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Management of Metastatic and/or Unresectable Pheochromocytoma and Paraganglioma

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Background

Pheochromocytomas (PCC) and paragangliomas (PGL), collectively referred to as PPGL, are neuroendocrine tumours arising from chromaffin cells of the autonomic nervous system. PCCs originate in the adrenal medulla, while PGLs develop in extra-adrenal sympathetic and parasympathetic paraganglia. The overall incidence of PPGL is 0.66 cases per 100 000 people per year[1]. Up to 40% are now recognized to be associated with a germline mutation[2], and metastatic PPGL (mPPGL) occurs in 15-25% of cases[3].

PPGL poses clinical challenges because of its heterogeneous presentations and the complexity of care. Management requires coordinated input from endocrinology, genetics, surgery, nuclear medicine, medical oncology and radiology for optimal care. This guideline focuses on the multidisciplinary management of metastatic and/or unresectable PPGL, emphasizing evidence-based approaches to diagnosis, treatment, and follow-up to optimize patient outcomes in this difficult subset of rare tumours. While emerging literature explores molecular cluster-based approaches in mPPGL, current evidence remains limited, and cluster-specific treatment strategies have not been incorporated into this guideline.

Guideline Questions

1. Should patients with primary PPGL or mPPGL undergo germline genetic testing? When?
2. How to work up and diagnose patients with mPPGL?
3. Which PPGL patients should be put under surveillance and what is best practice for these patients?
4. What treatment is recommended for patients with PPGL?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to April 2024, with additional targeted searches conducted in August 2024, January 2025 and October 2025 to identify newly published relevant literature. The specific search strategy, search terms, and search results are presented in Appendix A, and evidence tables are available upon request. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: National Comprehensive Cancer Network (NCCN)[4], United Kingdom Cancer Genetics Group (UKCGG)[5], North American Neuroendocrine Tumor Society (NANETS)[3], and European Society for Medical Oncology (ESMO)[6].

Target Population

The following recommendations apply to adult cancer patients with metastatic and/or unresectable pheochromocytoma and paraganglioma.

Recommendations

While literature explores molecular targeted therapies in metastatic pheochromocytoma and paraganglioma, treatment algorithms by clusters have not been incorporated into this guideline. This will be revised as new data emerges.

Evaluation

1. All patients with metastatic PPGL should be screened for catecholamine secretion[7-9] via serum measurement or 24-hour urine collection. *(Level of Evidence: V, Strength of Recommendation: B)*
    - First line: metanephrine, normetanephrine
    - Second line: 3-methoxytyramine (3-MT)

2. All patients with mPPGL should be offered genetic screening[2,3]. *(Level of Evidence: V, Strength of Recommendation: B)*

3. Perform the following imaging for staging at diagnosis/localization of primary[2-4,8,10-12] *(Level of Evidence: IV, Strength of Recommendation: B)*:
    a. Cross sectional imaging
        - Multiphasic CT or MRI of abdomen and pelvis and enhanced CT of chest.
        - HNPGL: enhanced CT or MRI of neck.
    b. Functional imaging (Vertex to Thigh)
        - For HNPGL, extra adrenal sympathetic PGL, multifocal, metastatic, SDHx mutation: Use SSTR based, Ga-68 DOTATATE PET/CT or PET/MRI.
        - For SDHx mutation, extra adrenal, multifocal, metastatic, or rapidly progressing: Use FDG PET/CT as second choice.
        - For sporadic PCC or inherited PCC associated with NF1, HIF2A, PHD1/2, RET, VHL, MAX: Use FDOPA PET/CT
            - If there is no access to FDOPA, Ga-68 Dotatate may be done instead.
        - I-123-MIBG imaging is not preferred but may be used when the preferred scans are not available.
        - Bone only disease: SSTR based as first line unless SDHx or poorly differentiated/ aggressive disease.

