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Aleksandra Sobiborowicz[1, 2], Anna M. Czarnecka[1, 3], Anna Szumera-Ciećkiewicz[4, 5], Piotr Rutkowski[1], Tomasz Świtaj[1]

[1]Department of Soft Tissue/Bone, Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Medical Faculty, Medical University of Warsaw, Warsaw, Poland
[3]Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences Warsaw, Poland
[4]Department of Pathology and Laboratory Diagnostics, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[5]Department of Diagnostic Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

Diagnosis and treatment of malignant PEComa tumours

Address for correspondence:
Dr n. med. Tomasz Świtaj
Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy
ul. Roentgena 5, 02–781 Warszawa
Phone: 22 546 20 31, fax: 22 643 93 75
e-mail: tomasz.switaj@coi.pl

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ABSTRACT

PEComa (PEC tumours; perivascular epithelioid cell tumours) is a family of rare tumours of mesenchymal origin, consisting of epithelial perivascular cells expressing melanocytic and myioid markers. This group includes benign tumours — such as angiomyolipoma (AML) of the kidney, and poorly differentiated malignant PEComa tumours with potential for an aggressive clinical course, which is the main focus of this review. PEComas are most often diagnosed in middle-aged women as extensive tumours located in the abdominal cavity or pelvis, manifesting as pain and complaints related to pressure on nearby organs. PEComa tumours should be differentiated from gastrointestinal stromal tumours (GIST), leiomyosarcoma, melanoma metastasis, chromophobic renal cell carcinoma, clear cell sarcoma, and other clear cell component tumours. Somatic inactivating mutations within the *TSC1*/*TSC2* genes, resulting in excessive activation of the mTORC1 complex, are characteristic for this group of tumour. Recently, a separate PEComa subgroup has been distinguished, characterised by the presence of the *TFE3* gene fusion, which also causes increased activity of the mTOR signalling pathway. Negative prognostic factors that indicate an increased risk of PEComa malignant biology are most often: tumour size > 5 cm, increased cytological and nuclear atypia, infiltration of surrounding tissues and blood vessels, presence of necrosis, and high mitotic activity. Radical resection remains the primary treatment method for PEComas because these tumours are characterised by high resistance to radiation and chemotherapy. In the case of locally advanced or metastatic disease, only single reports of short-term responses to palliative chemotherapy containing doxorubicin, gemcitabine, or ifosfamide are available in the literature. There are an increasing number of reports, in the form of several case reports and a few retrospective analyses, about the potential effectiveness of using mTOR inhibitors in unresectable cases. These drugs result in a reduction in primary tumour size and metastasis, as well as symptom relief, with controllable side effects. Unfortunately, case reports of complete resistance to mTOR inhibitor therapy are also available.

Key words: PEComa, perivascular epithelioid cell, mTOR

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Introduction

PEComa (PEC tumours; perivascular epithelioid cell tumours) is a family of rare tumours of mesenchymal origin composed of perivascular epithelioid cells (PEC) [1]. This group includes angiomyolipomas (AML), clear-cell sugar tumours (CCST) — pulmonary and extrapulmonary (PEST, primary extrapulmonary sugar tumour), lymphangioleiomyomatosis (LAM), clear-cell myomelanocytic tumours (CCMMT), and primary cutaneous PEComas (CCCMT, cutaneous clear cell myomelanocytic tumours). PEComa NOS (not otherwise specified) is a joint term for a broad group of tumours with perivascular epithelioid differentiation, not qualifying for the remaining subgroups of the PEComa family (AML, LAM, CCST, CCMMT). According to the WHO classification, in the PECOma NOS both benign PEComa NOS as well as clinically challenging tumours with

a higher degree of malignancy are included (malignant PEComa NOS). A malignant PEComa encountered by clinical oncologists in their practice is abdominopelvic perivascular epithelioid cell sarcoma — the so-called malignant PEComa [2, 3]. In the largest analysis performed so far encompassing 234 PEComa NOS cases described in the literature, epithelioid AML subtypes occurring outside the kidneys were also qualified [3]. In a collective analysis of 100 cases of PEComa-NOS, 38 cases were locally advanced with an infiltration of surrounding organs, and four patients developed metastases — these patients were qualified into the malignant PEComa group (Figure 1) [4]. Altogether fewer than 100 cases of malignant PEComa have been described in the literature [3, 5], and 13 of them concerned changes within bones [6].

Epidemiology

The age of the patients at the time of PEComa diagnosis is most commonly in the range of 38.9–56 years [7, 8], but PEComa cases in children have also been described [9, 10]. All reviews indicate more common PEComa occurrence in women (54–86.9% of cases) [11, 12], also after exclusion of sex-specific locations from the analysis [3].

