

# Low-grade oncocytic tumor (LOT) - a new renal entity ready for a prime time: An updated review

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**Summary.** Low-grade oncocytic tumor (LOT) of kidney has been recently proposed as a new renal entity. LOT was identified in the spectrum of oncocytic renal tumors with overlapping features between oncocytoma and eosinophilic chromophobe renal cell carcinoma, or it has been labelled as one of those entities in prior studies and in practice. LOT is often a single, relatively small tumor, found in a non-syndromic setting, but rare examples of multiple LOTs or admixed with other tumors have been found in patients with tuberous sclerosis complex. LOT typically has solid architecture, and it is composed of eosinophilic cells, with round to oval 'low-grade' nuclei, lacking irregularities and showing focal perinuclear halos. Sharp transition into edematous stromal areas, with scattered or loosely arranged cells are frequently found. LOT has a consistent immunohistochemical profile with diffuse reactivity for cytokeratin 7 and absent (or rarely weak) expression for CD117, a profile different from oncocytoma and eosinophilic chromophobe renal cell carcinoma. Similarly, in contrast to those entities, it also lacks or shows only weak expression for FOXI1. Recent studies have shown that LOT has a molecular/genetic profile different from other renal tumors, with frequent alterations affecting the *MTOR/TSC* pathway genes. LOT demonstrates either disomic pattern or deletions of 19p13, 19q13 and 1p36, and lacks complete chromosomal losses or gains. In all published studies to date, LOT has shown benign behavior. In this review, we summarize the evidence from recently published studies, which strongly supports the conclusion that LOT is a distinct and unique renal entity.

**Key words:** Low-grade oncocytic tumor, LOT, Oncocytoma, Chromophobe renal cell carcinoma, Unclassified renal tumor, Unclassified renal carcinoma, Hybrid tumor, TSC, MTOR

## Introduction

Low-grade oncocytic tumor (LOT) has been recently proposed to represent a separate and distinct renal entity (Trpkov and Hes, 2019; Trpkov et al., 2019). LOT has been primarily identified within the spectrum of oncocytic renal tumors with overlapping features between oncocytoma and eosinophilic chromophobe renal cell carcinoma (eo-ChRCC) that are difficult to subclassify precisely. Such tumors have also been labelled with various modifiers, including: “oncocytic, NOS”, “oncocytic, low-grade”, “unclassified oncocytic”, “borderline”, “hybrid” (or “with hybrid features”), and with “uncertain/low malignant potential” (Williamson et al., 2017; Trpkov et al., 2019). Importantly, LOT has a readily recognizable set of morphologic features and a consistent immunoprofile with negative CD117 and diffusely positive (Cytokeratin) CK7. A proportion of such cases in some large uropathology centers were also diagnosed either as oncocytoma (Kravtsov et al., 2021) or as eo-ChRCC (Trpkov et al., 2019; Morini et al., 2022). The initial study by Trpkov et al. comprised 28 individual cases collected from 4 centers, all found in a non-syndromic setting (Trpkov et al., 2019). They included tumors initially reported as “eo-ChRCC”, “oncocytic tumor, favor oncocytoma” or “low-grade oncocytic tumor, unclassified”, demonstrating diffuse reactivity for CK7, but negative CD117 (Trpkov et al., 2019). In addition to the sporadic and individual LOTs occurring in a non-syndromic setting, recent studies have also reported some patients harboring multiple LOTs, or LOTs occurring together with other tumors and angiomyolipomas (AML) in patients with tuberous sclerosis complex (TSC) (Schreiner et al., 2010; Lerma et al., 2021; Kapur et al., 2022; Morini et al., 2022).

In some studies, prior to 2019, examples of LOT

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have also been considered as eo-ChRCC or oncocytoma (Kuroda et al., 2013; Davis et al., 2014). For example, 4 cases morphologically very similar to LOT were included in the TCGA cohort, and were labelled “eo-ChRCC”; these cases however lacked any copy number alterations (Davis et al., 2014). In another study, 5 cases designated as “ChRCC, oncocytic variant” with “strong resemblance to renal oncocytomas”, and diffuse CK7 positivity, but lacking CD117 reactivity, were found on fluorescence in situ hybridisation (FISH) to have multiple (at least 4) chromosomal losses of chromosomes 7, 10, 13, 17, and 21 (Kuroda et al., 2013). However, no subsequent or follow-up studies were published on this entity to further validate and corroborate these initial findings. In TSC patients, some cases labelled as “ChRCC-like” that showed diffuse CK7 reactivity and were mostly CD117 negative, may in fact represent examples of LOT (Guo et al., 2014). Similarly, Schreiner et al. described 4 solid tumors in a patient with TSC, 2 of which were labelled “unclassified” and had morphologic and immunohistochemical features, in our view, consistent with LOT (Schreiner et al., 2010).

