METASTATIC RISK FACTORS IN PHEOCHROMOCYTOMA/PARAGANGLIOMA

© Dina V. Rebrova[1]*, Olga I. Loginova[1], Sergey L. Vorobyev[2], Natalya V. Vorokhobina[3], Evgenia S. Kozorezova[2], Fedor A. Indeykin[2], Tatyana V. Savelyeva[1], Ilya V. Sleptsov[1], Roman A. Chernikov[1], Elisey A. Fedorov[1], Arseny A. Semenov[1], Igor K. Chinchuk[1], Shamil Sh. Shikhmagomedov[1], Mikhail A. Alekseev[1], Vladimir F. Rusakov[1], Leonid M. Krasnov[1]

[1]Saint Petersburg State University, Saint Petersburg State University Hospital, St. Petersburg, Russia
[2]National Clinical Center of Morphological Diagnostic, St. Petersburg, Russia
[3]North-Western State Medical University n.a. I.I. Mechnikov, St. Petersburg, Russia

Currently, all pheochromocytoma/paraganglioma (PPGLs) are considered malignant due to metastatic potential. Consequently, PPGLs are divided into «metastatic» and «non-metastatic». Metastatic PPGLs can be with synchronous metastasis (metastases appear simultaneously with the identified primary tumor) or metachronous (metastases develop after removal of the primary tumor). The term metastatic PPGLs is not used in the presence of tumor invasion into surrounding organs and tissues, without the presence of distant metastases of lymphogenic or hematogenic origin.
It is generally believed that about 10% of pheochromocytomas and about 40% of sympathetic paragangliomas have metastatic potential. On average, the prevalence of PPGLs with the presence of metastases is 15–20%.
Risk factors for metastatic PPGLs are widely discussed in the literature, the most significant of which are groups of clinical, morphological and genetic characteristics. The review presents a discussion of such risk factors for metastatic PPGLs as age, localization and type of hormonal secretion of the tumor, the size and growth pattern of the adrenal lesion, the presence of necrosis and invasion into the vessels, the tumor capsule surrounding adipose tissue, high cellular and mitotic activity, Ki-67 index, expression of chromogranin B and S100 protein, the presence of genetic mutations of three main clusters (pseudohypoxia, kinase signaling and Wnt signaling).
Over the past two decades, a number of authors have proposed various predictor factors and scales for assessing a probability of metastatic PPGLs. The review contains detailed description and comparison of sensitivity and specificity of such predictor scales as PASS, GAPP, M-GAPP, ASES and COPPS.

KEYWORDS: pheochromocytoma; paraganglioma; metastatic pheochromocytoma/paraganglioma; malignant pheochromocytoma/paraganglioma; PASS scale; GAPP scale.

ФАКТОРЫ РИСКА РАЗВИТИЯ МЕТАСТАТИЧЕСКОЙ ФЕОХРОМОЦИТОМЫ/ПАРАГАНГЛИОМЫ

© Д.В. Реброва[1]*, О.И. Логинова[1], С.Л. Воробьев[2], Н.В. Ворохобина[3], Е.С. Козорезова[2], Ф.А. Индейкин[2], Т.В. Савельева[1], И.В. Слепцов[1], Р.А. Черников[1], Е.А. Федоров[1], А.А. Семенов[1], И.К. Чинчук[1], Ш.Ш. Шихмагомедов[1], М.А. Алексеев[1], В.Ф. Русаков[1], Л.М. Краснов[1]

[1]Санкт-Петербургский государственный университет, Клиника высоких медицинских технологий им. Н.И. Пирогова, Санкт-Петербург, Россия
[2]Национальный клинический центр морфологической диагностики, Санкт-Петербург, Россия
[3]Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия

