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Renal Oncocytoma: An Algorithm for Diagnosis and Management

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ABSTRACT

Renal oncocytoma is an uncommon tumor that exhibits numerous features which are characteristic but not necessarily unique. Percutaneous biopsy is a safe method of diagnosis. However, differentiation from other tumor subtypes often requires sophisticated analysis and is not universally feasible. This is why, surgical management can be considered as a first-line treatment or after surveillance. Potential triggers for change in management are: tumor size >3 cm, stage progression, kinetics of size progression (>5 mm/y), and clinical change in patient or tumor factors. Long-term follow-up data are lacking and greater centralization should be considered to reach adequate management.

1- Introduction:

In 1942, Zippel reported the first case of renal Oncocytoma (RO) [1]. This uncommon benign tumor of the renal parenchyma accounts for 3-7 % of all solid renal masses [2]. When tumors of less than 4 cm are considered, its incidence increases to 18% [3]. The differentiation of RO from renal cell carcinoma (RCC) is challenging and imaging characteristics alone are unreliable. Histopathological diagnosis remains the reference standard. However, renal mass biopsy (RMB) prior to surgical intervention can be inconclusive [4]. In addition, the finding of RO on RMB does not exclude malignancy because some hybrid tumors associate chromophobe RCC and RO [5].

The aim of this article is to present a thorough literature review about RO, in order to elucidate the different aspects of this uncommon tumor. Based on this review, we will propose an algorithm for the diagnosis and the management of RO.

2- Material and methods:

This narrative review summarizes recent evidence on RO. We performed a search of the literature up to June 2019 using the Medline computerized database of the US National Library of Medicine, the Cochrane database, and Google Scholar. The search was carried out using the following Medical Subject Headings (MeSH) and free-text terms: Renal oncocytoma, small renal masses, and renal mass biopsy. The number of records identified was more than 500, which were limited to systematic reviews, randomized controlled trials, prospective nonrandomized studies, cohort, and retrospective non-randomized studies. The majority of these articles have been excluded at the first screening due to irrelevance or data duplicates and at the end, only fifty-three full-text articles were selected for a qualitative synthesis.

The PRISMA guidelines for the reporting of this study were used to perform an accurate research checklist and report.

3- Results:

3.1.Clinical presentation

Older patients (seventh decade of life) are mainly affected by RO. Up to 75% of these patients are asymptomatic and their tumors are often incidentally discovered by imaging during a workup for other conditions. Symptoms which are found in about one third of patients include most

commonly flank or abdominal pain and hematuria [3,6–8]. Uncommonly, a flank mass is palpable [6]. Occasionally, hypertension may be the presenting complaint and rare familial cases have been described, including patients diagnosed with Birt-Hogg-Dubé syndrome [9].

Differential diagnoses include other neoplasms with eosinophilic or oncocytic cytoplasm, primarily chromophobe RCC, clear-cell RCC with eosinophilic cytoplasm, oncocytic variant of papillary RCC and less commonly oncocytoid RCC occurring after neuroblastoma and epithelioid angiomyolipoma [10].

3.2.Imaging

Unfortunately, it is difficult to distinguish RO from RCC on the imaging appearance, and both usually end up resected. ROs appear as sharply demarcated lesions of variable size, but often are large at presentation [11]. Their typical tomographic images are described as homogeneous hypervascular masses with subsequent washout in the delayed phase. A central sharp stellate scar is seen in RO in one-third of cases, especially in large tumors. However, it can also be present in RCC [12]. Distinguishing features include the evidence of metastasis and/or aggressive infiltration of the adjacent structures, which strongly orient toward the diagnosis of RCC. In addition, up to 13% of patients have multiple RO, and up to 32% have concurrent RCC, this is why it is important to carefully evaluate both kidneys on imaging [13]. Main radiologic findings in renal oncocytoma are presented in Figure 1.

3.2.1. Computed Tomography

ROs are slightly hyperattenuating relative to the normal kidney parenchyma, on non-enhanced computed tomography (CT) images. However, on the nephrographic phase after contrast enhancement, they appear less attenuating than the renal parenchyma [14]. Tumors are

homogeneous, well-encapsulated with clear margins and smooth contour. Their size range is from 3 to 10 cm, and in symptomatic patients, the lesions are usually larger than 5 cm [15]. The already mentioned central hypoattenuating scar (called stellate scar) may be observed in 33% of cases. This scar mimics the central necrosis commonly found in RCC and cannot be easily differentiated from it on CT, despite the advances of multisection scanning and high-resolution thin sections through the kidneys [16].