After the initial description of LOT, several groups have re-evaluated their institutional files and archives and have assembled retrospective LOT cohorts. In sum, these studies have confirmed, further validated, and expanded the knowledge on LOT, and have supported the notion that LOT is a separate entity (Akgul et al., 2021; Lerma et al., 2021; Guo et al., 2021; Kravtsov et al., 2021; Kapur et al., 2022; Morini et al., 2022). In the recent update on novel, emerging and provisional renal entities by the Genitourinary Pathology Society (GUPS) (Trpkov et al., 2021), LOT was proposed to represent a “provisional entity”, requiring further validation. Most recently, LOT has been shown to harbor ubiquitous MTOR/TSC mutations (Lerma et al., 2021; Kapur et al., 2022; Morini et al., 2022). In all published studies to date, containing over 100 patients, all reported tumors have behaved indolently. There was no evidence of local

tumor progression, recurrence and/or metastatic disease in any of the reported cases, therefore further justifying the term “tumor”, rather than “carcinoma” for this entity. Thus, based on the accumulated evidence, it appears that LOT truly represents a distinct renal entity that needs to be fully recognized, owing to its characteristic morphology, CD117-/CK7+ immunoprofile, its uniform MTOR/TSC mutations, and its benign behavior. This updated review aims to summarize the evidence from the recently published studies on LOT (Table 1), to present a cogent argument that LOT is indeed a unique renal entity, ready for “prime time”.

### Clinical features, demographics, hereditary and other tumor associations and behavior

The findings from the published studies regarding the features of LOT are shown in Table 1. LOT typically appears as a single, sporadic tumor, found in a non-syndromic setting. They are usually discovered incidentally, but patients can also present with flank pain, hematuria or anemia (Kapur et al., 2022). LOT is usually found in older patients, with a mean age of 62.7 years, but has been identified in patients spanning a broad age range from 10 to 87 years. Overall, there was a slight female predilection (M:F=1:1.3), although the gender distribution has been somewhat variable in the published studies. Rare examples of LOT have also been documented in patients with TSC; in toto, 5/109 (4.6%) of all reported patients with LOT had a TSC. Although LOT is typically found as a single tumor, multiple tumors with LOT morphology, measuring from a few millimetres up to 14.2 cm, have also been reported, either in patients with end-stage kidney disease (Kravtsov et al., 2021), or in patients with TSC (Lerma et al., 2021; Kapur et al., 2022). Overall, 8/109 (7.3%) of all reported cases have occurred as multiple tumors, either exclusively in association with other LOTs or with other tumor types. For example, one study reported 4 patients in whom LOT has been found together with

**Table 1.** Clinical and molecular characteristics of low-grade oncocytic tumor (LOT) of kidney in the published studies.

Author	No. of patients	Mean age, (range) years	Male/Female	No. of tumors	Median size, (range) cm	Multiple tumors	Pre-existing syndromes	Molecular/ genetic analysis	Follow-up
Trpkov et al., 2021	28	66 (49-78)	10/18	28	3 (1.1-13.5)	0	0	Deletions of 19p13.3, 19p13.11 and 1p36.33	ANED
Kravtsov et al., 2021	29	67 (27-87)	13/16	54*	3.4 (0.2-14.2)	3**	2 (TSC)	No CCND1 rearrangements	ANED
Kapur et al., 2022	7	75 (63-86)	2/5	22	3.1 (0.5-7.8)	1#	1 (TSC)	MTOR (x4), TSC1 (x1), RHEB (x1) mutations	ANED
Morini et al., 2022	10	66 (42-83)	1/9	10	4.8 (2.5-8.5)	0	0	MTOR (x7), TSC1 (x1) mutations	ANED
Akgul et al., 2021	23	66 (22-84)	14/9	23	4.0 (1.6-10.5)	0	0	N/A	ANED
Lerma et al., 2021	4	42.5 (10-61)	3/1	20	N/A (0.1-7.5)	4##	2 (TSC)	TSC1 (x2), neg. for FLCN, PTEN, FH, VHL mutations	ANED
Guo et al., 2021	8	56.6 (39-70)	4/4	8	4.5 (2-8)	0	0	N/A	ANED
Total	109	62.7 (10-87)	47/62 (1/1.3)	165	N/A (0.1-14.2)	8	5		ANED

ANED: Alive, no evidence of disease; TSC: tuberous sclerosis complex; N/A: Not available. \*: Number of tumors in one patient reported as more than 20. The total number of tumors is at least 54. \*\*: One patient with more than 20 bilateral tumors in the setting of end-stage renal disease; 2 patients had 5 and 3 tumors, respectively, all diagnosed as LOT. #: One patient has 6 tumors on the right side and 10 on the left side, all diagnosed as LOT. ##: All 4 patients had co-existent other tumors: eosinophilic solid and cystic RCC, eosinophilic vacuolated tumor, RCC with fibromyomatous stroma, angiomyolipoma, and/or papillary adenoma.

