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Justine Gantzer, Maud Toulmonde, François Séverac, Ali N. Chamseddine, Celine Charon-Barra, et al.. PEC-PRO: A new prognostic score from a series of 87 patients with localized perivascular epithelioid cell neoplasms (PEComas) treated with curative intent. *Cancer*, 2024, 130 (13), pp.2304-2314. <10.1002/cncr.35277>. <hal-04533834>

HAL Id: hal-04533834

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Submitted on 5 Apr 2024

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ORIGINAL ARTICLE

PEC-PRO: A new prognostic score from a series of 87 patients with localized perivascular epithelioid cell neoplasms (PEComas) treated with curative intent

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Funding information

French Sarcoma Clinical Reference Network; Institut National Du Cancer, Grant/Award Number: PRTK-2020-046

Abstract

Background: Perivascular epithelioid cell neoplasms (PEComas) encompass a heterogeneous family of mesenchymal tumors. Previously described clinicopathologic features aimed at distinguishing benign from malignant variants but lacked prognostic value.

Methods: This retrospective analysis examined clinicopathologic data from patients who had localized PEComa across French Sarcoma Network centers. The authors analyzed 12 clinicopathologic features in a Cox proportional hazard framework to derive a multivariate prognostic risk model for event-free survival (EFS). They built the PEComa prognostic score (PEC-PRO), in which scores ranged from 0 to 5, based on the coefficients of the multivariate model. Three groups were identified: low risk (score = 0), intermediate risk (score = 1), and high risk (score \geq 2).

Results: Analyzing 87 patients who had a median 46-month follow-up (interquartile range, 20–74 months), the median EFS was 96.5 months (95% confidence interval [CI], 47.1 months to not applicable), with 2-year and 5-year EFS rates of 64.7% and 58%, respectively. The median overall survival was unreached, with 2-year and 5-year overall survival rates of 82.3% and 69.3%, respectively. The simplified Folpe

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classification did not correlate with EFS. Multivariate analysis identified three factors affecting EFS: positive surgical margins (hazard ratio [HR], 5.17; 95% CI, 1.65–16.24; $p = .008$), necrosis (HR, 3.94; 95% CI, 1.16–13.43; $p = .030$), and male sex (HR, 3.13; 95% CI, 1.19–8.27; $p = 0.023$). Four variables were retained in the prognostic model. Patients with low-risk PEC-PRO scores had a 2-year EFS rate of 93.7% (95% CI, 83.8%–100.0%), those with intermediate-risk PEC-PRO scores had a 2-year EFS rate of 67.4% (95% CI, 53.9%–80.9%), and those with high-risk PEC-PRO scores had a 2-year EFS rate of 2.3% (95% CI, 0.0%–18.3%).

Conclusions: The PEC-PRO score reliably predicts the risk of postoperative recurrence in patients with localized PEComa. It has the potential to improve follow-up strategies but requires validation in a prospective trial.

KEYWORDS

necrosis, perivascular epithelioid cell neoplasms (PEComas), positive margins, prognostic, sex, vascular invasion

INTRODUCTION

Perivascular epithelioid cell neoplasms (PEComas) are rare sarcomas defined by the World Health Organization (WHO) classification as mesenchymal tumors composed of perivascular epithelioid cells with unique histologic properties and usual expression of melanocytic and smooth muscle markers.^{1–3} PEComas encompass a heterogeneous family, with the most common subtypes being angiomyolipoma, lymphangioleiomyomatosis, and PEComa-not otherwise specified (NOS), occurring in various anatomic locations. At the molecular level, PEComas are characterized by mutations in *TSC1* or *TSC2*, leading to mTOR pathway activation, *TFE3* gene fusion, or *FLCN* truncating mutations.^{4–6}

Clinically, PEComas can present as either indolent tumors or aggressive metastatic disease. In 2005, Folpe et al. described six tumor features associated with the malignant behavior of PEComas-NOS, including tumor size >5 cm, high nuclear grade and cellularity, necrosis, vascular invasion, mitotic rate >1/50 high-power fields (HPF), and infiltrative growth pattern.⁷ These characteristics classify PEComas-NOS as benign (no features present), of uncertain malignant potential (one feature present), or malignant (two or more features present). Unlike a large majority of soft tissue sarcomas, the community of expert sarcoma pathologists does not recommend use of the French National Federation of Centers for the Control of Cancer grade to assess tumor aggressiveness but, rather, advocates for the classification of Folpe and colleagues. In 2012, a simplified version of this classification, based on tumor size ≥ 5 cm and mitotic rate >1/50 HPF, was proposed.⁸

However, it remains unknown which combination of features predicts the clinical outcome of patients who have localized disease because of the scarcity and heterogeneity of published cases in the literature.^{4,6,9–15} Despite the emergence of data on advanced

PEComas,^{14,16} clinical data and outcomes for localized PEComas are still lacking.¹⁷ Therefore, understanding the natural history of localized tumors is crucial to define prognostic factors and optimize patient follow-up and adjuvant treatments.

To address this issue, we conducted a retrospective multicenter study to describe the natural history of localized PEComas-NOS, analyze the features associated with event-free survival (EFS), and build a prognostic score to identify different prognostic groups.

