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Uterine perivascular epithelioid cell tumors (PEComa) and the accuracy of proposed classification systems in predicting the malignant versus non-malignant behavior

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HIGHLIGHTS

- Uterine PEComas not associated with tuberous sclerosis complex are rare mesenchymal tumors.
- Uterine PEComas have heterogeneous clinical presentation overlapping with uterine leiomyomas.
- Uterine PEComas are often diagnosed after hysterectomy, and proposed adjuvant treatments are inconstant and heterogeneous.
- The modified Folpe classification was the most accurate in predicting the malignant versus non-malignant behavior of PEComas.
- Changing the PEComa size to ≥8 cm and number of mitotic figures per 50 high power fields to ≥5 may increase the accuracy.

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ABSTRACT

Objective. To compare the accuracy of available classification systems (Folpe, modified Folpe, Bennet, and Schoolmester) in predicting the behavior of uterine Perivascular Epithelioid Cell tumors (PEComas).

Methods. We reviewed the pathology registry to identify all uterine PEComas treated at our center. We conducted a systematic literature review searching electronic databases from inception to November 2023. We included all references reporting at least one case of uterine PEComa; cases associated with tuberous sclerosis complex were excluded. Patient-level data were extracted by identified records. Survival analysis was used to assess the accuracy of all proposed classification systems to classify uterine PEComas as malignant versus non-malignant.

Results. Six uterine PEComas were treated at our center. The literature search identified 101 uterine PEComas from 32 studies. Eighty-five out of 107 PEComas (28 studies and our series) reported enough follow-up data and details to apply all four classifications. The modified Folpe classification demonstrated the highest hazard ratio (HR) for relapse (HR:8.63; 95% confidence interval [CI] 2.06–36.1) and death due to PEComa (HR:6.8, 95% CI:0.89–51.6) for malignant versus non-malignant PEComas. Changing the cut-off of PEComa size to ≥8 cm and mitotic figures per 50 high power fields to ≥5, the HR for recurrence lowered (HR:6.26; 95% CI 2.20–17.80), but HR for death increased (HR:10.3; 95% CI 1.35–77.80).

Conclusions. The modified Folpe classification was the most accurate in predicting the PEComa behavior. Changing the cut-off of PEComa size and number of mitotic figures may improve the accuracy in predicting death due to disease.

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Contents

1. Introduction . . . 36
2. Material and methods . . . 36
   2.1. Retrospective study . . . 36
   2.2. Systematic review . . . 36
      2.2.1. Study selection and quality assessment . . . 37
      2.2.2. Data extraction . . . 37
   2.3. Statistical analysis . . . 37
3. Results . . . 37
   3.1. Retrospective case series . . . 37
      3.1.1. Summary of the 6 cases of uterine PEComas treated at the AOUI Verona . . . 38
   3.2. Literature search results . . . 38
      3.2.1. Quality assessment . . . 38
      3.2.2. Summary of the 101 cases of uterine PEComas from the literature review. . . . 38
   3.3. The accuracy of the classification systems in predicting PEComa behavior . . . 39
   3.4. Characteristics associated with recurrence-free and cause-specific survival . . . 39
4. Discussion. . . . 39
5. Conclusion . . . 42

Source of funding . . . 42
Ethical standards . . . 42
CRediT authorship contribution statement. . . . 42
Appendix A. Supplementary data . . . 42
References . . . 42

1. Introduction

Perivascular epithelioid cell tumors (PEComas) are a rare subtype of mesenchymal tumors composed of distinctive perivascular epithelioid cells (PEC) immunohistochemically characterized by the coexpression of muscle and melanogenetic markers [1–5]. The uterus is a common localization in women [2]. Presentation symptoms are heterogeneous, and in almost all cases, uterine PEComas are diagnosed after the pathological examination due to their overlapping clinical presentation with uterine leiomyomas [3,6].

The main concern after diagnosis is predicting the disease behavior, given that uterine PEComas include both benign and malignant tumors [7]. Different classification systems to predict prognosis and guide treatment have been proposed based on the pathological characteristics of the primary tumor: Folpe, modified Folpe, Bennet, and Schoolmester classifications [3,7–10]. However, which classification is more appropriate is unclear. Folpe et al. [7] classified PEComas as benign, uncertain malignant, and malignant based on pathologic characteristics (size ≥5 cm, infiltrative growth pattern, high nuclear grade, and cellularity, mitotic rate >1 mitotic figure per 50 HPF, necrosis, and vascular invasion). In 2015, Conlon et al. [9] revised the Folpe classification system to increase accuracy by defining malignant PEComa if necrosis or two or more high-risk features were present. Schoolmester et al. [10] published a different classification system with a higher threshold for the malignant group and, therefore, higher specificity for malignant diagnosis, combining benign and uncertain malignancy into one group. In 2018, Bennet et al. [3] modified the Schoolmester system, reducing the number of features for defining malignancy.

The rarity of the disease impedes the standardization of the classification system to predict PEComa behavior and consequent definition and evaluation of treatment options [11]. Although surgical resection is currently considered the first choice of treatment, subsequent PEComa management strategies are undefined [12,13].

Based on this scenario, the present study aimed to provide additional evidence on uterine PEComas, summarizing all cases published in the literature along with a series treated at our center and evaluating the accuracy of proposed classification systems to predict PEComa behavior using patient-level data.

2. Material and methods

2.1. Retrospective study

We retrospectively reviewed the prospectively collected pathology registry to identify all cases of uterine PEComa diagnosed and treated at the AOUI Verona between January 1994 and November 2023. We excluded cases with a clinically suspected or genetically confirmed diagnosis of tuberous sclerosis complex (TSC), frequently characterized by multiple PEComas with more malignant behavior and possible difficult discrimination between recurrence and second primary PEComa [31,35]. Demographic characteristics and preoperative, surgical, and postoperative treatment data were retrospectively retrieved from medical records, including pathology reports and follow-up data. The same expert gynecologic pathologist (GM) revised and confirmed all identified cases.

