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Outcomes of Patients with Metastatic Phaeochromocytoma and Paraganglioma: a Systematic Review and Meta-analysis

Oksana Hamidi, D.O.[1], **William F. Young Jr., M.D.**[1], **Lucinda Gruber, M.D.**[2], **John Smestad**[3], **Qi Yan**[4], **Oscar J. Ponce, M.D.**[5,6], **Larry Prokop**[5,7], **M. Hassan Murad, M.D.**[5,8], and **Irina Bancos, M.D.**[1]

[1]Division of Endocrinology, Diabetes, and Nutrition, Mayo Clinic, Rochester, MN, USA

[2]Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

[3]Mayo Clinic Medical Scientist Training Program, Mayo Clinic, Rochester, MN, USA

[4]Department of Surgery, Mayo Clinic, Rochester, MN, USA

[5]Evidence-based Practice Center, Mayo Clinic, Rochester, MN, USA

[6]Unidad de Conocimiento y Evidencia, Universidad Peruana Cayetano Heredia, Lima, Peru

[7]Mayo Clinic Libraries, Mayo Clinic, Rochester, MN, USA

[8]Division of Preventive Medicine, Mayo Clinic, Rochester, MN, USA

Summary

Objective—The outcomes of patients with metastatic phaeochromocytoma (PHEO) and paraganglioma (PGL) are unclear. We performed a systematic review and meta-analysis of baseline characteristics and mortality rates of patients with metastatic PHEO and PGL (PPGL).

Design—Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science and references of key articles were searched from inception to 2016.

Patients—Selected studies comprised at least 20 patients with metastatic PPGL and reported baseline characteristics and follow-up data.

Measurements—Reviewers extracted standardized data and assessed risk of bias of each study using a modified Newcastle-Ottawa tool. Random-effects meta-analysis was used to pool event rates across studies.

Results—Twenty retrospective noncomparative studies reported on 1338 patients with metastatic PHEO (685, 52.9%) and PGL (611, 47.1%), diagnosed at a mean age of 43.9±5.2 years. Mean follow-up was 6.3±3.2 years. Of 532 patients with reported data, 40.4% had synchronous

Address all correspondence and requests for reprints: Irina Bancos, M.D., Division of Endocrinology, Diabetes, and Nutrition, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905, Tel +1 507-286-1387, Fax +1 507-284-5745, bancos.irina@mayo.edu.

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metastases. Five-year (7 studies, n=738) and 10-year (2 studies, n=55) mortality rates for patients with metastatic PPGL were 37% (95% CI, 24–51%) and 29% (95% CI, 17–42%), respectively. Higher mortality was associated with male sex (RR 1.50) and synchronous metastases (RR 2.43).

Conclusions—Available low quality evidence from heterogeneous studies suggests low mortality rates of patients with metastatic PPGL. Male sex and synchronous metastases correlated with increased mortality. The assessment of outcomes of patients with metastatic PPGL has been inadequate, indicating the need for carefully planned prospective studies.

Keywords

phaeochromocytoma; paraganglioma; succinate dehydrogenase; mortality; neoplasm metastasis

1. Introduction

Phaeochromocytoma (PHEO) and paraganglioma (PGL) are rare neuroendocrine tumours derived from chromaffin tissues of the adrenal medulla and extra-adrenal paraganglia, respectively. PHEO and PGL (PPGL) can occur sporadically or as inherited genetic syndromes, primarily multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau (VHL) disease, neurofibromatosis type 1 (NF1), and mutations in succinate dehydrogenase subunits (*SDHx*)[1–4].

Approximately 2–13% of patients with PHEO and 2.4–50% with PGL have been reported to have metastatic disease with differences mainly due to selection bias[5–7]. Reported survival rates of patients with metastatic PPGL vary considerably between studies, with 5-year survival rates ranging from 12% to 84%[2,8–12]. Due to the rarity of this disease, variability of malignancy definitions, fragmented nature of studies, and small numbers of patients, there is no clear and consistent documentation of the outcomes in patients with metastatic PPGL. Therefore, a more accurate survival estimation of patients with metastatic PPGL is warranted.

The aim of this study was to perform a systematic review and meta-analysis to evaluate clinical characteristics of patients with metastatic PPGL and reported mortality rates. We also sought to identify predictive features correlating with shorter survival in patients with this rare disease.