4. Perform the following imaging for locally unresectable or metastatic disease surveillance/radioligand treatment eligibility[3,4,8,11,13,14] *(Level of Evidence: V, Strength of Recommendation: B)*:
    a. Cross sectional imaging
        - Multiphasic CT or MRI of the chest, abdomen, pelvis and neck (for HNPPGL) every 3-12 months. Follow up intervals may be adjusted based on specific patient characteristics at the provider's discretion.
    b. Functional imaging
        - Use the same ligand as baseline for comparability.

- For treatment eligibility: Use SSTR-PET/CT or SSTR-PET/MRI and MIBG SPECT/CT or other agents that have theranostic applications.
- For SSTR/MIBG negative disease or rapidly progressive disease: Use dual imaging with FDG-PET/CT to assess for discordant disease; the utility of FDOPA PET/CT in the assessment of discordant disease is still under investigation but may be considered in selected cases.

Management of Endocrinopathies

5. Use alpha blockade for hypertension and catecholamine excess symptoms[4,8,15]. *(Level of Evidence: V, Strength of Recommendation: B)*

6. Use beta-blockers for hypertension or catecholamine-induced tachyarrhythmia only after established alpha blockade[2-4,15]. *(Level of Evidence: V, Strength of Recommendation: B)*

7. Use calcium channel blockers as adjuvant therapy for hypertension refractory to combined alpha and beta blockade[3,4,15]. *(Level of Evidence: V, Strength of Recommendation: B)*

8. Use individualized management for hypertensive emergency in mPPGL based on concurrent or underlying complications/comorbidities[2-4]. *(Level of Evidence: V, Strength of Recommendation: B)*

9. Consider conducting regular diabetes screening for patients with mPPGL[2-4,16]. *(Level of Evidence: V, Strength of Recommendation: B)*

10. Use antiresorptive therapies (bisphosphonate or denosumab) to reduce the risk of skeletal events[3,4,17]. *(Level of Evidence: V, Strength of Recommendation: C)*
    a. 4mg zoledronic acid annually, if vitamin D >50 nmol/L.

Systemic Treatment Options for Metastatic or Unresectable Disease

11. Radioligand treatments
    a. Use I-131-MIBG for MIBG positive tumours[18-20]. *(Level of Evidence: III, Strength of Recommendation: A)*
    b. Use Lutetium Dotatate for somatostatin receptor positive tumors (Krenning score ≥3)[21,22] *(Level of Evidence: III, Strength of Recommendation: B)*.

The choice between agents is currently based on uptake of the corresponding diagnostic modality; in case of concordant uptake choice of treatment is based on several parameters such as toxicity or other parameters in a personalized approach[10]

    c. For discordant disease (FDG positive, Dotatate/MIBG ±), consider chemotherapy[23]*(Level of Evidence: V, Strength of Recommendation: C)*.

12. Chemotherapy and other agents
    a. For limited unresectable metastatic disease, use radiation therapy, local ablative therapy, or transarterial chemoembolization[3,4,6,24]. *(Level of Evidence: III, Strength of Recommendation: B)*

b. For asymptomatic diffuse unresectable metastatic disease, use surveillance[3,4,25-28]. *(Level of Evidence: IV, Strength of Recommendation: B)*
c. For SSTR-positive slowly progressing disease, use somatostatin analogs (SSAs) [3,8,29,30] *(Level of Evidence: IV, Strength of Recommendation: C)*.
d. For moderately to rapidly progressive disease use either:
    - Sunitinib[31,32]*(Level of Evidence: I, Strength of Recommendation: A)*
    - Cabozantinib[7,33,34] *(Level of Evidence: III, Strength of Recommendation: C)*
        - Cabozantinib is not funded in Alberta. It is currently available through compassionate access
    - For high tumor burden, numerous bone metastases, or visceral crisis, use CVD chemotherapy (cyclophosphamide, vincristine, dacarbazine)[35]. *(Level of Evidence: V, Strength of Recommendation: C)*
    - For PPL/PPGL with VHL syndrome use belzutifan (HIF2A inhibitor)[36] via Special Access Program. *(Level of Evidence: III, Strength of Recommendation: A)*
        - Belzutifan is not funded in Alberta. It is currently available through compassionate access.
e. For locally advanced or metastatic PPGL not amenable to surgery or curative treatment, use belzutifan 120mg orally once daily[36]*(Level of Evidence: V, Strength of Recommendation: B)*

