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# Update on Gastrointestinal Pecomas: Molecular Pathogenesis and Risk Stratification

**Khandakar B**[*1,2,3]

[1]Department of Pathology and Laboratory Medicine, USA
[2]Donald and Barbara Zucker School of Medicine, Northwell Health, USA
[3]North Shore University Hospital and Long Island Jewish Medical Center, USA

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***Corresponding author:** Binny Khandakar, Department of Pathology and Laboratory Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Northwell Health and North Shore University Hospital and Long Island Jewish Medical Center, New York, USA, Email: binnykhandakar@gmail.com

## Abstract

Perivascular epithelioid cell tumors (PEComas) represent a rare family of mesenchymal neoplasms with distinctive morphological and immunophenotypic features. Gastrointestinal PEComas constitute an uncommon subset with variable clinical behavior, ranging from benign localized lesions to malignant and metastatic neoplasms. Accurate diagnosis requires integration of histologic features, immunohistochemical analysis demonstrating myomelanocytic differentiation, and exclusion of mimics such as gastrointestinal stromal tumors, metastatic melanoma, and epithelioid smooth muscle tumors.

Central to the pathogenesis of PEComas is dysregulation of the mTOR signaling pathway. TSC1 and TSC2 alterations underlie mTOR activation in a significant proportion of conventional PEComas, whereas a subset of cases harbor TFE3 gene rearrangements that define a biologically and clinically distinct subgroup. These molecular features not only clarify pathogenetic mechanisms but also support targeted therapeutic strategies, most notably mTOR inhibitors, which have demonstrated meaningful clinical activity in advanced or unresectable disease. Risk stratification remains challenging, as existing criteria—particularly those proposed by Folpe and colleagues—were developed from heterogeneous cohorts and incompletely predict behavior in gastrointestinal sites.

Emerging evidence suggests the incorporation of additional features such as Ki-67 index, necrosis, mitotic activity, and molecular alterations may improve prognostic accuracy. Comprehensive surgical excision remains the primary treatment for localized tumors, while systemic therapy, particularly mTOR pathway inhibition, is reserved for recurrent, unresectable, or metastatic disease. Continued multidisciplinary collaboration, expanded molecular profiling, and development of prospective registries are essential to refine risk prediction, therapeutic selection, and long-term management of gastrointestinal PEComas.

**Keywords:** PEComa; Gastrointestinal tract; mTOR pathway; TFE3 rearrangement; Molecular diagnostics; Targeted therapy

## Abbrevations

PEComas: Perivascular Epithelioid Cell Tumors; WHO: World Health Organization; PECs: Perivascular Epithelioid Cells; mTOR: Mammalian Target of Rapamycin; GAP: GTPase-Activating Protein; GIST: Gastrointestinal Stromal Tumor; CTOS: Connective Tissue Oncology Society; NGS: Comprehensive molecular profiling; LOH: Loss of Heterozygosity; CTOS: Connective Tissue Oncology Society; WHO: World Health Organization.

## Introduction

PEComas are uncommon mesenchymal neoplasms first recognized as a distinct entity by the World Health Organization (WHO) in 2002, subsequently refined in 2013 and 2020 classifications [1,2]. These tumors are characterized by perivascular epithelioid cells (PECs) exhibiting dual myomelanocytic differentiation, showing both smooth muscle and melanocytic immunophenotypic features [3].

While most commonly arising in the kidney and uterus, gastrointestinal tract involvement represents approximately 15-25% of extracutaneous PEComas [4,5]. The gastrointestinal PEComa family encompasses several entities, including clear cell "sugar" tumors and malignant PEComas. Understanding their molecular underpinnings, particularly mTOR pathway alterations, has significant diagnostic and therapeutic implications [6].

### Epidemiology and Clinical Features

**Demographics:** Gastrointestinal PEComas demonstrate a female predominance (approximately 3:1 ratio), typically presenting in the fourth to sixth decades of life [7,8]. However, cases across all age groups, including pediatric patients, have been documented [9]. Approximately 30% of patients with PEComas have tuberous sclerosis complex (TSC), though this association is less pronounced in gastrointestinal sites compared to retroperitoneal or uterine locations [10].

**Anatomic Distribution:** Within the gastrointestinal tract, PEComas most frequently involve the colon and rectum (30-40%), followed by the small intestine (20-25%), stomach (15-20%), and mesentery and omentum (10-15%) [4,11,12]. Other sites including pancreas, liver, and esophagus are rare.

**Clinical Presentation:** Most gastrointestinal PEComas present as incidental findings or with nonspecific symptoms. Abdominal pain or discomfort occurs in 40-50% of cases, gastrointestinal bleeding in 15-25%, palpable mass in 10-15%, while obstruction is rare [13,14]. Incidental imaging findings account for 20-30% of cases.

### Pathologic Features

**Gross Pathology:** Gastrointestinal PEComas typically present as well-circumscribed, solid masses ranging from 1 to 20 cm with a median size of 4-6 cm [15]. The cut surface varies from tan-white to gray, occasionally with hemorrhage or necrosis in larger or malignant examples. Most tumors are intramural, though submucosal and subserosal variants occur [16].