2. Materials and Methods

A. Eligibility criteria

This study was performed based on a protocol that was designed in advance. The results of this review are reported according to PRISMA statement (preferred reporting items for systematic reviews and meta-analysis)[13]. We searched for original prospective and retrospective comparative and noncomparative studies that enrolled patients with metastatic PPGL (as defined by authors of original studies).

B. Inclusion and exclusion criteria

We included studies that described at least 20 patients with metastatic PPGL and reported baseline characteristics and follow-up data. Eligible studies were not restricted to any language. In case of multiple studies describing an overlapping cohort of patients, only the study which comprised the largest number of subjects and/or the longest duration of follow-up was included for this review. We included studies regardless their publication status. We excluded all non-original research studies and case reports. Because highly selected cohorts can overestimate or underestimate mortality rate, we also excluded studies reporting on a selected group of patients with metastatic PPGL (e.g., only patients with bone metastases or only those undergoing chemotherapy)

C. Data Sources and Search Strategies

A comprehensive search of several databases from each database's inception to December 9, 2016, any language, was conducted (Supporting Information). The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Scopus, and Web of Science. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies evaluating selected outcomes in patients with metastatic PHEO and PGL. Experts in the field were consulted and the references from primary studies were scanned to identify studies missed by the search strategy. The actual strategy is available in the appendix.

D. Selection of studies

All studies obtained from the search were entered into reference manager software (EndNote). Reviewers (O.H, L.G., J.S.) working independently and in duplicate reviewed all titles and abstracts of the identified studies and selected full text manuscripts for eligibility. Many of the identified studies retrieved by our search were non-relevant or non-original and were excluded at this phase. Full text screening was then performed in duplicate to assess eligibility for final inclusion. Disagreements at full text screening were resolved by consensus or referral to the full text of the study.

E. Data extraction and management

Potentially relevant studies were retrieved for detailed assessment. Working independently and in duplicate four reviewers (O.H., L.G., J.S, and Q.Y.) used standardized data collection form that was developed based on the protocol to extract information from each eligible study. Disagreements between reviewers were resolved by consensus or referral to the full text of the study.

For all included studies, the following data were extracted: first author, year of publication, study design, setting (country, referral centre, database), population studied, number of subjects with metastatic PHEO and PGL, genetic mutation status, duration of follow-up, age at diagnosis of primary tumour and metastatic spread, functional status (defined by elevated urine or plasma catecholamines and/or metanephrines), size of primary tumour, location of metastases, systemic and regional treatments, overall survival, and 5- and 10-year survival

rates. The outcomes of interest were focused on factors associated with shorter survival and higher mortality risk.

F. Methodological quality and risk of bias assessment

The present meta-analysis is based on observational studies. Risk of bias and quality of each study were assessed by reviewers working independently and in duplicate using a modified Newcastle-Ottawa tool, which included assessment of the following: a) how the sample represented the population of interest, b) how the data on metastatic PPGL was collected, c) sufficient follow-up period for the outcomes to occur (at least 5 years of follow-up); d) adequacy of follow-up (the proportion of patients assessed at the completion of the study); and e) how the outcome was assessed. Elements of risk of bias assessment were used to explore potential heterogeneity. Disagreements were resolved by consensus or by referring to the full text of the study. Determination of exposure (baseline characteristics and survival outcomes) was adequately reported in thirteen studies.

G. Statistical analysis: summary measures and synthesis of results

We conducted a meta-analysis using the random-effects model to pool estimates from the included studies. We calculated the cumulative incidence of mortality at 5, 10 and overall (longest follow-up) years for patients with: PHEO, PGL, skull base and neck PGL, and *SDHB*-positive tumours. We also assessed the effects of synchronous vs metachronous metastasis and male vs female sex on mortality risk. All statistical analyses were performed using Stata v14.0 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

We used the I^2 statistic to assess for heterogeneity across individual studies and to estimate the percentage of total between-study variation (ranging from 0 to 100%)[14]. I^2 values of 25, 50 and 75% respectively indicate low, moderate, and high inconsistency across studies (heterogeneity) not explained by chance. Given the expected clinical heterogeneity and within-study variability, a random effects model was used.

3. Results

A. Study selection

The initial search yielded 804 unique records for title and abstract screening; of these, 28 studies were selected for detailed assessment (Figure 1a). After full text assessment, 8 studies comprised a population already described in the publications included in our review; they were excluded because they described the smaller sample sizes and/or shorted duration of follow-up. Finally, a total of 20 studies were included in the present analysis. Eighteen studies were written in English, one in French, and one in Chinese (all familiar to authors). Of these, only 13 studies contained sufficient data to be included in the quantitative meta-analysis.