MATERIALS AND METHODS

Patient population

This was a retrospective, multicentric analysis of all PEComa cases included in the French Sarcoma Clinical Reference Network (NETSARC+; <http://www.netsarc.org>, Accessed December 18, 2023) centers of the French Sarcoma Group and in one Belgian center. De-identified data from patients, including patient and tumor characteristics, treatments, and outcomes, were collected for patients who were treated between 2005 (the year of publication of the Folpe classification) and 2021. All cases included were reviewed by a local sarcoma expert pathologist on the basis of morphologic criteria and immunohistochemical profile to be classified according to the *WHO Classification of Soft Tissue Sarcomas*. Included patients had to have a localized tumor and a diagnosis of PEComa-NOS. Patients were excluded if their follow-up was less than 6 months, if they did not undergo surgery, or if their relapse status and vital status were unknown. The study was approved by the Strasbourg University Hospital Ethical Committee (FC/dossier 2019-6), was conducted in accordance with the Declaration of Helsinki, and was registered on ClinicalTrials.gov (identifier NCT03916575).

Statistical analysis

Patient and tumor characteristics were described using numbers and proportions for categorical variables, medians with interquartile ranges (IQRs) for continuous variables, or medians, means, and ranges for age. EFS was defined as the time from surgery to the first documented evidence of recurrence or death from any cause. Overall survival (OS) was defined as the time between diagnoses and death from any cause. EFS and OS were censored at the time of the last follow-up. Survival curves were estimated using the Kaplan–Meier method.

Prognostic factors associated with EFS were identified using a multivariate Cox model. First, a univariate analysis was performed using 12 clinicopathologic features, including age, male sex, tumor size (>5 cm), high mitotic rate (>1/50 HPF), high nuclear grade and cellularity, presence of tumor necrosis, presence of vascular invasion, presence of lymph node invasion, the simplified Folpe classification, positive surgical margins (defined as R1–R2),¹⁸ the receipt of adjuvant radiotherapy, and the receipt of perioperative systemic treatment. The multivariate model was then built, including variables with clinical relevance and/or *p* values < .1 in the univariate analysis. The results are presented as hazards ratios (HRs) with 95% confidence intervals (CIs). Missing data were handled using multiple imputation by chained equations with 50 imputed data sets.^{19,20} All estimates were calculated for each imputed data set and then combined using the rules according to Rubin.²¹

To create the PEComa prognostic score (PEC-PRO), a stepwise variable selection procedure using the Akaike information criterion was performed on the multivariate Cox model. The score was then built based on the coefficients of the variables retained in the prognostic model. All coefficients of the variables retained in the model were divided by the smallest coefficient and then rounded to the unit to attribute a certain number of points to the patient when the characteristic was present. The discriminative power of the score was assessed using cross-validation based on bootstrap resampling to compute the C-index on all imputed data sets at different times of the follow-up (see Figure S1). To ensure the absence of interaction, models were used to test pairwise interactions between each variable of the score.

Given the moderate number of patients in our study, three prognostic groups (low, intermediate, and high risk) were determined from the PEC-PRO score using thresholds that minimized the Akaike information criterion of the model among all possible combinations (see Figure S2). A *p* value < .05 was considered statistically significant. Statistical analyses were performed with R software, version 4.1.1 (R Core Team, 2021).

RESULTS

Patients and tumor characteristics

Overall, 87 of 166 patients identified met the inclusion criteria (Figure 1). All patients' characteristics are detailed in Table 1.

The median patient age was 52 years (range, 13–84 years) with a female predominance (*n* = 63; 72.4%). At diagnosis, greater than 95%

of patients had a good Eastern Cooperative Oncology Group performance status of either 0 or 1. Sixteen patients had a history of previously treated cancer (19.3%). The most frequent primary sites of PEComas-NOS were the uterus (*n* = 15; 17.2%), kidney (*n* = 14; 16.1%), soft tissues (*n* = 12; 13.8%), liver (*n* = 10; 11.5%), and the retroperitoneum and pelvis (*n* = 9 for each; 10.3%). The median tumor size was 6 cm (IQR, 3.2–10.0 cm); and, of the 69 tumors assessed for lymph node invasion, six had lymph node invasion (6.9%).

Details on previously described worrisome histologic features

The classifications proposed by Folpe et al. were rarely reported as such by pathologists, whereas most tumor features were reported, except those with an *infiltrative growth pattern*. Among patients for whom histologic features were known, 65.3% (*n* = 47 of 72) had tumors with a high mitotic rate, and 60.5% (*n* = 46 of 76) had tumors >5 cm (Table 1). Moreover, 56.6% of patients (*n* = 43 of 76) had tumors with high nuclear grade and cellularity, whereas only 35.2% (*n* = 25 of 71) and 35.5% (*n* = 22 of 62) had tumors with necrosis and vascular invasion, respectively.