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other tumors typically seen in TSC patients, including eosinophilic solid and cystic renal cell carcinoma (ESC RCC), eosinophilic vacuolated tumor (EVT), RCC with fibromyomatous stroma (RCC FMS), AML, and papillary adenoma (Lerma et al., 2021).

In the published studies, follow-up was available for 92/109 (84.4%) patients with a mean follow-up of 42.5 months (range 0 to 344 months) (Trpkov et al., 2019; Akgul et al., 2021; Guo et al., 2021; Lerma et al., 2021; Kravtsov et al., 2021; Kapur et al., 2022; Morini et al., 2022). All reported LOTs to date with available follow-up have behaved indolently, with no evidence of disease progression, including either local progression, recurrence and/or metastatic disease.

### Pathologic features

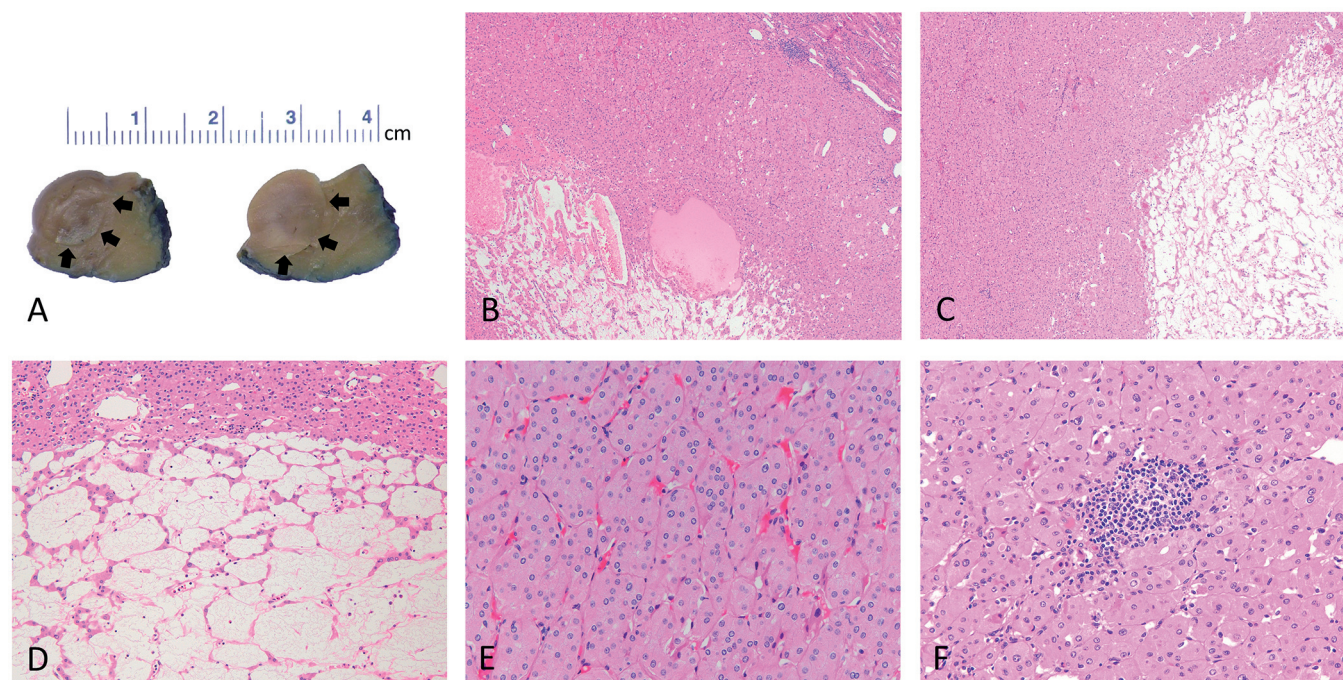
#### Macroscopic features and stage

LOT has a mahogany or tan/yellow-brown cut surface and is typically a solid tumor (Fig. 1A). The median tumor size was between 3 and 4.8 cm; the largest studies documented a median size between 3 and 4 cm (Trpkov et al., 2019; Akgul et al., 2021; Kravtsov et al., 2021). The reported size however had a broad range from 0.1 to 14.8 cm; of note, very small LOTs measuring only a few millimetres have typically been documented in patients harboring multiple tumors. In cases where stage was reported, 83.4% of LOTs were

either stage pT1a (52.6%) or pT1b (30.8%); stages  $\geq$ pT2 were reported in 16.6% patients (pT2a: 7.7%; pT2b: 3.8%; and pT3a: 5.1%).