B. Risk of bias assessment

Characteristics of the risk of bias assessment are shown in Figure 1b. All studies were observational and were of moderate-to-high risk of bias. Samples were not sufficiently

representative in most studies (10 out of 13). Most of the included studies had insufficient or unclear duration of follow-up. Outcomes were adequately reported in all 13 studies. Clear description of how metastatic PPGL was defined and diagnosed was used in all articles.

C. Study characteristics

Individual study characteristics are shown in Table 1. Included studies were published between 1992 and 2016. Nineteen studies were classified as retrospective cohort studies, and 1 study was classified as an inception cohort study. The studies were mostly conducted in Europe (n=9) and Asia (n=6), and the U.S. (n=5). In 2 manuscripts, only metastatic PPGL originating from skull base and neck were studied; in 3 studies, only metastatic PHEOs were assessed; in 2 studies, only patients with genetic mutation testing were studied.

As expected, studies used different definitions of metastatic PPGL. In 11 studies, diagnosis was made when metastases were present in nonchromaffin sites in accordance with the World Health Organization (WHO) classification criteria of endocrine tumours [15,16]. In 2 studies, metastatic PPGL was defined as the presence of distant metastases, local invasion[17] or histologic features (Phaeochromocytoma of the Adrenal gland Scaled Score)[18]. We were not able to exclude data of patients with local invasion or histologic features from the study cohort. However, since the presence of metastases met our inclusion criteria for defining metastatic PPGL, we decided to include these studies for our review.

D. Descriptive analysis of baseline characteristics

Twenty studies were qualitatively analysed for baseline characteristics of patients with metastatic PPGL. A total of 1338 patients were described (Table 2). Of these, distinction between PHEO and PGL was available in 1139 patients with 685 (56.5%) metastatic PHEO and 611 (46.7%) metastatic PGL. The patients were followed for a mean of 6.3±3.2 years (range of means, 2.2–13.7 years).

Eight studies reported on genetic testing of patients with metastatic PPGL[12,19–25]. In 3 studies, absence of *SDHB* mutation was confirmed by genetic testing in all patients with metastatic PPGL[19,20,25]. In the other 5 studies, *SDHB*-negative patients were those who a) tested negative for *SDHB* mutation, b) tested positive for other mutations, c) met clinical criteria for NF1, or d) did not undergo genetic testing. Of 484 patients reported in these studies, 172 (35.5%) patients with metastatic PPGL had a *SDHB* mutation. Other reported mutations included: 12 patients with *VHL*[12,19,22,26–28], 9 MEN2A[12,18,24,28,29], 5 NF1[19,22,26], 5 *SDHD*[20,22,23], 2 *SDHC*[12,22], 2 familial/syndromic[24], 1 Turner syndrome[18], and 1 MEN1[12].

Mean age at primary tumour diagnosis was 43.9±5.2 years for the entire population, 46.5±5.0 years in patients with PHEO, and 43.85±5.2 years in patients with PGL. *SDHB*-positive patients were diagnosed with primary tumour at a mean age of 34.9±4.6 years and *SDHB*-negative patients were diagnosed at a mean age of 40.5±0.7 years. Mean time to development of metastases was 3.6±1.9 years. In studies where onset of metastases was reported, synchronous metastases were noted in 215 out of 532 patients (40.4%). Similarly, in studies where presenting symptoms were described, adrenergic symptoms were present in 176 out of 266 patients (66.2%). Of 367 tumours, 308 (83.9%) were functional. Mean

primary tumour size was 7.5±1.3 cm. PHEOs were 8.3±0.5 cm and PGLs were 6.2±1.3 cm. In patients with a *SDHB* mutation, mean tumour size was 6.4±0.4 cm; and in *SDHB*-negative patients, mean tumour size was 7.7±0.4 cm. Surgical resection of primary tumours was reported in 308 out of 367 patients (83.9%).

Distribution of metastases in patients with metastatic PPGL in reported studies was: 53.5% (211/394) bone[18,19,21–23,25–27,29], 41.6% (155/371) lymph nodes[18,19,21,22,25–27,29], 38.0% (150/394) mediastinum and lungs[18,19,21–23,25–27,29], 31.1% (122/394) liver[18,19,21–23,25–27,29], 17.4% (34/195) abdomen and pelvis[18,19,21,22,29], and 3.8% (3/80) brain[19,29].

