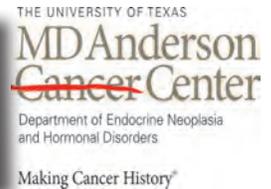




**Malignant Pheochromocytomas and Paragangliomas:
 Clinical Predictors of Malignancy and Systemic
 Therapeutic Approaches**



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The World Health Organization defines pheochromocytoma (PHEO) as a tumor arising from the adrenal medulla and paraganglioma (PGL) as a tumor arising from the paraganglia outside the adrenal medulla. PGLs are located in the head, neck, thorax, abdomen, and pelvis, and can be classified as parasympathetic and sympathetic depending on their origin. Parasympathetic PGLs are mainly located in the head and neck; these tumors may be locally invasive but rarely develop metastases and are not discussed here. Approximately 10-17% of PHEO/PGLs are metastatic. Treatment against metastatic disease includes systemic chemotherapy and radiopharmaceutical agents that are mostly nonspecific and indiscriminately target dividing cells. Patients with metastatic tumors have high morbidity and mortality rates from excessive catecholamine secretion, cardiovascular complications, and bulky disease, for which no curative treatment is available. The 5-year overall survival rate for patients with metastatic tumors ranges is approximately 50%. However, over the last decade our understanding of the genetic and molecular causes of PHEO/PGL has markedly improved. Up to 50% of metastatic cases could be associated with hereditary germline mutations. Additionally, many sporadic metastatic PHEO/PGLs share a similar molecular profile with hereditary tumors. This knowledge is now leading to the development of new therapies based on the molecular mechanisms involved in the formation of malignant PHEO/PGLs. In this review, we will describe clinical predictors of malignancy that could determine the aggressiveness of follow-up and treatment and our current systemic therapeutic approaches for patients with unresectable disease.

Clinical Predictors of Aggressiveness and Overall Survival

There are three recognized clinical predictors of

malignancy and survival: 1. Primary tumor size, 2. Primary tumor location (adrenal vs. extraadrenal), and 3. Germline SDHB mutations. A primary tumor size larger than 5 cm is associated with a shorter overall survival and an increased risk of metastases. Metastases in PHEOs smaller than 5 cm in size are uncommon.

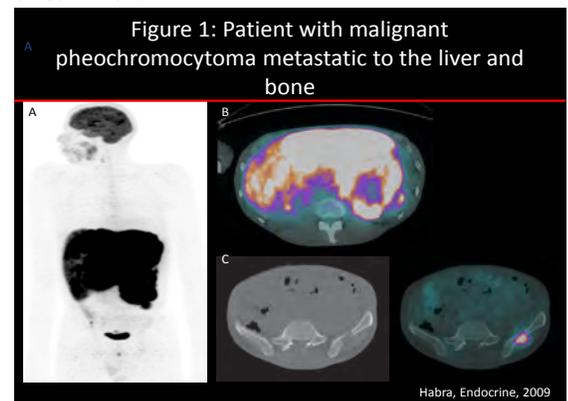


Figure 1: Patient with malignant pheochromocytoma metastatic to the liver and bone

Sympathetic PGLs located in the abdominal (Zuckerkind organ, paraaortic, perirenal, etc), pelvic (bladder), and thoracic cavities are frequently malignant and metastases may be seen in up to 70% of cases. Although in most metastatic sympathetic PGLs the primary tumor is larger than 5 cm in size, in up to 20% of metastatic PGLs the primary tumor is smaller than 5 cm. (Continued on Page 2)

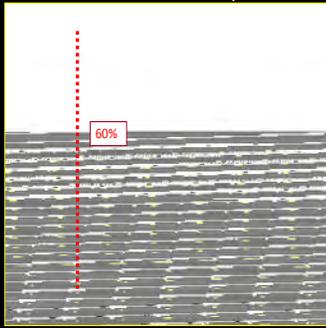
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An extra-adrenal location is associated with a double risk of death when compared with a primary tumor size larger than 5 cm making an extraadrenal location a stronger predictor of metastases, and survival. Nevertheless, whenever metastatic, both PHEOs and PGLs exhibit a similar overall survival suggesting that metastatic PHEO/PGL oncopathogenesis overlaps. Metastatic disease and decreased survival are observed in approximately 50% of patients with PHEO/PGLs associated with SDHB mutations. SDHB metastatic tumors are more aggressive than other metastatic tumors not associated with SDHB mutations. Although most SDHB tumors are PGLs, several metastatic PGLs are sporadic and not associated with SDHB mutations. Therefore, the higher prevalence of malignancy in PGLs cannot be explained by an association of genetic background and tumor site alone.