#### Microscopic Features

LOT lacks a well-formed capsule at the periphery and usually has a solid, compact nested, and focal tubular or tubuloreticular growth. The cells have an eosinophilic (“oncocytic”) cytoplasm, round to oval, low-grade nuclei that lack prominent irregularities (or “raisinoid” features), and often have delicate perinuclear clearings (or halos) (Trpkov and Hes, 2019; Trpkov et al., 2019). A frequent and helpful feature is the presence of sharply delineated, edematous stromal areas, containing scattered, irregularly distributed individual cells, elongated (“myoid”) cells, and/or cord-like cell formations, mimicking a tissue culture. Such areas convey a picture of individual “boats in a bay” arrangement, in contrast with the more substantive cell aggregates, typically seen in the central areas of an oncocytoma that exhibit “archipelagenous growth”. Stromal areas often contain fresh hemorrhage, or rarely, fibrin deposition. Small lymphocytic clusters can be found in the solid tumor areas. Atypical morphologic features, including significant cell atypia, nuclear pleomorphism, increased mitotic activity, and coagulative necrosis are typically absent. The microscopic features of LOT are illustrated in Fig. 1B-F.



**Fig. 1.** Macroscopic and microscopic features of low-grade oncocytic tumor (LOT). **A.** Grossly, LOT is typically a small, mahogany-brown tumor (arrows) or it can show tan-yellow color. **B-D.** LOT has solid or compact nested growth with sharp transition into areas of loose stroma, containing either scattered individual cells (“boats in a bay”) or resembling disorganized tissue culture. **E.** At higher magnification, LOT is composed of eosinophilic cells with delicate, round to oval nuclei, focally showing perinuclear halos. **F.** Small lymphocytic aggregates can also be seen in the solid areas.