Localized Treatment Options for Unresectable Disease or Focused Metastatic Lesions[4,37-40]

13. Head and neck paraganglioma-localized/unresectable-disease control *(Level of Evidence: III, Strength of Recommendation: B)*
    a. Observation can be considered for asymptomatic or slow-growing, low-volume unresectable disease.
    b. Radiation therapy (RT) can be considered for unresectable disease, medically inoperable patients, patients who decline surgical intervention, or tumour progression after incomplete resection.
    c. Stereotactic radiosurgery (SRS; 13-18 Gy in one fraction for small lesions [diameter of <3 cm] located superior to the level of the T2/T3 interspace) or fractionated stereotactic radiation therapy (FSRT; 21-30 Gy in 3-5 fractions for larger lesions) are recommended.
    d. For patients not eligible for SRS or FSRT, proton therapy referral or photon therapy with intensity-modulated RT/volumetric modulated arc therapy are options (45-54 Gy in 25-30 fractions or a hypofractionated regimen).

14. Pheochromocytoma-Localized/unresectable-disease control *(Level of Evidence: IV, Strength of Recommendation: B)*
    a. Observation can be considered for asymptomatic or slow-growing, low-volume unresectable disease.
    b. Radiation therapy can be considered for unresectable disease with or without cytoreductive (R2) resection, in medically inoperable patients, or recurrent disease.

c. Stereotactic body RT or intensity-modulated RT/volumetric modulated arc therapy are options. A dose >40 Gy is recommended for malignant pheochromocytoma.

15. Metastatic PPGL-Palliative *(Level of Evidence: IV, Strength of Recommendation: B)*
    a. Observation can be considered for asymptomatic or slow-growing, low-volume metastatic disease.
    b. Palliative RT can be considered for oligometastatic disease and/or symptomatic metastatic sites such as in the bone, brain, or soft tissue sites (e.g., for pain relief, spinal cord compression, or hypertension). Techniques and dose regimens for RT are based on the anatomic location. Stereotactic radiosurgery can be considered for patients with brain metastases.

Note: There are no randomized studies to guide sequencing of treatments. The only placebo controlled randomized study for management of metastatic disease is the FIRSTMAPP[31] study that showed antitumor activity of sunitinib in 78 patients.

Discussion

Evaluation

Catecholamine Secretion:

PPGLs often secrete catecholamines[8], contributing to their clinical manifestations. Sympathetic PPGLs, which have a higher metastatic potential, commonly produce catecholamines such as epinephrine, norepinephrine, and dopamine, whereas parasympathetic PPGLs (e.g., head and neck) typically do not secrete catecholamines and exhibit lower metastatic risk[7]. Given the potential for catecholamine-related complications, all patients with metastatic PPGL should be screened for catecholamine secretion[7,8].

Due to the short half-life of epinephrine and norepinephrine, direct measurement is less reliable. Instead, their metabolites are assessed via serum measurement or 24-hour urine collection[8]: metanephrines, normetanephrine, and 3-methoxytyramine (3-MT). In patients with SDHB or SDHD mutations, dopamine elevations are particularly relevant, necessitating comprehensive testing[41]. Clinicians should coordinate with clinical biochemistry to arrange 24-hour urine catecholamine analysis for accurate diagnosis and monitoring.

Genetic Testing:

Up to 40% of pheochromocytoma and PPGL are now recognized to be associated with germline mutations, with key driver genes including SDHx, VHL, RET, NF1, and others, among which SDHB carries the highest metastatic risk[2]. All patients with mPPGL should be offered genetic screening to guide prognosis, identify associated syndromes, and facilitate cascade screening of family members[2,41].

In Alberta, screening is conducted via the hereditary PPGL predisposition panel (including SDHA, SDHB, SDHC, SDHD, SDHAF2, MAX, TMEM127, VHL, FH, NF1), which can be ordered through Connect Care by endocrinologists without requiring a medical genetics consultation. Patients with positive results or variants of uncertain significance (VUS) should be referred to medical genetics for further evaluation. For ordering details, refer to the Alberta Precision Laboratories information sheet.