В настоящее время все феохромоцитомы/параганглиомы (ФЕО/ПГ) считаются злокачественными, поскольку обладают метастатическим потенциалом. ФЕО/ПГ разделяют на «метастатические» и «неметастатические». Метастатические ФЕО/ПГ» могут быть с синхронным метастазированием (метастазы появляются одновременно с выявленной первичной опухолью) или метахронным (метастазы развиваются после удаления первичной опухоли). Термин «метастатическая ФЕО/ПГ не применяется при наличии инвазии опухоли в окружающие органы и ткани, без наличия отдаленных метастазов лимфогенного или гематогенного происхождения.
Принято считать, что около 10% ФЕО и около 40% симпатических ПГ обладают метастатическим потенциалом. В среднем распространенность ФЕО/ПГ с наличием метастазов составляет 15–20%.
В литературе широко обсуждаются факторы риска метастатической ФЕО/ПГ, наиболее значимыми из которых считаются группы клинических, морфологических и генетических признаков. В обзоре представлено обсуждение таких факторов риска метастатической ФЕО/ПГ, как возраст, локализация и тип гормональной секреции опухоли, размер и характер роста новообразования, наличие некроза и инвазии в сосуды, капсулу опухоли, окружающую жировую клетчатку, высокая клеточность и митотическая активность, индекс Ki-67, экспрессия хромогранина B и белка S100, наличие генетических мутаций из трех основных кластеров (псевдогипоксии, киназного сигналинга и сигналинга *Wnt*).

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На протяжении последних двух десятилетий рядом авторов предложены различные предикторные факторы и шкалы для оценки вероятности развития метастатической формы ФЕО/ПГ. В обзоре подробно представлено описание и сравнение чувствительности и специфичности предикторных шкал PASS, GAPP, M-GAPP, ASES и COPPS.

КЛЮЧЕВЫЕ СЛОВА: феохромоцитома; параганглиома; метастатическая феохромоцитома/параганглиома; злокачественная феохромоцитома/параганглиома; шкала PASS; шкала GAPP.

Pheochromocytoma (PCC) is a tumour that develops from chromaffin cells of the adrenal medulla; paraganglioma (PGL) is a tumour that develops from sympathetic or parasympathetic ganglia [1]. Clinical manifestations and morphological structure of these tumours are identical. The most frequent symptom of PPGLs is elevated blood pressure. Probable courses include paroxysmal arterial hypertension with development of sympathoadrenal crises and persistent arterial hypertension that is resistant to antihypertensive therapy. Approximately 10% of PPGLs are asymptomatic [2]. These tumours are most often discovered incidentally through radiological examinations and require more in-depth tests to determine the nature of the incidentaloma in order to assess the need for surgery and preoperative preparation [3].

The division of PPGLs into benign and malignant, which persisted until the 4th revision of the WHO classification (2017), has become irrelevant. All PPGLs are now considered malignant by definition, as they have metastatic potential. In this regard, PPGLs are divided into "metastatic" and "non-metastatic" [4]. Metastatic PPGLs can develop synchronous metastasis (metastases appear simultaneously with the identified primary tumour) or metachronous (metastases develop after removal of the primary tumour) [5]. The term "metastatic PPGLs" is not used in the presence of tumour invasion into surrounding organs and tissues if no distant metastases of lymphogenic or hematogenic origin exist.

It is generally believed that about 10% of PCCs and about 40% of sympathetic PGLs have metastatic potential [6]. Parasympathetic PGLs in the head and neck metastasise rarely [7]. On average, the prevalence of PPGLs with metastases is 15%–20% [6, 8].

In most cases of sporadic PPGLs, surgical removal of the primary tumour results in complete cure [9]. The most common opinion in the literature is that in the event of metastatic lesions, five-year survival rate does not exceed 50% [10, 11]. More optimistic data were obtained in a study by Hamidi O. *et al.* (2017), in which a large cohort of patients showed much higher five-year survival rates than previously thought, both overall and specifically for metastatic PPGLs group: 85.4% and 88.2%, respectively; 10-year survival rates were 72.5% and 77.9%, respectively. This demonstrated an overall relatively favourable prognosis even for the common form of the disease [12]. However, to date, it is not uncommon for this pathology to be detected on autopsy only [13–16].

According to the literature, synchronous PPGLs metastases are detected in 35%–50% of cases [17]. Analysis of data on patients with adrenal and retroperitoneal neoplasms who underwent surgery at St. Petersburg State University Hospital in 2010–2022 showed that metastases were detected in only six out of 285 patients (2.1%) with PCCs and abdominal PGLs. Metachronous secondary deposits can be detected several years after removal of the primary tumour [12, 17]; therefore, the European Society of Endocrinology recommends ten-year follow-up of all patients with PPGLs [18]. In addition, there is a recommendation for lifelong follow-up of patients at high risk of developing metastatic PPGLs [18], but to date there are no reliable ways to assess the metastatic potential of these tumours.

