Conclusions: Multi-tier grading systems outperform the 2004/2016 WHO in predicting recurrence and T1+ progression in NPUC, with the 4-tier system providing the most precise risk stratification. Ki67 further enhances prognostic accuracy, identifying thresholds that predict recurrence and progression. These findings support using multi-tier grading combined with Ki67 to guide individualized treatment and surveillance strategies.

Lab Invest 106 (2026) 105132

https://doi.org/10.1016/j.labinv.2025.105132

845 | Diagnostic Utility of CD56 in the Immunohistochemical Assessment of Eosinophilic Vacuolated Tumor

Ngoc-Nhu Jennifer Nguyen[1], Michelle Hirsch[2], Liang Cheng[3], Maria Tretiakova[4], Abbas Agaimy[5], Asli Yilmaz[6], Farshid Siadat[7], Fadi Brimo[8], Ting Zhao[9], Chin-Lee Wu[10], Costantino Ricci[11], Michelangelo Fiorentino[12], Büşra Yaprak Bayrak[13], Mahmut Akgul[14], Katrina Collins[15], Ekta Jain[16], Cristina Magi-Galluzzi[16], Andrew Evans[17], Rola Saleeb[18], Khaleel Al-Obaidy[19], Michelle Downes[20], Dimitrios Korentzelos[21], Kiril Trpkov[7], Ankur Sangoi[22], [1] *Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON;* [2] *Brigham and Women's Hospital, Boston, MA;* [3] *Alpert Medical School of Brown University, Providence, RI;* [4] *University of Washington, Seattle, WA;* [5] *Universitätsklinikum, Erlangen, Germany;* [6] *Alberta Precision Laboratories, University of Calgary, Calgary, AB;* [7] *University of Calgary, Calgary, AB;* [8] *McGill University, Montreal, QC;* [9] *Massachusetts General Hospital, Harvard Medical School, Boston, MA;* [10] *Massachusetts General Hospital, Boston, MA;* [11] *S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy;* [12] *Alma Mater Studiorum-University of Bologna, Bologna, Italy;* [13] *Kocaeli University School of Medicine, Izmit, Turkey;* [14] *Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [15] *Indiana University School of Medicine, Indianapolis, IN;* [16] *The University of Alabama at Birmingham, Birmingham, AL;* [17] *University of Toronto, Vaughan, ON;* [18] *St. Michael's Hospital/University of Toronto, Toronto, ON;* [19] *McLaren Health Pathology, Flint, MI;* [20] *Sunnybrook Health Sciences Centre, Toronto, ON;* [21] *University of Pittsburgh Medical Center, Pittsburgh, PA;* [22] *Stanford University, Stanford, CA*

Disclosures: Ngoc-Nhu Jennifer Nguyen: None; Michelle Hirsch: None; Liang Cheng: None; Maria Tretiakova: None; Abbas Agaimy: None; Asli Yilmaz: None; Farshid Siadat: None; Fadi Brimo: None; Ting Zhao: None; Chin-Lee Wu: None; Costantino Ricci: None; Michelangelo Fiorentino: None; Büşra Yaprak Bayrak: None; Mahmut Akgul: None; Katrina Collins: None; Ekta Jain: None; Cristina Magi-Galluzzi: None; Andrew Evans: None; Rola Saleeb: None; Khaleel Al-Obaidy: None; Michelle Downes: None; Dimitrios Korentzelos: None; Kiril Trpkov: None; Ankur Sangoi: None

Background: Eosinophilic vacuolated tumor (EVT) is an emerging renal oncocytic tumor in the 2022 World Health Organization classification. Prototypical morphologic features include eosinophilic cytoplasm with large, optically clear vacuoles and enlarged nuclei with prominent nucleoli. However, its immunoprofile, characterized by positivity for CD117, cathepsin K, CD10 and GPNMB with variable KRT7/KRT20 expression, overlaps with other entities in the morphological differential diagnosis. We have anecdotally noted that EVTs are often positive for CD56, and herein explore the diagnostic sensitivity and specificity of CD56 in a large cohort of eosinophilic renal neoplasms including EVT.

