Clinical features and outcomes of metastatic pheochromocytoma treated by cytotoxic chemotherapy

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Abstract. Cytotoxic chemotherapy, including cyclophosphamide, vincristine, and dacarbazine (CVD) therapy, is widely used to treat metastatic pheochromocytoma and paraganglioma. Because these diseases are rare, studies are needed to establish treatment strategies. This was a single-center and retrospective study to analyze the efficacy of chemotherapy for patients with metastatic pheochromocytoma and paraganglioma diagnosed in 1983–2020. Clinical characteristics, tumor volume response, biochemical response based on catecholamine level, overall survival, and progression-free survival were evaluated. Patients with a complete response or partial response in tumor volume or catecholamine level were classified as responders. Sixteen patients were administered chemotherapy for a median of 16.5 cycles (interquartile range, 10–42). The tumor volume response was classified as follows: partial response (N = 4), stable disease (N = 9), and progressive disease (N = 3) (disease control rate = 81%). The biochemical responses were as follows: complete response (N = 2), partial response (N = 5), no change (N = 3), and progressive disease (N = 1) (disease control rate = 91%). The 5-year survival rate was 50% (95% confidence interval [CI], 21–74%) and median overall survival was 4.4 years (95% CI, 2.4 years–not reached). Overall survival and progression-free survival between responders and nonresponders were not statistically different. One patient developed myelodysplastic syndrome during CVD therapy. In conclusion, chemotherapy achieved disease control among more than half of patients, although survival did not differ between responders and nonresponders. Further fundamental research and prospective trials are needed to analyze the efficacy of CVD therapy.

Key words: Pheochromocytoma, Paraganglioma, Chemotherapy, Secondary malignancy

PHEOCHROMOCYTOMA (PCC) and paraganglioma (PGL) are rare tumors occurring in the primary sites of the adrenal medulla and extra-adrenal tissues, respectively. The incidence of these tumors is approximately 0.6–0.8 cases per 100,000 person-years [1, 2]. Most PCC and PGL (PPGL) cases are non-cancerous; however, around 10–30% of PPGL cases are cancerous and characterized by metastasis [3]. The common metastatic sites are the liver, lungs, lymph nodes, and bones [4]. Several strategies for treating metastatic PPGL have been developed on a case-by-case basis. If few primary and metastatic sites are present, tumor resection is recommended. For metastatic PPGL, both symptom management and systemic treatment are necessary [5]. High catecholamine levels sometimes cause severe complications such as cardiomyopathy, venous thromboembolism, and hypertensive crisis. Thus, surgical reduction of the tumor and reduction of the catecholamine level via appropriate medications for reducing the disease burden are essential for PPGL management. For example, if patients have persistent hypertension due to excessive adrenergic stimulation, alpha- and beta-blockers are optimal for lowering blood pressure. Moreover, even if the tumor is not completely resectable, surgically reducing tumor size locally is still advised to reduce catecholamine release [6]. Additionally, external radiotherapy is recommended to ease painful symptoms secondary to...
bone metastasis [7]. For systematic disease control, administration of the radiotherapeutic agent iobenguane I 131 and chemotherapy is recommended; indications of these treatments depend on several factors such as metastatic site, iobenguane I 131 uptake, performance status, and patient preference [8]. Metastatic PPGL is mainly treated by cytotoxic chemotherapy. Particularly, for patients with rapid progression, a high tumor burden, and multiple metastases, chemotherapy should be considered. Chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) was established approximately 30 years ago and has been the main regimen used to treat metastatic PPGL [9]. However, few prospective trials and retrospective studies have been performed because of the rarity of this cancer [10-14]. Thus, we analyzed metastatic PPGL cases to evaluate the efficacy of chemotherapy.