2.2. Systematic review

We systematically reviewed the literature by searching in the electronic databases Scopus, PubMed/MEDLINE, and Science Direct from inception to November 2023. The search strategy (Supplementary material) included combinations of the medical terms "Perivascular epithelioid cell neoplasms," "PEComa," and "uterus." We included all references published in English reporting at least one case of uterine PEComa confirmed at the pathologic evaluation with a clinical or genetic exclusion of tuberous sclerosis complex (TSC); uterine PEComa cases with

another concomitant synchronous malignancy were also excluded. No selection criteria were applied to the study design or type of publication.

2.2.1. Study selection and quality assessment

Two authors independently screened the titles and abstracts of identified references (SG, FAF). The full text of the potentially eligible publications was retrieved and independently assessed for eligibility by two other reviewers (SG, PCZ), who assessed the risk of bias after inclusion. Any disagreement over the eligibility of studies or risk of bias assessment was resolved through discussion with a fourth author (SU). The references of all identified studies were systematically revised to identify other eligible publications. Moreover, available literature reviews were retrieved to search for possible additional publications in the reference lists. Risk of bias assessment was performed following the modified 8-questions Newcastle Ottawa scale for case series and case reports proposed by Murad et al. [14]. The review was reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. It was not registered on PROSPERO as per the register policy.

2.2.2. Data extraction

A standardized form was used to extract data from included studies. We collected demographic characteristics, symptoms, surgical data, immunohistochemical and pathological features, treatment strategy, and follow-up details for each reported case of uterine PEComa confirmed at the pathologic evaluation with a clinical or genetic exclusion of TSC and without concomitant malignancy.

2.3. Statistical analysis

Standard descriptive statistics were used as appropriate. Patient-level data were used to test the accuracy of available classification systems to predict malignant versus non-malignant behavior. Recurrence-free survival was defined as the interval between primary surgery and the diagnosis of recurrence; cause-specific survival was defined as the interval between primary surgery and death due to PEComa. In cases without the event of interest, the length of follow-up was defined as the months between primary surgery and the last follow-up.

We applied the proposed classification systems (Folpe [7], modified Folpe [9], Schoolmester [10], and Bennet [3] classifications) to each identified case of uterine PEComa, classifying each case as malignant or non-malignant. Because Folpe and modified Folpe scores propose three risk categories (malignant, benign, and uncertain malignant potential), we merged the benign and uncertain malignant groups, conforming to the proposed classification by Schoolmester and Bennet (malignant versus non-malignant) (Table 1) [3,7,9,10].

The missing patient-level data were handled by assuming a random missing. Only studies with at least one PEComa case with the availability of follow-up data regarding recurrence-free, cause-specific survival and enough details to allow the classification of malignant versus non-malignant for all four classifications were included. Therefore, cases of PEComa in which applying all four classifications was impossible or without follow-up data were excluded from the following analyses.

Agreement between the four classifications in classifying PEComas as malignant versus non-malignant was estimated with Cohen's Kappa. Kaplan-Meier curves and log-rank tests were used to compare malignant versus non-malignant groups regarding recurrence-free and case-specific survival for each classification system. Univariate Cox proportional hazards regression analysis was performed to estimate hazard ratios (HRs) for recurrence and death due to PEComa for the malignant group using the non-malignant group for each proposed classification as the reference.

In the same group of PEComas, univariate and multivariable Cox regression analyses were used to identify anatomopathological and immunohistochemical features associated with recurrence-free and cause-specific survival. The best multivariable models predicting oncologic outcomes were selected using the Akaike information criterion minimization. In the case of continuous variables, Cox regression analysis implementing penalized splines function was used to describe the relationship between these variables and recurrence-free or cause-specific survival.

A two-tailed p-value <0.05 was considered statistically significant. Statistical analysis was performed using R statistical language version 4.2.2 [16].

3. Results

3.1. Retrospective case series

We identified six cases of uterine PEComa diagnosed and treated at the AOUI Verona without clinically suspected or genetically confirmed

Table 1
Summary of Folpe, modified Folpe, Schoolmester, and Bennet classifications.

	Folpe	Modified Folpe	Schoolmester	Bennet	Current study
Benign	**No worrisome features** *(PEComa size ≥5 cm†, infiltrative growth pattern, high nuclear grade, and cellularity, mitotic rate >1 per 50 HPF†, necrosis, vascular invasion)*	**≤1 worrisome feature** *(PEComa size ≥5–<10 cm, infiltrative growth pattern, mitotic rate 2–3 per 50 HPF, no necrosis, lymphovascular invasion)*	**≤3 worrisome features** *(PEComa size ≥5 cm, high-grade nuclear atypia, necrosis, lymphovascular invasion, mitotic rate ≥1 per 50 HPF)*	**≤2 worrisome features** *(PEComa size ≥5 cm, high-grade nuclear atypia, necrosis, lymphovascular invasion, mitotic rate >1 per 50 HPF‡)*	**Non-malignant**
Uncertain malignant potential	Only nuclear pleomorphism/multinucleated giant cells or Only PEComa Size >5 cm	**1 worrisome feature** *(PEComa size ≥10 cm, isolated marked atypia, mitotic rate ≥4 per 50 HPF, no necrosis, lymph vascular invasion)*			
Malignant	**≥2 worrisome features** *(PEComa size ≥5 cm†, infiltrative growth pattern, high nuclear grade, and cellularity, mitotic rate >1 per 50 HPF†, necrosis, vascular invasion)*	**Necrosis or ≥2 worrisome features** *(PEComa size ≥5 cm, infiltrative growth pattern, mitotic rate >1 per 50 HPF, lymphovascular invasion, marked atypia)*	**≥4 worrisome features** *(PEComa size ≥5 cm, high-grade nuclear atypia, necrosis, lymphovascular invasion, mitotic rate ≥1 per 50 HPF)*	**≥3 worrisome features** *(PEComa size ≥5 cm, high-grade nuclear atypia, necrosis, lymphovascular invasion, mitotic rate >1 per 50 HPF‡)*	**Malignant**