### Microscopic Features

The histologic spectrum of PEComas is broad, but characteristic features can be identified [17,18]. The cellular composition typically consists of epithelioid to spindle cells with clear to granular eosinophilic cytoplasm, distinct cell borders, vesicular nuclei with small nucleoli, and a characteristic perivascular arrangement. Cells often display a radial arrangement around vessels creating a nesting or pseudopapillary pattern.

Regarding cytoplasmic features, the clear cytoplasm results from glycogen accumulation (PAS-positive, diastase-sensitive), while granular eosinophilic cytoplasm reflects abundant mitochondria and smooth muscle differentiation [19]. Architecturally, PEComas may display nested or alveolar patterns (most common), fascicular patterns, pseudopapillary patterns, solid sheets, or mixed patterns.

The vascular component is characteristic, with PEComas demonstrating intimate association with blood vessels and tumor cells radiating from thin-walled or ectatic vessels [20].

**Immunohistochemistry:** The diagnostic immunophenotype reflects myomelanocytic differentiation [21,22]. Melanocytic markers are typically positive, including HMB-45 (80-100% positive, most sensitive), Melan-A/MART-1 (70-90%), MiTF (60-80%), and cathepsin K (variable). Smooth muscle markers show variable positivity: SMA (60-80%), desmin (30-60%), caldesmon (30-50%), and MSA (50-70%).

PEComas are typically negative for S100 protein (usually negative, occasionally focal), cytokeratins, CD117/c-KIT, DOG1, and CD34 (negative in tumor cells but highlights vessels). The combination of HMB-45 and SMA positivity is highly characteristic and aids in distinguishing PEComas from other gastrointestinal mesenchymal tumors, particularly gastrointestinal stromal tumors (GISTs) [23].

**Molecular Markers:** Immunohistochemistry for phosphorylated ribosomal S6 protein (p-S6), a downstream target of mTOR, is positive in most PEComas and reflects pathway activation [24]. Cathepsin K positivity has emerged as a useful adjunct marker [25].

## Molecular Pathogenesis

**Mtor Pathway Dysregulation:** The fundamental molecular aberration in PEComas involves constitutive activation of the mammalian target of rapamycin (mTOR) pathway, a central regulator of cell growth, proliferation, metabolism, and angiogenesis [26,27]. The TSC1-TSC2 complex functions as a GTPase-activating protein (GAP) for RHEB (Ras homolog enriched in brain). In its GDP-bound state, RHEB is inactive; however, when bound to GTP, RHEB potently activates mTOR complex 1 (mTORC1) [28].

The TSC1-TSC2 complex promotes conversion of RHEB-GTP to RHEB-GDP, thereby inhibiting mTORC1. Loss of TSC1 or TSC2 function results in accumulation of RHEB-GTP, constitutive mTORC1 activation, hyperactivation of downstream effectors (S6K, 4E-BP1), enhanced protein synthesis and cell growth, and metabolic reprogramming [29].

## Genetic Alterations

- **TSC1/TSC2 Inactivation:** Germline mutations in TSC1 (chromosome 9q34) or TSC2 (chromosome 16p13.3) cause tuberous sclerosis complex, a multisystem disorder with hamartomatous manifestations [30]. Patients with TSC have increased susceptibility to PEComas, particularly in kidney and liver.

In sporadic PEComas (without TSC), somatic alterations affecting TSC1/TSC2 occur in approximately 40-50% of cases [31,32]. These alterations include loss of heterozygosity (LOH), point mutations, deletions, and epigenetic silencing.

- **FE3 Gene Rearrangements:** A subset of PEComas (15-30%) harbor TFE3 gene fusions involving chromosome Xp11.2 [33,34]. TFE3 belongs to the MiTF/TFE family of transcription factors that regulate lysosomal biogenesis and autophagy. Common TFE3 fusion partners include PSF-TFE3, SFPQ-TFE3, DVL2-TFE3, and NONO-TFE3.

TFE3-rearranged PEComas show distinctive features including nested/alveolar architecture, abundant clear cytoplasm, strong nuclear TFE3 immunoreactivity, often weaker or absent HMB-45 expression, younger patient age, and association with TSC1/TSC2 wild-type status [35]. TFE3 fusions drive tumorigenesis through constitutive transcriptional activation, upregulation of E-box genes, enhanced melanocytic and autophagy programs, and possible mTOR pathway cross-activation [36].

**Other Molecular Alterations:** Additional recurrent alterations include RAD51B rearrangements (rare) [37], NTRK3 fusions (rare) [38], TP53 mutations (associated with malignant behavior) [39], PTEN loss (alternative mechanism of mTOR activation) [40], and PIK3CA mutations (activate PI3K-AKT-mTOR pathway) [41].

## Signaling Pathway Integration

The pathogenesis of PEComas involves convergence on mTOR pathway hyperactivation through multiple mechanisms [42]. These include direct mTORC1 activation through TSC1/TSC2 loss, upstream activation via PI3K-AKT pathway alterations (PIK3CA mutations, PTEN loss), transcriptional programs driven by TFE3 fusions promoting growth and melanocytic differentiation, and metabolic reprogramming with enhanced glycolysis and biosynthetic capacity.