Materials and Methods

Patient characteristics and study design

In this retrospective, single-center, observational study, we reviewed the medical records of 44 patients who were diagnosed with PPGL from January 1983 to June 2020. The Institutional Review Board of The Cancer Institute Hospital of JFCR approved this study, which was conducted in accordance with the Helsinki Declaration on human experimentation. After excluding patients with localized PPGL who had undergone complete resection by surgery and had not been administered chemotherapy, 16 patients were selected. We obtained information on sex, age, cancer type (PCC or PGL), recurrence status (patients who were initially diagnosed with localized PPGL and later recurred as a metastatic disease), metastatic site, catecholamine levels, past medical history, family history, smoking and alcohol intake history, chemotherapy regimen, total chemotherapy courses undertaken, tumor response (tumor volume and biological response), progression-free survival (PFS), and overall survival (OS). Moreover, information on the date of initial diagnosis, surgery, relapse, progression, and death was obtained. Primary site, metastasis, and tumor volume were evaluated based on radiological findings including computed tomography (CT), 18F-fluorodeoxyglucose-positron emission tomography/CT, and magnetic resonance imaging. The primary objective was to determine the clinical benefit of systemic chemotherapy in these patients. We also examined the clinical features of patients who developed secondary malignancy after undergoing chemotherapy. A reduction in tumor volume and catecholamine levels signified the efficacy of chemotherapy. OS and PFS were also analyzed. We defined OS as the duration from the date of chemotherapy initiation to the date of final follow-up or death, and patient information was censored when the last follow-up date was confirmed without death. PFS was defined as the duration from the date of chemotherapy initiation to the date of detection of disease progression according to the response of the tumor volume. The metastasis-free duration was considered as the period from initial PPGL diagnosis to metastasis diagnosis, whereas relapse-free duration was defined as the period from complete cure to relapse.

Chemotherapeutic treatment

PPGL is typically treated with cytotoxic agents such as cyclophosphamide, vincristine, dacarbazine, and doxorubicin, and our study included patients treated with these agents. CVD therapy consists of cyclophosphamide (750 mg/m²) on day 1, vincristine (1.4 mg/m²) on day 1, and dacarbazine (600 mg/m²) on days 1 and 2 every 21–28 days. We excluded patients who were administered only drugs without anti-tumor activities such as zoledronate. The use of meta-iodobenzylguanidine labeled with 131-iodine (131-I-MIBG, iobenguane I 131) throughout the clinical course was accepted. Patients with a good performance status without any significant organ dysfunction and who suffered from symptoms secondary to the tumor, accompanied by a large tumor volume, or had elevated catecholamine levels, were considered to start chemotherapy. After regulatory approval of 131-I-MIBG as advanced medical care in Japan in 2015, patients with at least one site of abnormal MIBG uptake were referred to institutions offering 131-I-MIBG to determine the application of this treatment.

Evaluation of the effects of chemotherapy

Radiological tumor volume response

We reviewed the patient’s medical records and radiological findings including CT and magnetic resonance imaging. Response Evaluation Criteria in Solid Tumors, version 1.1 was used to assess the tumor complete response (CR, disappearance of measurable tumor), partial response (PR, at least a 30% decrease in the sum of target lesions), progressive disease (PD, at least 20% increase in the sum of target lesions), or stable disease (SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) [15]. The radiological tumor volume response was typically assessed after every 3–4 cycles of chemotherapy; however, no protocol was established at our institution because of this study was retrospective and based on the test schedule applied, which depended on the physician’s choice and patient’s condition.

Biochemical response

The biochemical response was defined as changes in
the levels of serum or urine catecholamine and its derivatives from baseline levels. Serum or urine catecholamine levels were evaluated at each cycle of chemotherapy and obtained as needed based on the physicians’ judgment. The degree of response was defined according to a previous study as follows: CR (normalization of hormonal levels), PR (≥25% reduction in hormonal levels), NC (no change, <25% reduction and <25% increase), and PD (≥25% increase in hormonal levels) [14].

**Responder criteria**

Patients who exhibited CR or PR in terms of a reduction in tumor volume and/or biochemical parameters (levels of serum or urine catecholamine) were considered as responders, whereas patients who exhibited SD or PD in the tumor volume response and NC or PD in the biochemical response were considered as nonresponders.

**Factors affecting tumor response**

The effects of sex, age, cancer type (PCC or PGL), metastatic transformation, surgery history, metastatic site, catecholamine levels, family history, smoking, alcohol intake, and other pathological features on the tumor response and survival were statistically analyzed.

**Adverse event evaluation**

Adverse events that occurred during chemotherapy were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 to determine the relationship between chemotherapy and secondary malignancy [16]. As adverse event details were not documented in the medical records of all patients, we analyzed only the available details. Adverse event information of patients with secondary malignancy was evaluated separately in detail.