The Folpe malignancy classification could be established for 73.6% of tumors (*n* = 64) and, using the simplified Folpe classification, for 86.2% of tumors (*n* = 75). According to the Folpe classification, 31.3% of tumors (*n* = 20) were benign, 3.1% (*n* = 2) were of uncertain malignant potential, and 65.6% (*n* = 42) were malignant. According to the simplified Folpe classification, 21.3% of tumors (*n* = 16) were benign, 40% (*n* = 30) were of uncertain malignant potential, and 38.7% (*n* = 29) were malignant.

Surgery and perioperative treatments

All included patients underwent surgical resection of their primary tumor. Of those patients, four received neoadjuvant therapy using either mTOR inhibitors (*n* = 2) or anthracycline-based chemotherapy (*n* = 2). Among the 83 patients for whom surgical resection margin status was available, 74.7% (*n* = 62) had R0 resection margins, 12.1% (*n* = 10) had R1 resection margins, and 13.2% (*n* = 11) had R2 resection margins. Adjuvant treatment was received by five patients using either anthracycline-based chemotherapy (*n* = 2), mTOR inhibitors (*n* = 1), or hormonotherapy (*n* = 1) and was not specified for one patient. Regarding radiotherapy, of the 83 patients for whom receipt was unknown, only 12.1% of patients (*n* = 10) had received radiotherapy, all as adjuvant treatment.

Association of clinicopathologic tumor features with event-free survival

With a median follow-up of 46 months (IQR, 20–74 months), 55 patients (63.2%) were alive with no evidence of disease, eight patients (9.2%) were alive with disease, and 24 patients (27.6%) had died from disease progression. Thirty-four patients (39.1%) had a

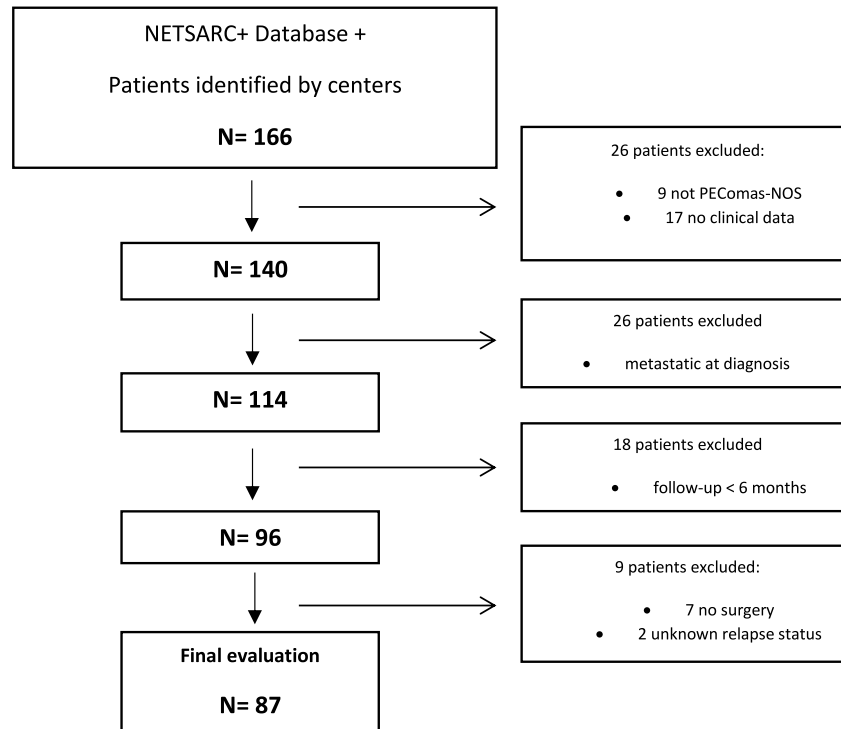


FIGURE 1 Study flow chart. NETSARC+ indicates the French Sarcoma Clinical Reference Network; PEComas-NOS, perivascular epithelioid cell neoplasms, not otherwise specified.

recurrence; and, among these, 79.4% ($n = 27$) had a distant recurrence, whereas 20.6% ($n = 7$) had a locoregional recurrence. Eighty six percent of patients who had a local recurrence had positive margins compared with only 33% of those who had a distant recurrence. The median EFS was 96.5 months (95% CI, 47.1 months to not applicable [NA]). The EFS rates were 64.7% (95% CI, 55.3%–75.8%) at 2 years and 58% (95% CI, 47.9%–70.2%) at 5 years (Figure 2A). According to the Folpe classification, the 2-year EFS rates were 88.4% (95% CI, 77.4%–99.4%), 73.3% (95% CI, 40.4%–100%), and 46.3% (95% CI, 31.4%–61.2%) for benign, uncertain malignant, and malignant tumors, respectively. According to the simplified Folpe classification, these rates were 71.6% (95% CI, 52.8%–90.4%), 77.4% (95% CI, 62.5%–92.2%), and 46.6% (95% CI, 28.5%–64.6%) for benign, uncertain malignant, and malignant tumors, respectively. The OS rates were 82.3% (95% CI, 74.2%–91.2%) at 2 years and 69.3% (95% CI, 59.2%–81.2%) at 5 years, whereas the median OS was not reached (Figure 2B).

