Paraganglioma as a risk factor for bone metastasis

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Abstract. Malignant pheochromocytoma (PHEO) and paraganglioma (PGL) (PHEO and PGL: PPGL) are frequently associated with bone metastasis. Bone metastasis requires long-term management and may lead to skeletal-related events (SREs) that remarkably reduce patients’ quality of life (QOL). The aim of this study was to elucidate the risk factors for developing bone metastasis in patients with PPGL. The medical records of 40 consecutive adult patients with malignant PPGL at the National Hospital Organization Kyoto Medical Center between 2006 and 2016 were reviewed. SREs were defined as pathologic fracture, spinal cord compression, and the need for bone irradiation and/or surgery. PHEO (20/40) and PGL (20/40) were each present in 50% of the patients. Bone was the most frequent site of metastasis, detected in 60% (24/40). Bone metastasis was more frequent in patients with PGL (16/20, 80%) than in patients with PHEO (8/20, 40%) (p = 0.02). Half (12/24) of the patients with bone metastasis had at least one SRE. Extra-skeletal invasion of the spine, defined as local infiltration to the surrounding tissue beyond the cortical bone, was more frequently observed in patients with bone metastasis associated with SREs than without them (p = 0.001). Careful follow-up and management are warranted especially in patients with PGL as a risk factor for bone metastasis and with extra-skeletal invasion of the spine as risk factor of SREs.

Key words: Pheochromocytoma, Paraganglioma, Bone metastasis, Skeletal-related events

PHEOCHROMOCYTOMA (PHEO) and paraganglioma (PGL) are rare diseases characterized by the production of catecholamines [1]. Malignant PPGL accounts for 10% of the patients [2, 3], and several studies also reported high rates of recurrence or metastatic disease after surgical resection [4-6]. Currently, effective therapy is not established for patients with malignant PPGL [4, 5].

The most common site of distant metastasis of malignant PPGL has been reported to be the bone, accounting for about 70% of metastases [7, 8], as is the case with many other solid tumors (e.g. breast cancer and prostate cancer) [9]. Interaction of circulating primary tumor cells with the bone microenvironment has been suggested to cause a positive feedback loop of tumor growth and bone destruction, and may result in skeletal-related events (SREs) such as pathological fractures, spinal cord compression, the requirement for surgery or radiotherapy, and malignant hypercalcemia [9-11]. Patients with bone metastasis are at risk of complicating immobilization, loss of dependence, decreased quality of life (QOL), and reduced survival [12]. Moreover, medical costs may significantly increase in the terminal stage of life, particularly after the development of SREs [11]. Although SREs frequently occur in patients with malignant PPGL associated with bone metastasis [8], the risk factors for bone metastasis in malignant PPGL are not well defined. The objective of the current study was to investigate risk factors for bone metastasis and development of SREs in patients with malignant PPGL.

Materials and Methods

We reviewed the medical records of 40 consecutive adult patients with malignant PPGL at our institution...
between 2006 and 2016. None of the patients in this study had any blood relationships. Patients accompanied with other malignant tumors which frequently develop bone metastasis such as breast cancer or prostate cancer. Although—patients received administration of bone-targeting agents (bisphosphonate or denosumab) to prevent SREs, no patients developed vertebral fractures after discontinuation of denosumab. We defined the malignancy based on a presence of metastasis to non-chromaffin tissue sites at the first diagnosis as well as an occurrence of metastatic lesions during the follow-up period. Medical records documented the baseline clinical characteristics as follows: age, gender, height and weight, family history of PPGL, genetic disease, plasma and urine catecholamine levels, and location, size, Ki-67 index, and Ki-67 positive cell rate (>2%) of the primary tumor which was highly suggestive malignancy [13]. The functioning type of catecholamine was determined as follows [14]: if the plasma or urine adrenaline levels were abnormally high, the type was determined to be adrenergic, regardless of the presence of elevated noradrenaline levels. If the noradrenaline levels were high in the absence of elevated adrenaline levels, the type was determined to be noradrenergic.

Bone metastasis was diagnosed by computed tomography (CT) and at least one imaging modality including magnetic resonance imaging (MRI), iodine-131(or 123)-meta-iodobenzylguanidine (MIBG), 99mTc-bone scintigraphy, or fluorine-18-fluoro-2-deoxy-D-glucose (18F-FDG) positron emission tomography (PET)-CT. Although not all imaging modalities were conducted in each patient, there was no apparent difference of positive rate between different modalities beside CT in all PPGL and between PHEO and PGL by each imaging modality (data not shown). Image interpretation of the presence of bone metastasis was conducted by two radiologists and was confirmed by 2 endocrinologists as attending physicians.

