The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Management of Metastatic and/or Unresectable Pheochromocytoma and Paraganglioma

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Abstract: This manuscript is the result of the North American Neuroendocrine Tumor Society consensus conference on the medical management and surveillance of metastatic and unresectable pheochromocytoma and paraganglioma held on October 2 and 3, 2019. The panelists consisted of endocrinologists, medical oncologists, surgeons, radiologists/nuclear medicine physicians, nephrologists, pathologists, and radiation oncologists. The panelists performed a literature review on a series of questions regarding the medical management of metastatic and unresectable pheochromocytoma and paraganglioma as well as questions regarding surveillance after resection. The panelists voted on controversial topics, and final recommendations were sent to all panel members for final approval.

Key Words: metastatic pheochromocytoma, metastatic paraganglioma, management, treatment, surveillance

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Pheochromocytomas and paragangliomas (PPGLs) are tumors of the autonomic nervous system found within the adrenal medulla or extra-adrenal paraganglia, respectively. Pheochromocytoma (PCC) and paraganglioma (PGL) occur in 2 to 8 per million people.[1] Metastatic PPGL (mPPGL) occurs in up to 15% to 25% of people with primary PPGL and can have a long latency period. Pheochromocytomas and PGLs metastasize to the lymph nodes (80%), bones (71%), liver (50%), and lungs (50%).[2] Metastatic disease can be diagnosed at the time of the primary tumor discovery or even as long as 20 years later.[3] People with mPPGL have a 5-year survival rate between 50% and 70%,[4–7] meaning for some individuals, living with mPPGL is a chronic condition, whereas others, unfortunately, will have progressive disease with a subset of those having rapidly progressing, very aggressive disease. Furthermore, in some patients, a primary PPGL may occur in a location where surgical resection cannot be accomplished safely and other therapies are required to control both hormone secretion and tumor growth. Significant advances in the diagnosis and treatment of mPPGL have occurred in the last few years, including improved somatostatin receptor (SSTR)–based nuclear imaging, the first Food and Drug Administration (FDA)–approved therapy for mPPGL, and an increase in clinical trials. Here, we make expert recommendations on the diagnosis, management, treatment, and surveillance of metastatic and/or unresectable PPGL.

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MATERIALS AND METHODS

The expert panel for the North American Neuroendocrine Tumor Society mPPGL guidelines consisted of 18 participants, including 3 endocrinologists, 4 medical oncologists, 4 surgeons, 2 radiologists/nuclear medicine physicians, 1 nephrologist, 1 pathologist, 1 interventional radiologist, 1 radiation oncologist, and 1 endocrine cancer researcher. The panelists met in person in October 2019 and debated all topics through a series of short presentations that reviewed the key literature. After the in-person meeting, panelists voted on questions designed to address areas of controversy and/or those with limited data. For these guidelines, after excluding any abstentions, we defined "consensus" as no more than 1 oppositional vote and "significant majority" as 75% agreement or greater. The full document and the recommendations in the document were circulated to the panelists for final approval.

RESULTS

Inherited Predisposition to PPGL

Up to 40% of PPGL arise in patients with germline pathogenic variants in at least 1 of 12 well-studied susceptibility genes leading to predisposition syndromes (Table 1).[8] The classic cancer predisposition syndromes associated with PPGL are Neurofibromatosis type 1 (NF1), Multiple Endocrine Neoplasia type 2 (MEN2), and von Hippel–Lindau (VHL) disease caused by germline pathogenic variants in *NF1*, *RET*, and *VHL*, respectively. These syndromes most often are associated with secreting unilateral or bilateral PCC. Metastatic disease is rare in patients with MEN2- and VHL-associated PPGL. Although PPGL tumors are rare in patients with NF1, mPPGL can occur in up to 12% of NF1-associated PPGL.[9] Hereditary PGL-PCC Syndrome is caused by pathogenic germline variants in the *Succinate Dehydrogenase Subunit* (*SDHx*) genes (*SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2*), and combined, the *SDHx* genes account for the largest group of hereditary PPGL. Pathogenic germline variants in any of these genes are predisposed to PPGL with varying age-related penetrance based on the gene and a smaller but increased risk of clear cell renal cell carcinoma (RCC) and gastrointestinal stromal tumors.[10,11] Metastatic PPGL is rare in *SDHC*-, *SDHD*-, and *SDHAF2*-associated PPGL, but the risk is higher with *SDHB* (25%–50% by the age of 60 years)[12] and *SDHA* (12% by the age of 70 years).[13] There are other susceptibility genes that are significantly less frequently mutated in patients with PPGL including *TMEM127*, *MAX*, and *FH*. Additional genes have been proposed as susceptibility genes, including *MDH2*, *PHD1*, *PHD2*, *KIF1B*, *SLC25A11*, *GOT2*, *DLST*, and *DNMT3A* (as well as *EPAS1*/*HIF2A* as somatic mosaic).[14–22] Given the rarity of PPGL associated with all of these genes, the true risk of mPPGL is less well understood.[23]

Of patients with mPPGL, approximately 40% to 45% will have a known heritable pathogenic variant. The most commonly associated gene with mPPGL is *SDHB* (over 40% of mPPGL cases), but mPPGL can be associated with sporadic tumors and with any of the other susceptibility genes albeit at a lower rates.[24,25] The knowledge of the germline pathogenic variant, or lack thereof, will have implications for surveillance of the patient and identification of their at-risk family members. If the patient carries a susceptibility gene pathogenic variant, they may be at risk for developing additional malignancies or other conditions, therefore requiring ongoing monitoring, and their blood relatives should be offered site-specific genetic testing. If the blood relative tests positive for the known familial pathogenic variant, that individual should be screened for life for syndrome-associated tumors based on syndrome-specific guidelines, which are outside the scope of this manuscript.[26–29]

Recommendation

We recommend that all patients with primary PPGL or mPPGL have clinical germline genetic testing and recommend family cascade testing if the patient carries a susceptibility gene pathogenic variant (consensus).

TABLE 1. Inherited Genetics of PPGL

Gene	Syndrome	Risk of PPGL	Primary PPGL Location	Risk of mPPGL	Other Associated Features
NF1	Neurofibromatosis type 1	1%–13%	PCC (rare case reports of PGL)	~12%	Neurofibromas, Lisch nodules, café au lait spots, optic gliomas, skeletal dysplasia
VHL	von Hippel–Lindau syndrome	20%	PCC (bilateral) (rare case reports of PGL)	<5%	RCC (clear cell type), pancreatic NETs, hemangioblastomas of the CNS including retina
RET	Multiple Endocrine Neoplasia type 2	50%	PCC (bilateral) (rare case reports of PGL)	<5%	Medullary thyroid cancer, primary hyperparathyroidism
SDHA	Hereditary PGL-PCC syndrome	*SDHA*: 10%	*SDHA*: PGL, PCC	*SDHA*: 12%	RCC (clear cell type), GIST
SDHB	Hereditary PGL-PCC syndrome	*SDHB*: 25%	*SDHB*: PGL, HNGPL, PCC	*SDHB*: 25%–50%	RCC (clear cell type), GIST
SDHC	Hereditary PGL-PCC syndrome	*SDHC*: low	*SDHC*: HNPGL (unifocal), thoracic PGL	*SDHC*: <5%	RCC (clear cell type), GIST
SDHD	Hereditary PGL-PCC syndrome	*SDHD*: 45%	*SDHD*: HNPGL (multifocal), PGL, PCC	*SDHD*: <5%–8%	RCC (clear cell type), GIST
SDHAF2	Hereditary PGL-PCC syndrome	*SDHAF2*: low	*SDHAF2*: HNPGL (multifocal)	*SDHAF2*: low	RCC (clear cell type), GIST
TMEM127		Low	PCC, PGL less common	<5%	RCC
MAX		Unknown	PCC	Unclear	
FH	Hereditary leiomyomatosis and RCC syndrome	Low	PGL	May be high	RCC (papillary type), cutaneous leiomyomas, uterine fibroids

GIST indicates gastrointestinal stromal tumor.

Definition of Metastatic PCC/PGL

The definition of mPPGL is the identification of tumor spread to a location that does not normally have paraganglionic tissue.[1] Only 3 such sites have been proven to definitively qualify as having no paraganglionic tissue, including bone, brain, and lymph node; however, metastatic disease can involve any organ.

Primary PGLs can occur almost anywhere in the body. The distinction between multifocal primary PPGL and metastatic spread of a PPGL is important for optimal patient management. Patients with hereditary predisposition to PPGL are likely to have multifocal primary tumors, and risk for metastatic disease varies depending on the gene. For example, *SDHD* pathogenic variant carriers have high incidence of multifocal primary PPGL, which are usually multiple head and neck PGLs (HNPGLs) but can be anywhere along the parasympathetic and sympathetic chain from skull base to pelvis, and low risk for metastatic disease.[10] As such, patients with multifocal primary tumors can often be managed with surgical resection, local therapy, or active observation. When the multifocal disease is within organs such as lung or liver, it may be more difficult to distinguish primary from metastatic disease.[30] Interestingly, for academic purposes, the extent or burden of disease does not determine if the lesions are metastatic or multifocal. Instead, there are some other factors that might help distinguish the two. For example, those with multifocal disease and sporadic PPGL (where there is no known hereditary predisposition gene pathogenic variant) are more likely to have metastatic disease. In addition, primary pulmonary PGLs tend to be found centrally, whereas a peripheral lesion is more likely to be metastatic; similarly, primary paraganglias in the liver are most commonly found in or near the hilum of the liver.[31] In addition, there are some morphologic markers that may be helpful in the distinction (see pathology discussion later). However, for clinical care, although the location within the organ and molecular and histopathologic markers may be useful to distinguish between multifocal and metastatic disease in these locations, this distinction may not matter, especially when the disease is unresectable (recommendation: significant majority). For clinical care purposes, any evidence of PPGL tumor to nonprimary tumor sites can be considered as metastatic disease (recommendation: significant majority).

In some cases, recurrence in the surgical bed can occur after resection of a PPGL. Most often, this is because of tumor spillage or incomplete resection with regrowth of residual tumor. However, especially in patients with germline predisposition to these lesions, it is also possible that it represents new disease arising in nearby paraganglia or residual adrenal tissue. This explains why recurrence seems to be more common in patients with MEN2 or VHL.[32–36] Regrowth or recurrence in the surgical bed should not be identified as mPPGL. However, management of recurrence can be just as complex as for metastatic disease, particularly when a lesion is deemed surgically unresectable.

Pathology of Metastatic PCC/PGL

The histologic morphology of PPGL that will give rise to metastasis is usually similar to that of nonmetastatic lesions. These tumors are composed of solid nests of round to oval cells that are known as "zellballen." The intervening stroma is usually highly vascular. The tumor cells have abundant granular amphophilic or basophilic cytoplasm; in some tumors, the cells are more elongated and almost spindle shaped. Some tumors have unique morphology: tumors associated with VHL disease have more prominent clear cytoplasm and stromal edema,[37] and those associated with *SDHx* disease may have more prominent and abundant granular eosinophilic cytoplasm. The nuclei vary from uniform with vesicular chromatin to atypical with hyperchromasia; mitoses are generally scarce and necrosis is not usually a feature of these tumors. The PPGL tumor cells have reactivity for neuroendocrine markers including nuclear INSM1 and cytoplasmic synaptophysin and chromogranin, but unlike epithelial neuroendocrine tumors (NETs), they are negative for keratins. Pheochromocytomas and PGLs usually express tyrosine hydroxylase, if from sympathetic chain, and nuclear GATA3, and there is a network of scattered S100-positive sustentacular cells.

Immunohistochemistry can be used to support the diagnosis of mPPGL versus multifocal primary disease, although there are no firm criteria. Both primary and metastatic tumors stain for INSM1, synaptophysin, chromogranin, and tyrosine hydroxylase, as well as nuclear GATA3. However, primary tumors usually have numerous sustentacular cells that stain intensely for S100 protein, whereas metastatic foci may completely lack these highly specialized and unique structural stromal cells that theoretically should not travel with the tumor cells to metastatic foci.[38]

It is not possible to identify which primary PPGLs will give rise to metastatic disease from ones that will not metastasize. The ability to predict metastasis from examination of a primary tumor is desirable; however, no single marker has been shown to predict the development of metastatic disease. In other NETs, the Ki-67 proliferation index can be used to characterize the aggressive potential of disease; however, the association with PPGL is not known.[39] In The Cancer Genome Atlas study, Ki-67 protein expression by immunohistochemistry was performed on a subset of 62 primary PPGL cases and correlated with the presence of metastatic disease, but long-term follow-up was unavailable for most cases.[40] Therefore, it is unclear at this time if Ki-67 index is predictive of aggressive disease (recommendation: consensus). No definitive studies in PPGL exist, and therefore, a recommendation for cutoffs of Ki-67 index cannot be made.

Several studies have proposed histopathologic criteria that can be applied to predict risk of developing metastatic disease (Table 2), but the results have been controversial. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) is a system based on architecture and cellular morphology, invasion, necrosis, and proliferation, where a score less than 4 supposedly is not associated with metastatic spread.[41] This scoring system has limitations. First, it was designed specifically for adrenal PCCs and was not validated for PGLs. Second, it is subject to interobserver variability[42] and, therefore, has not proven to be reproducible. Third, there are some intuitive inconsistencies. For example, all tumors are either graded as monotonous when the nuclei are bland or not monotonous when they have pleomorphic nuclei. Intuitively, pleomorphism should predict a worse tumor, yet profound pleomorphism receives a lower score than monotony (1 vs 2 points), the latter of which is a feature of the majority of tumors.

The Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) was designed to also include extra-adrenal tumors to overcome 1 limitation of PASS.[43] In addition to histologic and cytologic features, it incorporates the degree of tumor cell proliferation using immunohistochemistry for the Ki-67 antigen that is expressed in replicating nuclei, and it has the added advantage of determining the catecholamine profile. This grading system classifies tumors as score of 0 to 10; well-differentiated tumors have a score of 2 or less, moderately differentiated tumors are scored 3 to 6, and poorly differentiated tumors have scores of 7 or greater.[43] The risk of metastasis correlates with score, and the time to metastasis inversely correlates with score, consistent in a separate retrospective cohort study.[44] However, the morphologic feature points also have a lack of clarity regarding definitions. Furthermore, the system has not yet been clinically validated in prospective studies.

Neither PASS nor GAPP incorporates molecular data, such as *SDHB* germline pathogenic variants, which is an important correlate of metastatic behavior.[45] A recent third proposal attempted to address this by combining the PASS and GAPP scores with SDHB immunohistochemistry,[46] because loss of SDHB immunoreactivity suggests a mutation in any one of the *SDHx* genes. However, this system has not yet been clinically validated, and it is important to note that SDHB immunohistochemistry can be incongruent in some cases.[47] Given this, there was no consensus that SDHB immunohistochemistry should be routinely done on all PPGL pathology specimens. In North America, clinical genetic testing almost always is covered by medical insurance and is more reliable than immunohistochemistry. If clinical genetic testing for *SDHB* pathogenic variants cannot be done for some reason, SDHB immunohistochemistry can be considered as an alternative.

In summary, the pathology of mPPGLs is poorly documented. The literature is confounded by mostly retrospective studies with short follow-up time, which can be problematic given the long latency for developing metastatic disease in many patients. Furthermore, many reports fail to consider the possibility of multifocal primary disease in patients with genetic predisposition to the development of these tumors. Prospective studies are needed to assess some of the proposed histopathologic scoring systems, and the future may require a combination of histopathology plus knowledge of hereditary susceptibility gene pathogenic variants and somatic genetic results, the latter of which are not yet used routinely in the clinical setting (see section Tumor-Associated (Somatic) Genetics).

Clinical Predictors of Metastases, Prognosis, and Survival

As outlined previously, PPGL is classified into either nonmetastasized and metastasized tumors, but histologic features are not reliable indicators. However, predicting the likelihood of metastatic disease remains an important question when encountering patients with a primary PPGL as it will strongly influence patient survival, initial clinical and presurgical evaluation (eg, whether to search for any distant metastases, the extent of metastasis), as well as follow-up care. Prognostic parameters regarding survival of patients with mPPGL can provide important information, particularly when deciding on the aggressiveness of therapy, which ranges from an active observation approach to surgical resection to antineoplastic therapy.

The rationale for determining metastatic potential before surgery is that it might influence the surgical approach.[48] The detection of metastasis could make a surgery either more inclusive, including metastasectomy, or less aggressive, focusing on debulking. Features of the primary tumor postsurgically might influence the decision on whether, and to what degree, to conduct postsurgical evaluation for the presence of metastasis, and on how closely a patient will need to be followed. It is important to keep in mind, however, that the majority of PPGL do not metastasize, and therefore, a full imaging evaluation, such as a staging procedure, is neither necessary nor justified for every single patient with primary PPGL.

Presurgical tumor characteristics that make metastatic disease more likely are large tumor size (>5 cm for PCCs, >4 cm for PGLs), gross large vessel invasion, extra-adrenal location, and germline predisposition with an *SDHB* pathogenic variant.[43,49] Although these characteristics are not statistically significant in predicting biological behavior in all retrospective analyses, the majority of studies suggest that these characteristics confer a higher likelihood of metastatic tumors.[4,43,45,49–51] Carriers of *SDHB* pathogenic variants have an overall increased risk of developing metastatic disease of approximately 25% to 50%,[12] yet it must be noted that less than half of individuals with mPPGL have an *SDHB* pathogenic

TABLE 2. Histopathologic Criteria to Predict Risk of Developing Metastatic Disease

Scoring System	PASS (Range, 0–20)		GAPP (Range, 0–10)	
Architecture	Large nests or diffuse growth	2	Zellballen	0
			Large irregular nests	1
			Pseudorosettes	1
Cytology	High cellularity	2	Low cellularity (<150 cells/10 mm^2)	0
	Cellular monotony	2		
	Spindle cells	2	Moderate cellularity (150–250 cells/10 mm^2)	1
	Nuclear pleomorphism	1		
	Nuclear hyperchromasia	1	High cellularity (>250 cells/10 mm^2)	2
Invasion	Vessels	1	Vascular or capsular	1
	Tumor capsule (if present)	1		
	Periadrenal adipose tissue	2		
Necrosis	Focal or confluent necrosis	2	Comedo necrosis	2
Mitoses	>3/10 High-power fields	2		
	Atypical mitoses	2		
Ki-67 labeling index			<1%	0
			1%–3%	1
			>3%	2
Catecholamine type			Epinephrine type (E or E + NE)	0
			Norepinephrine type (NE or NE + DA)	1
			Nonfunctioning type	0
Summary score interpretation	Potential for clinically malignant behavior	≥4	Well-differentiated	0–2
			Moderately differentiated	3–6
			Poorly differentiated	7–10

E, epinephrine; NE, norepinephrine; DA, dopamine.

variant.[24] In addition, it is suggested that the presence of dopamine secretion, or elevated levels of its metabolite methoxytyramine, was more often associated with metastatic disease in a retrospective study.[52] However, in view of the very limited availability of methoxytyramine testing in North America, and the lack of prospective studies, it is not recommended to be checked routinely.

Postsurgical tumor characteristics associated with metastatic or persistent disease can be obvious, such as persistent elevation of metanephrine levels or distant lymph node metastases identified on pathology.

Recommendation

We recommend patients with primary PPGL to have preoperative clinical germline genetic testing (significant majority), as this may change preoperative evaluation for metastatic disease if the patient carries an *SDHB* pathogenic variant (significant majority). If seeing a genetic counselor and obtaining testing will take months, resection of the primary tumor should not be delayed.

An evaluation for metastatic disease should be considered upon diagnosis of a PPGL, and presurgical characteristics should be assessed to help direct surgical options (see section Imaging Studies to Detect and Evaluate for mPPGL). Evaluation for metastatic disease should also be considered after surgery based on postsurgical characteristics to help direct surveillance. Although no single cutoff of suggestive findings can be defined, we suggest considering evaluation for metastatic disease in patients with any concerning features (Table 3). Some suggest that lymphovascular or capsular invasion and tumor necrosis are concerning histopathologic features, but alone, these have not been borne out (no consensus).

Characteristics Impacting Patient Survival in the Setting of mPPGL

Very few studies explore factors predictive of survival in patients with metastatic mPPGL. Five-year overall survival in those with metastatic disease ranges from 50% to 70%,[4–6,53] making mPPGL a chronic illness for many patients. Some patients do have rapidly progressive disease and, unfortunately, succumb more quickly to their disease. To prognosticate survival, treating physicians need to take into account patient- and disease-specific factors.

With regard to patient-specific factors, considerations are not different from other cancers. Decreased performance status, age, age-related frailty, and presence of other comorbidities are likely to influence the disease course and treatment-related toxicity, adverse effects, and complications.[54] Disease-specific factors that have been shown to confer worse prognosis are related to disease extent, such as presence of distant versus regional metastasis, presence of synchronous metastases at the time of diagnosis, and size of the primary tumor.[4,6,55,56] Lung metastases as well as biochemical phenotype of dopamine or methoxytyramine secretion might also be associated with a decreased overall survival.[6] In addition, patients with mPPGL that secrete metanephrine and/or normetanephrine have hemodynamic and other hormonal adverse effect challenges, which can impact morbidity and mortality beyond those with nonsecreting tumors. Interestingly, although predisposing to metastatic disease, *SDHB*-related PPGL do not seem to show a more aggressive course.[6] However, data on the association of these disease characteristics with patient outcome are conflicting. One large study explored the natural history of mPPGL over the course of the first year after diagnosis without treatment. At 1 year, there was 50% progression, and yet they found no association with any analyzed risk factors with progression.[7] In our clinical experience, the rate of disease progression over 6 to 12 months serves as a good marker for overall prognosis.

TABLE 3. Presurgical and Postsurgical Characteristics of Potentially Aggressive PPGL

Characteristics		Consensus on Factor Being Risk Factor for Metastatic or Aggressive Disease
Presurgical		
Large tumor size	>5 cm (adrenal)	Significant majority
	>4 cm (extra-adrenal)	Significant majority
Gross vessel invasion	Present	Consensus
Germline *SDHB* pathogenic variant	Present	Significant majority
Postsurgical		
Tumor with adjacent LN involvement	Present	Consensus
Persistently elevated metanephrine levels even 8 wk postoperative	Present	Consensus
Ki-67 or mitotic index	High	No consensus on cutoff points of either 2% or 5%

American Joint Committee on Cancer Staging for PPGL

Recently, the American Joint Committee on Cancer (AJCC) eighth edition included staging guidelines for PPGL, which had not been included previously.[57] The staging system is based on the recognition of clinical predictors of metastases and survival in the context of tumor size, location, and presence and location of metastatic disease. The current AJCC eighth edition TNM model lacks nuances important for this unique tumor type. For example, it does not include HNPGLs.[58] In addition, because it was published before the latest World Health Organization definitions, it uses the old terms benign and malignant. With the 2017 World Health Organization definitions,[1] experts in the field strongly believe that all PPGLs have metastatic potential and prefer the terms metastatic and nonmetastatic. Nevertheless, the AJCC eighth edition guidelines do make the assumption that all PPGLs have the potential to metastasize, and the guidelines are a step forward toward associating stage with outcomes to help manage and treat patients with PPGL.[57] We summarize the AJCC eighth edition guidelines for TMN staging below and in Table 4.

The AJCC Tumor Origin (T) category uses primary tumor size and tumor location. Size is defined as the measurement of the longest axis of the primary tumor in millimeters. There are some data to support the T categorization. Retrospective studies have evaluated size as a prognostic factor. Pheochromocytomas larger than 5 cm are associated with an increased risk of metastasis and shorter OS.[4] Although metastatic disease can arise from smaller PCC, it is uncommon. Regardless of size, the AJCC considers all extra-adrenal PGLs to be of increased risk (with HNPGLs not included in the staging system). The extra-adrenal location is associated with twice the risk of death from disease compared with a primary PCC larger than 5 cm, making extra-adrenal location a strong predictor of aggressiveness, metastasis, and decreased survival.[4] Nevertheless, once metastatic, PCC and PGL have similar overall survival.[4] No studies have addressed

TABLE 4. Eighth Edition of AJCC Staging Guidelines for PPGL

Definition of Tumor Origin (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T1	PCC size <5 cm in greatest dimension, no extra-adrenal invasion
T2	PCC size ≥5 cm, sympathetic PGL of any size, no extra-adrenal invasion
T3	Tumor of any size with invasion of surrounding tissues (eg, liver, pancreas, spleen, kidneys)

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Lymph node positive

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Distant metastasis to only bone
M1b	Distant metastasis to only lymph nodes/liver or lung
M1c	Distant metastasis to bone plus multiple other sites

Anatomic Stage and Prognostic Groups—PCC/Sympathetic PGL

Tumor Origin	Regional Lymph Nodes	Distant Metastasis	Stage
T1	N0	M0	Stage I
T2	N0	M0	Stage II
T1	N1	M0	Stage III
T2	N1	M0	Stage III
T3	N0	M0	Stage III
T3	N1	M0	Stage III
Any T	Any N	M1	Stage IV

whether the extent of invasion of the primary tumor affects overall prognosis or ability to predict outcome.

The AJCC Regional Lymph Node (N) category is based on metastases found in regional lymph nodes or not. However, to date, no studies have assessed regional lymph nodes metastases as predictors for outcome in mPPGL. This category is largely based on data from other cancer types.

The AJCC Distant Metastases (M) category is based on distant metastasis being defined as evidence of disease in organs where chromaffin cells are not normally present. Using the presence and location of metastatic disease is reasonable for survival prediction. Several studies have demonstrated that the presence of distant metastases portends a worse survival. In fact, only 50% to 70% of patients with distant metastases are alive 5 years after initial diagnosis.[4–6,53] In addition, the location of distant metastases has been found to be important. Patients who only had skeletal metastases exhibit a significantly longer overall survival when compared with patients with or without skeletal metastases but with metastases in other organs such as the liver and lungs (12 vs 5 vs 7.5 years, respectively; log-rank test $P = 0.005$).[4]

Overall, the eighth edition of AJCC offers a starting place for stage grouping of PPGL, despite the limitations. The AJCC staging will provide uniform data collection to be used to evaluate statistical models to predict clinical response. Other variables unique to PPGL may need to be collected in the future (ie, *SDHB* germline status), and consideration must be given for using the same staging for HNPGLs, which are currently not included in the AJCC eighth edition.

Recommendation

Although we feel that many of the current elements and definitions of the AJCC eighth edition staging system for PPGL do not account for the unique characteristics of these tumors, we do recommend the implementation of this system because it will increase data available for better understanding prognostic indicators for survival (consensus). The AJCC staging will facilitate a common language, use an existing infrastructure to capture essential data (Commission of Cancer and American College of Surgeons), and unify a means of abstracting outcomes (National Cancer Database).

