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Clinical Profile, Outcomes, and Predictors of Malignant Pheochromocytoma and Paraganglioma: Insights From a Single-Center Cohort

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ABSTRACT

Background: Malignant pheochromocytoma and paraganglioma (mPPGL) are not so common and the factors predicting the metastatic behavior are not well understood.

Methods: This retrospective cohort study included 218 patients with PPGL managed at our center over a period of 11 years (2013–2024). The clinical profile and treatment outcomes of patients with mPPGL were studied and were compared with non-metastatic PPGL(non-mPPGL).

Results: Thirty-six patients had mPPGL and the median age at diagnosis of metastases was 39.5 years(range 10–62). Twenty-one(58.3%) patients had synchronous metastases and 15(41.7%) developed metachronous metastases after a median duration of 76 months(range 13–270 months) from the diagnosis of the primary tumor. Metastases were detected in 100% of patients who had 18FDG(4/4) and 68 Ga DOTATATE(4/4) PET-CT, 97.2% (35/36) with CT/MRI and 79.3%(23/29) with 131I MIBG scan. Surgery was the primary treatment in 78%, and 131I MIBG therapy was administered to 19(52.8%) patients. Eleven patients succumbed due to metastatic disease and among them nine died within a year of diagnosis of metastases, the median survival at last follow-up was 31.5 months (range 3–96). On comparing mPPGL($n = 36$) and non-mPPGL($n = 182$), we found that patients with mPPGL had larger tumors (8.8 ± 5.2 vs. 6.3 ± 3.3, $p = 0.001$), had less frequent adrenergic symptoms and more often had extra-adrenal tumors.

Conclusion: Malignant PPGLs had a variable clinical course and were amenable to multimodal therapeutic strategies with a favorable outcome in about 67% of the patients. Although mPPGL had larger tumor diameter compared to non-mPPGL, no particular size cut-off could accurately predict metastases. Adjuvant 131I MIBG therapy is a useful treatment option in resource limited settings.

Devika Nandakumar and Remya Rajan considered joint first authors.

1 | Introduction

Pheochromocytoma and paragangliomas (PPGL) are rare neuroendocrine tumors that arise from chromaffin tissue of the adrenal medulla and neural crest derivatives of extra-adrenal sympathetic or parasympathetic paraganglia respectively [1]. Metastatic pheochromocytoma and paragangliomas (mPPGL) are defined by the presence of tumor cells in non-chromaffin tissues such as lymph nodes, bones, liver, or lungs. PPGLs are predominantly indolent tumors [2] and about 15-20% of PPGLs are associated with metastases [1, 3]. Recurrence of PPGL has been reported in about 5% of cases over 5 years and, about 40% of the disease recurrence is due to metastases [4]. Also, metastases have been reported up to 15 years after initial diagnosis of tumors thought to be benign [5].

At initial presentation, in the absence of synchronous metastases, tumor size greater than 5 cm, location of the primary tumor (sympathetic paraganglioma), non-secretory status or dopamine secretion, tumor necrosis, and germline succinate dehydrogenase B (*SDHB*) mutation may predict metastatic disease, aggressiveness and poor outcome among PPGL [6–10]. Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) and the Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) are the available histological scores that predict the risk of aggressive behavior/malignancy in these tumors. However, studies have shown that they are useful tools to predict tumors with low risk of metastasis (rule out metastases) rather than predicting the high-risk ones [11–13].

There is limited data from the Indian subcontinent on the clinical behavior of malignant PPGL and the factors predicting it. In this study, we analyzed the clinical and biochemical parameters, imaging and treatment outcomes of patients with malignant PPGL managed at our center. Also, we compared their characteristics with non-metastatic PPGL (non-mPPGL) to identify the factors that may predict metastasis at presentation.

2 | Methods

This retrospective cohort study included patients with PPGL managed at our center over a period of 11 years from 2013 to 2024. The study was approved by the institution review board (IRB No: 16147) which determined that informed consent was not required for review of medical records alone. The study included 218 patients with PPGL managed at our center over the study period. Among them, 36 patients had metastatic PPGL. The clinical, biochemical, imaging profile and treatment outcomes of patients were obtained from the electronic medical records.

