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Contents

Bimonthly Volume 8 Number 5 October 28, 2020

EVIDENCE REVIEW

REVIEW

META-ANALYSIS

World Journal of Meta-Analysis

Bimonthly Volume 8 Number 5 October 28, 2020

Contents

ABOUT COVER

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EVIDENCE REVIEW

Current trend in the diagnosis and management of malignant pheochromocytoma: Clinical and prognostic factors

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Abstract

Pheochromocytomas are tumors arising from the chromaffin cell of the adrenal gland and paragangliomas as tumors from extra-adrenal sympathetic chromaffin cells. The combined yearly incidence of pheochromocytoma and paraganglioma (PPGL) is approximately 0.8 per 100000 person/year. Malignant pheochromocytoma is defined only by the presence of metastasis, as there is no confirmatory histology or biomarkers. The most common metastatic sites of these chromaffin tumors are the lymph node, bone, lungs, and liver. This review focuses on relevant clinical and immunohistological factors that are predictive of malignant PPGL or metastasis and determinants of prognosis. Findings showed that the risk of malignant PPGL, along with disease survival, is closely associated with age, primary tumor size, gender, synchronous metastasis, and absence of surgical excision. Other essential biomarkers or immunohistology investigated were galectin-3, COX-2, nm-23, microRNA-210, ERBB-2 overexpression and succinate dehydrogenase subunit mutation, which were predictive of malignancy as well as disease prognosis. Curative resection is possible but most metastatic diseases are amenable to radiopharmaceuticals and chemotherapy due to late presentation. Other therapeutic options, like molecular-targeted therapy, are still undergoing clinical trials.

Key Words: Chromaffin; Malignancy; Metastatic; Paraganglioma; Pheochromocytoma; Prognosis

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Core Tip: The diagnosis of malignant pheochromocytoma/paraganglioma (PPGL) is challenging. To date, confirmatory histology and biomarkers are still lacking. Data from recent studies have shown various biomarkers and genetic mutations that are predictive of malignancy, metastasis and disease prognosis of PPGL, but primary tumor size, male sex and synchronous metastasis have revealed consistent association with malignant PPGL and its prognostication.

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INTRODUCTION

The World Health Organization (WHO) in 2004 defined pheochromocytomas as tumors arising from the chromaffin cell of the adrenal gland and paragangliomas as tumors from extra-adrenal sympathetic chromaffin cells or parasympathetic nonchromaffin cells of the head and neck[1]. Pheochromocytoma and paraganglioma (PPGL) are histologically similar, with both secreting catecholamine (norepinephrine), but pheochromocytoma may also secrete epinephrine[2]. The combined yearly incidence of PPGL is approximately 0.8 per 100000 person/year[3]. Although the majority of PPGL are benign, about 10% to 31% are metastatic[3,4]. According to the WHO, malignant pheochromocytoma is defined only by the presence of metastasis[4].

Despite PPGL being mostly sporadic, nearly 40% are linked to somatic and/or germline mutations in at least 20 known susceptibility genes associated with the pathogenesis of these tumors[5]. PPGL can also occur with hereditary syndromes and genetic testing in patients may be required[5].

Genetically, PPGL with associated succinate dehydrogenase subunit B (SDHB) germline mutations may require a stringent follow-up, as the risk of malignancy is almost 40% and these tumors display aggressive behaviors[6]. Biochemical studies using plasma-free metanephrines or 24-h urine collection for fractionated metanephrines can rule-out PPGL in most instances.

Currently, no diagnostic molecular or histological marker exists for malignancy and most patients are diagnosed with malignant PPGL after they have developed unresectable disease and metastatic disease[7]. The most common metastatic sites of these chromaffin tumors are the lymph node, bone, lungs, and liver[8]. The 5-year survival without metastasis has been reported to be approximately 89.3%[8]. When metastasis is detected, the prognosis is usually poor, with a 5-year survival rate of only 60%[9]. Most of these cases then resort to systemic chemotherapy or radiopharmaceutical agents, such as metaiodobenzylguanidine. These therapies lead mostly to partial radiographic response, disease stabilization, and symptomatic control in about 40% of cases[7,9].

