

CLINICAL PRACTICE GUIDELINE

Japan Endocrine Society Clinical Practice Guideline for the Diagnosis and Management of Pheochromocytoma and Paraganglioma 2025

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Abstract. Pheochromocytomas and paragangliomas are characterized by two key features: endocrine disorders with excessive catecholamine secretion and a hereditary or metastatic nature, making early diagnosis and treatment crucial. This clinical practice guideline is a revision of the 2018 edition, which considers recent advances in clinical practice and changes to the health insurance coverage in Japan. Patients presenting with symptoms such as palpitations, headaches, hypertension, or abdominal tumors should undergo screening and confirmation with measurement of fractionated catecholamines and their metabolites in the blood and urine. When the tumor is located in the adrenal glands, it is diagnosed as a pheochromocytoma; when it is located outside the adrenal gland and confirmed by ¹²³I-MIBG scintigraphy or ¹⁸F-FDG PET, it is diagnosed as a paraganglioma. Treatment begins with inhibiting catecholamine action using α -blockers, and if that is insufficient, metyrosine is used in combination, followed by laparoscopic tumor removal. Given the metastatic potential, long-term postoperative follow-up is essential. Even in cases of metastasis, tumor debulking should be considered. Treatment options are selected based on the amount of remaining tumor, symptom severity, and lesion progression, including CVD chemotherapy or radionuclide therapies such as ¹³¹I-MIBG or ¹⁷⁷Lu-DOTATATE. Genetic testing guides the management of different variants, and significant progress has been made in molecularly targeted drug trials. Therefore, further advances in individualized and long-term management are required.

Key words: Pheochromocytoma and paraganglioma, Catecholamine, Neuroendocrine tumor, Metastatic potential, Genetic disease

Introduction

Pheochromocytoma (PCC) is a classic endocrine tumor first reported by the German pathologist Felix Fraenkel in 1886. Charles H. Mayo described its clinical characteristics in 1926, establishing its significance as a representative adrenal disease that causes endocrine hypertension. Together with paraganglioma (PGL), PCCs are collectively referred to as pheochromocytomas and paragangliomas (PPGLs). It is characterized by the overproduction of catecholamines, hypertension, and potential metastasis to the bones, lungs, liver, and lymph nodes in 10–20% of patients.

Advances in hormone measurements and imaging have made the diagnosis of typical cases more straightforward. However, as it is a rare disease encountered by various specialists, there is a need for standard treatment guidelines. Supported by the Ministry of Health, Labour, and Welfare, the Japan Endocrine Society, the Japan Agency for Clinical Research and Development, and the National Center for Global Health and Medicine, the authors published pheochromocytoma treatment guidelines in 2010, 2012, and 2018 [1]. Significant advances have been made in pathology, diagnosis, and treatment, and the 2018 guideline has been revised for 2025. Key updates include: 1) a change in the disease concept of PPGL, which is clearly defined as a neuroendocrine tumor according to the WHO Classification of Endocrine and Neuroendocrine Tumours, 2) refinement of the man-

agement algorithm and diagnostic criteria, 3) application of new biochemical tests and imaging tests in clinical practice in Japan, 4) the significance and precautions of genetic testing in clinical practice, 5) addition of a description of new radionuclide therapy, 6) addition of a description of head and neck paragangliomas, and 7) addition of a description of the diagnosis and treatment of pediatric cases. Following the Minds Clinical Practice Guideline Creation Manual, the revision process required significant time and effort.

Methods

Purpose

This clinical practice guideline aims to improve and standardize the clinical practice of PPGL in Japan by updating the 2018 PPGL guideline [1]. The revisions were achieved by providing answers to major topics such as statements with certainty regarding the evidence and strengths of the recommendations.

The basic concept of the revision

This task has been positioned as an important clinical issue by the Japan Endocrine Society. This revision was based on the Japan Endocrine Society's "Pheochromocytoma and Paraganglioma Treatment Guideline 2018" [1]. However, it was created considering the following points: objective, specific, up-to-date, and practical contents, Minds' evaluation comments on the PPGL

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Abbreviations: ¹²³I-MIBG, Iodine-123 metaiodobenzylguanidine; ¹³¹I-MIBG, Iodine-131 metaiodobenzylguanidine; ¹⁸F-FDG, Fluorine-18 fluorodeoxyglucose; ¹⁸F-FDG PET, Fluorine-18 fluorodeoxyglucose positron emission tomography; ¹⁸F-FDG PET/CT, Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography; ¹⁸F-FDOPA, Fluorine-18 fluorodihydroxyphenylalanine; ¹⁷⁷Lu-DOTATATE, Lutetium-177-DOTA-Tyr3-Octreotate; 3-MT, 3-methoxytyramine; ACPA-J, advancing care and pathogenesis of intractable adrenal diseases in Japan; ACE-Is, angiotensin-converting enzyme inhibitors; AJCC, American joint committee on cancer; ALP, alkaline phosphatase; ARBs, angiotensin receptor blockers; BMA, bone-modifying agents; BUN, blood urea nitrogen; CAIX, carbonic anhydrase IX; CVD, cyclophosphamide, vincristine, and dacarbazine; CR, complete response; CRP, C-reactive protein; CT, computed tomography; CgA, chromogranin A; DBH, dopamine beta-hydroxylase; ECG, electrocardiogram; EBM, evidence-based medicine; EM staining, Elastica-Masson staining; EVG staining, Elastic van Gieson staining; FH, fumarate hydratase; GBq,

gigabecquerel; GAPP, Grading of Adrenal Pheochromocytoma and Paraganglioma; HE staining, hematoxylin and eosin staining; HU, Hounsfield units; HNPG, head and neck paraganglioma; ICHUSHI, Japanese database of medical literature (Igaku Chuo Zasshi); IMIC, international medical information center; LA, laparoscopic adrenalectomy; LESS, laparoendoscopic single-site surgery; LDH, lactate dehydrogenase; MEN2, multiple endocrine neoplasia Type 2; MIBG, metaiodobenzylguanidine; Minds, medical information network distribution service; MRI, magnetic resonance imaging; NEN, neuroendocrine neoplasm; NF1, neurofibromatosis Type 1; NGS, next-generation sequencing; OA, open adrenalectomy; PCC, pheochromocytoma; PET, positron emission tomography; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; PGL, paraganglioma; PR, partial response; PRRT, peptide receptor radionuclide therapy; PPGL, pheochromocytomas and paragangliomas; RECIST, Response Evaluation Criteria in Solid Tumors; RCT, randomized controlled trial; RANKL, receptor activator of nuclear factor kappa-B ligand; RET, rearranged during transfection; SDH, succinate dehydrogenase; SDHB, succinate dehydrogenase subunit B; SDHx, succinate dehydrogenase complex subunit x; SRE, skeletal-related events; SSTR, somatostatin receptor; TH, tyrosine hydroxylase; TNM, the primary tumor, lymph node and metastasis; VHL, Von Hippel-Lindau; VMA, vanillylmandelic acid; WHO, world health organization.

guideline 2018, and registration in the Minds “Clinical Practice Guidelines Registry” (https://minds.jcqh.or.jp/guide_author/infodetail/T0012403). The target readers of the guidelines are physicians, public health nurses, nurses, dietitians, and pharmacists engaged in the management of hypertension and PPGL. Task force members comprise specialists in various fields, such as endocrinology and metabolism, hypertension, urology, endocrine surgery, radiology, nuclear medicine, genetic medicine, and pathology. The Japan Endocrine Society approved these procedures.

Method of preparation

The preparation process followed the stipulations of the Minds Manual for Guideline Development (Tokyo: Japan Council for Quality Health Care, 2020 edition). We selected the literature for the guideline in two steps: primary screening using a systematic review process developed by the EBM Research Center of the International Medical Information Center (IMIC) (Tokyo, Japan).

Details of the first literature search are as follows:

- 1) Retrospective search from January 2018 to August 2022.
- 2) Databases: MEDLINE, The Cochrane Library, ICHUSHI web
- 3) Language: English (in principle)
- 4) Target study design: All designs, including observational studies, RCTs, clinical trials, systematic reviews, meta-analyses, and guidelines.
- 5) Papers with a high level of evidence

A total of 793 articles were selected after the primary screening. The systematic review committee members conducted secondary screening based on various objective criteria and a critical literature review.

Determination of the strength of evidence and recommendation

Core statements are described for each topic. The strength of the evidence for each statement was determined, in principle, following Minds (2020). The importance of each paper was objectively evaluated by considering the study design, whether it was a multi-center or single-center study, the number of cases, and so on. The strength of the evidence was determined based on a comprehensive evaluation of the papers (Table 1).

The strength of the recommendation for each statement was determined comprehensively, considering the strength of the evidence, benefits, and harm to patients, risk of bias, and nonlinearity (Table 2).

Consensus process and approval process

Committee members meticulously reached a consensus on the statement for each topic, strength of evidence, strength of recommendations, and content of evidence. We conducted an online modified Delphi consensus process, a reliable method that ensures objectivity and eliminates bias. For multiple proposals, we held an individual online vote and, in principle, adopted the majority opinion. We repeated the Delphi Consensus Round as necessary and included counterproposals in the text to ensure a thorough process. The task force’s advisors, the Peer Review Committee, and the Committee of the Clinically Important Issues of the Japan Endocrine Society (Chairman) reviewed the revised guideline draft to ensure the objectivity and neutrality of the statements and explanatory evidence with related literature. In addition, the revised version was provided for public comments from members of the Japan Endocrine Society before final approval by the Japan Endocrine Society.

Table 1 Certainty (strength) of the overall evidence

Strength	Explanation
A (Strong)	Strong confidence that the effect estimate is appropriate to support the recommendation
B (Medium)	Moderate confidence that the effect estimate is appropriate to support the recommendation
C (Weak)	Limited confidence that the effect estimate is appropriate to support the recommendation
D (Very Weak)	Very little confidence that the effect estimate is appropriate to support the recommendation

Table 2 Recommendation level (strength of recommendation)

Recommendation level	Explanation
1	Recommends whether the treatment should be performed or not
2	Suggests that the treatment be performed or not performed

Disclosure and management of conflicts of interest (COI)

This guideline was supported in part by the Japan Endocrine Society, the Study of Advancing Care and Pathogenesis of Intractable Adrenal Diseases in Japan (ACPA-J) from the National Center for Global Health and Medicine, Japan (27-1402, 30-1008 and 24A1004), and the Clinical Research Center, Ijinkai Takeda General Hospital, Kyoto, Japan. The task force received no funding or remuneration for this guideline from commercial sources or other entities.

The chair, vice chair, and all committee members were subject to disclosure of appropriate COI management in strict accordance with the Japan Endocrine Society's "Common Guidelines for Conflicts of Interest (COI) in Clinical Research" and the Japan Medical Association's Guidance on Eligibility Criteria for Developing Clinical Practice Guidelines (Japan Medical Association Conflict of Interest Committee, March 2017).

Chapter I: Pheochromocytoma/paraganglioma

I-1 Epidemiology

Statements

- I-1-1 The estimated number of patients, according to a nationwide epidemiological survey conducted in 2009, was approximately 2,900 cases per year (C).
- I-1-2 The survey showed no difference between men and women; the estimated onset age was mainly under 50, and the prevalence increased with age (C).
- I-1-3 The location of tumors was approximately 83% in the adrenal gland (pheochromocytoma, PCC), approximately 17% outside the adrenal gland (paraganglioma, PGL). Malignant* cases accounted for 10–15% of the total, and the incidence of malignant* was approximately three times higher in PGL than in PCC (C).
- I-1-4 The age-adjusted incidence rate is approximately 5 cases per million person-years and has increased over time. This increase is thought to be due to an increase in patients diagnosed with incidental tumors with small tumor diameters and low catecholamine production, as well as an increase in the number of endocrine and imaging tests performed (C).
- I-1-5 Due to the high frequency of hereditary diseases, it is necessary to treat the patient and blood relatives with caution, considering potential diseases (2C).

*Currently called metastatic

Evidence

A. Epidemiological surveys in Japan

The Takeda, Nawata, and Naruse Research and Study groups of the Ministry of Health, Labour, and Welfare's "Adrenal Hormonal Production Disorders Research Group" conducted a nationwide epidemiological survey in Japan.

1) Survey by Takeda Research and Study group

Four hundred ninety-three cases were reported over ten years, with a slight female predominance. The ages at onset ranged from 7 to 81 years, with an average of 41 years for men and 42 years for women. The most common ages were in their 30s and 40s for men and 40s and 50s for women. Familial onset was observed in 4.7% of the cases. Benign tumors accounted for 89%, of which 84% were adrenal and 15.7% were extra-adrenal. Malignant tumors accounted for 11%, of which 56.3% were adrenal and 39.6% were extra-adrenal. Approximately 7.6% of intra-adrenal tumors were malignant, while approximately 23.6% of extra-adrenal tumors were malignant. The tumor diameters ranged from 1 to 25 cm. During follow-up, 50 patients died of tumor-related complications, including perioperative complications [2].

2) Survey by the Nawata Research and Study group

The survey period was one year in 1997, and 17,740 facilities nationwide were surveyed. There were 1,030 patients, with a male-to-female ratio of 1.1:1 and an average onset age of 46.3 years for men and 41.2 years for women. Among the patients, 66.3% had hypertension (38.5% paroxysmal type, 28.3% persistent type), and 33.7% were asymptomatic. Malignant, familial, extra-adrenal, and bilateral adrenal cases accounted for 5.0–11.3%. The tumor resection rate was 91.8%, with success rates of 93.1% and an 8.1% incidence of intraoperative and postoperative shock, respectively. Endoscopic tumor resection was performed in 15% of the cases, with a success rate of 89.7% and an intraoperative accident rate of 5.1%. Among these patients, 81.4% were cured or improved, 13.7% remained unchanged or worsened, 1.8% died, and 3.1% were unknown [3].

3) Survey by the Naruse Research and Study group

The Ministry of Health, Labour, and Welfare conducted a nationwide epidemiological survey in 2009. The primary survey randomly selected 2,387 facilities from general and university hospitals and surveyed 5,912 departments. Patients visiting these hospitals from April 2008 to March 2009 were surveyed, with an estimated 2,600 benign and 320 malignant cases and a malignancy rate of 11.0%. The secondary survey included 47.1% male and 52.9% female patients, with a mean age of 55.3 years for benign and 53.0 years for malignant cases. The estimated age of onset was under 50 years in approximately 50% of all cases, both benign and malignant.

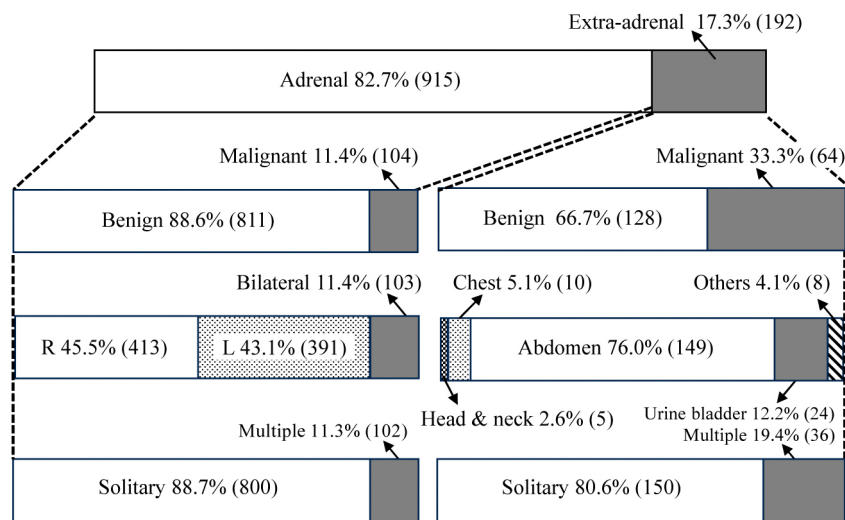


Fig. 1 Distribution of pheochromocytoma and paraganglioma inside and outside the adrenal gland, proportion of malignancies, tumor location, and proportion of multiple lesions (count excluding unknown cases) (references 4 and 5).

Abbreviations: R, right side; L, left side. The numbers in parentheses indicate the number of cases.

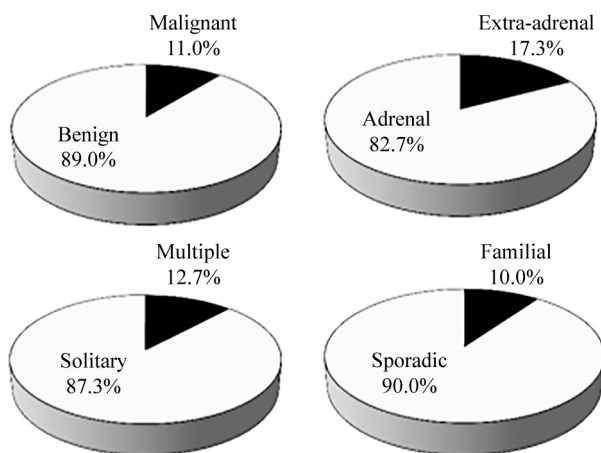


Fig. 2 Characteristics of all pheochromocytomas and paragangliomas (count excluding unknown cases) (references 4 and 5).

Approximately 82.7% of the tumors were in the adrenal gland, with no left or right side differences, and 17.3% were outside the adrenal gland, with more than 70% of these tumors in the abdomen (Figs. 1, 2) [4, 5].

B. Epidemiological studies overseas

Recent studies have reported changes in the incidence of PPGL. A Danish cohort study [6] of 567 patients from 1977 to 2015 showed the age-standardized incidence rate increased 4.8-fold from 1.4 to 6.6 per million person-years, mainly due to incidental detection in patients aged 50 or older with small tumors. As of December 2015, the prevalence of PPGL was 64.4 per million, with 89.1% of patients having unilateral PCC. A Canadian study [7]

from 2012 to 2019 identified 239 PPGL cases in a population of 5,196,368, with an incidence of 0.66 per 100,000 people per year, which was highest in those aged 60 to 79 years. A diagnostic algorithm estimated the incidence to be 0.54 per 100,000 people, which is higher than that in other global reports. A Dutch study [8] showed that the age-standardized incidence rate of PCC increased from 0.29 to 0.46 per 100,000 person-years between 1995–1999 and 2011–2015, while the age-standardized incidence rate of PGL was 0.08 and 0.11 per 100,000 person-years. Concurrently, the tumor size of PCC decreased, and the age at diagnosis increased, likely due to more frequent clinical examinations.

I-2 Endocrine investigations

Statements

- I-2-1 Factors like exercise, stress, body position, temperature, needle puncture, various foods, and medications can affect measured values (1B).
- I-2-2 Initial screening uses either random urinary fractionated metanephrines (over three times the upper limit after correcting for creatinine), blood fractionated catecholamines (over three times the upper limit), or plasma-free fractionated metanephrines (above the upper limit). All these tests can be done in an outpatient setting (1B).
- I-2-3 If screening criteria are met, perform functional confirmation tests for 24-hour urinary fractionated metanephrines (over three times the upper limit), 24-hour urinary fractionated catecholamines (over two times the upper limit), or plasma-free fractionated metanephrines (above the upper limit) (1B).

I-2-4 Note that some pheochromocytoma and paraganglioma (PPGL) cases show unclear catecholamine overproduction; thus, a definitive diagnosis should combine functional and imaging tests.

Evidence

A. Endocrinological diagnosis

1) Measurement precautions

Catecholamines and their metabolites can increase due to exercise, stress, body position, temperature, and puncture. Blood samples were collected from the forearm veins after the patient rested in bed using an indwelling needle. If this is impractical, the results are interpreted with potential false positives [9]. Avoid drugs and foods that affect catecholamine measurements (Table 3), although these effects vary among individuals [10]. Medications affecting catecholamines were discontinued before sample collection, although most antihypertensive drugs did not interfere. High-dose dexamethasone can induce hypertensive crises, thereby affecting measurements [11].

2) Measurement of catecholamines and metabolites

For biochemical diagnosis, the urinary fractionated metanephrines (metanephrine and normetanephrine), plasma-free fractionated metanephrines (metanephrine and normetanephrine), and urinary and blood catecholamines (adrenaline, noradrenaline and dopamine) were used (see PPGL clinical practice algorithm). Outside Japan, metanephrine, normetanephrine, and 3-methoxytyramine (3-MT) are recommended for diagnosis rather than fractionated catecholamines [12]. In Japan, the diagnostic accuracy of plasma-free metanephrines has not been fully verified, and 3-MT measurement is not covered by health insurance in Japan; therefore, fractionated catecholamines and metabolites are still used. The diagnostic significance of vanillylmandelic acid (VMA) has decreased with advances in metanephrine levels.

a) Plasma and urinary fractionated catecholamines

The plasma adrenaline and noradrenaline levels are typically high in patients with PCC. In contrast, only plasma noradrenaline levels were elevated in PGL. The half-lives of blood catecholamines are short, fluctuate widely, and overlap with those in non-PPGL cases. Western guidelines do not use plasma fractionated catecholamines

for diagnosis due to the lack of evidence for cutoff values. This guideline recommends cutoff values three times the upper limit of reference values for adrenaline and noradrenaline based on 24-hour urine collection values [13]. Diagnostic accuracy improves with plasma catecholamine concentrations (adrenaline + noradrenaline $\geq 2,000$ pg/mL), reaching 98% [14]. Plasma catecholamine levels may be normal in non-catecholamine-producing or small tumors (<2 cm in diameter). Urinary catecholamine excretion is more sensitive and specific for diagnosis, with recommended cutoff values of 2–3 times the upper limit of normal [13]. Urinary metanephrine and plasma-free fractionated metanephrines are more accurate diagnostic tools than plasma catecholamines or urinary catecholamine excretion [15–17].

b) Urinary fractionated metanephrines

Metanephrine and normetanephrine, stable metabolic products of adrenaline and noradrenaline, respectively, are produced by catechol-O-methyltransferase (COMT) in nerve terminals and target cells. In PPGL, these metabolites are useful biomarkers because of their stability and longer half-lives than those of catecholamines. Although random urinary fractionated metanephrines (corrected for creatinine) are practical for screening, 24-hour urine collection is more accurate. Random urine Cr correction provides comparable accuracy, particularly for morning samples [18–20]. There is no definitive diagnostic cut-off value, but false positives are common in stressed or critically ill patients. A value of 3–5 times the upper limit of normal is recommended to maintain specificity [21]. Cutoff values for 24-hour urine collection are ≥ 1.3 mg/day or ≥ 1.8 mg/day for metanephrine and normetanephrine [13, 14]. For adrenal incidentalomas, combining unenhanced CT attenuation values improves diagnostic accuracy [22]. PPGLs without elevated fractionated metanephrines may be PGLs that can metastasize [23].

c) Plasma-free fractionated metanephrines

PPGLs exhibit high COMT expression, releasing free metanephrines into the blood and urine. Over 90% of circulating metanephrine and 23–40% of normetanephrine are metabolites of adrenal catecholamines. Unlike catecholamines, which fluctuate with stimuli, free metanephrines are constantly secreted, making it highly diagnostic for PPGL [24, 25]. Normal free metanephrine

Table 3 Medications and foods that affect catecholamine measurements (Quoted from Ref. 10, with some modifications)

Medications	Tricyclic antidepressants, levodopa, drugs containing adrenergic receptor agonists (such as decongestants naphazoline nasal spray and tramazoline nasal spray), many psychotropic drugs (such as buspirone), prochlorperazine, clonidine discontinuation, ethanol, amphetamines, metoclopramide
Foods	Coffee containing caffeine, bananas, citrus fruits, vanilla ice cream, sweets containing vanilla, cheese containing tyramine, red wine, <i>etc.</i>

levels after repeated tests ruled out catecholamine-producing PPGL [26]. However, it has a high false-positive rate unless strict collection conditions are met (fasting, 20–30 minutes of supine rest, and freezing within 30 minutes of separation) [27].

Plasma remains stable at room temperature for approximately six hours [28]. Health insurance covers this test in Japan, similar to the EU and US. The ELISA method used in Japan may have a slightly lower accuracy than the LC-MS/MS and LC-ECD methods used abroad. Further verification of these cutoff values is required.

d) Plasma chromogranin A concentration

Chromogranin A, found in the secretory granules of adrenal medullary cells, is secreted with catecholamines and primarily excreted by the kidneys. It can be affected by factors such as decreased renal function. Although helpful in diagnosing non-catecholamine-producing PPGL, its sensitivity and specificity vary according to the method and report type. It also increases in other tumors, like neuroendocrine tumors and due to adrenal stimulation [29, 30], so it is currently used as an auxiliary diagnostic tool. Additionally, it is not covered by health insurance in Japan.

e) Others

Combining 3-methoxytyramine (3-MT), a dopamine metabolite, with plasma-free metanephrines enhances the diagnostic sensitivity [30]. Serum succinic acid levels may be a biomarker for patients with pathogenic *SDHB* gene variants [31].