Laboratory Workup to Diagnose and/or Follow Patients With mPPGL

All patients with primary PPGL should have biochemical evaluation before surgical resection and have α-blockade per Endocrine Society guidelines.[59] All patients should have plasma-free metanephrines or 24-hour urine metanephrines measured. Plasma catecholamines and 24-hour urine catecholamines have a lower sensitivity and specificity,[59] but it can be useful if evaluating for dopamine secretion. The presence of dopamine (or methoxytyramine if available) and discrepantly high levels of normetanephrine/metanephrine in relation to tumor size can suggest the presence of metastasis or an additional primary PPGL.[52] Patients with mPPGL with nonsecreting disease likely do not need further plasma or 24-hour urine metanephrines measured unless (1) they have a germline susceptibility gene pathogenic variant, as risk for additional primary PPGL is still present, or (2) they develop signs and symptoms of secreting disease. Chromogranin A can serve as a tumor marker in patients with mPPGL to follow disease progression.[60] However, there are many comorbid conditions (such as renal or liver disease) and medications (such as proton pump inhibitors) that can cause false-positive results,[61] which can lead to unnecessary anxiety for patients.

Recommendation

For individuals who had primary PPGL that were secreting, we recommend at least annual testing of plasma-free or 24-hour urine fractionated metanephrines to help detect recurrence or metastatic disease.

Although there may be cases when serum chromogranin A is helpful, such as for those with nonsecreting PPGL, we recommend against routine use of serum chromogranin A testing in all patients with metastatic or primary PPGL given the high false-positive rate (significant majority).

For those individuals with secreting mPPGL, we recommend that plasma-free or 24-hour urine fractionated metanephrines be monitored at least every 6 months (consensus). Small fluctuations in levels may be insignificant, whereas large increases may denote progression of disease.

Imaging Studies to Detect and Evaluate for mPPGL

In the preoperative evaluation for primary PPGL, all patients should have cross-sectional imaging of the body area where the primary tumor is localized. Imaging beyond this area should be reserved for patients with characteristics concerning for metastatic disease, as described previously. Initial studies should be done using

cross-sectional imaging. Although there are no definitive preferences for computed tomography (CT) or magnetic resonance imaging (MRI), both come with advantages and disadvantages. Although resolution is often better on CT scans, MRI tends to have a better sensitivity with regards to blood vessel invasion and detection of liver metastasis.[62]

Functional imaging scans often can more readily detect metastasis. Traditionally, iodine 123 meta-iodobenzylguanidine (^{123}I-MIBG) was most widely used, but this radionuclide has poor resolution and a lower detection rate compared positron emission tomography (PET)–based nuclear imaging modalities.[63,64] A recent study showed that the routine use of ^{123}I-MIBG imaging for any patient with PPGL only altered the initial approach to care in a very small minority of patients, and importantly, for half of that subset of patients, the therapy changes were based on false-positive results.[65] This low sensitivity is also true for ^{111}In-pentreotide scans, which may be more sensitive than MIBG for HNPGL.[66]

The PET/CT imaging modalities have higher sensitivity for detecting mPPGL. Although ^{111}In-pentreotide binds SSTRs, it has low sensitivity for most primary PPGL and mPPGL, whereas newer SSTR analogs that have been developed for use with PET/CT imaging, gallium 68 (^{68}Ga)–DOTATATE PET/CT (most commonly available in North America) and ^{68}Ga-DOTATOC PET/CT or ^{68}Ga-DOTANOC PET/CT, have high sensitivity. A prospective study on patients with *SDHB*-related mPPGL reported a 98.6% lesion-based detection rate on ^{68}Ga-DOTATATE PET/CT compared with an 86% lesion-based detection rate on F 18 fluorodeoxyglucose (^{18}F-FDG) PET/CT.[67] A retrospective study in pediatric patients with *SDHx*-related PPGL reported a 94% lesion-based detection with ^{68}Ga-DOTATATE PET/CT.[68] In patients with sporadic mPPGL, the lesion-based detection rate with ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT was 97.6% and 49.2%, respectively.[69] Taken together, these data suggest superiority of ^{68}Ga-DOTATATE PET/CT over ^{18}F-FDG PET/CT and anatomic imaging modalities to detect metastatic lesions. Importantly, SSTR imaging may also identify involved regional nodes that might be overlooked at the time of initial resection based on size alone. Some studies have used ^{18}F-DOPA PET and found it useful in rare subsets of disease, but this imaging modality is not widely available and used only in a research setting.[70]

Recommendation

A full staging with CT/MRI scan (chest/abdomen/pelvis) is a reasonable choice for presurgical workup in patients with concerning features for mPPGL (see prior section for risk stratification). Although we cannot recommend annual imaging for all patients with primary PPGL, for those at higher risk of metastatic disease, especially those with nonsecreting primary tumors, consider annual imaging. All patients with primary PPGL, regardless of known metastatic risk factors, should have annual plasma-free or 24-hour urine fractionated metanephrines to screen for recurrence or metastatic disease.

We recommend against the routine use of functional imaging in all patients with primary PPGL presurgically or postsurgically; however, if metastatic disease is strongly suspected, given the high sensitivity, and if available, SSTR PET/CT should be a first-line functional imaging modality when suspecting mPPGL given the high sensitivity (significant majority), and it can be safely used in the pediatric population. Somatostatin receptor PET/CT can be used to determine if the patient is likely to benefit from potential peptide receptor radionuclide therapy (PRRT) trials.

An ^{18}F-FDG PET/CT may be a useful alternative, particularly for patients with *SDHB*-associated mPPGL or rapidly progressive disease.

A ^{123}I-MIBG scan is required to select patients for ^{131}I-MIBG therapy; however, ^{123}I-MIBG sensitivity for the detection of metastatic lesions is inferior, in most cases, when comparing with ^{68}Ga-DOTATATE PET/CT and ^{18}F-FDG PET/CT (significant majority).

Imaging for Surveillance and Restaging of Patients With mPPGL Over Time

Typically, anatomical cross-sectional imaging is the most effective imaging for surveillance of mPPGL. Triple phase CT or MRI with contrast have proven sensitivity in the detection of mPPGL liver metastases.[62] Most studies suggest surveillance every 3 to 6 months for patients with mPPGL depending on rate of progression.[71–73] Given the variable rate of progression of mPPGL, the National Comprehensive Cancer Network guidelines recommend that, for locally unresectable or distant metastasis, cross-sectional imaging studies with CT or MRI are recommended every 3 to 12 months or use occasional functional imaging with ^{18}F-FDG PET/CT or SSTR PET (the latter preferred).[74] As discussed previously, functional imaging may be useful when there is suspicion for more disease than seen on cross-sectional imaging, but functional imaging is not recommended for routine surveillance given its cost and radiation exposure. There are no prospective studies to determine the frequency of the scans in patients undergoing systemic therapies.

Recommendation

We recommend surveillance imaging in patients with mPPGL with anatomical cross-sectional imaging with either CT or MRI every 3 to 6 months in the first year, and then if there is stable disease, every 6 to 12 months (consensus).

When patients with mPPGL are on systemic therapies, we recommend surveillance imaging with either CT or MRI at least every 3 to 6 months (consensus).

To evaluate liver metastasis, we recommend triple phase CT or MRI with contrast.

An SSTR PET should not be used routinely for continued surveillance. It may be helpful to repeat SSTR PET in the setting of suspected progression or to evaluate for therapeutic options (consensus). One exception may be for bone only metastatic disease; in this scenario, either SSTR or FDG PET/CT may be useful for routine imaging surveillance (significant majority).

Perioperative Blockade Before Systemic or Localized Therapies

High catecholamine production is associated with hypertension, diaphoresis, headaches, and palpitations among other symptoms and signs such as orthostatic hypotension, hyperglycemia, and anxiety. Before the use of α-blockade and modern anesthesia, mortality at the time of surgery for patients with PPGL was high; however, with current management, mortality is significantly reduced to 0% to 2%.[75] Given this knowledge, we recommend that all patients with a hormonally functional secreting mPPGL undergo preoperative or preprocedural blockade for 7 to 14 days before surgery/procedure and for most localized and systemic therapies to prevent periprocedural cardiovascular complications.[59,76] There is no consensus on which agents to use; however, retrospective studies support the use of α-adrenergic receptor blockers as the first choice and calcium channel blockers as second choice.[59] Calcium channel blocker use is not recommended as monotherapy.[77] Preoperative coadministration of β-adrenergic receptor blockers is indicated to control tachycardia only after administration of α-adrenergic receptor blockers and sufficient volume expansion to avoid the potential for hypertensive crisis

because of unopposed stimulation of α-adrenergic receptors. There is no evidence to support the preference of β1-selective adrenergic receptor blockers over nonselective β-adrenergic receptor blockers. Labetalol, as a mixed α and β receptor antagonist, should not be used as the initial therapy because it can result in paradoxical hypertension and hypertensive crisis given the 1:5 or 1:9 ratio of α to β antagonist action. Methyl-paratyrosine (metyrosine) inhibits catecholamine synthesis and may be used in combination with α-adrenergic receptor blockers for a short period before surgery to further stabilize blood pressure (BP) or used to help control symptoms related to catecholamine excess in those with mPPGL. Use of metyrosine is controversial with varying data. It has been shown in 1 study that, when used in combination with phenoxybenzamine, there were large hemodynamic swings with a wider range of intraoperative BP variations than those treated with phenoxybenzamine alone with no differences in postoperative outcomes,[78] whereas another study showed this combination to improve intraoperative hemodynamic stability and was associated with decreased cardiovascular morbidity.[79] Metyrosine is expensive, is not readily available, and has significant adverse effects, and as a result, it is being used less in clinical practice. Independent of medication regimen, treatment should also include a high-sodium diet and increased fluid intake. Preferred drugs and dosing recommendations are shown in Table 5.

It should be noted that a large observational case series of 110 patients with and 166 patients without α-blockade from 1 center found no differences in maximal intraoperative systolic BP and only a minor difference in mean maximal systolic arterial pressure between groups.[80] Of course, both groups had experienced anesthesiologists well prepared for treating PPGL for the surgical cases. Interestingly, 1 retrospective case series showed no difference in outcomes whether α-blockade was used perioperatively or not,[81] claiming that the anesthesiologist can control BP intraoperatively. Despite these data, we recommend strongly for the use of α-blockade for every surgical case of PPGL to prevent intraoperative hemodynamic instability given the variable experiences of anesthesiologists and surgeons.

When selecting which α-blocker to use, there are limited data supporting both competitive and noncompetitive α-blockers. Traditionally, nonselective noncompetitive α-blockers (phenoxybenzamine) were commonly used because of the nonselective, irreversible action at the level of the receptor and the long duration of action that provides more intraoperative hemodynamic stability.[76] The largest retrospective study of 87 patients demonstrated that α1-selective adrenergic receptor blockers when compared with nonselective α-blockers were associated with lower preoperative diastolic pressure, a lower intraoperative heart rate, better postoperative hemodynamic recovery with fewer adverse effects such as reactive tachycardia, and sustained postoperative hypotension.[82] More recently, a prospective randomized controlled trial compared phenoxybenzamine (nonselective, noncompetitive antagonist) to doxazosin (a selective competitive

TABLE 5. Medications Commonly Used for Hemodynamic Control in Patients With PPGL

Class of Drug	Drug Name	Average Dosing	Special Issues	Common Adverse Effects
α-Blockers				
Selective α1 blockers	Doxazosin	2–8 mg given every 12–24 h	Less potent than nonselective α-blockers	Orthostatic hypotension, dizziness, tachycardia
	Prazosin	2–5 mg given every 8 h	Less potent than nonselective α-blockers	Orthostatic hypotension, dizziness, tachycardia
	Terazosin	4–8 mg given every 12–24 h	Less potent than nonselective α-blockers	Orthostatic hypotension, dizziness, tachycardia
Nonselective α-blocker	Phenoxybenzamine	10–20 mg given every 8–12 h	Expensive, supply limited at times; irreversible binding to α receptors	Orthostatic hypotension, nasal congestion, tachycardia
β-Blockers				
Selective β1-blocker	Metoprolol tartrate	25–50 mg given every 12 h	Aim for heart rate <90/min	Fatigue, dizziness, asthma exacerbation
	Atenolol	25–50 mg given once or twice daily	Aim for heart rate <90/min	Fatigue, dizziness, asthma exacerbation
Nonselective β-blocker	Propranolol	20–40 mg given every 8–12 h	Aim for heart rate <90/min	Fatigue, dizziness, asthma exacerbation
α-Blockers and β-blockers				
	Labetalol	200–2400 mg daily	Used only after the α-blocker as labetalol is a more potent β than α antagonist	Fatigue, dizziness
	Carvedilol	6.25–50 mg given every 12 h	Used only after the α-blocker as carvedilol is a more potent β than α antagonist	Fatigue, dizziness
Calcium channel blockers				
	Amlodipine	5–10 mg daily	Nondihydropyridine calcium channel blocker preferred	Edema, headache
	Nifedipine	30–60 mg given every 12 h	Nondihydropyridine calcium channel blocker preferred	Edema, headache
Tyrosine hydroxylase inhibitor				
	Metyrosine	250–500 mg titrated up to every 6 h	It inhibits the regulatory enzyme of the catecholamine synthesis; not always available, expensive	Severe fatigue, extrapyramidal neurologic adverse effects, nausea, diarrhea, anxiety

antagonist) in 134 patients with primary PPGL and showed no difference in hemodynamic outcomes, with the phenoxybenzamine group requiring more preoperative β-blocker use and less intraoperative vasodilator agents.[83]

Some tumors secrete only dopamine, and there are no data on whether patients with these tumors should be α-blocked before systemic therapies or procedures. Most patients are asymptomatic with dopamine-secreting tumors. If symptoms are present, the most common one is hypotension. Some authors suggest that treatment with α-blockade is not indicated as it may lead to hypotension and cardiovascular collapse.[84] Others suggest treatment with shorter acting selective α1-blockade as patients can develop significant periprocedural complications and suggest that reversal of hypotension is easier to treat if it occurs than hypertensive crisis.[81] Metyrosine decreases dopamine synthesis and can also be useful for controlling symptoms in dopamine-secreting tumors if needed.