Invasion or infiltration into the perinephric fat or vessels has been described in oncocytomas [17,18] but regional lymphadenopathy and metastases are more typical findings of RCC. Occasionally calcification, necrosis, hemorrhage, and multifocal or bilateral tumors may be found. [19].

To help identify small RO, some studies have discussed the use of segmental enhancement inversion that is present when the renal oncocytoma is divided into 2 differently enhanced segments: there is a reversal of the relative degree of enhancement on the nephrographic phase images (120-180 seconds after contrast injection) compared to the corticomedullary phase images (30–40 seconds after contrast injection). Segmental enhancement inversion was mostly seen in oncocytomas smaller than 3 cm, while central scars were more often present in oncocytomas larger than 2.5 cm [9,20].

In their study on 43 patients with 53 RO and 123 patients with 128 RCC, Sasaguri et al used CT attenuation values and tumor texture (ie, heterogeneity and skewness) on biphasic contrast-enhanced CT to differentiate oncocytomas from many subtypes of RCCs [15].

Pano et al. used 4-phase CT to differentiate between RCC and oncocytomas in 97 patients. They found that lesion size more than 4 cm, the highest degree of lesion enhancement and its heterogeneity were the dominant features of RCC compared to RO [9].

3.2.2. Magnetic Resonance Imaging

ROs appear on magnetic resonance imaging (MRI) as well-defined and homogeneous masses, which are isointense to slightly hypointense when compared to the normal renal cortex on the non-enhanced T1 and T2 weighted sequences. However, slight T2 hyperintensity has also been reported [21]. When present, the stellate scar is hypointense on T1 and T2-weighted images. In contrast to CT imaging, MRI can differentiate the stellate scar from tumor necrosis. The latter appears hypointense on T1-weighted images and hyperintense on T2-weighted images and is a very important feature to rule out malignancy. Rarely, the central scar may appear bright on T2-weighted images [22]. However, it does not show enhancement in the center of the homogenously enhanced oncocytoma after the intravenous administration of Gadolinium-based contrast [23].

Despite the high confidence degree with MRI for detecting RO, it does not make a specific diagnosis. Thus, differentiating oncocytoma from RCC is not always possible with an accuracy of 84%, sensitivity of 90%, and specificity of 63% [19,21,23].

3.2.3. Nuclear Imaging

The differentiation of benign renal oncocytomas from renal cell carcinomas seems very promising using ^{99}Tc-sestamibi single-photon emission computed tomography (SPECT). Oncocytoma and hybrid oncocytoma/chromophobe tumors showed uptake of ^{99}Tc-sestamibi in

several studies, contrarily to other renal malignant tumors. RO with high fibrous component risk to be missed [24]. Exceptionally, some papillary tumors show sestamibi positivity that is much lower in intensity than oncocytoma or hybrid tumors. This imaging modality, showed a high true positive rate with a sensitivity of 96% and a specificity of 95.2%, as reported by Tzortzakakis and Gorin. Although observation might be safe for hybrid tumors, which didn't show evidence of aggressiveness after 10 years of follow-up, it is not for papillary tumors. Additional quantitative tools to estimate accurately the biological behavior of tumors and to provide a secure diagnosis are needed [24,25].

3.3.Pathology

3.3.1. Gross description

The gross appearance of RO is an important criterion. Tumors are well-circumscribed, unencapsulated, solid, homogenous with a brown amber cut surface similar to the normal renal parenchyma in color and different from the golden yellow cut surface of clear cell RCC where substantial hyalinization and fibrosis can also be present [2]. Five percent of RO are bilateral or multifocal and may invade renal capsule or renal vein. Twenty percent have gross hemorrhage but necrosis is rare [26]. As previously mentioned, the stellar scar is not specific for RO; it is not present in all tumors, and can also be found in chromophobe RCC and other slow-growing neoplasms [27]. RO size can range from small solid nodules to large masses mimicking high-stage RCC [9].

3.3.2. Microscopic description

The architecture under microscope is highly variable. RO are composed of oncocytes which are large cells with an intensely eosinophilic granular cytoplasm. This aspect is the result of the presence of a big number of mitochondria, the absence of glycogen and the scant lipid content

[28]. Mutations in the genome encoding nuclear and mitochondrial proteins, are believed to cause respiration defect with defective mitochondria, that normally should be removed by mitophagy, a selective form of autophagy. However, a defective autophagy is seen in RO, and is thought to produce benign instead of malignant tumors. It is attributed to metabolic-deficiency-induced Golgi disassembly and lysosome dysfunction, blocking the activation of lysosomal protease [29].