Metastases were considered to be synchronous if they were identified within 3 months of the diagnosis of the primary tumor. If identified beyond 3 months after diagnosis of the primary tumor, they were considered metachronous [8]. Clinical characteristics of bone metastasis were further detailed in terms of number (single or multiple), type (osteolytic or osteoplastic or mixed), and site of metastasis, Eastern Cooperative Oncology Group performance status (ECOG PS) at the time of diagnosis of bone metastasis, pain status (presence or absence of severe bone pain requiring analgesics), extra-skeletal invasion of the spine (defined as local infiltration of surrounding tissue beyond the cortical bone), and the use of bone-targeting agents (bisphosphonates and denosumab).

SREs were defined by clinical fracture, spinal cord compression, radiation to bone, surgery to bone, and hypercalcemia. Clinical fractures were defined as those identified during the evaluation of symptomatic patients and confirmed by written report of radiographic testing. Fractures involving the hands, feet, face, or skull were not included [15]. Spinal cord compression, manifesting as neurological impairment, back pain, or both, was confirmed radiographically. Radiation to bone was defined as radiation to palliate a painful bone lesion, radiation to treat or prevent fractures, radiation to treat or prevent spinal cord compression, or the use of bone-targeted radiopharmaceuticals. Surgery to bone was defined as surgical procedures to prevent imminent fractures or to treat pathological fractures or spinal cord compression.

Statistical analyses were performed with EZR statistical software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16]. Continuous variables were expressed as median and interquartile range. Categorical variables were expressed as number and percentage. Continuous variables were analyzed by Mann-Whitney U test, and categorical variables were analyzed by the Fisher exact test. p values <0.05 were considered statistically significant.

This study was approved by the ethical review board of the National Hospital Organization Kyoto Medical Center.

**Results**

**Baseline characteristics**

Clinical characteristics of the patients are shown in Table 1. The median follow-up period after the initial diagnosis of PPGL was 7 years (range, 1 month to 26 years), and the median duration before diagnosis of metastasis was 3 years (range, 0 to 23 years). PGLs were located in the thorax, abdomen, pelvis and urinary bladder.

**Clinical characteristics of bone metastasis**

We determined the frequency of each metastatic site in patients with malignant PPGL. Bone was the most frequent site of metastasis detected in 60% (24/40) of cases, followed by liver (53%: 21/40), lung (45%: 18/40), lymph nodes (33%: 13/40), peritoneal dissemination (33%: 13/40), and other (spleen in two patients, and
Bone metastasis in pheochromocytoma

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Brain in one patient). Bone metastases were predominantly osteolytic (92%: 22/24) and multiple (88%: 21/24). In addition, 36% of the patients (8/22) showed extra-skeletal invasion of the spine. One third (8/24) of patients had severe bone pain requiring analgesics. Most patients (92%: 22/24) had preserved ECOG PS at the time of diagnosis of bone metastasis, while two patients had an ECOG PS of 2. The most frequent site of bone metastasis was the spine (21 of 24, 88%), followed by the pelvis (16 of 24, 67%), ribs (14 of 24, 59%), sacrum (11 of 24, 46%), long bones (proximal and distal) (7 of 24, 25%), shoulder girdle (7 of 24, 25%), and skull (3 of 24, 13%). Bone-targeting agents were used for 33% (8/24) of the patients (six patients used bisphosphonates and two patients used denosumab).

### Risk factors for bone metastasis

Clinical findings were compared between patients with PPGL with and without bone metastasis (Table 2). The proportion of PGL was significantly higher in patients with bone metastasis than in patients without bone metastasis (67% vs. 25%, respectively; \( p = 0.02 \)). The prevalence of noradrenergic type was higher in patients with bone metastasis than without, but the difference was not statistically significant (\( p = 0.07 \)). There was no significant difference among groups in gender, age, rate of CVD chemotherapy, and tumor size. Bone was the only metastatic site with a significantly higher frequency in patients with PGL than PHEO (80% vs. 40%, respectively; \( p = 0.02 \)) (Table 3). In contrast, peritoneal dissemination was more prevalent in patients with PHEO than PGL, although the difference was not statistically significant.

### Clinical characteristics of SREs

We examined the clinical characteristics of SREs in patients with malignant PPGL associated with bone metastasis. Half (12/24) of the patients with bone metastasis had at least 1 SREs. Of those, 58% (7/12) developed 2 or more SREs during the follow-up period. The median interval between the diagnosis of bone metastasis and the development of the first SREs was 11.9 months (range, 0 months to 6.0 years). The most common event was radiation to bone (42%, 10/24), followed by spinal cord compression (21%, 5/24), surgery to bone (8%, 2/24) and clinical fracture (8%, 2/24). No patient had hypercalcemia. Bone-targeting agents were administered to eight patients with bone metastasis (33%, 8/24): 2 patients without SREs and 6 patients who already had at least 1 SRE.