HPF, high power fields.
† In the original Folpe classification, it is unclear how to consider 1 mitosis per 50 HPF and a PEComa of 5 cm. For the present study, we conformed to the modified Folpe classification.
‡ Bennet et al. removed 1 mitotic figure per 50 HPF as a worrisome feature compared to Schoolmester et al. No cases changed the classification in Bennet and Schoolmester classifications, whether using a mitotic rate >1 or ≥1 per 50 HPF.

diagnosis of tuberous sclerosis complex, including the first case of uterine PEComa reported in the literature [17]. Characteristics of included cases are summarized in Supplementary Table 1, and a detailed presentation of each case is reported as Supplementary material.

3.1.1. Summary of the 6 cases of uterine PEComas treated at the AOUI Verona

Median age was 49 (29–54) years; three (50%) women were postmenopausal. Initial clinical presentation was heterogeneous: postmenopausal uterine bleeding in 2 cases, hypermenorrhea in 2 patients, expulsion of material from the cervical canal in one case, and absence of symptoms in the latter. At ultrasounds, three PEComas were ≥7 cm and three ≤2 cm; in 4 (66.6%) cases, the PEComa involved the uterine body; the isthmus or cervix was involved in the others. In all six cases, ultrasound features overlapped with that of uterine leiomyomas.

Only one patient had a preoperative diagnosis by hysteroscopy and underwent type B radical hysterectomy plus pelvic lymphadenectomy and infracolic omentectomy. Overall, total hysterectomy and bilateral salpingectomy or salpingo-oophorectomy were performed in 4 cases, and myomectomy with uterine preservation in 2. After diagnosis, one case received adjuvant radiotherapy; none received chemotherapy.

Median follow-up was 25 (IQR: 24–63) months. Two cases recurred: one as pelvic mass surrounding the external iliac artery, the other as an intravascular disease in the hypogastric vein up to the inferior vena cava. Both patients underwent local excision of the disease and adjuvant chemotherapy. Five patients were alive at the end of the follow-up, and only one woman died 26 months after primary surgery. Complete immunohistochemical features of the six cases are reported in Supplementary Table 2.

3.2. Literature search results

The search strategy retrieved 439 items. After removing duplicates ($n = 124$), 283 studies were excluded because they did not report cases of uterine PEComa, because reporting cases of PEComa without pathological confirmation, because reporting only cases with a clinically suspected or genetically confirmed diagnosis of TSC or only cases without a clinical or genetic exclusion of TSC, or because describing the presence of another synchronous neoplasia. No references were excluded due to the language criteria. Finally, we included 32 studies in our review for 101 cases of uterine PEComa (Supplementary Table 3). Follow-up data regarding recurrence-free and cause-specific survival and enough details to allow the classification of malignant versus non-malignant for all four classifications (Folpe [7], modified Folpe [9], Schoolmester [10], and Bennet [3] classifications) were available in 28 studies for 79 PEComas, which were included in the evaluation of the four classification systems. The flowchart of study selection is shown in Supplementary Fig. 1.

3.2.1. Quality assessment

As per inclusion criteria, only uterine PEComa cases confirmed at the pathologic evaluation with a clinical or genetic exclusion of TSC were included; therefore, all 32 studies were considered compliant with question 2: “Was the exposure adequately ascertained?.”

Questions 3 “Was the outcome adequately ascertained?,” 7, “ Was follow-up long enough for outcomes to occur?” and 8 “Is the case (s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?” were addressed only in the 28 studies reporting enough details to allow the classification of malignant versus non-malignant for all four classifications (39 out of 48 PEComa cases (81.3%) without recurrence or death due to disease had a follow-up ≥12 months). Questions mostly relevant to adverse drug events (4, 5, and 6) were excluded. Answer to question 1 “Does the patient (s) represent(s) the whole experience of the investigator (centre) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?” was variably present in included studies (Supplementary Table 4).

3.2.2. Summary of the 101 cases of uterine PEComas from the literature review

Median age was 47.3 years (IQR 40–56). Clinical presentation was heterogeneous, unspecific, and not reported in 24 cases (23.7%). Atypical uterine bleeding (33.5%), pelvic pain (18.5%), growing myoma (13.5%), and adnexal mass (7%) were those more frequently reported. At preoperative imaging, mainly ultrasounds, uterine PEComas were usually reported as circumscribed lesions of the myometrium, almost constantly referred to as uterine leiomyomas. Data regarding vascularization of the lesion were rarely reported. The uterine corpus was the typical localization (58.6%), followed by the uterine cervix (9.2%), broad ligament (7%), and round ligament (1.2%). In most cases, the diagnosis was incidental at definitive pathology. Only a minority of cases (8.9%) were identified as advanced disease at diagnosis. The most frequent sites of metastasis were the lungs (55.6%) and pelvic lymph nodes (33.3%), followed by the liver and peritoneum. Diagnosis of advanced disease was before or after surgery based on whether presenting symptoms were gynecologic or non-gynecologic.