Mainly, the tumors are made of lined patterns of uniform round or polygonal cells. They appear as nests with alveolar or tubular structures closely packed at the periphery and separated centrally, leading to their dispersion in the edematous myxoid or hyalinized stroma [28]. The presence of other patterns (such as highly compact nested architecture or small papillary structures protruding into cystic spaces), resulting in a more solid appearance, can raise the concern of an eosinophilic variant of papillary RCC, making the diagnosis uncertain [26]. Clear cytoplasm may also be focally present, typically in the area of the central scar. Nuclei are uniform, small, round and central with evenly dispersed chromatin and smooth contour. Occasional degenerative atypia (bizarre nuclear pleomorphism), focal vacuoles and areas of fibrosis may also be present [9]. Mitotic activity is extremely rare, and finding more than one readily identifiable mitotic figure is worrisome or potentially incompatible with the diagnosis [26].

Unusually, tumors have an “oncoblastic” appearance with small cells and a scanty cytoplasm. They have similar immunohistochemical and molecular features of usual oncocytomas regarding most of the markers [28].

Although a proximal tubular origin was suggested at the beginning, most pathologists suggest nowadays a distal tubular origin. Renal oncocytoma and chromophobe RCC are thought to be closely related, arising from intercalated cells α and β respectively, with a subsequent divergent differentiation [28]. Main pathologic features of oncocytoma are presented in Figure 2.

3.3.3. Immunohistochemistry

The immunohistochemical profile of ROs show positivity for for CD117 (KIT), e-cadherin and S100A, and negativity to vimentin. Minimal staining is seen with cytokeratin 7 (CK7), contrarily to the stellar scars that exhibit increased staining. A new concept of low oncocytic tumor (LOT) has been described, where tumors look mostly like oncocytomas, but express positivity for CK7 and negativity for CD117. Nevertheless, those tumors are also benign without relapse or progression [30]. Another newly described entity is the concept of high-grade oncocytic (HOT) tumors, that show nested or tubular growth like the classical oncocytoma with uniform and large cells. They never show raisinoid-like (like chromophobe carcinoma) nuclei, but have predominant nucleoli (ISUP grade 3). They express normally CD117, but only half of them expresses CK7 [31].

3.4.Renal Mass Biopsy

Since 20–45% of SRM are benign, active surveillance could be a good option for most of them. This fact led to the increased use of RMB in the diagnosis of renal masses despite the controversy of this technique's diagnostic accuracy [32]. RMB has shown up to 80% diagnostic rate, with the ability to provide subtype and nuclear grade in the majority of the tumors [33]. However, this rate is lower in oncocytic lesions, as interpreting only a limited sampling of the lesion may not represent the entire tumor. Patel et al showed in their meta-analysis of 205 oncocytic RMB that the positive predictive value for oncocytoma diagnosis on RMB was 67%

with significant heterogeneity and wide confidence interval, indicating that the diagnostic accuracy varies greatly between studies and therefore between pathologists [4].

The pathological similarity of RO with other oncocytic lesions created a split among urologic pathologists whether it is preferable, after RMB, to give an outright diagnosis of oncocytoma (with typical features on biopsy sample) or to use more general terminology, such as “oncocytic neoplasm” [26].

It is difficult to differentiate oncocytoma and RCC especially on limited samples. ROs usually don’t show perinuclear halos, their cytoplasms are more uniformly granular, and they are nested with stromal edema [34]. As we already mentioned, immunohistochemical staining may also be helpful for differential diagnosis on RMB. Findings such as negative vimentin staining and positive KIT staining generally argue against papillary or clear cell RCC with eosinophilic cells [35]. Membranous positivity for KIT and negative staining for Vimentin is seen in both oncocytoma and chromophobe RCC. To differentiate those two tumors, other markers can be used, such as colloidal iron staining (Hale or modified Mowry) to better identify nuclear, stromal and cellular features [36,37]. Oncocytoma may show apical or weak focal fine cytoplasmic granules, compared to RCC that shows strong and diffuse microvacuolated cytoplasmic staining (Figure 2). However, those features might not be easily appreciated in small specimen biopsies, and some series showed variable staining of both tumors, which causes hesitation whether to base the treatment decisions on a biopsy sample or not [34]. Electron microscopy can also be useful and more cost effective than multiple immunohistochemical stains. Mostly, oncocytomas shows abundant mitochondria and absent or sparse microvesicles, while chromophobe RCC show numerous microvesicles and peripheral or abnormal mitochondria.