### Clinical risk factors for SREs

Various clinical parameters were compared between patients with and without SREs in patients with malig-

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**Table 1** Clinical characteristics of patients with malignant PPGL

| No. of patients | 40 |
|-----------------|--|
| Age at initial diagnosis, y | 43.3 ± 15.4 |
| Gender, male | 60% (24/40) |
| BMI, kg/m² | 22.2 ± 2.9 |
| Tumor location, PHEO: PGL | 1:1 (20:20) |
| Metastasis synchronous with primary tumor | 45% (18/40) |
| Family history of PHEO/PGL or genetic diseases | 10% (4/40) |
| Excess CA secretion† | 91% (32/35) |
| Functional type, adrenergic type: noradrenergic type | 1:1.9 (11:21) |
| Tumor size, mm†† | 93.3 ± 43.0 |
| Bone metastasis††† | 60% (24/40) |

Data are expressed as mean ± SD or proportion of patients (%)

BMI, body mass index; CA, catecholamine; PGL, paraganglioma; PHEO, pheochromocytoma; PPGL, pheochromocytoma and paraganglioma

† abnormally high plasma or urine catecholamine levels

†† max size of primary tumor

††† demonstrated by at least one imaging modality
nant PPGL associated with bone metastasis (Table 4). Extra-skeletal invasion of the spine was more commonly experienced in patients with SREs than in those without. SREs (73% vs. 0%, respectively; \( p = 0.001 \)). There was no significant difference between patients with and without SREs in the other clinical findings evaluated. The prevalence of 2 or more SREs during the follow-up period was also significantly higher in patients with extra-skeletal invasion of the spine than in those without (75% vs. 7%, \( p = 0.002 \)).

**Comparison of bone metastasis and SREs between PHEO and PGL**

Clinical characteristics of bone metastasis and SRE were compared between patients with malignant PHEO and PGL (Table 5). Noradrenergic type was more frequent in patients with malignant PGL than PHEO (\( p = 0.005 \)), while there was no significant difference of other clinical characteristics including age, gender, tumor size, and the rate of CVD chemotherapy between PGL and PHEO. There was not significant difference either Ki-67 index itself or proportion of Ki-67 positive cell rate (>2%) between PHEO and PGL. There was no significant difference of clinical characteristics of SRE such as prevalence of SRE at the time of bone metastasis, prevalence of 2 or more events of SRE during the follow-up period, and severity of SRE between the patients with PHEO and PGL associated with bone metastasis and SRE.

| Variable                  | With bone metastasis | Without bone metastasis | \( p \) value |
|---------------------------|----------------------|--------------------------|--------------|
| No. of patients           | 24                   | 16                       |              |
| Gender, male              | 67% (16/24)          | 50% (8/16)               | 0.34         |
| Age, y                    | 40 (33–51)           | 52 (34–58)               | 0.32         |
| PGL                       | 67% (16/24)          | 25% (4/16)               | 0.02*        |
| CVD chemotherapy          | 71% (17/24)          | 50% (8/16)               | 0.21         |
| Excess CA secretion†      | 95% (19/20)          | 87% (13/15)              | 0.56         |
| \( \geq 4 \text{times higher}^{11} \) | 12/19                | 11/13                    | 0.48         |
| \( 1–3 \text{times higher} \) | 7/19                 | 2/13                     |              |
| Noradrenergic type\({}^{11}{}^{11} \) | 75% (15/20)          | 40% (6/15)               | 0.07         |
| Tumor size, mm\(^{11}{}^{11} \) | 90 (60–150)         | 77 (64–103)             | 0.41         |

\( ^{†} \) abnormally high plasma or urine catecholamine levels
\( ^{11} \) 4-fold upper normal limit
\( ^{11}{}^{11} \) noradrenaline levels were high in the absence of elevated adrenaline levels
\( ^{11}{}^{11}{}^{11} \) max size of primary tumor

| Site of metastasis | PHEO | PGL | \( p \) value |
|-------------------|------|-----|--------------|
| No. of patients   | 20   | 20  |              |
| Bone              | 40% (8/20) | 80% (16/20) | 0.02* |
| Liver             | 65% (13/20) | 40% (8/20)   | 0.21    |
| Lung              | 40% (8/20) | 50% (10/20)  | 0.75    |
| Lymph nodes       | 35% (7/20) | 30% (6/20)   | 1.00    |
| Peritoneal dispersion | 45% (9/20) | 20% (4/20)   | 0.18    |