Patients with PPGL were diagnosed based on symptoms of catecholamine excess namely headache, palpitations, diaphoresis or abdominal pain or incidental diagnosis of an adrenal mass, with biochemical (urinary fractionated metanephrines or nor-metanephrines) and imaging confirmation. The clinical characteristics like the age of diagnosis, presenting symptoms (symptoms of catecholamine excess, pheochromocytoma crisis), coronary events or cerebrovascular complications, family history, and symptoms related to associated syndromes were recorded. Urinary fractionated metanephrines were analyzed using a competitive enzyme immune assay with a commercial ELISA kit (LDN GmbH & Co. KG, Nordhorn). The coefficients of variation (CV) for urinary metanephrines were 10.2% and that of urinary normetanephrines were 9.6%. Patients with urinary metanephrine and normetanephrine levels at least two times the upper limit of normal ($>700\,\mu g$/day and $>1200\,\mu g$/day, respectively) were classified as having secretory tumors [14, 15]. Imaging characteristics - computerized tomography (CT), magnetic resonance imaging (MRI) and all available functional images (FDG PETSCAN, ^{68}Ga DOTATATE PET Scan, or ^{131}I MIBG scan) were reviewed. The proportion of patients with adrenal pheochromocytoma or extra adrenal paraganglioma (PGL), unilateral or bilateral adrenal pheochromocytoma, tumor size, and presence of metastatic lesions, the site, number and location of metastases were recorded.

Details of the different modalities of treatment, time to recurrence or malignant progression and the duration of follow up were noted. Histopathology slides of the primary tumor and recurrent/metastatic tumors operated at our center were reviewed by a single pathologist for grading system for adrenal pheochromocytoma and paraganglioma (GAPP) score.

Synchronous metastatic disease was defined as the presence of distant metastases at initial presentation or within 3 months of the primary tumor diagnosis. Patients who developed metastatic disease ≥ 3 months after the diagnosis of the primary tumor were classified as having metachronous metastases [10]. Subjects carrying genetic mutations predisposing to PPGL, familial history of PPGL or its associated syndromic features, or presence of at least two National Institutes of Health criteria for diagnosing neurofibromatosis (NF1) syndrome were classified as inherited PPGL.

The various clinical, biochemical, radiological and histological characteristics were compared among patients with mPPGL and non-mPPGL.

The data was analyzed using SPSS version 21.0 (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) and R software version 4.x.x (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables such as age, duration of follow-up, median survival were reported using median(range); categorical variables were reported as frequencies and percentages. Clinical features such as gender, age, radiological characteristics, histological features were compared between patients with mPPGL and non-mPPGL. Univariate and multivariate logistic regression analysis were used to assess the factors predicting metastases. Survival analysis was performed using the Kaplan–Meier method and survival curves were constructed for patients with synchronous and metachronous metastases and differences between survival curves were assessed using the log-rank test. Kaplan–Meier curves and Gantt charts for treatment timelines were constructed using the survival, survminer, and ggplot2 packages in R. A p-value of <0.05 was considered statistically significant.

3 | Results

Our mPPGL cohort comprised of 36 patients. The median age at primary tumor diagnosis was 35.5 years (range 10–62 years) and 20 (55.6%) patients were males. Nineteen (52.8%) patients had pheochromocytoma only, 16(44.4%) patients had paraganglioma only and one patient had both pheochromocytoma and paraganglioma at primary presentation. The median duration of follow-up was 46 months (range 4-192 months).