Even nonsecreting metastatic lesions can be associated with substantial intraprocedural hemodynamic instability, and based on expert experience, periprocedural blocking is recommended. In those with nonsecreting disease, α-blockade is not needed for everyday use.

Based on limited data, we recommend the use of periprocedural α-blockade for 7 to 14 days before biopsy procedures (usually for an unrelated non-PPGL reason), radiofrequency ablation (RFA),[85,86] cryoablation, microwave ablation,[87] and chemoembolization procedures.[88–90] α-Blockade should be continued for 3 days after the procedure for those with nonsecreting tumors who were not already taking daily α-blockade.[85] α-Blockade should also be used with chemotherapy and systemic therapies, particularly with the use of tyrosine kinase inhibitors (TKIs); however, the duration of blocking is not well defined. Most advocate use of periprocedural α-blockade for patients receiving MIBG therapy.[91] There is conflicting evidence as to the need for α-blockade with radiation therapy.[92,93]

When a patient does not tolerate α-blockers, has adverse effects associated with increasing doses of α- and β-blockers, or has difficulty controlling BP on α- and β-blockers, additional medications are sometimes needed. Nondihydropyridine calcium channel blockers (eg, amlodipine, nifedipine) are most commonly used as second-line agents (Table 5). The main adverse effects of the calcium channel blockers are dependent edema and headaches, with dihydropyridine calcium channel blockers also causing constipation. In addition, angiotensin-converting enzyme (ACE) inhibitors (eg, benazepril, enalapril, lisinopril, ramipril) and angiotensin receptor blockers (ARBs) (eg, candesartan, irbesartan, losartan, olmesartan, valsartan) may help to improve BP in patients with PPGL. The most relevant adverse effects of the ACE inhibitors and the ARBs are cough, hyperkalemia, and rarely angioedema. The ACE inhibitors and ARBs are contraindicated during pregnancy.

There is no evidence from randomized controlled trials to determine the optimal target BP, but based on retrospective studies and expert experience, the goal should be a target BP of at least less than 130/80 mm Hg while seated and greater than 90 mm Hg systolic while standing with a target heart rate of less than 90 bpm before procedures and closer to 70-80 bpm, if possible, for long term control. These targets should be modified in each patient according to age and accompanying cardiovascular diseases. For all perioperative and periprocedural blockades, close monitoring of BP and heart rate is required, with adjustment of associated therapies in the immediate postprocedure period.

Recommendation

We recommend that all patients with metastatic or primary PPGL should be α-blocked 7 to 14 days before any procedure because the concentration of catecholamines within a PPGL may be high even if not secreted (consensus). After ablative or systemic therapies, α-blockade should be continued for at least 3 days to account for a tumor lysis–type release of hormones in those who had nonsecreting disease and were not already taking daily α-blockade.

Typical starting doses of α-blockers to give periprocedurally are phenoxybenzamine 10 mg every 12 hours or doxazosin 2 mg once daily or prazosin 1 to 2 mg once daily, all started at bedtime to temporize possible lightheadedness. For any of the α-blockers, titrate up to highest tolerated dose and BP goals every 2 to 3 days. Table 5 has the typical doses to reach with titration, but it is individualized for each patient.

β-Blockers should be used to treat tachycardia resulting from appropriate α-blockade in patients with metastatic or primary PPGL (consensus).

Hormonal Manifestations and Complications of Secreting mPPGL

The hormonal manifestations of mPPGL are mainly cardiovascular and include catecholamine-induced cardiomyopathy (takotsubo), myocardial infarction, hypertensive emergency or urgency, shock, syncope, arrhythmia, dissecting aortic aneurysm, acute kidney injury, and hemorrhagic or ischemic stroke. Treatment of hypertensive crisis is the same as for those with nonmetastatic disease and includes use of α-blockers with addition of β-blockers and calcium channel blockers as needed. Intravenous agents if needed include nicardipine, phentolamine, magnesium sulfate, and nitroprusside with addition of a β-blocker as needed.[76,94] Chronic treatment with α-blockade should be used for patients who are either hypertensive or who are symptomatic from secretory tumors. Metyrosine can also be used to reduce catecholamine production and for symptom control in patients with high catecholamine load, but there can be significant adverse effects at high doses.

Patients with mPPGL with secreting disease can also experience other systemic effects of high catecholamines, including decrease in gut motility, leading to severe constipation and even ileus, and hyperglycemia, leading to new-onset or worsening diabetes mellitus. In addition, secreting disease can contribute to worsening anxiety and other mood changes. The severe constipation can be life threatening and is preventable.[95] Patients should be counseled on staying hydrated, eating a diet rich in fiber, and the use of laxatives when needed. New-onset or worsening diabetes mellitus should be monitored for and treated as any other form of type 2 diabetes.[96]

There are no data on the long-term effects of secretory tumors in mPPGL and cardiovascular outcomes. There are no data on whether to consider echocardiograms or other routine cardiovascular monitoring and testing for patients with mPPGL.

Recommendation

Patients with secreting mPPGL should be evaluated in clinic with assessment of symptoms, BP and heart rate measurement, and plasma metanephrine levels every 3 to 6 months (consensus). Home BP assessment should also be encouraged. Symptoms and signs of anxiety, mood changes, severe constipation, and new-onset or worsening diabetes mellitus should be monitored for at each visit.

Consider doing a baseline echocardiogram in patients with mPPGL with highly elevated catecholamines, stable disease, and predicted long-term survival over 5 years (consensus), and consider repeating every 3 to 5 years depending on the life expectancy of the patient.

The Role of Surgical Debulking of Metastases in the Setting of mPPGL

There are no direct data to support or refute a benefit of resection of mPPGL. Pheochromocytoma and PGL are rare diseases, and mPPGL is even more uncommon, and current information is retrospective; therefore, the beneficial impact of surgical debulking cannot be assessed. Carefully planned prospective studies are needed. When resection will lead to no evidence of disease, it may be beneficial; when resection will leave residual metastatic foci, the benefits may be less clear. There are limited data on removing metastases. Series of pulmonary metastasectomy are limited,[97] but long-term survival has been reported in a few cases with isolated metastases.[98] There are data that low tumor burden portends a better overall survival compared with patients with high tumor burden.[55] Some potential benefits include the following. First, for those patients with functional tumors, the improvement in symptoms may be expected to be even greater if, after primary tumor removal, further tumor burden is decreased by resection of metastatic disease. Hypothetically, further decrease in catecholamines might decrease cardiovascular risk and other endocrine disorders that could lead to substantial morbidity and mortality.[99] Second, the decreased catecholamine secretion may portend improvement in adrenergic symptoms and make systemic chemotherapy more tolerable. Third, the decreased tumor load may increase the efficacy of subsequent treatments such as chemotherapy,[100] targeted therapy, and radionuclide therapy with agents such as ^{131}I-MIBG. Fourth, the decreased tumor burden may lessen the chance of anatomical complications related to the metastatic tumor location and growth.[55] Fifth, lower tumor burden may lead to a decreased expression of biomarkers associated with tumor development and spread, such as adrenomedullin.[101] This is not used clinically, but research studies suggest that this hormone is implicated in cell proliferation, survival, angiogenesis, immunosuppression, and development of bone metastases; therefore, debulking may have impact.[102,103]

Recommendation

Risks, benefits, and alternatives of debulking procedures for metastases should be considered in shared decision-making capacity with the patient and multidisciplinary teams. When possible, minimally invasive resection techniques of metastatic disease should be considered. Whether prior systemic or local therapies increase, the complication rate of resection is unclear.

Consideration for Removing the Primary Tumor in the Setting of mPPGL

The decision to resect the primary PPGL in the setting of known metastatic disease can be difficult, and the data are limited. Generally, if there is a high burden of metastatic disease, the patient has significant comorbidities, or the symptoms are minimal, then resection is likely not in the best interest of the patient. In contrast, if the patient has resectable metastatic disease, is relatively young, is predicted to have long survival, and has significant symptoms, then removing the primary may be palliative by reducing the disease burden.

Despite the absence of trials addressing this question, there are known factors that can be taken into account when trying to make the decision in individual patients. One study examined factors related to survival in 113 patients with mPPGL over a 15-year period.[55] Patients who had surgery (79% of the total) had a median overall survival of 148 months versus 36 months in those not having surgery ($P < 0.001$), and patients with metachronous metastases had higher overall survival over those with synchronous metastases (172 vs 63 months, $P < 0.001$). On multivariable analysis, the most significant variables for overall survival were surgery (hazards ratio [HR], 0.22), primary tumor size larger than 5 cm (HR, 9.7), PGL versus PCC (HR, 4.8), the presence of bone metastases in addition to liver and lung metastases (HR, 3.0), and high tumor burden (≥7 bone metastases, >50% liver replacement, or ≥3 pulmonary nodules >2 cm; HR, 2.5).[55] One explanation offered for the improvement in overall survival after resection of the primary was reduced cardiovascular events and decreasing future metastases. Because this is a retrospective study, one must be wary that the significant improvement in survival seen in the group with their primaries removed was influenced by selecting patients with more favorable disease for resection. This study addressed this to some extent by finding no difference in ECOG status in the 2 groups and propensity matching, although this only included functional status and sex and not tumor burden or number of metastases, because these were not found to be significantly different between the surgical and nonsurgical groups. Although the level of evidence must be considered weak because it is a cohort study, there are no randomized or larger studies addressing this issue, and therefore these conclusions represent the best available evidence.

If we accept that there is a benefit to resection of the primary PPGL in the setting of metastatic disease, then another important question is whether this should be performed open or laparoscopically. One review of the literature on laparoscopic removal of any adrenal malignancies found that the cons of this approach were port-site recurrence, tumor fragmentation, peritoneal dissemination of tumor, and local recurrence because of periadrenal invasion.[104] They concluded that laparoscopic resection of any adrenal malignancies should only be performed when complete resection with an intact capsule can be achieved, with early conversion to an open procedure if this does not seem achievable laparoscopically. In another series, resection of the primary PPGL in the setting of metastatic disease was performed in an open fashion in 75 patients and laparoscopically in 9.[55] The local recurrence rate for the entire cohort was 34%, but this was not significantly different in the laparoscopic versus open groups. Another study reviewed 96 patients undergoing adrenalectomy for hereditary primary PCC.[35] Recurrences occurred in 1% (1/82) of patients having open total adrenalectomy versus 12% having a laparoscopic approach. Although recurrences were more common in the laparoscopic than open group, this could be because of less familiarity of the laparoscopic approach at the time as this is an older study. Of note, an old and small case series reported 3 cases of pheochromocytosis in patients who had had prior laparoscopic adrenalectomies for primary PCC.[105] The primary tumors were larger and ranged in size from 5.5 to 6.5 cm, and the recurrences were detected by recurrent symptoms 3 to 4 years after adrenalectomy. Each patient had widespread peritoneal disease at exploration, which was thought to be because of laparoscopic disruption of the tumor or leaving an adrenal remnant behind at the original laparoscopic surgery. All patients had normalization of catecholamines for at least 6 months after primary tumor resection, suggesting that there were no overlooked sites of metastatic disease at the first operation.

It is difficult to draw definitive conclusions from these studies. The open approach would seem favorable for larger tumors (>5–6 cm), when there may be invasion of local structures, regional nodal disease, or when there are other sites of intra-abdominal disease. The laparoscopic approach would be expected to lead to quicker recovery, which could be warranted in cases of smaller tumors where removal of additional intra-abdominal disease is not necessary or ruled out (ie, when it is unresectable or in cases of extensive tumor burden where removing the primary is felt to be of benefit).

Recommendation

We recommend surgical resection of the primary PPGL in the setting of metastatic disease if the tumor is secreting, if removing the primary tumor will help prevent local anatomical complications (ie, gastrointestinal or urinary tract obstruction), or if systemic therapy is an option to help decrease tumor burden (consensus). If resection of the primary PPGL is to be performed, we recommend an open approach rather than laparoscopic approach for most primary PPGL larger than 5 to 6 cm.

We cannot recommend for or against removing a nonsecreting primary tumor in the setting of wide-spread bony metastases (significant majority). It may be helpful if the primary is at risk of causing local anatomical complications.

Consideration for Regional Lymphadenectomy

In the setting of mPPGL, if there is disease outside of the locoregional area, it is difficult to know whether removal of the local nodes will impact survival or symptoms. In 1 review of 113 patients with mPPGL, 69% of patients had recurrence in locoregional nodes, which was not impacted by the completeness of surgical resection of the primary tumor (R0, R1, or R2).[55] The extent of nodal dissection performed in these cases was not specified, and of note, in general, details of what constitutes lymph node dissection during adrenalectomy are limited in the literature.