Imaging:

Staging at Diagnosis/Localization of Primary.

Diagnostic imaging is essential for accurate staging and localization of the primary. Cross-sectional imaging is the primary method for initial evaluation, using multiphasic CT or MRI of the abdomen and pelvis, combined with enhanced CT of the chest. For HNPGL, enhanced CT or MRI of the neck should be performed to evaluate local extent and involvement.

Functional imaging from vertex to thigh is recommended in addition to cross-sectional imaging. Somatostatin receptor (STTR) based PET/CT or PET/MRI (Ga-DOTATATE) is the first choice for HNPGL, extra-adrenal sympathetic PGL, multifocal disease, metastatic disease, or tumors associated with SDHx mutation-associated tumours due to its high sensitivity. FDG PET/CT is a second option for these cases. 18F-FDOPA PET/CT is preferred for sporadic PCC or inherited PCC associated with NF1, HIF2A, PHD1/2, RET, VHL, or MAX mutations, due to its specificity in these genetic contexts. 123I-MIBG is not preferred due to its lower sensitivity compared to other modalities but may be used when the preferred scans are not available. For patients with bone-only disease, SSTR based first line imagining is recommended unless disease is SDHx or poorly differentiation/ aggressive[12].

Locally Unresectable or Metastatic Disease Surveillance/Radioligand Treatment Eligibility.

Surveillance imaging to monitor disease progression and to assess for radioligand is recommended every 3-12 months, individualized based on the patient. This should be cross-sectional, depending on the disease sites, combined with functional imaging. There is no strong evidence that IV administration of iodinated/gallium-based contrast increased risks of hypertensive crisis with functioning PPGL[42]. Functional imaging should use the same baseline ligand for comparability. Additional imaging may be performed for treatment eligibility, with FDG-PET-CT added for SSTR-negative or rapidly progressing disease.

Management

Management of Endocrinopathies:

Medical management with alpha blockade is indicated for hypertension and other symptoms of catecholamine excess (i.e. palpitations and diaphoresis)[15].

Beta-blockers are the next-line agent to control hypertension and /or catecholamine induced tachyarrhythmia, however, they should never be used without established alpha blockade due to risk

of precipitating hypertensive crisis[15]. Calcium channel blockers can be used as adjuvant therapy for hypertension refractory to combined alpha and beta blockade[15]. Best practices for management of hypertensive emergency in mPPGL has not been established and should be individualized based on other concurrent or underlying complications/comorbidities (i.e. ACS, acute kidney injury, CVA, pulmonary edema)[15]. Controlling chronic catecholamine excess through systemic therapy for mPPGL is paramount to preventing hypertensive crisis and other complications related to catecholamine excess[15].

Chronic catecholamine release can lead to insulin resistance and increased risk of type two diabetes mellitus[7], therefore individuals with mPPGL should be considered for regular diabetes screening.

PPGL have predilection to metastasize to bone and skeletal events are common including pain, fracture, and spinal cord compression[7,17,43]. Antiresorptive therapies with either bisphosphonate or denosumab are recommended to reduce the risk of skeletal events[17]. Bone turnover testing can be considered in absence of robust data. A 4mg annual dose of zoledronic acid is recommended, provided vitamin D is above 50 nmol/L.

Treatment Options for Metastatic or Unresectable Disease

Radioligand Treatments:

The management of unresectable of mPPGL hinges on a tailored approach guided by disease stability, imaging characteristics, and clinical parameters. For progressive disease, radioligand treatments such as I-131-MIBG are indicated for MIBG-positive tumors, while Lutetium Dotatate is appropriate for SSTR-positive tumors with a Krenning score ≥3. The choice between agents is currently based on uptake on the corresponding diagnostic modality; in case of concordant uptake choice of treatment is based on several parameters such as toxicity or other parameters in a personalized approach[10]. For discordant disease, characterized by FDG positivity with variable Dotatate or MIBG status, chemotherapy emerges as a viable consideration. The Radioligand Treatment Algorithm (Figure 1) shows a summary of the decision-making process for patients with mPPGL.