In univariate analysis, seven of the 13 tested features were associated with an increased risk of recurrence: male sex (HR, 2.78; 95% CI, 1.39–5.57; $p = .005$), tumor size >5 cm (HR, 2.43; 95% CI, 1.03–5.75; $p = 0.043$), high nuclear grade and cellularity (HR, 2.61; 95% CI, 1.13–6.04; $p = .026$), necrosis (HR, 4.40; 95% CI, 1.95–9.86; $p = .001$), vascular invasion (HR, 4.15; 95% CI, 1.75–9.86; $p = .002$), lymph node invasion (HR, 2.94; 95% CI, 1.24–6.99; $p = .017$), and positive surgical margins (HR, 2.43; 95% CI, 1.20–4.41; $p = .015$; Table 2). The simplified Folpe classification was not associated with

the risk of recurrence, although malignant cases showed a tendency toward decreased EFS (HR, 2.39; 95% CI, 0.88–6.46; $p = .083$). By using multivariate analysis, three features remained independently associated with EFS: positive surgical margins (HR, 5.17; 95% CI, 1.65–16.24; $p = .008$), necrosis (HR, 3.94; 95% CI, 1.16–13.43; $p = .030$), and male sex (HR, 3.13; 95% CI, 1.19–8.27; $p = .023$). Two other features presented important and clinically interesting HRs without being statistically significant: vascular invasion (HR, 2.53; 95% CI, 0.79–8.11; $p = .11$) and tumor size >5 cm (HR, 2.10; 95% CI, 0.65–6.82; $p = .201$).

The PEC-PRO score, a prognostic model of event-free survival

After the variable selection procedure in the multivariate model detailed above (see Materials and Methods), four variables were retained in the prognostic model and were identified as prognostic factors: sex, presence of necrosis, vascular invasion, and positive margins. The prognostic score, named PEC-PRO, was constructed using these four variables. The point scoring system was based on the regression coefficient of the model by attributing two points for tumors with necrosis and one point for the other factors: vascular invasion, positive margins, and male sex. The total point score for a patient is obtained by summing the points for each applicable characteristic. The final score ranged from 0 to 5. Patients were then

TABLE 1 Patient and tumor characteristics.

Population characteristics	No.	%
Age: Median [mean, range], years	52	[51.5, 13–84]
<30	9	10.3
30 to <45	18	20.7
45 to <60	28	32.2
60 to <75	24	27.6
≥75	8	9.2
Sex, female	63	72.4
Performance status (PS) ^a		
PS 0	60	81.0
PS 1	11	14.9
PS 2	3	4.1
Previous significant medical history ^b		
Previous cancer	16	19.3
None	64	80.7
Primary tumor site		
Uterus	15	17.2
Kidney	14	16.1
Soft tissues	12	13.8
Liver	10	11.5
Retroperitoneum	9	10.3
Pelvis	9	10.3
Gastrointestinal tract	7	8.1
Bladder	4	4.6
Head and neck	3	3.5
Lung	3	3.5
Peritoneum	1	1.1
Median tumor size [mean, interquartile range], cm ^c	6	[7.6, 3.2–10]
≤5	46	60.5
>5	30	39.5
High nuclear grade and cellularity ^d		
Present	43	56.6
Absent	33	43.7
Mitotic rate > 1/50 HPF ^e		
Present	47	65.3
Absent	25	34.7
Necrosis ^f		
Present	25	35.2
Absent	48	64.8
Vascular invasion ^g		
Present	22	35.5
Absent	40	64.5

TABLE 1 (Continued)

Population characteristics	No.	%
Lymph node status		
N0	63	72.4
N1	6	6.9
Nx	18	20.7
Folpe classification ^h		
Benign	20	31.3
Uncertain malignant potential	2	3.1
Malignant	42	65.6
Folpe simplified classification ⁱ		
Benign	16	21.3
Uncertain malignant potential	30	40.0
Malignant	29	38.7
Median follow-up [mean, interquartile range], months	46	[55.3, 20–74]
Vital status at the latest follow-up		
Alive without disease	55	63.2
Alive with disease	8	9.2
Dead	24	27.6

Abbreviation: HPF, high-power fields.

^aN = 74 (13 missing data).

^bN = 80 (seven missing data).

^cN = 76 (11 missing data).

^dN = 76 (11 missing data).

^eN = 72 (15 missing data).

^fN = 71 (16 missing data).

^gN = 62 (25 missing data).

^hN = 64 patients (23 missing data or not able to conclude because the information on the feature *infiltrative growth pattern* was discriminant).

ⁱN = 75 (12 missing data).

classified into the following categories: low risk (score of 0), intermediate risk (scores of 1, 2, or 3), and high risk (scores of 4 and 5) of recurrence. We note that there was no interaction between sexes or other variables on the PEC-PRO score. The correlations between previous prognostic classifications and the PEC-PRO score are detailed in Figure 3.