Design: A cohort of EVTs (n=40) and other eosinophilic kidney tumors (n=115) collected from 16 institutions were stained for CD56 and semi-quantitively scored as follows: 0 (≤2%), 1+ (2-10%), 2+ (10-50%), or 3+ (>50%). All diagnoses were made by genitourinary pathologists with the aid of immunohistochemical studies. Clinicopathologic features were recorded for EVTs including *MTOR/TSC1/TSC2* status when available.

Results: The median age of EVT patients was 51 years (range 13-80 years). The M:F ratio was 1:1.7. EVT specimens were: biopsy (n=5), partial nephrectomy (n=24), and radical nephrectomy (n=11). Next generation sequencing detected a *MTOR/TSC1/TSC2* variant in 11/13 EVTs. CD56 expression was found in 38/40 (95%) EVTs. Most EVTs (n=33/40, 82.5%) had 3+/diffuse CD56 expression (Figure 1) and this pattern of reactivity was found to be the most specific for EVT (Table 1). However, a 3+ pattern of CD56 expression was also seen in 12/35 (34.3%) oncocytomas, 1/20 (5%) eosinophilic solid and cystic (ESC) renal cell carcinomas (RCC), and 2/4 hybrid oncocytic tumors (Figure 2). Eosinophilic chromophobe RCC (n=11), eosinophilic clear cell RCC (n=7), SDH-deficient RCC (n=5), epithelioid angiomyolipoma (n=7), low grade oncocytic tumor (n=23), and urothelial carcinoma (n=5) were all/mostly negative for CD56, with rare cases showing at most a 1+ staining pattern.

Table 1
Sensitivity and specificity of CD56 for eosinophilic vacuolated tumor using different percent cut-offs to define CD56 positivity

CD56 positivity criteria	Sensitivity	Specificity
1+/2+/3+ expression	95.0% (38/40)	73.9% (85/115)
2+/3+ expression	90.0% (36/40)	78.3% (90/115)
3+ expression	82.5% (33/40)	87.0% (100/115)

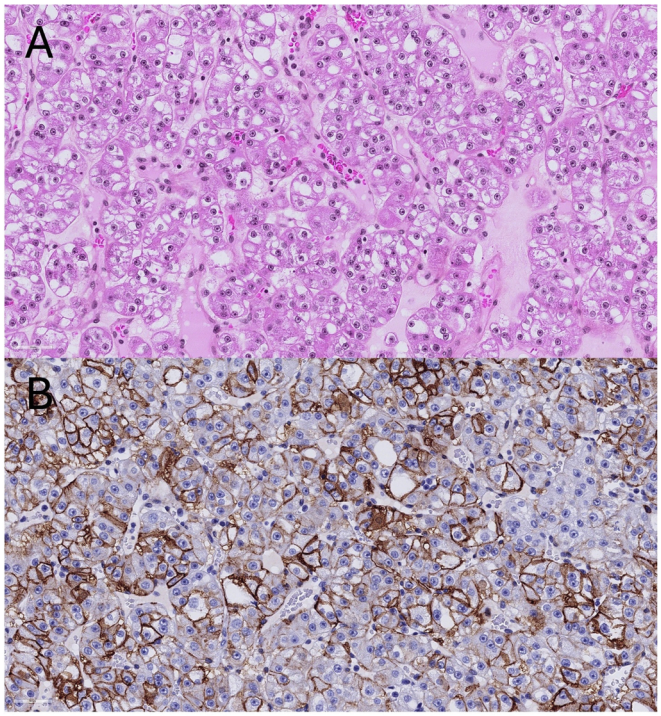


Figure 1. Diffuse CD56 expression in eosinophilic vacuolated tumor. (A) H&E, 400x magnification. (B) CD56, 400x magnification.

Figure 1 - 845.