Of 101 PEComas, 72.3% were ≥ 5 cm ($n = 73$). The tumor was composed mainly of epithelioid cells in 56.4% ($n = 57$) of cases and spindle cells in 17.8% ($n = 18$). Multinucleated giant cells were observed in 26 uterine PEComas (25.7%). High nuclear grade and cellularity were reported in 46 cases (45.5%), and nuclear pleomorphism was described in 50 cases (49.5%). The mitotic rate was ≥1 per 50 high power fields (HPF) in 68 cases (67.3%). Necrosis was observed in 45 cases (44.6%). The infiltrative growth pattern was reported in 39 cases (38.6%), and vascular invasion was present in 27 cases (26.7%). The immunochemical analysis reported a positive finding as follows: HMB-45 in 98.9% (92/93), cathepsin-k in 100% (49/49), Melan-A in 51.6% (42/81), and MITF in 85.7% (36/42) of tested cases. Smooth muscle markers were frequently reported in the literature and resulted positive as follows: smooth muscle actin was positive in 80% of tested cases (60/75), desmin in 72.2% (52/72), and h-caldesmon in 75% (36/48). Vimentin was positive in 66.7% of tested cases (18/27), S-100 in 17.2% (10/58), CD-10 in 29% (9/31), and CD-117 in three cases.

A standardized treatment approach was not observed. First-line treatment was reported in 89 out of 101 cases. Hysterectomy was performed in 78 cases (87.6%), with bilateral salpingo-oophorectomy in 55.1%. Lymph node dissection was implemented in 17 patients (19.1%). Myomectomy with preservation of the uterus was reported in 11 cases (12.4%). Neoadjuvant chemotherapy was proposed in 3 cases (3.4%) [18–20]. After primary surgery, adjuvant chemotherapy was administered in 21 cases (23.6%), in combination with radiotherapy in 35.7%. Chemotherapy agents were ifosfamide, dacarbazine, doxorubicin, vincristine, irinotecan, paclitaxel, doxorubicin, and mTOR inhibitors. Sirolimus demonstrated a short-term efficacy in reducing tumor size and central cavitation of pulmonary metastasis in one patient with uterine PEComa [21]. A combination of surgery and mTOR inhibitors was offered in three patients with advanced uterine PEComa, achieving in two cases a complete tumor regression [22]. Adjuvant radiotherapy alone was administered in 4 cases (4.5%).

The median follow-up was 18 months (1–175; IQR 12–33). Recurrence after first-line therapy was reported in 35 cases (34.7%) with a median time to recurrence of 9.5 (1–84; IQR 6–15) months. Recurrences most frequently involved the lung ($n = 21$; 60.0%), followed by the pelvis ($n = 11$; 31.4%), liver ($n = 6$; 17.1%), bone (n = 2; 5.7%), kidney (n = 2; 5.7%) and pelvic lymph nodes ($n = 3$; 8.6%). Treatment of recurrence was reported for 18 cases (51.4%). A combination of surgical, medical, and radiation therapy was administered in 8 cases (44.5%), and only surgical and medical treatment was proposed in 5 (27.8%) and 4 (22.1%) cases, respectively. A total of 15 deaths were reported, representing 14.9% of all PEComas and 42.9% of recurrences, with a median time to death of 17.5 (5–43; IQR 12–35.5) months.

Table 2
Agreement between the Folpe, modified Folpe, Bennet, and Schoolmester classifications in classifying PEComas as malignant versus non-malignant (Cohen's Kappa).

	Folpe	Modified Folpe	Schoolmester
Modified Folpe	0.887 (95% CI 0.78–0.99; $p < 0.001$)		
Schoolmester	0.205 (95% CI 0.11–0.31; $p = 0.002$)	0.251 (95% CI 0.13–0.37; <0.001)	
Bennet	0.479 (95% CI 0.32–0.63; <0.001)	0.566 (95% CI 0.41–0.72; <0.001)	0.533 (95% CI 0.37–0.70; <0.001)

3.3. The accuracy of the classification systems in predicting PEComa behavior

Follow-up data regarding recurrence-free and cause-specific survival and enough details to allow the classification of malignant versus non-malignant for all four classifications (Folpe [7], modified Folpe [9], Schoolmester [10], and Bennet [3] classifications) were available in 85 (79 from literature review [28 studies] and six from our series) out of 107 PEComas (101 from literature review [32 studies] and six from our series).

The measure of agreement between the four classifications is reported in Table 2. Regarding the 9 out of 85 PEComa cases with metastatic disease at diagnosis, the Folpe, modified Folpe, and Bennet classifications recognized all nine cases as malignant. Conversely, the Schoolmester classification regarded two cases as non-malignant.

Kaplan-Meier curves and the log-rank test showed a statistically significant lower recurrence-free survival in the group of malignant PEComa defined by the Folpe, modified Folpe, and Bennet classifications but not for the Schoolmester classification (Fig. 1). At least one recurrence was observed in all non-malignant groups.

Kaplan-Meier curves and the log-rank test showed a statistically significant lower cause-specific survival in the group of malignant PEComa defined by the Folpe, modified Folpe, and Bennet classifications but not for the Schoolmester classification (Fig. 2). One death due to PEComa was observed in the non-malignant group defined by the Folpe and modified Folpe classifications, three deaths in the group proposed by Bennet, and up to twelve deaths in the non-malignant group defined by Schoolmester.

The number of cases classified as malignant and non-malignant by each classification and the number of recurrences and deaths, along with median recurrence-free and cause-specific survival with 95% confidence intervals for each group, are reported in Table 3.

Estimated HRs for recurrence and death due to PEComa for the malignant group using as reference the non-malignant group for each proposed classification are reported in Table 4. The modified Folpe classification demonstrated the highest HR for relapse (HR 8.63; 95% CI 2.06–36.1) and death due to PEComa (HR 6.8, 95% CI 0.89–51.6). However, only the Bennet classification provided a statistically significant higher HR for death due to PEComa among malignant versus non-malignant cases (HR 4.3, 95% CI 1.22–15.2).