The 2-year EFS rates were 93.7% (95% CI, 83.8%–100.0%), 67.4% (95% CI, 53.9%–80.9%), and 2.3% (95% CI, 0.0%–18.3%) for the low-risk, intermediate-risk, and high-risk groups, respectively (Figure 4A). The median EFS was not reached for the low-risk group and was 96.4 months (95% CI, 28.1–104.3 months) for the intermediate-risk group, but it was only 3.4 months (95% CI, 2.6–7.5 months) for the high-risk group. For OS, the median was not reached for the low-risk and intermediate-risk groups, but it was 24.0 months (95% CI, 13 months to NA) for the high-risk group, with 4-year OS rates of 93.7% (95% CI, 83.3%–100.0%) and 71.8% (95% CI,

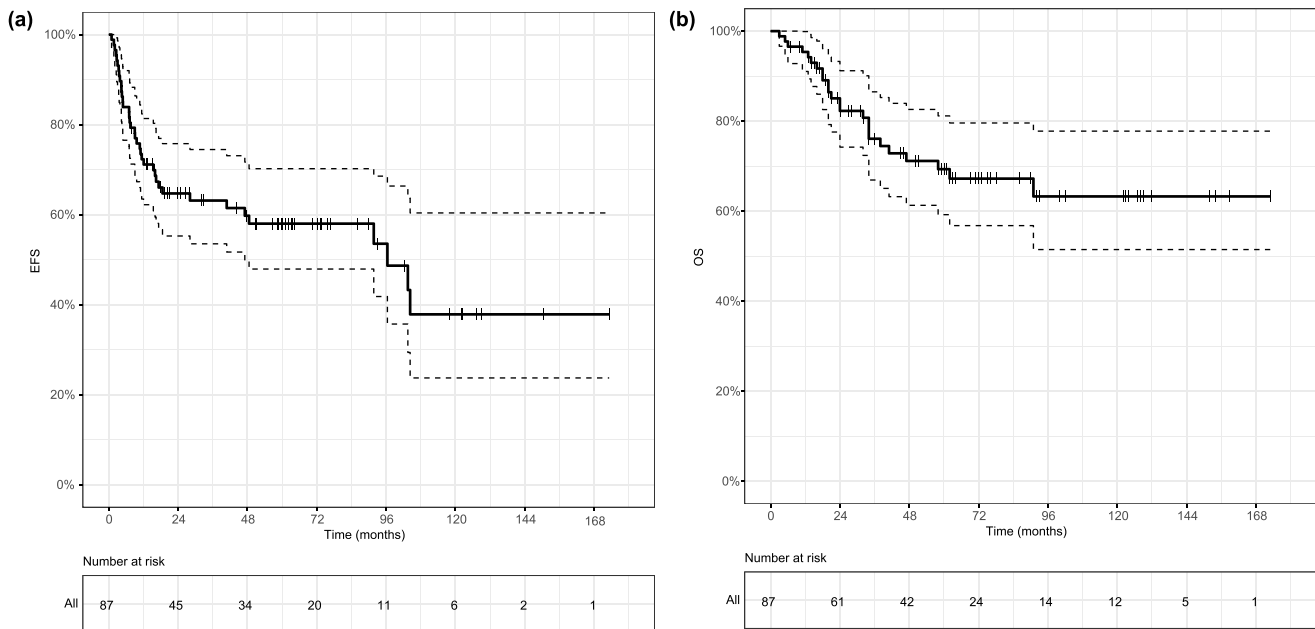


FIGURE 2 Kaplan-Meier (A) EFS and (B) OS curves. EFS indicates event-free survival; OS, overall survival.

56.8%–86.8%) for the low-risk and intermediate-risk groups, respectively, but only 25.3% (95% CI, 0.0%–50.5%) for the high-risk group (Figure 4B).

DISCUSSION

To our knowledge, we report herein the clinicopathologic features and outcomes of the largest cohort of patients to date with localized PEComas-NOS and with a significant median follow-up. The analysis allowed us to establish a prognostic score, enabling a subgroup risk stratification scheme that might be useful to optimize follow-up and adjuvant treatment recommendations.

Until now, the natural history of PEComas-NOS was not well understood. Based on pathologic features from 26 patients with a median follow-up of 30 months, in 2005, Folpe et al. proposed a classification to stratify these tumors as malignant, of uncertain malignant potential, or benign.⁷ However, these features can be missing on pathologic reports, leading to an inability to reach a conclusion on the classification. This issue was highlighted by Bleeker et al., who proposed a revised set of variables shortened to two pathologic features: the *simplified Folpe classification*.⁸ These classifications have been established to identify the features associated with relapse and thus malignant behavior but without taking in account neither the time to recurrence or OS. In our cohort, 28.4% and 22.6% of patients who had tumors classified as benign or with uncertain malignant potential developed recurrent disease. This was consistent with the absence of an association between the simplified Folpe classification and EFS, although a tendency toward a higher risk of EFS was observed for cases classified as malignant.

Our cohort shared clinical features that were similar to those previously reported.^{7,8,17,22} Among these features, male sex, positive surgical margins, and the presence of necrosis and/or vascular invasion were associated with poor EFS. Male sex was previously described as a poor prognostic factor in retroperitoneal sarcomas and also in specific carcinomas, explained by the finding that it was associated with significantly higher risks of all-cause death.^{23–25} Positive surgical margins are a described a poor prognostic factor common to all sarcomas.^{26–28}

Studies are needed to explore the role of molecular tumor alterations in predicting malignant potential.