Over the past two decades, various predictor factors and scales have been proposed by a number of authors to assess the likelihood of developing metastatic PPGLs. Risk factors can be divided into clinical, morphological and genetic groups.

CLINICAL FACTORS

Data on how various clinical factors affect PPGLs aggressive course and development of metastases are disparate and varied. In a retrospective study by Hamidi O. *et al.* (2017), older age is stated as one of the significant factors of rapid disease progression with a fatal outcome within five years [12]. On the contrary, Cho Y.Y. *et al.* (2018) considered an age under 35 to be a factor of higher risk for metastases [19], and Zelinka T. *et al.* (2011) – an age under 40 [20].

Some authors consider the nature of tumour secretion as a predictor of metastasis. Thus, Ayla-Ramirez M. *et al.* (2013) and Szalat A. *et al.* (2010) found that metastatic PPGLs rarely secrete adrenaline, while Eisenhofer G. *et al.* (2012) reported dopamine secretion as more characteristic for this type of tumours; Cho Y.Y. *et al.* (2018) and Zelinka T. *et al.* (2011) considered noradrenaline type of secretion as a risk of metastasis [6, 19, 20, 21, 22].

In a study by Hamidi O. *et al.* (2017), functional activity was detected in 197 out of 248 patients with metastatic PPGLs. From the data available for analysis, increased adrenergic secretion was found in 61 out of 177 patients (34.5%); noradrenergic secretion was found in 113 out of 177 patients (63.8%); dopaminergic secretion – in 71 out of 177 patients (42%). In 51 patients out of the 248 examined (21%), hormonal activity was absent [12].

The study by Stenman A. *et al.* (2019) obtained data on the association of elevated plasma chromogranin B levels and its increased expression in tumours with high PASS score, suggesting that this indicator could be used for preoperative assessment of the risk of metastatic PPGLs [23].

Many authors have shown that PGLs of extra-adrenal localisation have a higher metastatic potential compared to PCCs. In a study by Ayla-Ramirez M. *et al.* (2011) on a large cohort of 371 patients (267 PCCs and 104 PGLs), the incidence of secondary lesions was 25% in PCCs compared to 65%–70% in PGLs [6]. Out of 272 patients with metastatic PPGLs examined between 1960 and 2016 at Mayo Clinic, 36% had PCCs, 58% had PGLs, and 6% had both types of tumours simultaneously [12].

MORPHOLOGICAL FACTORS

Most authors agree that morphological markers of high probability of metastatic PPGLs development include tumour necrosis, diffuse growth of the neoplasm, high cellularity, invasion into blood vessels, tumour capsule, or the surrounding fatty tissue, high mitotic activity (>3 mitoses per 10 fields of view at ×400 magnification).

August C. *et al.* (2004) considered the PPGLs' weight to be the most informative factor in predicting a metastatic tumour: tumours weighing 100 g or more were statistically significantly more likely to be metastatic [24]. Similar data were obtained in the study by Wailly P. *et al.* (2012). These authors found a direct correlation of tumour size and mass with the detection of metastases [25]. Nevertheless, August C. *et al.* (2004) noted that 25% of patients with secondary lesions had PPGLs less than 100 g with a minimum weight of 22 g, while an 80-year-old patient with a 280 g neoplasm was found to have no metastases during the subsequent eight-year follow-up [24]. A study by Agarwal A. *et al.* (2010) suggested that tumour size greater than 6 cm is a prognostically unfavourable factor for a metastatic PCC, although in 2 out of the 6 examined patients tumours size was 4 cm [26].