\( ^{*} \) Fisher’s exact test. \( ^{*} p < 0.05 \). Data are expressed as proportion of patients (%)

PGL, paraganglioma; PHEO, pheochromocytoma
The results of the present study demonstrated that the prevalence of bone metastasis was more frequent in patients with PGL than in patients with PHEO, and PGL was the only risk factor for bone metastasis. Bone was

### Table 4  Comparison of parameters in patients with bone metastasis of malignant PPGL with and without SREs

| Variable                                | With SREs | Without SREs | p value |
|-----------------------------------------|-----------|--------------|---------|
| No. of patients                         | 12        | 12           |         |
| Gender, male                            | 58% (7/12)| 75% (9/12)   | 0.67    |
| Age, y                                  | 35 (32–40)| 49 (40–60)   | 0.09    |
| PGL                                     | 67% (8/12)| 67% (8/12)   | 1.00    |
| Noradrenergic type†                     | 89% (8/9) | 64% (7/11)   | 0.32    |
| Tumor size, mm††                       | 80 (60–125)| 150 (58–150) | 0.70    |
| Multiple tumors                         | 83% (10/12)| 91% (11/12)  | 1.00    |
| ECOG PS ≥ 2                            | 8% (1/12) | 8% (1/12)    | 1.00    |
| Non-osseous metastasis                  | 75% (9/12)| 67% (8/12)   | 1.00    |
| Extra-skeletal invasion of spine†††      | 73% (8/11)| 0% (0/11)    | 0.001*  |

Fisher’s exact test or Mann-Whitney U test. Data are expressed as proportion of patients (%) or median (range interquartile range), ECOG PS, Eastern Cooperative Oncology Group performance status; PGL, paraganglioma; SRE, skeletal-related event *p < 0.05.
† Noradrenaline levels were high in the absence of elevated adrenaline levels, with or without elevated dopamine levels
†† max size of the primary tumor
††† defined as local infiltration to surrounding tissue beyond the cortical bone

### Table 5  Comparison of clinical characteristics between patients with malignant PPGL

| Variable                                | PHEO | PGL  | p value |
|-----------------------------------------|------|------|---------|
| No. of patients                         | 20   | 20   |         |
| follow-up period after diagnosis of the malignancy, month | 36 (24–51) | 36 (28–54) | 0.99 |
| Age at initial diagnosis, y             | 53 (33–58) | 40 (33–47) | 0.21 |
| Gender, male                            | 60% (12/20) | 60% (12/20) | 1      |
| Metastasis synchronous with primary tumor | 40% (8/20) | 50% (10/20) | 0.75 |
| Family history of PHEO/PGL or genetic diseases | 15% (3/20) | 5% (1/20) | 0.77 |
| CVD chemotherapy                        | 65% (13/20) | 60% (12/20) | 1      |
| Excess CA secretion†                    | 89% (17/19) | 94% (15/16) | 1      |
| Noradrenergic type††                    | 37% (7/19) | 88% (14/16) | 0.005* |
| Tumor size, mm†††                       | 75 (63–100) | 89 (60–150) | 0.28   |
| Ki-67 index                             | 2 (1–11) | 5 (1–7) | 0.89    |
| [Ki-67 >2%]                             | [29% (2/7)] | [60% (3/5)] | 0.56   |

Fisher’s exact test or Mann-Whitney U test. Data are expressed as proportion of patients (%) or median (range interquartile range), *p < 0.05. CA, catecholamine; PGL, paraganglioma; PHEO, pheochromocytoma
† abnormally high plasma or urine catecholamine levels
†† noradrenaline levels were high in the absence of elevated adrenaline levels
††† max size of primary tumor

### Discussion

The results of the present study demonstrated that the
the only metastatic site that had a significantly higher frequency in patients with PGL compared with patients with PHEO. In addition, we also found that extra-skeletal invasion of the spine, defined as local infiltration of surrounding tissue beyond the cortical bone, was common in patients with malignant PPGL associated bone metastasis and SREs.

We showed that bone metastasis is the most common site of metastasis in patients with malignant PPGL, in agreement with previous studies [7, 8]. Excess catecholamines may be associated with the high prevalence of bone metastasis in patients with malignant PPGL, since previous studies demonstrated that catecholamines may affect bone metabolism [17, 18]. Bone metastasis could significantly affect patient QOL thorough the development of SREs in patients with malignant PPGL. It could be clinically very important to identify risk factors for bone metastasis and SREs for early diagnosis and possible intervention in patients with malignant PGL.