This review has focused on relevant clinical and immuno-histological factors that are predictive of malignant PPGL or metastasis. The review also highlights essential biomarkers that are relevant to prognostication of malignant PPGL. A succinct overview of the current standard of care is provided in the Discussion.

METHODOLOGY

An extensive literature search was conducted from 2000 to 2020 using the PubMed database and search engine. The keyword utilized was "clinical and prognostic factors of malignant pheochromocytoma". There were a total of 74 articles. The abstracts and full texts of 36 publications on malignant PPGL were reviewed after extraction of duplicate text.

After perusal of abstracts and full texts, 11 publications investigating the clinical parameters and biomarkers on the risk of malignancy, metastasis and prognosis were selected for qualitative and quantitative synthesis as projected in Table 1. All articles

Table 1 Clinical factors and biomarkers assessing the risk of malignancy and prognosis of pheochromocytoma and paraganglioma

Ref.	Study duration and type	Study population	Study protocol/objective	Study outcome
Choi *et al*[10], 2015	1997-2013, retrospective	345 pts	Prognostic factors associated with survival for PPGL	Poor survival: Older age and synchronous metastasis
De Wailly *et al*[11], 2012	1993-2009, retrospective	53 pts	New immunohistologic elements correlating to malignant PPGL	Risk of malignancy/recurrence: Tumor necrosis, Ki-67 index > 4% and pS100
Hamidi *et al*[12], 2017	1960-2016, retrospective	272 pts	Epidemiology and survival outcome of malignant PPGL	MOS: 24.6 years, DSS: 33.7 years; poor survival: Older age at diagnosis, male sex, synchronous metastasis, larger tumor size, elevated dopamine
Mei *et al*[13], 2019	1973-2013, retrospective	1014 pts	Survival pattern of malignant PPGL	Survival advantage: Younger age, female sex, surgical resection and origin from of aortic/carotid bodies
Ruff *et al*[14], 2019	Prospective	35 pts	Serum miR-210 levels as a biomarker of malignancy	Lower serum miR-210 expression level and larger primary tumor size strongly correlated with malignant disease
Zelinka *et al*[15], 2011	Retrospective	41 pts	Biochemical and clinical outcome of malignant PPGL	Metastatic pheochromocytoma presented at a significantly younger age, with larger tumor, tumor necrosis and more frequent secreted norepinephrine
Hamidi *et al*[16], 2017	Systemic review and meta-analysis of 20 studies	1338 pts	Baseline characteristics and outcome of patients with malignant PPGL	5-year and 10-year mortality rates of 37% (95%CI: 24%-51%) and 29% (95%CI: 17%-42%), respectively; male sex and synchronous metastases were associated with higher mortality
Saffar *et al*[17], 2011	1986-2006, retrospective	51 pts	Galectin-3, COX-2, and nm-23 to discriminate benign disease from malignancy	Negative nm-23, along with positive galectin-3 or COX-2 were predictive of malignancy, with a sensitivity of 100%
Suh *et al*[18], 2017	1988-2013, retrospective	176 pts	Variations in genomic expressions and mutations of malignant PPGL	mRNA expression of malignant PPGL was up-regulated in five pathways; disease-free survival rates were closely related the presence or absence of mutations
Szalat *et al*[19], 2011	1980-2008, retrospective	16 pts	Predictive features of malignancy in PPGL	High levels of chromogranin A at the time of diagnosis were associated with malignancy; 10-year survival rate after initial diagnosis was 50% and 25% after metastasis
Zhong *et al*[20], 2017	2002-2014, retrospective	414 pts	Clinical significance of biomarker nomogram in detecting malignancy and rate of metastasis	Tumor size, tumor location, vascular invasion, ERBB-2 overexpression and SDHB mutation were independent predictors of malignancy and metastasis

DSS: Disease-specific survival; MOS: Median overall survival; PPGL: Pheochromocytoma and paraganglioma; SDHB: Succinate dehydrogenase subunit B.

on benign pheochromocytoma exclusively were excluded from the study. All case reports and case series with less than 10 subjects were not eligible for inclusion.