In sarcoma, because available staging tumor-nodal-metastasis (TNM) classification has limited clinical value,²⁹ nomograms are preferred to assess the prognosis. The most frequently used nomogram is the *Sarcuator*, which was built for patients with extremity soft tissue sarcoma.³⁰ The PEC-PRO score works as a nomogram, adding a value of one or two features, depending on the presence of four clinicopathologic features. In the high-risk group of patients, almost 95% relapsed in the 2 years after their surgery, and approximately 75% had died of their disease after the fourth year. These patients need to be very closely monitored, and systemic perioperative treatment should be discussed by a multidisciplinary tumor board. In the intermediate-risk patients, greater than 30% relapsed in the 2 years after their surgery, and approximately 30% had died of their disease at 4 years after their surgery, also arguing for close monitoring. Conversely, less than 10% of patients in the low-risk group relapsed in the first 2 years and had died of their disease in the first 4 years. Therefore, the PEC-PRO score provides a practical tool for risk stratification in clinical practice and is more reliable than previous classifications.

TABLE 2 Univariate and multivariate analyses of clinicopathologic factors related to event-free survival.

Variable	Univariate analysis, HR [95% CI]	<i>p</i>	Multivariate analysis, HR [95% CI]	<i>p</i>
Median age, years				
Younger	1.00	.378	—	
Older	1.34 [0.69–2.61]			
Sex				
Female	1.00	.005 ^a	1.00	.023 ^a
Male	2.78 [1.39–5.57]		3.13 [1.19–8.27]	
Tumor size >5 cm				
Absent	1.00	.043 ^a	1.00	.201
Present	2.43 [1.03–5.75]		2.10 [0.65–6.82]	
Primary tumor site				
Uterus	1.00			
Kidney	0.65 [0.21–2.01]	.458	—	
Gastrointestinal tract	0.45 [0.09–2.12]	.312	—	
Soft tissue and head/neck	0.69 [0.29–1.64]	.404	—	
Others	0.86 [0.32–2.29]	.764		
High nuclear grade and cellularity				
Absent	1.00	.026 ^a	1.00	.946
Present	2.61 [1.13–6.04]		1.04 [0.31–3.46]	
Mitotic rate > 1/50 HPF				
Absent	1.00	.106	—	
Present	2.00 [0.85–4.68]			
Necrosis				
Absent	1.00	.001 ^a	1.00	.030 ^a
Present	4.40 [1.95–9.90]		3.94 [1.16–13.43]	
Vascular invasion				
Absent	1.00	.002	1.00	.110
Present	4.15 [1.75–9.86]		2.53 [0.79–8.11]	
Lymph node invasion				
Absent	1.00	.017 ^a	1.00	.530
Present	2.94 [1.24–6.99]		1.59 [0.34–7.48]	
Folpe simplified classification				
Benign	1.00		—	
Uncertain malignant potential	1.12 [0.88–3.24]	.833		
Malignant	2.39 [0.88–6.46]	.083		
Surgical margins				
Negative	1.00	.015 ^a	1.00	.008 ^a
Positive	2.43 [1.20–4.41]		5.17 [1.65–16.24]	
Systemic perioperative treatment				
Absent	1.00	.124	—	
Present	2.06 [0.81–5.26]			

(Continues)

TABLE 2 (Continued)

Variable	Univariate analysis, HR [95% CI]	<i>p</i>	Multivariate analysis, HR [95% CI]	<i>p</i>
Adjuvant radiotherapy				
Absent	1.00	.268	—	
Present	1.70 [0.65–4.41]			

Abbreviations: CI, confidence interval; HPF, high-power fields; HR, hazard ratio.

^aThese *p* values indicate a significant difference.