**Statistical analysis**

For continuous values, the mean, median, standard deviation, minimum, and maximum values were calculated. For categorical values, frequencies and percentages were determined. The Mann–Whitney U test was used to compare the mean and median of continuous values between two individual groups. The Fisher exact test was used to assess the association between two categorical values. Clinical outcomes such as OS and PFS were calculated by using the Kaplan–Meier method, and a log-rank test was used to compare survival curves between patient groups. Univariate and multivariate Cox proportional hazards models were adopted to identify prognostic factors. All tests were two-sided, and a value of \( p < 0.05 \) was considered as statistically significant. All statistical analyses were performed using EZR (a graphical user interface for R) that incorporates frequently used statistical functions [17].

**Results**

**Patient characteristics**

This retrospective study included 16 patients with metastatic PPGL who were administered cytotoxic chemotherapy at least once. Patient characteristics are summarized in Table 1. Among the 16 patients, nine (56%) responded to chemotherapy and were considered as responders. Chemotherapy-related details were available for all patients. Between responders and nonresponders, there was no difference in age, sex, cancer type, initial disease status, history of smoking and alcohol, family cancer history, and courses of chemotherapy including CVD. The prevalence of hypertension was significantly higher among responders (odds ratio = 15.5, \( p = 0.04 \)).

Detailed clinical information of each patient is summarized in Table 2. PCC was observed in seven patients and PGL in nine patients. The initial disease status was localized in 11 patients and metastasis was identified in five patients. The most common initial disease lesions were in the adrenal gland and retroperitoneum. A family history of cancer was noted in six patients, and 14 patients underwent surgical resection as the initial treatment. Genetic information, such as succinate dehydrogenase subunit (SDHx) gene mutations, was not collected in this study.

**Chemotherapeutic treatment**

The initial chemotherapy regimen included ACVD (doxorubicin, cyclophosphamide, vincristine, and dacarbazine), CVD, and VDC (vincristine, dacarbazine, and cyclophosphamide) (Table 2). ACVD therapy contains doxorubicin at 40 mg/m² in addition to the CVD regimen. The most common initial regimen was CVD (\( N = 12, \) 75%). The ACVD regimen was administered to three patients (19%) in their early 90s as an initial treatment and was replaced with CVD therapy once the maximum cumulative dose of doxorubicin was reached. Only one patient administered the VDC regimen (vincristine 1.4 mg/m², doxorubicin 75 mg/m², and cyclophosphamide 1,200 mg/m²) was first diagnosed with Ewing sarcoma; the regimen was changed from VDC to CVD after pathological review confirmed metastatic PGL. ¹³¹I-MIBG therapy was administered to three patients (19%). Radiotherapy for bone metastasis was conducted in seven patients (44%), and the efficacy of radiotherapy was not included in the radiological tumor volume response.

**Tumor response**

**Radiological tumor volume response**

Information on the tumor volume response was available for all patients (Table 2). Although no patients gained
Table 1  Characteristics of patients on the basis of their response to cytotoxic chemotherapy

