Review Article
The systems of metastatic potential prediction in pheochromocytoma and paraganglioma

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Received January 29, 2020; Accepted February 7, 2020; Epub March 1, 2020; Published March 15, 2020

Abstract: Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors that arising from the adrenal medulla or extra-adrenal autonomic ganglia. Traditionally, PPGL was classified as benign or malignant based on the presence of distant metastasis at the time of initial surgery. However, according to WHO 2017 Classification of Tumors of Endocrine Organs, all PPGL has metastatic potential. The term “metastatic” is used, replacing “malignant” in this group of tumors. The prediction of PPGL's metastatic potential is a clinical concern, although many relevant indicators such as genetics, histology, pathology and molecular biology markers have been proved to be related to the metastasis of PPGL, but none of them is 100% predictive; various types of prediction systems had been created, but previous studies had demonstrated that they still need to be validated in multicenter studies. There is no unified clinical standard to differentiate metastatic from non-metastatic and a highly effective prediction system is of urgent need. In this review, we summarized all reported prediction systems, including the PASS system, the GAPP system, the COPPs system and the ASES system. Additional potential indicators that related to metastatic PPGL were also introduced.

Keywords: Pheochromocytoma, paraganglioma, metastatic potential, prediction systems, PPGL

Introduction

Pheochromocytoma (PHEO) and paraganglioma (PGL), termed as PPGL, are rare neuroendocrine tumors that arising from the chromaffin cells of the adrenal medulla and extra-adrenal sympathetic or parasympathetic autonomic ganglia, respectively. About 80 to 85 percent of PPGL are pheochromocytoma, with an estimated annual incidence of 2-8 cases per million [1]. The main clinical characteristics of PPGL patients are recurring episodes of hypertension, palpitations, profuse diaphoresis and pallor. Nausea, vomiting, flushing and weight loss may be present in a few patients [2]. It has reported that approximately 0.1 to 1 percent of hypertension is due to PPGL [3, 4].

Traditionally, PPGL was classified as benign or malignant based on the presence of distant metastasis at the time of initial surgery. However, according to the update on adrenal tumors in 2017 WHO of endocrine tumors, all PPGL could have metastatic potential due to the lack of histological system endorsed for the biological aggressiveness of PPGL. The term “metastatic” is used, replacing “malignant” in this group of tumors.

Metastasis can be diagnosed only after the presence of metastasis in non-chromaffin site, but not local invasion into surrounding tissues [5]. Most PPGL are non-metastatic, which are not life-threatening and can be successfully cured by surgery, however, approximately 15-20% of them would finally metastasize [6, 7]. For patients with metastatic PPGL, the 5-year survival rate was lower than 50% [8, 9]. Metastasis can occur in months even decades after the initial diagnosis [10]. Thus, a proportion of patients with PPGL was considered as non-metastatic before surgery, while they were identified to have metastasis during follow up. It is of great significance to predict the metastatic potential in early stage, not only evaluate the risk of metastasis as well as survival and prognosis, but also guide doctors in taking active surgical intervention and strict follow-up.
European Society of Endocrinology Clinical Practice Guideline suggested that patients with high risk of metastatic potential should be followed-up for lifetime instead of 10 years [11]. A precise prediction of metastatic potential would be important. Besides, we would have a better understanding of the mechanisms of PPGL metastasis by predicting its metastatic potential, providing new insights into its drug targets.

Prediction of PPGL metastatic potential remains a clinical challenge. Although many relevant indicators have been proved to be related to the metastasis of PPGL [6, 12], none of them is 100% predictive; algorithms including the Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) grading system, the grading system for adrenal pheochromocytoma and paraganglioma (GAPP), the modified grading system for adrenal pheochromocytoma and paraganglioma (M-GAPP), the COPPs (Composite Pheochromocytoma/paraganglioma Prognostic Score) scoring system and ASES scoring system had been proposed [13-17], but previous studies had demonstrated that reproducibility of these systems needs to be validated in multicenter studies. In this review, we summarized all reported prediction systems and additional potential indicators that related to metastatic PPGL, aiming to help medical colleagues better understanding existing prediction systems from different perspectives and provide new insights into the prediction of PPGL metastatic potential.