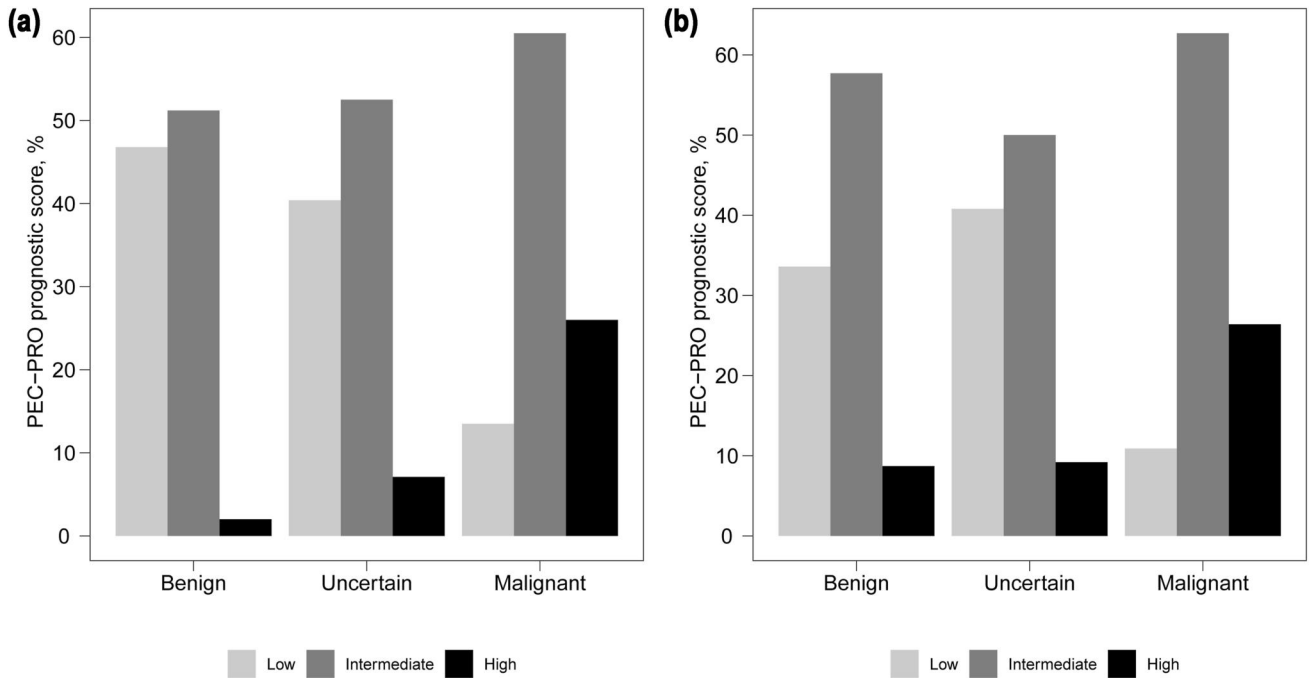


FIGURE 3 Correlation of the percentage (A) between the Folpe classification and the PEC-PRO prognostic score and (B) between the Folpe simplified classification and the PEC-PRO prognostic score. EFS indicates event-free survival; OS, overall survival; PEC-PRO, perivascular epithelioid cell neoplasm prognostic score.

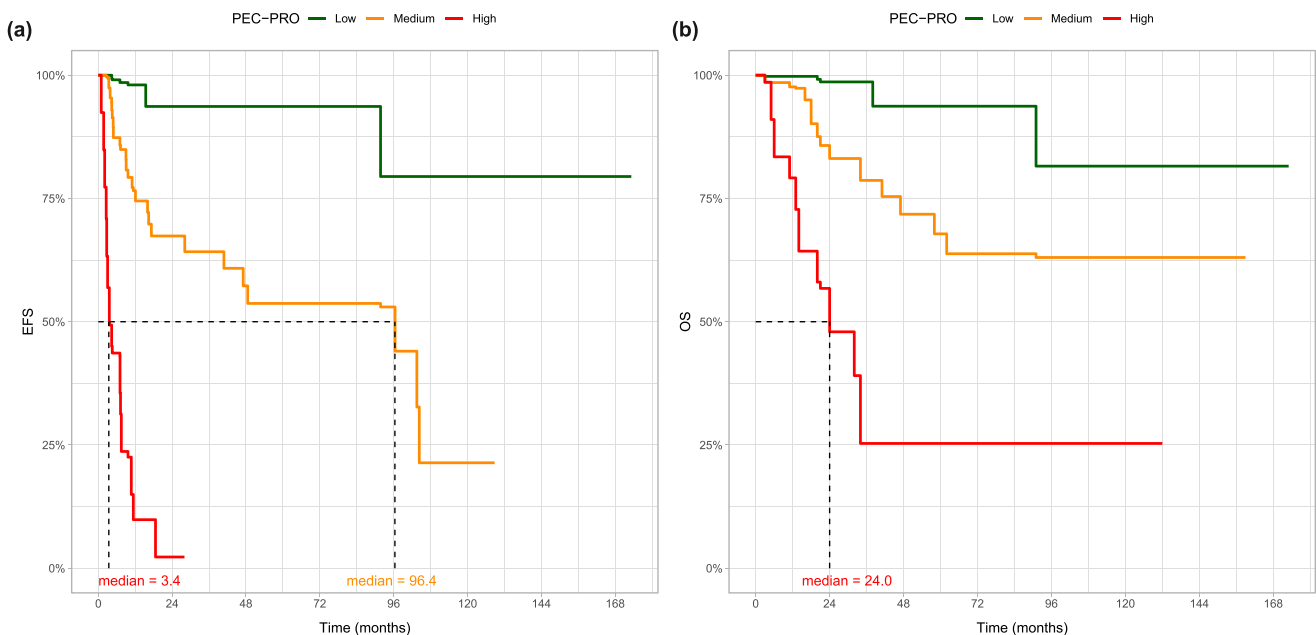


FIGURE 4 Kaplan-Meier (A) EFS and (B) OS curves according to the PEC-PRO prognostic score. EFS indicates event-free survival; OS, overall survival; PEC-PRO, perivascular epithelioid cell neoplasm prognostic score.