Mortality of patients with metastatic PPGL: meta-analysis

Results of the meta-analysis, stratified by the type of population, are shown in Figure 2a. All analyses were performed with a random effects model. Overall, 5- and 10-year mortality rates of patients with metastatic PPGL ranged 43%–63% (11 studies; n=1047), 24%–51% (7 studies; n=738), and 17–42% (2 studies; n=55), respectively. Overall and 5-year mortality rates in patients with PGL were 46% (95% CI, 18–75%; 3 studies; n=309) and 22% (95% CI, 17–27%; 2 studies, n=246), respectively. Overall and 5-year mortality rates in patients with metastatic PHEO were 53% (95% CI, 42–63%; 5 studies; n=449) and 42% (95% CI, 37–48%; 3 studies; n=349), respectively. Overall and 5-year mortality rates in patients with metastatic skull base and neck PGL reported in studies ranged 34%–56% (2 studies; n=84) and 27%–48% (2 studies; n=84), respectively. For patients with a *SDHB*-mutation, overall mortality ranged 35%–55% (2 studies; n=96). There was substantial heterogeneity (I^2 values over 50%) in analyses of overall and 5-year mortality.

Factors associated with higher relative risk (RR) of mortality were: male sex (RR 1.50; 95% CI, 1.11–2.02) and synchronous metastases (RR 2.43; 95% CI, 1.01–5.85) (Figure 2b). These analyses were homogeneous.

4. Discussion

A. Principal findings

The present systematic review and meta-analysis aimed to assess baseline characteristics and outcomes of patients with metastatic PPGL. Over a third of the patients had a *SDHB* germline mutation and were younger at primary tumour diagnosis, compared with *SDHB*-negative patients. The majority of metastatic PPGL tumours were functional and were associated with adrenergic signs and symptoms. More than 40% of patients presented with synchronous metastases.

We found that the 5- and 10-year mortality rates for patients with metastatic PPGL were 37% and 29%, respectively. We also showed that male sex and synchronous metastases were associated with shorter survival and worse outcomes. These data indicate that outcomes of patients with metastatic PPGL are heterogeneous and widely variable, possibly related to the referral bias and duration of follow-up.

SDHB mutations are thought to be highly associated with metastatic PPGL, with rates of developing metastases up to 50%- 90% in some studies[1,12,19,30–32]. Previous studies have also reported that *SDHB* mutation was associated with shorter survival rates than other PPGL types[1,2,12,19,30–32]. However, in many studies the outcomes of metastatic PPGL are unreliable based on small sample size, inadequate follow-up time, evaluation of a specific selected cohort, and referral bias. Although we were not able to analyse the risk of mortality in patients with *SDHB* mutations, overall mortality of this cohort was 45%. By excluding studies that sampled less than 20 patients with metastatic PPGL and seeking to analyse consecutive patients, the results from our meta-analysis showed that the pooled survival estimation in *SDHB*-mutation carries is higher than previously appreciated. Therefore, with the results of this study, it is possible to inform patients with metastatic PPGL more adequately concerning their prognosis.

B. Limitations

The 20 studies showed a high risk of bias and were inadequate for assessing outcomes of patients with metastatic PPGLs. The first important limitation is inconsistent definition of metastatic PPGL. In 2004, the WHO stated that metastatic PHEO are diagnosed only by the documented presence of metastases, and less emphasis was placed on local invasion[15]. However, in 2007 the Armed Forces Institute of Pathology Fascicle Tumours of the Adrenal Glands and Extra-adrenal Paraganglia defined malignancy as “extensive local invasion or documentation of metastases”[33]. Although some studies determined metastatic diagnosis based on local invasion, the extent of local invasion to adjacent tissues does not necessarily indicate higher risk towards development of metastases[2]. Use of various definitions of metastatic PPGL might have led to wide ranges of mortality rates. This limitation indicates that the studies were prone to selection bias, thereby potentially falsely lowering the mortality risk.

Mortality of patients with metastatic PPGL could have been misrepresented because of insufficient follow-up in some studies. Since most studies included patients with manifested disease, of whom a substantial proportion were in tertiary care centres, we assume that most included index cases with a higher than average risk of harbouring aggressive metastatic PPGL. Hence, this referral bias might also overestimate the mortality risk of metastatic PPGL. Although our results suggest that *SDHB*-negative tumours were larger than *SDHB*-positive tumours, the results of such descriptive statistics can be due to chance.