Ayla-Ramirez M. et al. (2011) reported decreased survival in patients with tumour size greater than 5 cm, but 16% of patients with metastatic forms (3 PCCs and 11 PGLs) had neoplasms smaller than 5 cm. Moreover, the possibility of tumour spread even in small neoplasms of 2 cm with simultaneous metastases in lymph nodes and tumours of 1 cm with bone metastasis detected one year after surgery was demonstrated on several patients [6]. In Zelinka T. *et al.* (2011), the median size of PCCs was larger in the metastatic group (8 cm vs. 5.8 cm); however, the minimum and maximum sizes were not significantly different (2.4 cm vs. 2 cm and 17 cm vs. 16 cm, respectively) [20]. Hamidi O. *et al.* (2017) obtained evidence of a high positive correlation between large tumour size and the risk of secondary lesions and rapid disease progression, with size greater than 6 cm considered as an important independent risk factor. Nevertheless, in this large cohort, metastatic PCCs with minimum size of 3 cm and PGLs with minimum size of of 0.9 cm occurred [12]. Thus, tumour size and mass cannot be considered a reliable prognostic criterion for metastatic spread of PPGLs.

A number of authors consider tumour necrosis as one of the prognostic factors of metastatic spread [20, 25, 27].

When it comes to determining the metastatic potential of chromaffin tissue tumours and the informativeness of the proliferative activity index, the authors' views differ. In Kulkarini M.M. *et al.* (2016), when examining ten PPGLs, a Ki-67 value of more than 3% was found only in two of the three metastatic PPGLs (elevated in two PGLs and not elevated in one PCC), while all seven non-metastatic neoplasms had a Ki-67 value under 3% [28]. In a study by Wailly P. *et al.* (2012), all seven PCC patients with established tumour metastases had a Ki-67 over 4%, but one out of the 46 cases with no distant lesions identified had a Ki-67 at 11% [25]. August C. *et al.* (2004) performed comparative genomic hybridisation of 41 PPGLs, which did not provide reliable evidence of chromosomal aberrations characteristic for the metastatic form of the disease. In this study, metastatic PPGLs were found to have higher proliferative activity with a MIB-1 index over 5%, and a weak membrane expression of CD44-S protein was observed [24]. Nevertheless, even though the aforesaid studies show that the described markers reflect increased proliferative activity and impaired ability to differentiate cells in metastatic PPGLs, some methodological limitations preclude deeming these indicators to be convincing enough for practical recommendations.

Data on the role of reduced number of Sertoli cells and, consequently, S100 protein expression as a predictor of metastatic spread of PPGLs are contradictory. In a study by Kulkarini M.M. *et al.* (2016), out of three cases with distant tumour spread, weak S100 immunoreactivity was found in two patients and moderate in one patient. In the seven non-metastatic cases, S100 expression was moderate to strong [28]. Unger P. *et al.* (1991) and, more recently, Wailly P. *et al.* (2012) considered the absence of S100 expression to be a reliable histopathological marker of high risk of secondary lesions [26, 29]. However, Bialas M. *et al.* (2013) showed a high variability of S100-positive cell counts depending on the part of tumour selected; therefore, this parameter cannot be deemed a reliable standardised marker of PCC/PGL metastasis risk [30]. Thus, the use of S100 protein expression as a risk factor is limited by contradictory results of studies, which is probably due to small sizes of samples represented therein.

GENETIC FACTORS

It is currently believed that about 40%–50% of PPGLs are associated with genetic mutations, even where no unfavourable family history exists [31]. Hereditary syndromes and currently known genetic mutations associated with PPGLs development can be divided into three main groups: those leading to cellular pseudohypoxia, those associated with disorders of kinase signalling and those associated with disorders of *Wnt* signalling [32] (Table 1).

The disease pathogenesis with mutations in genes of the pseudohypoxia group (*SDHA, SDHB, SDHC, SDHD, SDHAF2, FH, VHL, EPAS1*) is associated with excessive activation of hypoxia inducible factors (HIFs) in the absence of hypoxia. This group of neoplasms is characterised by a more aggressive course [32]. A number of studies established that tumours in patients with a pathogenic variant of the *SDHB* gene have the highest metastasis potential (up to 40%–50%) [6, 12, 33-35]. The amount of succinate in the tumour as measured by high-performance liquid chromatography – mass spectrometry (HPLC/MS), is higher in metastatic PPGLs compared to non-metastatic ones, which is due to *SDHB* gene mutations [36]. Meanwhile, the incidence of secondary lesions with defects in *SDHA, SDHC* and *VHL* genes is relatively low [32]. In AylaRamirez M. *et al.* (2011), about one half of metastatic PPGLs cases were associated with *SDHB* positive mutation, and the majority of such patients were diagnosed with PGLs. At the same time, only one patient from 89 metastatic PPGLs was found to have a rare *SDHC* mutation [6]. Similar data were obtained in a study by Hamidi O. *et al.* (2017) based on data of examination of 272 patients with metastatic PPGLs, of whom 81 (30%) had genetic syndromes, including 42 cases (15.4% of the total number and 52% of all genetically tested) due to *SDHB* mutation. In contrast, *SDHC* mutation was identified in only two out of the 272 patients (0.7%) [12]. *SDHD*