B. Suppression and provocation tests

The clonidine suppression test involves administering clonidine, a central α_2 -adrenergic receptor agonist, to suppress noradrenaline secretion. This suppression was absent in catecholamine-secreting PPGL. After discontinuing sympathetic nerve-blocking drugs (e.g., β -blockers) for over 48 hours and resting the patient for 20 minutes, clonidine (0.15 to 0.3 mg) is administered orally. In healthy individuals, adrenaline and noradrenaline levels dropped below 50% of the baseline or below 500 pg/mL. However, these levels remain unchanged in patients with catecholamine-secreting PPGL [32]. This test helps diagnose noradrenaline-type PPGL, with clonidine loading showing promise using plasma-free normetanephrine concentrations [33].

Although glucagon and metoclopramide loading tests have been used previously, they are not recommended because of their low specificity and the risk of hypertensive crisis [34]. Phentolamine is used for blood pressure control during surgery and to treat constipation; however, it is not recommended for diagnosis because of the risk of severe hypotension.

I-3 Imaging diagnosis

Statements

- I-3-1 When pheochromocytoma and paraganglioma (PPGL) is suspected, imaging is used to locate the tumor, assess its spread, and check for metastasis to guide treatment (1A).
- I-3-2 CT provides high spatial resolution but lacks disease specificity. It helps identify primary PPGL tumors and metastatic lesions, particularly in the lungs and liver (1B).
- I-3-3 MRI offers high contrast resolution but has low disease specificity. It is beneficial for differentiating adrenal cortical tumors, paraganglioma (PGL) (especially head and neck lesions), and metastatic lesions. MRI is preferred over CT for frequent exams or in children to avoid radiation exposure (1B).
- I-3-4 ^{123}I -MIBG scintigraphy is highly specific for PPGL diagnosis (1A) but may yield false positives and negatives. It helps diagnose PGLs and metastases, but its diagnostic sensitivity is inferior to that in primary tumors of pheochromocytoma (PCC) (2C). A thyroid block is recommended to reduce radiation exposure to the thyroid and avoid affecting diagnostic accuracy for medullary thyroid cancer and nearby neck lesions (2C).
- I-3-5 ^{18}F -FDG PET effectively detects metastatic lesions in PPGL and often has a higher detection rate than ^{123}I -MIBG scintigraphy, especially for *SDHx* gene pathogenic variants (2C).

Evidence

A. Role of imaging

Imaging methods for PPGL include CT, MRI, and nuclear imaging, such as ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy and ^{18}F -FDG PET (Table 4) (see the PPGL clinical practice algorithm). Imaging is performed when blood and urine tests suggest PPGL to determine the presence, origin, spread, and metastasis of the tumor. Imaging is crucial for 1) diagnosing bilateral, multiple, and metastatic lesions; 2) guiding surgical planning and evaluating the primary lesion's relationship with surrounding organs and blood vessels; 3) diagnosing recurrence and metastasis during postoperative follow-up.

The accuracy of imaging varies based on the location of the lesion and tumor characteristics. Imaging is the key to treatment planning and is highly sensitive and specific for lesion detection [35, 36]. The considerations included facility access, costs, and contraindications. The benefits and disadvantages of this method are listed in Table 4.

Table 4 Benefits and disadvantages of diagnostic imaging in PPGL

Methods	Features	Disadvantages
CT	• High spatial resolution • Characteristic imaging pattern (Relatively high attenuation [unenhanced CT attenuation value >10 HU]; dense staining in the arterial phase and washed out in the late phase)	• Not disease-specific • Differentiation from adrenal cancer and metastasis is necessary
MRI	• High contrast resolution • Characteristic imaging pattern (Low signal on T1 weighted image, high signal on T2 weighted image; no signal reduction in the opposed phase of chemical shift imaging; dense staining in the arterial phase and washout in the late phase)	• Not disease-specific • Differentiation from adrenal cancer and metastasis is necessary
¹²³ I-MIBG Scintigraphy	• High disease specificity • Easy whole-body search	• Sensitivity is low due to low spatial resolution • Detection sensitivity is low in metastatic and <i>SDHx</i> gene pathogenic variant-positive cases
¹¹¹ In-octreotide Scintigraphy	• High disease specificity • High detection sensitivity even in cases positive for <i>SDHx</i> gene pathogenic variants	• Low sensitivity due to low spatial resolution
¹⁸ F-FDG PET	• Highly concentrated in malignant tumors and inflammation, with high sensitivity • Easy whole-body search	• Not disease-specific
¹⁸ F-FDOPA PET	• High disease specificity • High sensitivity even in metastatic and <i>SDHx</i> gene pathogenic variant-positive cases	• Not approved in Japan

HU, Hounsfield units; *SDHx*, succinate dehydrogenase complex subunit x

B. CT

The CT offers excellent spatial resolution and can depict lesions approximately 5 mm in size. It provides precise anatomical details, such as tumor morphology and its relationship with the surrounding organs. However, CT is not specific for differentiating adrenal tumors. PCCs are often large, with possible necrosis, cysts, or hemorrhage, complicating their differentiation from adrenal cancer or metastases [37]. Calcification is present in about 10% of PCCs, while adrenal cortical adenomas contain fat, which usually have unenhanced CT attenuation values of 10 Hounsfield units (HU) or less. PCCs lack fat and have unenhanced CT attenuation values of 20 HU or more, suggesting a higher likelihood of PCC if fat is absent [37]. The sensitivity of CT for PCC detection is approximately 90% [35]. Although less sensitive for PGLs, CT is useful for screening and detecting metastases, especially in the *SDHx* gene with pathogenic *SDHx* variants [35, 38]. CT texture analysis is currently under development [39]. PCCs often show early staining on contrast-enhanced CT, with washout observed in the late phase [37] (Fig. 3). Caution is needed because these features can also appear in adrenal cancers or metastases. For surgical planning, assessing tumor-vessel relationships is crucial, and contrast-enhanced CT is recommended as the first choice by

international guidelines [40]. In Japan, written informed consent, monitoring of blood pressure and ECG, and preparation of phentolamine (Regitin®) are advised in accordance with the “Precautions for Patients with Specific Backgrounds” in the product labeling when iodinated contrast agents are used for PPGLs.

C. MRI

The MRI is valuable for diagnosing adrenal tumors because of its distinct imaging characteristics: low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and heterogeneous signal patterns in PCCs [41]. Unlike CT, MRI can identify small amounts of fat using chemical-shift imaging, which aids in tumor differentiation. If there is no signal reduction on opposed-phase images compared to in-phase images (signal reduction rate <10%), the tumor is more likely to be a PCC than a cortical adenoma (Fig. 4). MRI, with its high-contrast resolution, is particularly effective in detecting PGLs, recurrence, and metastasis. It is beneficial for head and neck lesions and *SDHx* pathogenic variants, showing a sensitivity of 85–90% and a specificity of approximately 95% [38].

PPGL metastases commonly involve the bones, lungs, liver, and lymph nodes. Although CT and MRI can effectively depict small lymph nodes and lung metastases because of their high spatial resolution, their

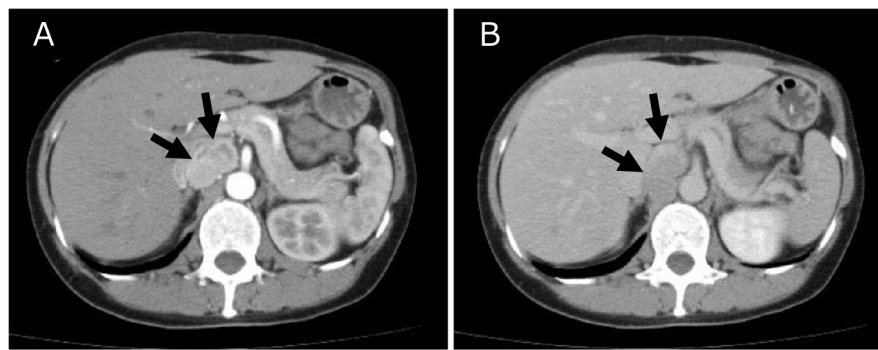


Fig. 3 Contrast-enhanced CT of right adrenal pheochromocytoma

The tumor was stained with a contrast medium in the early contrast phase (A), and washout of the contrast medium was observed in the late contrast phase (B) (arrow).

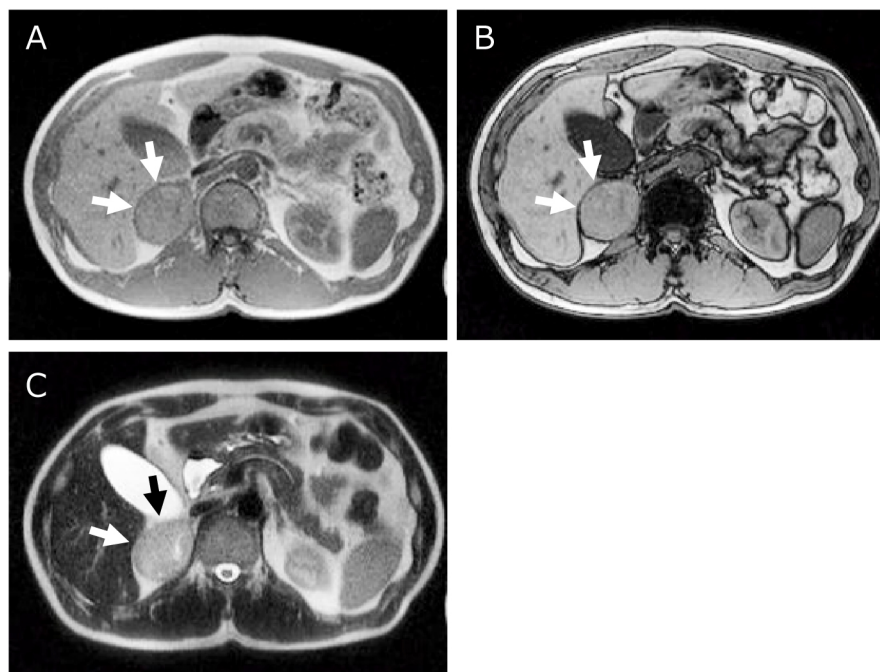


Fig. 4 MRI of right adrenal pheochromocytoma

The tumor signal did not decrease in the opposing phase (B) compared to the in-phase (A) on the gradient-echo T1-weighted image (arrow), indicating that it did not contain fat. The tumor showed a heterogeneous, high signal on T2-weighted imaging (C).

disease specificity remains low [36]. MRI is preferred for frequent examinations and in children to avoid radiation exposure. Contrast-enhanced MRI often shows a strong early contrast, similar to CT, without an increase in catecholamine levels. The effectiveness of diffusion-weighted MRI in diagnosing metastatic lesions in PPGL remains debatable [37, 42].

D. ^{123}I -MIBG scintigraphy

Although CT and MRI offer high spatial resolution, qualitative diagnosis is often difficult due to postoperative changes or artifacts. In contrast, ^{123}I -MIBG scintigraphy is valuable for the qualitative and functional

diagnosis of neuroendocrine tumors, including PPGL.

^{123}I -MIBG is a guanidine-like compound taken up by cells *via* the noradrenaline transporter, making it specific to neuroendocrine tumors. It emits gamma rays suitable for imaging and does not emit beta-rays such as ^{131}I , reducing the need for thyroid blocking. However, thyroid blocking is recommended to prevent a reduction in diagnostic accuracy due to potential accumulation in the thyroid. Potassium iodide (50–150 mg/day) or Lugol's solution (5–10 drops/day) should be administered three days before the test and continued until the day of imaging. Reserpine and tricyclic antidepressants should be

discontinued one week before the test, as they inhibit MIBG uptake. ^{123}I -MIBG accumulation in adrenal tumors indicates a high likelihood of PCC, although normal adrenal glands can also accumulate MIBG, which requires careful interpretation. The sensitivity and specificity of ^{123}I -MIBG for PCC were greater than 90% [43]. However, detection sensitivity was lower in poorly differentiated cases, PGL, multiple cases, *SDHx* pathogenic variants, and hereditary PPGL [44].

MIBG also accumulates in normal organs, such as the salivary glands and myocardium. The accumulation in atypical organs is indicative of metastasis. Despite its usefulness, MIBG's spatial resolution limits its ability to detect small lesions and affects its diagnostic ability for liver metastases. For metastatic PPGL, the sensitivity is approximately 90% [43, 44] (Fig. 5A); however, ^{18}F -FDG PET was superior for detecting metastasis and *SDHx* variant-positive cases [36, 44, 45].

Whole-body evaluation with ^{123}I -MIBG scintigraphy and PET studies is useful in cases with large primary lesions, PGL, or *SDHx* gene pathogenic variants. We also evaluated the indications for ^{131}I -MIBG internal therapy. ^{123}I -MIBG also detects other neuroendocrine tumors, such as neuroblastoma and medullary thyroid carcinoma, but is less effective for PPGL.

E. ^{18}F -FDG PET

^{18}F -FDG PET is a valuable imaging tool for diagnosing PPGLs and detecting increased glucose metabolism, which is often higher in tumors with high proliferation rates. Although ^{18}F -FDG does not have high specificity

for tumors and can accumulate in normal adrenal glands, liver, and bone marrow, it is beneficial in certain contexts.

1) Detection sensitivity: PPGLs often showed increased ^{18}F -FDG accumulation with a detection sensitivity of 70–80% [36, 44] (Fig. 5B).

2) Diagnostic value: ^{18}F -FDG PET is highly diagnostic, especially when ^{123}I -MIBG scintigraphy shows low diagnostic ability, such as for *SDH* pathogenic variants. It effectively evaluates metastatic lesions and assesses treatment efficacy [36, 38, 44, 45].

3) False positives: ^{18}F -FDG PET can show false positives due to uptake by the brown adipose tissue [46]. Radiomic analysis of ^{18}F -FDG PET data may enhance diagnostic accuracy [47].

F. Other imaging tests

1) ^{111}In -Octreotide (Pentetreotide) scintigraphy: This imaging method visualizes somatostatin receptors (SSTR2 and SSTR3), which are overexpressed in many PPGLs, particularly in those with *SDHB* pathogenic variants. It showed a higher positivity rate in cases such as ^{123}I -MIBG. Combining ^{111}In -octreotide scintigraphy with MRI and CT can enhance diagnostic accuracy [38].

2) ^{68}Ga -DOTATATE PET: This PET scan is highly sensitive for diagnosing primary head and neck PGLs irrespective of genetic pathogenic variants [48]. It is also helpful for identifying SSTR-positive neuroendocrine tumors treatable with ^{177}Lu -DOTATATE, approved by health insurance in Japan in 2021.

3) Bone scintigraphy: This test detects metastatic bone tumors. As the tracer reflects bone formation, it is less

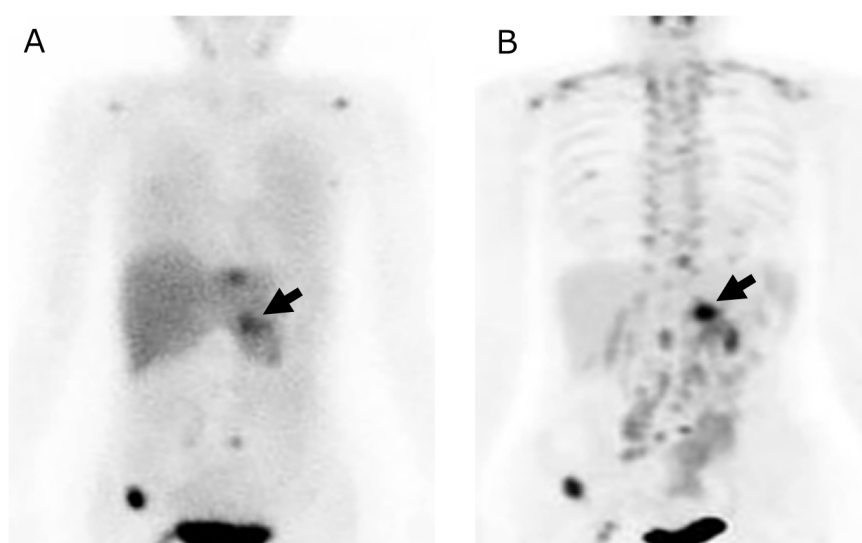


Fig. 5 ^{123}I -MIBG scintigraphy and ^{18}F -FDG PET in a case of paraganglioma

^{123}I -MIBG scintigraphy (A) showed multiple abnormally high accumulations in the shoulders, vertebrae, sacrum, right ilium, and right ischium. The primary tumor was located in the upper left abdomen (arrow). ^{18}F -FDG PET (B) showed multiple bone metastases and a high accumulation of ^{18}F -FDG in the primary tumor. The accumulations observed around the clavicle and vertebral bodies were considered to be brown adipose tissue.

effective for detecting osteolytic metastases, commonly found in metastatic PPGL.

I-4 Medical Treatment

Statements

- I-4-1 Sufficient inhibition of excess catecholamine action is essential to manage blood pressure and prevent cardiovascular complications in perioperative and nonoperative cases of functional pheochromocytoma and paraganglioma (PPGL) (1C).
- I-4-2 Selective α_1 -blockers are the first-choice drugs (1B). If blood pressure reduction is insufficient, combine them with calcium antagonists or metyrosine (2C).
- I-4-3 Combine with β -blockers for tachycardia/tachyarrhythmia, myocardial damage, heart failure, or ischemic heart disease (2C). Administering a β -blocker before an α_1 -blocker is contraindicated (1A).
- I-4-4 A normal salt diet or saline infusion is recommended before surgery to prevent orthostatic hypotension and avoid hemodynamic changes during surgery and excessive postoperative hypotension (2C).
- I-4-5 If catecholamine overproduction is unclear, α_1 -blockers are generally unnecessary. However, a comprehensive assessment of clinical findings is needed before prescribing α_1 -blockers before surgery (2D).

Evidence

A. Principles of preoperative and post-diagnostic treatment

1) Inhibition of excess catecholamine action in preoperative and non-surgical cases of functional PPGL

Surgical resection is the primary treatment option for PPGL. Surgery can induce excessive catecholamine secretion, causing severe cardiovascular complications, including hypertensive crisis, arrhythmia, ischemic heart disease, pulmonary edema, and multiple organ failure. Post-tumor resection carries a risk of severe hypotension and hypoglycemia due to an abrupt drop in catecholamine levels. Therefore, optimizing the blood pressure, heart rate, and circulating plasma volume before and after surgery is essential. Nonsurgical treatment methods and goals are similar to those used during the perioperative period.

2) Selective α_1 -blockers

While no randomized controlled trials exist for preoperative treatment, sufficient preoperative treatment, including α -blockers, has reduced perioperative mortality to below 3%. α -blockers should be administered at least 7 to 14 days before surgery, starting with the usual dose

and gradually increasing to target blood pressure and heart rate. Oral α -blockers available in Japan are selective α_1 -blockers (e.g., prazosin, doxazosin, urapidil). Systematic reviews/meta-analyses [49, 50], randomized controlled trials [51], and prospective controlled trials [52] demonstrate that nonselective α -blockers outperform selective α -blockers in regulating blood pressure and hemodynamics during surgery. No significant differences were observed in perioperative complications or deaths. Doxazosin, which has a long duration of action, is a commonly used drug. The initial dose was 1–2 mg/day, titrated up to 16 mg every 2–3 days until the target blood pressure was reached. As the first dose may cause orthostatic hypotension, it should be administered before bedtime.

α - β -blockers like labetalol and carvedilol are not recommended due to their substantial β -blocking effects, risking hypertensive attacks. Labetalol also interferes with imaging results by inhibiting the accumulation of ^{131}I -MIBG. α_1 -blockers are unnecessary for non-catecholamine-producing PPGL. However, clinically distinguishing hormone production is challenging; therefore, the necessity of treatment should be comprehensively evaluated, considering factors such as ^{123}I -MIBG uptake and cystic degeneration within the tumor.

3) Other antihypertensive drugs

When the antihypertensive effects of α -blockers are insufficient, cause significant side effects, or when vasospastic angina occurs, calcium antagonists are administered. A recent randomized trial comparing the effects of amlodipine and prazosin on intraoperative hemodynamics found that prazosin was superior in controlling blood pressure spikes above 160 mmHg, but there was no difference in the prevalence of hypotension and its duration. Thus, amlodipine may serve as an alternative to prazosin [53].

For severe catecholamine excess or tachycardia/tachyarrhythmia induced by α -blockers, β -blockers are added several days after sufficient α -blocker administration (several days later). Administering a β -blocker before an α -blocker is contraindicated, as it may cause a hypertensive attack due to enhanced vasoconstriction from catecholamines' action and inhibited vasodilation from β_2 receptor blockade.

4) Catecholamine synthesis inhibitor

Metyrosine (Demser[®]), a catecholamine synthesis inhibitor, blocks tyrosine hydroxylase, thereby reducing catecholamine production. It is effective when α -blockers are insufficient, particularly for catecholamine cardiomyopathy and intractable hypertension. The starting dose is 0.5 g/day in Japan, with effects observed within 2–3 days. The goal is to normalize blood pressure in patients with hypertension and reduce the urinary

fractionated metanephrines by at least 50% in patients with normotension. If ineffective, the dose can be increased to a maximum of 4 g/day, with an optimal dose being 2–3 g/day.

A multicenter open-label study in Japan showed a 33% achievement rate for reducing urinary fractionated metanephrines by 50% after 12 weeks (67% preoperatively and 23% nonsurgically) [54]. Preoperative administration may improve intraoperative outcomes [55], and its use should be considered for high-risk surgeries involving high catecholamine production.

The main adverse events include central nervous system symptoms (*e.g.*, drowsiness, insomnia, and anxiety), extrapyramidal symptoms (approximately 10%), and diarrhea, even at small doses. Caution is needed for activities requiring alertness (*e.g.*, driving) and when using alcohol, anxiolytics, sleep-inducing drugs, haloperidol, and phenothiazines. Patients should drink at least 2 L/day to prevent crystalluria and urinary stones. If needle-shaped crystals are detected in the urine, water intake should be increased, and if persistent, the dosage is reduced or metyrosine is discontinued. However, its safety in pregnant and lactating women in Japan has not yet been established.

5) Treatment Goals and Duration

There is no solid evidence regarding the optimal preoperative blood pressure or heart rate. However, the following targets have been proposed: sitting blood pressure <130/80 mmHg, orthostatic systolic blood pressure at least 90 mmHg, heart rate of 60–70 bpm sitting, 70–80 bpm standing [49]. For organ damage caused by long-term catecholamine excess (*e.g.*, cardiomyopathy, myocardial infarction), initiate α -blockers early to prepare for surgery.

6) Correction of circulating blood volume

Start a normal salt diet (9 g/day) on the third day of α -blockers, adjusting intake according to blood pressure reduction and orthostatic hypotension to manage decreased circulating blood volume. It takes 7–14 days for the plasma volume to increase. Additionally, 1–2 L of saline is infused from the evening before surgery until surgery.

B. Postoperative Treatment

Specific postoperative complications of PPGL include severe hypotension and hypoglycemia. Postoperatively, patients should be managed in an ICU with frequent monitoring of blood pressure, heart rate, and plasma glucose levels. Persistent hypotension is common in patients with large tumors and severe catecholamine overproduction. Preoperative α -blockers reduce the risk of persistent hypotension and vasopressor resistance. If hypotension occurs, it is managed with vasopressors and fluid replacement [49]. Plasma glucose should be monitored

for 48 hours postoperatively, especially in patients previously treated with insulin or oral hypoglycemic agents. Hypoglycemia is treated with an intravenous glucose solution.

I-5 Surgical Treatment

Statements

- I-5-1 Tumor resection by surgery is the first-line treatment (1A).
- I-5-2 Laparoscopic or robot-assisted laparoscopic adrenalectomy is the standard for small pheochromocytoma (PCC) (1B).
- I-5-3 Open surgery is recommended for large tumors or suspected invasion into surrounding organs (2C).
- I-5-4 Consider surgical removal of the primary tumor, even in metastatic pheochromocytoma and paraganglioma (PPGL), to extend survival (2C).
- I-5-5 Consider partial adrenalectomy in familial PCC cases with a high risk of bilateral adrenal lesions or post-contralateral adrenalectomy (2C).