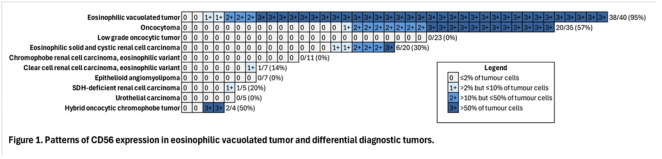


Figure 1. Patterns of CD56 expression in eosinophilic vacuolated tumor and differential diagnostic tumors.

Figure 2 - 845.

Conclusions: Our findings support the utility of CD56 as an adjunct diagnostic tool in the workup of kidney tumors (along with CD117, cathepsin K, GPNMB, KRT7, KRT20, SDHB, and CD10) when EVT is a consideration in the differential diagnosis. Diffuse CD56 showed high sensitivity and moderate specificity for EVT. Importantly, the presence of diffuse CD56 excluded most types of RCC except a small subset of ESC RCC.

Lab Invest 106 (2026) 105133

https://doi.org/10.1016/j.labinv.2025.105133

846 | Eosinophilic Vacuolated Tumor with Worrisome Morphologic Features May Have Metastatic Potential

Ngoc-Nhu Jennifer Nguyen[1], Michelle Hirsch[2], Liang Cheng[3], Maria Tretiakova[4], Abbas Agaimy[5], Asli Yilmaz[6], Farshid Siadat[7], Katrina Collins[8], Fadi Brimo[9], Büşra Yaprak Bayrak[10], Mahmut Akgul[11], Ting Zhao[12], Chin-Lee Wu[13], Michelangelo Fiorentino[14], Costantino Ricci[15], Ekta Jain[16], Cristina Magi-Galluzzi[16], Rola Saleeb[17], Andrew Evans[18], Khaleel Al-Obaidy[19], Michelle Downes[20], Dimitrios Korentzelos[21], Kiril Trpkov[7], Ankur Sangoi[22],

[1] *Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON;* [2] *Brigham and Women's Hospital, Boston, MA;* [3] *Alpert Medical School of Brown University, Providence, RI;* [4] *University of Washington, Seattle, WA;* [5] *Universitätsklinikum, Erlangen, Germany;* [6] *Alberta Precision Laboratories, University of Calgary, Calgary, AB;* [7] *University of Calgary, Calgary, AB;* [8] *Indiana University School of Medicine, Indianapolis, IN;* [9] *McGill University, Montreal, QC;* [10] *Kocaeli University School of Medicine, Izmit, Turkey;* [11] *Brigham and Women's Hospital, Harvard Medical School, Boston, MA;* [12] *Massachusetts General Hospital, Harvard Medical School, Boston, MA;* [13] *Massachusetts General Hospital, Boston, MA;* [14] *Alma Mater Studiorum-University of Bologna, Bologna, Italy;* [15] *S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy;* [16] *The University of Alabama at Birmingham, Birmingham, AL;* [17] *St. Michael's Hospital/University of Toronto, Toronto, ON;* [18] *University of Toronto, Vaughan, ON;* [19] *McLaren Health Pathology, Flint, MI;* [20] *Sunnybrook Health Sciences Centre, Toronto, ON;* [21] *University of Pittsburgh Medical Center, Pittsburgh, PA;* [22] *Stanford University, Stanford, CA*

Disclosures: Ngoc-Nhu Jennifer Nguyen: None; Michelle Hirsch: None; Liang Cheng: None; Maria Tretiakova: None; Abbas Agaimy: None; Asli Yilmaz: None; Farshid Siadat: None; Katrina Collins: None; Fadi Brimo: None; Büşra Yaprak Bayrak: None; Mahmut Akgul: None; Ting Zhao: None; Chin-Lee Wu: None; Michelangelo Fiorentino: None; Costantino Ricci: None; Ekta Jain: None; Cristina Magi-Galluzzi: None; Rola Saleeb: None; Andrew Evans: None; Khaleel Al-Obaidy: None; Michelle Downes: None; Dimitrios Korentzelos: None; Kiril Trpkov: None; Ankur Sangoi: None

Background: Eosinophilic vacuolated tumor (EVT) is described in the 2022 World Health Organization classification as an emerging renal tumor with *TSC1/TSC2/MTOR* mutation(s). Approximately 60 clinically indolent cases have been reported. However, we have encountered EVTs with potentially aggressive morphologic features. The frequency and clinical significance of these findings remain unknown and prompted the current study.