We have done the univariate analysis of factors responsible for the bone metastasis, although there was no significant difference in gender, age, tumor size, and catecholamine type between the groups. PGL was shown to be the only risk factor for bone metastasis (data was not shown). In addition, it was also shown that bone was the only metastatic site that had a significantly higher frequency in patients with PGL compared with patients with PHEO. Previous reports demonstrated that the prevalence of malignancy in patients with PGL is higher (45–70%) than in patients with PHEO (6.6–25%), a phenomenon possibly related to a higher association with SDHB, SDHD and VHL genetic mutations, which leads to a higher malignant potential through activation of hypoxia/angiogenesis pathways and VEGF over-expression [4, 19, 20]. PPGL cells have been demonstrated to intensely express CXCR4 which is closely associated with formation of bone metastasis in patients with breast or prostate cancer [8, 21]. In addition, NA has been shown to increases chemokine stromal cell-derived factor-1 (SDF-1) as the ligand of chemokine receptor CXCR4 [22]. It is therefore suggested that PGL may be prone to bone metastasis through its predominant production of noradrenaline, although whether excess noradrenaline and/or underlying genetic mutations such as SDHB are responsible for the metastasis remain to be elucidated.

In our study, patients with bone metastases of malignant PPGL also had a high prevalence of SREs. Risk factors for the development of SREs have not been clarified. Extra-skeletal invasion of the spine was frequently observed in patients with bone metastasis associated with SREs in malignant PPGL. Local infiltration to surrounding tissue beyond the cortical bone, especially the posterior cortical bone, could carry a risk of epidural spinal cord compression [23]. The destruction of the cortical bone may cause vertebral body collapse and displacement of the body fragments into the epidural space with eventual spinal cord and/or nerve root compression [23]. In addition, extra-skeletal invasion of the spine may also cause pain and pathologic fractures by expansion of the tumor, and mechanical instability of the spine. Thus, early intervention for the prevention of SREs may be especially important for patients with extra-skeletal invasion of the spine [23, 24]. Although bone-targeting agents have been shown to reduce SREs in patients with advanced solid tumors [25], the effectiveness of bone-targeting agents in patients with malignant PPGL has not been elucidated.

The present study has several limitations. The retrospective nature of our study and cohort study of a small number are important limitations. An institutional selection bias of single-center studies could be the second limitation. Number of the patients with PHEO and PGL was identical in our cohort despite of that PGL is generally less common. It could be attributed to our institutional characteristics which is specialized for more intractable and aggressive diseases. Thereby, the prevalence of SREs may be overestimated due to the institutional bias. Moreover, because of its characteristics, surgery of primary tumor was less likely to do. Accordingly, we had not too many histological data including Ki-67 index. And our institution had not evaluated the surgical margin status routinely, thus statistically enough data of them and the number of R0 surgery were not available. In addition, since the primary tumor has been operated many years ago in the different hospitals, information related to surgery (i.e. surgical margin status, the R0 surgery) and histopathological findings (i.e. Ki-67 positive rate and GAPP score) was very limited to evaluate the effects of these possible confounding factors on the present results. Since these factors could related to the malignant nature of the tumor, study on their correlation with the bone metastasis will be important. Therefore multicenter prospective studies in patients with malignant PPGL are needed.

Moreover, different imaging modality may affect the diagnosis of bone metastasis and the results of the present study, since not all type of modality was conducted in all patient. The present study was however not a
quantitative/semi-quantitative comparison of the number and size of bone metastasis between PHEO and PGL, which needs more objective definition of the bone metastasis.

Another important limitation of the study is the lack of the data of pheochromocytoma-sensitive gene mutation. Factors for bone metastasis could be clarified by multivariate logistic analysis only after including the genetic mutation data as well as increasing the sample size of the study. Genetic mutation, especially that of SDHB, is one the important factor related to the malignant nature of PPGL. However, since genetic testing has not been a standard diagnostic procedure in Japan, it was not feasible to include that mutation in the present analysis. Systematic analysis of SDHB mutation waits establishment of clinical sequence of genomic medicine including the health care system. Furthermore, no systematic analysis of bone turnover markers such N-telopeptide of type I collagen, and measurement of bone mineral density by dual X-ray absorptiometry as a risk factor for SREs [12] was conducted in this study. Finally, correlation of bone pain with SREs should be investigated with a standardized questionnaire for evaluating bone pain.

Conclusion

Careful follow-up and management are warranted in patients with PGL as a possible risk factor for bone metastasis and with extra-skeletal invasion of the spine as a risk factor for SREs.

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Disclosure

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