Table 1: Groups of genetic mutations associated with development of pheochromocytoma/paraganglioma

Genetic mutations group	Genes
Causing cellular pseudohypoxia	*SDHA, SDHB, SDHC, SDHD, SDHAF2, FH, VHL, EPAS1*
Associated with impaired kinase signalling	*RET, NF1, TMEM127, HRAS, MAX*
Associated with impaired Wnt signalling	*CSDE1, MAML3*

and *SDHAF2* gene mutations are more frequently associated with development of head and neck PGLs with a low risk of metastasis [7]. In hereditary leiomyomatosis syndrome and renal cell carcinoma caused by inactivating mutations of the fumarate hydratase (*FH*) gene, PPGLs occur in under 1% of cases; however, out of this number, more than 50% have an aggressive course with metastasis [32].

Kinase signalling mutations (*RET, NF1, TMEM127, HRAS, MAX*) lead to changes in the activity of such kinase signalling pathways as RAS/RAFG/MAPK and PI3K/AKT/mTOR, which is accompanied by tumour initiation and progression [32]. This type of neoplasia is characterised by lesion multifocality and high relapse rate [37]. In hereditary syndromes in this group, cases of metastatic PPGLs have been described, but their incidence is extremely rare.

CSDE1 and *MAML3* genes lead to oncogenesis by activation of *Wnt* and *Hedgehog* signalling pathways [32]. There are few studies on these mutations. It is believed that neoplasms of this group are characterised by the most aggressive course, active metastasis, and frequent relapses [37]. In addition, there are data on the association of metastatic PPGLs with somatic mutations in *SETD2* and *ATRX* genes, as well as with the activating mutation of the *TERT* promoter [38].

Due to established association between the prevalence of metastatic PPGLs and specific gene mutations, many researchers point to the need for genetic testing of all patients with newly diagnosed disease [39–41]. Late performance of genetic testing has been found to be associated with increased risk of relapse and decreased survival [42]. At the same time, one cannot ignore high financial burden on the public healthcare system if genetic panels would be routinely used for all patients with PPGLs [43]. Taking this factor into account, some authors recommend screening for certain categories of patients only: for example, for those aged under 20 and with family history or any clinical indicators of hereditary disease, as well as for all the patients with sympathetic PGLs [8, 44].

PREDICTOR SCALES

Based on clinical, morphological and genetic factors, various predictor scales have been established to predict the risks of metastatic PPGLs; these scales have both advantages and limitations.

THE PASS SCALE

Pheochromocytoma of the Adrenal gland Scaled Score (PASS) was proposed in 2002 by Thompson L.D.R. and was the first system created to predict PCCs' metastatic potential [45]. In that study, Thompson L.D.R. evaluated the morphological parameters of 100 surgically removed PCC in patients with a ten-year follow-up history after surgery: 50 with benign tumours and 50 with malignant tumours; in the latter group, 33 had distant metastases [45].

The PASS scale includes 12 histological features, each scoring 1 or 2 points; the maximum score is 20. If the total score is 4 or more, the tumour's malignancy potential is considered high.

PASS Criteria:

1) Large nests or diffuse cell growth (2 points)
2) Central or extensive necrosis foci (2 points)
3) High cellularity (2 points)
4) Cell monomorphism (2 points)
5) Spindle-shaped cells (2 points)
6) Mitosis figures – more than 3 in 10 consecutive fields of view (2 points)
7) Atypical mitosis figures (2 points)
8) Invasion into fatty fibre (2 points)
9) Vascular invasion (1 point)
10) Capsular invasion (1 point)
11) Marked cellular polymorphism (1 point)
12) Nuclear hyperchromia (1 point).

Although the PASS system was developed to assess PCCs' malignant potential, subsequent studies have shown its efficacy in assessing PGLs as well [10, 46, 47].