RMB can facilitate appropriate management in patients who are candidates for nonsurgical treatment [35]. Though, the risk of selective sampling of the tumors and the probability of missing malignant sampling in hybrid tumors is not resolved yet [34].

Table 1 summarizes the main radiologic and pathologic features in favor of RO or RCC.

3.5.Evolution

The rate of benign findings after nephrectomy for small renal masses (SRM) has been as high as 21% to 34% [37,38]. To avoid unnecessary surgeries for these benign tumors, studies have suggested RMB before definite treatment. However, concerning RO, the management remains controversial since the definitive diagnosis relies on careful microarchitectural examination and immunohistochemical evaluation that cannot be confirmed on biopsy most of the time [39]. Therefore, the need to better characterize the natural evolution of RO is crucial to potentially decrease the need for treatment.

The growth rate (GR) of RO was studied in many previous works. Kawaguchi et al reported a GR of 0.16 mm monthly or 0.20 cm annually for proven oncocytoma, and this finding was similar to the GR of other SRM [40]. Another meta-analysis showed a mean GR of 0.28 cm annually for SRMs followed up by imaging, with no statistically significant difference between RO and RCC [41]. The similarity in GR between RO and RCC was also shown in a Canadian prospective phase II clinical trial of active surveillance for SRMs [42]. Neuzillet et al, reported a mean GR of 0.7 and 2.4 mm annually for non-surgically and surgically treated RO respectively without identifying the predicting factors of positive growth that remain unclear so far. In addition, they noted that patients with RO treated non-operatively did not experience symptoms progression despite documented tumor growth on imaging [43]. A large-scale nephrectomy

series showed that despite growing, the average size of benign tumors including RO was significantly smaller than that of RCC tumors [37,43].

Large tumors are not exclusively RCC since giant ROs have been reported through the literature [44]. Even when features of aggressiveness, perinephric fat or vascular invasion, are associated with RO those tumors have a non-malignant behavior and have excellent prognosis [17,18]. The metastatic progression is still virtually unknown [45].

3.6.Management

For many years, the standard treatment for RO has been surgical extirpation. Nephrectomy for both malignant and benign tumors has been associated with major complications. Hemorrhage into the collecting system, leak of urine, ureteral strictures and thermal injuries of adjacent bowels are known complications of surgical treatment [34]. A recent large retrospective national study in the United Kingdom on 1202 patients, showed that the complication rate associated with surgical removal of a renal oncocytoma was not negligible. Even though the majority had minimally invasive surgery, 20% developed in-hospital complications from which 18.9% were Clavien-Dindo grade 3 or above [46]. However, the recent advances in robotic-assisted surgeries, specifically in high-volume centers, are improving post-surgical outcomes by offering higher degrees of freedom of movements, dexterity and a 3D vision [47]. In fact, robotic partial nephrectomy has a significant positive effect on achieving better postoperative renal function and higher trifecta outcome, which is defined by warm ischemia time $\leq$ 25 min, absence of positive surgical margin, and complications $\leq$ Clavien-Dindo grade 2 [47].

Given the benign nature of oncocytoma, surgical management may represent overtreatment in small renal oncocytomas that are asymptomatic [46]. The debate concerning the necessity of

surgery for RO is continuous, especially with the increased practice of pre-treatment biopsy and the increasing knowledge of its indolent natural history, despite the occasional presence of apparently invasive features such as lymphovascular and renal capsular involvement [17,18,45].

Tumor ablation was shown to be more cost-effective and safer than surgery for SRMs and could be an interesting alternative option [48].

Since the majority of RO has a slow annual GR, in well-selected patients active surveillance could be also a safe way for management [44]. Conservative management is especially beneficial in patients with multiple comorbidities, for whom renal function preservation is vital [33]. Active surveillance is even widely used in patients with small RCCs who are not candidates for surgery and it may be a safe management option for T1 oncocytomas confirmed on biopsy [41,45]. In this perspective, the European guidelines state that RO can be managed with active surveillance if a histological diagnosis has been attained [49]. However, a few concerns have been discussed concerning active surveillance. In fact, the coexistence of RCC and oncocytoma is seen in 10% to 32% of patients with RO [50,51]. This surprisingly high occurrence brings into question whether we should consider surgical management until more accurate methods become available to distinguish RO from RCC and to rule out the presence of coexistent malignant tumors.