The lymphatic drainage of the adrenal glands was reported in detail in 1966[106] and gives insight into the nodes at risk from adrenal tumors. Based on the adrenocortical carcinoma literature,[107,108] lymph nodes potentially at risk on the left include those that extend from the crus superiorly, to the renal hilum inferiorly, and to the right side of the aorta medially. On the right, the at-risk nodes extend from the lower edge of the liver above to the renal pedicle below, and the lateral edge of the inferior vena cava medially. In PPGL, studies are limited discussing the value of lymph node dissection. An older study described 7 patients with malignant PCC with long-term follow-up and found that lymph node dissection at initial operation, close follow-up, and aggressive resection of recurrences were associated with improved recurrence-free intervals.[109] A limitation to older studies is the definition of "malignant" disease at the time was unclear. A case report of symptomatic PCC recurring in the adrenal bed and retroperitoneal nodes in an adolescent 8 years after initial adrenalectomy reported normalization of BP after resection, suggesting at least palliative benefit to resecting the recurrent disease in regional nodes.[110] A larger study described patterns of recurrence in 129 patients after adrenalectomy for PCC, 11 of whom had nodal or distant metastases at the time of operation.[111] Twenty-five patients developed recurrence or died due to PCC (3 others died perioperatively), including 16 patients with normalization of catecholamines after initial surgery. Nine patients who did not have metastatic disease determined at the first operation developed recurrence, 5 with distant metastases, and 4 had nodal involvement (who had partial response to reintervention). Of note, 10 patients developed contralateral adrenal gland disease, and it was unclear if these were new primary tumors versus metastases.

Recommendation

We cannot recommend for or against routine regional lymph node dissection given the limited data (significant majority). The available studies suggest that lymph node dissection should be considered at initial surgery for larger or locally invasive tumors, or when involved nodes are suggested by preoperative imaging or intraoperative exploration, as these patients will be at high risk for recurrence in regional nodes. Resection of recurrence in regional nodes may also be justified for relief of symptoms or for improvement in survival in selected cases with limited disease.

Radioguided Surgery

The use of radioactive isotopes can be a valuable adjunct to localization of regional nodes or metastases. This can take the form of nonselective radiolabeled agents, such as sulfur colloid, that are taken up in lymph nodes draining from the injection site or isotopes that are specifically taken up in tumor tissue through cell-surface receptor binding and internalization.[112] The use of radioguided surgery (RGS) has been limited for PPGL, but there have been a few isolated case reports and case series. In a series of 8 patients with HNPGLs, each patient had an ^{111}In-pentreotide scan and was explored within 24 hours using a γ-probe.[113] The mean tumor-to-background ratio was 3, and the counts fell to background after removal in all but 1 case, where residual tumor was detected. Two additional case reports described 1 patient each with PCC who developed recurrences 15 or 25 years after initial primary diagnosis.[114,115] Both reports describe the use of γ-probes after ^{123}I-MIBG scans, which were helpful to detect the metastatic lesions intraoperatively. One case noted recurrence 6 months later, suggesting that RGS was not entirely successful. The other case described pheochromocytosis seen at exploration, and the probe allowed them to detect small lesions that may have been missed without it.[115]

The largest and most recent study using RGS in patients with NETs examined results of 44 patients explored after injection of ^{68}Ga-DOTATATE.[116] In this series, there were only 3 patients with PPGL, where 6 tumors were found at exploration. Several important things were learned from this experience, including that a tumor-to-background ratio of greater than 2.5 seemed to have the highest sensitivity, but there were still many false-negatives. The authors felt ^{68}Ga-DOTATATE could be preferable to ^{123}I-MIBG or ^{111}In-pentetreotide because the imaging characteristics are superior, but with its half-life of only 68 minutes, it must be given intraoperatively. The number of patients with PPGL in this study was limited, so it is unclear if the findings are directly applicable to this group.

Recommendation

Given limited data, we cannot recommend for or against RGS (consensus). We suggest that RGS may have utility in patients with mPPGL for helping to localize occult nodal metastases, determining adequacy of surgical margins, and helping to detect small tumors that might not be visible or obscured by scar tissue. There are several different isotopes available, and the timing of exploration after injection, kiloelectron volt settings to best detect γ-photon radiation, radiation exposure, and scatter will differ between isotopes.[117] It is not clear what the best approach for RGS in mPPGL is at this time, but it would be logical to use the isotope with which the metastasis was detected (^{123}I-MIBG or ^{68}Ga-DOTATATE) and to have experience using these isotopes intraoperatively to fully realize its potential.

Interventional Oncology: Biopsy, Ablation, and Embolotherapy

Biopsy

Because PPGLs are highly vascular neoplasms that often secrete catecholamines, percutaneous biopsy has been associated with life-threatening hemorrhage, hypertensive crisis, capsular disruption with tumor implantation, and death.[118] Frequently, the diagnosis of PPGL can be made based on biochemical testing, eliminating the need for a diagnostic biopsy. We recommend

against routine biopsy of suspected or known PPGL. Nonetheless, in some cases of mPPGL, tissue acquisition can be important to patient management, such as investigating actionable somatic mutations. The 2018 American College of Radiology/Society of Interventional Radiology/Society for Pediatric Radiology Practice Guidelines for Percutaneous Biopsy do not specifically address biopsy of PPGL.[119] As we discussed previously in the section on perioperative blockade, we recommend α-blockade before biopsy of a known or suspected functioning tumor with elevated catecholamines and/or metanephrines. The presence of an anesthesiologist to manage acute hemodynamic complications is also a consideration.

Recommendation

Biopsy of known or suspected mPPGL should not be routinely performed, but if necessary, it should be performed under α-blockade (consensus). Monitored anesthesia care should be considered.

Ablation

There are no controlled trials for ablation in mPPGL. Most of the literature is case reports and small series. Attempts at adrenal ablation using percutaneous ethanol injection failed to achieve complete response across a range of histologic tumor types. Injection of PCC was associated with major hemodynamic adverse events.[88] Chemical ablation is also not recommended for this disease.

One series reported on RFA of 7 PCC metastases to liver or bone.[86] All patients were premedicated for 7 to 21 days with phenoxybenzamine, atenolol, and α-methyl-paratyrosine to a target BP of 110 to 120 mm Hg systolic and 60 to 70 mm Hg diastolic with home BP monitoring. Procedures were performed under general anesthesia, continuous arterial pressure monitoring, and a nitroprusside infusion with supplementary medication for BP control as needed. Catecholamines were measured intraprocedurally and demonstrated release of epinephrine and norepinephrine during electrode manipulation and during application of radiofrequency current in all subjects. Complete ablation was achieved on the first attempt in 6 metastases after short-term follow-up; 1 bone lesion required a second procedure for evidence of residual viable tumor on a scan 6 months later.

Another study reported on different types of ablation of 123 metastases in 31 patients (24 PCC, 7 PGL).[85] Of those, 63 (51%) were osseous, 54 (44%) liver, and 6 in other locations. Radiofrequency ablation was used in 61% of procedures, cryoablation in 33%, and percutaneous ethanol injection in 4 subjects. Indications were control of catecholamine excess, local pain, or local control to prevent skeletal-related events or other complications. Most functional tumors received alpha blockade similar to the previously described series. Technical success was 94%. Eighty metastases had imaging follow-up. Among these, 69 (86%) achieved local control, which was equal for RFA and cryoablation. Local control was 94% in liver (all RFAs), 88% for bone cryoablation, and 74% for bone RFA. Pain control was achieved in 100% of evaluable subjects for whom pain was the indication; control of catecholamine excess was achieved in 80% of evaluable subjects. Hospital admission for BP management was required after 12% of procedures.

Recommendation

Percutaneous image-guided thermal (radiofrequency or cryo) ablation is effective for symptom control and prevention of skeletal-related events from oligometastatic mPPGL and should be performed under α-blockade and monitored anesthesia care, because release of vasoactive hormones is expected (consensus).

Embolization

There are no controlled trials of embolotherapy in patients with mPPGL. Embolization is frequently reported in the preoperative setting to reduce blood loss and mitigate hormone release. A meta-analysis of 25 studies encompassing 1326 subjects concluded that preoperative embolization of carotid body tumors significantly reduces blood loss and operative time with no change in stroke, transient ischemic attack, or cranial nerve injury.[89] Another meta-analysis of 22 studies encompassing 578 subjects reached the same conclusion.[120] In contrast, a separate meta-analysis of 15 studies encompassing 470 subjects found no improved outcomes from preoperative embolization of carotid body tumors.[121]

Embolization has been performed before adrenalectomy for large or ruptured PCC and to control symptoms from unresectable primary and metastatic lesions. There are only case reports and outcomes are variable. There are several case reports of chemoembolization of liver metastases, suggesting that this can be done safely with improvement in tumor-related symptoms.

Recommendation

Preoperative embolization may be useful before resection of primary HNPGLs to reduce blood loss and operative time (significant majority).

There is no evidence supporting routine preoperative embolization for abdominopelvic PPGL (consensus).

Chemoembolization can be performed safely for local control/symptom management from PPGL liver metastases (consensus).

Cytotoxic Chemotherapy

Systemic treatment for mPPGL may include the use of cytotoxic chemotherapies such as cyclophosphamide/vincristine/dacarbazine (CVD) or temozolomide-based treatments. The CVD treatment has shown both tumor and biochemical responses in mPPGL, but data are based on small, single-arm, or retrospective studies.[100,122–126] Of note, these studies used older tumor response and biochemical response criteria, which varied between studies and differ from current standards. The largest of the retrospective studies was a meta-analysis of 4 publications evaluating CVD.[124] All 4 publications reported radiographic responses (50 patients), and 2 reported biochemical responses (35 patients). Radiographic partial responses were seen in 37% of patients and biochemical partial responses in 40%; complete responses were rare. Mean cycles to see effect was not reported.

Temozolomide is a newer oral alkylating agent that has shown efficacy in pancreatic NETs (ECOG 2211).[127] Temozolomide is also effective in mPPGL demonstrating both tumor and biochemical responses, but like with CVD, data are based on small retrospective studies.[128–130] A new prospective randomized clinical trial for mPPGL will examine temozolomide versus temozolomide plus olaparib and opened in 2020 (Alliance A021804). This is the only cytotoxic chemotherapy trial currently available. In summary, there is little prospective evidence to guide the choice of cytotoxic chemotherapy (CVD vs temozolomide), timing, or duration in mPPGL.

Adverse effect profiles should be considered when selecting a specific cytotoxic chemotherapy regimen. Temozolomide has a more favorable adverse effect profile than CVD. Temozolomide may cause mild cytopenias, nausea, vomiting, and fatigue; prophylactic antiemetics are generally recommended before each temozolomide dose. Some antiemetics are thought to theoretically be

able to precipitate a catecholamine crisis, which is another reason to ensure α-blockade in patients receiving cytotoxic chemotherapy. The adverse effects of CVD are similar to those associated with temozolomide, although they are usually more severe. There is a small but cumulative risk of developing myelodysplastic syndrome with alkylating agents, including temozolomide and dacarbazine; thus, some prior temozolomide-based studies have limited the total duration of treatment to 1 year.

At present, there are no proven predictive biomarkers to inform the selection of CVD or temozolomide in mPPGL. *SDHB* germline pathogenic variants may predict response to CVD[5] or temozolomide,[128] the latter thought to be due to *SDHB*-associated PPGL having global hypermethylation including the *MGMT* promoter (ie, gene for DNA repair enzyme methylguanine methyltransferase). The currently ongoing prospective study of temozolomide versus temozolomide with olaparib in mPPGL (Alliance A021804) will collect *SDHx* germline and MGMT deficiency status. This trial will provide important information about predictive biomarkers in mPPGL.

Recommendation

Cytotoxic chemotherapy should be considered first line when patients have bulky disease (defined as many large metastases) (significant majority) or symptomatic or rapidly progressive disease (consensus).

Targeted Molecular Therapy Options

Pheochromocytomas and PGLs are characterized by increased microvascular density and elevated expression of angiogenic factors such as the vascular endothelial growth factors and their receptors, the platelet-derived growth factor receptor β, endothelin receptors, and angiopoietin 2.[131,132] Angiogenesis is an important hallmark for mPPGL development. Case reports published a decade ago suggested that potent TKIs with antiangiogenic properties may benefit patients with mPPGL.[133,134] Axitinib, cabozantinib, lenvatinib, pazopanib, and sunitinib are TKIs evaluated in phase 2 clinical trials for patients with mPPGL.[135–137] All these drugs have been associated with tumor size reduction and durable disease stabilization.[132] RECIST partial responses of 13%, 36%, and 37% were noted in the phase 2 clinical trials with sunitinib, axitinib, and cabozantinib, respectively.[132] However, the results of the phase 2 clinical trials with axitinib and pazopanib revealed that a substantial number of patients developed grade 3 and 4 cardiovascular toxicity.[135] These trials titrated the dose of axitinib and pazopanib up, and during the drug titration, several patients experienced adverse events and some were not able to continue treatment. Toxicity was likely because of a combination of factors including BP exacerbation caused by direct vascular toxicity and excessive catecholamine release because of tumor destruction. Conversely, preliminary results derived from the phase 2 clinical trial with cabozantinib (NCT02302833) show no severe cardiovascular toxicity. This trial titrates the dose of cabozantinib down based on patient's tolerability, and preliminary results reveal what seems to be an impressive PFS of 16 months.[132,136] Although overall response to sunitinib is low, patients with germline pathogenic variants in *RET* or in *SDHx* may derive greatest benefit.[137,138]

Multiple phase 2 trials have demonstrated the antineoplastic effects of antiangiogenic TKIs in patients with mPPGL. Therefore, TKIs can be considered as a therapeutic option, although participation in ongoing clinical trials with TKIs is encouraged. Because of associated cardiovascular toxicities with TKIs, patients must be prepared with α- and β-blockers and other antihypertensives before treatment is started. Furthermore, providers must be prepared to manage labile BP and potential catecholamine crisis. Therefore, careful follow-up and aggressive antihypertensive dosage adjustments before and during therapy is needed. The dose of the TKI may need to be adjusted down in response to high BP.