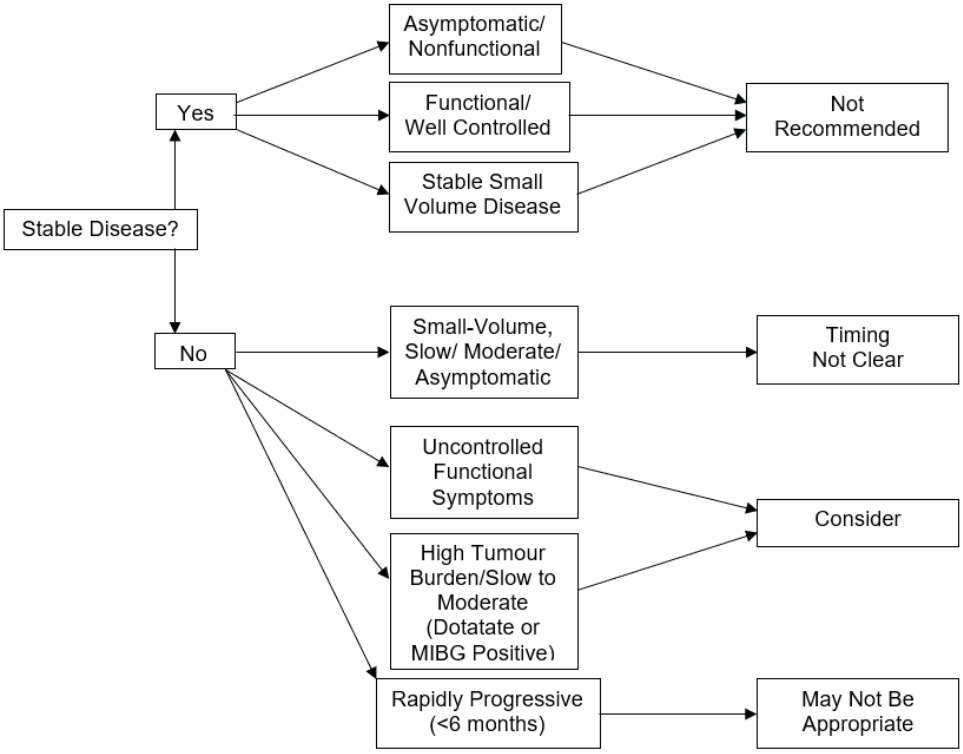

Figure 1: Radioligand treatment algorithm

Chemotherapy and Other Agents:

In the realm of chemotherapy and other agents, limited unresectable metastatic disease can be addressed through radiation therapy, local ablative therapy, or transarterial chemoembolization[3,4,6,24]. Asymptomatic diffuse unresectable metastatic disease may be managed with surveillance, avoiding active treatment unless progression occurs[3,4,25-28]. For slowly progressing SSTR-positive disease, SSAs offer a targeted option[3,8,29,30], while moderately to rapidly progressive disease may benefit from sunitinib or cabozantinib[22,31,32,44-46].

In scenarios involving high tumor burden, numerous bone metastases, or visceral crisis, CVD chemotherapy (cyclophosphamide, vincristine, dacarbazine) is advised[35], with belzutifan recommended for PPL/PPGL with VHL syndrome[36].

Localized Treatment Options for Unresectable Disease or Focused Metastatic Lesions:

In unresectable, asymptomatic, or slow-growing low-volume disease, observation is increasingly accepted as a safe alternative, reflecting the indolent biology of many skull-base tumours[3,24,28,39]. When intervention is required, radiation therapy provides excellent long-term tumour control with preservation of function. Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) have emerged as preferred approaches for small-to-moderate-sized lesions, achieving local control rates exceeding 95 % with low rates of new cranial neuropathy[38]. For larger lesions or those in

close proximity to critical structures, conventional fractionated photon therapy (IMRT/VMAT) or proton therapy offers durable control with acceptable toxicity[3,37,39,40].