Several studies have evaluated the diagnostic accuracy of the PASS system, but the results have been inconsistent. It should be noted that before the 2017 revision of the WHO morphological classification, the term "malignant PCC" was used not only for metastatic forms, and therefore it is difficult to compare the results of studies from different years. Thus, as noted above, the follow-up data of the malignant PCC group presented in Thompson L.D.R. (2002) on whose basis the PASS scale was developed stated that the metastatic form was diagnosed only in 33 patients out of 50 [45].

August C. *et al.* (2004) analysed 43 cases of PPGLs graded as malignant by PASS: 37 adrenal and 6 extra-adrenal localisations. In the course of follow-up one patient was diagnosed with MEN 2A syndrome, and metastases were detected in 20 patients. Thus, in the described sample, the method's sensitivity was 100%, whereas its specificity was 0% [24]. In contrast, good results were obtained in a study by Szalat *et al.* (2010) through evaluating 16 cases of metastatic PPGLs, of which eight patients had histological material available for analysis: 7 PCCs and 1 PGLs. Out of the analysed tumours, seven cases had a PASS score over 4, whereas one PCC case had a PASS score under 4, with 87.5% method sensitivity. When analysing 19 neoplasms with no detectable metastases during a five-year follow-up using the PASS scale, all PCCs were found to have scored less than 4 points with a 100% specificity. However, the authors report a possible low reproducibility of some morphological parameters, such as nuclear hyperchromia and marked cellular polymorphism; therefore, in this work, revision of all tissue specimen was performed by one morphologist [21].

More convincing are the meta-analysis data of a large cohort of 809 PCCs, in which 102 out of 105 malignant forms (in different publications, these PCCs included those with diagnosed metastasis and those with invasion into neighbouring organs and tissues, as well as those with tumour relapse) scored 4 or more points in PASS with a 97% sensitivity. The analysis showed a rather low specificity of 68%, as only 480 of 704 non-metastatic PCCs were found to have a score under 4 [46].

Kulkarini M.M. *et al.* (2016) presented data from 4 PGLs cases. Metastasis were identified in two patients with a PASS scale sensitivity and specificity score of 100% [28]. A meta-analysis by Stenman A. *et al.* (2019) obtained less optimistic results from the analysis of 42 PGLs, of which 13 metastatic tumours had a total score at or over 4 (100% sensitivity); however, in the nonmetastatic forms, the same result was obtained in 8 out of 29 patients, whereas 21 out of the 29 examined ones had a total score under 4 (72% specificity) [46]. Even lower results were obtained by Agarwal A. *et al.* (2010), in which a PASS score >4 points was found in 5 out of 6 patients with metastatic PCCs (83% sensitivity) and in 27 out of 84 nonmetastatic cases (67.9% specificity) [26].

According to many authors, application of the PASS histological scale is limited due to low reproducibility of morphological features in different studies [10, 46, 47].

THE GAPP SCALE

The Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) was proposed by Kimura N. *et al.* in 2014 [48]. The GAPP model is based on the PASS algorithm with significant changes: exclusion of the most variable histological parameters; retention of only four criteria (histological pattern, cellularity, comedonecrosis, and invasion into the capsule and blood vessels); addition of immunohistochemical parameters (Ki-67 proliferation index) and clinical characteristics (laboratory data – type of catecholamine secretion). Unlike the PASS scale, the GAPP diagnostic system is designed for both PCCs and PGLs. As suggested by the authors, based on the results of characteristic scores, all PPGLs tumours are divided into three groups: highly differentiated (0–2 points), moderately differentiated (3–6 points) and low differentiated (7–10 points). Highly differentiated tumours are assumed to have less metastatic potential and better overall survival; however, even in the original study, the specificity of this grading was 96%: 4 of 111 patients had metastases, and five-year survival rate was 100%. Metastasis were detected in 21 out of 35 patients with moderately differentiated PPGLs (60%) and in 15 out of 17 patients (88%) with highly differentiated masses; five-year survival rates were 67% and 22%, respectively [48].