Anatomical location

Among the most common locations for PEComa development are the uterus, skin, the liver, and the colon [3, 13]. Moreover, large malignant PEComas are diagnosed especially in the extraperitoneal space [14]. Many anatomical locations have been described for PEComas. In a large analysis 24 pancreatic PEComa cases were presented, of which half were localised in the head of the pancreas [12] and numerous PEComas of the digestive tract [11, 15], including the stomach [16], the ileus [17] and the colon [18]. Moreover, single cases in various locations have been described: the greater omentum [19], the gall bladder [20], the common bile duct [21], the breast [22], the thigh bone [6], rib [23], skull base [24], heart [25], pericardium [26], the prostate [27, 28], ovary [29], nasal cavity [30], throat [31], eye socket [10], urinary bladder [32], lung [33], and the groin [34].

Diagnosis

PEComa is quite often (approx. 20% of the cases) diagnosed by chance in an imaging examination performed for other indications [12]. The symptomatic form, most commonly locally advanced, manifests by pain and discomfort in the area of the tumour and by weight loss [12, 35], and in the case of PEComa localised in the uterus by a bloody discharge [36]. A biopsy is required for the diagnosis.

Metastases are most commonly described in the lungs — cases of pneumothorax caused by tumour infiltration [37], and in the liver and bones. Metastases to the extraperitoneal space have also been described as well as the central nervous system, ovary, adrenal glands, peritoneum, intestinal wall, skin, stomach, and lymph nodes [3, 4, 35, 37, 38]. For this reason, the diagnosis of malignant PEComa requires a complete evaluation of the staging as in the case of other sarcomas [39]. Dissemination in patients with primary tumours in the pelvis or lower limb first takes place to the lung (90%); 77.8% of tumours encompassing the kidneys and the mesentery first metastasise to the liver, and in turn tumours in the adrenal glands and extraperitoneal tissues initially give metastases to the peritoneum and lungs [40]. As metastases often occur after many years and predictive markers for their development are not known, patients after PEComa resection, especially of tumours > 8 cm, require observation for many years after surgical treatment [4]. Metastases in patients with PEComa can develop even up to 10 years after resection of the primary tumour [41].

Pathomorphology

PEC (perivascular epithelioid cells) do not have a corresponding normal cell type and simultaneously express differentiation markers for muscle cells and melanocytes. PEComas are composed of epithelioid and spindle-shaped cells with a light and eosinophilic cytoplasm with a sporadic presence of granularities. Cell nuclei are small and cylindrical; the nucleolus is rarely visible. The cells form nests or bands, often radially surrounding blood vessels [42]. In PEComa cells from the colon obtained by thin needle biopsy the presence of eosinophilic cytoplasmic inclusions has been described [43]. Elongated fusiform cells in PEComas are characterised by distinct fibres specific for smooth muscle, while the epithelioid component in general does not contain a large amount of such fibres. A PEComa may thus be composed of fusiform cells with elongated nuclei and thus present a myoid phenotype, or it may contain cells with a clearly eosinophilic cytoplasm and a more visible epithelioid phenotype; both these types of cells occur next to each other in the tumour (Fig. 1) [4].

In immunohistochemical staining typically co-expression of melanocytic markers is observed:

— HMB-45 in 92–100% [36, 44, 45];
— Melan A/Mart1 in 23–88% [36, 46];
— transcriptional factor MITF; nuclear expression in 50–92% [36, 44];