Seven (19.4%) patients presented with the classical triad of headache, sweating and palpitations. Sixteen (44.4%) patients had at least one symptom related to catecholamine excess (sweating/palpitations/tremors/headache), 13(36.1%) patients presented with symptoms of mass effect such as abdominal pain, abdominal mass or neck swelling and 7(19.4%) patients were incidentally diagnosed to have PPGL on imaging done for other causes. Twenty-nine (80.6%) patients with mPPGL were secretory which included 22 predominantly norepinephrine secreting and seven epinephrine secreting tumors. All the pheochromocytomas ($n = 19$) were unilateral. Among the paragangliomas ($n = 17$), eleven patients had solitary (64.7%) and seven patients (41.2%) had multifocal tumors. Five patients had two tumors and, two patients had three paragangliomas. The paraganglioma tumor sites included abdominopelvic ($n = 15$) followed by skull base ($n = 4$) and thoracic ($n = 2$). The median diameter of the primary tumor was 7.6 cm (range 2.7–25 cm). Twenty patients (55.6%) underwent genetic testing; initially targeted screening was performed based on the clinical presentation (Multiple Endocrine Neoplasia – *MEN2*/Von Hippel Lindau syndrome - *VHL/SDHx*) and if negative clinical exome sequencing was performed using next generation sequencing. Nine (45%) patients carried a pathogenic variant in PPGL susceptibility genes. Six patients carried mutations in *SDH* genes [2 *SDHB*, 2 *SDHC*, 1 *SDHD*, 1 *SDHAF2* (SDH assembly factor 2)] and one patient each harbored mutations in *VHL, RET* (re-arranged during transfection), and *MAX* (MYC associated factor X) genes.

Twenty-one (58.3%) patients presented with synchronous metastases and 15(41.7%) patients developed metachronous metastases over a median duration of 76 months (range 13–270 months). The time duration from diagnosis of the primary tumor to detection of metastases is shown in Figure 1. The most common sites of metastases were liver (54.5%), lungs (45.4%) and bone (45.4%). The imaging modalities for detection of metastases included FDG PET CT (4/4) and ^{68}Ga DOTATATE PET CT (4/4), CT/MRI- (35/36, detection rate- 97.2%) and I^{131} MIBG (23/29, detection rate- 79.3%).

Thirty (80.5%) patients underwent surgical resection of the primary tumor/s as the first treatment and 11(30.6%) patients developed recurrence at the site of the primary tumor following surgery. The median time to local recurrence was 60 months (range 18-270). The mean (SD (standard deviation)) GAPP score was 4.5 ± 1.9. Nineteen (52.8%) patients received ^{131}I MIBG therapy in our cohort. The other modalities of treatment included chemotherapy (22.2%) (CVD regime: cyclophosphamide, vincristine and dacarbazine/cisplatin and etoposide/capecitabine), radiotherapy (13.9%), tyrosine kinase inhibitors (8.3%), Temozolomide and ^{177}Lutetium DOTATATE therapy (5.6% each), octreotide LAR and Sirolimus (2.8% each). The treatment details of individual patients are shown in Figure 2.