Design: Through multi-institutional collaboration, 36 EVTs resected between 2004 and 2025 were evaluated for worrisome morphologic features including invasion into large vessels, fat, the pelvicalyceal system, or lymphatic/small vessels, as well as increased mitotic activity, necrosis and large size (≥7 cm). EVTs were diagnosed using established diagnostic features, including eosinophilic cells with prominent cytoplasmic vacuoles and nucleoli plus immunohistochemistry (CD117, KRT7, KRT20, CD10 and/or cathepsin K). In a subset of EVTs, somatic tumor testing for *TSC1/TSC2/MTOR* variants was performed. Events (metastasis, recurrence, progression, and disease-specific death), treatment received, and clinical status at last follow-up were collected via review of the electronic patient records.

Results: Patient age ranged from 13 to 80 years (median 51). The M:F ratio was 1:1.8. EVTs were resected by partial (n=22) or radical (n=14) nephrectomy, with tumor size ranging from 1.1 to 15.5 cm (median 2.7). Eleven of 13 sequenced EVTs had a *TSC1* (n=2), *TSC2* (n=5) *or MTOR* (n=4) mutation. One additional patient had clinically suspected tuberous sclerosis. Seven of 36 (19.4%) EVTs had worrisome morphologic features (Table 1): 5 tumors measured ≥7 cm, 3 showed fat invasion (Figure 1), 2 had large vessel invasion (Figure 2), and 2 invaded lymphatic/small vessels. No increased mitotic activity or necrosis was identified. Median follow-up time for 17 patients was 12 months (range 1-67). One patient had regional lymph node (LN) metastases at nephrectomy with no progression on follow-up. Another patient with no nodal disease at presentation developed regional and distant LN metastases 9 and 24 months post nephrectomy, respectively. All patients were alive at last follow-up.

Table 1. Clinicopathologic characteristics and clinical outcomes of eosinophilic vacuolated tumors with worrisome morphologic features

Patient	Age (years)	Gender	Specimen	Tumor size (cm)	Actionable molecular alterations	Worrisome morphologic features	Events	Post-nephrectomy treatment	Clinical status at last follow-up	Follow-up time (months)
#1	59	M	Partial nephrectomy	7.5	*MTOR* mutation	• Large vessel invasion • Extensive lymphatic/small vessel invasion • Size ≥7 cm	• Regional lymph node metastases proven on biopsy (9 months after nephrectomy) • Distant lymph node metastases on imaging (24 months after nephrectomy)	• Adjuvant chemotherapy • Retroperitoneal lymph node dissection	Alive with distant lymph node metastases	29
#2	27	F	Radical nephrectomy and retroperitoneal lymph node dissection	7.0	*MTOR* mutation	• Renal sinus fat invasion • Size ≥7 cm	Regional lymph node metastases (at the time of nephrectomy)	None	Alive with no disease	4
#3	80	M	Radical nephrectomy	15.5	None	• Perinephric fat invasion • Renal sinus fat invasion • Lymphatic/small vessel invasion • Size ≥7 cm	None	None	Alive with no disease	3
#4	78	M	Partial nephrectomy	1.5	N/A	Perinephric fat invasion	None	None	Alive with no disease	12
#5	50	M	Partial nephrectomy	1.9	*MTOR* mutation	Large vessel invasion	None	None	Alive with no disease	10
#6	13	F	Radical nephrectomy	10.0	N/A	Size ≥7 cm	None	None	Alive with no disease	17
#7	73	M	Partial nephrectomy	7.0	None	Size ≥7 cm	None	None	Alive with no disease	11