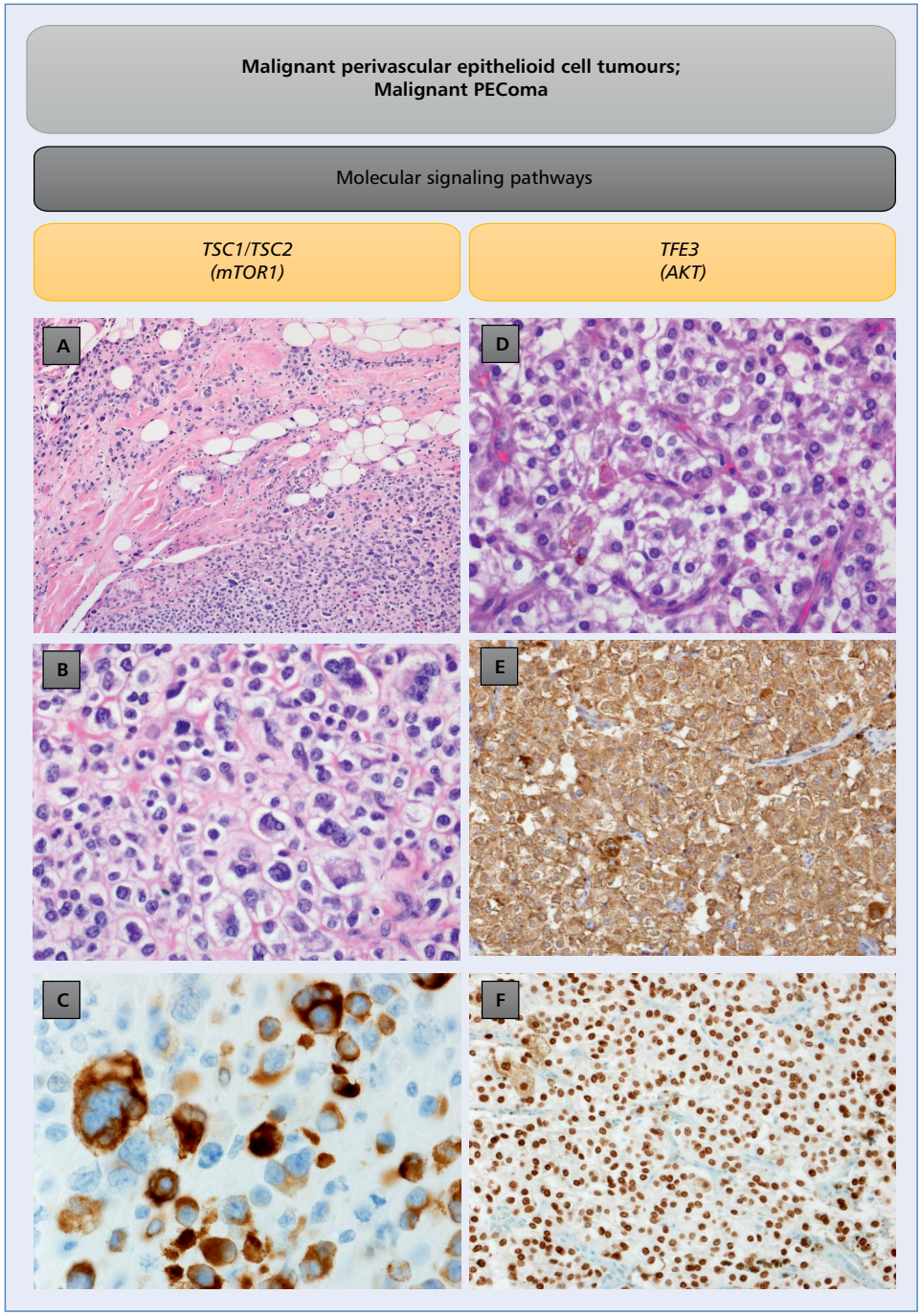

Figure 1. Malignant tumors of the PEComa family. **A**. As per definition, malignant PEComas is characterized by infiltrative growth type (HE, 40×); **B**. In addition, they PEComas characterized by high grade cytological atypia (HE, 400×); **C**. Tumor cells express HMB-45, which, together with SMA and Cathepsin K, are typical immunohistochemical markers (600×); **D**. Malignant PEComa with the presence of cells with pale and granular abundant cytoplasm (HE, 400×); **E**. Strong expression of Cathepsin K (200×); **F**. Strong nuclear expression of TFE3 (200×) — rearrangement of the TFE3 gene confirmed by fluorescence *in situ* hybridization and next generation sequencing

— S100; rare nuclear and cytoplasmic expression in 8–33% [44, 46];
and smooth muscle:
— desmin 36–100% [36, 44];
— smooth muscle actin (SMA) 59–93% [4, 44, 46];
— caldesmon 75–92% [36, 45].

Among additional PEComa markers cathepsin K is mentioned; its expression was observed in all analysed cases [45, 47], and transcriptional factor TFE3 (transcription factor binding to IGHM enhancer 3) was observed in 29–38% of cases regardless of the rearrangement of the *TFE3* gene [36, 44]. PNL2 has been

proposed as a new marker with high sensitivity and specificity in the differentiation of PEComa and AML (expression described in 89% of cases) from other neoplasms derived from kidneys, which do not express this marker [48]. In immunohistochemical analysis PEComas also stain positive for vimentin, CD-31, and CD-34 and are negative for CgA (chromogranin A), Syn (synaptophysin), CK (creatine kinase), CD117, CD10, AFP (alpha-fetoprotein), and EMA (epithelial membrane antigen). There are single reports about positive results of staining for progesterone receptor [49]. Cytoplasmic expression of CD10, a marker used in differential diagnosis of renal cell carcinoma metastases to the skin, has also been detected in skin PEComas [50]. In four cases of malignant-PEComa-NOS formed in the colon, the thigh, elbow, and bladder a strong nuclear overexpression of cyclin D1 was observed [51].

Macroscopically PEComa tumours are pink, yellow-brown, or white in cross section, with a differentiated consistency. In about 20% of cases, bleeding into the tumour or the presence of necrosis are observed [45]. The tumour capsule, typical for sarcomas, is absent, but the tumours are described as well limited from surrounding tissue [11, 35]. PEComa tumours are characterised by a rich vascularisation from branching capillaries to thicker arterioles, often with a hyalinised wall [42]. In 13–19% of PEComa cases an increased hyalinisation of the stroma is observed and the lack of the rich vascularisation typical for classical cases; this variant has been described as the sclerosing variant [36, 46]. Malignant PEComa is characterised by a high degree of histological malignancy, high cellularity, a high mitotic index (> 1/50 HPF), the presence of necrosis, and the possibility of infiltration of surrounding tissues and blood and lymphatic vessels [44].