**Existing prediction systems**

**PASS scoring system**

The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) grading system was created by Thompson in 2002, which was the earliest grading system for detecting the potential of biologically aggressive behavior of PHEO. The establishment of PASS grading system was based on 12 individually histologic features including large nests or diffuse growth (>10% of tumor volume), central (middle of large nests) or confluent tumor necrosis (not degenerative change), high cellularity, cellular monotony, tumor cell spindling (even if focal), mitotic figures >3/10 HPF (high-power field), atypical mitotic figure(s), extension into adipose tissue, vascular invasion, capsular invasion, profound nuclear pleomorphism and nuclear hyperchromasia. These features are endowed with different points, thereby discriminating non-metastatic PHEO from metastatic PHEO (based on the analysis of the overall tumor features of 100 patients) on the basis of the total score of patients’ features. In the PASS system, a PHEO is defined as “benign” fashion when its score is <4; otherwise (PASS score ≥4), biologically aggressive, with a total score of 20 (Table 1) [13]. Features including large nests or diffuse growth (>10% of tumor volume), central (middle of large nests) or confluent tumor necrosis (not degenerative change), high cellularity, extension into adipose tissue, vascular invasion, capsular invasion and a high count of mitotic had been widely accepted to be associated with metastasis in the PASS system [12].

Many studies assessed the predictive ability of PASS grading system [18, 19], but the results are inconsistent. In 2004, August et al evaluated the PASS system in 37 cases of PHEO, including 14 cases of malignancy, which found that all 14 cases of malignancy were assigned score ≥4 points, with a 100% sensitivity; and 23 cases of benign PEO had a score ≥4 points, with a specificity of 0% [20]. This study indicated that the PASS system does not have a strong ability to distinguish non-metastatic PHEO from PHEO with a PASS score ≥4. However, Szalat et al produced different results in 2010 with the study of 26 cases, including 7 metastatic tumors. Among 7 cases of metastatic PHEO, 6 were scored ≥4, 1 case had a score <4, with the sensitivity to be 86%. But all the 19 cases of non-metastatic PHEO had a PASS score <4, with a specificity of 100% [21]. Number of cases recruited in the studies may be the cause of the inconformity. In a recent meta-analysis which counted 809 PHEO cases with 105 metastatic cases, 102 were scored with ≥4 points, with a sensitivity of 97%. However, among the remaining 704 non-metastatic cases, 224 had PASS score ≥4 points, and only 480 cases were less than 4 points, with a specificity of 68%. These studies indicate that PASS grading system is of high sensitivity and low specificity. The accuracy rate of metastatic prediction results (PASS ≥4 points) is 31% (102/(102+224)); while accuracy rate of non-metastatic prediction results (PASS <4 points) is 99% (480/(3+480)) [22]. It means
that the prediction to be non-metastatic is more credible than that of metastatic. One study showed that PASS grading system gets a higher specificity when considered PHEO to be metastatic with a score of 6 rather than 4. This may be a way to increase the reliability and use of the PASS system [17].

Although the PASS grading system is established for pheochromocytoma only, other studies classify paraganglioma according to the PASS system, and the results show that the PASS system also has a similar ability to predict the malignant behavior of paraganglioma [19].

The evaluation of metastatic potential is a research concern. Being the earliest grading system, the establishment of PASS system is of great significance and provides a foundation for subsequent research. Although metastatic prediction results of the PASS system are not satisfactory, the non-metastatic prediction ability makes it a great value in specific clinical applications. Though, this system also has its shortcomings. For example, only histological characteristics were considered, while other influencing factors such as gene mutation [23], tumor characteristics [24] and clinical characteristics of patients were ignored [16]. In addition, there are too many histological features to be observed, which makes it easily influenced by the subjective evaluation, thus causing errors [25]. These disadvantages limited the development of the PASS system and encouraged the creation of other comprehensive prediction systems.