This molecular framework explains the myomelanocytic phenotype (MiTF/TFE regulation of melanocytic genes), sensitivity to mTOR inhibitors, morphologic diversity, and variable biological behavior [43].

## Implications For Targeted Therapy

Understanding mTOR pathway dependence has therapeutic implications. mTOR inhibitors (sirolimus, everolimus) demonstrate efficacy in advanced PEComas [44,45], with objective response rates of 40-50% and disease stabilization in an additional 30-40%. These agents are particularly effective in TSC-associated and metastatic disease.

Mechanisms of resistance include feedback activation of PI3K-AKT pathway, alternative proliferative signals, and tumor heterogeneity [46].

## Differential Diagnosis

Gastrointestinal PEComas must be distinguished from several entities.

## Gastrointestinal Stromal Tumor (GIST)

Key distinguishing features separate GISTs from PEComas. GISTs are CD117+, DOG1+, and melanocytic markers negative, while PEComas are HMB-45+, CD117-, and DOG1-. Molecularly, GISTs harbor KIT or PDGFRA mutations [47].

**Clear Cell Sarcoma (Soft Tissue Melanoma):** Clear cell sarcoma shows S100 strong positivity and harbors EWSR1-ATF1 or EWSR1-CREB1 fusions, while PEComas are typically S100 negative and have TSC or TFE3 alterations. Additionally, clear cell sarcoma shows more consistent melanocytic differentiation with melanin [48].

**Epithelioid Smooth Muscle Tumors:** Epithelioid smooth muscle tumors have melanocytic markers that are negative or focal, show conventional smooth muscle marker patterns, and may overlap in morphology, requiring a panel approach [49].

### Melanoma

Melanoma is S100 diffusely positive and often shows melanin pigment, while clinical correlation is essential. Molecularly, BRAF, NRAS, and NF1 mutations are common in melanoma [50].

### Paraganglioma

Paragangliomas are chromogranin and synaptophysin positive with sustentacular cells that are S100+, while PEComas have negative neuroendocrine markers. Paragangliomas may show clear cytoplasm and nesting [51].

**Renal Cell Carcinoma (Metastatic):** Renal cell carcinomas are PAX8+, cytokeratin+, and melanocytic markers negative (except rare cases), while PEComas are PAX8- and cytokeratin-. Clinical and radiologic correlation is important [52].

**Risk Stratification:** Accurate risk assessment is critical for management decisions. Multiple classification systems have been proposed.

**Folpe Criteria (2005)**: Folpe AL, et al. [53] proposed the most widely used system based on analysis of 26 PEComas (including non-gastrointestinal sites) [53]. The worrisome/malignant features include size ≥5 cm, infiltrative growth pattern, high nuclear grade, high cellularity, mitotic activity ≥1/50 HPF, necrosis, and vascular invasion.

Risk categories are defined as benign (no worrisome features), uncertain malignant potential (nuclear pleomorphism/multinucleated giant cells ONLY, or size >5 cm ONLY), and malignant (≥2 of the above features). Clinical correlation shows that the metastatic rate in the malignant category is approximately 50%, the benign category shows rare recurrence or metastasis, and the uncertain potential category demonstrates intermediate behavior (10-15% adverse outcomes).

### Limitations Of Folpe Criteria

Several limitations have been recognized. The criteria were based on heterogeneous anatomic sites with a small sample size. Some "benign" PEComas have metastasized, the system does not incorporate molecular features, and gastrointestinal-specific behavior may differ [54].

### Modified Risk Stratification Systems

**Schoolmeester JK, et al. [55] - Gynecologic PEComas:** This system proposed refined criteria for uterine PEComas, identifying high-risk features [55]. Size >5 cm receives 2 points, while infiltrative growth, high nuclear grade, mitoses ≥1/50 HPF, necrosis, and vascular invasion each receive 1 point. A score ≥4 indicates high risk for recurrence/metastasis.

**Doyle Criteria (2014):** Doyle emphasized that even tumors lacking classic malignant features may behave aggressively [56]. The criteria proposed close follow-up for all PEComas >3 cm or with any concerning features.

### Gastrointestinal-Specific Considerations

Limited data specific to gastrointestinal PEComas suggest certain high-risk features [57,58]. These include size >8 cm (may be more relevant than 5 cm cutoff), significant necrosis (>10% tumor area), mitotic activity >2/50 HPF, marked nuclear atypia, infiltrative borders, and lymphovascular invasion.

Additional predictive factors include Ki-67 proliferative index >10% associated with aggressive behavior [59], TP53 alterations suggesting worse prognosis [39], and TFE3-rearranged PEComas with variable behavior requiring further study [60].

### Proposed Integrated Risk Assessment

An integrated approach incorporating traditional histologic parameters and molecular features is proposed. Low risk tumors have size <5 cm, are well-circumscribed, show low nuclear grade, have mitoses <1/50 HPF, no necrosis, no vascular invasion, and Ki-67 <5%.

Intermediate risk tumors have size 5-8 cm OR focal infiltration OR moderate nuclear atypia OR mitoses 1-2/50 HPF OR Ki-67 5-10%. High risk tumors have size >8 cm OR diffuse infiltration OR high nuclear grade OR mitoses >2/50 HPF OR necrosis present OR vascular invasion present OR Ki-67 >10% OR TP53 mutation.