Evidence

Primary tumor resection in metastatic PPGL is associated with over 3.5 times lower mortality risk and longer survival compared to chemotherapy only [56]. In catecholamine-producing PPGL, resection improves survival and alleviates symptoms such as hypertension and constipation [56]. Tumor debulking, even if not curative, can provide clinical benefits, and may improve prognosis with metastatic tumor resection, although more evidence is needed.

A. Position of Surgical Treatment and perioperative management

Surgical resection is the primary treatment for a possible permanent cure of PPGL. However, excessive catecholamine production and neovascularization in PPGL lead to an increased risk of bleeding during surgery. Complication rates and perioperative deaths were high from the 1970s to the 1990s [10]. The development of perioperative management, including proper preoperative α -blocker administration and strict intraoperative management by an experienced anesthesiologist, significantly reduced the mortality to under 3% and the complication associated with laparoscopic adrenalectomy to under 8% (see Chapter I-4 Medical Treatment) [10]. Some advocate for similar management, even for normotensive PPGL [57].

B. Surgical methods

Open and laparoscopic surgeries (including robot-assisted) are available options. The choice depends on the tumor size, adhesion to surrounding tissues, and the experience of the surgical team. Benign tumors ≤ 6 cm in diameter are generally suitable for laparoscopic surgery.

However, open surgery is recommended for tumors >6 cm due to high risk of bleeding and the potential for complications, such as severe hypertension, tumor rupture and local recurrence [40]. Open surgery is also preferred if invasion or adhesion to the surrounding organs is suspected [40]. Although laparoscopic surgery for PGL is debatable, it can be considered for small tumors without signs of organ invasion [40].

1) Laparoscopic Adrenalectomy/Robot-Assisted Laparoscopic Adrenalectomy

Laparoscopic surgery includes laparoscopic adrenalectomies (LA) and robot-assisted laparoscopic adrenalectomy (RAA). LA involves trocar placement and pneumoperitoneum using forceps during surgery. LA was first performed in 1992 and has been recognized as a minimally invasive and safe procedure covered by insurance since 1996 in Japan. Laparoendoscopic single-site surgery (LESS), a variant of LA, offers better cosmetic outcomes and reduced postoperative pain but may involve rougher forceps manipulation. RAA, covered by insurance since 2022 in Japan, offers advantages over LA and open surgery, including enhanced precise operations due to 3D imaging, an enlarged view, flexible forceps tips, and image stabilization.

Meta-analyses comparing open adrenalectomy (OA) and laparoscopic adrenalectomy (LA) for PCC indicate that LA offers superior outcomes, including reduced intraoperative hemodynamic instability, blood loss, and postoperative recovery [58, 59]. However, these results should be interpreted with caution, as LA is primarily used for smaller tumors. For tumors ≥ 6 cm, the conversion rate to open surgery was high (7.7%), with severe complications occurring more frequently in converted cases [60]. Therefore, LA for large PCCs requires a skilled surgical team and careful case-by-case consideration.

A randomized controlled trial comparing robot-assisted laparoscopic adrenalectomy (RAA) and LA found similar operation times for both methods. However, RAA resulted in reduced blood loss and shorter operative times (excluding docking) in patients with high preoperative blood normetanephrine levels [61]. RAA was significantly more expensive than LA but showed no difference in perioperative complications or hospital stay. In PCC with tumors ≥ 5 cm, RAA demonstrated lower rates of conversion to open surgery, reduced intraoperative blood loss, and fewer blood pressure fluctuations [62, 63]. The RAA appears advantageous for larger tumors due to its flexible forceps tip, although further data are.

Since 2004, the Japan Society of Endoscopic Surgery and the Japanese Society of Urological Endoscopy and Robotics have worked to enhance laparoscopic safety through certifications and guidelines. These include the

“Guidelines for Robot-Assisted Surgery in the Urological Field” and the “Urological Robot-Assisted Surgery Education Program,” mandating adherence to these guidelines and obtaining informed consent [64].

2) Partial Adrenalectomy

Partial adrenalectomy can prevent lifelong steroid replacement and acute adrenal insufficiency in patients with familial PCC. However, it may result in steroid dependence and tumor recurrence in the remaining adrenal glands. A multicenter study across 45 institutions in 19 countries ($n = 625$, 849 adrenal surgeries, median follow-up of eight years) assessed outcomes such as steroid dependence, recurrence, metastasis, and mortality [65]. Among those who underwent partial adrenalectomy, 23.5% remained steroid-dependent postoperatively. Among these 377 patients with steroid dependence, 18% experienced acute adrenal insufficiency, resulting in two deaths. Recurrence occurred in the ipsilateral adrenal gland in 13% of cases. Metastasis was observed in 1.3% of patients, with no significant difference between total and partial adrenalectomies (1/301 [0.3%] vs. 7/324 [2%], $p = 0.07$) [65]. Four out of eight patients with metastasis had germline *VHL* pathogenic variants (2% of all *VHL* disease cases), whereas only one multiple endocrine neoplasia type 2 (MEN2) patient had metastasis (0.3% of all MEN2 cases). Partial adrenalectomy does not reduce survival rates [65, 66]. It is recommended for patients with bilateral PCC, tumors ≤ 5 cm, and a high risk of future PCC. Each case requires evaluation based on surgeon expertise and the risks of reoperation or acute adrenal insufficiency after total adrenalectomy. Informed consent must be obtained, and partial adrenalectomy should follow unilateral adrenalectomies.

Imai *et al.* analyzed 144 MEN2 patients from the MEN Consortium in Japan to determine codon-specific penetrance of PCCs [67]. Patients with codons 918 and 634 variants may have higher recurrence rates in the ipsilateral adrenal glands after partial resection. Gene-phenotype correlations suggest that pathogenic variant locations should guide surgical decisions. At least one-third of the adrenal glands must remain intact to preserve adrenal cortex function [65]. The adrenal gland, typically small and poorly visible during surgery, is nourished by multiple arteries. Therefore, peri-adrenal dissection should be minimized to avoid damaging the nutrient vessels. Preserving the central adrenal vein is not crucial because collateral circulation often develops if ligated [68]. For tumors ≥ 5 cm, preserving the normal adrenal cortex can be challenging; thus, careful surgical planning and intraoperative ultrasound are recommended.

I-6 Hypertensive crisis

Statements

- I-6-1 Hypertensive crisis can arise from various triggers during the clinical course of pheochromocytoma and paraganglioma (PPGL). Early diagnosis and specific treatment are essential due to poor prognosis from severe hypertension and cardiovascular complications (1A).
- I-6-2 Intravenous phentolamine is administered, followed by an intravenous infusion. After the acute phase, switch to oral doxazosin, a selective α_1 -blocker (1B).

Evidence

A. Triggers

Hypertensive crises can occur due to various triggers during the clinical course, causing severe hypertension, tachycardia, and circulatory failure due to excess catecholamines. Its incidence is 3–11% [69, 70], with a mortality rate of approximately 15% [71]. The triggers included daily activities, pregnancy, medications, and procedures [72] (Table 5). Overseas guidelines [40] state that non-ionic iodine contrast agents are safe for PPGL and recommend contrast CT as the first imaging choice. When using iodine contrast for PPGL in Japan, it is advised to follow the “Cautions for patients with specific backgrounds” in the product labeling (see Chapter I-3 Imaging diagnosis).

High-dose dexamethasone can cause severe hypertensive crises; therefore, glucocorticoids should be used with caution if PPGL is suspected [11]. Metastatic PPGL treatments, such as chemotherapy, ^{131}I -MIBG therapy, and TAE, can induce hypertensive crises due to tumor collapse. Patients should be educated about triggers and informed of potential crisis risks during diagnosis and treatment, with preparations made for emergencies.

B. Diagnosis

Symptoms of excess catecholamines include headache,

palpitations, sweating, and marked blood pressure fluctuations. Other symptoms include chest pain, apical ballooning syndrome [73], acute heart failure, pulmonary edema, and shock. Signs of dehydration, elevated serum protein, BUN/creatinine ratio, hematocrit, LDH, ALP, potassium, increased neutrophil-predominant WBCs, and CRP suggest tumor destruction and inflammation. Elevated plasma catecholamine levels, renin activity, and aldosterone concentrations due to decreased plasma volume can lead to multiple organ failure, including pleural effusion as well as liver and renal failure, known as PCC multisystem crisis (PMC).

C. Treatment

Therefore, hospitalization is required. The first treatment choice is intravenous administration of phentolamine (Regitin®), a nonselective α -blocker, administered as a continuous infusion due to its short duration. Calcium antagonists and nitrates are combined as necessary. The initial goal is to maintain the diastolic blood pressure at 110 mmHg or less, reducing it to approximately 160/100 mmHg within 2–6 hours. Phentolamine induces tachycardia by increasing noradrenaline release. If tachycardia occurs, β -blockers are administered orally, except during emergencies, to prevent fatal arrhythmias [74]. For multiple organ failure, continuous hemofiltration dialysis or extracorporeal cardiopulmonary support may improve survival, requiring collaboration with other departments [71, 75]. Once the acute phase resolves, patients are transitioned to oral α_1 -blockers like doxazosin.

I-7 Diagnosis of non-catecholamine-producing PPGL

Statements

- I-7-1 Since non-catecholamine-producing pheochromocytoma and paraganglioma (PPGL) is often metastatic and negative on MIBG scintigraphy, careful and comprehensive investigation with

Table 5 Triggers of hypertensive crisis in pheochromocytoma and paraganglioma

Triggers in daily life	• Bent posture • Exercise • Abdominal bruising • Overeating • Foods high in tyramine (aged natural cheese, red wine, <i>etc.</i>) • Drinking alcohol • Sneezing • Urination • Defecation • Stress • Smoking • Pregnancy
Procedures and examinations	• Abdominal palpation • Enema examination • Tumor biopsy • Iodine contrast agent ¹⁾
Medications	• Dopamine receptor antagonists (metoclopramide [Primperan®]) ²⁾ • Glucagon • β -blocker monotherapy • Tricyclic antidepressants • SNRIs • MAO inhibitors • High-dose dexamethasone ³⁾
Other treatments	• Chemotherapy (CVD chemotherapy) • Radiation therapy (^{131}I -MIBG internal irradiation, external irradiation) • Transcatheter arterial embolization (TAE) • Radiofrequency cryoablation • Contrast medium

¹⁾ Refer to Chapter I-3 Imaging diagnosis.

²⁾ Both oral and injectable medications are contraindicated. The dopamine D2 receptor antagonist domperidone does not cause hypertensive attacks, and there are no contraindications listed in the package insert, but caution is required, similar to that for metoclopramide.

³⁾ Do not administer more than 2 mg of dexamethasone.

SNRIs, serotonin noradrenaline reuptake inhibitors; MAO, monoamine oxidase; CVD, cyclophosphamide, vincristine, and dacarbazine.

MRI, contrast CT, and nuclear imaging for somatostatin receptors is mandatory (1C).

I-7-2 Differential diagnosis from other neuroendocrine tumors is often complicated by findings that extend beyond histopathological diagnosis (C).

I-7-3 PPGL is first diagnosed through pathological examination after surgery in many cases (C).

Evidence

A. Diagnosis

Non-catecholamine-producing PPGLs are frequently PGLs, and the sensitivity of ^{123}I -MIBG scintigraphy is low, making diagnosis difficult. A comprehensive diagnosis must be made based on the MRI, contrast-enhanced CT and ^{18}F -FDG PET findings. Nuclear imaging of somatostatin receptors is also helpful; however, differentiating them from other neuroendocrine neoplasms (NENs) can be challenging, depending on the tumor's location (see Chapter I-3 Imaging diagnosis). Consequently, diagnosis is often based on the pathological findings obtained after surgery. Given that many cases of non-catecholamine-producing PPGLs are metastatic, careful and comprehensive diagnosis using different modalities and early treatment are essential.

Regardless of advancements in measurement methods, 2.9–8.9% of PPGL cases remain non-catecholamine-producing, with negative plasma and urine catecholamines and their metabolites [15, 76, 77]. In the ACPA-J study conducted in Japan, urinary metanephrine and normetanephrine levels were within the reference range in 6.2% of the enrolled PPGLs [23]. Compared with catecholamine-positive PPGLs, the frequency of PGL, frequency of metastasis, and rate of negative ^{123}I -MIBG scintigraphy results were significantly higher in non-catecholamine-producing PPGLs.

A study of cases at the Mayo Clinic reported a high frequency of metanephrine, normetanephrine, and catecholamines within the normal range in 20.6% of PPGLs with metastasis [78]. In the ACPA-J group, the frequency of normal blood metanephrine and normetanephrine levels was 18.8% in PPGLs with metastasis [23]. On the other hand, it has been reported that the concentration of catecholamine metabolites is higher in PPGLs with metastasis than in those without metastasis [79]. This finding can be attributed to the higher production capacity of a larger tumor volume.

B. Genetic Background

In non-catecholamine-producing PPGL, it has been reported that cases positive for *SDHB* gene pathogenic variants have a high frequency of metastasis [80, 81] and tumors that are pathologically negative for tyrosine hydroxylase (TH) and do not produce catecholamines are often found [82]. A correlation between positive *SDHD*

pathogenic variants and non-catecholamine production has been previously reported [83]. In addition, it has been reported that cases positive for *SDHB/SDHD* gene pathogenic variants have a high frequency of PGLs [84] and that the sensitivity of ^{123}I -MIBG scintigraphy is low [35]. Positive *SDHx* pathogenic variants may be one of the factors behind the high frequency of PGLs, metastasis, and negative rate of MIBG scintigraphy in non-catecholamine-producing PPGL.

I-8 Diagnosis and treatment of head and neck paragangliomas

Statements

I-8-1 Since most HNPGs are non-catecholamine-producing and typically asymptomatic, the diagnosis of PGL is usually based on the imaging characteristics and location of the tumor. For catecholamine-producing tumors, follow the endocrine tests for standard methods (1C).

I-8-2 Approximately one-third of cases, whether sporadic or hereditary, show dopamine overproduction. Measuring the dopamine metabolite 3-methoxytyramine (3-MT) is recommended but is not covered by health insurance in Japan (1B).

I-8-3 Hereditary head and neck paragangliomas (HNPGs) often involve *SDHD* germline pathogenic variants. Genetic testing is recommended for all cases of HNPGs due to the tendency for multiple lesions (1C).

I-8-4 Imaging is crucial for detecting primary, multiple, and metastatic tumors. Whole-body contrast MRI, skull base contrast CT, and nuclear imaging techniques such as ^{18}F -FDG PET/CT and ^{123}I -MIBG scintigraphy are recommended (1C).

I-8-5 Fine needle cytology is not recommended for pathological diagnosis due to its low accuracy (2D).

I-8-6 Most HNPGs are endocrinologically inactive and grow slowly, so surveillance therapy is preferred to minimize postoperative complications. However, surgical resection or radiation therapy is advised for high-risk groups. For multiple lesions or distant metastases, multidisciplinary approaches, including radionuclide therapy and chemotherapy, are recommended (1C).

Evidence

HNPGs are rare neuroendocrine tumors arising from the nonchromaffin cells of the parasympathetic nervous system [85]. Formerly known as glomus tumor, it now falls under the WHO classification of HNPG. With an incidence of 0.5 per million, it primarily affects women aged 30–50 [86]. HNPGs are classified according to

their site of origin as follows: approximately 60% are carotid body tumors (CBT), 30% are jugular bulb tympanum PGL, and 10% are vagus nerve PGL. Sporadic HNPGLs may also arise from the larynx, orbit, trachea, thyroid gland, and nasal cavity [86, 87].

A. Catecholamine production

While HNPGL originates from the parasympathetic paraganglia, they have been shown to produce excess noradrenaline and normetanephrine in only 4% of cases [88]. A study of 152 cases found significant secretion in only 9.2% of cases and 7.7% of tumors, with most cases showing less than a five-fold increase above the standard upper limit [89]. Evaluation of catecholamine production is crucial for perioperative management. Measurement of the plasma-free fractionated metanephrines or the fractionated metanephrines in 24-hour urine is essential. Additionally, approximately one-third of HNPGL cases, whether sporadic or hereditary, show excessive dopamine production. Therefore, measuring the dopamine metabolite 3-methoxytyramine (3-MT) is beneficial (not covered by health insurance in Japan) [90].

B. Genetic Background

Hereditary HNPGL often involves germline pathogenic variants in the *SDHD* gene. Baysal *et al.* found *SDHD* variants in 50% of cases, which increased to 70% when *SDHB* variants were also present. The lifetime risk of familial occurrence in *SDHD*-positive cases was 75% [91]. Hereditary *SDHD* variants frequently present as multifocal lesions. A Japanese cohort study of 370 PPGLs found a high prevalence of pathogenic variants in 77 HNPGLs (51.9%), with 28.6% and 22.1% for *SDHD* and *SDHB* and 1.3% for *SDHC*. Notably, only 27.5% of cases with pathogenic variants had a family history [92]. Therefore, genetic testing is recommended for all patients with HNPGL after appropriate genetic counseling and informed consent, regardless of family history.

C. Imaging

HNPGLs are often multifocal but rarely metastasize (6–19%) [93]. Whole-body imaging is essential, with contrast-enhanced MRI of the head and neck helping differentiate primary lesions from schwannomas [94]. High-resolution CT of the skull base has also been used for jugular bulb tympanic PGLs. A whole-body MRI of the chest, abdomen, and pelvis is recommended to detect multifocal and metastatic tumors, including coronal T1-weighted images, STIR images, and transverse fat-suppressed T2-weighted images from the skull base to the kidneys [86].

Nuclear imaging techniques, such as somatostatin receptor scintigraphy and ^{18}F -FDG PET/CT, are useful for staging HNPGLs. ^{68}Ga -DOTATATE PET/CT, which targets SSTR2 widely expressed in HNPGLs, can detect

tumors smaller than 1 cm, with some reports showing 96% detection [90]. However, the test is not covered by health insurance in Japan. ^{18}F -FDG PET/CT is useful in *SDHx* gene-positive cases. ^{123}I -MIBG scintigraphy has low sensitivity for HNPGL and is indicated only when radionuclide therapy with ^{131}I -MIBG is planned [90].

D. Preoperative pathological diagnosis

Fine-needle cytology is not recommended for HNPGL because of the risk of hypertensive emergencies and bleeding in catecholamine-producing tumors. Fine needle cytology has also been reported to misdiagnose all five thyroid PGLs as follicular tumors [95]. Therefore, this procedure is avoided.

E. Treatment

1) Surveillance therapy

Most HNPGLs are non-catecholamine-producing and grow slowly, with a mean annual growth diameter of 0.4 mm for jugular bulb tympanic PGLs and 1.6 mm for carotid body and vagus nerve PGLs [86]. Approximately 40% of patients showed no growth during follow-up [90]. Surveillance therapy is preferred for asymptomatic patients to avoid postoperative complications. Follow-up will include contrast-enhanced head and neck MRI at six months, annually for three years, every other year for six years, and every three years thereafter. Surgical resection is recommended for high-risk cases such as tympanic PGL, jugular bulb PGL with hearing loss or pulsatile tinnitus, significant skull base compression, catecholamine production, rapid growth, and metastasis [86]. Preoperative embolization for hypervascularity is attempted, but there is a lack of consensus on its effectiveness [90].

2) Surgical treatment and external radiation

Radical resection of HNPGLs has a high incidence of postoperative complications, such as swallowing problems and airway obstruction (54–60%) [96]. Gamma-knife radiation therapy is recommended as an adjuvant or sole treatment for local tumor control in patients with suspected postoperative complications and metastasis. A meta-analysis of 11,174 cases reported local tumor control in 94.2% of cases, with 48.6% showing no growth and 45.6% experiencing shrinkage. Local tumor control rates were 96% after five years and 93.4% after ten years, with a median radiation dose of 15 Gy [96].

3) Chemotherapy and radionuclide therapy

CVD chemotherapy is used for inoperable HNPGLs and those with distant metastases. Radionuclide therapy with ^{131}I -MIBG, covered by insurance in Japan since 2022, has shown effectiveness in a meta-analysis of ^{123}I -MIBG cases, with a 5-year survival rate of 37% and a 10-year survival rate of 29% [97].

I-9 Diagnosis and treatment in pregnancy

Statements

- I-9-1 Early diagnosis and treatment of pheochromocytomas and paragangliomas (PPGLs) are crucial due to the high mortality rates for both mother and child when PPGL is not adequately treated before delivery (1B).
- I-9-2 Ultrasound or MRI is recommended for imaging examinations due to their safety and ease. CT and ¹²³I-MIBG scintigraphy should only be performed if the diagnostic benefits outweigh the disadvantages from the perspective of radiation exposure (1B).
- I-9-3 Selective α -blockers are the first choice for systemic management and blood pressure control before delivery, but calcium antagonists (nifedipine, amlodipine) should also be combined if necessary (2C).
- I-9-4 If tumor removal is to be performed before delivery, it is recommended to do so in the second trimester up to 24 weeks of pregnancy (2C).

Evidence

A. Epidemiology

The incidence of PPGL-complicated pregnancies is rare, affecting only 0.007% of pregnant women [98]. Historically, maternal and fetal mortality rates were 12–18% and 40–50%, respectively. Since 2000, advancements in care have reduced these rates to 0% and 12% in patients diagnosed and treated before birth, respectively. However, because mortality remains high (29%) in cases diagnosed after birth [99], early diagnosis and treatment are crucial. Women with a family history of PPGL should undergo biochemical and imaging tests before pregnancy [100].

B. Major symptoms

Symptoms of PPGL (hypertension, palpitations, headache, and sweating) often mirror those observed in non-pregnant patients and may become more pronounced as pregnancy progresses. Mechanical stimulation of the tumor by uterine enlargement or fetal movement can exacerbate the symptoms [101]. Distinguishing PPGL from pregnancy-induced hypertension is challenging.

C. Diagnosis

1) Biochemical diagnosis

Screening should include the urinary fractionated metanephrines (creatinine corrected), blood fractionated catecholamines, and plasma-free fractionated metanephrines. Pregnancy can increase urinary catecholamine levels, which complicates interpretation [102]. Clonidine testing is not contraindicated but should be used cautiously because of insufficient diagnostic sensitivity and specificity.

2) Imaging diagnosis

Ultrasound is preferred for safety but may miss small tumors. MRI, with a sensitivity similar to CT (90–100%), is beneficial for detecting PGLs and late pregnancy [101, 103]. MRI has been reported to be safe for pregnant women and fetuses [103, 104]; gadolinium contrast agents are not recommended because of safety concerns. CT and ¹²³I-MIBG scintigraphy are generally avoided because of radiation risks. If necessary, reducing radiation exposure and obtaining informed consent are essential [105].

D. Treatment

1) Medical treatment

α -blockers are the first choice for blood pressure control and should be initiated at diagnosis, not just before delivery [100, 103]. β -blockers may be used for tachycardia but are associated with intrauterine growth retardation. Calcium antagonists such as nifedipine and amlodipine can be combined if α -blockers are insufficient. Magnesium sulfate may be useful in cases of preeclampsia or severe hypertension [106]. Metyrosine is not recommended due to the limited safety data. ARBs, ACE-Is, and direct renin inhibitors are contraindicated. In cases of hypertensive crisis, phentolamine is preferred as the first option, and if blood pressure is not reduced sufficiently, intravenous administration of nicardipine should be considered [107].

2) Surgical treatment

Tumor removal is recommended before 24 weeks of gestation, if feasible [98, 103], although recent studies suggest no significant advantage over medical treatment [99, 100]. For diagnoses after 24 weeks, medical management should continue until the fetus is viable, and then consider postoperative tumor removal should be considered.

3) Delivery

In patients who undergo tumor resection before delivery, both cesarean and vaginal delivery are options. For patients who do not undergo resection, a cesarean section is recommended, as vaginal delivery poses a higher risk of catecholamine release due to uterine contractions and fetal descent. However, in cases where catecholamine levels are relatively low, small tumors, or where the tumor is located outside the abdominal or pelvic region, it has been suggested that vaginal delivery may be safe [100]. Careful consideration must be given in advance for each case.