It was unclear in the majority of studies how the metastatic PPGL cases were selected. Most studies reported on a selected non-consecutive group of patients with metastatic PHEO and/or PGL, had unclear number of patients lost to follow-up, and allowed insufficient duration of follow-up for outcomes to occur. Additionally, 2 studies recruited subjects from the national and international registries [9,10]. Although these databases are typically well validated for epidemiologic and clinical studies on cancers [34–36], some data are inherently limited, such as patient comorbidities, sites of metastases, and pertinent biochemical and genetic studies (not collected in SEER).

We were able to quantitatively analyse 13 cohort studies, with follow-up durations ranging from 2.2 and 13.7 years. The paucity of cohort studies with a long-term follow-up duration

poses a risk of overrepresentation of patients with rapidly progressive disease and thus overestimation of mortality from metastatic PPGL. Of note, the 10-year mortality rate appeared lower than the 5-year mortality rate, signifying a substantial bias in patient selection and lack of sufficient follow-up. The paucity of genetic information is probably related to the fact that many genetic mutations (including SDHx gene mutations) have only been described quite recently. However, it is reported that metastatic disease can occur more than 20 years after initial diagnosis of primary tumour [37,38]. The lack of long-term follow-up in the 2 included cohort studies [metastatic PPGL with overall survival 1.5 years[26]; therapy naïve metastatic PPGL with 5 year survival 44% (95%CI: 31–59%)[22]] may have resulted in the selection of rapidly progressive disease and thus overestimation of the mortality of metastatic PPGL.

Two studies exclusively examined patients with skull base and neck PGL[10,21] and 3 studies only included patients with metastatic PHEO[18,39,40]. Inclusion of these studies into computation of pooled survival could have skewed our results, since it is postulated that patients with metastatic PPGL originating from skull base or neck have better survival compared to metastatic disease originating from PHEO or PGL from other sites.

Another important limitation is a variety of metastatic assessments, thereby increasing heterogeneity of the included studies. This could have biased the risk estimates. For example, in some studies, the diagnostic evaluation relied also on clinical information reported by other care givers. We aimed to use elements of risk of bias assessment to explore potential heterogeneity between studies, but due to the small number of included studies, performing a sensitivity analysis was not feasible.

C. Generalizability of study results

Studies assessing the survival of patients with metastatic PPGL were included in the meta-analysis. However, most studies included patients from international registries, while the accurate outcomes and survival rates may vary in different countries. Furthermore, these registries mostly comprised symptomatic patients treated in tertiary care centres, were largely retrospective in nature, with registration of patients at a single point in time and little to no entry of follow-up data. These selection mechanisms prohibit simple generalizations of the study results.

D. Recommendations for future research

This meta-analysis assessed the overall, 5- and 10-year mortality rates of patients with metastatic PPGL carrying specific risk factors (male sex, synchronous metastases). However, only one study was conducted in a prospective manner. Heterogeneous reporting of variables and length of follow-up in the available studies on metastatic PPGL do not allow for a more in-depth or additional analysis of variables associated with a more aggressive disease. As metastatic PPGL is a rare disorder, we suggest that it would be of great benefit to perform a large multicentre retrospective study on non-selected patients with metastatic PPGL to include detailed characteristics of clinical, biochemical, imaging, and genetic variables and evaluate outcomes. Multicentre collaboration enables a larger sample size of patients with metastatic PPGL and allows a subgroup analysis in this heterogeneous

disorder. Data from a well-designed, large sample size retrospective study will be extremely valuable not only to determine an evidence-based monitoring approach for such patients, but also to design a multicentre longitudinal long-term prospective observational study after agreement on such approach.

5. Conclusion

In conclusion, the present study shows that the mortality of patients with metastatic PPGL is highly variable, depending on the presence of risk factors. Overall pooled 5- and 10-year mortality rates were 37% and 29%. Male sex and synchronous metastases were associated with increased mortality risk. Mortality of patients with metastatic PPGL varied considerably in the included studies due to methodological differences, including selection bias. Past studies have been inadequate for assessing outcomes of patients with metastatic PPGL. Further research is indicated to provide accurate prognostic information for patients with metastatic PPGL,