Our study has several limitations, including its retrospective design and the limited number of patients. However, to our knowledge, this cohort is the largest published to date on a very rare disease diagnosed by expert pathologists. Of course, the PEC-PRO score needs further validation in larger and independent series, retrospective studies, and then, ideally, prospective studies within the international sarcoma community to decide which patients could benefit from adjuvant therapies through a clinical trial based on the PEC-PRO score.³¹

Conclusion

We describe prognostic factors of localized PComas-NOS. By using a weighted combination of clinicopathologic features, the PEC-PRO score reliably predicts the risk of postoperative recurrence. It has the potential to better improve follow-up strategies and personalize adjuvant treatments. The findings of this retrospective analysis require clinical validation.

AUTHOR CONTRIBUTIONS

Justine Gantzer: Writing—original draft, conceptualization, methodology, investigation, data curation, resources, visualization, formal analysis, and writing—review and editing. **Maud Toulmonde:** Writing—review and editing and resources. **François Severac:** Formal analysis, methodology, visualization, and writing—review and editing. **Ali N. Chamseddine:** Resources and writing—review and editing. **Céline Charon-Barra:** Resources and writing—review and editing. **Charles Vinson:** Resources and writing—review and editing. **Alice Hervieu:** Resources and writing—review and editing. **Agathe Bourgmayer:** Resources, writing—review and editing, and data curation. **François Bertucci:** Writing—review and editing and resources. **Thomas Ryckewaert:** Writing—review and editing and resources. **Thibaud Valentin:** Writing—review and editing and resources. **Nelly Firmin:** Writing—review and editing and resources. **Loïc Chaigneau:** Writing—review and editing and resources. **Emmanuelle Bompas:** Writing—review and editing and resources. **Philippe Follana:** Writing—review and editing and resources. **Nathalie Rioux-Leclercq:** Writing—review and editing and resources. **Pauline Soibinet-Oudot:** Writing—review and editing and resources. **Laurence Bozec:** Writing—review and editing and resources. **François Le Loarer:** Writing—review and editing and resources. **Noëlle Weingertner:** Writing—review and editing and resources. **Christine Chevreau:** Writing—review and editing and resources. **Florence Duffaud:** Writing—review and editing and resources. **Jean-Yves Blay:** Writing—review and editing and resources. **Jean-Emmanuel Kurtz:** Writing—review and editing and resources. **Patrick Schöffski:** Writing—review and editing and resources. **Mehdi Brahmi:** Writing—review and editing and resources. **Gabriel G. Malouf:** Conceptualization, supervision, formal analysis, project administration, funding acquisition, and writing—review and editing.

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ACKNOWLEDGMENTS

We thank the patients of all the centers for agreeing to participate in this project. This work was supported in part by grants from the INCA (PRTK-2020-046) and the French Sarcoma Clinical Reference Network.

CONFLICT OF INTEREST STATEMENT

Philippe Follana reports personal/consulting fees from GlaxoSmithKline; fees as an expert witness from Daiichi Sankyo Europe GmbH, Eli Lilly and Company, and GlaxoSmithKline; and travel expenses from Novartis Pharmaceuticals Corporation outside the submitted work. Patrick Schöffski reports personal/consulting fees from Adcendo, Amryt Pharma Holdings Ltd., Avacta Life Sciences, Blueprint Medicines Corporation, Boehringer Ingelheim, Cogent Therapeutics LLC, Curio Science, Deciphera Pharmaceuticals Inc., Ellipses Pharma, Eisai, Exelixis Inc., Genmab, IDRx, LLX Solutions, Medpace, Merck, Moleculin Biotech, NEC Oncolmmunity AS, PharmaMar, Regeneron Pharmaceuticals, Servier Pharmaceuticals LLC, Sonata Therapeutics, Telix Pharmaceuticals, Transgene, and UCB Biopharma SRL outside the submitted work. Jean-Yves Blay reports

research funding from the French Sarcoma Clinical Reference Network, INTERgroupe coopérateur français dans le domaine des SARComes (INTERSARC), LYon Recherche Innovation contre le CANcer+ (LYRICAN+), European reference network for all rare adult solid cancers (EURACANoRes NV), Eisai, G1 Therapeutics, PharmaMar, Genmab, Merck, Sartar Therapeutics, INA Therapeutics, and Adcendo; and personal/consulting fees from Deciphera, Ellipses Pharma, Transgene, Exelixis, Boehringer Ingelheim, Studiercentrum voor Kernenergie, SQZ Biotechnology, Adcendo, PharmaMar, Merck, Medspace, Cogent Biosciences, Eisai, Curio Science, LLX Solutions, Servier, Genmab, Biolumina, Sanofi, Regeneron, Moleculin Biotech, Avacta Life Sciences, Amryt Pharma, and UCB Boxer Capital outside the submitted work. Gabriel G. Malouf reports research funding from MSD Avenir and personal/consulting fees from Bristol Myers Squibb, Ipsen Pharma SAS, and Merck Sharpe and Dohme outside the submitted work. The remaining authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Gantzer J, Toulmonde M, Severac F, et al. PEC-PRO: a new prognostic score from a series of 87 patients with localized perivascular epithelioid cell neoplasms (PEComas) treated with curative intent. *Cancer*. 2024;1-11. doi:[10.1002/cncr.35277](https://doi.org/10.1002/cncr.35277)