**GAPP and Modified-GAPP scoring system**

The grading system for adrenal pheochromocytoma and paraganglioma (GAPP) was designed by Kimura et al both for pheochromocytoma and paraganglioma in 2014, which was based on the PASS grading system by excluding some poorly concordant histological features [26] and aimed to predict the metastatic potential.
and the prognosis of patients. Compared to the PASS, the GAPP grading system was presented by 6 parameters which including 4 histological features (histological pattern, cellularity, comedo-type necrosis, capsular/vascular invasion) received from PASS and another 2 new immunohistochemical and biochemical features (Ki67 labelling index and catecholamine type). Similarly, these features were endowed with different points, with a total score of 10 (Table 1). Depending on the patient’s total points scored by their tumor characteristics, it was graded into three types: well-differentiated (WD, 0-2 points), moderately differentiated (MD, 3-6 points) and poorly differentiated (PD, 7-10 points). Different differentiated types were related to different metastatic potential and 5-year survival rates. The study contained 163 tumors, including 40 metastatic tumors. On the basis of the GAPP grading system, approximately 68% (111 cases) were graded into well-differentiated (WD), 22% (35 cases) were moderately differentiated (MD), and 10% (17 cases) were poorly differentiated (PD). Of these PPGLs, 4 WD, 21 MD and 15 PD tumors were metastatic, while the 5-year survival rates of the patients were 100% for WD, 67% for MD and 22% for PD tumors, respectively. The WD group showed a significant low metastatic rate (4%) and a perfect 5-year survival rate (100%) when compared to the MD group (with 60% metastatic rate and 67% 5-year survival rate) and PD group (with 88% metastatic rate and 22% 5-year survival rate). Thus, WD tumors were considered as low risk of metastasis, and MD or PD tumors were likely to be highly metastatic tumors (GAPP score ≥3). In addition, there was an important correlation between the GAPP score and the time of metastasis. Therefore, it is possible to predict metastatic potential and prognosis of patients according to their tumor score and corresponding differentiated levels based on GAPP [14].

A previous study had been carried out to validate the prediction ability of the GAPP grading system. It was found that the GAPP grading system has a similarly high sensitivity, low specificity, low prediction accuracy rate of metastatic tumors and an excellent prediction accuracy rate of non-metastatic PPGL compared to the PASS system. This result seemed like that excluding some nonspecific histological features of PPGL was compensated by adding Ki67 labelling index and catecholamine type [22].

A Ki67 proliferative index above 3 to 5% has been reported to be associated with an increased risk of metastasis in PPGL [23]. As a kind of neuroendocrine tumor, catecholamine secreting was the most noteworthy characteristic of PPGL, and the type of catecholamine (noradrenaline-type) was also an important risk factor for metastasis [11]. The combination of these two features and original 4 histological parameters was an improvement for the GAPP grading system when compared to PASS, but still ignored important factors which were reported to be associated with metastasis and prognosis such as tumor size and location [5]. Foremost, succinate dehydrogenase gene subunit B (SDHB) mutation, which has been widely accepted as a high-risk factor for metastasis has not been added into this system [3]. In the previous study, 8 MD and 5 PD tumors were negative for SDHB immunohistochemistry (which was useful to detect SDHB mutation), with a metastatic rate of 77% (10/13), while none of the 111 cases of WD tumors showed negative for that. It suggested that a combination of negative of SDHB immunohistochemistry with the GAPP grading system might be useful to predict metastatic potential [14]. This promoted the production of M-GAPP grading system.