This system requires validation in larger gastrointestinal PEComa cohorts.

### Molecular Diagnostics

**Immunohistochemical Approaches:** A standard diagnostic panel should include melanocytic markers (HMB-45 mandatory, Melan-A, MiTF), myoid markers (SMA, desmin), exclusionary markers (S100, cytokeratins, CD117, DOG1), proliferation marker Ki-67, pathway activation marker p-S6 (indicates mTOR activation), and TFE3 (nuclear staining suggests rearrangement) [61].

**Molecular Testing:**

**FISH (Fluorescence In Situ Hybridization):** TFE3 break-apart probe identifies TFE3 rearrangements and is particularly useful when HMB-45 is weak/negative but

morphology is suggestive [62].

**Next-Generation Sequencing (NGS):** Comprehensive genomic profiling can identify TSC1/TSC2 mutations/deletions, gene fusions (TFE3, RAD51B, NTRK), TP53 alterations, PIK3CA/PTEN alterations, and therapeutic targets [63].

**Copy Number Analysis:** Copy number analysis may detect TSC1/TSC2 deletions and assess for complex genomic alterations in aggressive tumors.

### Molecular Features and Prognosis

Emerging evidence suggests molecular subgroups correlate with behavior. TSC-altered PEComas show classic myomelanocytic phenotype, variable behavior based on histologic features, and are mTOR inhibitor responsive [64].

TFE3-rearranged PEComas occur in younger patients, often show aggressive features (large size, necrosis), have uncertain response to mTOR inhibitors, and may benefit from TFE3-directed therapies under investigation [65]. TP53-mutated PEComas are associated with malignant histology, higher proliferation, worse prognosis, and potential resistance to standard therapies [39].

### Clinical Management

**Surgical Resection:** Complete surgical excision remains the primary treatment for localized gastrointestinal PEComas [66]. This includes wide local excision with negative margins, while lymphadenectomy is generally not indicated as nodal metastases are rare. Laparoscopic versus open approach depends on size and location. The 5-year disease-free survival after R0 resection is 60-80% for low-risk tumors and 30-50% for high-risk tumors.

### Adjuvant Therapy

**mTOR Inhibitors:** For high-risk or incompletely resected tumors, mTOR inhibitors are considered [67,68]. Sirolimus (Rapamycin) 2-6 mg daily (target trough 5-15 ng/mL) or Everolimus (Afinitor) 10 mg daily may be used.

The evidence basis includes case series showing disease stabilization, responses in TSC-associated PEComas, though limited randomized data exists with mostly case reports and small series. Duration is typically continued until progression or intolerable toxicity, though optimal duration is undefined.

**Conventional Chemotherapy:** Limited efficacy has been reported with anthracycline-based regimens and gemcitabine/docetaxel. These are generally reserved for mTOR-resistant progressive disease [69].

### Advanced/Metastatic Disease

For unresectable or metastatic PEComas [70,71], first-line therapy consists of mTOR inhibitors (sirolimus or everolimus) with response rates of 40-50% and disease stabilization in an additional 30-40%.

Second-line options include clinical trials when available, chemotherapy (doxorubicin-based, gemcitabine/docetaxel), and combination strategies (mTOR inhibitor + PI3K inhibitor under investigation). Targeted therapy for fusion-positive tumors includes MET inhibitors under investigation for TFE3-rearranged tumors (based on TFE3 target genes) and NTRK inhibitors (larotrectinib, entrectinib) for NTRK-rearranged tumors, which are rare but actionable.

Regarding immunotherapy, data is limited and PD-L1 expression is variable, though case reports of responses to checkpoint inhibitors exist [72].

### Surveillance

Risk-stratified follow-up is recommended [73]. For low-risk tumors, clinical exam and imaging (CT/MRI) should be performed every 6 months for 2 years, then annually for 5 years, as most recurrences occur within 3 years.

For intermediate/high-risk tumors, surveillance should occur every 3-4 months for 2 years, every 6 months for years 3-5, annually thereafter, with lifelong surveillance given that late recurrences have been reported.

Regarding imaging modalities, CT chest/abdomen/pelvis is preferred, MRI for selected cases, and PET-CT may identify metabolically active disease.

## Future Directions

### Molecular Therapeutics

Ongoing research focuses on dual PI3K/mTOR inhibitors to overcome feedback activation [74], AKT inhibitors to target upstream pathway components, autophagy modulation based on TFE3 biology, and combination strategies including mTOR inhibitor plus chemotherapy or targeted agents.

### Biomarker Development

Areas of investigation include circulating tumor DNA (ctDNA) for monitoring, predictive biomarkers for mTOR inhibitor response, resistance mechanisms, and immune microenvironment characterization [75].

### Molecular Classification

Efforts are underway toward comprehensive molecular taxonomy integrating transcriptomic profiling, methylation patterns, proteomic signatures, and clinical-molecular correlations.

### Rare Fusion Partners

Work continues on identification and characterization of novel fusion events, their functional consequences, and specific therapeutic vulnerabilities.