Preoperative RMB has a positive predictive value of 67% for oncocytic lesions [4]. A systematic review of large-volume center series has reported a biopsy median diagnostic accuracy rate of 90.3%. Those results show a beneficial role of RMB which might, in combination with other clinical assessment factors, help in the preoperative diagnosis and the subsequent prevention of the morbidity associated with overtreatment [52]. On the other hand, in a recent systematic review on RMB series, 11 of 46 cases initially diagnosed as oncocytic tumors on biopsy were

found to be RCC after surgery, which makes surgical treatment regardless of the biopsy results, a good argument [5]. In order to improve the decision making concerning RO, a large single-center series (144 biopsied oncocytic tumors) suggested and used morphological features and expression markers that can aid in the distinction between RO and malignancy on RMB. The concordance between biopsy and final histology was 94% [53].

4- Conclusions

Renal oncocytoma (RO) is an uncommon tumor that follows a benign course regardless of tumor size or degree of local invasiveness. It exhibits numerous features that are characteristic but not necessarily unique. Currently, only surgical resection with pathologic examination can reliably make the diagnosis.

Surgical treatment morbidity can be significant and if surgery is done, partial nephrectomy should be performed when technically possible, even for larger lesions.

Percutaneous biopsy is a safe diagnostic method that can redirect patients toward less morbid management options, including active surveillance or ablation, although differentiation from other tumor subtypes often requires sophisticated analysis and is not universally feasible.

Notwithstanding, long-term follow-up data are lacking and greater centralization for the work up and treatment of RO should be considered, to offer sufficient local expertise in making accurate diagnosis. This is why, reference centers are needed in order to develop a translational evaluation that can lead to adequate management. Finally, in recapitulation of our review and until the appearance of clear guidelines, we propose an algorithm for the diagnosis and management of renal oncocytomas (Figure 3).

Table 1. Major radiologic and pathologic features in favor of renal oncocytoma or renal cell carcinoma.

Diagnostic tools	Favor Renal Oncocytoma	Favor Renal Cell Carcinoma
Imaging		
Computed tomography (1)	▪ Homogeneous ▪ Well-encapsulated with clear margins ▪ Stellate scar ▪ Spoken-wheel-like enhancement ▪ Segmental enhancement inversion	▪ Lymph node enlargement ▪ Metastasis ▪ Heterogeneous enhancement ▪ Lower nodule enhancement in the excretory phase in relation to the unenhanced phase
Magnetic resonance imaging (2,3,4)	**Tumor**: ▪ Well-defined, homogeneous masse ▪ Isointense to slightly hypointense on the non-enhanced T1 and T2	**Tumor**: ▪ Isointense on T1 ▪ Hyperintense on T2 ▪ Loss of signal intensity within the solid portions of the tumor on opposed phase images compared with in-phase ▪ Cystic changes within the solid tumor ▪ Enhancement of viable component
	Stellate scar: ▪ Hypointense on T1 and T2 ▪ No enhancement in the center of the homogenously enhanced oncocytoma	**Tumor necrosis**: ▪ Hypointense on T1 ▪ Hyperintense on T2 ▪ No enhancement
Sestamibi nuclear imaging (5, 6)	▪ High uptake	▪ Negative or low uptake
Pathology		
Macroscopic appearance (7)	▪ Brown amber cut surface similar to the normal renal parenchyma in color	▪ Golden yellow cut surface with hyalinization and fibrosis
Cytologic features (8)	▪ **Nuclei**: round and regular membrane, no perinuclear halos ▪ **Cytoplasm**: uniformly granular ▪ **Architecture**: nested with stromal edema ▪ **Entrapped normal tubules**: present	▪ **Nuclei**: pleomorphism, irregular membrane, perinuclear clearing, intranuclear pseudoinclusions ▪ **Cytoplasm**: heterogeneous texture ▪ **Architecture**: sheet-like or trabecular pattern ▪ **Entrapped normal tubules**: absent
Hale's colloidal iron stain (8)	▪ Apical or weak focal fine cytoplasmic granules	▪ Strong, diffuse microvacuolated cytoplasmic staining
Electron microscopy (8)	▪ **Microvesicles**: absent or sparse ▪ **Mitochondria**: abundant	▪ **Microvesicles**: numerous ▪ **Mitochondria**: peripheral or abnormal
Genome analysis (9)	▪ Diploid pattern or near-diploid aneuploidy	▪ Hypodiploid
Immunohistochemistry (10)	▪ KIT, e-cadherin, S100A + ▪ Vimentin -	▪ KIT - ▪ Vimentin +