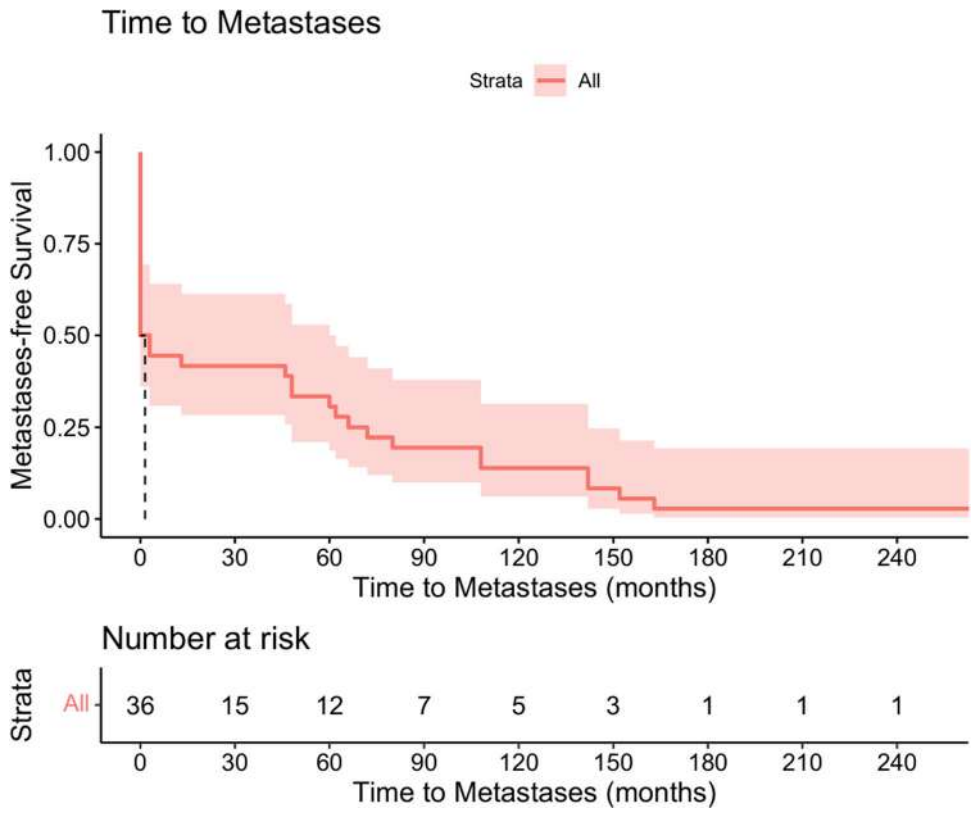

FIGURE 1 | Time taken for metastases from the diagnosis of initial tumor in months.