## Discussion

### Integration of Molecular and Morphologic Features

The evolving understanding of gastrointestinal PEComa pathogenesis demonstrates the critical interplay between molecular alterations and morphologic phenotype. The recognition that mTOR pathway hyperactivation represents the central pathogenic mechanism unifies our understanding of these diverse tumors. This molecular framework not only explains the characteristic myomelanocytic differentiation but also provides rational therapeutic targets. The demonstration that most PEComas, regardless of TSC mutation status, exhibit activation of mTOR signaling (as evidenced by p-S6 positivity) validates the use of mTOR inhibitors across the spectrum of these neoplasms.

However, the identification of TFE3-rearranged PEComas as a distinct molecular subset challenges the notion of PEComas as a homogeneous entity. These fusion-positive tumors demonstrate several distinctive features: they occur in younger patients, often lack or show weak HMB-45 expression (which can create diagnostic challenges), and are associated with wild-type TSC1/TSC2 genes. The mechanism by which TFE3 fusions lead to the PEComa phenotype remains incompletely understood, though transcriptional activation of melanocytic differentiation programs and possible cross-talk with mTOR signaling pathways are implicated. Whether TFE3-rearranged PEComas respond similarly to mTOR inhibitors as TSC-altered tumors remains an open question requiring further clinical investigation.

The presence of TP53 mutations in a subset of aggressive PEComas adds another layer of molecular complexity. TP53 alterations are well-established drivers of malignant behavior across cancer types, and their presence in PEComas appears to confer worse prognosis. This finding suggests that comprehensive molecular profiling may refine risk stratification beyond traditional histologic parameters. As next-generation sequencing becomes more accessible, integration of molecular features (TSC1/TSC2 status, TFE3 rearrangements, TP53 mutations, PIK3CA alterations) with morphologic assessment may enable more personalized prognostication and treatment selection.

### Diagnostic Challenges and Practical Approaches

Despite characteristic features, diagnosis of gastrointestinal PEComas can be challenging. The histologic spectrum is broad, with varying proportions of epithelioid versus spindle cells, clear versus eosinophilic cytoplasm, and different architectural patterns. Some cases may show predominantly spindle cell morphology mimicking smooth muscle tumors, while others with clear cell morphology may suggest metastatic renal cell carcinoma or clear cell sarcoma.

The immunohistochemical profile, while distinctive, is not absolute. Not all PEComas express all melanocytic markers, and the intensity of staining can vary. HMB-45 remains the most sensitive marker, but TFE3-rearranged PEComas may show weak or absent staining, creating potential diagnostic pitfalls. In such cases, nuclear TFE3 immunoreactivity should prompt consideration of FISH analysis for TFE3 rearrangement. Conversely, focal or weak expression of melanocytic markers in what otherwise appears to be a smooth muscle tumor should raise consideration of PEComa.

The differential diagnosis with GIST is particularly important in the gastrointestinal tract. Both can present as intramural masses with epithelioid morphology. However, the immunophenotypes are essentially mutually exclusive: GISTs express CD117 and DOG1 but lack melanocytic markers, while PEComas show the reverse pattern. In rare cases where immunohistochemistry is ambiguous, molecular testing for KIT/PDGFRA mutations (supporting GIST) versus TSC1/TSC2 alterations or TFE3 rearrangements (supporting PEComa) can be definitive.

The practical approach to diagnosis should include a comprehensive immunohistochemical panel upfront, incorporating melanocytic markers (HMB-45, Melan-A, MiTF), myoid markers (SMA, desmin), and exclusionary markers (S100, cytokeratins, CD117, DOG1). Addition of TFE3 immunohistochemistry is increasingly recommended, particularly for tumors with weak melanocytic marker expression or in younger patients. Proliferative index (Ki-67) and p-S6 (indicating mTOR pathway activation) provide additional diagnostic and prognostic information.

### Risk Stratification: Current State and Future Refinements

Risk stratification of gastrointestinal PEComas remains imperfect. The Folpe criteria, while widely used, were

developed from a heterogeneous cohort including various anatomic sites, and their applicability to gastrointestinal PEComas specifically requires validation. The finding that some tumors lacking traditional malignant features have metastasized indicates that our current risk assessment tools are inadequate.

Several issues complicate risk stratification. First, the optimal size cutoff for gastrointestinal PEComas may differ from other sites. While 5 cm is the standard threshold in Folpe criteria, some evidence suggests that 8 cm may be more predictive for gastrointestinal lesions. This site-specific variation likely reflects differences in clinical detection (gastrointestinal tumors may be detected earlier due to symptoms) and biological behavior.

Second, the binary assessment of features (present/absent) in Folpe criteria may not capture the full spectrum of risk. For example, is a tumor with 2 mitoses per 50 HPF equivalent in risk to one with 20 mitoses per 50 HPF? Both would be classified as "malignant" by having ≥1 mitosis per 50 HPF plus one other feature, yet clinical experience suggests quantitative differences in mitotic activity correlate with outcome. The Schoolmeester scoring system for gynecologic PEComas attempts to address this by creating a weighted point system, though it requires validation for gastrointestinal sites.

Third, current systems do not incorporate molecular features, which increasingly appear prognostically relevant. Integration of TP53 mutation status, proliferative index (Ki-67), and possibly TFE3 rearrangement status into risk models may improve predictive accuracy. The proposed integrated risk assessment presented in this review represents an attempt to synthesize traditional morphologic parameters with emerging molecular markers, but prospective validation in large cohorts is essential.