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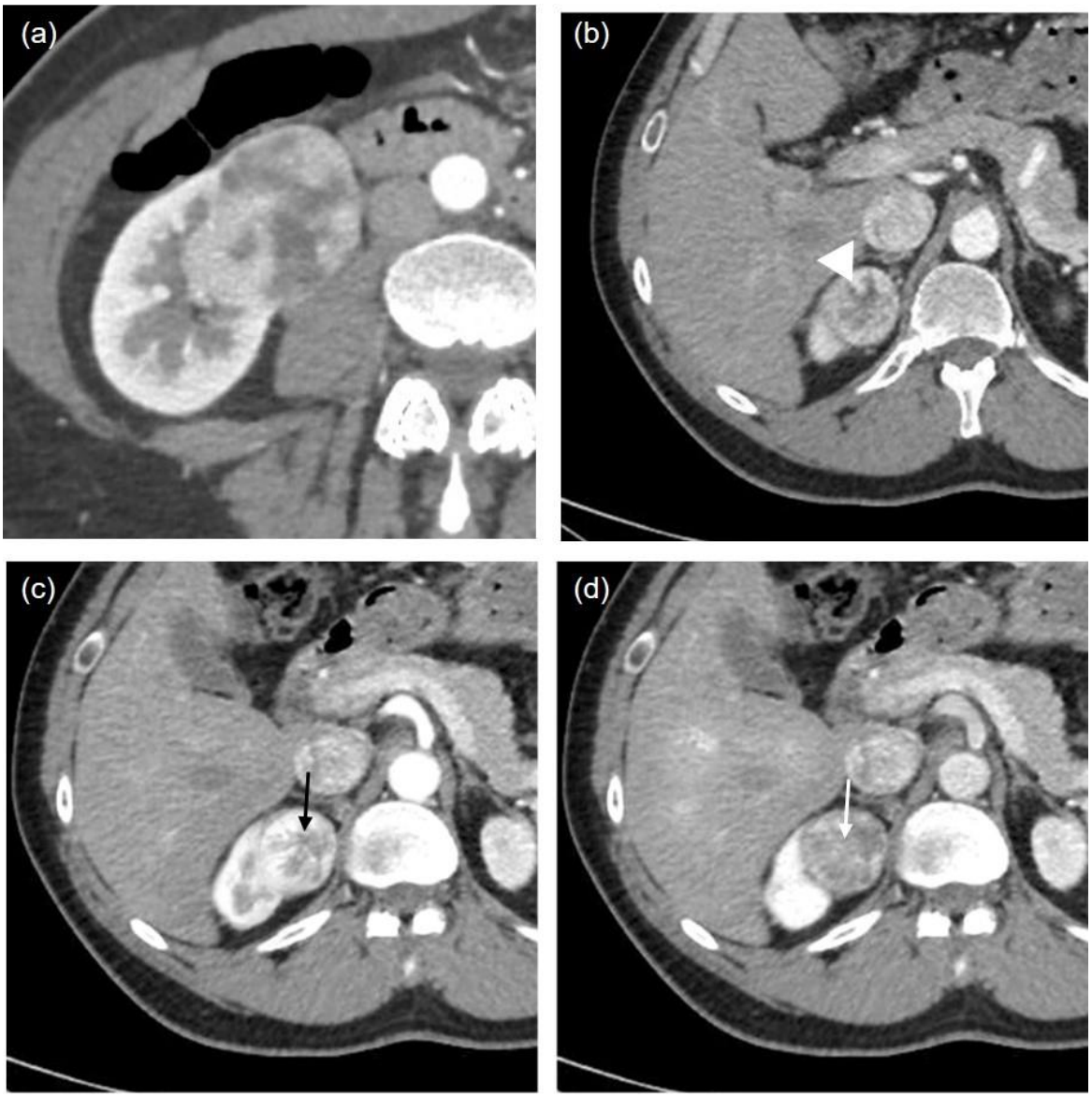