3.4. Characteristics associated with recurrence-free and cause-specific survival

In the 85 PEComas with follow-up data, characteristics associated in univariate Cox regression analysis with recurrence-free survival were the PEComa size (HR 1.14; 95% CI 1.07–1.22; $p < 0.001$), the presence of infiltrative growth (HR 2.19; 95% CI 1.04–4.61; $p = 0.032$), high cellularity (HR 2.98; 95% CI 1.53–5.81; $p = 0.001$), and necrosis (HR 3.87; 95% CI 1.82–8.25; $p < 0.001$), and the number of mitotic figures per 50 HPF (HR 1.01; 95% CI 1.01–1.02; $p < 0.001$). MELAN A positivity was associated with higher HR for recurrence (HR 3.99; 95 CI 1.39–11.5; $p = 0.003$), whereas progesterone positivity with lower (HR 0.09; 95% CI 0.02–0.49; $p = 0.005$) (Supplementary Table 5). In multivariable analysis, only the number of mitotic figures per 50 HPF was independently associated with recurrence-free survival (Supplementary Table 6); the best multivariable Cox regression model predicting the risk of recurrence included the presence of necrosis (HR 3.45; 95% CI 1.33–8.95; $p = 0.006$) and the number of mitotic figures per 50 HPF (HR 1.01; 95% CI 1.00–1.02; $p = 0.004$).

Characteristics associated in univariate Cox regression analysis with cause-specific survival were the PEComa size (HR 1.18; 95% CI 1.07–1.30; $p = 0.002$), the presence of necrosis (HR 4.50; 95% CI 1.28–15.8; $p = 0.008$), and the number of mitotic figures per 50 HPF (HR 1.01; 95% CI 1.01–1.02; $p < 0.001$) (Supplementary Table 7). In multivariable analysis, only the number of mitotic figures per 50 HPF was independently associated with cause-specific survival (Supplementary Table 8); the best multivariable Cox regression model predicting the risk of death due to PEComa included the PEComa size (HR 1.14; 95% CI 1.03–1.27; $p = 0.021$) and the number of mitotic figures per 50 HPF (HR 1.01; 95% CI 1.00–1.02; $p = 0.01$). The relationship between the risk of death due to PEComa and the number of mitotic figures per 50 HPF and PEComa size are depicted in Supplementary Fig. 2. Relative death rate was higher than 1.00 for PEComa size ≥8 cm and ≥ 5 mitotic figures per 50 HPF.

Based on the above observations, we tested a classification defining malignant PEComa in the presence of necrosis or two or more worrisome features: PEComa size ≥8 cm, ≥ 5 mitotic figures per 50 HPF, infiltrative growth, high nuclear grade atypia, and lymph vascular invasion. Kaplan-Meier curves and log-rank test reported a statistically significant difference in recurrence-free and cause-specific survival between malignant and non-malignant groups (Supplementary Fig. 3). Four out of 35 non-malignant PEComas recurred, but only one died due to disease, whereas 33 out of 50 malignant cases recurred, and 15 died due to PEComa. Median recurrence-free and cause-specific survival and 95% confidence intervals are reported in Table 5. HR for recurrence was lower than Folpe and modified Folpe classifications but higher than Bennet and Schoolmester (HR 6.26; 95% CI 2.20–17.80). Conversely, HR for death due to PEComa was the highest (HR 10.3; 95% CI 1.35–77.80).

4. Discussion

The present study summarizes the available evidence on uterine PEComas not associated with TSC. They represent a rare mesenchymal tumor; clinical presentation is unspecific and overlapping with uterine leiomyomas, and preoperative diagnosis is highly uncommon. Surgical and adjuvant treatments are heterogeneous. Among the four proposed classifications, the modified Folpe was the most accurate in predicting the malignant behavior, which was associated with the PEComa size, the number of mitotic figures per 50 HPF, and necrosis. Changing the PEComa size cut-off to ≥8 cm and the number of mitotic figures per 50 HPF cut-off to ≥5 may increase the accuracy in separating malignant (and possibly fatal) cases from non-malignant ones.

Our case series and the systematic review consistently reported a mean age at diagnosis of 47 years. Although age ranged between 29 and 56 years, the perimenopausal period was the most frequently affected. Notably, the heterogenous clinical presentation overlaps with the symptoms of this age and uterine fibromatosis [23]. Atypical uterine bleeding, menstrual irregularities, pelvic mass, and pelvic pain were reported by almost two-thirds of patients.