Fourth, the category of "uncertain malignant potential" in the Folpe system encompasses a heterogeneous group with intermediate outcomes (10-15% adverse events). Better stratification of this group would enable more tailored management. Some features traditionally considered worrisome, such as nuclear pleomorphism alone, may not carry significant risk in the absence of other findings, while combinations of features in the intermediate range (moderate mitotic activity, moderate nuclear atypia, intermediate size) may warrant closer surveillance.

The rarity of gastrointestinal PEComas makes development of validated, site-specific risk stratification systems challenging. Multi-institutional collaborative efforts and tumor registries will be essential to accumulate sufficient cases for robust statistical analysis. International collaboration, such as through organizations like the Connective Tissue Oncology Society (CTOS), may facilitate such efforts.

**Therapeutic Implications of Molecular Insights:** The recognition that mTOR pathway dysregulation is central to PEComa pathogenesis represents a paradigm of molecularly-targeted therapy. The clinical efficacy of mTOR inhibitors (sirolimus, everolimus) in advanced PEComas, while based primarily on case series and small cohort studies, demonstrates meaningful responses where chemotherapy has shown limited benefit. Response rates of 40-50% with additional disease stabilization in 30-40% represent substantial clinical activity for a soft tissue sarcoma.

However, several therapeutic challenges remain. First, not all patients respond to mTOR inhibitors, and mechanisms of primary resistance are poorly understood. While TSC1/TSC2-altered tumors are most clearly mTOR-dependent, whether TFE3-rearranged PEComas show similar sensitivity remains unclear. Prospective studies correlating molecular subtype with treatment response are needed.

Second, resistance to mTOR inhibition, when it develops, may result from feedback activation of upstream signaling (particularly PI3K-AKT pathway) or activation of alternative proliferative signals. This mechanism of resistance has been well-documented in other mTOR-dependent cancers and has motivated investigation of dual PI3K/mTOR inhibitors or combination strategies. In PEComas, rational combination approaches might include mTOR inhibitors with PI3K or AKT inhibitors, though toxicity of such combinations requires careful evaluation.

Third, the optimal duration and timing of mTOR inhibitor therapy remain undefined. Should high-risk localized PEComas receive adjuvant mTOR inhibition after complete resection? Current practice varies, with some centers offering adjuvant therapy for tumors with multiple high-risk features while others reserve mTOR inhibitors for recurrent or metastatic disease. The lack of randomized data makes evidence-based recommendations difficult. Given the generally chronic disease course and the need for prolonged therapy when mTOR inhibitors are used, patient selection and discussion of risks/benefits are critical.

Fourth, the identification of rare but actionable alterations such as NTRK fusions expands the therapeutic landscape. While NTRK fusions are rare in PEComas, their presence predicts dramatic responses to NTRK inhibitors (larotrectinib, entrectinib) based on experience in other tumor types. This finding reinforces the value of comprehensive molecular profiling, particularly for advanced or treatment-refractory cases.

The role of conventional chemotherapy in PEComas remains limited and poorly defined. Anthracycline-based regimens, the backbone of soft tissue sarcoma chemotherapy, show modest activity at best. Gemcitabine/docetaxel combinations have demonstrated some responses, but consistent efficacy data are lacking. Chemotherapy is generally considered for patients with progressive disease despite mTOR inhibition or those who cannot tolerate targeted therapy.

Immunotherapy represents an emerging area of interest. Limited data exist on immune checkpoint inhibitor efficacy in PEComas, though case reports of responses have been published. The immune microenvironment of PEComas is incompletely characterized, with variable PD-L1 expression reported. Further investigation of immune features and immunotherapy trials for PEComas are warranted, particularly as combination strategies (immunotherapy plus targeted therapy) show promise in other sarcoma subtypes.

## Surveillance and Long-Term Management

The natural history of gastrointestinal PEComas, particularly low-risk tumors after complete resection, remains incompletely defined due to rarity and relatively short follow-up in most published series. Most recurrences occur within the first 3 years after resection, though late recurrences beyond 5 years have been documented, justifying extended surveillance.

Risk-stratified surveillance protocols balance the need to detect recurrent disease at a treatable stage against the costs, radiation exposure, and patient burden of frequent imaging. For low-risk tumors (small, well-circumscribed, low mitotic activity, no necrosis), less intensive surveillance may be appropriate, though consensus on minimal follow-up is lacking. For high-risk tumors, more aggressive surveillance is clearly indicated given the substantial risk of recurrence.

The optimal imaging modality remains debated. CT provides excellent anatomic detail and is widely available, though involves radiation exposure—a consideration for younger patients requiring years of surveillance. MRI offers similar anatomic resolution without radiation and may be preferred for selected patients, particularly children or young adults. PET-CT may provide functional information about metabolically active disease and could be considered for staging or assessing response to therapy, though its role in routine surveillance is unclear.

Pattern of recurrence influences surveillance strategies. Gastrointestinal PEComas most commonly recur in the liver or peritoneum, though lung metastases also occur. This pattern suggests that abdominal and chest imaging should be included in surveillance protocols. The rarity of lymph node metastases indicates that routine nodal imaging beyond what is captured in standard chest/abdomen/pelvis CT is not necessary.