ELIGIBILITY

A total of 11 articles met the desired objective for further qualitative analysis. All studies with research methodology emphasizing clinical and immuno-histological factors that are predictive of malignant PPGL or metastasis were selected (Figure 1).

The selected articles were reviewed for study type and duration, study population, study protocol/objectives, clinical parameters, biomarker, and study outcome. The retrieved information was analyzed and reflected in the main text of the Results and Discussion.

The term "pheochromocytoma and paraganglioma" was used concurrently and abbreviated as PPGL.

EVIDENCE SYNTHESIS

A total of 11 studies[10-20] were synthesized (1 systematic review, 1 meta-analysis, 1 prospective study, and 9 retrospective studies) to include 3755 patients with malignant

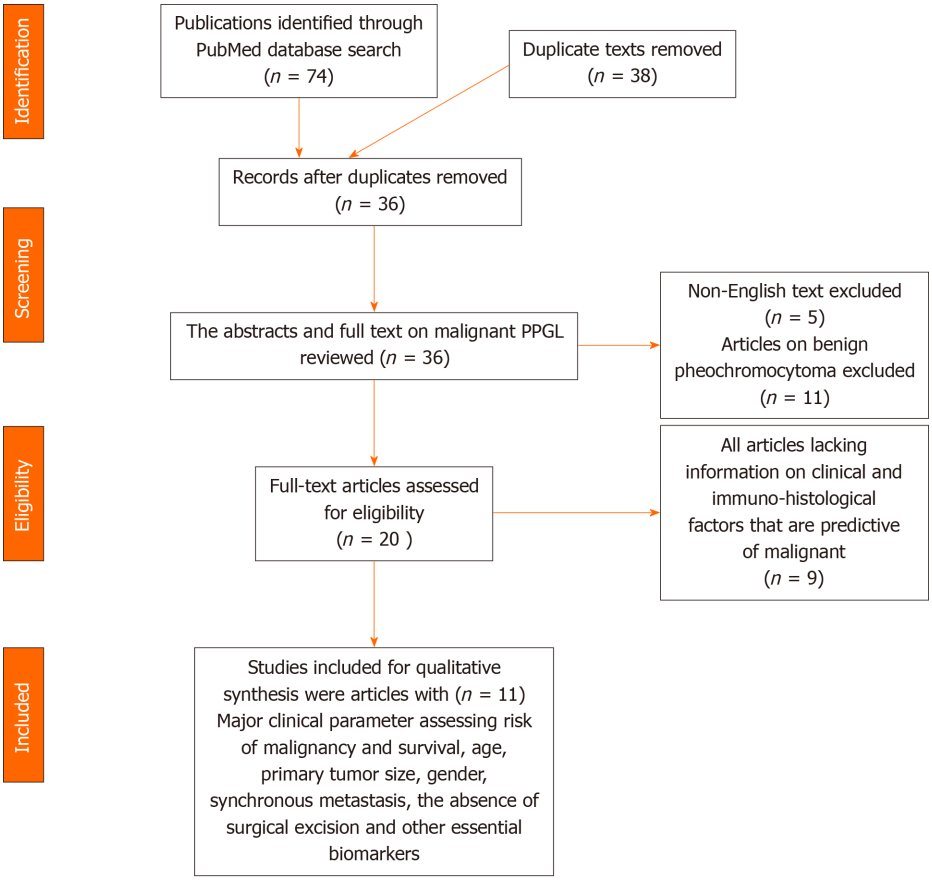

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart outlining the selection of articles for qualitative analysis.