| Clinical features | All patients | Responders | Nonresponders | p       |
|-------------------|--------------|------------|---------------|---------|
| Number of patients| 16           | 9          | 7             | 0.07    |
| Age               |              |            |               |         |
| Median (IQR)      | 42.5 (38–47) | 45 (42–51) | 38 (36–42.5)  |         |
| Sex               |              |            |               | 1.00    |
| Male              | 12 (75)      | 7 (78)     | 5 (71)        |         |
| Female            | 4 (25)       | 2 (22)     | 2 (29)        |         |
| Cancer type       |              |            |               | 0.36    |
| Pheochromocytoma  | 7 (44)       | 5 (56)     | 2 (29)        |         |
| Paraganglioma     | 9 (56)       | 4 (44)     | 5 (71)        |         |
| Initial disease status |      |            |               | 1.00    |
| Benign           | 11 (69)      | 6 (67)     | 5 (71)        |         |
| Malignant         | 5 (31)       | 3 (33)     | 2 (29)        |         |
| Smoking           |              |            |               | 0.21    |
| Yes               | 7 (44)       | 4 (44)     | 3 (43)        |         |
| No                | 5 (31)       | 5 (36)     | 0 (0)         |         |
| NA                | 4 (25)       | 0 (0)      | 4 (57)        |         |
| Alcohol           |              |            |               | 1       |
| Yes               | 7 (44)       | 5 (56)     | 2 (29)        |         |
| No                | 6 (38)       | 4 (44)     | 2 (29)        |         |
| NA                | 3 (19)       | 0 (0)      | 3 (43)        |         |
| Previous cancer history |      |            |               | NA      |
| Yes               | 0 (0)        | 0 (0)      | 0 (0)         |         |
| No                | 13 (81)      | 8 (89)     | 5 (71)        |         |
| NA                | 3 (19)       | 1 (11)     | 2 (29)        |         |
| Secondary malignancy |        |            |               | 0.51    |
| Yes               | 2 (13)       | 2 (22)     | 0 (0)         |         |
| No                | 11 (69)      | 6 (67)     | 5 (71)        |         |
| NA                | 3 (19)       | 1 (11)     | 2 (29)        |         |
| Family history of cancer |      |            |               | 1       |
| Yes               | 6 (38)       | 4 (44)     | 2 (29)        |         |
| No                | 4 (25)       | 3 (33)     | 1 (14)        |         |
| NA                | 6 (38)       | 2 (22)     | 4 (57)        |         |
| Initial chemotherapy |        |            |               |         |
| ACVD              | 3 (19)       | 2 (22)     | 1 (14)        |         |
| CVD               | 12 (75)      | 7 (78)     | 5 (71)        |         |
| VCD               | 1 (6)        | 0          | 1 (14)        |         |
| Courses of chemotherapy |      |            |               | 0.40    |
| Median (IQR)      | 16.5 (10–42) | 18.0 (15–45) | 13 (8–37.5)  |         |
| Courses of CVD    | 16.5 (5.5–42) | 18.0 (15–45) | 6 (2.5–37.5) | 0.27    |
| Malignancy free duration (year) |     |            |               | 0.87    |
| Median (IQR)      | 0.82 (0–5.7) | 0.69 (0–5.2) | 0.95 (0.1–4.7) |         |
| Initial lesion    |              |            |               | 1       |
| Single            | 12 (75)      | 7 (78)     | 5 (71)        |         |
| Adrenal gland     | 4 (25)       | 3 (33)     | 1 (14)        |         |
| Retroperitoneum   | 4 (25)       | 2 (22)     | 2 (29)        |         |
| Bladder           | 2 (13)       | 1 (11)     | 1 (14)        |         |
| Vagus nerve       | 1 (6)        | 0 (0)      | 1 (14)        |         |
| Vertebral         | 1 (6)        | 1 (11)     | 0 (0)         |         |
| Multiple          | 4 (25)       | 2 (22)     | 2 (29)        |         |
| Hypertension      |              |            |               | 0.04    |
| Yes               | 10 (63)      | 8 (89)     | 2 (29)        |         |
| No                | 6 (38)       | 1 (11)     | 5 (71)        |         |