The modified grading system for adrenal pheochromocytoma and paraganglioma (M-GAPP) was proposed by Koh et al in 2017, which is a combination of the loss of SDHB staining and some significant parameters (histological pattern, comedo-type necrosis, vascular invasion, Ki67 labeling index (%), catecholamine type) in the GAPP grading system (Table 1). In this study, the M-GAPP system was proved to have a higher prediction accuracy rate of metastatic tumors (10/19, 53%) than GAPP system (12/40, 30%) [15]. But in our review, we found that the M-GAPP was worse than GAPP grading system in specificity, sensitivity and accuracy rate of prediction results (Table 2).

Actually, neither GAPP nor M-GAPP grading system had a credible prediction accuracy rate of metastatic tumors (Table 2). Both of them were insufficient and need to be further validated in multicenter studies. It is of urgent need to
establish new predictive models to evaluate metastatic potential for PPGL.

**COPPs scoring system**

The COPPs (Composite Pheochromocytoma/paraganglioma Prognostic Score) scoring system, proposed by Pierre in 2019, is composed of three clinical-histopathological features (tumor size, necrosis, vascular invasion) combined with proliferation index PS100 and SDHB inactivation to predict PHEO/PGL metastasis risk and progression-free survival (PFS) [17].

In this study, a total of 147 cases of PPGL were collected in a single center (107 cases of PHEO and 40 cases of PGL), including 9 cases of metastasis (2 cases of PHEO and 7 cases of PGL). The collected clinical data included age, gender, date of the surgery, hypertension, size and location of tumor, genetic status, and follow-up data of patients. The expression of MCM6, Ki67, PS100 and SDHB was analyzed with immunohistochemistry. These collected data were used for multivariate and univariate analyses associated with metastasis status and progression-free survival. It was found that these variables (extra-adrenal localization, SDHB mutation, necrosis, cellular monotony, mitosis (>3/10 HPF, HPF = high-power field), capsular invasion, vascular invasion, loss of SDHB, PS100 negativity, size >7 cm, age, MCM6 LI) were significant correlated with metastasis status, while those (PS100, Ki-67, MCM6, vascular invasion, mitosis (>3/10) HPF, cellular monotony, high cellularity, necrosis, SDHB mutation, tumor size, metastasis) parameters were significant correlated with progression-free survival (PFS).

Among these parameters that were significant in univariate analysis, five were independently associated with metastasis status: focal or confluent necrosis, tumor size >7 cm, vascular invasion, PS100 loss, SDHB loss, which formed the COPPs grading system. These 5 different characteristics were endowed with different score, it is considered high risk of metastatic if the COPPs score ≥3 points, otherwise considered low risk (Table 1). Sensitivity and specificity of COPPs were 100% (9/9) and 92.4% (122/132), respectively. The accuracy rate of metastatic prediction results (COPPs ≥3 points) was 47.4% (9/19), and non-metastatic (COPPs <3 points) prediction results was 100% (122/122) (Table 2) [17].

Among these parameters included in COPPs grading system, tumor necrosis and vascular invasion also exist in PASS, GAPP, and M-GAPP grading system. The loss of SDHB was included in M-GAPP but not PASS or GAPP, which was proved to be associated with high risk of metastasis. Tumor size and loss of PS100 were reported to be related to metastasis in a previous study [27]. Compared with PASS and GAPP grading system, the COPPs grading system showed a similarly high sensibility and high prediction accuracy rate of non-metastatic PPGL, and had an increase in specificity, but still remains low or even lower in prediction accuracy rate of metastatic PPGL, which may be due to a small number of cases of metastatic PPGL (Table 2).

**ASES scoring system**

These grading systems, including PASS, GAPP, M-GAPP and COPPs, are mainly based on such characteristics of tumors: histopathological indicators, gene mutations, immunohistochemistry and molecular biological indicators (Table 1). However, many of the patient’s clinical characteristics such as age, tumor size, tumor location, secretory type of catecholamine may also be associated with metastatic potential [5, 17].