The basic pathological differential diagnosis for PEComa NOS (summarised in Table 1) encompasses: gastrointestinal stromal tumours (GIST), melanoma, renal cell, and adrenocortical carcinoma, especially the chromophobic type, clear cell sarcoma of tendon and aponeurosis — melanoma of the soft parts (CCS), alveolar soft part sarcoma (ASPS) [8, 52], paraganglioma, angiomyolipoma, and also gynaecological tumours such as endometrial stromal sarcoma with clear cell features or uterine tumour resembling sex cord tumour and other tumours with a clear cell component [4]. It is also important to distinguish them from tumours derived from smooth muscle (epithelioid leiomyosarcoma — LMS and epithelioid leiomyoma).

The diffuse and multimarker expression of proteins of melanocytic differentiation, which does not occur in other sarcomas, is highly indicative for the diagnosis of PEComas. Focal or weakly positive results of staining do not justify a PEComa diagnosis. Diagnosis of an angiomyolipoma can be excluded if neither lipid elements nor a biphasic cell population are present. However, PEComa and a monophasic epithelioid angiomyolipoma are probably very close diagnoses. An endometrial stromal

Table 1. Pathological differential diagnosis of PEComa NOS

Unit	Morphology	Immunohistochemical markers						Other characteristic properties
		HMB-45, Melan A	CD117	S100	CD10	SMA	TFE3	
PEComa	Perivascular proliferation of epithelioid and fusiform cells with light eosinophilic cytoplasm with granularities, nucleoli are visible	+	±	±	±	+	±	
GIST	Epithelioid and fusiform cells with light eosinophilic cytoplasm without granularities	–	+ (together with CD34)	–	–	–	–	*c-kit* and *PDGFA* mutations
Melanoma	Cells of different shapes. No clear nucleoli	+	–	+	–	–	–	*BRAF* mutations in approx. 50% of patients
Chromophobic RCC	Richly vascularised; epithelioid cells	–	+	–	+	–	–	
CCS	Nests of spherical or epithelioid cells, giant multinuclear cells present	+	–	+	–	–	–	Gene fusions: t(2:22)(q34;q12)(EWS-CREB11) t(12;22)(q13;q13)(EWS--ATF1)
ASPS	Cytoplasmic granularities, no epithelioid cells	–	–	–	–	±	+	Translocations t(X; 17)
LMS	Epithelioid and fusiform cells	–	±	±	+	+	–	

ASPS — alveolar soft part sarcoma; CCS — clear cell sarcoma; GIST — gastrointestinal stromal tumour; RCC — renal cell carcinoma; SMA — smooth muscle actin

sarcoma can be excluded due to the presence of a clear perivascular distribution of tumour cells and a diffuse, and not focal, positive staining HMB-45. PEComa can be distinguished from paraganglioma because the former is negative for staining for chromogranin A, synaptophysin, and protein S100, and the latter more commonly grows in the form of organoids. The expression of melanocyte markers (HMB-45 and MART-1/Melan-A) and the lack of immunoreactivity to cytokeratins and renal cell carcinoma counter a diagnosis of cancer and help to recognise a PEComa [51].

Genetics

In approx. 80% of PEComa cases deletions and/or loss of heterozygosity (LOH) are observed in the 16p13.3 region, at locus *TSC2*, leading to the loss of tuberin activity [7, 53]. Sporadically LOH is observed in the 9q34 region, locus *TSC1*, encoding hamartin [54]. Both proteins participate in forming a complex with GTPase activity, acting as an inhibitor of the mTOR (mTOR/S6K1/4E-BP1) signal pathway. Activation of the mTOR pathway leads to increased proliferation of cells and their differentiation into myocytes. The loss of the function of tuberin and/or hamartin leads to an excessive activity of the mTOR serine/threonine kinase, which is a target for the use of mTOR inhibitors in the therapy of patients with advanced PEComa [55]. These perturbations are often accompanied by mutations of the *TP53* gene, which is described in 63% of the cases in which this was analysed [7].

In spite of the frequent presence of *TSC2* somatic mutations, the occurrence of PEComa NOS/malignant PEComa is less tightly connected to tuberous sclerosis — a genetic syndrome caused by a germ-line mutation inactivating the *TSC1* or *TSC2* genes — in comparison to the remaining tumours from this family, e.g. LAM or AML. In the literature tuberous sclerosis occurred only among 0–6.25% of patients with PEComa [36, 44].

In recent years, taking into consideration molecular investigations, a second form of PEComa, characterised by rearrangements of the *TFE3* gene (Xp11.23) has been distinguished [7]. *TFE3* rearrangements were described earlier in renal cell carcinoma [56] and are also characteristic for alveolar soft part sarcoma [57]. Its product is a transcription factor of the MiTF/TFE family regulating the expression of genes dependent on the signal pathway of transforming growth factor β (TGF-β) [58]. Moreover, TFE3 takes part in the regulation of cellular metabolism via stimulation of lysosome formation and modification of the response to oxidative stress and increasing autophagy processes, resulting in activation of the mTORC1 signal pathway [59, 60]. For PEComa *SFPQ/PSF-TFE3* and *DVL2-TFE3* fusions have been described [7, 61].