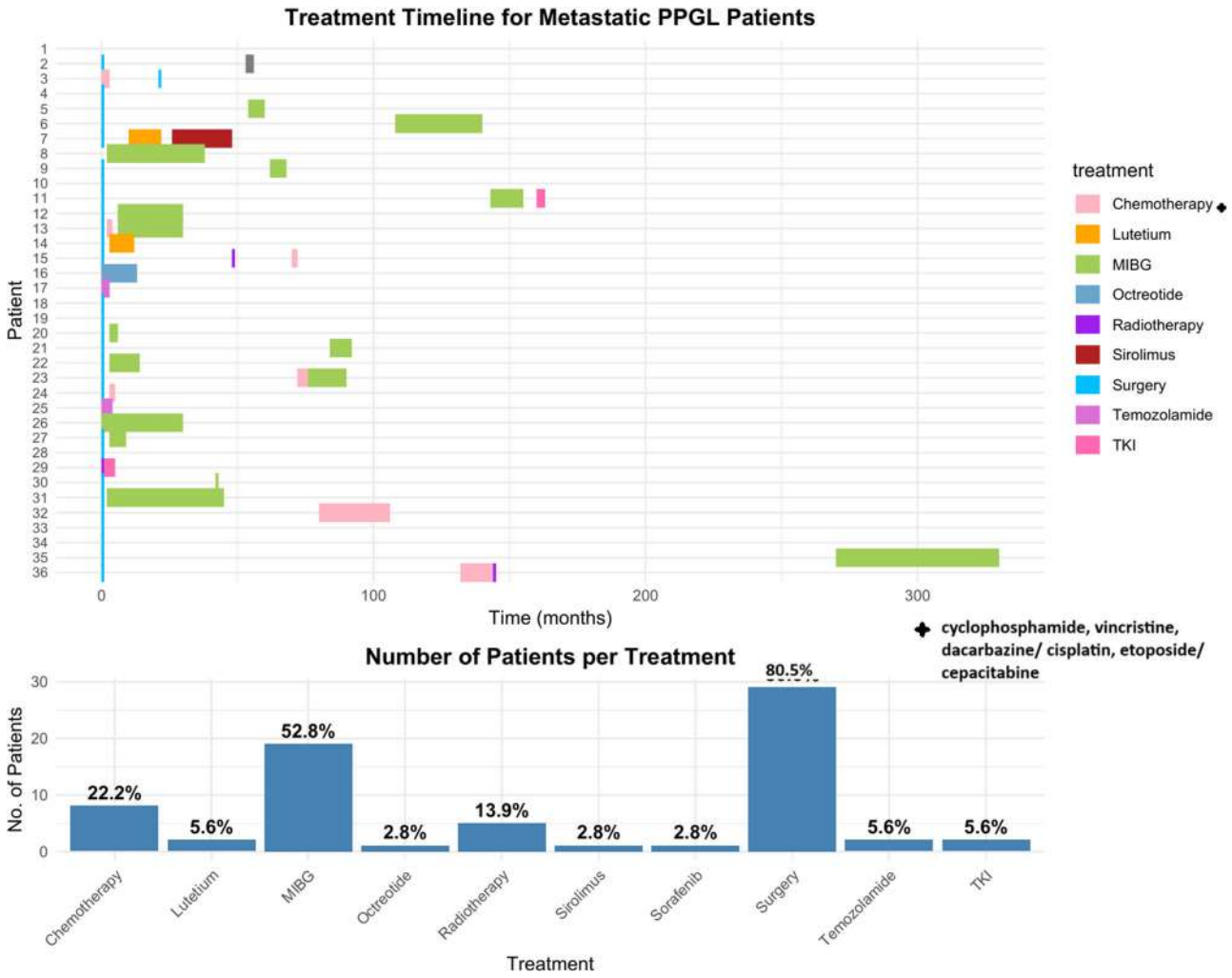

FIGURE 2 | Treatment received by the patients with metastatic PPGLs.

The median duration of follow-up after diagnosis of metastases was 31.5 months (range 3–96 months). Eleven (30.6%) patients succumbed due to metastatic disease and among them nine died within a year of diagnosis of metastases. One patient died in the postoperative period due to major vessel bleeding. At the last follow-up, 23(63.9%) patients were alive with disease and 1(2.8%) patient was disease free. A Kaplan–Meier survival curve of patients with metachronous or synchronous metastases is shown in Figure 3. Patients with synchronous metastases had a poor survival compared to those with metachronous metastases; however, this difference was not statistically significant ($p = 0.06$, Figure 3).

Our nonmalignant PPGL cohort (non-mPPGL) comprised of 182 patients and among them 95 (52.2%) were males. The mean age at diagnosis was 39.4 years (range 15–72 years). Comparison of the clinical, biochemical, imaging and histopathological parameters of patients with mPPGL and non-mPPGL is given in Table 1. It was found that patients with mPPGL had larger tumor diameter (8.9 ± 5.2 cm vs. 6.3 ± 3.3 cm, $p = 0.001$), less frequent adrenergic symptoms and more often were extra-adrenal in location (Table 1). On multivariate logistic regression, only tumor size was found to be an independent predictor of metastases (OR 1.18 95% CI 1.07–1.29, $p = 0.001$). On ROC analysis no definite tumor size cut-off could predict malignancy with good diagnostic accuracy.

4 | Discussion

The study describes a cohort of 36 patients with mPPGLs managed at our center over 11 years and highlights the challenges in management of these tumors. Metastatic PPGLs were larger and were more likely to be in extra adrenal location compared to non-mPPGLs. Most patients with mPPGL required multimodal therapy, and despite this about 31% succumbed.

Only 44% of our mPPGL patients experienced adrenergic symptoms, 36% presented with symptoms due to mass effect, and 20% were incidentally found on imaging, similar to other reports [10]. This highlights the importance of a high degree of clinical suspicion and thorough evaluation, as many malignant cases did not have classical symptoms at initial presentation, and > 50% were diagnosed due to mass effect or imaging done for other reasons. Similar to reports from other parts of the world, we found a larger proportion mPPGLs in extra-adrenal locations (47.2%) as compared to non-mPPGLs (24.1%). *SDHx* mutations presenting with paragangliomas