Quality of life considerations are important for patients requiring long-term surveillance and potentially chronic mTOR inhibitor therapy. The side effects of mTOR inhibitors—including mucositis, fatigue, metabolic disturbances, and immunosuppression—can significantly impact daily functioning. Balancing disease control with quality of life requires ongoing communication and shared decision-making. For some patients with slow-growing metastatic disease, intermittent therapy or drug holidays may be appropriate, though evidence supporting such approaches is limited.

## Pathologist's Role and Reporting Standards

The pathologist plays a critical role in PEComa diagnosis and risk assessment. Given the rarity of these tumors and the evolving understanding of their molecular features, pathologists should maintain a low threshold for consultation with colleagues experienced in soft tissue pathology when encountering potential PEComas.

Comprehensive pathology reporting should include specific elements that enable clinicians to make informed treatment decisions. Standard elements should include tumor size, anatomic location and depth, histologic subtype and architecture, cytologic features (epithelioid vs. spindle, clear vs. eosinophilic cytoplasm), nuclear grade, mitotic count per 50 HPF, presence/extent of necrosis, growth pattern (circumscribed vs. infiltrative), lymphovascular invasion, margin status, and stage if applicable.

Immunohistochemical results should be reported comprehensively, including both positive and negative markers. Reporting the intensity and extent of staining (e.g., "HMB-45: positive in 80% of tumor cells, strong intensity") provides more information than simple positive/negative designation. Ki-67 proliferative index should be reported as a percentage.

When molecular testing is performed, results should be clearly reported with interpretation. FISH results for TFE3 should specify whether rearrangement is present. NGS results should highlight actionable alterations and provide information on coverage and quality metrics.

Application of risk stratification criteria (Folpe or other system) should be explicit, with clear documentation of which features are present. A synthesis statement providing an overall assessment (e.g., "This tumor shows 3 of 7 Folpe

criteria for malignancy, placing it in the malignant/high-risk category") helps clinicians understand risk.

Recommendations for additional studies when appropriate (e.g., "Given weak HMB-45 expression, TFE3 immunohistochemistry or FISH may be informative") demonstrate thoughtful diagnostic approach and can guide additional workup.

## Gaps in Knowledge and Research Priorities

Despite advances in understanding PEComas, significant knowledge gaps remain. The pathogenesis of tumors without identifiable TSC1/TSC2 alterations or TFE3 rearrangements is unclear. What drives mTOR activation in these cases? Are there additional genetic or epigenetic mechanisms yet to be discovered? Comprehensive genomic studies including whole genome sequencing, transcriptomics, and epigenetic profiling may identify novel pathogenic mechanisms.

The cell of origin for PEComas remains debated. While the perivascular epithelioid cell is defined by its morphologic and immunophenotypic features, whether this represents a distinct normal cell population or a phenotype acquired through oncogenic transformation is unclear. Developmental studies and lineage tracing experiments could provide insights, though the rarity of these tumors makes such studies challenging.

The biology of TFE3-rearranged PEComas deserves focused investigation. How do TFE3 fusions create the myomelanocytic phenotype? What is the relationship between TFE3 and mTOR signaling in these tumors? Do TFE3-rearranged PEComas respond to mTOR inhibitors, and if so, through what mechanism? Clinical trials specifically enrolling TFE3-rearranged PEComas could address therapeutic questions.

Predictive biomarkers for mTOR inhibitor response are needed. While pathway activation (p-S6 positivity) indicates mTOR activity, it does not perfectly predict therapeutic response. Are there genomic, transcriptomic, or proteomic signatures that distinguish responders from non-responders? Can we identify resistance mechanisms prospectively? Development and validation of predictive biomarkers would enable more rational patient selection for targeted therapy.

The role of the immune microenvironment in PEComas is virtually unexplored. What immune cell populations infiltrate these tumors? Is there evidence of immune evasion mechanisms? Do PEComas with different molecular subtypes show distinct immune profiles? Comprehensive immune profiling could identify opportunities for immunotherapy and inform combination strategies.

Natural history studies with long-term follow-up are needed to understand the true behavior of PEComas across the risk spectrum. Many published series have relatively short median follow-up, and late recurrences may be underappreciated. Registry studies with extended follow-up would provide valuable prognostic data and could identify clinical or pathologic factors associated with late recurrence.

Quality of life and patient-reported outcome studies are lacking. What is the impact of diagnosis, treatment, and surveillance on patients' lives? How do patients perceive the balance between treatment benefits and side effects? Such studies could inform supportive care interventions and shared decision-making.

## Clinical Practice Recommendations

Based on current evidence, several clinical practice recommendations can be made, recognizing that the rarity of these tumors limits high-quality evidence. Complete surgical resection with negative margins should be attempted for all localized gastrointestinal PEComas when feasible. Pre-operative biopsy is appropriate to establish diagnosis, guide surgical planning, and enable molecular profiling that may inform adjuvant therapy decisions.