TSC2 mutations and *TFE3* gene rearrangements are mutually exclusive [7]. PEComa with a *TFE3* gene rearrangement has been described as differing in morphology, with a preponderance of epithelioid cells with a vesicular architecture and the lack of fusiform cells and no characteristic vascularisation. Lack of expression of smooth muscle actin (SMA) and desmin have also been observed [62]. However, the analysis only encompassed four cases, and in the literature there is also a case of a PEComa with a *TFE3* gene fusion with morphological properties typical for the classical form [42].

Among rare gene rearrangements described in PEComas are two cases of *RAD51B* fusions with *RRAGB/OPHN1* in a uterine PEComa and two cases of *HTR4-ST3GAL1* and *RASSF1-PDZRN3* fusions [7]. One case of malignant PEComa has been described in which next generation sequencing indicated a nonsense mutation (E1413*) in the *ATRX* gene (alpha thalassaemia-mental retardation, X linked) as the only genetic perturbation [63]. The loss of ATRX protein expression had been observed earlier in poorly differentiated soft tissue sarcomas [64] and was correlated with the phenomenon of alternative telomere elongation in leiomyosarcoma [65].

Treatment of locally advanced and metastatic disease

Radical resection is the mainstay of PEComa treatment because these tumours are characterised by resistance to chemotherapy and radiotherapy [3, 66]. In the described cases also the mastectomy of metastatic foci (lung, kidney, liver) permitted long-term control of the disease [4]. Because of the overarching importance of surgical treatment in order to obtain long-term survival, patients with initially recognised advanced disease have unfavourable prognoses because so far the importance and/or significance of adjuvant or neoadjuvant chemotherapeutic treatment has not been proven and it is currently not recommended, with the exception of clinical research protocols and application in reference centres [67]. A response to neoadjuvant stereotactic radiotherapy (SBRT; eight fractions of 7.5 Gy each) has also been observed in the case of a non-resectable liver PEComa. A decrease in the tumour size enabled radical resection, and the patient was disease-free after 21 months [68]. Chemotherapy has also been described as strongly decreasing the vascularisation but not the tumour size for PEComa (ifosfamide + vincristine + dactinomycin), which gives less blood loss during subsequent resection [51]. Three-component chemotherapy (epirubicin with cisplatin and ifosfamide) applied as a neoadjuvant allowed a decrease of tumour mass and resectability of a mass in the pelvis [69].

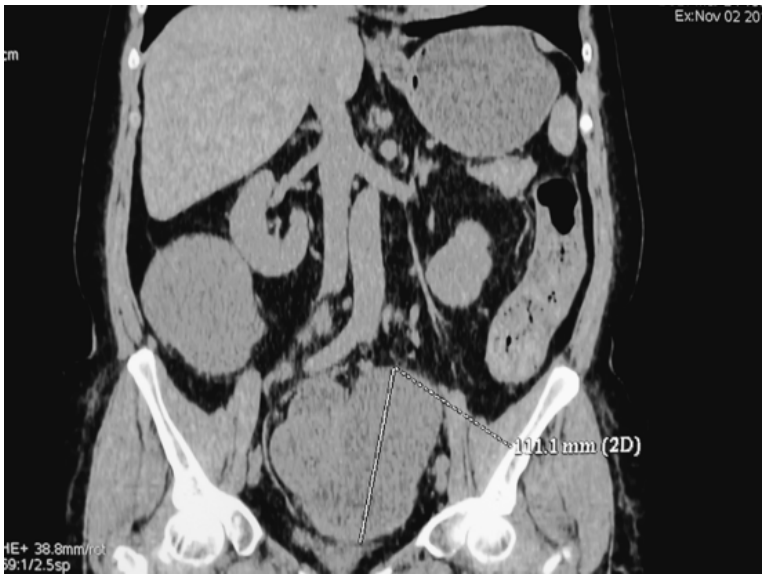

Figure 2. CT scan of PEComa — large pelvic and intraperitoneal tumours

Classical palliative chemotherapy yields few objective responses, although the use of Adriamycin in monotherapy has been described, as well as high dose ifosfamide, gemcitabine with docetaxel, and dacarbazine [67]. In a retrospective analysis of 53 patients with locally advanced or metastatic PEComa, the objective response rate (ORR) to chemotherapy based on gemcitabine or anthracyclines was only obtained in a small percentage of the patients (respectively, ORR = 20% and 13%), and progression-free survival (PFS) was: 3.4 and 3.2 months [70]. Moreover, only single cases of a response to doxorubicin and ifosfamide treatment were observed, e.g. a nine-month stabilisation of the disease obtained in a patient with a colon PEComa with metastases to the liver and a response in the form of a diminished mass of an upper limb PEComa by 80% after six cycles (PR, partial response) [71, 72]. Partial responses (PR) were also noted for dacarbazine treatment, complete responses (CR) for vincristine, and progression when imatinib treatment was used [51].