PPGL. The various objectives outlined essential clinical factors and immuno-histological factors that are predictive of malignant PPGL or metastasis. The major clinical parameters assessed for risk of malignancy and survival were age, primary tumor size, gender, synchronous metastasis, and absence of surgical excision. Other essential biomarkers/immunohistology features investigated were galectin-3, COX-2, nm-23, microRNA-210 (miR-210), and ERBB-2 overexpression, and SDHB mutation.

A retrospective study by Choi *et al*[10] of 345 patients treated for PPGL evaluating prognostic factors associated with survival for PPGL showed that the median survival was 7.2 years, with a 5-year survival rate of 75.4%. Univariate analysis revealed that older age (> 45 years), larger tumor size (> 6 cm), synchronous metastasis and lack of surgical excision correlated with poor survival. Further multivariate analysis showed that older age and synchronous metastasis were associated with poor overall survival.

De Wailly *et al*[11], in a review of 53 patients operated for PPGL, assessed for new immunohistological elements correlating to malignant pheochromocytoma and the findings indicated that the size and weight of pheochromocytoma were directly related to the Pheochromocytoma of Adrenal gland Scaled Score and malignancy[11]. The presence of tumor necrosis, Ki-67 index > 4%, and absence of pS100 indicated the need for close follow-up, as there was a high risk of malignancy or recurrence.

A retrospective review of 272 patients with malignant PPGL by Hamidi *et al*[12] assessing survivor outcome and predictors of shorter survivors displayed that the median overall survival was 24.6 years and disease-specific survival was 33.7 years. Older age at diagnosis, male sex, synchronous metastasis, larger tumor size, elevated dopamine, and not undergoing primary tumor resection were associated with shorter survival.

Review of the Surveillance, Epidemiology, and End Results program and Cancer Genome Atlas (commonly known as TCGA) database (data from 1973 to 2013) with 1014 patients to analyze epidemiology and survival pattern of malignant PPGL found that younger age, female sex, surgical resection, and origin from of aortic/carotid bodies conferred remarkable survival advantage[13]. Opposingly, distant metastasis was associated with a worse prognosis. ATRX was the most common oncogenic mutation in the metastatic group, while SHDB was higher among males.

A prospective study by Ruff *et al*[14] of 35 patients investigating serum miR-210 levels as a biomarker of malignancy revealed that the most common germline mutation involved SDHB[14]. Univariate analysis showed that lower serum miR-210 expression level and larger primary tumor size strongly correlated with malignant disease.

Zelinka *et al*[15] reported from a retrospective review investigating biochemical and clinical outcome of 41 cases of malignant pheochromocytoma to 108 cases of benign disease that patients with metastatic pheochromocytoma presented at a significantly younger age, with larger tumor, and more often secreted norepinephrine compared to benign pheochromocytomas.

The histological marker of potential malignancy of tumor necrosis was more consistent with metastatic pheochromocytoma. The median period to the development of metastasis from initial diagnosis was 3.6 years.

Results from a systematic review and meta-analysis of 20 retrospective studies of 1338 patients with malignant PPGL by Hamidi *et al*[16] showed that 40.4% of patients had synchronous metastasis. The 5-year and 10-year mortality rates were 37% (95% confidence interval (CI): 24%-51%) and 29% (95%CI: 17%-42%), respectively. Male sex and synchronous metastases were associated with higher mortality.

Retrospective data from Saffar *et al*[17] involving 55 cases of pheochromocytoma determining the concurrent expression of galectin-3, COX-2, and nm-23 to discriminate benign disease from malignancy showed that negativity for nm-23 along with positivity for galectin-3 or COX-2 were predictive of malignancy, with a sensitivity of 100%. Meanwhile, positivity of nm-23 along with dual negativity of COX-2 and galectin-3 showed a benign disease, with a 100% sensitivity.