IQR, interquartile range; NA, not available; ACVD, adriamycin, cyclophosphamide, vincristine, dacarbazine; CVD, cyclophosphamide, vincristine, dacarbazine; VCD, vincristine, cyclophosphamide, dacarbazine
| No | Sex | Age | Cancer type | Initial disease status | Initial lesions | Size of primary tumor before chemotherapy (maximum in diameter) | Past medical history | Family cancer history | Hormone functionality | Initial treatment | Chemotherapy | RT CVD cycles | Radiological tumor volume response | Biochemical response | MFD (year) | RFD (year) | PFS (year) | OS (year) | Status |
|----|-----|-----|-------------|-----------------------|----------------|----------------------------------------------------------------|---------------------|----------------------|---------------------|-------------------|---------------|----------------|--------------------------------|---------------------|-------------|-----------|-----------|--------|--------|
| 1  | M   | 46  | PCC         | Local                 | Adrenal gland (8) | 75 mm Pancreatitis, Lipoma, HTN (52), Gastric perforation | NA F (NE) | Resection | CVD No | Yes | 41 | 41 | SD | PD | 7.3 | 6.6 | 0.8 | 3.8 | Decayed |
| 2  | M   | 51  | PCC         | Local                 | Adrenal gland (8) | 38 mm HTN (40), Urdithiasis, DM (76) | NA F (NE) | Resection | ACVD, CVD No | No | No | 56 | 66 | PR | CR | 5.2 | 5.2 | 23.7 | 24.2 | Alive |
| 3  | M   | 38  | Metastatic  | Spine, Retroperitoneum | 85 mm HTN (16), DM (49) | Gastric cancer (5Ga) | F (NE) | Resection | ACVD, CVD, IFM, CVD Yes | Yes | 93 | 95 | SD | PR | NA | 7.2 | 7.1 | 12.1 | Decayed |
| 4  | F   | 25  | PGL         | Local                 | Retroperitoneum    | NA NA NA NF | Reection | ACVD, PTX Yes | Yes | 0 | 10 | SD | NC | 2.1 | 2.1 | 2.3 | 9.0 | Alive |
| 5  | F   | 42  | PCC         | Local                 | Adrenal gland (9) | None HTN (NA) | NA NA | Reection | CVD No | No | 10 | 10 | PR | NA | 0.4 | 0.4 | 0.6 | 0.9 | Alive |
| 6  | F   | 34  | PGL         | Local                 | Rarant laryngeal nerve | None | Graves’ disease (37) | NA | Resection | CVD No | No | 58 | 58 | SD | NA | 10.0 | 10.0 | 6.0 | 6.6 | Alive |
| 7  | F   | 45  | PGL         | Local                 | Retropetoneum | None ICH (51), Nephritic syndrome | F (NE) | Resection | CVD No | No | 31 | 31 | SD | PR | 10.9 | 10.9 | 3.4 | 5.0 | Decayed |
| 8  | M   | 43  | PCC         | Local                 | Bladder | None HTN (42), Tuberculosis | F (NE and DA) | Resection | CVD No | No | 34 | 34 | SD | NC | 0.3 | 0.3 | 2.9 | 3.5 | Decayed |
| 9  | M   | 38  | Metastatic  | Retropetoneum, Lung   | 57 mm | None Gastric cancer (Fa) | NA | Resection | CVD, Novel agents Yes | No | 6 | 6 | PD | NA | NA | 0.7 | 2.4 | Decayed |
| 10 | M   | 44  | PGL         | Metastatic            | Retropetoneum, Mediastinum, Lung, Bone | 149 mm HTN (NA) | Colorectal cancer (G,F), Brain tumor (Sa), Renal cancer (BRO) | NA Chemotherapy | CVD No | No | 15 | 15 | PR | NC | NA | 1.4 | 1.8 | Decayed |
| 11 | M   | 57  | PGL         | Local                 | Bladder | None HTN, DM | None F (NE and DA) | Resection | CVD, VDC, VDC, IE No | Yes | 2 | 13 | PD | NA | NA | 0.4 | 1.3 | Alive |
| 12 | M   | 38  | Metastatic  | Mediastinum, Bone, Liver | None Pulmonary HTN, ASD | NA NA | Chemotherapy VDC, VDC, IE No | Yes | 2 | 13 | PD | NA | NA | 0.4 | 1.3 | Alive |
| 13 | M   | 42  | PGL         | Local                 | Retropetoneum | None NA | NA F (NE) | Resection | CVD No | No | 3 | 3 | PD | NA | 1.0 | 1.0 | 0.8 | 1.8 | Alive |
| 14 | M   | 50  | PGL         | Metastatic            | Spine | None NA | F (NE) | Resection | CVD Yes Yes | 15 | 15 | SD | PR | NA | 1.0 | 1.0 | 4.3 | Alive |
| 15 | M   | 32  | PCC         | Local                 | Adrenal gland (5) | None ICH (31), HTN (51) | F (NE) | Resection | CVD No | No | 45 | 45 | SD | PR | 11.5 | 11.5 | 3.6 | 3.7 | Decayed |
| 16 | M   | 54  | PCC         | Local                 | Retropetoneum | None HTN (NA) | None F (NE) | Resection | CVD No | No | 4 | 4 | SD | CR | 0.7 | 0.4 | 0.3 | 0.3 | Alive |

M, male; F, female; PCC, pheochromocytoma; PGL, paraganglioma; ls, left; rs, right; HTN, hypertension; DM, diabetes mellitus; NA, not available; ICH, intracranial hemorrhage; ASD, atrial septal defect; GFa, grandfather; Mo, mother; Unc, uncle; Fa, father; BRO, brother; Fa, functional; NF, nonfunctional; NE, nonepinephrine; DA, dopamine; VDC, vincristine, doxorubicin, cyclophosphamide, dacarbazine; VD, vincristine, doxorubicin; VD, vincristine, dacarbazine; IFM, ifosfamide; PTX, paclitaxel; VDC, vincristine, doxorubicin, cyclophosphamide; IFM, ifosfamide; PD, partial response; SD, stable disease; NC, no change; PD, progressive disease; MFD, metastasis-free duration; RFD, relapse-free duration; PFS, progression-free survival; OS, overall survival.