E. Points to note in diagnosis and treatment

Early diagnosis and treatment are essential to minimize maternal and fetal risks. Collaboration with specialists in various fields is crucial. Treatment and diagnostic strategies should be individualized based on the tumor location.

I-10 Diagnosis and treatment of PPGL in children **Statements**

- I-10-1 Blood pressure should be measured in children with headaches, excessive sweating, palpitations, *etc.*, and pheochromocytoma and paraganglioma (PPGL) should be investigated if hypertension is observed (1B).
- I-10-2 Note that no pediatric reference values for endocrinological tests are useful for diagnosing PPGL (2C)
- I-10-3 First treatment choice is tumor removal, as in adults (2C).

Evidence

The standard diagnosis and treatment of PPGL in children have not been established in Japan or internationally [108]. Diagnostic triggers, clinical symptoms, important tests, and treatments differ between children and adults. Adults are often diagnosed with PPGL *via* treatment-resistant hypertension or adrenal incidentaloma, whereas children are usually diagnosed after symptoms such as hypertension, headache, hyperhidrosis, palpitations, reduced growth rate, and attention deficit hyperactivity disorder (ADHD) appear [108]. Active blood pressure measurements in children with these symptoms aid in the diagnosis of PPGL.

A. Diagnosis

Functional endocrine investigations for diagnosing PPGL include urinary metanephrine, catecholamine, and plasma-free fractionated metanephrines. Random urine metanephrine and normetanephrine/creatinine values are recommended for children because of difficulties in urine collection. The blood fractionated catecholamines fluctuate significantly, complicating their interpretation. No pediatric reference values are available for these tests. Early diagnosis of PPGL in asymptomatic children through surveillance is challenging. Imaging tests identified tumors, as suggested by endocrinological tests. Abdominal ultrasonography is simple but less effective in identifying adrenal tumors in children. MRI offers high contrast resolution, whereas CT involves radiation exposure, which should be minimized. ¹²³I-MIBG scintigraphy aids in diagnosing adrenal and extra-adrenal tumors and detecting metastases, although it also involves radiation exposure [40]. Somatostatin receptor PET/CT may better detect primary and metastatic tumors in children than CT/MRI, ¹²³I-MIBG scintigraphy, and ¹⁸F-FDG PET [109, 110].

B. Treatment

Tumor resection is the first choice of treatment for pediatric cases of metastasis, similar to that in adults. Preoperative blood pressure control focuses on α -blockers, although Japan does not specify the pediatric

dose for doxazosin. The choice between laparotomy and endoscopic surgery depends on the size of the child, suspected pathogenic gene variants, and hereditary tumor syndromes. The effectiveness of chemotherapy and internal radiotherapy in pediatric metastases remains unclear [111, 112].

C. Hereditary PPGL

PPGL may be linked to hereditary tumor syndromes such as von Hippel-Lindau disease. Even with pathogenic germline variants, childhood cases may not meet the clinical criteria for hereditary tumor syndromes. Family history and genetic testing are valuable, with a higher proportion of identified germline pathogenic variants in children (70–80%) compared to adults (30–40%) [108].

I-11 Histopathological diagnosis

Statements

- I-11-1 Immunostaining positive for Chromogranin A and negative for cytokeratin in tumor tissue is crucial for confirming the diagnosis (1A).
- I-11-2 The WHO Classification of Endocrine and Neuroendocrine Tumours has defined all pheochromocytomas and paragangliomas (PPGLs) as malignancies because of their metastatic potential since 2017 (A).
- I-11-3 Absence of immunostaining for SDHB indicates *SDHx* gene pathogenic variants, helping predict metastasis and recurrence (2B).
- I-11-4 Although the scoring scale based on a combination of pathological findings is a reference for evaluating the risk of metastasis in PPGL, further validation is needed for its long-term usefulness (2C).

Evidence

A. Key points in the pathological diagnosis of PPGL

Hematoxylin and eosin (HE) staining revealed irregularities in tumor cell size and nuclear and structural atypia in most PPGLs. The tumor tissue is vascular-rich and stroma-poor, making determination of vascular invasion challenging. D2-40 immunostaining for lymphatic invasion and Elastica-Masson (EM) or Elastica van Gieson (EVG) staining for venous invasion are essential. Metastasis was determined by the presence of tumor cells in non-chromaffin tissues. Immunohistochemistry for Chromogranin A (CgA) and cytokeratin (CAM5.2, AE1/AE3) must be used alongside HE staining; negative CgA and positive cytokeratin rule out PPGL. GATA3 is positive for PPGL but may also be positive in breast cancer and bladder urothelial carcinoma metastases [113]. If PPGL has not been diagnosed endocrinologically, staining with tyrosine hydroxylase (TH) or dopamine beta-

hydroxylase (DBH) is mandatory.

B. Pathological diagnosis of hereditary PPGL

SDHA, *B*, *C*, and *D* are critical genes of hereditary PPGL syndrome (HPPS). Germline pathogenic variants in *SDHB* are associated with a high incidence of abdominal PPGL, as well as metastasis and recurrence. *SDHB* immunostaining is negative in tumor tissue for patients with mutations in *SDHA*, *SDHB*, *SDHC*, or *SDHD* [114, 115], making it valuable for HPPS screening. *SDHA* immunostaining detects *SDHA* pathogenic variants [116, 117] but not for *SDHB*, *SDHC*, or *SDHD* variants.

SDHB and *SDHA* immunostaining are defined as “positive” when granular staining appears in the cytoplasm. Negative fumarate hydratase and positive 2-succinocysteine immunostaining are indicative of PPGL in hereditary leiomyomatosis-renal cell carcinoma syndrome. Positive carbonic anhydrase 9 (CAIX) immunostaining can identify PPGL in VHL disease. Positive α -inhibin immunostaining detects cluster 1 PPGL [113].

C. Prognostic markers for metastasis and recurrence

Scoring systems such as the Pheochromocytoma of the Adrenal Gland Scale (PASS), the Grading of Adrenal Pheochromocytoma and Paraganglioma (GAPP), and the Composite Pheochromocytoma/Paraganglioma Prognostic Score (COPPS), based on pathological or clinical findings, are used to predict PPGL metastasis and recurrence. However, further validation is required to confirm their long-term usefulness.

Given the poor prognosis for cases with *SDHB* pathogenic variants, screening for *SDHx* variants using negative *SDHB* immunostaining is essential [113]. A critical evaluation parameter is the Ki-67 positivity rate, an index of tumor proliferation associated with metastasis and recurrence risk in PPGL.

D. TNM Classification to PPGL

Due to its potentially malignant nature, the primary tumor, lymph node and metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC) is used for staging PPGL (See AJCC Cancer Staging Manual, 8th Edition, Springer, 2017). However, head and neck paraganglioma (HNPPGL) is excluded due to its low risk of metastasis.

I-12 Genetic testing and genetic counseling Statements

- I-12-1 Because 20–40% of pheochromocytomas and paragangliomas (PPGLs) are hereditary (carrying germline pathogenic variants in genes related to the onset of the PPGL), it is essential to take a detailed family history and medical history (1B).
- I-12-2 PPGL with *SDHB* pathogenic variants are highly metastatic (35–75%), serving as an indicator of distant metastatic risk (1C).

I-12-3 All PPGL patients should be informed about the high frequency of hereditary PPGL and the significance of, as well as considerations for, genetic testing (1B).

I-12-4 Genetic testing is performed at the patient’s discretion after genetic counseling, and analyses should be performed at a quality-guaranteed facility (1B). However, genetic testing and counseling for PPGL are not covered by health insurance in Japan, except in cases involving medullary thyroid carcinoma.

Evidence

A. Hereditary PPGL and driver genes

PPGLs are endocrine tumors with a high hereditary rate. The proportion of hereditary PPGLs with heterozygous germline pathogenic variants is reported to be 20–40% of all PPGL cases [40, 118, 119]. Comprehensive germline and somatic genetic testing, including analyses of fusion genes and copy number alterations, identified a molecular etiology in 95% of patients with PPGL [118]. Over 20 driver genes associated with PPGL, including those in germline and somatic lineages, have been identified.

Driver genes have recently been stratified into three clusters based on transcriptome analysis results [118, 120]: the pseudohypoxia-related cluster (clusters 1A and 1B), the kinase signal-related cluster (cluster 2), and the Wnt signal cluster (cluster 3). Specific genotype-phenotype correlations exist between each cluster and tumor phenotype, influencing factors such as tumor onset site, catecholamine secretion pattern (adrenergic or noradrenergic), diagnostic ability of imaging modalities, and metastasis risk. Consequently, personalized medicine—including optimal diagnostic methods and follow-ups—has been proposed for each cluster and driver gene [120].

Succinate dehydrogenase (*SDHx*) genes (*SDHA*, *SDHB*, *SDHC*, and *SDHD*), *VHL*, and *RET* are pivotal germline driver genes. The *SDHx* gene group, localized to the inner mitochondrial membrane, encodes succinate dehydrogenase subunit proteins of the TCA cycle. *SDHB* pathogenic variants are frequently associated with thoracic and abdominal PGLs and exhibit a high rate of metastasis (35–75%) [120]. The penetrance of PPGLs among carriers of the *SDHB* pathogenic variant is approximately 22% [121, 122]. Pathogenic *SDHD* variants frequently result in head and neck PGLs, especially carotid bodies, as primary lesions, with a penetrance higher than that of *SDHB* variants; 43% of cases manifest by the age of 60 years [121]. PPGLs follow an autosomal dominant manner; however, due to the genomic imprinting of the maternal allele, PPGLs in individuals

with *SDHD* mutations develop only when the pathogenic variant is inherited from the father. *VHL* is the gene responsible for von Hippel-Lindau disease (VHL disease), a hereditary tumor syndrome. The penetrance of PPGLs associated with VHL disease is approximately 15–20% [120]. VHL disease-associated PPGLs are characterized by early onset (average age at onset: 25.9–27.1 years), frequent bilateral PCC [92, 123], and a noradrenergic biochemical phenotype. *RET* is the gene responsible for multiple endocrine neoplasia type 2 (MEN2). The penetrance of MEN2-associated PCCs is approximately 60% and varies depending on genotype [67, 120, 124].

B. Proportion of hereditary PPGL in Japan

A cohort study of 370 Japanese PPGL probands reported a germline pathogenic variant rate of 32.4% [92]. The most common driver genes identified were *SDHB* (57 patients, 15.4%), *SDHD* (27 patients, 7.3%), and *VHL* (18 patients, 4.9%). A quarter of patients without a family history or genetic syndromic presentation had a germline pathogenic variant. The frequency of metastasis was significantly higher in patients with pathogenic variants than in those without (24.2% vs. 13.4%, respectively). Patients with pathogenic *SDHB* variants showed metastasis (36.8%). The frequency of hereditary PPGL is substantial, with *SDHB* pathogenic variants associated with a high incidence of metastasis in Japan, as reported in Europe and the USA.

C. How to proceed with a genetic diagnosis

1) Candidate patients for genetic testing

The clinical practice guidelines of the US Endocrine Society and the European Society of Endocrinology recommend genetic testing for “all” cases [12, 40]. However, as of April 2025, genetic testing for PPGL is not covered by health insurance in Japan, except for cases involving medullary thyroid cancer. Healthcare providers must ensure all PPGL patients receive accurate information regarding the high frequency of hereditary PPGL, the significance of genetic testing, and key considerations, enabling informed and voluntary decision-making regarding genetic testing.

2) Methods of genetic testing and target genes

The US Endocrine Society guideline recommends an algorithm to search for causative genes stepwise from clinical findings based on cost-effectiveness [40]. The recently developed multigene panel testing (MGPT) using next-generation sequencing (NGS) has significantly improved the detection rate and cost of pathogenic variants [125, 126]. Consensus guidelines have been published for the selection of target genes for MGPT using NGS in PPGL [127]. However, MGPT often results in a high identification rate of “variants of unknown significance (VUS).” Therefore, in cases where a genetic syndrome is evident from family history or

comorbid conditions (e.g., medullary thyroid carcinoma in MEN2, retinal and cerebellar hemangioblastoma in VHL disease, and café-au-lait spots in neurofibromatosis type 1), single-gene testing is recommended, with MGPT as a follow-up if the result is negative. In addition, genetic testing may also serve as an essential surrogate marker for *SDHx* pathogenic variants in cases with negative *SDHB* immunostaining in tumors [128].

Accurate and high-quality testing is essential to ensure results are effectively utilized in the medical management of patients with PPGL. MGPT for the PPGL driver genes can be performed as a non-insurance test at the Public Health Laboratory of the Kazusa DNA Research Institute (contact-based testing in April 2023). However, MGPT cannot fully detect pathogenic variants in the presence of exon deletions or duplications [125]. Additional analysis of copy number variants (CNVs) is required when appropriate.

D. Genetic counseling for hereditary PPGL

Germline genomic information is universal, predictable, and shareable. The “Guideline for Genetic Tests and Diagnosis in Medical Practice” by the Japanese Association of Medical Sciences (2022) recommends genetic counseling at the appropriate time as needed. Since genetic counseling is defined as a process that helps patients understand and adapt to the medical, psychological, and family impacts of the genetic involvement of a disease, it is desirable to provide team medical care in collaboration with doctors with extensive experience in treating the disease and those skilled in genetic counseling. Ongoing counseling should also be offered to patients with pathogenic variants and individuals with concerns about inheritance.

1) Significance in patients with PPGL

The significance of genetic testing in patients with PPGL is as follows:

1. Prediction of metastasis risk based on identified driver genes, with regular follow-up being essential for patients with pathogenic *SDHB* variants.
2. Possible early detection of concomitant diseases other than PPGL if a pathogenic variant is identified in *VHL* and *RET*.
3. Possible improvement of clinical outcomes of the patients by identifying *SDHB* or *VHL* pathogenic variants [129].
4. Possible chances of the relatives, if desired, to presymptomatic genetic testing.

Recent studies have proposed individualized treatments based on driver genes; however, this has yet to be established. Physicians engaged in genetic testing should fully understand this limitation and share it with patients who may undergo genetic analysis.

2) Significance in patients' blood relatives

Genetic testing and counseling have been proposed for family members, especially first-degree relatives, of patients with a pathogenic variant [125, 130].

The significance of genetic testing in patients' blood relatives is as follows:

1. If the pathogenic variant is positive, long-term surveillance leads to the early detection of PPGL, reduced risk of metastasis, and improved prognosis [131].
2. If the pathogenic variant is negative, the anxiety of developing PPGL is relieved, and unnecessary surveillance tests are avoided.

There is insufficient evidence for the effectiveness of surveillance for genes other than *SDHB*. Physicians should consider not only the clinical usefulness of genetic information for blood relatives but also the subject's wishes, family relationships, and the age and sex of the blood relatives before recommending genetic testing. In addition, relatives' genetic and surveillance tests are not covered by health insurance in Japan. Careful and comprehensive decision-making is mandatory before genetic testing is recommended.

I-13 Medical treatment algorithm according to genetic pathogenic variants

Statements

- I-13-1 Early genetic diagnosis after diagnosing pheochromocytoma and paraganglioma (PPGL) enables personalized medicine, optimizing diagnosis, treatment, and follow-up (1C).
- I-13-2 For PPGL with *RET*, *VHL*, or *NFI* pathogenic variants, lesions should be searched for per each syndrome's guidelines (1C).
- I-13-3 A treatment algorithm focusing on clinical characteristics like multiple and extra-adrenal lesions and the risk of metastasis from *SDHx* pathogenic variants can enhance PPGL care (1C).

Evidence

The 2014 Endocrine Society guideline recommends genetic testing in all cases [40]. The 2020 European Society of Hypertension guideline recommends using next-generation sequencing with a gene panel for candidate genes [132]. As the number of genetically diagnosed cases has increased overseas and the benefits of genetic testing have become apparent, management algorithms based on pathogenic variants have been proposed.

A. Clinical impact of genetic testing

A 15-year follow-up at a single institution showed that the referral rate of patients with PPGL to a specialized clinic for genetic testing increased from 26% to 94%, with a 50% positive test rate [133]. Genetic testing has

led to an increased preference for partial adrenalectomy in patients with *RET* or *VHL* variants, which are associated with a low risk [134]. A multicenter study in French institutions compared early (within one year) and late (more than seven years) detection of *SDHB*, *SDHC*, *SDHD*, and *VHL* variants. The early-detection group had smaller recurrent and metastatic tumor diameters and a higher 5-year survival rate after the onset [129].

B. Management algorithm according to genetic pathogenic variants

1) SDHx pathogenic variants

Evidence on the clinical characteristics of *SDHx* pathogenic variants, including *SDHB*, which is associated with a high risk of metastasis, is accumulating. Pathogenic *SDHx* variants may cause multiple extra-adrenal lesions and metastases, so the European Society of Nuclear Medicine guideline recommends imaging with ⁶⁸Ga-DOTATATE, ¹⁸F-FDOPA (not approved in Japan), or ¹⁸F-FDG [135]. Additionally, the effectiveness of peptide receptor radionuclide therapy (PRRT) [136], temozolomide [137], and sunitinib [138] (none covered by insurance in Japan) has been reported for metastatic lesions associated with *SDHx* pathogenic variants.

The consensus on screening for asymptomatic *SDHx* pathogenic variant carriers is that screening should be performed at age 6–10 years for *SDHB* pathogenic variants and at age 10–15 years for *SDHA*, *SDHC*, and *SDHD* pathogenic variants [130]. Monitoring clinical findings such as blood pressure, headache, palpitations, blood or urine fractionated metanephrines measurements, and MRI of the head, neck, chest, abdomen, and pelvis are recommended. Even if the initial screening is negative, annual clinical evaluation, fractionated metanephrines evaluation every two years, and MRI every 2–3 years are recommended [130].

Pathogenic variants of *SDHD* are characterized by a high incidence of nonfunctional head and neck paraganglioma (HNPGL), a low risk of metastasis (5%), and inheritance from the paternal side through imprinting. Considering these characteristics, a guideline focusing on the pathogenic variants of *SDHD* has been published [139]. As dopamine production is observed in 30% of cases, the diagnostic utility of blood 3-methoxytyramine (3-MT) (not covered by health insurance in Japan), a metabolic product, has been reported [140]. Given the high surgical risk associated with HNPGL, observation is considered for asymptomatic nonfunctional cases. In contrast, surgery is considered in cases with rapid tumor growth, head and neck compression symptoms, pain, cranial nerve symptoms, and catecholamine production.

A consensus statement has been published regarding the diagnosis and treatment of pathogenic *SDHB* variants [141]. Complete resection (R0) is recommended in cases

where surgery is possible, and laparotomy is recommended for large tumors of 6 cm or more. For postoperative follow-up in patients with elevated catecholamine levels, blood or urinary fractionated metanephrines, and blood 3-MT (not covered by insurance in Japan), testing is recommended within eight weeks post-surgery and annually thereafter. For imaging examinations, evaluation using CT or MRI is recommended within six months of surgery. Even if the 6-month follow-up is negative, it was suggested to continue searching for recurrent or metastatic lesions from the skull base to the pelvis using MRI at 1–2-year intervals. In metastatic PPGL with *SDHB* pathogenic variants, surgical treatment aimed at complete resection is prioritized; if symptomatic, debulking surgery is considered, even if complete resection is not possible. In cases of residual disease or complicated surgery, treatment options are selected individually: observation, radionuclide therapy (PRRT, ¹³¹I-MIBG), drug therapy (temozolomide, sunitinib, none of which are covered by insurance in Japan), or CVD chemotherapy, based on the patient's overall condition, tumor growth rate, tumor volume, and symptom status.

2) PPGL included in syndromes with other organ lesions (*RET*, *VHL*, *NFI* gene pathogenic variants)

Some germline pathogenic variants cause PPGLs to develop as a part of a syndrome that involves lesions in other organs. *RET* is the causative gene for multiple endocrine neoplasia type 2 (MEN2), *VHL* for Von Hippel-Lindau disease, and *NFI* for neurofibromatosis type 1. Lesions should be screened for, and specialist consultation should be performed according to the guidelines for each syndrome [142–144]. PPGL caused by pathogenic variants in these genes primarily manifest as adrenal gland involvement. Notably, pathogenic variants in the *RET* and *VHL* are characterized by a low risk of metastasis.

I-14 Prognosis and lifelong surveillance Statements

- I-14-1 Metastasis occurs in 10–15% of pheochromocytomas (PCCs) and 35–70% of paragangliomas (PGLs), with abdominal PGL particularly prone to metastasis. The median survival time for all patients with metastatic pheochromocytoma and paraganglioma (PPGL) is 7–22 years (C).
- I-14-2 Lifelong follow-up after surgery is recommended for hereditary PPGL. Sporadic PPGL cases with noradrenaline dominance, primary tumor diameter ≥ 5 cm, and PGLs outside the head and neck are at high risk of recurrence, long-term follow-up of 10 years or more (1C).

Evidence

A. Prognosis

Large-scale cohort studies report metastasis in 10–15% of PCCs and 35–70% of PGLs. The median survival time of patients with metastatic PPGL is 7–22 years. A meta-analysis indicated a 37% 5-year mortality rate and a 29% 10-year mortality rate for metastatic PPGL. The overall mortality rates were 46% and 53% for metastatic PGL and PCC, respectively. The overall mortality rate of head and neck PGL is 34–56% [120].

B. Postoperative follow-up

PPGLs are associated with recurrence (mostly distant metastasis) in 15–20% of cases, even after resection of the primary tumor [145, 146]. Some cases recur decades after surgery; therefore, long-term follow-up is necessary. The Endocrine Hypertension Working Group Position Statement/Consensus of the European Society of Hypertension [132] recommends measuring plasma-free fractionated metanephrines, 3-methoxytyramine (3-MT) (not covered by health insurance in Japan), and chromogranin A (not covered by health insurance in Japan) 2–6 weeks after surgery, explain to patients the possibility of future metastasis and the importance of follow-up, even if they normalize, and recommends annual follow-up for ten years. Lifelong follow-up is recommended for patients of young age with PGL, positive genetic pathogenic variants, and/or tumors 5 cm or larger in diameter.

In non-catecholamine-producing tumors, a blood test is performed 2–6 weeks after surgery to confirm that the patient is still not producing excess catecholamines, and the possibility of future metastasis, as well as the importance of follow-up observation, are explained to the patient. CT and MRI are performed periodically for ten years. However, no policy has been established for sporadic PCCs with tumors smaller than 5 cm in diameter that have not shown any recurrence for ten years.

A multicenter study demonstrated that the recurrence rate of sporadic PPGL was 14.7%, significantly lower than that of hereditary PPGL cluster 1 (47.5%) but similar to the 14.9% recurrence rate in hereditary PPGL cluster 2. Recurrence was diagnosed in 29.1% of cases 10 years after the initial diagnosis and in 17.7% of cases 15 years after the initial diagnosis. Predictive factors for recurrence included noradrenaline dominance, primary tumor diameter (≥ 5 cm), and extra-adrenal location [147].