A multigenomic analysis of data collected from 1988 to 2013 involving 176 patients by Suh *et al*[18] assessing the variations in genomic expressions and mutations of malignant PPGL with TCGA found that mRNA expression of malignant PPGL was up-regulated in five pathways, namely cell cycle (*BUB1*, *BUB1B*, *CCNB2*, *CDC2*, *ESPL1*), gap junction (*CDC2*, *PRKCB1*), calcium signaling (*CCNB2*, *CDC2*, *PRKCB1*), regulation of actin cytoskeleton (*DIAPH3*, *FGF18*, *IQGAP3*), and phosphatidylinositol (*PRKCB1*, *TTK*). Disease-free survival rates were closely related to the presence or absence of mutations, such as *RP11-798G7.5*, *HERC2*, *SETD2*, *TGDS*, *TRHDE*, *FKBP9*, and *BMS1*.

Data from Szalat *et al*[19] in a retrospective study of 16 patients from 1980 to 2008 identifying the predictive features of malignancy in PPGL displayed that high levels of chromogranin A at the time of diagnosis was associated with malignancy, metastasis and poor prognosis. The 10-year survival rate after initial diagnosis was 50% and 25% after metastasis is found.

A retrospective study by Zhong *et al*[20] randomly assigned 414 patients with PPGL to a training or validation group investigating the clinical significance of biomarker nomogram in detecting malignancy and rate of metastasis. The overall rate of metastasis was 10.6%. Univariate analysis revealed that primary tumor size, tumor location, vascular invasion, capsular invasion, ERBB-2 overexpression, and SDHB mutation were remarkably associated with malignancy[20]. Multivariate logistic regression analysis showed that tumor size, tumor location, vascular invasion, ERBB-2 overexpression, and SDHB mutation were independent predictors of malignancy and metastasis. Further analysis revealed that biomarker-based nomogram was useful for assessing the risk of metastasis compared to nomogram without biomarkers (ERBB-2 overexpression and SDHB mutation).

DIAGNOSIS

It has been proven that measurement of metanephrine is superior to other routine catecholamines and metabolites, like vanillylmandelic acid; therefore, the measurement of 24-h plasma metanephrine or fractionated urinary metanephrine is acceptable[21].

The role of imaging is to evaluate primary tumor, assess multifocality, and identify metastasis. Computed tomography scan and magnetic resonance imaging (commonly known as MRI) are ideal for primary tumors, with a sensitivity of 98%-100% for adrenal lesions[21]. MRI is more sensitive for extra-adrenal paraganglioma, with sensitivities of 93% *vs* 90% respectively.

Metaiodobenzylguanidine scintigraphy (I^{131}/I^{123}MIBG) has been used for decades to image neuroendocrine tumors because the uptake represents adrenergic innervation and catecholamine excretion. In patients with large tumors, inherited tumors or multifocal tumors, conventional imaging along with I^{123}MIBG or 18F-

fluorodeoxyglucose positron emission tomography can be used to detect metastases[22].

The American Joint Committee on Cancer has recently developed a staging criterion for malignant PPGL using the tumor-node-metastasis classification. The classification was based on certain parameters that allow the size of the primary tumor to reliably predict the presence of malignancy and shorter survival[23]. Patients with primary PPGL lager than 5 cm have a shorter overall survival than patients with smaller tumors[23]. Therefore, a pheochromocytoma lesser than 5 cm is stage as T_1. Tumors that are larger than 5 cm are staged T_2. Pheochromocytomas that invade surrounding structures, like the liver or kidney, requiring extensive surgery are staged T_3.

TREATMENT

Treatment for malignant PPGL is palliative; therefore, a shared decision-making is required for the patient's quality-of-life. Concerns are focused on the tumor growth, tumor hypersecretion, or the intervention itself. Bony metastasis to the spine is usually painful, with additional risk of spinal cord compression. Therefore, treatment of pain with nonsteroidal anti-inflammatory, analgesics, bisphosphonates, and radiotherapy are all viable options.