Recommendation

The TKIs could be a therapeutic option for patients with mPPGL, especially for those with tumors that do not express the noradrenaline transporter (MIBG nonavid), mixed tumors, and patients with contraindications for MIBG therapy (ie, bone marrow suppression due to bone metastases) or for any patients with rapid progression (consensus).

Neoadjuvant and Adjuvant Therapy

There are no prospective, retrospective, randomized, or nonrandomized studies evaluating the role of neoadjuvant chemotherapy in large numbers of patients with mPPGL. Considerations for neoadjuvant approaches remain individualized within specialized multidisciplinary teams with careful patient selection criteria. This approach may be considered for example in patients with large functional, symptomatic tumors, with or without metastatic disease, for which initial surgical resection is considered high risk and/or technically difficult and for which tumor shrinkage may enable R0 resection.[100] In this study, 2 patients had tumor shrinkage enabling surgical resection.

There are no retrospective, prospective, or randomized studies evaluating the outcomes of adjuvant chemotherapy for patients at high risk for developing mPPGL (metachronous metastases). The natural progression of mPPGL without treatment is that up to 46% experience a 1-year progression-free survival and 9% may have stable disease for 5 years.[7] Moreover, at present, there is a lack of well-defined consensus prognostic markers to reliably predict the development of metachronous metastatic disease. Thus, the rarity of this disease, the natural course of metastatic disease (slow growing in many patients) with a prolonged overall survival in many, combined with the lack of reliable prognostic markers and the long-term risks of systemic therapies (chemotherapy, TKIs, and/or radionuclide therapies) make it difficult to provide any recommendations regarding adjuvant chemotherapy for this disease type.

Recommendation

We cannot recommend for or against neoadjuvant or adjuvant therapy in patients with mPPGL given there are currently no data (consensus). Consideration for the use of neoadjuvant therapy can be considered on a case-by-case basis with multi-disciplinary team discussion.

Bone Metastases in Metastatic PCC/PGL

The skeletal system is 1 of the most common sites of metastatic disease in mPPGL, occurring in at least 60% to 70% of patients and limited to bone alone in 20% of patients.[2] Patients with bone metastases are at risk of skeletal-related adverse events, which include pain, pathologic fracture, neurologic complications resulting from cord compression, hypercalcemia (uncommon), and the need for surgery and/or radiation therapy because of disease morbidity. Up to 50% of patients with mPPGL experience a skeletal-related adverse event within a median of 12 months from initial diagnosis.[139] The median overall survival in 1 study of 128 patients with mPPGL was 12 years for bone limited disease, 7.5 years for nonosseous metastases, and 5 years for mixed osseous and nonosseous disease.[2] Furthermore, catecholamines may lower bone density as found in 1 study examining patients with catecholamine-secreting PPGL (not necessarily metastatic)

who were found to have lower trabecular bone scores than those with nonsecreting PPGL.[140]

There are no randomized controlled trials, or even open-label trials, to guide an evidence-based approach for the management of patients with metastatic bone disease in mPPGL; thus, treatments are guided by extrapolation from other oncologic therapeutic strategies and tailored to this particular tumor type based on expertise/expert opinion. Consideration of therapy and/or the goals of care in patients with metastatic bone disease in mPPGL, as in other cancer types, include the following parameters: evaluation of the extent of disease (structural integrity of bone, presence or absence of pathology fracture), rate of progression of bone disease, status of other metastatic foci, presence or absence of symptoms, including pain control, restore/preserve function, and prevent disease-related morbidity.

For patients with more focally extensive and/or wide-spread disease, whether on systemic therapy or not, consideration for antiresorptive or bone-targeted agents is recommended with either denosumab, zoledronic acid, or pamidronate. Bone-targeted agents are effective in preventing skeletal-related adverse events in other patients with cancer (breast, prostate, lung) with bone metastases and in reducing pathologic fractures and the need for radiation therapy. Denosumab seems to be the most effective in this setting.[141] The dosing and frequency of bone-targeted agents are not clearly established for patients with mPPGL. Commonly used therapies include denosumab 120 mg subcutaneous every 3 months or zoledronic acid 4 mg intravenous every 3 months and continued during disease progression.[142] It is important to consider that, in patients with mPPGL, particularly that is oligometastatic, their overall survival is greater than 5+ years, thus chronic use of bone-targeted agents must be balanced by uncertain benefits. The most common and/or relevant risks with bone-targeted agents are hypocalcemia, atypical fractures of femur, rebound vertebral fractures, and osteonecrosis of the jaw.[143] Thus, ensuring calcium and vitamin D levels are at target and completing a dental evaluation before the initiation of bone-targeted agents are recommended. Of note, abrupt cessation of denosumab therapy has been associated with an increased incidence of vertebral compression fractures.[144] Patient education regarding adherence to treatment schedule and/or switching to bisphosphonates if denosumab is stopped should be considered in patients on chronic denosumab therapy. If the bone disease progresses on 1 bone-targeted agent, and/or new bone disease develops, consideration may be given to switching to the alternative bone-targeted agent.

Beyond bone-targeted agents, cancer-directed treatment options for bone metastases may include the following: (1) focal therapies such as surgical resection/repair and/or ablative procedures such as external beam radiation-guided therapies and/or interventional radiology-guided thermal ablation and/or vertebroplasty; and (2) systemic therapies, which may include cytotoxic chemotherapy, TKIs, or radionuclide treatments.

Surgical interventions may be guided by decision tools, impending or presence of pathologic fracture, pain, and/or threat of neurologic compromise. Radiation therapy alone, or in combination after surgical intervention, may provide rapid pain relief as well as aide in tumor local control. Thermal ablation, such as RFA or cryoablation, and vertebroplasty have published efficacy in limited studies and may be options for patients not ideally suited for surgery and/or as an alternative to surgery. Such approaches are most often individualized and often done after discussion with a multidisciplinary team.[85,145]

Systemic antineoplastic therapies are indicated in the context of more widely metastatic disease that may or may not be symptomatic and/or rapidly progressive and for which focal therapies alone are unlikely to control overall disease burden. In a cohort of 52 patients, 17 responded to chemotherapy (33%), which included 12 of 17 with bone metastases.[100]

Recommendation

In patients with oligometastatic bony disease that is minimal or low volume, asymptomatic, stable or minimally progressive, and without evidence of urgently threatening structural compromise, surveillance alone may be reasonable.

If there is bony disease, consider bone-targeted agents such as denosumab 120 mg subcutaneous every 3 months or zoledronic acid 4 mg intravenous every 3 months and continued during disease progression (consensus). Because stopping denosumab may accelerate bone loss, we recommend its use only in those with renal function limiting the use of zoledronic acid.

Imaging for Bone Metastases

Twenty percent of patients with mPPGL present with only or predominantly bone metastasis.[2] In 1 large study of 128 patients, the lesion detection rate of bone metastasis was 95% with ^{18}F-FDG PET/CT compared with 70% with ^{123}I-MIBG.[2] An SSTR PET/CT may be even more sensitive for bony metastases in mPPGL.[67,69] In a study of 71 patients, sensitivity of bone scintigraphy with Tc 99m methylene diphosphonate in detection of bone metastasis in *SDHB*-associated mPPGL and non–*SDHB*-associated mPPGL was 95% and 70%, respectively, and overall sensitivity was 82%.[146] Part of the reason for low sensitivity is that the Tc 99m methylene diphosphonate is taken up by sites of active bone formation, not only in areas of bone metastases, but also in areas associated with degenerative disease, trauma, and inflammation.

Recommendation

We do not recommend routine use of bone scintigraphy with Tc 99m methylene diphosphonate because it is a nonspecific imaging method for detecting metastatic bone disease.

Based on the higher sensitivities of other functional imaging modalities, we recommend SSTR PET as a first-line imaging modality in mPPGL with bone involvement (significant majority). ^{18}F-FDG PET/CT can also be considered.

Radionuclide Therapy With MIBG

A hallmark of catecholaminergic cells, including those in many PPGL, is expression of the norepinephrine transporter for uptake of amines into vesicles in the cell. This expression has been exploited for both imaging and therapy using radiopharmaceuticals that are substrates for the norepinephrine transporter. Currently, the most successful radiopharmaceutical is MIBG (iobenguane), which is a guanethidine analog that can be labeled with radioactive iodine in the meta position. It was first described in 1980 as a myocardial imaging agent[147,148] and was quickly used to image the adrenal medulla with the first human experience imaging mPPGL.[149,150] In 1982, the first 5 patients treated with ^{131}I-MIBG were described,[151] and it has been used as an imaging and therapeutic tool since then.

When a radioactive drug is manufactured, there is a mixture of radioactive and nonradioactive molecules of the drug (in this case, MIBG containing either radioactive I 131 or stable I 127). The amount of radioactivity per unit mass of drug is the specific activity, relevant because the drug may have pharmacologic effects in addition to radioactive. The MIBG uptake via the norepinephrine transporter is a saturable, energy-dependent process, so low specific activity MIBG can competitively inhibit catecholamine reuptake leading to hypertension/cardiovascular effects and may

result in lower radiation doses to cancer cells. Most MIBG preparations are low specific activity (including the FDA-approved diagnostic agent), but the FDA-approved therapeutic form is a high specific activity formulation, which was used in the clinical trials for metastatic or nonresectable PPGL. In both cases, the generic drug name is iobenguane I 131.

There have been several published approaches to MIBG therapy for mPPGL that can be generally dichotomized into low dose or nonmyeloablative high dose, and myeloablative high dose with autologous stem cell support used commonly in neuroblastoma but much less frequently in mPPGL.[152–163] Although some series have compared different doses, none have directly compared low dose (typically ~74 MBq/kg; 2 mCi/kg in 4 cycles at 3-month intervals) to high dose (typically ~296 MBq/kg; 8 mCi/kg in 1–2 cycles given approximately 3 months apart). It seems likely that high-dose therapy results in faster response at the expense of more severe acute and subacute toxicity. Objective treatment response can be difficult to judge in mPPGL as it tends to have a relatively indolent course with modest anatomic changes as well as frequent bone metastases that are not measurable by anatomic imaging. The only prospective registrational trial to date treated hypertensive mPPGL patients with high specific activity MIBG at 296 MBq/kg up to a maximum of 18.5 GBq (500 mCi) in each of 2 treatments 3 to 6 months apart.[158] Overall, 25% of subjects had at least a 50% reduction in all antihypertensive drugs, lasting at least 6 months (range, 8–60 months); 49% of subjects had a 50% reduction in antihypertensives of any duration. Objectively, 23% of patients had RECIST partial response and a further 69% had stable disease, and 68% of patients with elevated chromogranin A at baseline had at least a 50% reduction. Interestingly, the highest proportion of biochemical response was at 12 months from the first treatment, highlighting the indolent natural history of mPPGL both in growth as well as in response to therapy. In patients with relatively indolent disease, low- and high-dose therapies seem to have similar long-term outcomes. Conversely, in patients with more aggressive disease, particularly those with *SDHB* germline pathogenic variants, high-dose therapy seems to be more effective (based on anecdotal data).

The use of MIBG therapy is indicated for patients with advanced mPPGL requiring systemic therapy and who have uptake in sites of disease on MIBG imaging. Because many patients have indolent disease, the optimal window for therapy is unclear. However, the presence of metastases alone is not an indication for therapy, and patients should have objective evidence of progression or symptoms that cannot be controlled conservatively. High specific activity MIBG (Azedra) is FDA approved for the treatment of patients at least 12 years old. Furthermore, MIBG is commonly given to very young children for the treatment of neuroblastoma. It should be noted that, in young children with mPPGL, their disease often bears many similarities to neuroblastoma and should often be treated more like neuroblastoma than adult mPPGL.

Each regimen of MIBG therapy can be considered individually, and patients who have clinical benefit may be retreated should they progress or have recurrent disease-related symptoms in the future. There is no preset limit on the cumulative activity of MIBG that can be given, but with increasing number of treatments comes increasing risk of dose limiting toxicity including myelosuppression and secondary malignancies.[154,158,162]

Although uptake on MIBG imaging is a predictor of response to therapeutic MIBG uptake, it is imperfect because of limitations of single photon/SPECT imaging. It is possible that PET analogs of MIBG for diagnostic use will serve as better predictors of response to therapy. No other predictors of favorable outcomes from treatment currently exist.

There is currently no clear role for adjuvant MIBG therapy after complete surgical resection, especially because in most cases primary resection cannot accurately determine whether a patient is likely to develop metastatic disease. In a patient with incomplete resection with gross residual disease, therapy could be considered if the patient otherwise meets criteria for requiring systemic therapy (progression, uncontrolled symptoms), although this is not, strictly speaking, adjuvant therapy. In most cases, the primary therapeutic consideration in such a case would be local therapy, for example, with external beam radiotherapy (RT).

There are no publications specifically addressing neoadjuvant MIBG therapy, although there are anecdotal reports of attempting to use MIBG therapy as a bridge to surgical resection in patients who are either unresectable or whose symptoms preclude safe surgery. Although this can be considered, anatomic change of mPPGL in response to MIBG (and, indeed, most if not all systemic therapies) is relatively slow, often requiring months or years before nadir is reached. If bridge to surgery is considered, a high-dose approach is likely to have a faster anatomic and symptomatic response.