Figure 2: Median Overall Survival of Individuals with Metastatic vs. Non-metastatic PHEO/PGL



Lymphatic and hematogenous dissemination is common happening more often into the lymph nodes, skeleton, liver, and lungs. Occasional cases have presented with metastases in the central nervous system, skin, and breast. Liver, pancreas, and kidney may be infiltrated because of tumor vicinity. Liver and lung metastases are associated with shorter survival. Bone metastases are common (70%) and two thirds of these patients may develop skeletal related events. PHEO/PGL metastases may be present at the time of diagnosis or may appear months or years later in up to 50% of cases. As expected, metachronous metastases are associated with a better overall survival when compared with synchronous metastases.

Systemic Therapies

¹³¹I-Metaiodobenzylguanidine (¹³¹I-MIBG)

¹³¹I-MIBG was reported for imaging PHEO/PGL in 1981 and for high-dose treatment of patients with metastatic PHEO/PGLs in 1984. In an effort to improve the response rate to ¹³¹I-MIBG, isotope infusions with very high activities (500-1,000 mCi) have been employed at the University of California, San Francisco. All patients had peripheral blood stem cells (PBSCs) collected in advance and cryopreserved. Grade 3-4 myelosuppression, occurred in 87% of these patients, but few required PBSCs. However, due to rare but serious complications after very-high dose ¹³¹I-MIBG, now, the ¹³¹I-MIBG activity is limited to ≤500 mCi for patients with PHEO/PGL. A universal optimal cumulative activity for ¹³¹I-MIBG cannot be established, since PHEO/PGL metastases vary in their response to ¹³¹I-MIBG. Higher cu-

mulative activities of ¹³¹I-MIBG appear to improve the response rate, but also increase the risk of myelodysplastic syndrome and leukemia. To minimize the risk of serious acute myelosuppression, intermediate ¹³¹I-MIBG activities of 9.25-13 GBq (250-350 mCi) may be administered during two or three hospitalizations to cumulative activities of about 18-30 GBq (500-800 mCi). The patient is then followed carefully. Re-treatment decisions must be individualized based upon each patient's response and the degree of continued avidity of PHEO/PGL metastases for MIBG. Interestingly there has been no correlation between whole-body absorbed dose and the grade of post-therapy thrombocytopenia or leukopenia. Patients who have received intermediate-high activities of ¹³¹I-MIBG must be monitored carefully for hematologic toxicity. Several months after receiving ¹³¹I-MIBG at cumulative activities of 18-30 GBq (500-800 mCi), patients received repeat CT/MRI imaging and diagnostic ¹²³I-MIBG scanning. Patients with progressive disease may be switched to chemotherapy. Patients who appear to be responding are followed carefully. Additional therapies with ¹³¹I-MIBG may be indicated for signs of recurrence or progression in patients whose metastases retain sufficient avidity for MIBG. Continued improvement in scanning and tumor markers can continue for up to two years after cumulative activities of ≥18.5 GBq (500 mCi). In patients receiving high-activity ¹³¹I-MIBG, the response rate was 22% by RECIST criteria. Minor responses occurred in another 35% of patients and stable disease occurred in 8%. Progressive disease was seen in 35%. Patients who had previously failed chemotherapy were less likely to respond to ¹³¹I-MIBG. The estimated overall 5-year survival (from time of ¹³¹I-MIBG treatment) was 64%. Patients have improved overall survival if they have responses by CT/MRI scanning or ¹²³I-MIBG diagnostic imaging. ¹³¹I-MIBG may shrink tumors, making very large tumors more resectable. Patients with metastatic PHEO/PGLs who qualify for ¹³¹I-MIBG therapy have a good chance for symptomatic improvement and possibly improved survival. However, about 40% of patients with metastatic PHEO/PGLs do not qualify for ¹³¹I-MIBG because of poor avidity. Another problem is that about 30% of selected treated patients fail to respond to ¹³¹I-MIBG and develop progressive disease within one year after treatment. Re-treatments with ¹³¹I-MIBG are limited by the progressive risk for myelodysplastic syndrome and acute myelogenous leukemia with very high cumulative activities. Also, with time, metastases tend to emerge that have little or no avidity for ¹³¹I-MIBG, resulting in progressive disease.

