisting of a prominent aggregate of normal renal tissue, which can be mischaracterized as renal tumors. Pseudotumors are often present on CT or MRI as an isoattenuated (iso-intensed) mass, which show enhancement similar to the renal parenchyma on post-contrast images. They can be congenital or acquired. Congenital pseudotumors include hypertrophic column of Bertin and renal hilar lips (81). Acquired pseudo-tumors are characterized by a focal compensatory hypertrophy adjacent to an area of scarring from previous inflammatory disease (82). Vascular anomalies, including renal artery aneurysm or arteriovenous fistula, may manifest as an enhancing renal mass when the contrast-enhanced portion of the examination is performed. These lesions are usually centrally located, and the observation that the mass is associated with and has the same attenuation of the vasculature is the clue to the diagnosis (83). Inflammatory masses, including inflammatory pseudotumor, focal pyelonephritis and renal abscess, may also mimic the appearance of renal neoplasm. However, comparison with a patient history, clinical and biochemical findings generally indicates the correct diagnosis (84).

When characterizing SRMs on CT or MRI, radiologist should be aware of imaging section...
thickness. Silverman et al. noticed that some of SRMs are too small to be completely characterized because diameters of such lesions are less than twice the reconstructed section thickness. For example, if 5 mm reconstructions are used, only renal masses of 10 mm and larger can be assured of being imaged principally through the mass. Although 3 mm reconstructions have been recommended, authors noticed that characterizing renal masses between 6 and 10 mm with CT may still be difficult (85). Jinkazi et al. showed that by using MSCT and 3mm thick-sections, the overall number of indeterminate renal masses was reduced in comparison with 5mm-thick sections (86).

**Conclusion**

A certain percentage of SRMs are benign tumors that have indolent clinical course, and these tumors usually require active surveillance instead of surgical or ablative treatment. In this regard, there is a need in defining distinct, radiologic, diagnostic criteria based on which radiologists will determine with certainty the type of the tumor. Diagnosis of SRMs has recently improved significantly due to intensive use of conventional imaging methods, as well as introducing new imaging techniques. CT, with MRI, remains the method of choice in the diagnosis of SRMs. Findings on CT sometimes should be supplemented with the MRI findings, especially in order to adequately categorize a complicated cyst using a Bosniak classification. US can be used in a long term follow-up, because of the advantages it has in terms of safety for the patient and low cost. The application of newer diagnostic methods, such as CEUS and DWMRI, showed good results, but the diagnostic criteria are still not sufficiently aligned. Therefore, it is necessary to conduct studies with a larger number of subjects in order to bring more concrete conclusions. Given the rapid and continuous progress of computer technique, it will be interesting to see if the diagnosis of renal tumors will continue to depend solely on the skill of the radiologist or will be based on the computer-assisted technique.

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RADIOLOŠKA DIJAGNOSTIKA MALIH TUMORA BUBREGA

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