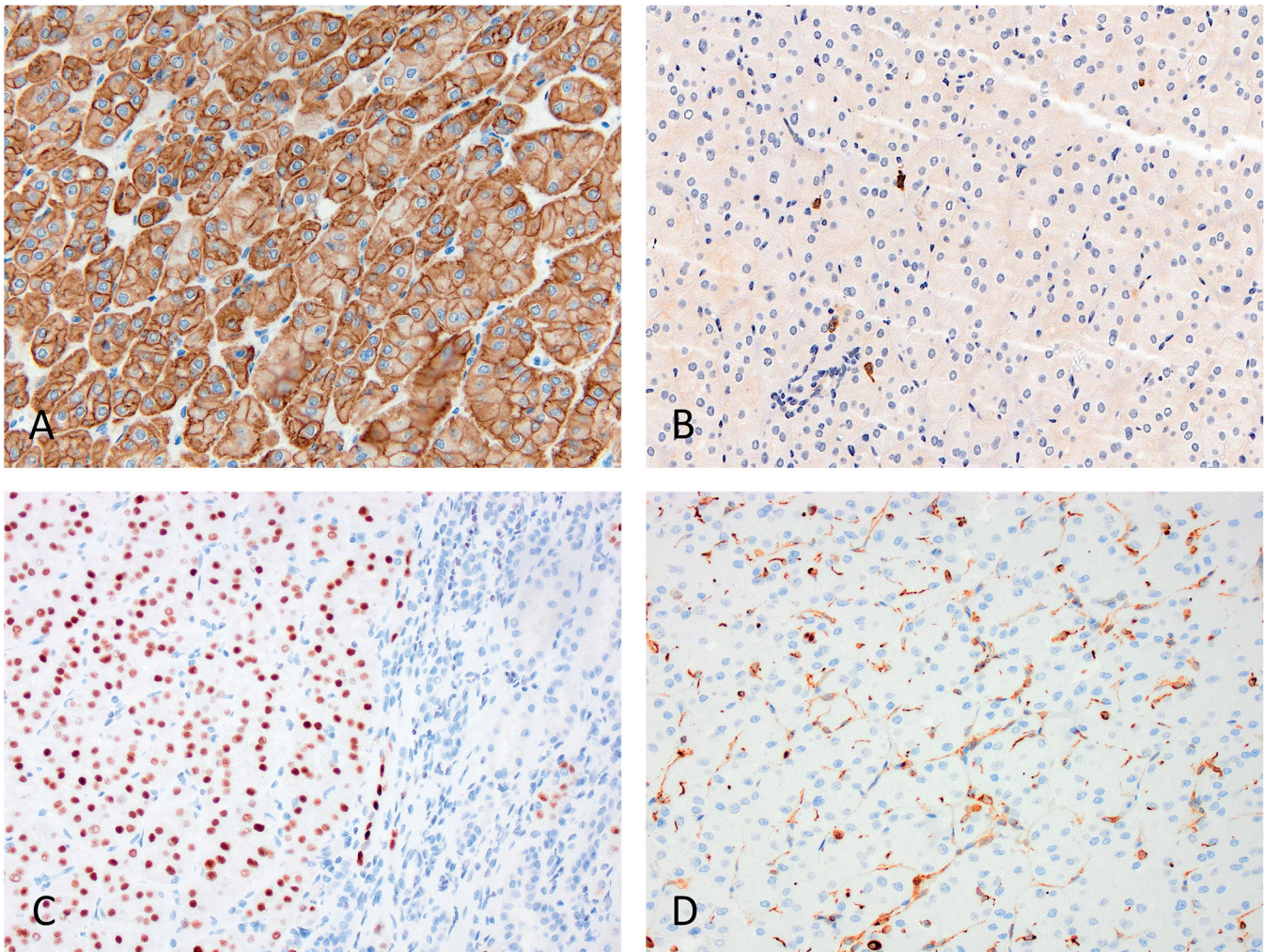


*Immunohistochemistry and electron microscopy*

LOT has a typical immunoprofile characterized by diffuse reactivity for CK7 and negative expression of CD117. Rare cases may show very weak and focal CD117 staining. The CK7+/CD117- profile would be unusual for an oncocytoma that typically exhibits only scattered (or patchy) CK7 positive cells and diffuse CD117 reactivity, or classic ChRCC that shows diffuse staining for both CK7 and CD117. LOT is also positive for PAX8, AE1/AE3, E-cadherin, BerEP4 and MOC31; fumarate hydratase (FH) and succinate dehydrogenase B (SDHB) are always retained (Trpkov et al., 2019; Kravtsov et al., 2021; Tong and Hu, 2021). LOT is negative for CA9, CK20, CK5/6, p63, CD15, HMB45, melan-A, cathepsin K, and vimentin. CD10 and AMACR can be either negative or focally positive. The

key immunohistochemical findings are illustrated in Fig. 2A-D.

Of note, although CK7+/CD117- profile strongly supports the diagnosis of LOT when the typical morphology is present, most recently it has been suggested that such an immunoprofile can also be seen in some “oncocytic renal neoplasms with diffuse keratin 7 immunohistochemistry” that exhibit more “oncocytoma-like” morphology (Mohanty et al., 2022). Whether these should be considered as part of the “LOT spectrum” remains an open question. This is particularly important when facing a scenario of a limited tissue in a needle biopsy specimen. It is well-known that some pathologists are unwilling to diagnose even oncocytoma on biopsy (Trpkov et al., 2021). Our approach has been to carefully consider the morphology in the context of the immunohistochemical profile, which we almost



**Fig. 2.** Key immunohistochemical features of low-grade oncocytic tumor (LOT). **A.** CK7 is diffusely positive. **B.** CD117 is typically completely negative (note rare positive mast cells). **C.** GATA3 shows diffuse and consistent nuclear expression (tumor periphery, tumor is shown on the left). **D.** Vimentin is negative (only the background stromal cells and the vessels are positive).



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always use in this setting. In fact, we have diagnosed some LOT cases on needle biopsy (illustrated in Trpkov et al., 2019). However, this may not always be possible, and in such a situation we would issue a descriptive diagnosis such as “*oncocyctic tumor, not further specified*”, and include a comment listing our differential diagnosis and/or preference(s). It has also been recently shown that LOT consistently and, at least focally, expresses p-S6 and p-4EBP1, both markers associated with MTOR pathway activation (Kapur et al., 2022; Morini et al., 2022). Absent or very low immunohistochemical expression of FOXI1 has also been recently found in LOT (Skala et al., 2020; Tong and Hu, 2021; Morini et al., 2022). Interestingly, FOXI1 is expressed in the intercalated cells of the distal renal tubules in the normal kidney, and is typically found both in oncocyctoma and in ChrCC, while it is negative in other renal tumors (Skala et al., 2020; Tong and Hu, 2021). For example, Tong and Hu reported that 8.6% of the evaluated cases considered as ChrCC and 27.8% of those considered as oncocyctoma, were negative for FOXI1, a pattern consistent with LOT (Tong and Hu, 2021). We have recently observed consistent and diffuse expression of GATA3 in LOT (unpublished observations and personal communication with Dr. Omar Hameed). In our experience, GATA3 is negative in oncocyctoma, although it is expressed in a wide variety of different neoplasms in various organs. Of note, one study reported reactivity for GATA3 in 51% (18/35) of ChrCC and 17% (6/35) of renal oncocyctomas (Miettinen et al., 2014); one can only speculate whether a proportion of these positive ChrCCs and oncocyctomas actually represent LOT.

Regarding the special stains in LOT, Muller–Mowry colloidal iron stain was found to be either negative or only luminal positive (Trpkov et al., 2019). On electron

microscopy, LOT shows abundant, closely packed cytoplasmic mitochondria, as found in oncocyctoma, which further supports and justifies the designation “oncocyctic” for the name of this entity (Siadat and Trpkov, 2020).

### Genetic, molecular and metabolomics features

The seminal LOT study that used an array comparative genomic hybridization and successfully evaluated 9 cases, found deletions at 19p13.3 (7/9), 1p36.33 (5/9) and 19q13.11 (4/90) (Trpkov et al., 2019). In 2/9 cases, a diploid chromosomal status was found, but no other consistent chromosomal gains or losses were identified (Trpkov et al., 2019). Although some features, such as loss of 1p36 and diploid pattern are common in renal oncocyctomas, it has been confirmed that *CCND1* rearrangements are not found in LOT (unlike in oncocyctoma which is frequently associated with *CCND1* rearrangements) (Kravtsov et al., 2021).