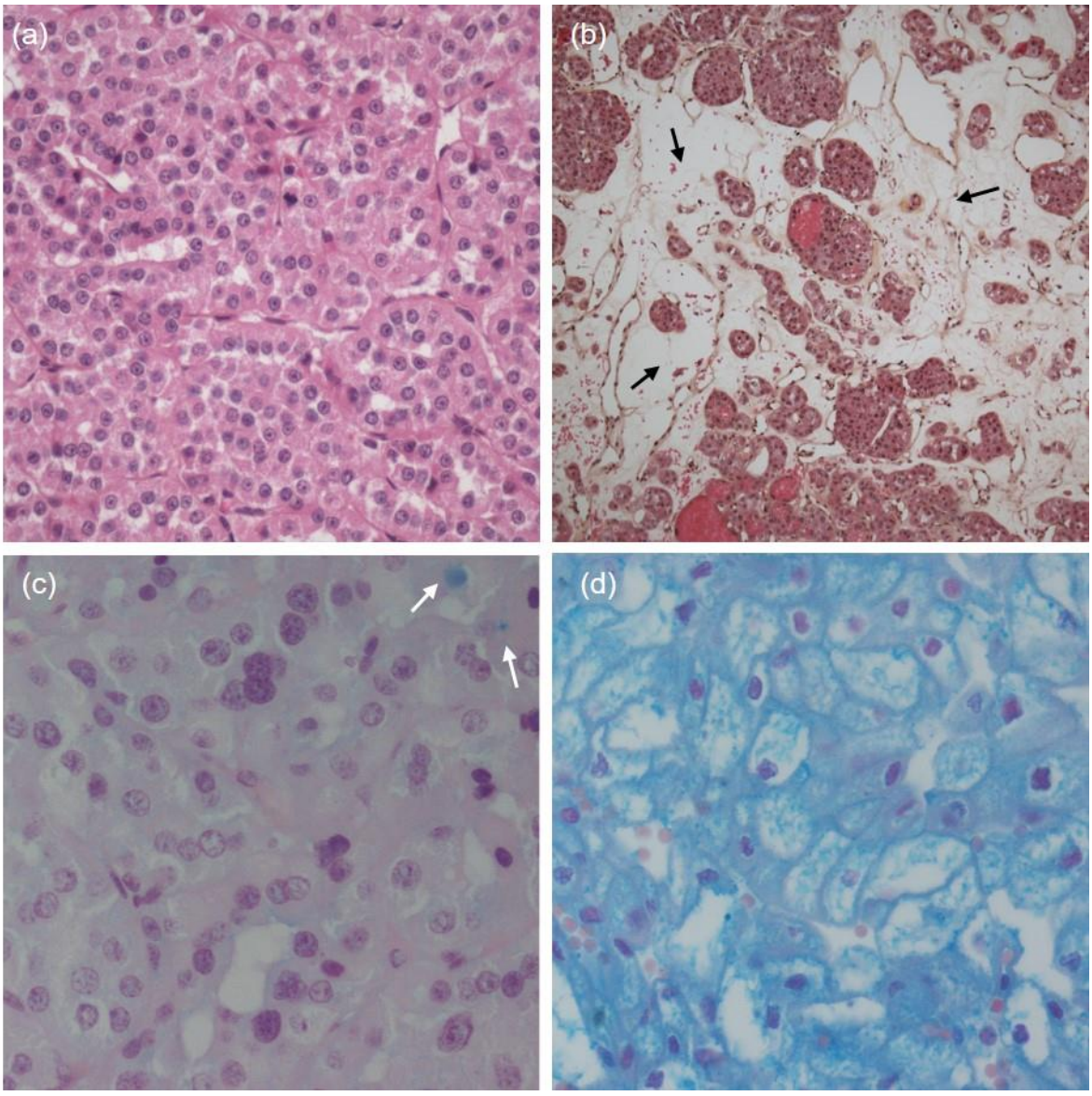
Figure 1. Computed tomography characteristics seen frequently in renal oncocytoma.