Based on the 2018 guideline, the postoperative follow-up algorithm shown in Fig. 6 is recommended, considering the recommendations of the European Society of Hypertension and Japan's health insurance system. In cases of preoperative catecholamine overproduction, blood pressure and biochemical tests were performed

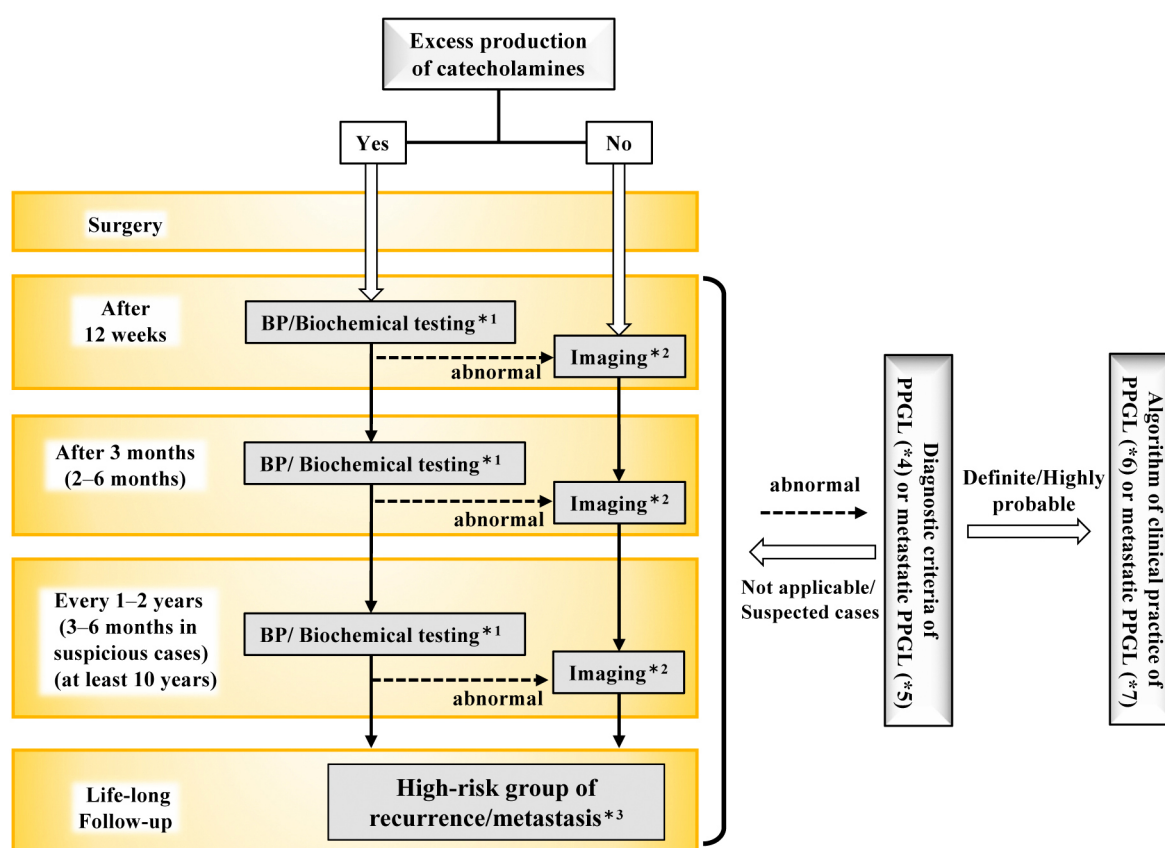


Fig. 6 Postoperative life-long survey algorithm of PPGL

*1 Measure random urine fractionated metanephrines/creatinine correction, plasma fractionated catecholamines, and/or plasma-free fractionated metanephrines (note that as of June 2025, there are restrictions on the number of times plasma-free fractionated metanephrines can be measured in Japan).

*2 ^{123}I -MIBG scintigraphy/CT/MRI/ ^{18}F -FDG PET will be performed as appropriate, depending on the functional conditions of the tumor.

*3 Young age, tumor diameter >5 cm, PGL, noradrenaline dominance, positive pathogenic gene variants, *etc.*

*4 Refer to Table 6.

*5 Refer to Table 7.

*6 Refer to Fig. 7.

*7 Refer to Fig. 8.

Abbreviations: BP, blood pressure; PPGL, pheochromocytoma and paraganglioma.

regularly, and imaging tests were performed if biochemical abnormalities were detected. Imaging tests are routinely performed in cases involving preoperative non-catecholamine production. In all cases, a minimum follow-up period of 10 years is recommended. Lifelong follow-up is recommended in cases with a high risk of recurrence or metastasis (young age, tumor diameter ≥ 5 cm or more, PGL, noradrenaline dominance, positive genetic pathogenic variants, *etc.*).

Chapter II: Metastatic Pheochromocytoma and Paraganglioma

II-1 Methods for assessing metastasis risk Statements

II-1-1 Pheochromocytomas and paragangliomas (PPGLs) are classified as malignant in the WHO classification; metastasis risk should be assessed at the initial diagnosis and during the disease (1B).

II-1-2 Metastasis is diagnosed if lesions are found in non-chromaffin tissues (B).

II-1-3 Factors useful for assessing metastasis risk include age at diagnosis, tumor size, catecholamine secretion pattern, timing of metastatic lesion diagnosis, tumor localization, disease type,

histopathological findings, *SDHB* gene pathogenic variants, and *SDHB* immunohistochemistry (1C).

Evidence

PPGLs are classified as potentially malignant according to the 2022 WHO classification of endocrine tumors [113] and require careful long-term follow-up [40]. Metastasis is diagnosed when lesions are found in non-chromaffin tissues (bone, lungs, liver, and lymph nodes). Differential diagnosis is difficult when PGLs first appear in solid organs, such as the lungs or liver [113]. Careful decision-making is necessary for PGLs with pathogenic genetic variants to distinguish metastatic lesions from multiple (synchronous or metachronous) lesions [113].

A. Clinical Findings and Staging

Factors associated with metastasis risk in PPGLs include young age, tumor size (≥ 4 –7 cm), and PGL [148–150]. Although metastatic PPGL (excluding head and neck paraganglioma [HNPPGL]) often presents with high levels of plasma normetanephrine and 3-methoxytyramine (3-MT) (not covered by health insurance in Japan) [151], metastasis is more prevalent in non-catecholamine-producing PPGLs [23]. In contrast, the post-surgery metastasis rates for sporadic PCC and HNPPGL are 3% [152] and 3.2% [153], respectively, indicating that PPGL is less linked to metastasis.

Independent prognostic factors for metastatic PPGL (excluding HNPPGL) include older age, larger tumor size, presence of metastases at initial diagnosis, multiple metastases, high levels of chromogranin A (not covered by health insurance in Japan), plasma fractionated metanephrines (≥ 5 times the upper limit), and elevated plasma 3-MT [78, 151, 153]. In HNPPGL, only high blood levels of 3-MT are correlated with disease-specific survival rates, which are higher than those of other metastatic PPGLs [151]. It should be noted that metastasis is not the sole factor determining poor prognosis, as not all metastatic cases have a poor prognosis, indicating the involvement of varying risk factors.

Nonchromaffin tissue lesions (liver, bone, lung, and lymph nodes) observed on MRI, CT, and ^{123}I -MIBG scintigraphy indicate metastasis. However, distinguishing between PGLs around the aorta is challenging. The US Endocrine Society guideline recommends ^{18}F -FDG PET for detecting metastatic PPGL, especially in cases with *SDHB* gene variants (sensitivity 74–100%) [40]. Recent studies have shown that ^{68}Ga -DOTATATE is more effective in localizing metastatic PPGL than ^{18}F -FDG PET, although it is not covered by health insurance in Japan [154].

The TNM classification of PPGL was introduced in the 8th edition of the AJCC Cancer Staging Manual (AJCC TNM classification) [155]. Due to its low risk of

metastasis, HNPPGL was not included in the classification.

B. Histopathological markers

Capsular and vascular invasions, which are pathologically significant, are not reliable predictors of metastasis in patients with PPGL. The PASS and the GAPP scores have been proposed for evaluating malignant behavior. A recent report found a weak correlation between the PASS scores and metastasis, whereas high GAPP scores were significantly correlated with metastasis [156]. The PASS scores also showed low inter-observer agreement [157]. However, the long-term usefulness of these scores requires further validation.

C. Genetic markers

Genetic variants related to the TCA cycle, such as *SDHx* and fumarate hydratase (*FH*), are associated with metastasis [158–160]. Cases positive for *SDHB* gene variants have a high metastasis rate (35–75%), with a meta-analysis showing a hazard ratio of 5.68 (95% CI 1.79–18.06, $p = 0.003$) [158]. The COPPS, which incorporates *SDHB* immunostaining, has been proposed to predict metastasis risk by focusing on tumor size, necrosis, vascular invasion, and negative S100 and *SDHB* immunostaining results. A COPPS score of 3 or more indicates a high risk of metastasis [148].

D. Efforts to Develop New Biomarkers

Molecular biological analysis is advancing with attempts to establish new biomarkers. miR-21-3p, a miRNA expressed explicitly in metastatic PPGL, may be a biomarker for treatment with mTOR inhibitors because of its role in activating the mTOR pathway [161]. Additionally, succinic acid accumulation in PPGL tissues, measured by liquid chromatography-mass spectrometry (LC-MS), can indicate the presence of *SDHx* gene variants [162]. Both approaches are in the research stage and require prospective studies for practical application.

II-2 Chemotherapy

Statements

- II-2-1 CVD chemotherapy, along with radionuclide therapy, is a standard systemic treatment covered by health insurance in Japan (A).
- II-2-2 CVD chemotherapy is expected to reduce tumor volume and catecholamines and may extend progression-free survival. However, there is no evidence of improvement in overall prognosis (B).
- II-2-3 In unresectable pheochromocytomas and paragangliomas (PPGLs), CVD chemotherapy is the first choice of systemic treatment when the disease progresses rapidly or when radionuclide therapy is not applicable (2C).
- II-2-4 In patients with positive nuclear imaging (^{123}I -

MIBG scintigraphy, somatostatin receptor scintigraphy), CVD chemotherapy and radionuclide therapy should be selected based on the rate of disease progression and feasibility (2C).

Evidence

A. Indications

In patients with surgically unresectable PPGL, combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD chemotherapy), along with radionuclide therapy, are systemic treatments covered by health insurance in Japan. CVD chemotherapy is the first choice when nuclear imaging (^{123}I -MIBG scintigraphy and somatostatin receptor scintigraphy) is negative, and the disease progression is rapid [120]. Patients should have an excellent overall condition, with no severe leukopenia, thrombocytopenia, or renal or liver dysfunction. However, when nuclear imaging is positive, there is no clear evidence regarding which CVD or radionuclide therapy should be the first choice. Decisions should consider each patient's specific situation and available medical resources. However, the efficacy and side effects of combining CVD chemotherapy with other antitumor drugs or ^{131}I -MIBG therapy remain unclear [163–167].

B. Methods

CVD chemotherapy involves administering cyclophosphamide ($750 \text{ mg/m}^2 \text{ BSA}$) on day 1, vincristine ($1.4 \text{ mg/m}^2 \text{ BSA}$) on day 1, and dacarbazine ($600 \text{ mg/m}^2 \text{ BSA}$) on days 1 and 2. This cycle was repeated every 21 days. Cyclophosphamide and dacarbazine doses increase by 10% each time until bone marrow suppression occurs. If blood findings or neurological side effects appear, the interval should be extended by one week, or the dose should be reduced [168]. The package insert of vincristine in Japan advises that the dose should not exceed 2 mg per administration to avoid side effects.

C. Efficacy

The effectiveness of CVD chemotherapy has been reported, including tumor reduction or elimination, decreased catecholamine levels, and improvement in hypertension. The first report by Averbuch *et al.* [168] demonstrated a complete tumor volume response in two cases and a partial response (PR) in six cases. Biochemical responses were complete in three cases and partial in eight—one patient discontinued treatment after four sessions owing to tumor growth and increased hormone levels during chemotherapy. Complete or partial tumor responses were observed in 57% of the patients, and complete or partial hormonal responses were observed in 79%.

A meta-analysis [169] of four cohort studies with 50

patients found a complete tumor response in 4%, a PR in 37%, and an unchanged response in 14% of patients. Among the 35 patients from the two cohort studies, biochemical responses were complete in 14%, partial in 40%, and unchanged in 20%, with a mean progression-free survival (PFS) of responders of 20 months [170] and 40 months [171]. Another study of 23 patients reported a 26% tumor volume response rate, 30% biochemical response rate, and a PFS of approximately eight years for responders, which was significantly longer than that for non-responders [172]. A small retrospective study [173] found that patients with *SDHB* variants had a longer PFS than those without variants.

Few studies have compared the long-term prognoses of patients who underwent CVD chemotherapy with those of patients who did not [170, 174–177]. There is no evidence that CVD chemotherapy contributes to improved survival rates.

D. Adverse effects

Most side effects are mild to moderate; however, hypertensive crises due to tumor lysis pose a severe risk. The side effects vary among patients; therefore, careful monitoring is crucial. However, chronic side effects of long-term drug administration remain unclear. Significant side effects are as follows: 1) fever, vascular pain, nausea, and vomiting; 2) bone marrow suppression; 3) liver dysfunction and peripheral neuropathy; 4) alopecia; and 5) hypertensive crisis [169].

II-3 Radionuclide therapy

Statements

- II-3-1 ^{131}I -MIBG and ^{177}Lu -DOTATATE internal radiation therapies are covered by health insurance for pheochromocytomas and paragangliomas (PPGLs) in Japan (A).
- II-3-2 ^{131}I -MIBG therapy is indicated for PPGLs with positive ^{123}I -MIBG scintigraphy and effectively decreases excess catecholamines (1B).
- II-3-3 ^{177}Lu -DOTATATE internal radiation therapy is indicated for PPGLs with positive somatostatin receptor scintigraphy (1B).

Evidence

A. ^{131}I -MIBG radiotherapy

It was approved in 2021 for unresectable PPGL with positive ^{123}I -MIBG scintigraphy results. Patients must be independent of their daily activities to ensure radiation protection for medical professionals. Due to the high doses and it emits a large amount of gamma rays in addition to beta rays, treatment must be performed in a radiation therapy room, with patients typically staying for 4–5 days. Adults receive 5.55–7.4 GBq intravenously over one hour. A total of 130 mg/day of potassium iodine was

administered 1–3 days before to seven days after treatment to prevent the thyroid accumulation of free ^{131}I .

1) Efficacy

A meta-analysis of 17 retrospective studies (243 cases) reported tumor volume response rates of 3% complete response (CR), 27% partial response (PR), and 52% stable disease (SD). The catecholamine response rate was 51%, and 21% remained unchanged [178]. In a Japanese phase I clinical trial (20 cases), Response Evaluation Criteria in Solid Tumors (RECIST) evaluation showed a CR of 10%, PR of 0%, and SD of 65%; scintigraphy evaluation showed a CR of 10%, PR of 25%, and SD of 40% [179].

In phase II clinical trial (17 cases), RECIST evaluation showed CR 0%, PR 6%, and SD 71%; scintigraphy evaluation showed CR 0%, PR 29%, and SD 47%; and the urinary catecholamine response rates were CR 0%, PR 24%, and SD 47%, similar to overseas results [180]. Multiple administrations of doses covered by insurance in Japan (up to 7.4 GBq) are thought to increase response rates [181]. The effectiveness of high-specific-radioactivity ^{131}I -MIBG preparations reported overseas cannot be directly compared with the low-specific-radioactivity preparations used in Japan.

2) Adverse Events

Nausea and vomiting occur in approximately 20% of patients soon after administration of antiemetics (5-HT₃ receptor antagonists) [182]. Hypothyroidism is considered a late non-hematological effect [182]. The side effects observed at high doses, such as hypertension and organizing pneumonia, are rare in Japan. Hematologic toxicity (grade 2 or lower) occurs in 10–20% of patients. A phase II clinical trial reported 81% lymphopenia (31% grade 3 or higher), 25% neutropenia, and 63% thrombocytopenia without grade 3 or higher cases. Hypertension was observed in 13% of the patients (6.3%, grade 3 or higher). [180].

B. ^{177}Lu -DOTATATE internal radiotherapy

It was approved for use in somatostatin receptor-positive neuroendocrine neoplasms by 2021. Lesion accumulation was confirmed by somatostatin receptor scintigraphy. In a 2022 notification by the Ministry of Health, Labour and Welfare, “PPGL” was listed for this drug [183]. It should be noted that insurance coverage approval varies by prefecture and case as of 2025. Due to the lack of large-scale clinical studies, the evidence for its effectiveness is not robust.

Although typically performed in a radionuclide therapy room, it can also be done in a general hospital room with appropriate protection and anti-contamination measures as described in academic society manuals [184].

Adults receive 7.4 GBq intravenously over 30 minutes, up to four times at 8-week intervals, with dosage

adjustments based on patient condition. An infusion of L-lysine hydrochloride and L-arginine hydrochloride (25 g each per 1,000 mL) is administered 30 minutes before treatment to reduce renal exposure.

1) Efficacy

A systematic review showed that ^{68}Ga -DOTA-SST (not approved in Japan) has a 93% lesion detection rate, which is significantly higher than the 38% achieved by $^{123/131}\text{I}$ -MIBG [185]. A meta-analysis of 12 papers [186] included patients who received 7–8 GBq of ^{177}Lu -DOTATATE every 2–3 months and patients with 3.7 GBq/m² of ^{90}Y -DOTATOC or 1.5–5.7 GBq of ^{90}Y -DOTATATE every 3–6 months. For the 201 patients with inoperable and metastatic disease, the response rate was 25% (95% CI: 19–32%), and the disease control rate was 84% (95% CI: 77–89%). Clinical and biological responses were 61% and 64%, respectively. No differences in antitumor effects were observed between the formulations. For comparison, a Japanese phase I/II clinical trial showed a 47% response rate for neuroendocrine tumors (excluding PPGL).

2) Adverse Events

A meta-analysis reported grade 3–4 neutropenia, thrombocytopenia, lymphopenia, and nephrotoxicity in 3%, 9%, 11%, and 4% of patients, respectively [186].

3) Procedures Required for Implementation

Given the high doses of radioactive pharmaceuticals used in radionuclide therapy, a thorough discussion within the hospital is necessary to determine their feasibility. Effective management of radiation exposure among medical staff, patient families, and the public is critical. A single department should not make decisions to administer these treatments. It is essential to establish an implementation system based on the consensus of relevant medical departments, including radiology/nuclear medicine and medical administration.

II-4 External beam radiation therapy

Statements

II-4-1 Stereotactic radiotherapy effectively controls local head and neck paraganglioma (HNPG) (1A).

II-4-2 Postoperative radiotherapy controls local tumors in incompletely resectable spinal paraganglioma (PGL) with local invasion (2B).

II-4-3 External beam radiation therapy may be effective for local control of pheochromocytoma (PCC) and PGL outside the head and neck (2C).

II-4-4 External beam radiation therapy has a low incidence of complications and is well-tolerated (1A).

Evidence

Due to its proximity to critical structures, surgical

treatment is complex, making external beam radiation therapy a viable option for HNPGLs [96]. Accordingly, most reports of external beam radiation therapy for PPGL have focused on HNPGLs. Although limited to PPGLs other than HNPGLs, retrospective cohort studies, case reports, and clinical experience have demonstrated the effects of external beam radiation therapy for the local control of bone and soft tissue metastases.

A. Efficacy

A systematic review of 37 articles included 1,144 cases treated with stereotactic radiotherapy, including jugular vein PGL (993 cases, 86.9%), tympanicum PGL (94 cases, 8.2%), carotid body tumors (28 cases, 2.4%), and vagus nerve PGL (16 cases, 1.4%). The median follow-up period was 44 months, with a local control rate of 94.2%. A median dose of 15 Gy (12–30 Gy) was required for over 90% of local control [96]. One report involving 81 patients across 13 facilities showed local control in 69 of 77 lesions. Among 20 patients treated with stereotactic radiotherapy, no PGL progression or side effects were noted in [187].

One systematic review of spinal PGLs included 143 studies involving 334 patients. Postoperative adjuvant radiation therapy was administered to 39 patients with nerve root invasion to achieve long-term tumor control without complications [188]. A retrospective cohort study (41 cases, 107 tumors) at the Mayo Clinic included 20 patients (30 lesions) treated with curative intent and 21 patients (77 lesions) treated with palliative intent. Treatments were indicated for local tumor control (66%), pain relief (22%), and spinal cord compression relief (12%). The sites treated were bone (69%), soft tissue (30%), and liver (1%). The median radiation dose was 40 Gy, with a median follow-up of 3.8 years. Five-year overall survival was 65% (79% for curative and 50% for palliative). All 11 lesions treated with stereotactic radiotherapy were controlled locally at a median of 3.0 years, with symptomatic improvement in 94% of cases [189].

B. Adverse events

A systematic review by Fatima *et al.* [96] reported side effects in 9.7% of gamma knives, 5.5% of linacs, and 4.3% of Cyberknife cases. Lassen-Ramshad *et al.* [187] noted late-onset side effects in 17 of 81 patients receiving conventional treatment; however, none received stereotactic radiotherapy. Palmisciano *et al.* [188] reported no complications in 39 patients who received adjuvant therapy for unresectable nerve root-involving tumors.

Breen *et al.* [189] reported grade 3 or higher side effects in 2 of 41 patients (premature menopause and sciatic nerve damage in a patient with pelvic metastasis) during the non-acute phase. No acute-phase side effects, such as hypertensive crisis, were observed.

II-5 Treatment of bone metastases

Statements

II-5-1 Metastatic pheochromocytoma and paraganglioma (PPGL) often metastasize to bone and cause skeletal-related events (SREs) such as pain, spinal cord compression, hypercalcemia, and pathological fractures, reducing patients' quality of life (B).

II-5-2 External radiation therapy and surgical treatments, similar to those used for other solid cancers, are recommended for bone metastases. Prompt diagnosis and treatment are necessary when symptoms of spinal cord compression are present (2C).

II-5-3 Bone-modifying agents (BMA) are an option for SRE prevention (2C).

Evidence

A. Frequency of Bone Metastasis

The bone is a common site of metastasis in many cancers, including PPGL. In a multicenter study, the bone metastasis rate was 71% (135/190) in PPGL and 73.7% (14/19) in head and neck paraganglioma (HNPGL), which was higher than that in the lungs, liver, and lymph nodes [151]. A survey by the Japan Research Group on Intractable Diseases found that the bone was the most common site of metastasis, accounting for 65% (55/77) of cases, with 90% being osteolytic lesions [190].

B. Mechanism of Bone Metastasis

Bone metastasis occurs when cancer cells proliferate in the bone marrow, with osteoclast-mediated bone resorption playing a crucial role in this process. Cancer cells secrete receptor activator of nuclear factor kappa-B ligand (RANKL) and other cytokines, stimulating osteoclasts and creating a vicious cycle between cancer cells and the bone [191, 192].

C. Skeletal-Related Events (SREs)

Bone metastasis can cause SREs, such as pain, pathological fractures, spinal cord compression, and hypercalcemia, decreasing patient quality of life (QOL) and worsening prognosis. The survival time for metastatic PPGL is approximately 12 years for bone-only metastasis, 7.5 years for non-bone metastasis, and five years for combined metastasis [193].

D. Treatment

1) Standard Treatment

Interdisciplinary and multidisciplinary treatments are essential. For bone metastasis in metastatic PPGL, the same approach used for other solid cancers should be followed. The Japanese bone metastasis treatment guideline recommends local therapy (surgery, radiation, and interventional radiology) and drug therapy (chemotherapy, BMA, and radionuclide therapy) [192]. Emergency

response is required for spinal cord compression and severe hypercalcemia. Imaging tests and appropriate treatments should be administered promptly.

2) Drug Therapy

BMAs such as zoledronic acid and denosumab inhibit bone resorption and are used to treat bone metastases in solid cancers. Regular BMA administration is recommended for bone metastases of lung, breast, and prostate cancers and can be used for metastatic PPGL, although evidence on administration timing and efficacy is limited. Side effects include medication-related osteonecrosis of the jaw, renal dysfunction, bone pain, acute-phase reactions, and atypical femoral fractures. Proper oral hygiene and dental care are recommended to reduce risks [192, 194].

II-6 Pain treatment

Statements

- II-6-1 Appropriate pain management is crucial for improving patient QOL (1B).
- II-6-2 Multidisciplinary treatment should be coordinated with related medical sections such as the palliative care unit (2C).
- II-6-3 Medications with a risk of inducing hypertensive crisis should be avoided (2C).

Evidence

A. Purpose of treatment

Metastatic PPGL often metastasizes to the bones, causing pain, spinal cord compression, and pathological fractures, leading to a reduced quality of life and a worse prognosis. Effective pain management is essential because of the prolonged disease course. The “WHO Cancer Pain Management Method” is a standard approach that significantly alleviates pain in patients with cancer. This method was updated in 2018 according to the “WHO Health Organization guideline for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents,” incorporating evidence-based practices. Japan’s “Guideline for Drug Therapy of Cancer Pain” [195] also references these guidelines. These guidelines are beneficial for treating metastatic PPGL pain with specific precautions.

B. How to use analgesics

Opioid therapy often requires measures to manage side effects, such as nausea, vomiting, and constipation. Common antiemetics include metoclopramide, domperidone, antihistamines, haloperidol, prochlorperazine, and olanzapine. Metoclopramide is contraindicated for PPGL due to the risk of hypertensive crisis, and domperidone should be used with caution. Therefore, prochlorperazine and chlorpromazine should be administered cautiously.