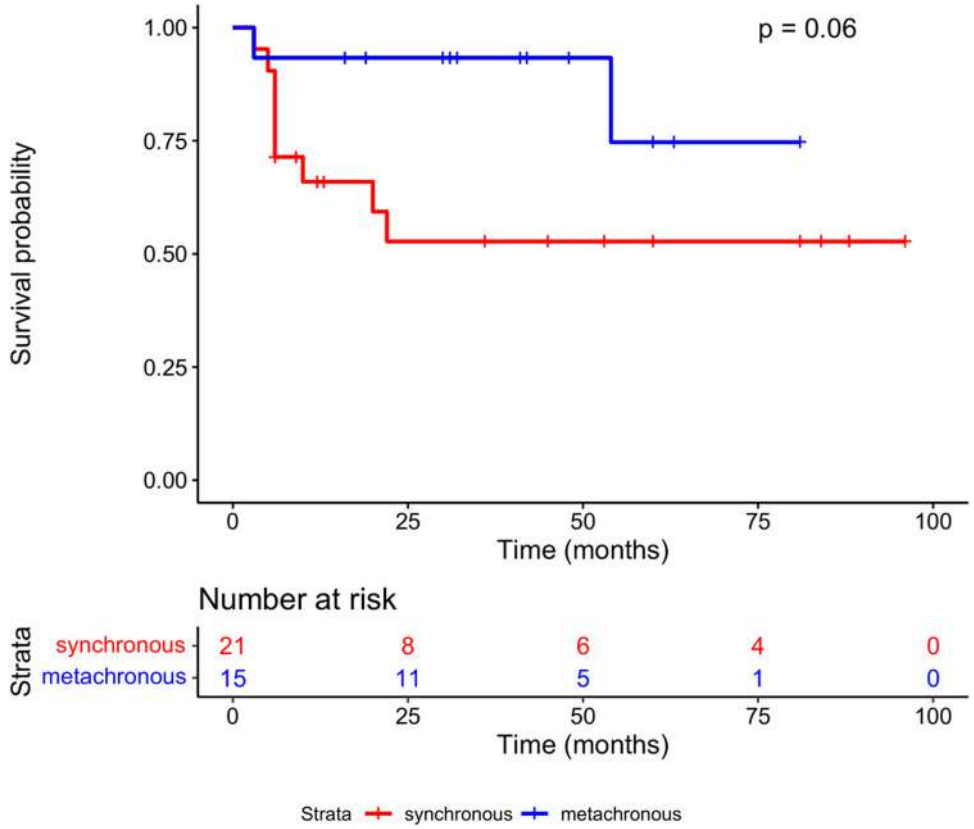

FIGURE 3 | The Kaplan–Meier curve showing the difference in survival among patients with metachronous and synchronous metastases.

TABLE 1 | Comparison of clinical, biochemical, radiological and histological characteristics among mPPGL and non-mPPGL.

Parameters	mPPGL $n = 36$	non-mPPGL $n = 182$	p value
Age (years) (mean ± SD)	36.3 ± 13.6	39.4 ± 14.5	0.232
Max tumor diameter (cm) (mean ± SD)	8.8 ± 5.2	6.3 ± 3.3	**0.001**
Gender *n* (%)			
Male	20 (55.6)	95 (52.2)	0.712
Female	16 (44.4)	87 (47.8)	
Adrenergic symptoms *n* (%)	16 (44.4)	112 (61.5)	0.060
Pheochromocytoma *n* (%)	20 (55.6)	147 (80.8)	**0.002**
Paraganglioma *n* (%)	17 (47.2)	44 (24.2)	**0.008**
Multifocal tumors *n* (%)	7 (41.2)	32 (17.5)	0.813
Secretory status *n* (%)	$N = 35$	$N = 181$	
Metanephrine secreting	7 (20)	61 (33.7)	0.649
Nor-metanephrine secreting	22 (62.9)	89 (49.2)	0.106
Non-secretory	6 (17.1)	30 (16.5)	1
GAPP score (mean ± SD)	4.5 ± 1.9	4.6 ± 2.5	0.764

have been recognized to be associated with increased risk of mPPGL [3, 9, 10].