Because of frequent genetic perturbations causing an increase in the activity of the mTOR signalling pathway, similarly as in other subgroups of this family of tumours, long-term response to treatment with mTOR inhibitors is observed [73]. Benson et al. (from the Royal Marsden Hospital) published a retrospective analysis of mTOR inhibitors in the treatment of advanced PEComas with metastases for 10 cases (eight women, two men, median age 47.5 years). Nine patients received sirolimus (median dose 4 mg/d *p.o.*) and one temsirolimus, at a dose of 25 mg/week intravenously. The reaction was evaluated according RECIST in 7/10 patients, PR was observed in 50% of cases, SD in 10%, and PD in 10%. In the three remaining patients, rapid progression took place in the first days of the treatment. Among the nine patients receiving sirolimus, the drug dose was decreased in five, and in four the treatment was intermittently stopped because of undesirable effects. Treatment was stopped in seven patients, in six of them because of disease progression. The one-year survival rate was 78.8%, and the survival time median was 2.4 years, with median observation time of 1.9 years [74]. In a retrospective analysis, application of mTOR inhibitors in patients with locally advanced or metastatic PEComa was demonstrated (ORR: 41%, PFS: 9 months), compared to classical chemotherapy based on gemcitabine or anthracyclines (ORR: 20% and 13%, PFS: 3.4 and 3.2 months) [70]. In another analysis encompassing five patients with PEComa metastases in the digestive tract, treated with sirolimus or everolimus, a clinical response was obtained in four (observation period 1 to 47 months), and in one patient progression and death occurred 23 months after diagnosis [11]. The remaining data about the use of mTOR inhibitors in this group of patients are from descriptions of cases. A 20-month disease stabilisation (SD) was observed in a patient with a disseminated form of kidney PEComa treated with sirolimus [75]. The therapy was complicated by strong undesirable effects during the first month of treatment, linked to the level of the drug in the blood of 156.8 ng/ml; this disappeared during five weeks after adjusting the dose. A pancreatic PEComa has been described in which resection was not performed and therapy with sirolimus was introduced, obtaining a partial response, which was maintained for 42 months [76]. A case of a patient with an advanced colon PEComa with metastases to the liver is known — after radical resection he received sirolimus as an adjuvant. In spite of treatment, local relapse occurred

Table 2. Cases of PEComa treated with mTOR inhibitors available in the literature

Author	Sex	Age	Tumour location	Metastases	Drug	Dose	Best outcome	Time to progression (months)	Follow-up (months)	Effect
Wagner et al. [79]	M	65	Extraperitoneal space	Lungs	Sirolimus	8 mg/d	PR	16	16	AWD
	M	70	Kidney	–	Sirolimus	1–4 mg/d	PR	12	12	AWD
	F	61	Uterus	Lungs	Sirolimus; sorafenib + sirolimus	2–8 mg/d	PR	3	7	DOD
Italiano et al. [78]	F	55	Uterus	Lungs, heart, liver	Temsirolimus	25 mg/week IV	PR	5,5	ND	AWD
	F	69	Uterus	Lungs	Neo. temsirolimus, adj. temsirolimus	25 mg/week IV	CR	ND	9	NED
Gennatas et al. [80]	F	63	Extraperitoneal space	Lungs, abdominal cavity	Everolimus	10 mg/d	PR	10	37	AWD
Dickson et al. [81]	F	24	Extraperitoneal space	–	Sirolimus	4 mg/d	CR	NR	22	NED
	F	40	Extraperitoneal space	Pelvic lymph nodes	Sirolimus	3–4 mg/d	CR	NR	16	NED
	M	57	Small intestine	Abdominal cavity	Sirolimus	4 mg/d	PR	NR	14	AWD
	F	37	Liver	–	Neo. everolimus	5 mg/d	PR	NR	6	NED
	M	65	Adrenal glands	Lungs, soft tissues	Sirolimus	1–4 mg/d	SD	ND	36	DOD
Scheppach et al. [72]	M	23	Colon	Liver	Sirolimus	2 mg/d	PD	4	23	DOD
Bergamo et al. [82]	F	31	Liver	–	Neo. sirolimus	2–3 mg/d	PR	NR	10	NED
Nakanishi et al. [83]	F	51	Extraperitoneal space	Liver	Temsirolimus	ND	SD	ND	5	DOD
Bunch et al. [84]	F	19	Uterus	–	Temsirolimus	25 mg/week IV	PR	NR	15	NED
Ghosh et al. [85]	F	57	Pelvis	Pleura, lymph nodes extraperitoneal space	Temsirolimus, sirolimus	25 mg/week IV; 2 mg/d	PR	NR; 3	10	DOD
Chen et al. [86]	F	71	Pelvis	–	Temsirolimus, everolimus	25 mg/week IV, 10 mg/d	SD	NR; 4	7	DOD
Weeber et al. [87]	M	56	Greater omentum	Liver, adrenal glands, extraperitoneal space	Everolimus	10 mg/d	CR	36	48	AWD
Sun et al. [88]	F	46	Uterus	Lungs, kidneys	Sirolimus	ND	PR	NR	7	AWD
Gao et al. [89]	F	47	Uterus	Lungs	Sirolimus + sorafenib	200–300 mg/d	CR	NR	7	NED