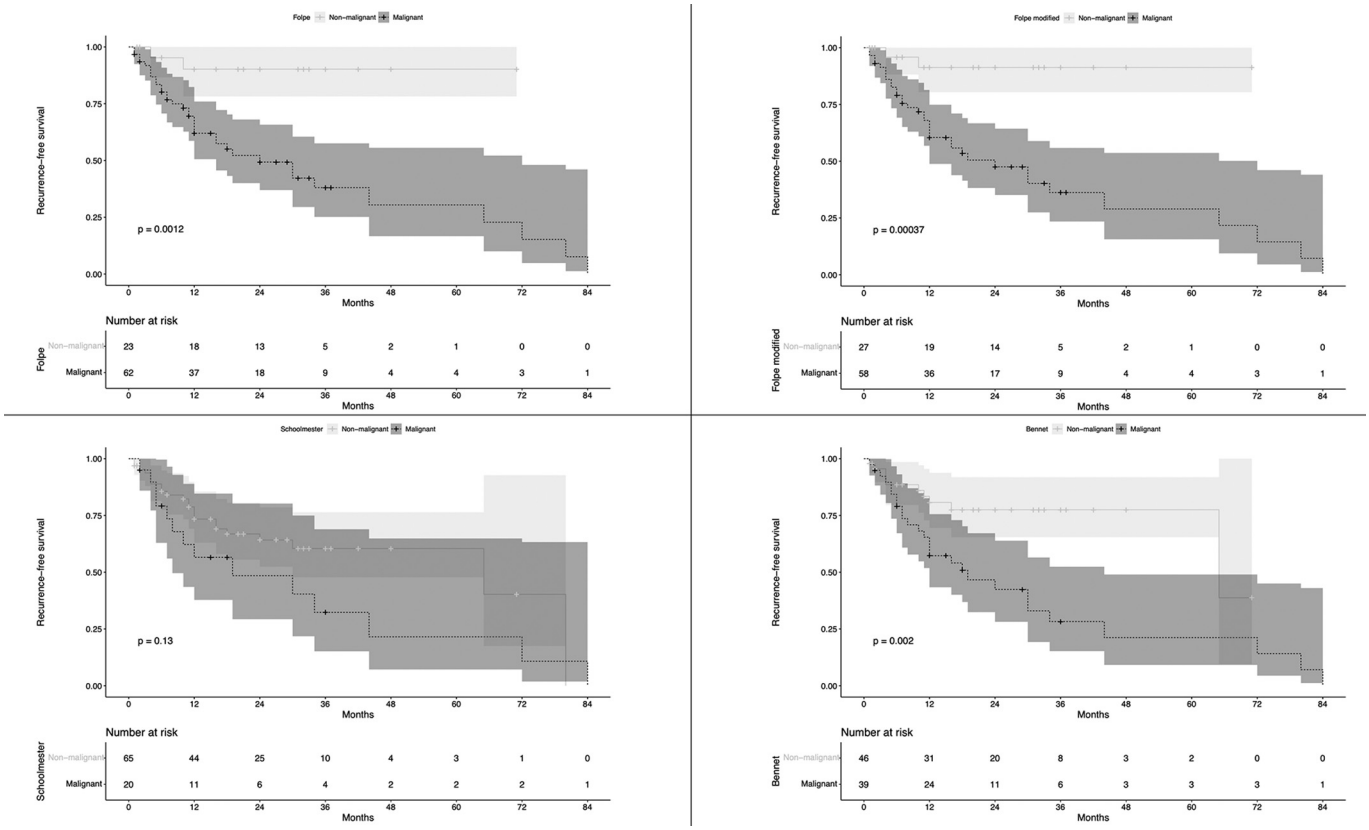

Fig. 1. Kaplan-Meier curves for recurrence-free survival of malignant versus non-malignant PEComas classified following the Folpe, modified Folpe, Schoolmester, and Bennet classifications.