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Figure 1a

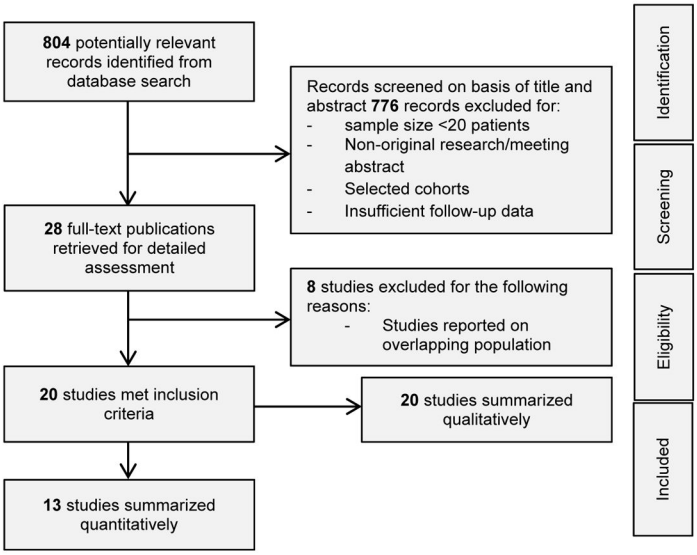

Figure 1b

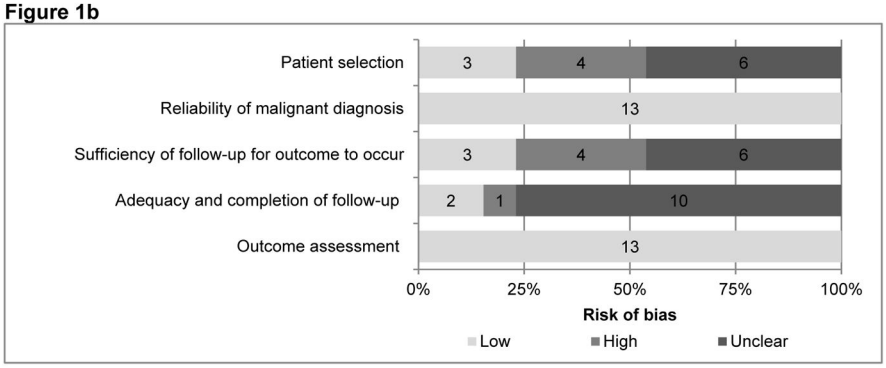

Figure 1.

Figure 1a PRISMA flow diagram of study selection.

Figure 1b Summary risk of bias based on the modified Newcastle-Ottawa tool.