For patients with unresectable, recurrent, or malignant disease, external-beam radiation therapy provides effective local control and symptom palliation. Retrospective series demonstrate that doses >40 Gy are associated with significantly improved long-term control compared with lower doses, supporting the use of definitive-dose radiotherapy in this setting[37,40]. Modern techniques such as intensity-modulated radiotherapy (IMRT/VMAT) or stereotactic body radiotherapy (SBRT), when anatomically feasible, further optimize the therapeutic ratio.

In the palliative management of mPPGL, observation remains appropriate for asymptomatic patients with low-volume or indolent disease, avoiding unnecessary treatment-related morbidity[3,28]. For symptomatic metastases, most commonly painful bone lesions or those threatening spinal cord compression, palliative external-beam radiotherapy provides rapid and durable symptom relief in the majority of patients[37,40]. Although brain metastases are rare in PPGL, stereotactic radiosurgery is a reasonable option when they occur[38]. Treatment techniques and dose-fractionation schedules should be individualized according to anatomic site, tumour volume, and proximity to critical organs.

Overall, high-quality randomized evidence is lacking due to disease rarity. Prospective cohort data, large retrospective series, and international consensus statements consistently support surgery as the preferred curative approach and modern radiotherapy techniques including SRS, FSRT, SBRT, IMRT/VMAT, and proton therapy as safe and effective alternatives for disease control in unresectable or symptomatic settings[37-40].

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Appendix A: Search Strategy

Database	Date	Search Strategy	Limits	Results
Pubmed	April 11, 2024	((pheochromocytoma[MeSH Major Topic]) OR (paraganglioma[Title/Abstract])) AND ((metastatic) OR (unresectable)) AND (genetic)	English language, full text, humans, 2019-current,	70
Pubmed	April 12, 2024	(((pheochromocytoma[MeSH Major Topic]) OR (paraganglioma[Title/Abstract])) AND ((metastatic) OR (unresectable))) AND ((diagnos*) OR (work-up))	English language, full text, humans, 2019-current, adult; no reviews or case studies	149
Pubmed	April 15,2024	((((pheochromocytoma[MeSH Major Topic])) OR (paraganglioma[Title/Abstract])) AND ((metastatic) OR (unresectable))) AND (surveillance)	English language, full text, humans, 2019-current, adult; no reviews or case studies	44
Pubmed	April 15,2024	((((pheochromocytoma[MeSH Major Topic])) OR (paraganglioma[Title/Abstract])) AND ((metastatic) OR (unresectable))) AND ((treatment) OR (management))	English language, full text, humans, 2019-current, adult; no reviews or case studies	127

Additional targeted searches were conducted in August 2024, January 2025, and October 2025 to identify newly published relevant literature.

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Endocrine Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Endocrine Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2026.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies or single arm trials
IV	Retrospective cohort studies or case-control studies
V	Case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2031. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

3-MT, 3-methoxytyramine; ACS, acute coronary syndrome; AE, adverse events; AHS, Alberta Health Services; CCA, Cancer Care Alberta; CT, computed tomography; CVA, cerebrovascular accident; CVD, cyclophosphamide, vincristine, dacarbazine; FDG, fluorodeoxyglucose; FDOPA, fluorodihydroxyphenylalanine; FSRT, fractionated stereotactic radiation therapy; HNPGL, head and neck paraganglioma; IMRT, intensity-modulated radiation therapy; mIBG, meta-iodobenzylguanidine; mPPGL, metastatic pheochromocytoma and paraganglioma; MRI, magnetic resonance imaging; OS, overall survival; PCC, pheochromocytoma; PET, positron emission tomography; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma; PRRT, peptide receptor radionuclide therapy; RT, radiation therapy; SBRT, stereotactic body radiation therapy; SDH, succinate dehydrogenase; SRS, stereotactic radiosurgery; SSA, somatostatin analog; SSTR, somatostatin receptor; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; VMAT, volumetric modulated arc therapy; VUS, variant of uncertain significance

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Endocrine Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

***Stella Koumna** reports receiving payments or honoraria for participation on advisory boards or speakers bureaus for Merck Canada, Novartis, and Ipsen.
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