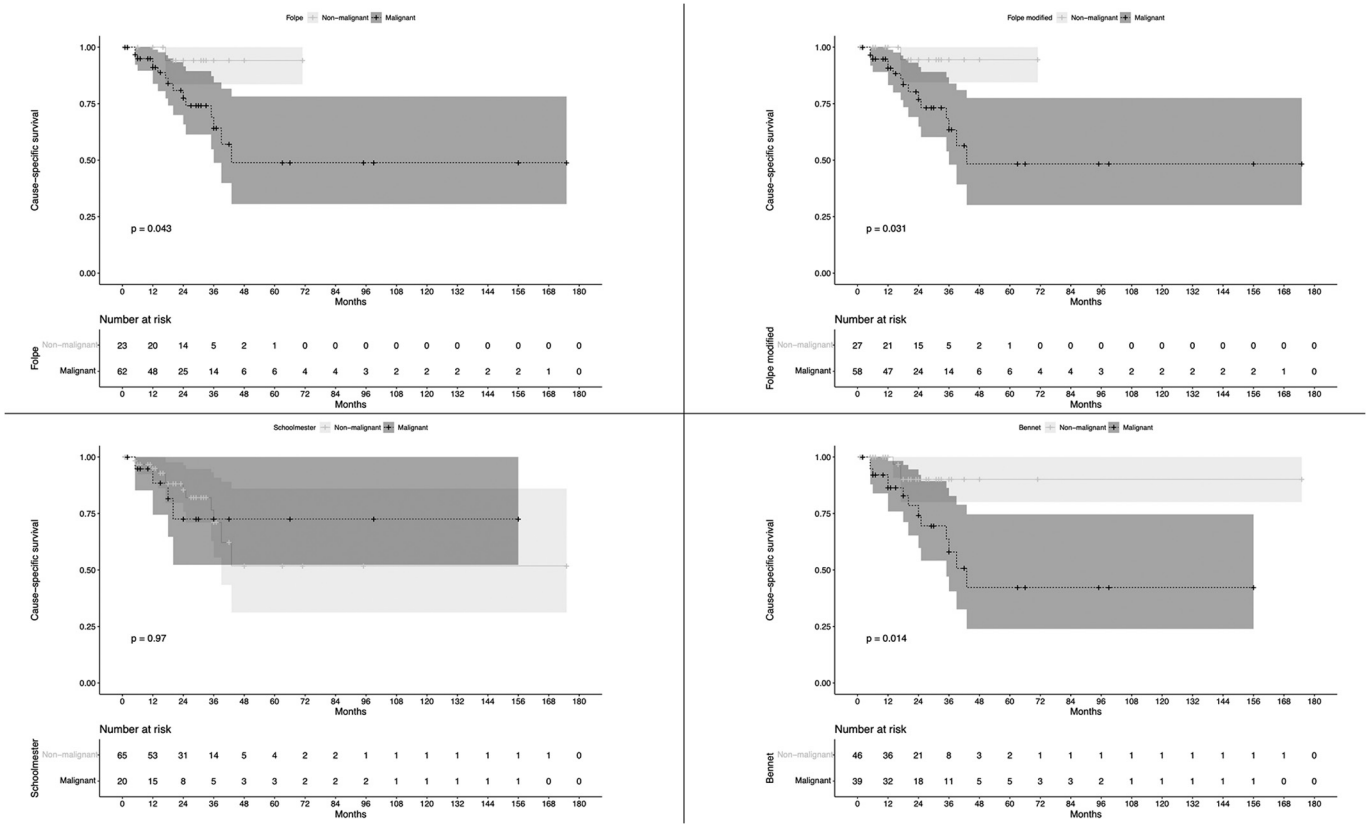

Fig. 2. Kaplan-Meier curves for cause-specific survival of malignant versus non-malignant PEComas classified following the Folpe, modified Folpe, Schoolmester, and Bennet classifications.

Table 3
The number of recurrences and deaths and median recurrence-free and cause-specific survival with 95% confidence intervals in non-malignant and malignant groups defined by the Folpe, modified Folpe, Schoolmester, and Bennet classifications.

Classification		Total cases	N Recurrences	% Events	Median RFS (months)
Folpe	Benign	23	2	9.7%	/
	Malignant	62	35	56.5%	24 (16–72)
Modified	Benign	27	2	7.4%	/
Folpe	Malignant	58	35	60.3%	24 (12–72)
Schoolmester	Benign	65	23	35.4%	65 (30 – /)
	Malignant	20	14	70%	19 (8 – /)
Bennet	Benign	46	10	21.7%	65 (65 – /)
	Malignant	39	27	69.2%	19 (12–44)
Classification		**Total cases**	**N Deaths due to PEComa**	**% Events**	**Median CSS (months)**
Folpe	Benign	23	1	4.4%	/
	Malignant	62	15	24.2%	43 (36 – /)
Modified	Benign	27	1	3.7%	/
Folpe	Malignant	58	15	25.9%	43 (36 – /)
Schoolmester	Benign	65	12	18.5%	43 (39 – /)
	Malignant	20	4	20%	/
Bennet	Benign	46	3	6.5%	/
	Malignant	39	13	33.3%	43 (35 – /)

N, number; RFS, recurrence-free survival; CSS, cause-specific survival; 7 out of 37 recurrences and 4 out of 16 deaths were observed in advanced diseases at diagnosis.

Similar to other mesenchymal tumors of the uterus [24], preoperative ultrasounds do not appear able to discriminate between uterine leiomyomas and uterine PEComas. Although some ultrasound findings were proposed associated with uterine PEComas, such as size >8 cm, peripheric vascularization, and cystic degeneration [25], PEComa cases with preoperative ultrasound imaging suggesting a different diagnosis than uterine leiomyomas were rare. As ultrasounds, magnetic resonance imaging failed to provide specific imaging for uterine PEComas, although magnetic resonance imaging demonstrated a role in other uterine mesenchymal tumors [26,27]. Lack of imaging features leads to the fact that a preoperative diagnosis is very uncommon and require every gynecologist to be aware of this rare and insidious entity, supporting the general recommendation of avoiding intrabdominal unprotected morcellation of the uterus or uterine masses during surgery [28–30].

Analysis of pathological examinations confirms the positivity of uterine PEComas to melanocytes and smooth muscle markers [31]. Although some cases were found negative for HMB-45, the melanocytes and smooth muscle markers at immunohistochemistry may allow differentiating PEComas from uterine endometrial stromal sarcoma [2,32] and the most challenging leiomyosarcoma.

Hysterectomy versus uterine conservative surgery was often chosen based on other indications, given the high rate of postoperative diagnosis. In the few cases with preoperative identification, hysterectomy was chosen by most authors and can be considered the first choice. However, the limited number of cases with follow-up data who underwent myomectomy cannot exclude conservative surgery in young women with non-malignant PEComas. Conversely, lymphadenectomy appears to be controversial and not supported. Indeed, as mesenchymal tumors, uterine PEComas are expected to have hematogenous metastases [2], which was confirmed by the high rate of reported hematogenous recurrences versus the few cases with lymphatic metastasis.

Data on postoperative management were even less conclusive. Adjuvant treatment, mainly chemotherapy with or without radiotherapy, was implemented in a minority of cases with heterogeneous chemotherapeutic agents. This did not allow us to provide any conclusion on the most recommended protocol. We chose radiation therapy in our series based on the high mitotic index and the increased neoangiogenesis [31]. However, the number of reported cases who received only radiotherapy was minimal, impeding any conclusion. Recently, the treatment with mTOR inhibitors showed antineoplastic activity in PEComas of different sites, including the uterus [22,33]. However, cellular apoptosis was not observed due to the cytostatic effect, and tumor progression is typically reported after treatment discontinuation [34]. Therefore, further research is mandatory to clarify the role of target therapy and all other adjuvant therapies in uterine PEComas after primary surgery.

One of the main limitations in comparing the various PEComa management options is the presence of four different classification systems, which introduces additional uncertainties in managing uterine PEComas. Before investigating the most appropriate treatment, standardizing the classification of malignant versus non-malignant is mandatory. Our results demonstrated only a partial agreement between the four methods, which implies that a subgroup of PEComas is differently regarded as malignant based on the chosen classification system. In this scenario, understanding the best method to classify uterine PEComas is a priority. Our results showed that only three out of four classification systems define two groups with statistically significantly different risks of recurrence and death due to disease and with different performances. The Cox regression analysis shows that the modified Folpe classification appears to have the highest accuracy in separating malignant from non-malignant uterine PEComas, whereas the Schoolmester has the lowest. Of note, Schoolmester and Bennet systems did not differ in the criteria for malignancy but in the adopted threshold (reduced from four to three features by Bennet), supporting as more effective a cautionary approach for uterine PEComas with intermediate anatomopathological features [3,10]. Based on these results, although no classification system was exempt from failures, the modified Folpe classification may be considered the best choice.