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Table 2 cont. Cases of PEComa treated with mTOR inhibitors available in the literature

Author	Sex	Age	Tumour location	Metastases	Drug	Dose	Best outcome	Time to progression (months)	Follow-up (months)	Effect
Liu et al. [90]	F	60	Small intestine	–	Sirolimus	2 mg/d	PD	1	ND	AWD
Binyamin et al. [91]	F	56	Kidney	Pubic bone, surgical scar	Everolimus	BD	PD	2	ND	AWD
Starbuck et al. [92]	F	30	Uterus	–	Temsirolimus, sirolimus	25 mg/week IV; 3 mg/d	PR	NR	36	AWD
Flechter et al. [93]	F	43	Uterus	–	Temsirolimus	25 mg/week IV	CR	NR	12	NED
	F	64	Uterus	Abdominal cavity	Temsirolimus	25 mg/week IV	PD	3	18	DOD
	F	35	Small intestine	Lungs, central nervous system	Everolimus	10 mg/d	SD	18	30	DOD
Batereau et al. [94]	F	26	Colon	Abdominal cavity, ovaries, bladder	Sirolimus	ND	PR	NR	36	AWD
Shaikh et al. [95]	F	20	Extraperitoneal space	Pleura	Everolimus	ND	PR	7	8	DOD
Rao et al. [96]	F	49	Pelvis	Periaortic lymph nodes	Sirolimus	ND	CR	NR	12	NED
	F	6	Heart	–	Neo. sirolimus	ND	SD	NR	24	NED
Varan et al. [97]	M	7	Eye cavity	–	Sirolimus	ND	PD	1	6	AWD
Tang et al. [98]	M	50	Abdominal cavity wall	Mediastinal lymph nodes, lungs, bones	Sirolimus	2–3 mg/d	PD	ND	ND	DOD
Machado et al. [67]	F	33	Greater omentum, small intestine	Liver	Temsirolimus	ND	SD	5	30	DOD
Westaby et al. [29]	F	54	Ovary	–	Sirolimus	ND	PD	1	6	DOD
Kwon et al. [99]	F	62	Uterus and vagina	Lungs, bones	Everolimus	25 mg/week IV	SD	NR	18	AWD
Hulova et al. [77]	F	28	Kidney	–	Everolimus	ND	SD	30	104	DOD
Saluja et al. [100]	F	28	Throat	–	Neo. everolimus	ND	PD	NR	6	NED
Raimondi et al. [75]	M	61	Kidney	Lungs	Sirolimus	1–5 mg/d	PR	NR	20	AWD
Gondran et al. [76]	M	17	Pancreas	–	Sirolimus	4–6 mg/d	PR	NR	42	AWD

Adj. — adjuvant treatment; AWD — alive with disease; ND — no data; DOD — dead of disease; NED — no evidence of disease; NR — not reached; Neo. — neoadjuvant treatment; CR — complete response; PD — progressive disease; PR — partial response; SD — stable disease

Table 3. Classification of PEComa NOS after [44]

Tumour size greater than 5 cm	**Benign** < 2 high risk characteristics and size < 5 cm
High degree of histological malignancy and high cellularity	**Uncertain malignancy potential** Size > 5 cm and no other high-risk characteristics OR nuclear pleomorphism/multinuclear giant cells
High mitotic index (> 1/50 HPF)	**Malignant** 2 or more high-risk characteristics
Presence of necrosis	
Infiltration of blood vessels	

along with new liver metastases [72]. A 36-month stabilisation of the disease has also been described in a patient with kidney PEComa with metastases to the lung as a response to everolimus [77]. Italiano et al. described a response to temsirolimus treatment in a patient after resection of a uterine PEComa with a single lung metastasis. A decrease in tumour size by 35% was observed with a subsequent lobectomy. The patient remained disease free for nine months after the surgery with continued temsirolimus therapy [78].

In spite of promising responses, cases of resistance to mTOR inhibitors have also been described in combination with resistance to chemotherapy or without it. Machado et al. described a case of resistance to both Adriamycin and ifosfamide in high doses as well as temsirolimus (SD for a period of five months), leading to the patient's death 30 months after the diagnosis [67]. As markers of expected response to sirolimus and everolimus, the following are indicated: the presence of *TSC1/TSC2* gene mutations and overexpression of ribosomal protein pS6-S235/236 [67]. Single cases of the use of this group of drugs in patients with PEComas described in the literature are summarised in Table 2.