C. How to use adjuvant analgesics

Various adjuvant analgesics are used to treat opioid-resistant pain, including neuropathic pain. These drugs do not primarily serve as analgesics but enhance the effect of analgesics under specific circumstances. Adjuvant analgesics include anticonvulsants, antidepressants, antiarrhythmics, N-methyl-D-aspartate (NMDA) receptor antagonists (*e.g.*, ketamine), corticosteroids, and bone-modifying agents (*e.g.*, zoledronic acid and denosumab). Tricyclic antidepressants require caution due to the risk of hypertensive crises. Corticosteroids are effective against pain caused by nerve compression, inflammation, increased intracranial pressure, and bone metastasis. However, they can induce hypertensive crises and should, therefore, be used with caution. Use the minimum effective dose, gradually reduce the dose, and discontinue if ineffective. Long-term use requires measures to manage side effects, such as hyperglycemia, gastric ulcers, and increased infection risk.

II-7 Management of gastrointestinal symptoms in PPGL

Statements

- II-7-1 Excess catecholamines cause constipation, paralytic ileus, megacolon, intestinal pseudo-obstruction, and intestinal perforation (C). Managing bowel movements from the mild stage is essential (2C).
- II-7-2 Intravenous infusion of phentolamine and oral metyrosine effectively improves intestinal peristalsis (1C).

Evidence

A. Frequency

Constipation occurs in approximately 5–13% of patients with PPGLs [196–198]. This symptom is prevalent in cases where noradrenaline is predominantly produced or where headaches, palpitations, sweating, and weight loss are present [199]. Severe cases may lead to paralytic ileus, megacolon [198], intestinal pseudo-obstruction [196, 200], and intestinal perforation [201]. These symptoms can aid in early diagnosis of PPGL.

B. Mechanism

Excess catecholamines stimulate α_2 and β_2 receptors in gastrointestinal smooth muscle, causing intestinal relaxation and decreased peristalsis. Due to stimulation of α_1 and α_2 receptors in the mesenteric arterial vascular smooth muscle, intestinal ischemia may also be involved [196, 201].

C. Treatment

Severe constipation may require more stimulants or osmotic laxatives than normal constipation. Blocking α_2 receptors is necessary to improve intestinal peristalsis.

Selective α_1 receptor blockers (e.g., doxazosin) are ineffective, whereas nonselective α receptor blockers (phentolamine, phenoxybenzamine) are effective [200, 202]. As phenoxybenzamine is unavailable in Japan, only phentolamine-injectable formulations can be used. The dosage varies, and there is no established protocol. During the administration of phentolamine, hypotension and gastrointestinal symptoms, such as abdominal pain and nausea, should be monitored. Metyrosine, a catecholamine synthesis inhibitor, is effective for severe constipation by inhibiting catecholamine synthesis [54, 203].

Chapter III: Perspectives

These guidelines have been significantly revised to incorporate progress since the 2018 guideline for treating PPGL [1]. Despite these advancements, the rarity of PPGL has resulted in limited evidence, leaving many diagnostic and treatment challenges unresolved.

A. Issues in diagnosis

1. Functional diagnosis: Plasma-free fractionated metanephrines, which are now covered by health insurance in Japan, are recommended overseas because of their superior sensitivity and specificity for blood fractionated catecholamines. However, strict regulations on blood collection conditions (time, meals, body position, and drug effects) and different methods (ELISA in Japan and mass spectrometry abroad) require further evidence to make it the first choice among conventional methods for the functional diagnosis of catecholamine overproduction.

2. Imaging diagnosis: Advanced imaging techniques, such as ^{68}Ga -DOTATE/PET, a somatostatin receptor imaging agent for neuroendocrine tumors, combined with CT, MRI, and PET, have improved the detection of PPGLs with catecholamine overproduction and metastases. However, future challenges include overcoming false positives and false negatives and ensuring efficient coordination among facilities that can perform testing.

3. Prediction of metastasis: While all PPGLs are potentially metastatic, only 10–20% show distant metastasis. Predicting the probability of metastasis at initial diagnosis is crucial and involves patient age, tumor size, catecholamine type, ^{18}F -FDG PET findings, histopathological findings, and *SDHB* gene variants. Considering these diverse factors, AI-based comprehensive judgment and establishing an algorithm based on it could be promising solutions for future development.

4. Genetic testing and response: About 20–40% of PPGL patients have pathogenic gene variants [130, 141, 204]. Educating patients and integrating genetic testing into medical practice can aid diagnosis, early detection,

family risk evaluation, prognosis prediction, and treatment selection. However, genetic testing is not covered by health insurance in Japan. It is necessary to establish a system for genetic counseling, highly accurate testing, feedback of results to actual medical practice, and effective long-term use of these results.

B. Issues in treatment

Although laparoscopic tumor resection is currently the first choice of treatment for PPGL, widespread applications of minimally invasive surgery, robot-assisted surgery, and partial adrenalectomy are expected. There is no established effective treatment for metastatic PPGL, which necessitates multidisciplinary approaches. In recent years, PPGL have been classified pathologically as a neuroendocrine tumor, making ^{177}Lu -DOTATATE internal radiation therapy applicable to PPGL.

Establishing evidence for the effectiveness of 1) combination therapy of CVD chemotherapy with other drugs, 2) immune checkpoint inhibitors, and 3) molecularly targeted drugs, the efficacy of which has been reported in RCTs using sunitinib, is expected. In clinical trials of rare diseases such as PPGL, disease registries such as the ACPA-J of the National Center for Global Health and Medicine Hospital in Japan are helpful research infrastructures. Developing individualized treatment algorithms based on genetic and molecular profiles is essential [205–208].

In addition to these issues in diagnosis and treatment, future efforts should focus on 1) understanding and preventing treatment-resistant PPGL, 2) establishing support systems for QOL and psychological aspects of patients with metastatic PPGL, 3) developing long-term monitoring and follow-up systems, and 4) a comprehensive overview of ongoing and planned clinical trials.

Chapter IV: Conclusions

Figs. 7, 8 illustrate the new algorithms for clinical practice in PPGL and metastatic PPGL, respectively. These algorithms were developed to incorporate all statements from each clinical step based on studies published in peer-reviewed journals providing updated evidence. Significant effort was made to maintain objectivity in the consensus process and recommendations, adhering to the Minds Manual for Guideline Development 2020. In clinical practice, the PPGL algorithm includes conditions required for PPGL screening, endocrine tests for screening and confirmation, imaging, clinical diagnosis, and treatments. Metastatic risks and follow-up algorithms (Fig. 6) should be assessed if no apparent metastatic lesions are detected. If metastatic or locally invasive lesions are apparent, the metastatic PPGL algorithm

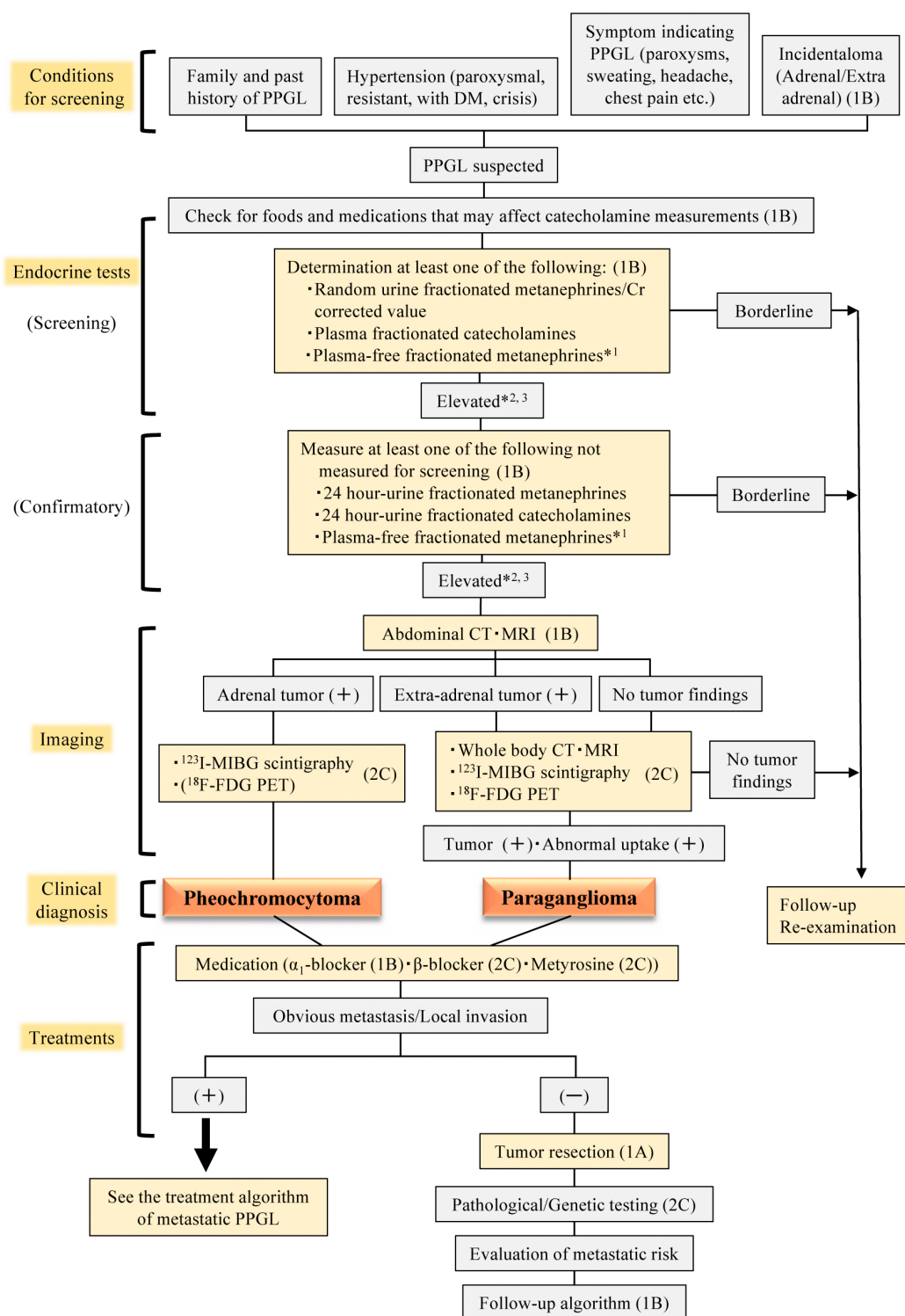


Fig. 7 Clinical practice algorithm for pheochromocytoma and paraganglioma in Japan

*1 Plasma-free fractionated metanephrines can be determined only once when performing a differential diagnosis of PPGLs under Japanese health insurance.

*2 The following are determined when those levels are three times higher than the upper limit of the reference range: random urine fractionated metanephrines/creatinine correction value, blood fractionated catecholamines, 24-hour urine fractionated metanephrines, and 24-hour urine fractionated catecholamines (PPGLs cannot be ruled out even if those values are below the set values).

*3 The following is determined when the levels are greater than the upper limit of the reference range:

Plasma-free fractionated metanephrins (PPGLs cannot be ruled out even if those values are below the set values).

Abbreviation: DM, diabetes mellitus; Cr, creatinine

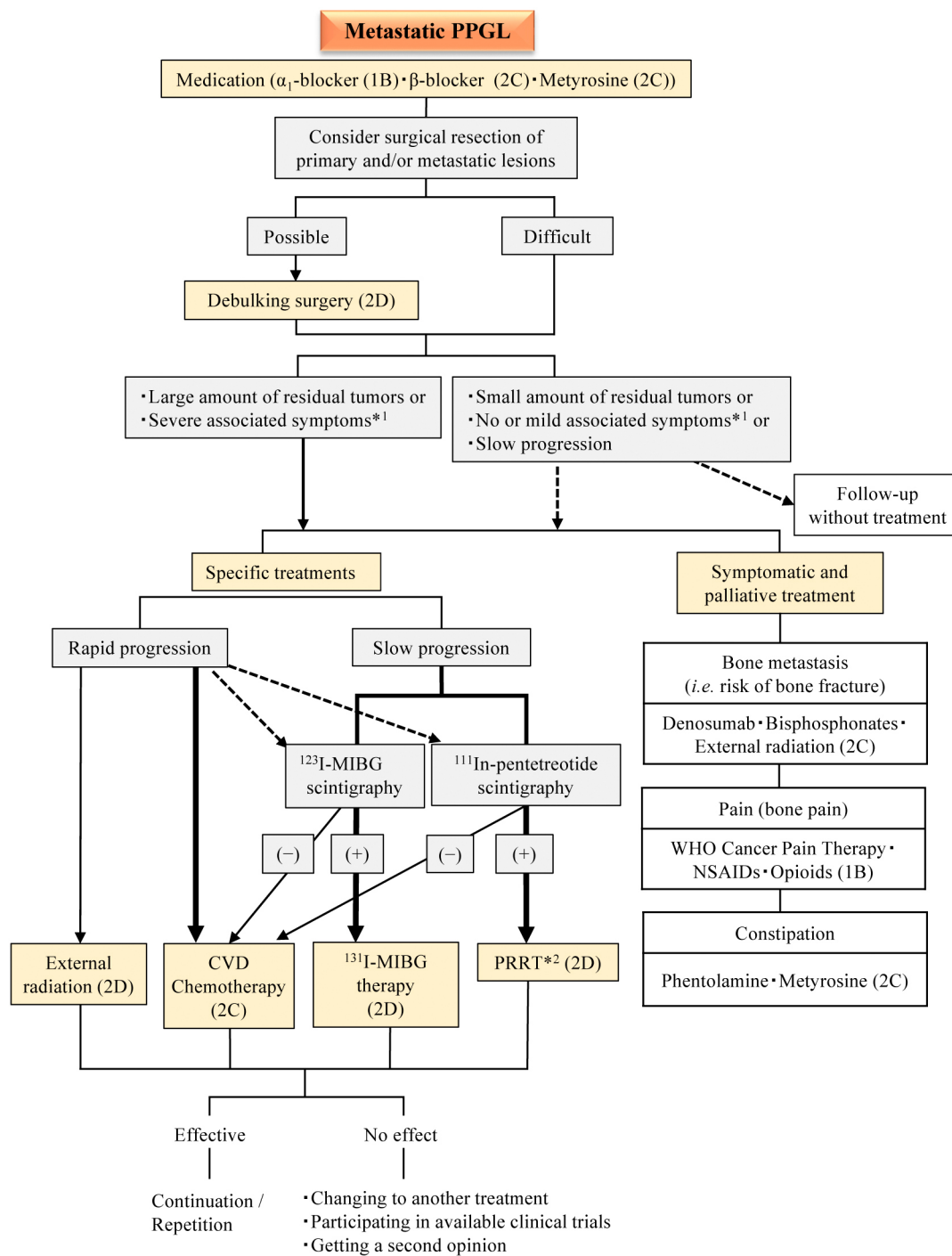


Fig. 8 Clinical practice algorithm for metastatic pheochromocytoma and paraganglioma

*1 Symptoms caused by excess catecholamines and localized symptoms caused by tumors

*2 PRRT: ^{177}Lu -DOTATATE internal therapy

The dashed arrow indicates treatment options.

Abbreviations: WHO, world health organization; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 6 Diagnostic criteria of PPGL

Required item		
1) Tumors suggesting origin from adrenal medulla or paraganglia ¹⁾		
Sub-items		
1) Pathological findings: characteristic findings of PPGL ²⁾		
2) Biochemical findings		
1 High levels of metanephrine or normetanephrine in 24-hour urine ³⁾		
2 High levels of adrenaline or noradrenaline in 24-hour urine ⁴⁾		
3 High levels of plasma-free metanephrine or normetanephrine ⁵⁾		
At least one finding of 1, 2, and 3 is positive.		
3) Imaging finding		
1 Avid ¹²³ I-MIBG uptake in the tumor ⁶⁾		
Decision	Definite cases	(1) Fulfill required item 1) and sub-item 1)
		(2) Fulfill required item 1) and sub-items 2) and 3)
	Probable cases	Fulfill required item 1) and sub-item 2)-1
	Suspected cases	(1) Fulfill required item 1) and sub-items 2)-2 or 2)-3
		(2) Fulfill required item 1) and sub-item 3)-1
	Excluded cases	Pseudopheochromocytoma, neuroblastoma, ganglioneuroma

¹⁾ Present or past. Any modality (CT or MRI)

²⁾ Most tumor cells must be positive for chromogranin A staining. If paraganglioma is suspected and all subitems 2) are negative, confirming the negative staining of the epithelial marker cytokeratin and positive staining of tyrosine hydroxylase (TH) or dopamine β-hydroxylase (DBH) is desirable.

^{3), 4)} Positive values if more than 3 times the normal upper limit. Repeated measurements are recommended as there are false positives and false negatives.

⁵⁾ Positive values if more than the normal upper limit. High values for at least metanephrine or normetanephrine. Caution is required for false positives and false negatives. (Japanese health insurance coverage is “only once for a differential diagnosis of pheochromocytoma”)

⁶⁾ 10–20% of PPGLs are negative on ¹²³I-MIBG scintigraphy. Furthermore, ¹²³I-MIBG is physiologically taken up by normal adrenal glands, and uptake can be asymmetric. Therefore, careful attention should be paid to the assessment and diagnosis of ¹²³I-MIBG accumulation in adrenal glands without obvious tumors. (See Chapter I-3 Imaging diagnosis)

PPGL, pheochromocytomas and paragangliomas; MIBG, metaiodobenzylguanidine

should be followed. Multidisciplinary therapeutic strategies encompass medical treatment, debulking surgery, chemotherapy, radionuclide therapy, and symptomatic and palliative care. Rational treatment choices must consider the patient preferences, QOL, cost-effectiveness, and the health insurance framework. Additionally, the diagnostic criteria for PPGL and metastatic PPGL (Tables 6, 7, respectively). The presence of tumors and pathological, biochemical, and imaging findings were rationally combined to draw a graded diagnosis from definite, probable, and suspected cases. Although PPGL are considered a potentially metastatic tumors, diagnosing metastatic PPGL requires pathological and imaging findings compatible with PPGL in non-chromaffin tissue tumors. Effective use of the diagnostic criteria and algorithm enhances the quality of PPGL medical care. A summary of this guideline is provided in a Graphical Abstract. Creating clinical practice guidelines is a significant task requiring considerable effort and cost. The clinical practice guideline of PPGL 2025 will contribute significantly to promoting national health by improving the quality of PPGL medical care.

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Table 7 Diagnostic criteria of metastatic PPGL

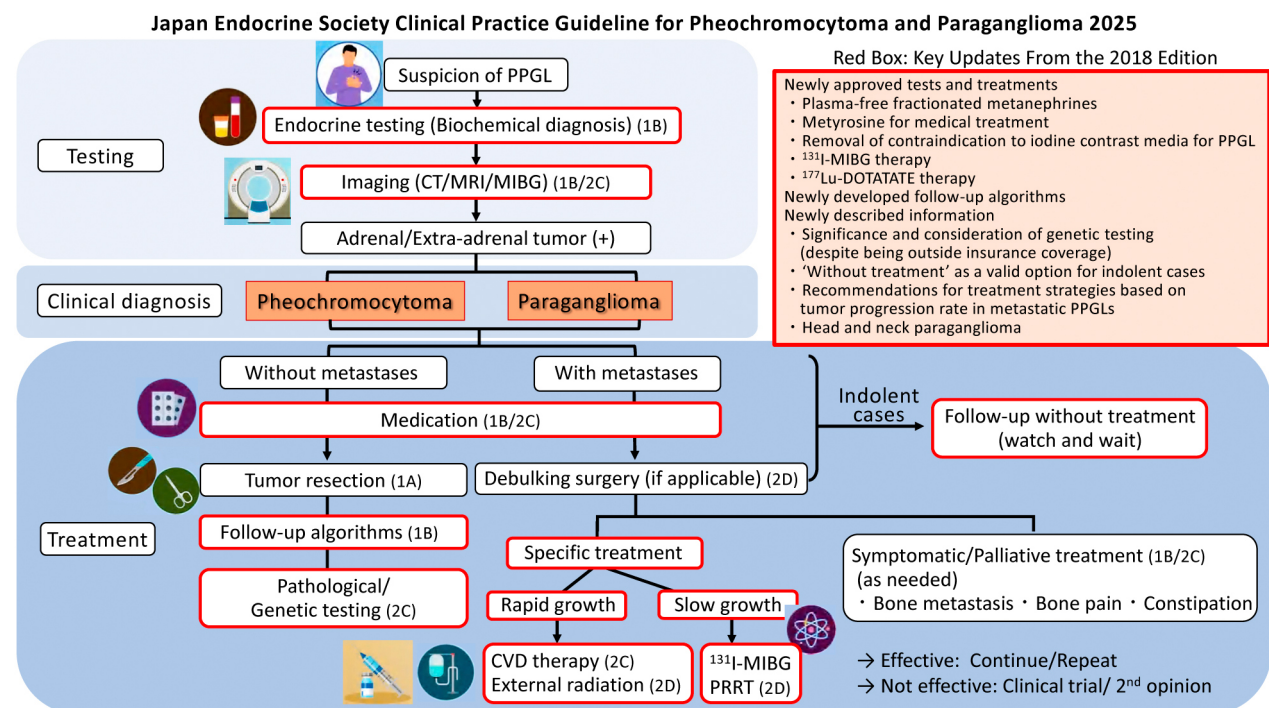
Required items		
1) Definite cases according to the diagnostic criteria for PPGL ¹⁾		
2) Presence of metastatic tumor in non-chromaffin tissue ²⁾		
Sub-items		
1) Pathological findings: Characteristic pathological findings of PPGL in the tumor in non-chromaffin tissue ³⁾		
2) Imaging findings: Avid ¹²³ I-MIBG uptake in the tumor in non-chromaffin tissue		
Decision	Definite cases	Fulfill required items 1) and 2), and sub-items 1) or 2)
	Suspected cases	Fulfill only required items 1) and 2)

¹⁾ Present or past period. Any modality (CT or MRI).

²⁾ Tumors in non-chromaffin tissues, such as the liver, lungs, bones, and lymph nodes.

³⁾ Most tumor cells must be positive for chromogranin A staining. In cases where paraganglioma is suspected and subitem 2) is negative, confirming the negative staining of the epithelial marker cytokeratin and positive staining of tyrosine hydroxylase (TH) or dopamine β-hydroxylase (DBH) is desirable.

PPGL, pheochromocytomas and paragangliomas; MIBG, metaiodobenzylguanidine



Graphical Abstract

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This clinical practice guideline summarizes the current standards for PPGL treatment. It is based on evidence from academic papers in Japan and overseas, medical practices in Japan, and expert opinions. Therefore, doctors in charge of medical treatment must fully consider

each patient's condition and the medical facility's situation and use it realistically and flexibly.

Notably, these clinical practice guidelines do not restrict the contents of individual medical treatments. The Japan Endocrine Society is responsible for the content of the clinical practice guidelines. However, it is also important to note that all responsibilities for individual medical treatment lie with the direct medical facility and the doctor in charge. Therefore, the doctors in charge must comply with Japan's health insurance system and domestic laws and regulations. Furthermore, all copyrights to these clinical guidelines belong to the Japan Endocrine Society.