* Only serum vanillylmandelic acid was measured and not able to determine the functionality. Biochemical response was assessed as NC.

** Novel agents are medications that were used in a phase 1 clinical trial.
CR, four (25%) achieved PR and nine (56%) achieved SD. The disease control rate (CR + PR + SD) was 81% (N = 13).

**Biochemical response**

Information on the level of serum and/or urine catecholamine and its derivatives was available for 11 patients. To evaluate the biochemical response, the serum catecholamine level was considered for 10 patients (serum norepinephrine level of nine patients and serum vanillylmandelic acid level of one patient), and the urine catecholamine level was considered for one patient. Biochemical CR was observed in two patients, whereas PR was observed in five patients. The disease control rate (CR + PR + NC) was 91% among these 11 patients. We classified one patient with non-catecholamine-secreting PGL in the no change (NC) category.

**Prognosis**

The median follow-up time for censored cases was 3.0 years (range, 0.3–24.2 years). The OS rate at five years for the 16 patients was 50% (95% confidence interval [CI], 21–74%). The median OS for the 16 patients was 4.4 years (2.4 years–not reached) and the median PFS for these patients was 2.3 years (0.7–3.6 years) (Fig. 1A–1B). The median OS for responders (N = 9) and nonresponders (N = 7) were 5.0 and 3.8 years, respectively. The Kaplan–Meier curves of OS and PFS in each group are shown in Fig. 1C–1D. There were no significant differences in OS and PFS between the two groups (p = 0.95 for OS and p = 0.22 for PFS). OS was also analyzed based on the tumor response only, biochemical response only, remission duration, and tumor pathology (PCC or PGL), but none of these factors were significant (Fig. 2A–2D). Age (≥50 years or <50 years), sex, smoking status, hypertension, and initial cancer status (localized or metastatic) were not associated with OS.

**Secondary malignancy**

Because of insufficient information available in the medical records, adverse events were not available for all patients. However, two patients developed secondary malignancy after or during chemotherapy. One patient was administered the second highest cycles of chemotherapy, whereas the other was administered the fourth highest among all 16 patients. Genetic tests such as next-generation sequencing for detecting somatic and germline mutations were not performed for these patients. Colorectal and gastric carcinoma were observed in one patient more than 20 years after the commencement of chemotherapy, and both cancers were successfully treated by surgery. Another patient developed therapy-related myelodysplastic syndrome (tMDS) during the 45th cycle of CVD chemotherapy administered for metastatic pheochromocytoma. During this cycle, this patient developed persistent pancytopenia, and a bone marrow test was performed. A cytogenetic test of the bone marrow aspirate showed a complex karyotype including deletions 7 and +5mar. The clinical course was complicated by the development of febrile neutropenia and frequent transfusions for myelosuppression. The patient died one month after tMDS was diagnosed. The clinical characteristics of the patients who developed secondary malignancy are summarized in Table 3.