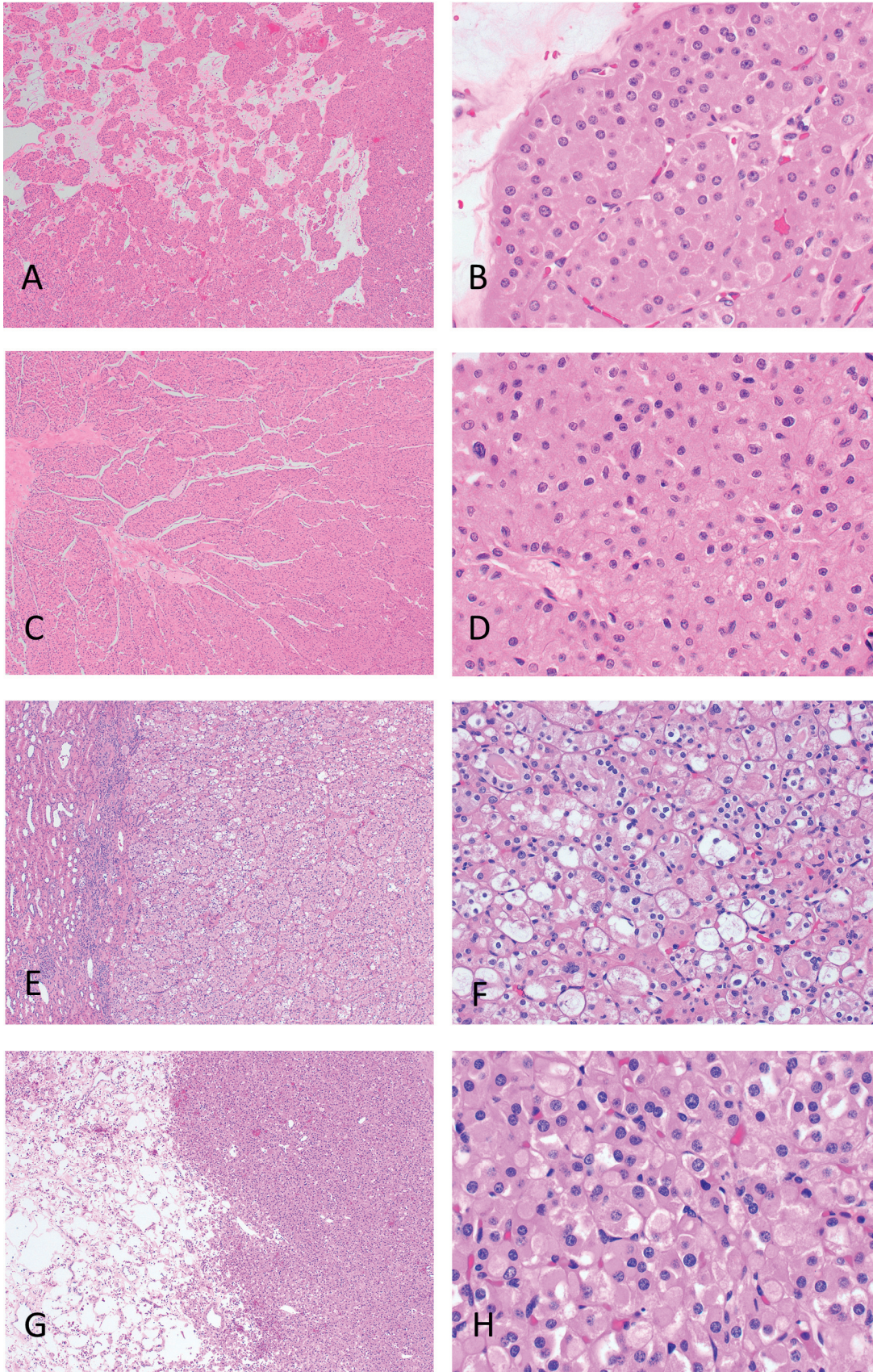
Evidence that LOT represents a distinct entity, different from ChrCC, and particularly from eo-ChrCC, can be derived from some genetic and molecular studies on ChrCC. ChrCC typically has multiple losses of chromosomes Y, 1, 2, 6, 10, 13, 17 and 21 (Paner et al., 2016). Three tumors considered as “eo-ChrCC” that were morphologically very similar to LOT were found in the TCGA cohort; however, they lacked any copy number alterations and only harbored *TSC/MTOR* mutations (Davis et al., 2014). Tong and Hu also recently reported 4 cases with striking morphologic similarities to LOT, which they labelled “eosinophilic chromophobe-like renal tumors” that had very low or null FOXI1 mRNA expression, distinct transcriptomic profiles, *MTOR* pathway mutations, and absence of any chromosomal losses (Tong and Hu, 2021). Skala et al.

**Table 2.** Salient morphologic and immunohistochemical features helpful in the differential diagnosis of low-grade oncocyctic tumor (LOT) vs. other similar renal eosinophilic tumors.