Recommendation

High specific activity ^{131}I-MIBG should be considered for patients requiring systemic therapy and who have MIBG-avid disease (consensus).

There is insufficient evidence to recommend the routine use of ^{131}I-MIBG in the adjuvant or neoadjuvant setting, although using it for a bridge to resectability can be considered, noting that dramatic anatomic responses are rare (consensus).

Adverse Events With ^{131}I-MIBG Therapy

As for patients with mPPGL undergoing any systemic therapy, patients should have their BP well controlled before treatment and should be on α/β-blockade at time of treatment. Inpatient therapy should be considered in patients with labile hypertension and is required for the high specificity MIBG therapy given the high mCi dosing. In the high specific activity ^{131}I-MIBG registration trial, which included 68 patients treated with ^{131}I-MIBG, no patient developed catecholamine crisis,[158] although per the package insert, 11% of patients developed worsening hypertension within 24 hours after treatment.[164] The most common chronic toxicity is bone marrow toxicity, including both cytopenias and subsequent development of leukemia.[158,164] The incidence of leukopenia, thrombocytopenia, neutropenia, and anemia of any grade was 41%, 49%, 39%, and 43% respectively, and grade 3 to 5 events occurred in 28%, 28%, 26%, and 14% of patients, respectively.[158] Caution should be taken in treating patients with preexisting renal failure, proteinuria, and labile hypertension. Per the ^{131}I-MIBG package insert, 7% of patients developed renal failure or acute kidney injury and 22% demonstrated a decrease in estimated glomerular filtration rate. In addition, in a low-specific activity formulation MIBG study, patients with proteinuria developed acute respiratory distress syndrome.[165] It is unclear if there is a risk of acute respiratory distress syndrome when using high-specific activity ^{131}I-MIBG treatment.

Radionuclide Therapy and Adverse Events With Lu 177 DOTATATE

Lu 177 (^{177}Lu) DOTATATE is FDA approved for gastroenteropancreatic NETs[166] and in clinical trials for metastatic or unresectable PPGL. ^{177}Lu-DOTATATE has shown efficacy in treating mPPGLs in small single-center series, but no formal studies are available.[167–170] The largest study to date evaluated 30 patients treated with ^{177}Lu-DOTATATE and reported a 23% overall

response rate.[170] A second study using ^{177}Lu-DOTATATE reported on 22 patients.[169] Radiographic response was seen in 2 of 22 patients, although half the patients had a greater than 50% decrease in uptake on posttreatment SPECT imaging.[169] ^{177}Lu-DOTATATE should be considered in patients who are negative on MIBG imaging, but positive on SSTR PET. In patients with heterogeneous uptake, one should consider imaging using both ^{123}I-MIBG and SSTR PET to determine which agent has uptake across the majority of the metastatic disease. It seems that ^{177}Lu-DOTATATE treatment has a lower rate of bone marrow toxicity compared with ^{131}I-MIBG, although this may be impacted by data using the older low specific activity ^{131}I-MIBG treatment and not the newer high specific activity formulation. In the largest study with ^{177}Lu-DOTATATE, 6 of 22 patients developed hematologic toxicity, with no cases of grade 3/4 toxicity, and 2 of 20 patients had cardiac failure thought to be because of catecholamine release.[170] Similar to ^{131}I-MIBG treatment, acute catecholamine crises can occur with ^{177}Lu-DOTATATE therapy, and patients' hypertension should be medically managed before treatment.

Recommendation

Preliminary data suggest potential clinical efficacy of ^{177}Lu-DOTATATE in a subgroup of patients with mPPGL; however, we suggest participation in a clinical trial if this therapy is considered (consensus).

Immunotherapy

Metastatic PPGLs are tumors characterized by pseudohypoxia that may prevent immune system recognition. Metastatic PPGLs are also characterized by a high rate of single germline pathogenic variants and a very low rate of somatic mutations; these tumors are expected to have low immunogenic antigen density and minimal inflammation.[171] The results of a phase 2 clinical trial with pembrolizumab for patients with mPPGL are now available.[172] Eleven patients who had at least progressive mPPGL in the last 6 months were included in the study. There were modest oncological responses with a nonprogression rate of 40% and a clinical benefit rate, defined as patients with an objective response or stable disease for at least 4 months, of 73%.[172] The objective response rate was 9%, and the progression-free survival was 5.7 months. Toxicity was in line with known treatment-related adverse events for pembrolizumab, including the overall most common fatigue, elevated liver enzymes, and anemia. Of interest, PDL-1 expression and the presence of inflammatory cells in the primary tumor did not seem to correlate with a therapeutic response. Response to immunotherapy did not seem to correlate with the genetic or hormonal status. The biggest limitation to this study is the small number of patients with mPPGL enrolled.

Recommendation

Immunotherapy may bring benefits to subgroups of patients with progressive mPPGLs. Given the very limited data and that the mechanisms that determine a positive response are unknown, we recommend immunotherapy be limited to clinical trials at this time (consensus).

Radiation Therapy

There is a long history of treating localized PGL in patients with unresectable tumors or with medical comorbidities who are not good candidates for surgery with RT.[173] Numerous reports have demonstrated excellent local control with either conventionally fractionated RT to 45 to 50 Gy, stereotactic radiosurgery (SRS), or fractionated stereotactic RT (SBRT).[174] Radiologically, there is minimal regression, and the predominant response is stable disease.[175]

Metastatic PPGLs are extremely rare, and there are no prospective data evaluating the use of RT in this setting. The most common site of metastatic disease requiring RT is to the bone. The role of RT in mPPGL is primarily for symptomatic relief and has historically been delivered with fractionated RT to doses of 30 to 40 Gy in 10 to 20 fractions.[92,176,177] In 1 retrospective study, 17 patients with mPPGL were treated with external beam radiation therapy (EBRT) to 22 distant metastatic sites, of which 15 (68%) were to bone metastases and 8 (36%) were to soft tissue metastases or residual tumor bed disease.[176] The median dose of EBRT was 40 Gy in 17 fractions of 2.25 Gy each. Seventy-six percent of patients had local control at 1 year or until death if this occurred in less than 1 year. Of those patients who lived longer than 1 year, the local control rate at 1 year was 90% (9/10); 1 patient of the 9 had in-field tumor progression at 2 years posttherapy. Also of note, 3 patients with elevated plasma catecholamines and metanephrines had a marked biochemical response post RT. In another retrospective study, 24 patients were treated with RT for 40 bone lesions, 4 in the central nervous system (CNS), and 3 in the abdomen.[177] The most common indications were pain (68%), CNS or spinal cord symptoms (10%), or for residual disease (21%). Patients were treated with either stereotactic radiation (mean, 21.9 Gy) or conformational EBRT (mean, 31.8 Gy). Stable disease was seen in 83% of patients, 17% had progression at a median of 22.5 months, and 81% had symptomatic improvement. Another retrospective study reported their experience with 41 patients and 107 sites, which were in bone (69%), soft tissue (30%), and liver (1%).[92] Local control at 5 years was achieved in 81% of lesions, and symptoms improved in 94%. Taken together, these studies found that radiation was generally well tolerated and useful for local control and relief of symptoms, with higher doses giving better control. Most patients had distant progression, and none reported hypertensive crises during therapy.

More recently, with the introduction of more sophisticated treatment planning and delivery techniques, single fraction SRS and fractionated SBRT have been used to deliver higher doses per fraction in few fractions with the goal of delivering a more radiobiologically effective dose while sparing normal tissue. Palliative RT for mPPGL is associated with excellent symptomatic control and durable local control. Both SRS and SBRT are also effective options, particularly for bone lesions. With only 1 to 5 treatments, SRS and SBRT can be easily integrated into a course of systemic therapy. Standard palliative doses of 30 to 35 Gy using 3 to 4 Gy per fraction can be used for larger tumors that are not amenable to SRS or SBRT.

Recommendation

Radiotherapy is a noninvasive therapy that can be effective for unresectable mPPGL disease, relieving pain, preventing pathologic fracture, and spinal cord compression, with good local control rates.

If bone metastases are in weight-bearing bones, we recommend radiation to those sites for stability (significant majority). Some patients may also require evaluation by orthopedics and/or neurosurgery to see if there will be benefit from other interventions in combination with radiation.

Use of "Cold" Somatostatin Analogs

Somatostatin analogs are effective treatments to prolong progression-free survival in patients with metastatic gastroenteropancreatic NETs with Ki-67 indices 10% or less.[178] We know that SSTRs are present on many mPPGLs based on uptake on SSTR

PET imaging. Therefore, it is hypothesized that perhaps somatostatin analogs would be useful to slow progression of mPPGL. There are several case reports with equivocal results. However, no prospective randomized trials for disease control have been conducted. One prospective cohort study of 10 patients with metastatic or recurrent PPGL examined the effects on catecholamine production after 3 monthly 20 mg Sandostatin LAR injections.[179] Only 6 of the 10 patients had octreotide scan positive disease at baseline. The authors concluded that somatostatin analog did not significantly change catecholamine secretion.[179] There was also no significant effect on any markers of tumor burden or decrease in symptoms, but there was a significant increase in hemoglobin A1C, suggesting treatment led to hyperglycemia. A second prospective crossover study compared short-term 1-day treatment with three 100 μg subcutaneous injections of octreotide compared with placebo in 10 patients with PPGL, and measured BP and catecholamine production.[180] The patients then underwent surgical resection of the primary tumor, and the tumor was evaluated for SSTR expression density. Overall, they found that the octreotide had no antisecretory effects and did not change BP or heart rate, although there was a statistically significant increase in blood glucose ($P < 0.01$).[180]

Recommendation

We cannot recommend for or against the use of somatostatin analogs for mPPGL given the lack of data. Somatostatin analogs can be considered for treatment for patients who have mPPGL, which is avid on SSTR imaging; however, lack of data and the cost of therapy must be part of the decision making process with the patient (consensus).

Consideration for Head and Neck PGLs

Head and neck PGLs are rare, comprising 0.6% of head and neck tumors, and they have a high hereditary component.[181] Furthermore, the majority of HNPGL are nonmetastatic, with only 15% to 19% being metastatic.[56,58] One challenge with the published data in this area is the definition used for "malignant" or metastatic HNPGL, with definitions not being entirely clear in the older studies. A review of the Surveillance, Epidemiology, and End Results Program database from 1973 to 2009 identified 86 patients with clinically aggressive or metastatic HNPGL.[56] Similarly, National Cancer Database reported 59 cases during an 11-year period (1985–1996).[182] The most frequent site for metastatic disease is regional lymph nodes (55%–69%) and distant sites (31%–45%). Risk of metastatic disease for HNPGL varies based on the primary site. It is lowest for carotid body tumors (3%–4%) and highest for orbital and laryngeal PGLs (25%)[183] (Table 6).

The majority of HNPGLs are indolent tumors. The 5-year survival for patients with HNPGL and regional metastases is 60% to 82%, whereas the 5-year survival for patient with metastatic disease to distant sites is 12% to 41%.[56,182] Analysis using the Surveillance, Epidemiology, and End Results Program database noted a median survival of 27 months and 15% 5-year survival for patients not receiving treatment for locally aggressive or metastatic HNPGL.[56] A single-center review of patients with aggressive or metastatic HNPGL noted that no patient had rapidly progressive disease, defined as less than 5-year survival from the time of diagnosis.[184]

TABLE 6. Risk of Metastatic Behavior of HNPGL

Primary Site	Metastatic Rate, %
Orbital	25
Laryngeal	25
Vagal	16–19
Jugulotympanic	5–6
Carotid body	3–4

Because of the rarity of the disease, optimal treatment for metastatic HNPGL is not well defined. Patients with regional lymph node metastases can be treated with surgery, radiation therapy, or both. In a series of 104 patients treated with definitive RT, the majority of whom were not surgical candidates, a local control rate of 96% was achieved.[185] The majority of patients (>90%) were treated with fractionated RT to a median dose of 4500 cGy in 25 fractions. In the small group of patients, RT doses were 6480 to 7440 cGy. A limitation to this study is that not all tumors were progressing before therapy; therefore, it is difficult to say if therapy changed the natural rate of progression.

Skull-based PGLs in the jugular foramen are particularly challenging. Surgical resection is associated with morbidity and cranial nerve deficits.[186] Reports using SRS with 5 fractions of 25 Gy have demonstrated local control rates of more than 95% and improvement in symptoms.[186,187] However, most patients treated with SRS have had small tumor size.

The majority of HNPGL express SSTRs (SSTR2).[188] However, the use of SSAs to treat clinically aggressive or metastatic HNPGL is only anecdotal with multiple small studies demonstrating minimal activity. In 1 case report of 8 patients with HNPGL given 30 mg somatostatin LAR monthly for 3 months, 1 patient had a response.[189] Another case series of 8 patients given octreotide 500 μg 3 times a day reported stable disease.[190] Despite ^{123}I-MIBG and ^{68}Ga-DOTATATE uptake in 50% to 100% of tumors in patients with metastatic HNPGL,[188] there are no prospective data regarding the utilization of ^{131}I-MIBG or ^{177}Lu-DOTATATE in this patient population.

Recommendation

In patients who have a metastatic HNPGL, with regional lymph node involvement, resection including lymph node dissection, followed by radiation therapy, can be considered (significant majority).