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References

- Naruse M, Japan Endocrine Society Taskforce on “Survey and guidelines for malignant pheochromocytoma (2018) Clinical practice guideline for the diagnosis and treatment of pheochromocytoma and paraganglioma 2018. *Folia Endocrinologica Japonica* 94 (Suppl Aug): 1–90 (In Japanese).
- Takeda R, Yasuhara S, Miyamori I, Sato T, Miura Y (1986) Pheochromocytoma in Japan: analysis of 493 cases during 1973–1982. *J Hypertens* 4 (Suppl 5): S397–S399.
- Takayanagi R, Miura K, Nakagawa H, Nawata H (2000) Epidemiologic study of adrenal gland disorders in Japan. *Biomed Pharmacother* 54 Suppl 1: 164s–168s.
- Naruse M, Taskforce of the research project for overcoming intractable diseases, Ministry of Health, Labour and Welfare of Japan (2010) Fiscal year 2010 report on the research of the advancement of diagnosis and treatment of pheochromocytoma (In Japanese).
- Tanabe A, Naruse M (2020) Recent advances in the management of pheochromocytoma and paraganglioma. *Hypertens Res* 43: 1141–1151.
- Ebbehoj A, Stochholm K, Jacobsen SF, Trolle C, Jepsen P, *et al.* (2021) Incidence and clinical presentation of pheochromocytoma and sympathetic paraganglioma: a population-based study. *J Clin Endocrinol Metab* 106: e2251–e2261.
- Leung AA, Pasiaka JL, Hyrcza MD, Pacaud D, Dong Y, *et al.* (2021) Epidemiology of pheochromocytoma and paraganglioma: population-based cohort study. *Eur J Endocrinol* 184: 19–28.
- Berends AMA, Buitenwerf E, de Krijger RR, Veeger N, van der Horst-Schrivers ANA, *et al.* (2018) Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. *Eur J Intern Med* 51: 68–73.
- Pommer G, Pamporaki C, Peitzsch M, Remde H, Deutschbein T, *et al.* (2022) Preanalytical considerations and outpatient *versus* inpatient tests of plasma metanephrines to diagnose pheochromocytoma. *J Clin Endocrinol Metab* 107: e3689–e3698.
- Lenders JW, Eisenhofer G, Mannelli M, Pacak K (2005) Pheochromocytoma. *Lancet* 366: 665–675.
- Barrett C, van Uum SH, Lenders JW (2015) Risk of catecholaminergic crisis following glucocorticoid administration in patients with an adrenal mass: a literature review. *Clin Endocrinol (Oxf)* 83: 622–628.
- Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, *et al.* (2016) European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a pheochromocytoma or a paraganglioma. *Eur J Endocrinol* 174: G1–g10.
- Kudva YC, Sawka AM, Young WF, Jr. (2003) Clinical review 164: The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab* 88: 4533–4539.
- Bravo EL (2004) Pheochromocytoma: current perspectives in the pathogenesis, diagnosis, and management. *Arg Bras Endocrinol Metabol* 48: 746–750.
- Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, *et al.* (2002) Biochemical diagnosis of pheochromocytoma: which test is best? *Jama* 287: 1427–1434.
- Sawka AM, Jaeschke R, Singh RJ, Young WF, Jr. (2003) A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* 88: 553–558.
- Grouzmann E, Drouard-Troalen L, Baudin E, Plouin PF, Muller B, *et al.* (2010) Diagnostic accuracy of free and total metanephrines in plasma and fractionated metanephrines in urine of patients with pheochromocytoma. *Eur J Endocrinol* 162: 951–960.
- Takekoshi K, Satoh F, Tanabe A, Okamoto T, Ichihara A, *et al.* (2019) Correlation between urinary fractionated metanephrines in 24-hour and spot urine samples for evaluating the therapeutic effect of metyrosine: a subanalysis of a multicenter, open-label phase I/II study. *Endocr J* 66: 1063–1072.
- Peitzsch M, Kaden D, Pamporaki C, Langton K, Constantinescu G, *et al.* (2020) Overnight/first-morning urine free metanephrines and methoxytyramine for diagnosis of pheochromocytoma and paraganglioma: is this an option? *Eur J Endocrinol* 182: 499–509.
- Sbardella E, Maunsell Z, May CJH, Tadman M, James T, *et al.* (2020) Random ‘spot’ urinary metanephrines compared with 24-h-urinary and plasma results in pheochromocytomas and paragangliomas. *Eur J Endocrinol* 183: 129–139.
- Kline GA, Boyd J, Sadrzadeh HSM, Leung AA (2021) Inpatient measurements of urine metanephrines are indistinguishable from pheochromocytoma: retrospective cohort study. *Am J Med* 134: 1039–1046.e1033.
- Ohno Y, Sone M, Taura D, Yamasaki T, Kojima K, *et al.* (2018) Evaluation of quantitative parameters for distinguishing pheochromocytoma from other adrenal tumors. *Hypertens Res* 41: 165–175.
- Kawashima A, Sone M, Inagaki N, Okamoto K, Tsuiki M, *et al.* (2021) Pheochromocytoma and paraganglioma with negative results for urinary metanephrines show higher risks for metastatic diseases. *Endocrine* 74: 155–162.
- Casey R, Griffin TP, Wall D, Dennedy MC, Bell M, *et al.* (2017) Screening for pheochromocytoma and paraganglioma: impact of using supine reference intervals for plasma metanephrines with samples collected from fasted/seated patients. *Ann Clin Biochem* 54: 170–173.
- Chen Y, Xiao H, Zhou X, Huang X, Li Y, *et al.* (2017) Accuracy of plasma free metanephrines in the diagnosis of

- pheochromocytoma and paraganglioma: a systematic review and meta-analysis. *Endocr Pract* 23: 1169–1177.
26. Tanaka Y, Isobe K, Ma E, Imai T, Kikumori T, et al. (2014) Plasma free metanephrines in the diagnosis of pheochromocytoma: diagnostic accuracy and strategies for Japanese patients. *Endocr J* 61: 667–673.
 27. Därr R, Kuhn M, Bode C, Bornstein SR, Pacak K, et al. (2017) Accuracy of recommended sampling and assay methods for the determination of plasma-free and urinary fractionated metanephrines in the diagnosis of pheochromocytoma and paraganglioma: a systematic review. *Endocrine* 56: 495–503.
 28. Wang K, Gao X, Zhang W, Sun N, Xie L, et al. (2021) Study of stability and interference for catecholamines and metanephrines, 3-methoxytyramine: key point of an accurate diagnosis for pheochromocytoma and paraganglioma. *Scand J Clin Lab Invest* 81: 564–572.
 29. Bílek R, Vlček P, Šafařík L, Michalský D, Novák K, et al. (2019) Chromogranin A in the laboratory diagnosis of pheochromocytoma and paraganglioma. *Cancers (Basel)* 11.
 30. Liu L, Xie W, Song Z, Wang T, Li X, et al. (2022) Addition of 3-methoxytyramine or chromogranin A to plasma free metanephrines as the initial test for pheochromocytoma and paraganglioma: Which is the best diagnostic strategy. *Clin Endocrinol (Oxf)* 96: 132–138.
 31. Lamy C, Tissot H, Faron M, Baudin E, Lamartina L, et al. (2022) Succinate: a serum biomarker of SDHB-mutated paragangliomas and pheochromocytomas. *J Clin Endocrinol Metab* 107: 2801–2810.
 32. Eisenhofer G, Goldstein DS, Walther MM, Friberg P, Lenders JW, et al. (2003) Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab* 88: 2656–2666.
 33. Tsiomidou S, Pamporaki C, Geroula A, Van Baal L, Weber F, et al. (2022) Clonidine suppression test for a reliable diagnosis of pheochromocytoma: When to use. *Clin Endocrinol (Oxf)* 97: 541–550.
 34. Lenders JW, Pacak K, Huynh TT, Sharabi Y, Mannelli M, et al. (2010) Low sensitivity of glucagon provocative testing for diagnosis of pheochromocytoma. *J Clin Endocrinol Metab* 95: 238–245.
 35. Lumachi F, Tregnaghi A, Zucchetta P, Cristina Marzola M, Cecchin D, et al. (2006) Sensitivity and positive predictive value of CT, MRI and ¹²³I-MIBG scintigraphy in localizing pheochromocytomas: a prospective study. *Nucl Med Commun* 27: 583–587.
 36. Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, et al. (2012) Staging and functional characterization of pheochromocytoma and paraganglioma by ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography. *J Natl Cancer Inst* 104: 700–708.
 37. Corral de la Calle MA, Encinas de la Iglesia J, Fernández-Pérez GC, Repollés Coboleda M, Fraino A (2022) Adrenal pheochromocytoma: Keys to radiologic diagnosis. *Radiologia (Engl Ed)* 64: 348–367.
 38. Gimenez-Roqueplo AP, Caumont-Prim A, Houzard C, Hignette C, Hernigou A, et al. (2013) Imaging work-up for screening of paraganglioma and pheochromocytoma in SDHx mutation carriers: a multicenter prospective study from the PGL-EVA Investigators. *J Clin Endocrinol Metab* 98: E162–E173.
 39. De Leo A, Vara G, Paccapelo A, Balacchi C, Vicennati V, et al. (2022) Computerized tomography texture analysis of pheochromocytoma: relationship with hormonal and histopathological data. *J Endocrinol Invest* 45: 1935–1944.
 40. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, et al. (2014) Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 99: 1915–1942.
 41. Gerson R, Tu W, Abreu-Gomez J, Udare A, McPhedran R, et al. (2022) Evaluation of the T2-weighted (T2W) adrenal MRI calculator to differentiate adrenal pheochromocytoma from lipid-poor adrenal adenoma. *Eur Radiol* 32: 8247–8255.
 42. Takano A, Oriuchi N, Tsushima Y, Taketomi-Takahashi A, Nakajima T, et al. (2008) Detection of metastatic lesions from malignant pheochromocytoma and paraganglioma with diffusion-weighted magnetic resonance imaging: comparison with ¹⁸F-FDG positron emission tomography and ¹²³I-MIBG scintigraphy. *Ann Nucl Med* 22: 395–401.
 43. Jacobson AF, Deng H, Lombard J, Lessig HJ, Black RR (2010) ¹²³I-meta-iodobenzylguanidine scintigraphy for the detection of neuroblastoma and pheochromocytoma: results of a meta-analysis. *J Clin Endocrinol Metab* 95: 2596–2606.
 44. King KS, Chen CC, Alexopoulos DK, Whatley MA, Reynolds JC, et al. (2011) Functional imaging of SDHx-related head and neck paragangliomas: comparison of ¹⁸F-fluorodihydroxyphenylalanine, ¹⁸F-fluorodopamine, ¹⁸F-fluoro-2-deoxy-D-glucose PET, ¹²³I-metaiodobenzylguanidine scintigraphy, and ¹¹¹In-pentetreotide scintigraphy. *J Clin Endocrinol Metab* 96: 2779–2785.
 45. Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Ling A, et al. (2007) Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. *J Clin Oncol* 25: 2262–2269.
 46. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, et al. (2009) Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 360: 1509–1517.
 47. Noortman WA, Vriens D, de Geus-Oei LF, Slump CH, Aarntzen EH, et al. (2022) [(18)F]FDG-PET/CT radiomics for the identification of genetic clusters in pheochromocytomas and paragangliomas. *Eur Radiol* 32: 7227–7236.
 48. Archier A, Varoquaux A, Garrigue P, Montava M, Guerin C, et al. (2016) Prospective comparison of (68)Ga-DOTATATE and (18)F-FDOPA PET/CT in patients with various pheochromocytomas and paragangliomas with

- emphasis on sporadic cases. *Eur J Nucl Med Mol Imaging* 43: 1248–1257.
49. Fagundes GFC, Almeida MQ (2022) Perioperative management of pheochromocytomas and sympathetic paragangliomas. *J Endocr Soc* 6: bvac004.
 50. Zawadzka K, Więckowski K, Małczak P, Wysocki M, Major P, *et al.* (2021) Selective vs. non-selective alpha-blockade prior to adrenalectomy for pheochromocytoma: systematic review and meta-analysis. *Eur J Endocrinol* 184: 751–760.
 51. Buitenwerf E, Osinga TE, Timmers H, Lenders JWM, Feelders RA, *et al.* (2020) Efficacy of α -Blockers on hemodynamic control during pheochromocytoma resection: a randomized controlled trial. *J Clin Endocrinol Metab* 105: 2381–2391.
 52. Zhu CY, Hong JC, Kamdar NV, Hu MY, Tseng CH, *et al.* (2022) Comparison of preoperative alpha-blockade for resection of paraganglioma and pheochromocytoma. *Endocr Pract* 28: 889–896.
 53. Jaiswal SK, Memon SS, Lila A, Sarathi V, Goroshi M, *et al.* (2021) Preoperative amlodipine is efficacious in preventing intraoperative HDI in pheochromocytoma: pilot RCT. *J Clin Endocrinol Metab* 106: e2907–e2918.
 54. Naruse M, Satoh F, Tanabe A, Okamoto T, Ichihara A, *et al.* (2018) Efficacy and safety of metyrosine in pheochromocytoma/paraganglioma: a multi-center trial in Japan. *Endocr J* 65: 359–371.
 55. Gruber LM, Jasim S, Ducharme-Smith A, Weingarten T, Young WF, *et al.* (2021) The role for metyrosine in the treatment of patients with pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* 106: e2393–e2401.
 56. Roman-Gonzalez A, Zhou S, Ayala-Ramirez M, Shen C, Waguespack SG, *et al.* (2018) Impact of surgical resection of the primary tumor on overall survival in patients with metastatic pheochromocytoma or sympathetic paraganglioma. *Ann Surg* 268: 172–178.
 57. Lafont M, Fagour C, Haissaguerre M, Darancette G, Wagner T, *et al.* (2015) Per-operative hemodynamic instability in normotensive patients with incidentally discovered pheochromocytomas. *J Clin Endocrinol Metab* 100: 417–421.
 58. Fu SQ, Wang SY, Chen Q, Liu YT, Li ZL, *et al.* (2020) Laparoscopic versus open surgery for pheochromocytoma: a meta-analysis. *BMC Surg* 20: 167.
 59. Li J, Wang Y, Chang X, Han Z (2020) Laparoscopic adrenalectomy (LA) vs. open adrenalectomy (OA) for pheochromocytoma (PHEO): a systematic review and meta-analysis. *Eur J Surg Oncol* 46: 991–998.
 60. Schweitzer ML, Nguyen-Thi PL, Mirallie E, Vriens M, Raffaelli M, *et al.* (2019) Conversion during laparoscopic adrenalectomy for pheochromocytoma: a cohort study in 244 patients. *J Surg Res* 243: 309–315.
 61. Ma W, Mao Y, Zhuo R, Dai J, Fang C, *et al.* (2020) Surgical outcomes of a randomized controlled trial compared robotic versus laparoscopic adrenalectomy for pheochromocytoma. *Eur J Surg Oncol* 46: 1843–1847.
 62. Isiktas G, Nazli Avci S, Ergun O, Krishnamurthy V, Jin J, *et al.* (2022) Laparoscopic versus robotic adrenalectomy in pheochromocytoma patients. *J Surg Oncol* 126: 460–464.
 63. Fu SQ, Zhuang CS, Yang XR, Xie WJ, Gong BB, *et al.* (2020) Comparison of robot-assisted retroperitoneal laparoscopic adrenalectomy versus retroperitoneal laparoscopic adrenalectomy for large pheochromocytoma: a single-centre retrospective study. *BMC Surg* 20: 227.
 64. Japanese Society of Endourology and Robotics (2020) Clinical guidelines for urological laparoscopic surgery. https://www.jsee.jp/wordpress/wp-content/themes/jsee/assets/pdf/guideline_2020.pdf accessed on March 1, 2023 (In Japanese).
 65. Neumann HPH, Tsoy U, Bancos I, Amodru V, Walz MK, *et al.* (2019) Comparison of pheochromocytoma-specific morbidity and mortality among adults with bilateral pheochromocytomas undergoing total adrenalectomy vs. cortical-sparing adrenalectomy. *JAMA Netw Open* 2: e198898.
 66. Bhambhani HP, Daneshvar MA, Peterson DJ, Ball MW (2021) Partial versus total adrenalectomy for pheochromocytoma: a population-based comparison of outcomes. *Int Urol Nephrol* 53: 2485–2492.
 67. Imai T, Uchino S, Okamoto T, Suzuki S, Kosugi S, *et al.* (2013) High penetrance of pheochromocytoma in multiple endocrine neoplasia 2 caused by germ line RET codon 634 mutation in Japanese patients. *Eur J Endocrinol* 168: 683–687.
 68. Castinetti F, Taieb D, Henry JF, Walz M, Guerin C, *et al.* (2016) Management of endocrine disease: outcome of adrenal sparing surgery in heritable pheochromocytoma. *Eur J Endocrinol* 174: R9–R18.
 69. Riester A, Weismann D, Quinkler M, Lichtenauer UD, Sommerer S, *et al.* (2015) Life-threatening events in patients with pheochromocytoma. *Eur J Endocrinol* 173: 757–764.
 70. Ando Y, Ono Y, Sano A, Fujita N, Ono S, *et al.* (2022) Clinical characteristics and outcomes of pheochromocytoma crisis: a literature review of 200 cases. *J Endocrinol Invest* 45: 2313–2328.
 71. Whitelaw BC, Prague JK, Mustafa OG, Schulte KM, Hopkins PA, *et al.* (2014) Pheochromocytoma [corrected] crisis. *Clin Endocrinol (Oxf)* 80: 13–22.
 72. Prys-Roberts C, Farndon JR (2002) Efficacy and safety of doxazosin for perioperative management of patients with pheochromocytoma. *World J Surg* 26: 1037–1042.
 73. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, *et al.* (2016) Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 18: 8–27.
 74. Sloand EM, Thompson BT (1984) Propranolol-induced pulmonary edema and shock in a patient with pheochromocytoma. *Arch Intern Med* 144: 173–174.
 75. Sauneuf B, Chudeau N, Champigneulle B, Bouffard C, Antona M, *et al.* (2017) Pheochromocytoma crisis in the

- ICU: a french multicenter cohort study with emphasis on rescue extracorporeal membrane oxygenation. *Crit Care Med* 45: e657–e665.
76. Eisenhofer G, Prejbisz A, Peitzsch M, Pamporaki C, Masjkur J, et al. (2018) Biochemical diagnosis of chromaffin cell tumors in patients at high and low risk of disease: plasma versus urinary free or deconjugated O-methylated catecholamine metabolites. *Clin Chem* 64: 1646–1656.
 77. Heavner MG, Krane LS, Winters SM, Mirzazadeh M (2015) Pheochromocytoma diagnosed pathologically with previous negative serum markers. *J Surg Oncol* 112: 492–495.
 78. Hamidi O, Young WF, Jr., Iñiguez-Ariza NM, Kittah NE, Gruber L, et al. (2017) Malignant pheochromocytoma and paraganglioma: 272 patients over 55 years. *J Clin Endocrinol Metab* 102: 3296–3305.
 79. Feng F, Zhu Y, Wang X, Wu Y, Zhou W, et al. (2011) Predictive factors for malignant pheochromocytoma: analysis of 136 patients. *J Urol* 185: 1583–1590.
 80. Gimenez-Roqueplo AP, Favier J, Rustin P, Rieubland C, Crespin M, et al. (2003) Mutations in the SDHB gene are associated with extra-adrenal and/or malignant pheochromocytomas. *Cancer Res* 63: 5615–5621.
 81. Amar L, Bertherat J, Baudin E, Ajzenberg C, Bressac-de Paillerets B, et al. (2005) Genetic testing in pheochromocytoma or functional paraganglioma. *J Clin Oncol* 23: 8812–8818.
 82. Timmers HJ, Pacak K, Huynh TT, Abu-Asab M, Tsokos M, et al. (2008) Biochemically silent abdominal paragangliomas in patients with mutations in the succinate dehydrogenase subunit B gene. *J Clin Endocrinol Metab* 93: 4826–4832.
 83. Dreijerink KMA, Rijken JA, Compaijen CJ, Timmers H, van der Horst-Schrivers ANA, et al. (2019) Biochemically silent sympathetic paraganglioma, pheochromocytoma, or metastatic disease in SDHD mutation carriers. *J Clin Endocrinol Metab* 104: 5421–5426.
 84. Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, et al. (2004) Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. *JAMA* 292: 943–951.
 85. Kimura N, Shiga K, Kaneko KI, Oki Y, Sugisawa C, et al. (2021) Immunohistochemical expression of choline acetyltransferase and catecholamine-synthesizing enzymes in head-and-neck and thoracoabdominal paragangliomas and pheochromocytomas. *Endocr Pathol* 32: 442–451.
 86. Lloyd S, Obholzer R, Tysome J (2020) British skull base society clinical consensus document on management of head and neck paragangliomas. *Otolaryngol Head Neck Surg* 163: 400–409.
 87. Williams MD (2017) Paragangliomas of the head and neck: an overview from diagnosis to genetics. *Head Neck Pathol* 11: 278–287.
 88. Kimura N, Asa SL, Gill AJ, Tischler AS (2024) Head and neck paraganglioma. In: WHO head and neck tumours (5th) Part B. World Health Organization, Lyon, France: 655–658.
 89. Smith JD, Ellsperman SE, Basura GJ, Else T (2021) Re-evaluating the prevalence and factors characteristic of catecholamine secreting head and neck paragangliomas. *Endocrinol Diabetes Metab* 4: e00256.
 90. Cleere EF, Martin-Grace J, Gendre A, Sherlock M, O'Neill JP (2022) Contemporary management of paragangliomas of the head and neck. *Laryngoscope Investig Otolaryngol* 7: 93–107.
 91. Sandow L, Thawani R, Kim MS, Heinrich MC (2023) Paraganglioma of the head and neck: a review. *Endocr Pract* 29: 141–147.
 92. Yonamine M, Wasano K, Aita Y, Sugawara T, Takahashi K, et al. (2021) Prevalence of germline variants in a large cohort of Japanese patients with pheochromocytoma and/or paraganglioma. *Cancers (Basel)* 13.
 93. Moskovic DJ, Smolarz JR, Stanley D, Jimenez C, Williams MD, et al. (2010) Malignant head and neck paragangliomas: is there an optimal treatment strategy? *Head Neck Oncol* 2: 23.
 94. Malla SR, Bhalla AS, Manchanda S, Kandasamy D, Kumar R, et al. (2021) Dynamic contrast-enhanced magnetic resonance imaging for differentiating head and neck paraganglioma and schwannoma. *Head Neck* 43: 2611–2622.
 95. Satturwar SP, Rossi ED, Maleki Z, Cantley RL, Faquin WC, et al. (2021) Thyroid paraganglioma: a diagnostic pitfall in thyroid FNA. *Cancer Cytopathol* 129: 439–449.
 96. Fatima N, Pollom E, Soltys S, Chang SD, Meola A (2021) Stereotactic radiosurgery for head and neck paragangliomas: a systematic review and meta-analysis. *Neurosurg Rev* 44: 741–752.
 97. Hamidi O, Young WF Jr, Gruber L, Smestad J, Yan Q, et al. (2017) Outcomes of patients with metastatic pheochromocytoma and paraganglioma: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 87: 440–450.
 98. Harrington JL, Farley DR, van Heerden JA, Ramin KD (1999) Adrenal tumors and pregnancy. *World J Surg* 23: 182–186.
 99. Biggar MA, Lennard TW (2013) Systematic review of pheochromocytoma in pregnancy. *Br J Surg* 100: 182–190.
 100. Bancos I, Atkinson E, Eng C, Young WF, Jr., Neumann HPH (2021) Maternal and fetal outcomes in pheochromocytoma and pregnancy: a multicentre retrospective cohort study and systematic review of literature. *Lancet Diabetes Endocrinol* 9: 13–21.
 101. Oliva R, Angelos P, Kaplan E, Bakris G (2010) Pheochromocytoma in pregnancy: a case series and review. *Hypertension* 55: 600–606.
 102. Zuspan FP (1970) Urinary excretion of epinephrine and norepinephrine during pregnancy. *J Clin Endocrinol Metab* 30: 357–360.
 103. Lenders JWM, Langton K, Langenhuijsen JF, Eisenhofer G (2019) Pheochromocytoma and pregnancy. *Endocrinol Metab Clin North Am* 48: 605–617.