In a meta-analysis by Stenman A. *et al.* (2019), GAPP system sensitivity in 175 PCCs cases, of which four were considered malignant (with metastases or local relapse), was 50%: two patients had a tumour score of 3 or more, whereas the other two had a grade under 3. 35 nonmetastatic cases had a GAPP score of 3 or more, whereas 136 scored less than 3, thus the specificity was 80%. A 100% sensitivity of the prognostic algorithm was obtained for PGLs: all four metastatic cases included in the analysis scored 3 or more points. However, GAPP scale specificity for this sample was 68%, as 10 out of 31 and 20 out of 31 nonmetastatic PGLs scored ≥3 and <3, respectively [46]. In Britvin T.A. *et al.* (2021), a significant positive correlation between the PASS and GAPP systems and between both these scales with the size of PCCs was established [49].

MODIFIED M-GAPP SCALE

A modified GAPP scale for PPGLs (M-GAPP) was proposed by Koh J.M. *et al.* (2017) [50]. Such an important prognostic factor as *SDHB* gene mutation in tumour cells was added to GAPP scoring system criteria. However, diagnostic accuracy of this scale did not improve: 12 out of 34 (35.3%) tumours with a PASS score ≥4, 12 out of 40 (30%) moderately or low differentiated by GAPP and 10 out of 19 (52.6%) with MGAPP score ≥3 turned out to be metastatic [50]. According to a meta-analysis by Wang Y. *et al.* (2020), M-GAPP scale sensitivity was 67%, specificity - 84%, which was even lower than the similar evaluation by GAPP system [10].

ASES SCALE

Cho Y.Y. *et al.* (2018) proposed a clinical prognostic scale for assessing metastatic potential ASES – short for Age, Size, Extra-adrenal (extra-adrenal localisation), and Secretory (hormonal secretion), based on evaluation of data from 333 patients (305 PCCs and 28 PGLs), of whom 23 had metastases (18 PCCs and 5 PGLs) [19]. Age up to 35 years inclusive, tumour size of 6 cm or more, extra-adrenal localisation and noradrenaline type of secretion are each scored 1 point on this scale. With a total score of 2 or more, the sensitivity of this scale was 61% (14/23) and specificity was 80% (248/310). The 10year survival rate of patients with a score ≥2 was 30% and <2 was 86% [19]. Despite the low diagnostic accuracy of this scale, the possibility of prognostic assessment of the metastatic potential of the tumour enables one to speak about the importance of taking into account not only PPGLs histopathological characteristics but their clinical features as well [10].

COPPS SCALE

The Composite Pheochromocytoma/paraganglioma Prognostic Score (COPPS) was proposed in 2019 by Pierre C. *et al.* and includes three clinicopathological characteristics (tumour size, presence of necrosis and vascular invasion) and immunohistochemical characteristics (loss of *S100* and *SDHB* expression) [27]. In this study, data from 147 patients (107 PCCs and 40 PGLs) were assessed, of whom nine had metastases (2 PCCs and 7 PGLs). The analysis found a statistically significant positive correlation between high risk of metastatic PPGLs and such parameters as extra-adrenal tumour localisation, *SDHB* gene mutation, tumour necrosis, cellular monomorphism, >3 mitoses in 10 fields of view at x400 magnification, capsular and vascular invasion, loss of *S100* and *SDHB* gene expression, size over 7 cm, age over 40, and *MCM6* expression level. In addition, combined majority of these parameters correlated with progression-free survival rates.

Of these parameters, only five were independently associated with metastatic PPGLs: tumour size over 7 cm (1 point), vascular invasion (1 point), tumour necrosis (5 points), loss of *S100* gene expression by tumour cells (2 points), loss

Table 2: Comparing various morphological scales designed to determine the risk of metastatic pheochromocytoma/paraganglioma

Scale name	PASS	GAPP	M-GAPP	ASES	COPPS
First proposed	Thompson L.D.R. (2002) [45]	Kimura N. *et al.* (2014) [48]	Koh J.M. *et al.* (2017) [50]	Cho Y.Y. *et al.* (2018) [19]	Pierre C. *et al.* (2019) [27]
Applicable for pheochromocytoma	+	+	+	+	+
Applicable for paraganglioma		+	+	+	+
Age				+	
Tumour size				+	+
Type of catecholamine secretion		+	+	+	
Extra-adrenal localisation				+	
Morphological criteria:					
large nests or diffuse cell growth	+	+	+		
necrosis foci	+	+	+		+
high cellularity	+	+	+		
cell monomorphism	+				
spindle-shaped cells	+				
over 3 mitoses in 10 consecutive view fields	+				
atypical mitosis figures	+				
fatty tissue invasion	+				
vascular invasion	+	+	+		+
capsular invasion	+	+	+		
marked cell polymorphism	+				
nuclear hyperchromia	+				
Ki-67 proliferation index		+	+		
Loss of *S100* expression					+
SDHB gene mutations in tumour cells			+		+