Table 4
Univariate Cox proportional hazards regression analysis for recurrence and death due to PEComa.

Classification		HR for recurrence	95% CI	HR for death due to PEComa	95% CI
Folpe	Benign	reference		reference	
	Malignant	7.45	1.78–31.2	6.21	0.82–47.1
Modified	Benign	reference		reference	
Folpe	Malignant	8.63	2.06–36.1	6.80	0.89–51.6
Schoolmester	Benign	reference		reference	
	Malignant	1.71	0.85–3.43	1.03	0.33–3.19
Bennet	Benign	reference		reference	
	Malignant	3.03	1.44–6.35	4.30	1.22–15.2

N, number; HR, hazard ratio; 37 recurrences out of 85 PEComas; 16 deaths due to PEComa out of 85 PEComas

Table 5
Median recurrence-free and cause-specific survival with 95% confidence intervals in benign and malignant groups defined by the proposed classification and univariate Cox regression analysis for recurrence and death due to PEComa.

	Total cases	N Recurrences	% Events	Median RFS (months)
Benign	35	4	11.4%	65 (65 – /)
Malignant	50	33	66.0%	18 (12–44)
	Total cases	**N Deaths due to PEComa**	**% Events**	**Median CSS (months)**
Benign	35	1	2.9%	/
Malignant	50	15	30.0%	43 (35 – /)
	HR for recurrence	**95% CI**	**HR for death due to PEComa**	**95% CI**
Benign	reference		reference	
Malignant	6.26	2.20–17.80	10.3	1.35–77.80

N, number; HR, hazard ratio; RFS, recurrence-free survival; CSS, cause-specific survival

However, there is much room for improving the categorization of this disease. In fact, although a small proportion of cases is misclassified, the modified Folpe classification provided fewer cases classified as non-malignant than the other two systems. This implies that a large proportion of patients classified as malignant will never recur. In this regard, changing the cut-off value to ≥8 cm for the PEComa size and to ≥5 for the number of mitotic figures per 50 HPF may improve the classification. Additionally, investigating characteristics associated with oncologic outcomes highlights the potential role of MELAN-A and hormone receptors as markers of malignant and non-malignant nature, respectively. Unfortunately, the number of cases with these markers, particularly hormone receptors, was limited.

The systematic review of the literature following PRISMA guidelines allowed the identification of all cases of uterine PEComa published in the literature. The use of patient-level data for almost all identified PEComas, along with our case series, one of the largest in the literature, allowed testing all four classifications on the same PEComa population. This method allowed a direct comparison of the four classifications and removed the influence of confounders related to differences between centers and cases. Finally, our results are strengthened by excluding cases associated with the TSC, frequently characterized by multiple PEComas with more malignant behavior and possible difficult discrimination between recurrence and second primary PEComa [31,35]. In this regard, our results do not apply to about 9% of PEComas associated with TSC, which should be ruled out after diagnosis [7,20,36].

As a systematic review and retrospective study, we could summarize only data reported in identified studies and medical records of included patients. Therefore, potentially relevant data were lacking in a variable proportion of PEComas, limiting the number of cases available for a quantitative analysis. The rarity of uterine PEComas and incomplete data reporting represents the main limitation in providing definitive recommendations. Indeed, although we tried to identify and include all cases of uterine PEComas published in the literature, the estimated 95% confidence intervals for HRs suggest that the number of observations is still limited to achieve definitive conclusions. Regarding the test of available classification systems, as stressed by Schoolmeester et al. [10] and Bennet et al. [3], we merged the uncertain and benign groups of the Folpe and modified Folpe classifications. However, how to consider uncertain malignant cases is unclear. An additional challenge is the need to standardize the definition and guarantee the reproducibility of parameters included in the available classification systems of uterine PEComas. Therefore, a further limitation is the impossibility of a central review of all PEComas cases used to test the classification systems. Finally, including advanced PEComas for testing the classification systems may be considered a limitation. However, we included such cases because the assessment of malignant versus non-malignant in incidental postoperative diagnosis is paramount to guide an appropriate staging by imaging, and results showed that the advanced stage does not imply the classification of the PEComa as malignant. Regarding the new proposed classification, caution is needed, given that no external validation was performed. Moreover, results regarding oncologic outcomes are affected by adjuvant therapies. In this regard, the small number of cases and the use of heterogeneous protocols limit the influence of adjuvant treatments on observed results, although they impeded providing data regarding their efficacy. Finally, TSC was not excluded by genetic test in all included cases.

5. Conclusion

A classification system for uterine PEComa is challenging but crucial for appropriate management. The modified Folpe classification appears to have the highest accuracy, although further studies are mandatory to validate our observation and potentially improve PEComa classification, including additional immunohistochemical or genetic factors. Unifying the PEComa classification is essential to investigate this rare entity further.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration. The Institutional Review Board approved the study, and all included participants gave consent for case presentation and anonymized data collection and analysis for research purposes.

CRediT authorship contribution statement

Simone Garzon: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Anna Caliò:** Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization. **Filippo Alberto Ferrari:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Cesare Quintino Iannicello:** Writing – review & editing, Data curation. **Pier Carlo Zorzato:** Writing – review & editing, Writing – original draft, Data curation. **Mariachiara Bosco:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Elena Piazzola:** Writing – review & editing, Supervision. **Guido Martignoni:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Antonio Simone Laganà:** Writing – review & editing, Validation, Methodology. **Andrea Mariani:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Stefano Uccella:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2024.06.007.

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