104. Young WF Jr (2007) Endocrine hypertension. In: Melmed S, Polonsky KS, Larsen PR (eds.) *Williams Textbook of Endocrinology* (11th). Elsevier, Philadelphia, USA: 522–530.
105. Japan Society of Obstetrics and Gynecology, Japan Association of Obstetricians and Gynecologists (2020) Guidelines for obstetric practice in Japan 2020 (In Japanese).
106. Gruber LM, Young WF Jr, Bancos I (2021) Pheochromocytoma and paraganglioma in pregnancy: a new era. *Curr Cardiol Rep* 23: 60.
107. Japan Society for the Study of Hypertension in Pregnancy (2021) Guidelines for pregnancy-induced hypertension disorders 2021 (In Japanese).
108. Kuo MJM, Nazari MA, Jha A, Pacak K (2022) Pediatric metastatic pheochromocytoma and paraganglioma: clinical presentation and diagnosis, genetics, and therapeutic approaches. *Front Endocrinol (Lausanne)* 13: 936178.
109. Jha A, Ling A, Millo C, Gupta G, Viana B, *et al.* (2018) Superiority of (68)Ga-DOTATATE over (18)F-FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (SDHx)-related pheochromocytoma and paraganglioma in the pediatric population. *Eur J Nucl Med Mol Imaging* 45: 787–797.
110. Jaiswal SK, Sarathi V, Malhotra G, Hira P, Shah R, *et al.* (2021) The utility of (68)Ga-DOTATATE PET/CT in localizing primary/metastatic pheochromocytoma and paraganglioma in children and adolescents—a single-center experience. *J Pediatr Endocrinol Metab* 34: 109–119.
111. Virgone C, Andreetta M, Avanzini S, Chiaravalli S, De Pasquale D, *et al.* (2020) Pheochromocytomas and paragangliomas in children: Data from the Italian Cooperative Study (TREP). *Pediatr Blood Cancer* 67: e28332.
112. Yen K, Lodish M (2021) Pheochromocytomas and paragangliomas. *Curr Opin Pediatr* 33: 430–435.
113. Mete O, Asa SL, Gill AJ, Kimura N, de Krijger RR, *et al.* (2022) Overview of the 2022 WHO classification of paragangliomas and pheochromocytomas. *Endocr Pathol* 33: 90–114.
114. van Nederveen FH, Gaal J, Favier J, Korpershoek E, Oldenburg RA, *et al.* (2009) An immunohistochemical procedure to detect patients with paraganglioma and pheochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. *Lancet Oncol* 10: 764–771.
115. Kimura N, Takekoshi K, Horii A, Morimoto R, Imai T, *et al.* (2014) Clinicopathological study of SDHB mutation-related pheochromocytoma and sympathetic paraganglioma. *Endocr Relat Cancer* 21: L13–L16.
116. Korpershoek E, Favier J, Gaal J, Burnichon N, van Gessel B, *et al.* (2011) SDHA immunohistochemistry detects germline SDHA gene mutations in apparently sporadic paragangliomas and pheochromocytomas. *J Clin Endocrinol Metab* 96: E1472–E1476.
117. Burnichon N, Brière JJ, Libé R, Vescovo L, Rivière J, *et al.* (2010) SDHA is a tumor suppressor gene causing paraganglioma. *Hum Mol Genet* 19: 3011–3020.
118. Fishbein L, Leshchiner I, Walter V, Danilova L, Robertson AG, *et al.* (2017) Comprehensive molecular characterization of pheochromocytoma and paraganglioma. *Cancer Cell* 31: 181–193.
119. Jiang J, Zhang J, Pang Y, Bechmann N, Li M, *et al.* (2020) Sino-European differences in the genetic landscape and clinical presentation of pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* 105.
120. Nölting S, Bechmann N, Taieb D, Beuschlein F, Fassnacht M, *et al.* (2022) Personalized management of pheochromocytoma and paraganglioma. *Endocr Rev* 43: 199–239.
121. Andrews KA, Ascher DB, Pires DEV, Barnes DR, Vialard L, *et al.* (2018) Tumour risks and genotype-phenotype correlations associated with germline variants in succinate dehydrogenase subunit genes SDHB, SDHC and SDHD. *J Med Genet* 55: 384–394.
122. Benn DE, Zhu Y, Andrews KA, Wilding M, Duncan EL, *et al.* (2018) Bayesian approach to determining penetrance of pathogenic SDH variants. *J Med Genet* 55: 729–734.
123. Li SR, Nicholson KJ, McCoy KL, Carty SE, Yip L (2020) Clinical and biochemical features of pheochromocytoma characteristic of Von Hippel-Lindau syndrome. *World J Surg* 44: 570–577.
124. Japan Endocrine Society (2014) Handbook for diagnosis and treatment of multiple endocrine neoplasia syndrome (In Japanese).
125. Muth A, Crona J, Gimm O, Elmgren A, Filipsson K, *et al.* (2019) Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. *J Intern Med* 285: 187–204.
126. Horton C, LaDuca H, Deckman A, Durda K, Jackson M, *et al.* (2022) Universal germline panel testing for individuals with pheochromocytoma and paraganglioma produces high diagnostic yield. *J Clin Endocrinol Metab* 107: e1917–e1923.
127. Toledo RA, Burnichon N, Cascon A, Benn DE, Bayley JP, *et al.* (2017) Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary pheochromocytomas and paragangliomas. *Nat Rev Endocrinol* 13: 233–247.
128. Oudijk L, Gaal J, de Krijger RR (2019) The role of immunohistochemistry and molecular analysis of succinate dehydrogenase in the diagnosis of endocrine and non-endocrine tumors and related syndromes. *Endocr Pathol* 30: 64–73.
129. Buffet A, Ben Aim L, Leboulleux S, Drui D, Vezzosi D, *et al.* (2019) Positive impact of genetic test on the management and outcome of patients with paraganglioma and/or pheochromocytoma. *J Clin Endocrinol Metab* 104: 1109–1118.
130. Amar L, Pacak K, Steichen O, Akker SA, Aylwin SJB, *et al.* (2021) International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. *Nat Rev Endocrinol* 17: 435–444.
131. Davidoff DF, Benn DE, Field M, Crook A, Robinson BG, *et al.* (2022) Surveillance improves outcomes for carriers of SDHB pathogenic variants: a multicenter study. *J Clin*

- Endocrinol Metab* 107: e1907–e1916.
132. Lenders JWM, Kerstens MN, Amar L, Prejbisz A, Robledo M, et al. (2020) Genetics, diagnosis, management and future directions of research of pheochromocytoma and paraganglioma: a position statement and consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension. *J Hypertens* 38: 1443–1456.
 133. Asban A, Kluijfhout WP, Drake FT, Beninato T, Wang E, et al. (2018) Trends of genetic screening in patients with pheochromocytoma and paraganglioma: 15-year experience in a high-volume tertiary referral center. *J Surg Oncol* 117: 1217–1222.
 134. Nockel P, El Lakis M, Gaitanidis A, Yang L, Merkel R, et al. (2018) Preoperative genetic testing in pheochromocytomas and paragangliomas influences the surgical approach and the extent of adrenal surgery. *Surgery* 163: 191–196.
 135. Taïeb D, Hicks RJ, Hindié E, Guillet BA, Avram A, et al. (2019) European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of pheochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging* 46: 2112–2137.
 136. Kolasinska-Ćwikła A, Pęczkowska M, Ćwikła JB, Michałowska I, Pałucki JM, et al. (2019) A clinical efficacy of PRRT in patients with advanced, nonresectable, paraganglioma-pheochromocytoma, related to SDHx gene mutation. *J Clin Med* 8.
 137. Perez K, Jacene H, Hornick JL, Ma C, Vaz N, et al. (2022) SDHx mutations and temozolomide in malignant pheochromocytoma and paraganglioma. *Endocr Relat Cancer* 29: 533–544.
 138. O’Kane GM, Ezzat S, Joshua AM, Bourdeau I, Leibowitz-Amit R, et al. (2019) A phase 2 trial of sunitinib in patients with progressive paraganglioma or pheochromocytoma: the SNIPP trial. *Br J Cancer* 120: 1113–1119.
 139. Taïeb D, Wanna GB, Ahmad M, Lussey-Lepoutre C, Perrier ND, et al. (2023) Clinical consensus guideline on the management of pheochromocytoma and paraganglioma in patients harbouring germline SDHD pathogenic variants. *Lancet Diabetes Endocrinol* 11: 345–361.
 140. Richter S, Qiu B, Ghering M, Kunath C, Constantinescu G, et al. (2022) Head/neck paragangliomas: focus on tumor location, mutational status and plasma methoxytyramine. *Endocr Relat Cancer* 29: 213–224.
 141. Taïeb D, Nölting S, Perrier ND, Fassnacht M, Carrasquillo JA, et al. (2024) Management of pheochromocytoma and paraganglioma in patients with germline SDHB pathogenic variants: an international expert Consensus statement. *Nat Rev Endocrinol* 20: 168–184.
 142. Japan Endocrine Society (2013) Guidelines for the diagnosis of multiple endocrine neoplasia syndrome: actual condition and guidelines for diagnosis and treatment. <https://www.j-endocrine.jp/uploads/files/edu/MEN.pdf> accessed on June 26, 2023 (In Japanese).
 143. Research group for standardization and actual condition survey of hereditary diseases causing various endocrine abnormalities (2017) Guidelines for the diagnosis and treatment of von Hippel-Lindau disease (VHL) 2017. https://www.kochi-u.ac.jp/kms/hs_urol/pdf/vhl_2017ver.pdf accessed on May 19, 2023 (In Japanese).
 144. Neurofibromatosis Type 1 Clinical Guidelines Revision Committee, Japanese Dermatological Association (2018) Guidelines for the diagnosis and treatment of neurofibromatosis type 1 (Recklinghausen disease). https://www.dermatol.or.jp/uploads/uploads/files/NF1_GL.pdf accessed on June 26, 2023 (In Japanese).
 145. Amar L, Fassnacht M, Gimenez-Roqueplo AP, Januszewicz A, Prejbisz A, et al. (2012) Long-term post-operative follow-up in patients with apparently benign pheochromocytoma and paraganglioma. *Horm Metab Res* 44: 385–389.
 146. Parasiliti-Caprino M, Lucatello B, Lopez C, Burrello J, Maletta F, et al. (2020) Predictors of recurrence of pheochromocytoma and paraganglioma: a multicenter study in Piedmont, Italy. *Hypertens Res* 43: 500–510.
 147. Li M, Prodanov T, Meuter L, Kerstens MN, Bechmann N, et al. (2023) Recurrent disease in patients with sporadic pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* 108: 397–404.
 148. Pierre C, Agopianz M, Brunaud L, Battaglia-Hsu SF, Max A, et al. (2019) COPPS, a composite score integrating pathological features, PS100 and SDHB losses, predicts the risk of metastasis and progression-free survival in pheochromocytomas/paragangliomas. *Virchows Arch* 474: 721–734.
 149. Dhir M, Li W, Hogg ME, Bartlett DL, Carty SE, et al. (2017) Clinical predictors of malignancy in patients with pheochromocytoma and paraganglioma. *Ann Surg Oncol* 24: 3624–3630.
 150. Wachtel H, Hutchens T, Baraban E, Schwartz LE, Montone K, et al. (2020) Predicting metastatic potential in pheochromocytoma and paraganglioma: a comparison of PASS and GAPP scoring systems. *J Clin Endocrinol Metab* 105: e4661–4670.
 151. Pamporaki C, Prodanov T, Meuter L, Berends AMA, Bechmann N, et al. (2022) Determinants of disease-specific survival in patients with and without metastatic pheochromocytoma and paraganglioma. *Eur J Cancer* 169: 32–41.
 152. Holscher I, van den Berg TJ, Dreijerink KMA, Engelsman AF, Nieveen van Dijkum EJM (2021) Recurrence rate of sporadic pheochromocytomas after curative adrenalectomy: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 106: 588–597.
 153. Hescot S, Curras-Freixes M, Deutschbein T, van Berkel A, Vezzosi D, et al. (2019) Prognosis of malignant pheochromocytoma and paraganglioma (MAPP-Prono Study): a European network for the study of adrenal tumors retrospective study. *J Clin Endocrinol Metab* 104: 2367–2374.
 154. Kan Y, Zhang S, Wang W, Liu J, Yang J, et al. (2018) (68)Ga-somatostatin receptor analogs and (18)F-FDG

- PET/CT in the localization of metastatic pheochromocytomas and paragangliomas with germline mutations: a meta-analysis. *Acta Radiol* 59: 1466–1474.
155. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, *et al.* (2017) The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging. *CA Cancer J Clin* 67: 93–99.
 156. Kimura N, Takayanagi R, Takizawa N, Itagaki E, Katabami T, *et al.* (2014) Pathological grading for predicting metastasis in pheochromocytoma and paraganglioma. *Endocr Relat Cancer* 21: 405–414.
 157. Wu D, Tischler AS, Lloyd RV, DeLellis RA, de Krijger R, *et al.* (2009) Observer variation in the application of the pheochromocytoma of the adrenal gland scaled score. *Am J Surg Pathol* 33: 599–608.
 158. Crona J, Lamarca A, Ghosal S, Welin S, Skogseid B, *et al.* (2019) Genotype-phenotype correlations in pheochromocytoma and paraganglioma: a systematic review and individual patient meta-analysis. *Endocr Relat Cancer* 26: 539–550.
 159. Lee H, Jeong S, Yu Y, Kang J, Sun H, *et al.* (2020) Risk of metastatic pheochromocytoma and paraganglioma in SDHx mutation carriers: a systematic review and updated meta-analysis. *J Med Genet* 57: 217–225.
 160. Castro-Vega LJ, Buffet A, De Cubas AA, Cascón A, Menara M, *et al.* (2014) Germline mutations in FH confer predisposition to malignant pheochromocytomas and paragangliomas. *Hum Mol Genet* 23: 2440–2446.
 161. Calsina B, Castro-Vega LJ, Torres-Pérez R, Inglada-Pérez L, Currás-Freixes M, *et al.* (2019) Integrative multi-omics analysis identifies a prognostic miRNA signature and a targetable miR-21-3p/TSC2/mTOR axis in metastatic pheochromocytoma/paraganglioma. *Theranostics* 9: 4946–4958.
 162. Wallace PW, Conrad C, Brückmann S, Pang Y, Caleiras E, *et al.* (2020) Metabolomics, machine learning and immunohistochemistry to predict succinate dehydrogenase mutational status in pheochromocytomas and paragangliomas. *J Pathol* 251: 378–387.
 163. Srimuninnimit V, Wampler GL (1991) Case report of metastatic familial pheochromocytoma treated with cisplatin and 5-fluorouracil. *Cancer Chemother Pharmacol* 28: 217–219.
 164. Jirari A, Charpentier A, Popescu S, Boidin P, Eisenmann B (1999) A malignant primary cardiac pheochromocytoma. *Ann Thorac Surg* 68: 565–566.
 165. Nakane M, Takahashi S, Sekine I, Fukui I, Koizumi M, *et al.* (2003) Successful treatment of malignant pheochromocytoma with combination chemotherapy containing anthracycline. *Ann Oncol* 14: 1449–1451.
 166. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, *et al.* (2006) Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. *J Clin Oncol* 24: 401–406.
 167. Sisson JC, Shapiro B, Shulkin BL, Urba S, Zempel S, *et al.* (1999) Treatment of malignant pheochromocytomas with ¹³¹I metaiodobenzylguanidine and chemotherapy. *Am J Clin Oncol* 22: 364–370.
 168. Averbuch SD, Steakley CS, Young RC, Gelmann EP, Goldstein DS, *et al.* (1988) Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. *Ann Intern Med* 109: 267–273.
 169. Niemeijer ND, Alblas G, van Hulsteijn LT, Dekkers OM, Corssmit EP (2014) Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 81: 642–651.
 170. Huang H, Abraham J, Hung E, Averbuch S, Merino M, *et al.* (2008) Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. *Cancer* 113: 2020–2028.
 171. Tanabe A, Naruse M, Nomura K, Tsuike M, Tsumagari A, *et al.* (2013) Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine in patients with malignant pheochromocytoma and paraganglioma. *Horm Cancer* 4: 103–110.
 172. Asai S, Katabami T, Tsuike M, Tanaka Y, Naruse M (2017) Controlling tumor progression with cyclophosphamide, vincristine, and dacarbazine treatment improves survival in patients with metastatic and unresectable malignant pheochromocytomas/paragangliomas. *Horm Cancer* 8: 108–118.
 173. Fishbein L, Ben-Maimon S, Keefe S, Cengel K, Pryma DA, *et al.* (2017) SDHB mutation carriers with malignant pheochromocytoma respond better to CVD. *Endocr Relat Cancer* 24: L51–L55.
 174. Edström Elder E, Hjelm Skog AL, Höög A, Hamberger B (2003) The management of benign and malignant pheochromocytoma and abdominal paraganglioma. *Eur J Surg Oncol* 29: 278–283.
 175. Noshiro T, Honma H, Shimizu K, Kusakari T, Watanabe T, *et al.* (1996) Two cases of malignant pheochromocytoma treated with cyclophosphamide, vincristine and dacarbazine in a combined chemotherapy. *Endocr J* 43: 279–284.
 176. Tada K, Okuda Y, Yamashita K (1998) Three cases of malignant pheochromocytoma treated with cyclophosphamide, vincristine, and dacarbazine combination chemotherapy and alpha-methyl-p-tyrosine to control hypercatecholaminemia. *Horm Res* 49: 295–297.
 177. Nomura K, Kimura H, Shimizu S, Kodama H, Okamoto T, *et al.* (2009) Survival of patients with metastatic malignant pheochromocytoma and efficacy of combined cyclophosphamide, vincristine, and dacarbazine chemotherapy. *J Clin Endocrinol Metab* 94: 2850–2856.
 178. van Hulsteijn LT, Niemeijer ND, Dekkers OM, Corssmit EP (2014) (¹³¹I)-MIBG therapy for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 80: 487–501.
 179. Wakabayashi H, Inaki A, Yoshimura K, Murayama T, Imai Y, *et al.* (2019) A phase I clinical trial for

- [(131)I]meta-iodobenzylguanidine therapy in patients with refractory pheochromocytoma and paraganglioma. *Sci Rep* 9: 7625.
180. Inaki A, Shiga T, Tsushima Y, Jinguji M, Wakabayashi H, *et al.* (2022) An open-label, single-arm, multi-center, phase II clinical trial of single-dose [(131)I]meta-iodobenzylguanidine therapy for patients with refractory pheochromocytoma and paraganglioma. *Ann Nucl Med* 36: 267–278.
 181. Yoshinaga K, Oriuchi N, Wakabayashi H, Tomiyama Y, Jinguji M, *et al.* (2014) Effects and safety of ¹³¹I-metaiodobenzylguanidine (MIBG) radiotherapy in malignant neuroendocrine tumors: results from a multicenter observational registry. *Endocr J* 61: 1171–1180.
 182. Shilkrot M, Bar-Deroma R, Bar-Sela G, Berniger A, Kuten A (2010) Low-dose iodine-131 metaiodobenzylguanidine therapy for patients with malignant pheochromocytoma and paraganglioma: single center experience. *Am J Clin Oncol* 33: 79–82.
 183. Ministry of Health, Labour and Welfare (2022) <https://www.mhlw.go.jp/content/12404000/000914217.pdf> accessed on August 1, 2025 (In Japanese).
 184. Japan Radiological Society (2021) http://jsnm.org/wp_jsnm/wp-content/uploads/2021/08/%E7%97%85%E5%AE%A4%E3%83%9E%E3%83%8B%E3%83%A5%E3%82%A2%E3%83%AB.pdf accessed on August 1, 2025 (In Japanese).
 185. Han S, Suh CH, Woo S, Kim YJ, Lee JJ (2019) Performance of (68)Ga-DOTA-conjugated somatostatin receptor-targeting peptide PET in detection of pheochromocytoma and paraganglioma: a systematic review and metaanalysis. *J Nucl Med* 60: 369–376.
 186. Satapathy S, Mittal BR, Bhansali A (2019) ‘Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: a systematic review and meta-analysis’. *Clin Endocrinol (Oxf)* 91: 718–727.
 187. Lassen-Ramshad Y, Ozyar E, Alanyali S, Poortmans P, van Houtte P, *et al.* (2019) Paraganglioma of the head and neck region, treated with radiation therapy, a rare cancer network study. *Head Neck* 41: 1770–1776.
 188. Palmisciano P, Sagoo NS, Haider AS, Ogasawara C, Ogasawara M, *et al.* (2022) Primary paraganglioma of the spine: a systematic review of clinical features and surgical management in cauda equina *versus* non-cauda equina lesions. *World Neurosurg* 161: 190–197.e120.
 189. Breen W, Bancos I, Young WF, Jr., Bible KC, Laack NN, *et al.* (2018) External beam radiation therapy for advanced/unresectable malignant paraganglioma and pheochromocytoma. *Adv Radiat Oncol* 3: 25–29.
 190. Tanabe A, Naruse M, Kinuya S, Katabami T (2011) Clinical characteristics of malignant pheochromocytoma: analysis of 77 cases by the Ministry of Health, Labour and Welfare Research Group on Intractable Diseases. Program of 84th Annual Meeting of Japan Endocrine Society O3-6-13 (Abstract). *Folia Endocrinologica Japonica* 87: 288 (In Japanese).
 191. Yoneda T, Hiraga T (2005) Crosstalk between cancer cells and bone microenvironment in bone metastasis. *Biochem Biophys Res Commun* 328: 679–687.
 192. Japanese Society of Medical Oncology (ed) (2022) Guidelines for the management of bone metastasis (2nd). Nankodo, Tokyo, Japan (In Japanese).
 193. Ayala-Ramirez M, Palmer JL, Hofmann MC, de la Cruz M, Moon BS, *et al.* (2013) Bone metastases and skeletal-related events in patients with malignant pheochromocytoma and sympathetic paraganglioma. *J Clin Endocrinol Metab* 98: 1492–1497.
 194. Kishimoto H, Ogino H, Kitagawa Y, Nomura T, Arai S, *et al.* (2023) Pathology and management of medication-related osteonecrosis of the jaw. Osteonecrosis of the Jaw Committee Position Paper 2023 https://www.jsoms.or.jp/medical/pdf/work/guideline_202307.pdf accessed on August 1, 2025 (In Japanese).
 195. Hisahara K (2014) Adjuvant analgesics. In: Japanese Society for Palliative Medicine, Committee for Palliative Care Guidelines (ed) Guidelines for pharmacologic management of cancer pain 2014. Kanehara Shuppan, Tokyo, Japan: 78–83 (In Japanese).
 196. Mullen JP, Cartwright RC, Tisherman SE, Misage JR, Shapiro AP (1985) Pathogenesis and pharmacologic management of pseudo-obstruction of the bowel in pheochromocytoma. *Am J Med Sci* 290: 155–158.
 197. Mason LD, Prentice WM, Whitelaw BC (2009) An unusual case of severe constipation due to metastatic pheochromocytoma. *J Pain Symptom Manage* 37: e5–e7.
 198. Sweeney AT, Malabanan AO, Blake MA, de las Morenas A, Cachecho R, *et al.* (2000) Megacolon as the presenting feature in pheochromocytoma. *J Clin Endocrinol Metab* 85: 3968–3972.
 199. Thosani S, Ayala-Ramirez M, Román-González A, Zhou S, Thosani N, *et al.* (2015) Constipation: an overlooked, unmanaged symptom of patients with pheochromocytoma and sympathetic paraganglioma. *Eur J Endocrinol* 173: 377–387.
 200. Yamaguchi S, Shibata H, Miyashita K, Kurihara I, Murai-Takeda A, *et al.* (2010) Gastrointestinal pseudo-obstruction after debulking surgery of malignant pheochromocytoma, improved by intravenous administration of alpha-adrenergic receptor blocker, phentolamine. *Hypertens Res* 33: 753–754.
 201. Karri V, Khan SL, Wilson Y (2005) Bowel perforation as a presenting feature of pheochromocytoma: case report and literature review. *Endocr Pract* 11: 385–388.
 202. So KW, Tsui HL, Tsang KH (2021) Colonic pseudo-obstruction as a rare complication of pheochromocytoma. *Eur J Case Rep Intern Med* 8: 002421.
 203. Osinga TE, Kerstens MN, van der Klauw MM, Koornstra JJ, Wolffenbuttel BH, *et al.* (2013) Intestinal pseudo-obstruction as a complication of paragangliomas: case report and literature review. *Neth J Med* 71: 512–517.
 204. Neumann HPH, Young WF, Jr., Eng C (2019) Pheochromocytoma and Paraganglioma. *N Engl J Med* 381: 552–565.

205. Kong G, Callahan J, Hofman MS, Pattison DA, Akhurst T, *et al.* (2017) High clinical and morphologic response using (90)Y-DOTA-octreotate sequenced with (177)Lu-DOTA-octreotate induction peptide receptor chemoradiotherapy (PRCRT) for bulky neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 44: 476–489.
206. Corssmit EPM, Snel M, Kapiteijn E (2020) Malignant pheochromocytoma and paraganglioma: management options. *Curr Opin Oncol* 32: 20–26.
207. Favier J, Pacak K, Clifton-Bligh R (2024) Advancements and challenges in pheochromocytoma and paraganglioma research: a collection of insights. *Endocr Relat Cancer* 31.
208. Baudin E, Goichot B, Berruti A, Hadoux J, Moalla S, *et al.* (2024) Sunitinib for metastatic progressive pheochromocytomas and paragangliomas: results from FIRSTMAPPP, an academic, multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet* 403: 1061–1070.
209. The Japan Endocrine Society (2025) Clinical Practice Guideline for the Diagnosis and Management of Pheochromocytoma and Paraganglioma 2025. *Folia Endocrinologica Japonica* 101 (Suppl Jun): 1–119 (In Japanese).