**Discussion**

Although several types of molecular-targeted agents such as tyrosine kinase inhibitors and mTOR inhibitors have been used to treat metastatic PPGL, cytotoxic chemotherapy including the CVD regimen remains a mainstream option for treating metastatic PPGL [10, 18]. However, evidence to support the superior effect of this chemotherapy type is limited. Several cytotoxic agents have been studied as PPGL treatment options since the late 20th century, and the CVD regimen is thought to be the most common. A meta-analysis of four studies evaluated the tumor volume response after CVD administration for treating PPGL and reported pooled percentages of CR, PR, and SD of 4%, 37%, and 14%, respectively; analysis of the biological response showed that the pooled percentages of CR, PR, and SD were 14%, 40%, and 20%, respectively [19]. One limitation of this meta-analysis is that the total number of patients was only 50, and the four included studies were retrospective and observational in nature without a control arm because of the rarity of PPGL [11-14]. Nomura et al. compared the survival curves of patients with PPGL who were administered CVD therapy with those of patients who were not administered CVD therapy and reported no significant survival difference between these two groups [20]. Three independent studies consistently reported no difference in survival rates between nonresponders and responders to chemotherapy, although the definition of the response and statistical comparison methods were different in each study, and OS tended to be longer in responders [11, 13, 14]. Similarly, we compared the OS based on the response to chemotherapy, which revealed no significant difference between the two groups. This may be partly explained by the limited number of patients and slow-growing nature of PPGL [21]. In contrast, another study performed in Japan demonstrated the survival benefit of CVD treatment when patients were divided into PD and non-PD (CR + PR + SD) groups [22]. We did not compare the PD and non-PD groups because of the small number of patients. Our study also showed that the
The incidence of hypertension was higher in responders than in nonresponders. In our study, responders were defined as those who showed a response in the tumor volume or catecholamine levels. Therefore, patients with a greater tumor burden which was fast-growing nature may accompany higher catecholamine levels leading to hypertension [23]. This may result in a better response to chemotherapy in patients with hypertension. The prognostic factors of PPGL remain poorly defined, and it is unknown whether the presence of hypertension leads to better or worse outcomes in patients with PPGL [24]. Another potential reason for the higher incidence of hypertension in responders was the limited number of participants in our study. Thus, further studies of larger number of patients are needed to determine the clinical and molecular factors that can predict a better response and survival in patients with PPGL.

Generally, genetic mutations are frequently observed in patients with PPGL, such as those in RET, VHL, NF1, and SDHx (SDHA, SDHB, SDHC, SDHD, and SDHAF2) [3]. A recent study reported that patients with metastatic PPGL with an SDHB mutation exhibited longer PFS after CVD treatment [25]. However, most patients in our study did not undergo genetic evaluation because next-generation sequencing for patients with metastatic cancer was only recently approved in Japan (June 2019). Rather
than cytotoxic chemotherapy, multitarget inhibitors such as sorafenib and sunitinib have been considered as possible targeted therapies for treating metastatic PPGL, as most VHL- and SDHx mutation-associated tumors exhibit high vascularization [26-28]. However, multitarget inhibitors are not approved in Japan and no patients were administered targeted therapies. The CVD regimen is considered as a relatively safe therapy option because of the small number of adverse events [29].

Common adverse events associated with the CVD regimen include myelosuppression, gastrointestinal toxicities including nausea and vomiting, and peripheral neuropathy, but most patients can tolerate treatment with the development of these adverse events at a moderate level [14]. However, in our study, one patient developed tMDS and another patient developed secondary malignancy (colorectal and gastric cancer) after undergoing multiple cycles of CVD treatment. A previous observational study reported that a patient who developed tMDS with a complex karyotype including deletions 5 and 7 was compatible with the long-term use of an alkylating agent after 24 cycles of CVD and radiation therapy for

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**Fig. 2** OS between responders and nonresponders in terms of tumor volume reduction (A) and in terms of reduction in biochemical response (B), OS based on metastasis-free duration (C) and tumor pathology (PCC or PGL) (D). Kaplan–Meier curves showing the overall survival of patients with (solid line) and without (dashed line) tumor volume reduction (A), with (solid line) and without (dashed line) a decrease in catecholamine levels (B), in patients whose metastasis-free duration was more than five years (solid line) and five years or less (dashed line) (C), and in patients whose tumor pathology was PCC (solid line) and PGL (dashed line) (D). CI, confidence interval; HR, hazard ratio; OS, overall survival; MFY, metastasis-free years; PCC, pheochromocytoma; PGL, paraganglioma.
According to the WHO 2016 classification for hematopoietic and lymphoid tumors, the patient included in our study developed MDS with excess blasts-2 and a complex karyotype including deletions 7 and +5mar, which may have been associated with the alkylating agent four years after administering radiotherapy for bone metastasis and during the 45th cycle of CVD therapy. Two major classes of therapy-related myeloid neoplasms have been associated with alkylating agents and topoisomerase II inhibitors. The CVD regimen specifically includes two alkylating agents, cyclophosphamide and dacarbazine, and therapy cycles tend to be longer because of the indolent nature of PPGl. Alkylating agents cause approximately 70% of therapy-related myeloid neoplasms and are frequently accompanied by del(5q) or −7/del(7q) karyotype abnormalities [30].