of *SDHB* gene expression (1 point). Based on these, a COPPS scale with a maximum score of 10 points was created, on which a score of ≥3 points indicates a high metastatic potential of the tumour. The sensitivity of this prognostic system was 100% and specificity was 92.4% (Table 2) [27].

CONCLUSION

PPGLs are recognised as malignant tumours, but establishing their metastatic potential is challenging. The predominantly morphological features and scoring scales proposed by different authors do not have sufficient sensitivity and specificity to reliably determine the prognosis of tumour disease. At present, an individual approach to the assessment of prognosis, taking into account both clinical, morphological and genetic features, is the most rational. Due to the absence of reliable markers for determining metastatic potential, PPGLs patients, as per clinical recommendations, are subject to lifelong follow-up. It seems that, in the future, accumulation of data of in-depth preoperative examination with the purpose of detection of simultaneous metastases and regular followup of patients after surgical treatment to detect metastases combined with development of the most specific morphological and genetic features will enable to increase the sensitivity and specificity of metastasis risk indicators for this group of patients.

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AUTHORS INFO

***Dina V. Rebrova**, MD, PhD; ORCID: 0000-0002-7840-4174; SPIN-код: 6284-9008; e-mail: endocrinology@list.ru

Olga I. Loginova, MD, PhD; ORCID: 0000-0002-2484-4895; e-mail: olga7.smirnova@gmail.com
Tatyana V. Savelyeva, MD; ORCID: 0000-0002-2846-4056; SPIN-код: 9740-6360; e-mail: taleon76@yandex.ru
Natalya V. Vorokhobina, MD, PhD, Prof.; ORCID: 0000-0002-9574-105X; SPIN-код: 4062-6409; e-mail: natvorokh@mail.ru
Vladimir F. Rusakov, MD, PhD; ORCID: 0000-0002-6807-778X; SPIN-код: 1345-3530; e-mail: rusvf@mail.ru
Leonid M. Krasnov, MD, PhD; ORCID: 0000-0003-4449-0251; SPIN-код: 355848; SCOPUS ID: 7003572477;
e-mail: krasnov.surg@mail.ru
Ilya V. Sleptsov, MD, PhD; ORCID: 0000-0002-1903-5081; SPIN-код: 2481-4331; e-mail: newsurgery@yandex.ru
Roman A. Chernikov, MD, PhD; ORCID: 0000-0002-3001-664X; SPIN-код: 7093-1088; e-mail: yaddd@yandex.ru
Elisey A.Fedorov, MD, PhD; ORCID: 0000-0002-1294-811X; SPIN-код: 5673-2633; e-mail: elick@yandex.ru
Arseny A. Semenov, MD, PhD; ORCID: 0000-0001-6760-0025; SPIN-код: 6724-2170; e-mail: arseny@thyro.ru
Igor K. Chinchuk, MD, PhD; ORCID: 0000-0001-6986-1034; SPIN-код: 6252-6710; e-mail: dr.chinchuk@bk.ru
Mikhail A. Alekseev, MD; ORCID: 0000-0001-5643-5204; e-mail: miha_decor@mail.ru
Sergey L. Vorobyev, MD, PhD; ORCID: 0000-0002-7817-9069; SPIN-код: 5920-0603; e-mail: slvorob@gmail.com
Evgenia S. Kozorezova, MD; ORCID: 0000-0002-3659-7510; SPIN-код: 8523-5817; e-mail: kozorezovaes@yandex.ru
Fedor A. Indeikin, MD; ORCID: 0000-0002-1436-2235; SPIN-код: 4627-4445; e-mail: f.indeickin@yandex.ru
Shamil S. Shikhmagomedov, MD; ORCID: 0000-0002-3876-6306; SPIN-код: 3262-7588;
e-mail: shihmagomedov@yandex.ru

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