### Table 2. Sensibility, specificity, and prediction rate of different grading systems

<table>
<thead>
<tr>
<th></th>
<th>PASS</th>
<th>GAPP</th>
<th>M-GAPP</th>
<th>COPPs</th>
<th>ASES</th>
<th>Average or total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases of PPGL</td>
<td>100</td>
<td>163</td>
<td>72</td>
<td>141</td>
<td>333</td>
<td>809</td>
</tr>
<tr>
<td>Cases and proportion of PHEO</td>
<td>100 (100%)</td>
<td>127 (78%)</td>
<td>63 (88%)</td>
<td>105 (74%)</td>
<td>305 (92%)</td>
<td>700 (87%)</td>
</tr>
<tr>
<td>Cases and proportion of Metastatic PPGL</td>
<td>33* (33%)</td>
<td>40 (25%)</td>
<td>15 (21%)</td>
<td>9 (6%)</td>
<td>23 (7%)</td>
<td>120 (15%)</td>
</tr>
<tr>
<td>Sensibility</td>
<td>100% (33/33)</td>
<td>90% (36/40)</td>
<td>67% (10/15)</td>
<td>100% (9/9)</td>
<td>61% (14/23)</td>
<td>85% (102/120)</td>
</tr>
<tr>
<td>Specificity</td>
<td>75% (50/67)</td>
<td>87% (107/123)</td>
<td>84% (48/57)</td>
<td>92% (122/132)</td>
<td>80% (248/310)</td>
<td>83% (575/689)</td>
</tr>
<tr>
<td>Accuracy rate of non-metastatic prediction result</td>
<td>100% (50/50)</td>
<td>96% (107/111)</td>
<td>91% (48/53)</td>
<td>100% (122/122)</td>
<td>97% (248/257)</td>
<td>97% (575/593)</td>
</tr>
<tr>
<td>Accuracy rate of metastatic prediction result</td>
<td>66% (33/50)</td>
<td>69% (36/52)</td>
<td>53% (10/19)</td>
<td>47% (9/19)</td>
<td>18% (14/76)</td>
<td>47% (102/216)</td>
</tr>
</tbody>
</table>

* 17 of the 50 patients did not develop malignant clinical behavior.
Systems predicting PPGL metastatic potential

28-31]. And the ASES system is established in 2018 which only consisted of 4 clinical characteristics of patients (age, tumor size, extra-adrenal location and secretory type) based on multiple clinical parameters, aiming to evaluate the metastatic potential of PPGL [16].

In this study, a total of 333 patients were enrolled in the research, including 305 PHEO and 28 PGL. Metastasis occurred in 23 patients, including 18 PHEO and 5 PGL. Clinical characteristics including age, gender, height, weight, BMI, tumor size, location and preoperative fractionated metanephrines were collected. The patients were then divided into two groups based on whether the tumor had metastasized: 310 in the non-metastatic group and 23 in the metastatic group. Then the collected data were analyzed by multiple factors between two groups, and 4 clinical features were finally determined according to the data analysis results. In ASES grading system, any of these 4 parameters was scored 1 point if it was present, otherwise scored 0 point. A tumor more than or equal to 2 points was considered to be high risk of metastasis [16]. For parameters of ASES grading system, tumor size was first added into such grading system (COPPs was created after ASES system). Although tumor size was reported to be related to metastatic PPGL or rapid progress in previous studies [24, 27], it has also been reported that there is no significance in tumor size between metastatic and non-metastatic PPGL [18, 32]. So it’s still uncertain whether tumor size is a risk factor of metastasis or not.

In a previous study, the primary tumor location was a stronger indicator of metastasis than tumor size [5]; but recently, it was revealed that tumor location was not associated with metastasis [33]. These two uncertain risk factors may have a negative impact on the predictive value of the ASES prediction model.