Diagnosis	Key distinguishing features	Immunohistochemistry
Low-grade oncocyctic tumor (LOT)	Solid sheets and compact nests, may show focal transition to tubuloreticular areas (more centrally) Sharply delineated edematous stromal areas with loose and irregular cell growth ('boats in a bay' arrangement); may show frequent hemorrhage Round to oval nuclei, without irregularities, often with perinuclear 'halos'	CD117- CK7+ GATA3+ (limited data)
Oncocyctoma	Diffuse, nested, tubulocystic growth Central stromal areas with 'archipelagenous' growth containing larger cell nests or aggregates Round to oval nuclei that lack perinuclear 'halos'	CD117+ CK7-/+ (usually only scattered cells) GATA3- (limited data)
Chromophobe RCC, eosinophilic	Solid growth, typically no stromal areas Cells with more prominent membranes, irregular (raisinoid) nuclei and perinuclear 'halos'	CD117+ CK7+ (can be variable) GATA3-/+ (limited data)
Hybrid oncocyctic tumor (Birt-Hogg Dubé syndrome)	Often multiple tumors with solid or nested growth, and 'hybrid' (oncocyctoma/chromophobe-like) look, no stromal areas Often scattered cells with clear cytoplasm (mosaic pattern) Typically round to oval nuclei, perinuclear halos may be present	CD117+ CK7-/+ (usually only scattered cells) Cathepsin K+/- (limited data)
SDH-deficient RCC	Solid to focal tubulocystic growth Edematous stromal areas may be present with scattered cells ('boats in a bay' arrangement) Cells with flocculent cytoplasm and cytoplasmic vacuoles Round to oval (low-grade) nuclei, no nuclear irregularities, lack perinuclear halos (if typical morphology)	CD117- CK7- SDH- AE1/AE3- (often)



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**Fig. 3.** Several entities can be considered in the differential diagnosis of low-grade oncocyctic tumor (LOT). **A.** On low magnification, oncocyoma has an “archipelagenous growth” in the central areas, with cells forming larger nests. **B.** At high magnification, oncocyoma cells have a homogeneous eosinophilic cytoplasm and round to oval nuclei without perinuclear ‘halos’. **C.** Eosinophilic variant of ChRCC has a broad trabecular or diffuse growth at low magnification. **D.** The cells at higher magnification have irregular (raisinoid) nuclear shapes and perinuclear ‘halos’. **E.** In Birt–Hogg–Dubé syndrome, patients often have multiple and bilateral renal tumors with ‘hybrid’ morphology between oncocyoma and eosinophilic variant of ChRCC. The tumor is non-encapsulated with solid growth, and scattered cells with clear cytoplasm (“mosaic pattern”) can be seen even at low magnification. **F.** At higher power, the cells have an equivocal morphology between oncocyoma and eosinophilic variant of ChRCC and there are scattered cells with clear cytoplasm (“mosaic pattern”). **G.** SDH-deficient RCC shows solid growth with sharply delineated edematous areas with rare cells (“boats in a bay”), resembling LOT at low magnification. **H.** At high magnification, the cells have more flocculent cytoplasm and cytoplasmic vacuoles, with round to oval, low-grade nuclei, without nuclear irregularities and perinuclear ‘halos’.



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recently found that *LINC01187* was a specific ChRCC biomarker using an RNA in situ hybridization method (Skala et al., 2020). They however found negative *LINC01187* and very low levels of nuclear FOXI1 in two tumors initially considered as eo-ChRCC, in which both markers should have been expressed (Skala et al., 2020). Ultimately, both tumors were found to harbor *MTOR* gene mutations and diploid pattern, as well as absence of any copy number, a molecular profile suggestive of LOT (Skala et al., 2020). Complete absence of any chromosomal losses was also found in 41.7% of cases considered eo-ChRCC, in a large ChRCC study (Ohashi et al., 2019). The most important reason why LOT in many of the studies is included as eo-ChRCC is due to the lack of strict diagnostic criteria for eo-ChRCC in the 2016 WHO classification, with the sole requirement that eo-ChRCC is “almost purely composed of eosinophilic cells” (Paner et al., 2016). Detailed genetic and molecular studies are also infrequently performed in routine practice on such cases. As an additional confounder, tumors morphologically identical to LOT that showed diffuse CK7 reactivity and mutations in *TSC1* or *TSC2*, were labelled with descriptive terms (Tjota et al., 2020). For example, one study reported a group of 15 tumors, designated “eosinophilic renal tumors”, with morphologic and immunohistochemical features identical to LOT that had mutations involving the TSC/MTOR pathway (Tjota et al., 2020).