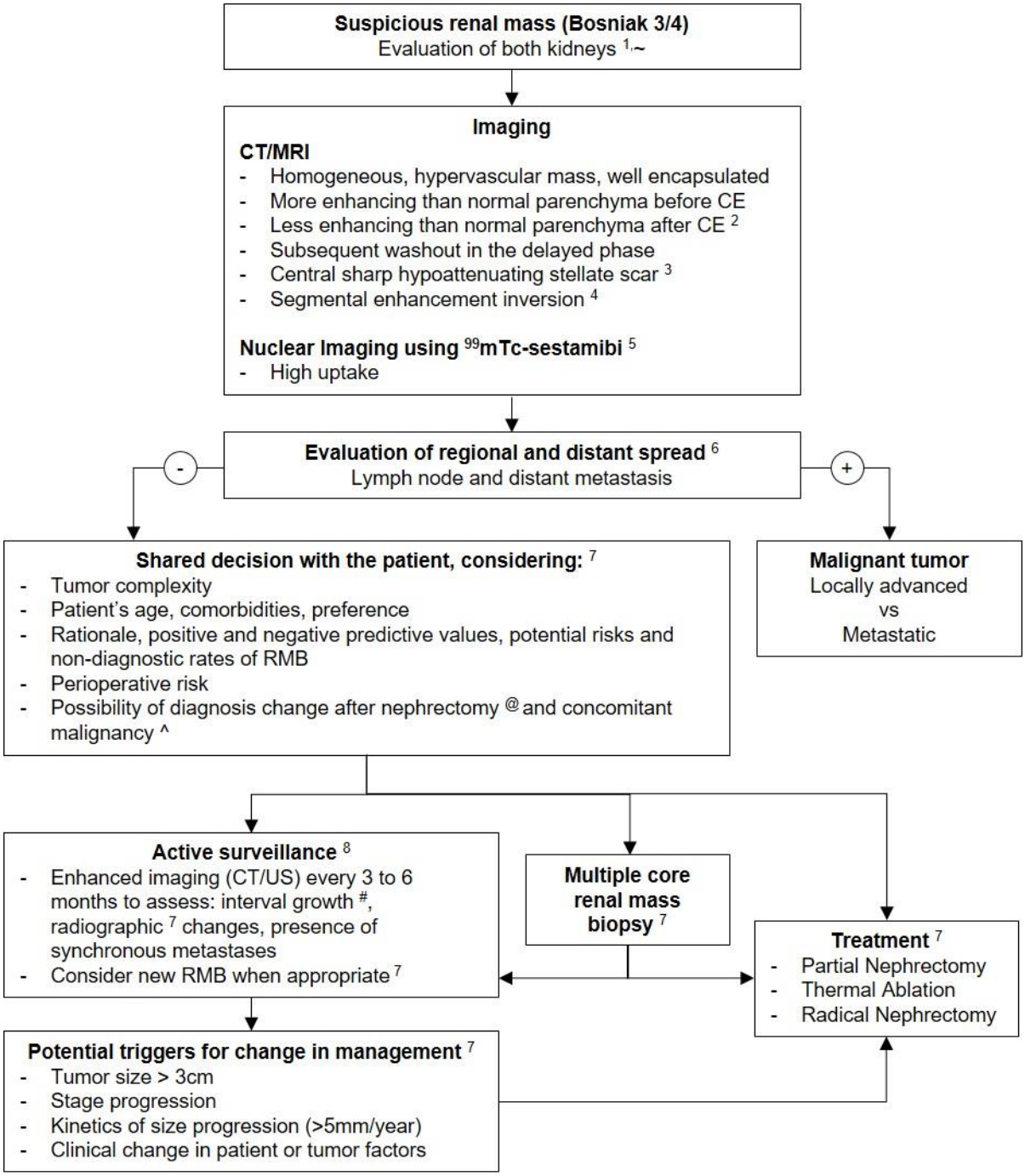
(a) Contrast-enhanced CT image showing a well-defined round tumor less attenuating than normal parenchyma. (b) Contrast-enhanced CT image showing a stellate scar (white triangle) at the center of the tumor. (c, d) Contrast-enhanced CT image showing segmental enhancement inversion of renal oncocytoma between nephrographic (black arrow) and corticomedullary (white arrow) phases.

Figure 2. Histologic sections of renal oncocytoma and chromophobe renal cell carcinoma.



(a,b,c) Renal oncocytoma showing eosinophilic, uniform cells with regular round nuclei with absence of mitosis and atypia. Cells show insular growth and are arranged in nests or in small islets divided by loose connective stroma (black arrows). Apical and weak staining pattern is visible with Hale's colloidal iron staining (white arrows). (d) Chromophobe renal cell carcinoma showing diffuse positivity for Hale's colloidal iron staining, with "raisinoid" nuclei having irregular contour.

Figure 3. Algorithm for diagnosis and management of renal oncocytoma.



CT: computed tomography; MRI: magnetic resonance imaging; CE: contrast enhancement; Tc: technetium; US: ultrasonography

~ : 5% are bilateral or multifocal [1]

@ : Post-nephrectomy, renal cell carcinoma was diagnosed in 31.2% and other benign lesions were found in 4.2% [8]

^ : Concomitant renal cell carcinoma in 32% of cases [9]

: Majority of oncocytomas have slow progression <14mm/year [9]

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