Figure 2a

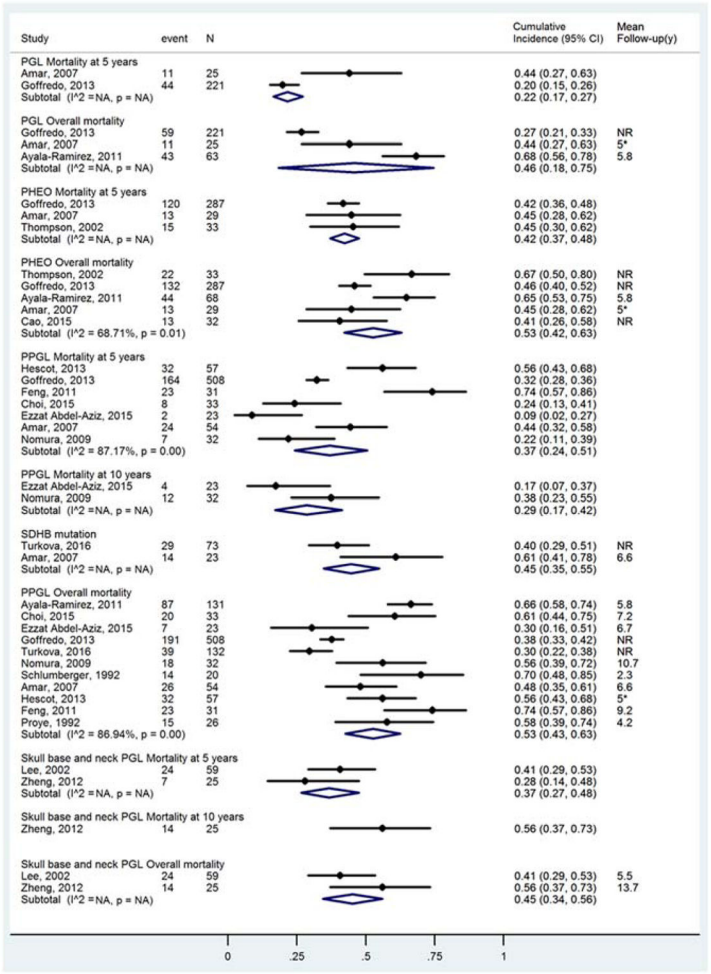

Figure 2b

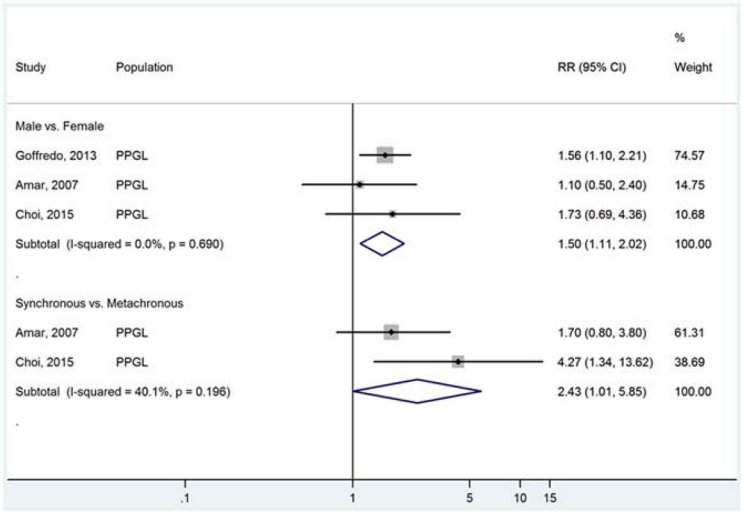

Figure 2.

Figure 2a Meta-analysis of mortality in patients with metastatic PPGL.

Footnote: The size of the boxes is proportional to the weight of each study.

Abbreviations used: NR, not reported.

Figure 2b Factors associated with higher mortality risk.

Footnote: Abbreviations used: RR, relative risk.

Table 1

Characteristics of included studies

Study description					Malignant PHEO/PGL			Mutation analysis		Metastatic diagnosis			
Author, year	**Country**	**Study design**	**Data collection**	**Population studied**	***N* (women)**	**PHEO**	**PGL**	***SDHB*-negative**	***SDHB*-positive**	**Age at diagnosis (years)**	**Age at metastases (years)**	**Synchronous**	**Duration of follow-up**
Proye, 1992	France	Retrospective (single centre)	1971–1991	Surgically managed benign and metastatic PPGL	26 (NR)	13	13			51.3			49.8 months (0–86)
Schlumberger, 1992	France	Retrospective (single centre)	1985–1990	Metastatic PPGL	20 (4)	16	4			40 (11–76)		11	28 months (3–352)
Glodny, 2001	Germany	Retrospective (single centre)	1967–1998	Benign and metastatic PPGL	29 (11)	22	7			39.2±21.9			NR
Lee, 2002	USA	Retrospective (national databasemulticentre)	1985–1996	Metastatic skull base and neck PGL	59 (30)	--	59			44	44	59	65.5 months
Mignon, 2002	France	Retrospective (multicentre)	1992–2002	Benign and metastatic PHEO	27 (17)	27				47 (13–74)			NR
Thompson, 2002	USA	Retrospective (single centre)	1970–1997	Surgically managed benign and metastatic PHEO	33 (17)	33				48.3(9–80)			NR
Dannenberg, 2003	Netherlands Frances Switzerland	Retrospective (multicentre)	1973–1997	Benign and metastatic PPGL	24 (12)	18	6						NR
Amar, 2007	France	Retrospective (multicentre)	NR	Metastatic PHEO and thoraco-abdominal PGL with genetic testing	54 (25)	29	25	49	23	37.9±13.9	42.0±13.8	24	79 months (IQR 24–190)
Nomura, 2009	Japan	Inception cohort (single centre)	1985–2006	Metastatic PPGL	32 (14)	12	20						10.7±9.4 years (range 0.5–39.7)
Ricketts, 2010	UK	Retrospective (unclear)	NR	Benign and metastatic PPGL with *SDHB* and *SDHD* mutations	42 (NR)	?	?		40				NR
Ayala-Ramirez, 2011	USA	Retrospective (single centre)	1960–2009	Benign and metastatic PHEO & sympathetic PGL	131 (NR)	68	63		9			67	5.8 years (range 0.01–57.3)
Feng, 2011	China	Retrospective (single centre)	1999–2008	Surgically managed benign and metastatic PPGL	31 (13)	17	14			43.1±17.5		13	110 months (range 6–246)
Zheng, 2012	China	Retrospective (single centre)	1975–2010	Benign and metastatic skull base and neck PGL	25 (13)	--	25		4	40±5 (range17–71)			13.7±8.3 years
Goffredo, 2013	USA	Retrospective (national database/multicentre)	1988–2009	Metastatic PPGL in adults	508 (244)	287	221			53.5±15. PHEO 51.2 ±16.1 PGL			NR
Hescot, 2013	France	Retrospective (multicentre)	2001–2011	Therapy-naïve metastatic PPGL	57 (24)	27	30	29	20	49±15		25	27 months (range 6–62)