Ultimately, the ASES system showed a low sensibility of 61% (14/23) and a specificity of 80% (248/310). The prediction accuracy rate of non-metastatic PPGL and metastatic PPGL was 97% (248/257) and 18% (14/76), respectively (Table 1). Compared with the other four systems, the ASES system has the most cases of PPGL, but relatively low proportion of metastatic cases, fewer parameters including uncertain factors, all of which may lead to the lowest prediction accuracy rate of metastatic result and the least clinical application value of these systems. However, ASES system only focuses on the clinical characteristics of PPGL and can also achieve a good prediction accuracy of non-metastatic tumors, which suggests that we cannot ignore the clinical characteristics of PPGL in the establishment of new standards in the future.

Potential indicators for predicting metastasis

In the previous section, we briefly introduce several existing predictive systems. Each of these systems has its advantages and disadvantages, and some of them have clinical application value. However, these scoring systems have not been validated in multicenter clinical trials and have not been widely accepted by the clinicians. In addition to these histopathological indicators, SDHB gene mutation, molecular markers, immunohistochemistry and clinical features contained in these scoring systems, there are many other potential factors associated with metastasis. We will present some of the current reporting indicators, which are not part of the above-mentioned predictive system. These risk factors may help to establish new predicting models in the future.

PPGL was the most heritable tumor in humans [34]. Gene mutations play a major role in the occurrence of heredity PPGL. The latest research shows that about 35%~40% of the occurrence of PPGL is related to at least 27 gene mutations, mainly including SDHx (SDHA, SDHB, SDHC, SDHD, SDHAF2), VHL, RET, NF1, HRAS, MAX, ATRX, FH, KIF1B, EPAS1 and so on [35]. SDHB gene mutation has long been declared to be associated with metastatic PPGL [36], and the loss of SDHB immunohistochemistry has been already added into grading systems like M-GAPP and COPPs. A study showed that three novel genes MYCN, CYO5B and VCL were significantly higher in metastatic PPGL compared with non-metastatic PPGL [37]. Telomerase activity and ATRX mutations are independent risk factors for metastasis and are associated with clinical progression of PPGL [38, 39]. Besides, mutations including SDHD [11], MAX [40], FH [41], TERT [42, 43], SLC25A11 [44], MAML3 [45] had also been reported to be related to metastatic PPGL. Gene mutations not only affect the risk of metasta-
sis, but also the patient’s tumor location, biochemical characteristics, overall prognosis and clinical syndromes [46, 47]. For example, the VHL gene mutation can cause the von Hippel-Lindau syndrome (VHL disease), while NF1 syndrome was caused by NF1 gene mutation [48, 49]. So genetic testing is of great importance to PPGL patients and can guide patients’ follow-up and predict prognosis. According to genetic test guideline, SDHB, SDHD, VHL, FH, RET and NF1 should be tested. SDHA, SDHAF2, SDHC, TMEM127, MEN1 and MAX is recommended to be tested [50]. Although we focus on linking genetic mutations to the risk of metastasis, the importance of genetic mutation status is not only about metastasis, but more importantly, guiding our management and treatment through genotypes.

Actually, except genetic mutations, there are many additional molecular markers had the potential to become indicators in the future. It was reported that earliest molecular markers including EPAS1, VEGF, nm23-H1, TIMP-4 and other factors was related to metastatic PPGL, but some of them like OCT4, S-100, c-Erb2 and CD34 had low reproducibility in later studies, which may be confounded by the SDHB mutation [6, 51]. A recent study has shown that weak CHGB protein expression is associated with high PASS score [52], suggesting that CHGB levels may be a new biomarker for predicting malignant biological behavior of PPGL. In addition, recent biomarkers like miRNAs [53-55], long non-coding RNAs (IncRNA) [56, 57], ERBB-2 over expression [58], Hsp90 [51], high levels of plasma methoxytyramine [29],CNTN4 protein expression [59] may also have the potential to become metastatic indicators in the future. The discovery of metastasis-related molecular markers can not only help diagnose metastatic PPGL, but also help discover drug target of PPGL [48].