There were several limitations to our study. This study was a retrospective analysis of chemotherapy without a control arm, and the number of patients included was limited. Thus, evaluating the efficacy of CVD therapy itself was difficult, and further studies comparing the

| Table 3 Details of patients who developed secondary malignancy |
|---------------------------------------------------------------|
| Patients with secondary malignancy | No. 2 | No. 15 |
| Type of secondary malignancy (age of diagnosis) | Colorectal cancer (74), Gastric cancer (79) | MDS (48) |
| Sex | M | M |
| PCC/PGL diagnosis age | 51 | 32 |
| PCC/PGL | PCC | PCC |
| Initial status | Benign | Benign |
| Initial lesion | Adrenal gland (left) | Adrenal gland (left) |
| Past medical history | Hypertension (40), Urolithiasis (37), DM (76) | Intracranial hemorrhage (31), Hypertension (NA) |
| Medication for hormonal symptoms | NA | Doxazosin, Nifedipine |
| Initial catecholamine levels (serum) | | |
| Epinephrine (pmol/L) | 164 | 573 |
| Norepinephrine (pmol/L) | 1,596 | 38,954 |
| Dopamine (pmol/L) | NA | 372 |
| Family cancer history | NA | Prostate Cancer (Father) |
| Smoking | None | None |
| Alcohol | None | None |
| Initial treatment for PCC/PGL | Resection (51) | Resection (32) |
| Ki-67 (%) of resection specimen | NA | <1 |
| Malignancy diagnosis age | 51 | 44 |
| Malignancy-free duration (year) | 5.2 | 11.5 |
| Metastatic site | Lymph node | Bone, adrenal gland |
| Chemotherapy | ACVD × 12 | CVD × 45 |
| | CVD × 56 (stopped at 65 years old) | |
| 131-I-MIBG | None | None |
| Radiation therapy | No | Yes (44) |
| Best response (RECIST) | PR | SD |
| Best response (Biochemical) | CR | PR |
| PFS (year) | 23.7 | 3.6 |
| OS (year) | 23.7 | 3.7 |
| Deceased | No | Yes (Due to MDS) |

131-I-MIBG: meta-iodobenzylguanidine labeled with 131-I; MDS: myelodysplastic syndrome, PCC; pheochromocytoma, PGL; paraganglioma, NA; not available, MIBG; metaiodobenzylguanidine, ACVD; adriamycin + cyclophosphamide + vincristine + dacarbazine, CVD; cyclophosphamide + vincristine + dacarbazine, RECIST; response evaluation criteria in solid tumors, PFS; progression-free survival, OS; overall survival
survival benefit between CVD therapy and other treatments are needed to assess the therapeutic efficacy. This limitation can be addressed by a meta-analysis that includes the results of our study. An additional limitation of our study is that catecholamine levels were mainly detected in the serum rather than in the plasma or urine metanephrines. This is because plasma and urine metanephrines measurement was approved in Japan in 2019 and most patients in this study started chemotherapy before this approval. This study also lacks information on adverse events for all patients. This research also lacks information on pathological features, including predictive markers (e.g., pheochromocytoma of the adrenal gland scaled score or Ki-67 index). Moreover, information to genetic mutations and pathological prognostic factors that may have affected the response to chemotherapy was insufficient. Radiation therapy and 131I-MIBG treatment were also administered to a few patients and may have affected their survival, leading to accurate analysis of the benefit of CVD treatment.

**Conclusion**

In this retrospective study, more than half of patients gained tumor control based on both the tumor volume and catecholamine levels. We also found that cytotoxic chemotherapy or mainly CVD therapy administered for treating metastatic PPGL led to no significant survival difference between responders and nonresponders. Because more than half of the patients showed a reduction in the tumor volume or catecholamine levels, the CVD regimen should still be the main option for controlling tumor progression and improving catecholamine-related complications. However, rare but lethal complications such as tMDS can develop, possibly because of long-term chemotherapy in patients with PPGL as reported in one of our patients. Therefore, further research that directly compares the survival benefit and long-term toxicity of CVD therapy with that of other treatment options is necessary to establish CVD therapy as a primary treatment option for metastatic PPGL. The rarity of this disease complicates randomized trials; our retrospective cohort study may contribute to future meta-analyses as additional data become available.

**Disclosure**

The authors declare that they have no conflict of interest.

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**Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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