Additional strong evidence has also emerged recently of the involvement of the *MTOR* pathway genes in LOT. Morini et al. recently identified variations in *MTOR* pathway related genes in 80% (8/10) of evaluated LOT cases, including *MTOR* (7/8) and *TSC1* (1/8) (Morini et al., 2022). Similarly, Kapur et al. found somatic, likely activating, mutations in *MTOR* (4/6) and *RHEB* (1/6) in 6 evaluable LOTs; additionally, one patient with multiple bilateral LOTs had a pathogenic germline mutation in *TSC1* (1/6) (Kapur et al., 2022). Lerma et al. found *TSC1* germline mutations in 2 TSC patients who had multiple LOTs, along with other renal tumors seen in TSC patients, such as ESC RCC, EVT, RCC FMS, and AML (Lerma et al., 2021).

Although *TSC/MTOR* mutations support a diagnosis of LOT when the typical morphology and

immunoprofile are present, they are not specific or pathognomonic for LOT. Such mutations can be found in TSC patients, and even much more frequently in a sporadic setting, associated with renal neoplasms such as LOT, EVT, ESC RCC and RCC FMS, as well as AML (or PEComa) (Trpkov et al., 2021). *MTOR* pathway abnormalities are however not unique for this group of tumors and have also been documented in a wide variety of other renal tumors such as clear cell RCC, papillary RCC, ChRCC, acquired cystic disease associated RCC, and in some unclassified aggressive RCCs (Trpkov et al., 2021).

Papathomas et al. used a combination of <sup>99m</sup>Tc-sestamibi SPECT/CT and tissue microarray analysis to evaluate a metabolic signature for various renal eosinophilic tumors (Papathomas et al., 2020). <sup>99m</sup>Tc-sestamibi SPECT/CT positive renal tumors typically included ChRCC. Of the 7 cases considered initially as ChRCC, 2 were reclassified as LOT upon expert review, and these 2 tumors were <sup>99m</sup>Tc-sestamibi SPECT/CT negative and demonstrated a metabolomics signature different from ChRCC and oncocytoma (Papathomas et al., 2020).

### Differential diagnosis

The salient distinguishing features on morphology and immunohistochemistry between LOT and some eosinophilic renal tumors are summarized in Table 2 and are illustrated in Fig. 3A-H. Common eosinophilic renal tumors that need to be distinguished from LOT include oncocytoma and ChRCC, particularly the eo-ChRCC. Other less common renal tumors in the differential include those found in Birt-Hogg-Dubé syndrome that show ‘hybrid’ or overlapping features between an oncocytoma and ChRCC, as well as SDH-deficient RCC, in its typical form, and without dedifferentiation. LOT also regularly shows retained expression of SDHB on immunohistochemistry. Although other renal tumors with eosinophilic features may also be included in the broader differential, such as clear cell RCC, papillary RCC, MITF RCC (TFE3 and TFEB), ESC RCC, EVT (HOT) and epithelioid AML, their morphologies and immunoprofiles are sufficiently distinctive from LOT to

**Table 3.** Summary features of Low-grade Oncocytic Tumor (LOT) of kidney.

Clinical, gross features and behavior	Microscopic features	Immunohistochemistry	Molecular and genetic findings
Older patients, wide age range	Solid growth (no macrocysts)	CK7 diffusely positive	MTOR, TSC1 and RHB mutations
Mostly solitary and non-syndromic, rare in TSC patients (typically multiple)	Eosinophilic (oncocytic) cells, no distinct cell membranes	CD117 negative (rare cases weak positive)	Some cases had deletions of chromosomes 19p, 19q and 1p, or are diploid
Smaller tumors, tan to mahogany brown, no capsule	Bland, low-grade nuclei, lacking irregularities and large nucleoli, focal perinuclear halos	Vimentin negative	No other chromosomal losses or gains
Uniformly indolent behavior	Sharply demarcated loose stromal areas, often with hemorrhage, containing scattered eosinophilic cells	p-S6 and p-4EBP at least focally positive	
		FOXI1 negative or weak/focal	
		GATA3 diffusely positive	

necessitate further elaboration.

## Conclusions

In this updated review, we have summarized the accumulated evidence and knowledge on LOT, since its initial description to date. In our view, and following the existing principles of renal tumor classification, LOT fulfils the required set of criteria to be recognized as a distinct renal entity in the WHO classification of renal neoplasia. LOT has readily distinguishable morphologic, immunohistochemical, genetic and molecular features (summarized in Table 3), and it has uniformly benign behavior. Such characteristics separate LOT from other similar renal tumors. Moreover, in our experience, and based on some published studies, LOT appears to be not so rare in practice. For example, large retrospective studies have shown that LOT represents about 4% of cases considered to represent either oncocytoma (Kravtsov et al., 2021) or ChRCC (Morini et al., 2022), or about 6.7% of “unclassified RCC or low-grade oncocytic/eosinophilic renal neoplasms” (Akgul et al., 2021). Thus, LOT encompasses and carves off a sizable proportion from the “oncocytic” or “eosinophilic” tumors that routinely pose diagnostic challenges and are typically signed-out descriptively and imprecisely. We expect that this updated review will further promote the awareness of this entity and will stimulate additional retrospective, prospective, collaborative and other studies to fully validate LOT as a distinct renal entity.

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