Comprehensive pathologic evaluation including morphologic assessment, full immunohistochemical panel, proliferative index, and consideration of molecular testing (particularly TFE3 immunohistochemistry and/or FISH, NGS for high-risk or recurrent tumors) should be standard. Multidisciplinary discussion including surgical oncology, medical oncology, and pathology is recommended for all cases.

Risk stratification using established criteria (Folpe or modified systems) should be performed, recognizing limitations and incorporating molecular features when available. For high-risk tumors (particularly those with incomplete resection, multiple adverse features, or TP53 mutations), discussion of adjuvant mTOR inhibitor therapy is reasonable, though benefits remain unproven. Patient preference and tolerance for side effects should guide decisions.

Risk-stratified surveillance with clinical examination and cross-sectional imaging (CT or MRI) of chest, abdomen, and pelvis should be implemented. Surveillance intensity and duration should reflect tumor risk level, with more aggressive follow-up for high-risk tumors and extended surveillance given potential for late recurrence.

For unresectable, recurrent, or metastatic disease, mTOR inhibitor therapy (sirolimus or everolimus) represents first-line systemic treatment based on best available evidence. Enrollment in clinical trials should be encouraged when available. Conventional chemotherapy or experimental agents may be considered for mTOR inhibitor-refractory disease.

Comprehensive molecular profiling (NGS) should be strongly considered for advanced disease to identify rare actionable alterations (NTRK fusions, etc.) that may guide targeted therapy selection. Consultation with sarcoma specialists at high-volume centers is recommended for management of advanced disease.

## Future Perspectives

The field of PEComa research and clinical management is rapidly evolving. Integration of advanced molecular techniques into routine practice will likely refine our diagnostic and prognostic approaches. Single-cell sequencing technologies may provide unprecedented insight into PEComa biology, revealing tumor heterogeneity and identifying rare cell populations that drive progression or resistance.

Liquid biopsy approaches using circulating tumor DNA may enable non-invasive monitoring of disease and early detection of recurrence. Such technologies could reduce the imaging burden for patients under surveillance and provide molecular insights into disease evolution.

Precision medicine approaches will increasingly guide therapy selection. Beyond mTOR inhibitors, emerging targeted therapies directed at specific molecular vulnerabilities may expand treatment options. For TFE3-rearranged tumors, agents targeting TFE3-driven transcriptional programs or downstream effector pathways are under investigation in other fusion-positive sarcomas and may prove applicable to PEComas.

Combination therapeutic strategies will likely be necessary to overcome resistance and improve outcomes. Rational combinations might include mTOR inhibitors with PI3K/AKT inhibitors, immunotherapy, or chemotherapy. Preclinical models of PEComas, currently limited, would accelerate evaluation of such combinations.

International collaboration through networks like CTOS and sarcoma registries will be essential for advancing knowledge about these rare tumors. Standardized data collection, tissue banking, and collaborative clinical trials will enable progress impossible for individual institutions.

Patient advocacy and engagement will play important roles in driving research and improving care. As patients become more informed and connected through social media and patient organizations, their voices will shape research priorities and clinical trial design.

## Conclusion

Gastrointestinal PEComas represent a distinctive group of mesenchymal neoplasms characterized by myomelanocytic differentiation and mTOR pathway dysregulation. Accurate diagnosis requires integration of morphologic features, comprehensive immunohistochemistry, and increasingly, molecular characterization. Recognition of molecular subgroups, particularly TFE3-rearranged tumors, expands our pathogenetic understanding and may identify specific therapeutic vulnerabilities.

Risk stratification using established histologic criteria, supplemented by proliferative indices and molecular markers, guides management decisions, though current systems require refinement and validation for gastrointestinal sites specifically. Complete surgical resection remains the cornerstone of treatment for localized disease, with mTOR inhibitors providing rational targeted therapy for high-risk, unresectable, or metastatic PEComas based on pathway biology.

Despite substantial progress in understanding PEComas, significant questions remain regarding pathogenesis, optimal risk stratification, predictive biomarkers for therapy response, and long-term outcomes. The rarity of gastrointestinal PEComas necessitates collaborative multi-institutional efforts, comprehensive tumor registries, and well-designed clinical trials to advance the field.

Pathologists play a critical role in accurate diagnosis, comprehensive characterization, and appropriate risk assessment of these tumors. As molecular diagnostics become more accessible, integration of genomic information with traditional morphologic and immunophenotypic assessment will enable increasingly personalized diagnosis and prognostication.

Future advances will likely include refined molecular taxonomy, development of predictive biomarkers, novel targeted therapies beyond mTOR inhibition, and rational combination strategies. Liquid biopsy technologies may enable non-invasive monitoring, while deeper understanding of tumor biology will identify additional therapeutic vulnerabilities.

For clinicians managing patients with gastrointestinal PEComas, a multidisciplinary approach incorporating

surgical oncology, medical oncology, pathology, and radiology expertise optimizes outcomes. Risk-stratified surveillance enables early detection of recurrence, while targeted therapies based on molecular features provide treatment options for advanced disease.

The evolving understanding of gastrointestinal PEComas exemplifies precision medicine in oncology—integration of molecular insights with clinical and pathologic features to guide individualized management. Continued research, international collaboration, and patient engagement will drive further progress in improving outcomes for patients with these rare and biologically fascinating tumors.

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