In patients with unresectable primary HNPGL, RT represents the best studied option (consensus). The use of SRS has shown mixed results in case report studies. ^{131}I-MIBG or ^{177}Lu-DOTATATE is also a possible option if HNPGL uptake with ^{123}I-MIBG or ^{68}Ga-DOTATATE can be confirmed, respectively, although studies confirming benefits in HNPGL are lacking (consensus).

Consideration for Fertility Preservation Before Systemic Treatment for Younger Patients

Cancer therapy often affects reproductive organs, leading to impaired pubertal development, hormonal regulation, fertility, and sexual function. The impact of treatment-related infertility is dependent on the type of treatment, the degree of exposure, and the age of the patient.

The degree of gonadal toxicity has been assessed after exposure of multiple chemotherapeutic agents. The highest risk of gonadal toxicity in men and women has been demonstrated with treatment by alkylating agents alone or in combination with other drugs. It has been reported that treatment with a lifetime cumulative dose greater than 7.5 g of alkylating agents in men is associated with permanent azoospermia, and an average lifetime cumulative dose of 5.2 g in women is associated with the onset of amenorrhea.[191,192] The associated risk of vincristine monotherapy is considered to be very low risk in women and men.[193,194] Data are limited to small case series for dacarbazine and

temozolomide. Both have been associated with a transient drop in spermatogenesis, but data are lacking in women.[194–196]

The tolerance of normal tissues to radionuclides is variable. Much of the variability is attributed to the differences in dosimetry methodology and the heterogeneous distributions of the radionuclides. There are no data regarding the impact of radionuclide therapies on fertility; however, the package inserts for ^{177}Lu-DOTATATE and ^{131}I-MIBG both discuss risk of temporary or permanent infertility with therapy and provide estimated absorbed doses to the ovaries and testes.[164,166]

Recommendation

Although the risks are different for specific treatment options, we recommend following the American Society of Clinical Oncology guidelines and advocate that all patients of reproductive age diagnosed with cancer should be informed of the potential for gonadal toxicity and the options to preserve future fertility (consensus). These options include harvesting sperm or oocytes and freezing sperm, oocytes, or blastocysts. Patients who choose the option of fertility preservation should be referred to appropriate reproductive specialists before the initiation of cancer-based therapies. The discussion on fertility preservation also opens the opportunity to address preimplantation genetic diagnosis for patients with hereditary syndromes predisposing to PPGL. This involves testing germ cells before implantation and selecting those without known pathogenic variants in susceptibility genes.

Consideration for Stem Cell Preservation Before Systemic Therapy

Hematologic sequelae, in the form of myelosuppression, have been described as a result of most forms of cytotoxic treatment. The degree of impact is dependent upon the type of treatment, degree of exposure, and past exposure to marrow-toxic therapies. When the treatment risk of hematologic toxicity is significant, as is most commonly seen with chemotherapy myeloablative regimens, stem cell preservation has been used and consists of peripheral blood stem cell leukopheresis before the administration of myeloablative treatments, and reinfusion after treatment effect is assessed.

Different chemotherapies have different toxicity profiles. Independent of the particular agent, transient hematologic toxicities are commonly seen. In long-term follow-up of combination regimens including alkylating agents in a variety of cancers, the risk of therapy-related myeloid malignancy, acute myeloid leukemia, or myelodysplastic syndrome (MDS) ranges from 1% to 5%.[197–199] In studies that included therapy with alkylating agents in mPPGL, the reported transient hematologic toxicity ranges from 10% to 30%; none of the studies reported treatment-associated hematologic malignancy.[122,123,128]

Hematologic toxicities have also been reported with the administration of PRRT for NETs.[200–202] Any grade hematologic toxicities have been reported to be approximately 10%. The incidence of therapy-related myeloid neoplasm, acute leukemia, or MDS was reported as high as 2.9%. No clear association has been demonstrated with burden of disease, in particular bone involvement, and risk of hematologic toxicity.[200–202]

Hematologic toxicity also exists with MIBG therapy. With high specific activity MIBG, acute leukemias and MDS were reported in 6.8% of the 88 patients who received a therapeutic dose.[158,164] A clear association has been described between the dose of conventional low specific activity MIBG and hematologic toxicity.[154,159,203–207] With MIBG, the degree of marrow toxicity is reportedly more significant to that reported with chemotherapy and PRRT. Most notably, persistent marrow dysfunction is described in many of the trials, with an incidence of 8% to 12%. However, because of the small number of patients in these trials the dose, toxicity association has not been clearly defined.[154,159,203–207] Based on the concern for hematologic toxicity, some studies using high-dose MIBG have included stem cell preservation in the pretreatment protocol. Only 1 study of 50 patients noted persistent marrow toxicity in 4 patients that required autologous stem cell rescue.[154]

In the treatment of mPPGL, peripheral blood stem cell preservation use has been limited to high-dose low specific activity conventional MIBG therapy. Although hematologic toxicities are significant after high doses of chemotherapy, PRRT, and MIBG, the current data highlights deficiencies in our knowledge regarding extent and durability of hematologic toxicities with sequential therapies and the role of preexisting hematologic risk factors. And, of note, little to no data are known about the longer-term effects of the FDA-approved high specific activity MIBG.

Recommendation

We cannot recommend for or against stem cell preservation (consensus). Stem cell preservation is not standard of care. However, any patient with preexisting cytopenias, or one who is being considered for sequential therapy with an alternate therapeutic modality, should be considered for a hematologic consultation to discuss the risk of durable marrow toxicity and the clinical indication for stem cell preservation.

Tumor-Associated (Somatic) Genetics

The landscape of somatic mutations and their contribution to mPPGL are still poorly defined.[40,208,209] Somatic driver events involving the *MAML3* cotranscription factor through amplification and/or fusion to upstream partners have emerged as candidates associated with aggressive and/or mPPGL,[40,210] although its prevalence has not yet been precisely defined. Somatic *NF1*, *VHL*, and *HRAS* mutations have also been described in mPPGL.[40,210,211] Approximately one third of all mPPGL do not have a clearly recognizable initiating driver mutation.[40]

Somatic events in genes involved in cellular immortalization, such as *TERT* and *ATRX*, are common features of many cancers[212] and have also been reported in mPPGL. *ATRX* mutations often co-occur with germline *SDHB* mutation or with other germline or somatic mutations.[208,213,214] This profile suggests that *ATRX* mutations function as a modifier event, which might contribute to the tumor transformation rather than its initiation. Likewise, somatic activation of the telomerase reverse transcriptase gene, *TERT*, by promoter methylation, mutation, translocation, amplification or overexpression is overrepresented in mPPGLs, often co-occurring with other driver mutations.[215,216] *ATRX* and *TERT* disruptions tend to occur in a mutually exclusive manner in PPGLs.[216] Importantly, these 2 markers seem to confer independent risk for metastatic potential and patient survival.[216] Data from a single retrospective study suggest that *ATRX/TERT* aberrations contribute to approximately 70% of mPPGLs.[216] However, as *ATRX* or *TERT* defects have also been detected in non-mPPGLs, it remains to be determined whether these tumors will eventually progress to metastasis, thus supporting a role for ATRX/TERT as markers of tumor transformation and potential predictors of poor prognosis. Prospective studies with long-term follow-up are needed to verify these promising findings.

Finally, somatic alterations in microRNAs (in particular, miR-21-3p/miR-183-5p)[217] and DNA methylation (eg, *RDBP* gene)[218] have retrospectively been correlated with metastatic risk of PPGLs. These studies deserve further investigation in prospective analyses.

Consideration for Tumor Specific (Somatic) Genetic Testing

Somatic genetic testing is currently used to guide management of multiple sporadic cancers; however, this practice has not been adopted in mPPGL outside of academic research settings due to limited data.

If confirmed by future prospective studies, identification of certain somatic events, such as *ATRX* or *TERT* alterations and *MAML3*-fusions, may have value for prognostic prediction in mPPGL.[40,219] In addition, identification of potentially actionable somatic genetic lesions holds promise as a potential guide for therapy selection in mPPGLs. A larger body of work is still needed to define the ideal composition and format of a somatic panel to test PPGL.

Currently, *SDHB* germline pathogenic variant is the best molecular indicator of increased risk for metastatic disease.[220] Immunohistochemistry for SDHB (loss of SDHB staining) has been demonstrated to serve as a surrogate of SDHB function (ie, germline pathogenic variant).[221,222] Therefore, SDHB immunohistochemistry has been proposed as a complement to the evaluation of germline *SDHB* variants of uncertain significance.[219] However, there are cases of incongruent results with clinical genetic testing as discussed previously, which makes this an imperfect marker. Furthermore, any disruption of the SDH complex by pathogenic variants in other subunits may make SDHB immunohistochemistry negative. Nevertheless, SDHB staining may serve as an initial screen for SDHB dysfunction or germline pathogenic variant in centers where germline genetic testing of PPGLs is not yet broadly available. Adopting SDHB staining would require the establishment of robust and well-defined protocols for SDHB immunohistochemistry as well as guidelines for evaluation and interpretation of results, which are not straightforward.

Recommendation

Given limited data, we cannot recommend routine clinical use of somatic genetic testing for mPPGL at this time, but we are optimistic there may be benefit in the future (significant majority). For now, somatic testing should be considered research.

Using Germline and/or Somatic Genetics to Predict Prognosis or Response to Therapy

As described previously, certain germline and somatic mutations have been associated with risk for metastatic disease. However, whether these mutations also predict patient outcome has not been fully defined. Approximately 40% to 50% of patients carrying an *SDHB* germline pathogenic variant do not develop metastases over prolonged follow-up.[216,220] On the other end of the spectrum, some patients with germline *FH* pathogenic variants[223] or *MAML3* somatic fusion or amplification[40,210] do not have metastases, although long-term follow-up is required to determine outcome because some metastases can develop even 20 years after initial tumor diagnosis. Thus, it seems that metastatic risk and outcomes may be determined by distinct factors. This is a critically important issue that can impact patient management and should be addressed by future well-designed prospective studies with long-term follow-up.

Few studies have addressed the role of driver mutations in therapeutic response of mPPGLs, but emerging retrospective data suggest that patients with *SDHB* germline pathogenic variants show better response to CVD than non-*SDHB* carriers.[5] In addition, patients with germline pathogenic variants in *RET* and *SDHB* with mPPGLs had better outcome after sunitinib[137,138] or temozolomide[128] treatment, although these were small retrospective cohorts. These studies seem to support the notion that, although the risk of metastatic disease is unquestionably higher in carriers of an *SDHB* mutation, among patients with metastatic disease, the presence of an *SDHB* mutation may in fact be associated with better outcome and greater therapeutic response. The retrospective nature of the studies above limits further interpretation, but these observations should be evaluated in prospective studies as they have the potential to impact patient care.

The Future of Molecular Markers as Predictors of Metastases, Prognosis, and Survival

Detection of tumor-derived material in blood or other fluids, also known as liquid biopsy, has become feasible and can potentially be used for early-stage detection, treatment monitoring, and identification of recurrent or residual disease in solid cancers.[224] However, the clinical validity and utility of liquid biopsies is still being evaluated, as this method is highly dependent on the shedding rate and the degree of heterogeneity of each tumor. The detection of circulating tumor material in PPGLs is limited to a few studies of microRNA and exosomal DNA.[217,225] A question that remains open is whether somatic events that are relevant for tumor outcome can be potentially tracked in patients by liquid biopsy and outperform existing biomarkers. For example, metanephrines have been long established as a reliable indicator of tumor burden in secreting PPGLs.[226] Another consideration is that well-established driver mutations in mPPGLs, such as *SDHB* pathogenic variants, are detectable in the germline and can be easily assessed by routine molecular screening. Additional studies are needed to demonstrate the value and applicability of liquid biopsies for management of patients with mPPGL.

GAPS IN KNOWLEDGE

Although significant progress in the field has been made over the last 2 decades, many questions remain about how to predict metastatic/aggressive disease and how best to treat it. For example, "Are there molecular markers in the primary PPGL which will predict metastatic spread?" "When should we intervene with systemic therapy in individuals with mPPGL versus continue with active observation?" "Are outcomes improved if the primary tumor is removed in the setting of low-volume metastatic disease?" "Can we predict with molecular markers that individual's disease will respond to which therapy?" "Are combination therapies more effective than monotherapy?"

To address many of these questions, the lack of preclinical models has been a huge barrier. Human cell lines have been difficult to create, and the limited animal models lack features of the human disease.[227] Recently, a xenograft and cell line model was developed for SDH-deficient PGL from rats with heterozygous germline *Sdhb* mutation.[228] The mRNA expression profile for the PGL is similar to the human pseudohypoxia mRNA expression subgroup suggesting validity of the model. Additional cell lines, organoids, and animal models are needed to be able to study the heterogeneous mPPGL and test novel therapies.

DISCUSSION

Metastatic PPGL is a rare disease, and although there are no known cures, patients can live with the disease for a long time. Because the disease can be indolent, active observation is an option even in the setting of widely metastatic disease. Local therapies including surgical resection, radiation therapy, embolization, or ablation can be useful in certain settings for symptomatic control or in limited metastatic disease. Systemic therapies are recommended for those patients with progressive disease and include radionuclide therapy, cytotoxic chemotherapy, and targeted

therapies. High levels of evidence for any of these therapies is lacking. There is also limited follow-up even for retrospective studies. Given the limitations of the data as well as the heterogeneity of this patient population, especially given the high degree of hereditary predisposition, we recommend that clinical care for patients with mPPGL be given at expert centers within a multidisciplinary environment. Participation in clinical trials is encouraged as novel treatments are being investigated.

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