Metastatic PPGLs had a significantly larger mean tumor diameter (8.8 ± 5.2 cm) compared to non-mPPGLs (6.3 ± 3.3 cm, $p = 0.001$), and tumor size was found to be an independent predictor of metastases on multivariate logistic regression analysis (*OR* 1.18, p 0.001). Khadilkar et al. have also reported larger tumor diameter in malignant PPGL as compared to non-mPPGL (8.3 ± 4.1 cm vs. 5.7 ± 2.3 cm, $p = 0.0001$) [9]. In a study

by Schovanek et al. in SDHB-related PPGL, tumors ≥ 4.5 cm were linked to earlier metastasis ($p = 0.003$), and those larger than 5.5 cm were associated with worse overall survival ($p = 0.008$) [7].

We found that > 80% of mPPGLs and non-mPPGLs were functional, and a larger proportion of mPPGL were normetanephrine secreting tumors, though the difference was not statistically significant. In a study by Khadilkar et al., 81.9% of non-mPPGL were functioning tumors compared to 72.2% of malignant cases, with more metanephrine-secreting tumors among non-mPPGL [9]. Eisenhofer et al. noted significant differences in catecholamine secretion profiles between metastatic and non-metastatic tumors, with metastatic tumors showing altered and lower catecholamine secretion [16].

Surgery was the most commonly employed modality of initial treatment in our mPPGL cohort (78%), and about 31% developed recurrence rate at the primary site on follow-up. Other studies have reported similar rates of local recurrence of about 33% [10]. The median follow-up duration for mPPGL patients was 46 months from the primary diagnosis and 31.5 months after metastases detection, with 55.5% having synchronous metastases. Metachronous metastases developed in 44.4% of patients, after a median follow-up of 76 months (6.3 years). Hamidi et al. also reported synchronous metastases in 35% of patients, while 65% developed metachronous metastases at a median of 5.5 years [10]. This highlights the need for long-term follow-up of these tumors even if they exhibit indolent behavior at diagnosis.

At the last follow up, 66.6% of our patients were alive with disease, while 30% succumbed to metastatic disease, mostly within 1 year of diagnosis of metastases. The availability of multimodal treatment options like chemotherapy and targeted therapies, and response to ^{131}I MIBG and ^{177}Lutetium DOTATATE therapy have significantly improved the survival of patients with metastatic PPGL [17]. In our cohort, a large proportion of patients (53%) received ^{131}I MIBG as an adjuvant therapy, which is affordable to most of our patients who have to pay for their treatment. A meta-analysis of 27 studies (608 patients with PPGL) found no statistically significant difference in the unweighted mean progression free survival (PFS) between ^{131}I MIBG and ^{144}Lutetium PRRT (25.4 vs. 29.6 months, $p = 0.787$; 95% CI [−5.9, 14.1]). With linear regression models, ^{131}I MIBG overall PFS was on an average 10 months lower when compared with ^{144}Lutetium PRRT, with adrenal tumors responding better to PRRT [18].

Among the factors predicting mPPGL, though extra adrenal tumor location was a significant predictor on univariate analysis, only larger tumor size emerged as a significant predictor after multivariate analysis. Other studies have also reported that larger tumors are more likely to be malignant (9, 10), and in addition *SDHB* mutation, non-secreting tumors, and extra-adrenal tumor location have been associated with mPPGL [7–9].

To our knowledge, this is the largest series of mPPGL from a single center from India. Comprehensive description of clinical course and treatment outcomes of 36 cases of malignant PPGL managed at a single center remains the strength of the study. The retrospective nature of the study, nonavailability of methoxy-tyramine level (not done routinely at our center) and genetic analysis in half of our patients in the malignant cohort are the limitations of this study.

5 | Conclusion

Malignant PPGLs had a variable clinical course and were amenable to multimodal therapeutic strategies with a favorable outcome in about 67% of the patients with mPPGL. Although, mPPGL had larger tumor diameter compared to non-mPPGL, there was no definite size cut-off that could predict metastases. Adjuvant ^{131}I MIBG therapy is a useful treatment option to prolong PFS in resource limited settings.

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The authors have nothing to report.

Data Availability Statement

Data generated during the study may be available from the corresponding author on a reasonable request.

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