Study description					Malignant PHEO/PGL			Mutation analysis		Metastatic diagnosis			
Author, year	**Country**	**Study design**	**Data collection**	**Population studied**	***N* (women)**	**PHEO**	**PGL**	***SDHB*-negative**	***SDHB*-positive**	**Age at diagnosis (years)**	**Age at metastases (years)**	**Synchronous**	**Duration of follow-up**
Cao, 2015	China	Retrospective (single centre)	2003–2012	Metastatic PHEO	32 (15)	32	--			40.12±12.18 synchronous; 47.13±11.29 metachronous		17	51 months In synchronous 41 months in metachronous
Choi, 2015	Korea	Retrospective	1997–2013	Benign and metastatic PPGL	33 (20)	27	6			43.6±17.4 PHEO 40.2±9.7 PGL			7.2 years (2.2–19.9)
Ezzat Abdel-Aziz, 2015	US	Retrospective (multicentre)	1983–2012	Benign and metastatic PPGL	23 (9)	9	14		1	45 (5–71)		8	80 months (5–300)
Khadilkar, 2016	India	Retrospective (multicentre)	2000–2015	Benign and metastatic PPGL	20 (10)	10	10		2	39.3±13.4		13	NR
Turkova, 2016	USA	Retrospective (single centre)	2000–2014	Metastatic PPGL	132 (55)	38	94	59	73	35±16	41±16	23	NR

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Table 2

Description of included patients

	Value	Total no. patients in cited studies	No. of studies (citations)
Baseline characteristics			
Total *N*	1338		20 [9,10,12,17–29,39–42]
Women	533 (46.7%)	1139	17 [9,10,17–19,21–28,39–42]
PHEO	685 (52.9%)	1212	17 [9,12,17–19,22–29,39–42]
PGL	611 (47.1%)	1204	16 [9,10,12,17,19,21–29,41,42]
SDHB mutation	172 (35.5%)	484	8 [12,19–25]
Adrenergic signs and symptoms	176 (66.2%)	266	9 [18,22–24,26,29,39,41,42]
Functional	308 (83.9%)	367	8 [19,22,24–26,28,29,39]
Surgical resection of primary tumours	698 (84.8%)	823	10 [9,10,17,18,22,23,26,28,29,40]
Synchronous	215 (40.4%)	532	10 [12,17,19,22–26,40,41]
Time to metastases, yrs	3.6±1.9	339	7 [19,22–26,28]
Duration of follow-up, yrs	6.3±3.2 Range of means, 2.2–13.7	523	12 [10,12,17,19,21–23,26,28,29,40,41]
Age at primary tumour diagnosis			
Overall, yrs	43.9±5.2	1109	16 [9,10,18,19,21–26,28,29,39–42]
PHEO, yrs	46.5±5.0	406[a]	5 [9,18,28,39,40]
PGL, yrs	43.85±5.2	311[a]	4 [9,10,21,28]
SDHB-positive, yrs	34.9±4.6	105[b]	3 [12,19,25]
SDHB-negative, yrs	40.5±0.7	186	2 [19,25]
Tumour size			
Overall, cm	7.5±1.3	995	10 [9,12,18,19,21,24,25,40–42]
PHEO, cm	8.3±0.5	420[a]	4 [9,12,18,40]
PGL, cm	6.2±1.3	309[a]	3 [9,12,21]
SDHB-positive, cm	6.4±0.4	96b	2 [19,25]
SDHB-negative, cm	7.7±0.4	186	2 [19,25]

Categorical data presented as number (percentages).

Continuous data presented as mean±SD.

[a] Total number of patients with PHEO and PGL in cited studies, respectively.

[b] Total number of patients with *SDHB* mutation in cited studies.

Abbreviations used: yrs, years.