Patients with malignant PPGL may already present with cardiovascular complications from excess catecholamine, like acute adrenergic cardiomyopathy, arrhythmia, myocardial infarction, stroke, and sudden death[22,24]. For patients who may require surgery, preoperative control of blood pressure and adrenergic outflow is crucial to prevent adverse events. The first pharmaceutical agent of choice is an alpha-blocker preferably, either noncompetitive (phenoxybenzamine) or competitive (doxazosin, prazosin, and terazosin)[25,26]. Beta-blockers may be needed to prevent or ameliorate reflex tachycardia or orthostatic hypotension associated with the alpha-blocker. If the pressure is not controlled by an alpha- or beta-blocker, calcium channel inhibitor or metyrosine are alternatives[26]. Liberal salt and fluid intake are encouraged to promote intravascular expansion.

The only definitive treatment for PPGL is surgical resection. Though surgery may not be curative in most scenarios, it offers long-term disease remission in some patients. Patients with malignant PPGL and isolated metastasis can have a better result with surgery. In patients with incurable disease, resection can reduce the catecholamine hypersecretion and avoid complication of tumoral compression on vital organs[21,22]. Accurate preoperative imaging is crucial to assess the vasculature of the tumor. The tumor should be dissected without capsular infraction. It is advised that the veins be ligated first, to prevent excess catecholamine release into circulation. If regional lymph nodes are assessed preoperative or intraoperatively, a regional lymphadenectomy should be performed[21,22].

I^{123} MIBG is frequently being investigated as a treatment option for metastatic PPGL. It is recommended as the first-line treatment in patients with slow-growing I^{123} MIBG-positive metastasis. Treatment can be administered as both fractionated low dose and high dose; both are shown to have considerable efficacy[27]. A systematic review and meta-analysis of 17 studies involving 243 patients with malignant PPGL evaluating the effect of I^{131} MIBG therapy on tumor volume in patients with malignant PPGL showed that the complete response was 3%, partial response was 27% and stable disease was 52%[28]. Separate analysis showed better hormonal response among paraganglioma than pheochromocytoma.

Chemotherapy may have a role in the management of malignant PPGL. The best recommended chemotherapeutic protocol includes cyclophosphamide, vincristine, and dacarbazine (CVD) administered as (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2, and dacarbazine 600 mg/m^2 on day 1 and dacarbazine 600 mg/m^2 on day 2). A systematic review and meta-analysis of four studies, by Niemeijer *et al*[29], using chemotherapy with CVD involving a pool of 50 patients with PPGL revealed varying response of malignant PPGL to CVD[29]. The pooled percentages were 4% for complete response (95%CI: 1%-15%), 37% for partial response (95%CI: 25%-51%) and 14% for stable disease (95%CI: 7%-27%). Sub analysis of two studies also showed varying response of catecholamine excess, with complete response in 14% (95%CI: 6%-30%), partial response in 40% (95%CI: 25%-57%), and stable hormonal response in 20% (95%CI: 10%-36%)[29].

Molecular-targeted therapies, like receptor tyrosine kinase inhibitors, mTORC1 inhibitors, HIF-2α antagonist and SSTR2 analogues, are still investigational[3,7]. Receptor tyrosine kinase inhibitors like unitinib, cabozantinib, axitinib and pazopanib are considered to have potential therapeutic benefits and still part of ongoing clinical

trials[7,9,30].

CONCLUSION

The diagnosis of malignant PPGL is challenging. To date, confirmatory histology and biomarkers are still lacking. The presence of metastasis is still being considered as a reference for malignancy. Data from recent studies have shown various biomarkers and genetic mutations that are predictive of malignancy, metastasis and disease prognosis of PPGL. Biomarkers like galectin-3, COX-2, nm-23, miR-210, ERBB-2 overexpression and SDHB mutation have shown correlation to malignant PPGL and disease prognosis. However, primary tumor size, male sex and synchronous metastasis have revealed consistent association with malignancy PPGL and prognostication.

Most malignant PPGL may not be amenable or curable with surgical excision. As such, radiopharmaceuticals and chemotherapy are alternative treatment options. Other therapeutic options, like molecular-targeted therapy, are still undergoing clinical trials.

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