Regarding new drugs, recently a case of a one-year disease stabilisation in response to pazopanib combined with nivolumab has been described in an advanced PEComa of the lower limb with metastases to bones and lungs [63]. Potential benefits of using angiogenesis inhibitors in patients with advanced PEComa have been described, but only a very small percentage of objective responses have been achieved, mainly in the form of disease stabilisation: ORR = 8.3%, PFS = 5.4 months [70].

Survival — prognostic factors for PEComa-NOS

Among PEComa-NOS tumours, both clinically benign tumours as well as rapidly progressing tumours with disease dissemination are observed. Folpe et al. proposed the division of PEComas into three categories of risk: benign tumours, tumours with an uncertain malignancy potential, and malignant tumours, on the basis of the presence of the high-risk characteristics presented in Table 3 [44].

The prognostic suitability of the above-mentioned criteria was evaluated in a large review, encompassing 234 PEComa NOS cases available in the literature [3]. Among tumours classified as benign according to the Folpe criteria no relapses of the disease were observed. However, among cases in which a relapse did occur, tumours classified as malignant constituted 81.6% (median time to relapse 23 months). In about 30% of all cases the tumours were malignant (local relapse or disease dissemination took place), and tumours evaluated as malignant according to Folpe constituted 51% of these tumours [3]. 10.6% of cases led to death because of the disease, and seven of them were diagnosed at the moment of dissemination or in a non-resectable stage, and in 13 relapse occurred after resection [3]. In the same paper a significant correlation was demonstrated between tumour size over 5 cm ($p = 0.04$, RR = 6.16, 95% Cl: 1.04–117.4), a high mitotic index (> 1/50 HPS) ($p < 0.01$, RR = 6.96, 95% Cl: 2.2–26.7), low degree of cellular differentiation — Grade 3 ($p = 0.03$, RR = 3.35, 95% Cl: 1.17–9.42), and a higher risk of PEComa relapse after resection [3]. The primary location in skin was linked to a lower risk of local relapse after resection. In 20 of the described cases not one relapsed ($p = 0.002$, RR = 6.2×10^{-7}, 95% Cl: not calculable), whereas relapse occurred in 11.1% of cases located in the liver and in 33.3% of cases concerning extraperitoneal space [3].

In another analysis concerning PEComas localised in female sex organs, the following were among factors significantly correlated with a risk of recurrence or metastases: size greater than 5 cm ($p = 0.0048$), presence of necrosis ($p = 0.0014$), infiltration of lymph vessels ($p = 0.0006$), pronounced nuclear atypia ($p = 0.0192$), and mitotic activity > 1/50 HPF ($p = 0.011$) [36]. In an investigation focused on digestive tract PEComas, there were distant metastases in 37% of patients, and a higher risk of their occurrence was correlated with the following: pronounced nuclear atypia ($p = 0.0033$), disseminated pleomorphism ($p = 0.02$), and the presence of ≥ 2 mitoses/10 HPF ($p = 0.0002$) [11]. In another

analysis concerning digestive tract PEComa, local relapse did not occur, and the presence of distant metastases after resection was observed in 37.1% of patients, with a median of time to occurrence of metastases of six months [35].

In an analysis encompassing PEComas localised in female sex organs, 66% of cases were treated by surgery alone, and the average OS after resection was 24.8 months. The age of the patient was a negative OS predictor. In patients with disseminated disease treated by surgery with adjuvant chemotherapy or radiotherapy the average OS was 17.8 months, and in those treated only systemically or by radiotherapy it was 20.7 months. Patients with initial disseminated disease had a shorter OS regardless of the selected treatment method [35].

Summary

Malignant PEComa tumours are most frequently diagnosed in middle-aged women as extensive tumours localised in the abdominal cavity or pelvis, presenting as pain from the tumour progression and problems linked to pressure on surrounding organs. These tumours, because of expression of melanocyte and myoid markers and the presence of poorly differentiated epithelioid cells, should be differentiated from stromal neoplasms of the digestive tract, leiomyosarcoma, melanoma metastases, chromophobic type of renal cell carcinoma, clear cell sarcoma, and other neoplasms with a clear cell component. Somatic inactivating mutations within the *TSC1/TSC2* genes and fusions of the *TFE3* gene resulting in excessive activation of the mTORC1 complex are characteristic for these tumours. Among negative prognostic factors indicating an increased risk of malignant PEComa biology the most commonly included are: tumour size > 5 cm, pronounced cytological and nuclear atypia, infiltration of surrounding tissues and blood vessels, the presence of necrosis and high mitotic activity. Radical resection remains the main method of PEComa treatment because these tumours show a high resistance to radiotherapy and chemotherapy. There are increasing numbers of reports about the potential effectiveness of using mTOR inhibitors in non-resectable cases. These drugs cause a decrease in the size of the primary tumours and metastases and a decrease in the ailments, and the undesirable actions can be controlled. Unfortunately, cases have also been described of complete resistance to treatment with mTOR inhibitors.

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