Last but not least, imaging plays an important role in the diagnosis and staging of tumors. The radiomics refers to the extraction of valuable information by analyzing a large amount of standard data with high-throughput medical images including computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI), which has a very large potential to establish a descriptive or predictive models [60, 61]. Recent studies have shown promising results of radiomics in oncological practice, including tumor discrimination and subtype classification and in assessing treatment responses. Although there was little research of radiomics in patients with PPGL, recent studies showed that radiomics can help differentiate subclinical pheochromocytoma from lipid-poor adenoma, which is difficult using traditional imaging analysis [62, 63]. This promising result laid a solid foundation for the application of radiomics in predicting metastatic potential of PPGL.

Discussion

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors characterized by the secretion of catecholamine and recurrent episodes of hypertension. According to WHO 2017 Classification of Tumors of Endocrine Organs, all PPGL have metastatic potential. The term “malignant PPGL” and “benign PPGL” were abandoned and replaced by “metastatic PPGL” and “non-metastatic PPGL”. Metastatic PPGL and non-metastatic PPGL differ greatly in terms of follow-up, prognosis and survival rate, and metastasis can only be determined when metastasis occurs. Therefore, how to predict the metastasis potential at an early stage has become a clinical concern and an urgent problem to be resolved.

Many indicators, such as histopathology, genetic mutations, biomarkers, and clinical characteristics, have been declared to be associated with metastasis, but none of the individual factors was 100% correlated. So, it is a challenge to establish a new, convenient, highly specific and standard evaluation system by combining multiple influencing factors. Several prediction systems were established from 2002 to 2019. The original PASS system was consisted only by histopathological indicators, which were too numerous and complex, and some of them were not specific to PPGL; GAPP was created by excluding some nonspecific parameters on the bases of PASS, and combined both Ki-67 and catecholamine type, which was the first time the clinical characteristics of the tumor were considered (catecholamine type); M-GAPP was modified by selecting several factors that had a high correlation with PPGL in GAPP, and added SDHB gene mutation (which was proved to be highly corre-
lated with metastasis), the first time gene mutation was incorporated into the scoring system. While COPPS incorporated tumor size (another clinic characteristic), ASES was completely based on the clinical characteristics of patients.

In studies about these five scoring systems, the number of cases collected was ranged from 72 to 333 (with a total of 809 cases), PHEO proportion was ranged from 74% to 100% (with a total of 700 cases), and the percentage of confirmed metastases was ranged from 6% to 33% (with an average proportion of 15%). It can be seen that all scoring systems have high prediction accuracy rate of the non-metastatic PPGL that may be related to the fact that non-metastatic samples account for the majority when the system is established, which has clinical application value. From the comparison of COPPS, ASES system and other systems, we can see that the proportion of malignant tumors in cases will affect the accuracy of prediction results when the scoring system is established, and the increase of the number of cases and proportion of metastatic tumors can improve the reliability of metastatic prediction results (Table 2). ASES system is only based on clinical characteristics, showing the worst sensitivity and the lowest metastatic prediction accuracy rate in the five systems, which suggesting that we can not only consider on one aspect of a factor when trying to establish a scoring system. Factors including pathology, clinical characteristics, molecular marker, gene mutation and other factors should be discussed in the same time. ASES consisted of 4 factors while PASS included 12 factors. The small number of factors in the ASES system and large number of factors in the PASS system may be lead to a low specificity of ASES and a low specificity of PASS.

PPGL is a rare disease. Its low incidence and uncertainty of metastasis time make it difficult to carry out clinical research and to establish a clinical prediction model. Our review focused on the prediction of metastatic potential in patients with PPGL, and we mainly introduced the predictive system that has been established by analyzing their scoring rules, sensitivity, specificity, accuracy rate of prediction results and the clinical application value. We also reviewed additional reported factors which related to the metastatic ability of PPGL, hoping to inspire readers from different perspectives and help the establishment of the new system in the future.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 8190-2727), Natural Science Foundation of Hunan Province, China (No. 2018JJ6133) and Innovation-Driven Project of Central South University (No. 020CX046).

Disclosure of conflict of interest

None.

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