Current "carrier-added" MIBG preparations contain mostly "cold" ¹²⁷I-MIBG. In these preparations, ¹²⁷I-MIBG may reduce the therapeutic efficacy of ¹³¹I-MIBG, due to competitive inhibition of uptake into PH/PGL tumors. Therefore, a noncarrier-added ¹³¹I-MIBG (Ultratrace MIBG, Azedra) has been developed. A clinical trial has been completed to determine the efficacy and safety of noncarrier-added ¹³¹I-MIBG.

Systemic Chemotherapy

Systemic chemotherapy plays an important role in the treatment of metastatic PH/PGL. However, a clear understanding of the value of individual drugs and their combinations has been very difficult to determine, mainly because of the rarity of these tumors.

(Continued on page 3)

Upcoming Events

American Association of Clinical Endocrinologists (AACE) 22nd Annual Meeting and Clinical Congress May 1-5, 2013. Phoenix, AZ. (www.aace.com)

American Society of Clinical Oncologists (ASCO) 13th Annual Meeting May 31-June 4, 2013. Chicago, IL. (<http://chicago2013.asco.org/>)

ENDO: The Endocrine Society Annual Meeting 2013. June 15-18, 2013. San Francisco, CA. (www.endo-society.org)

American Diabetes Association (ADA) 73rd Scientific Sessions. June 21-25, 2013. Chicago, IL. (www.scientificsessions.diabetes.org)

The Second World Congress on Thyroid Cancer. July 10-14, 2013. Toronto, CA. (www.thyroidworldcongress.com)

ThyCa Conference 2013. 16th International Thyroid Cancer Survivors' Conference September 27-29, 2013. Philadelphia, Pennsylvania. (www.thyca.org)

American Society for Bone and Mineral Research (ASBMR) 2013 Annual Meeting. Oct 12-15, 2013. Baltimore, MD. (www.asbmr.org)

83rd Annual Meeting of the American Thyroid Association October 16-20, 2013. San Juan, Puerto Rico (www.thyroid.org)



(Jimenez Vasquez, continued)

Cyclophosphamide and dacarbazine based regimens combined with vincristine (CVD) and/or doxorubicin (CVDD, CDD) are the best studied regimens. Combined chemotherapy with cyclophosphamide (750 mg/m² d 1), vincristine (1.4 mg/m² d1), and dacarbazine (600 mg/m² d1 + 2) (CVD) was introduced against metastatic PHEO/PGL in 1985 as this combination demonstrated effectiveness in patients with neuroblastoma, a tumor that shares a similar origin with PHEO/PGL. Recently, in the largest published study to date, of 52 patients treated with different chemotherapy regimens, only those treated with cyclophosphamide-dacarbazine based chemotherapy (CVD, CDD, CVDD) exhibited clinical benefits. The clinical benefits were observed in 40% of patients treated with these protocols and included a tumor size reduction as demonstrated by cross sectional imaging and a better blood pressure control in association with dose reduction or discontinuation of antihypertensives. In patients who responded to chemotherapy and had metastatic disease at diagnosis the median overall survival was 6.4 years whereas for non-responders was 3.7 years. Responders had a marginally significant longer survival ($p=0.095$), that remained significant ($P=.05$; hazard ratio, 0.22; 95% CI, 0.05-1.0) in a Multivariate Cox proportional hazard model when adjusted for tumor size. Age, gender, race, primary tumor size and location, number of metastatic sites, timing of metastasis, and genetic background did not predict a positive response to chemotherapy, leaving pending the determination of which factors may predict a good response. In most patients cyclophosphamide and dacarbazine-based chemotherapy was well-tolerated. The duration of treatment is still to be determined.

Other regimens that have been tested in smaller numbers of patients include (1) cisplatin and 5-fluorouracil, (2) etoposide, carboplatin, vincristine, cyclophosphamide, and doxorubicin, (3) cyclophosphamide and methotrexate, (4) Ifosfamide, (5) temozolomide, and (6) streptozocin with varying combinations of other agents. Most of these regimens have been shown to be either ineffective or effective in so few patients that no evidence-based conclusions can be drawn about their utility for treating metastatic PHEO/PGL.

Before initiating chemotherapy, adequate alpha and beta blockage is required. Alpha methyl-tyrosine to inhibit catecholamine synthesis is

strongly recommended if available and not contraindicated. In children this drug is not recommended as they seem sensitive to its side effects. The follow-up of patients treated with chemotherapy should include frequent clinical visits and radiographic and biochemical studies. To determine tumor size reduction we recommend CT/MRI and/or bone scan every three months. Pain, blood pressure, and performance status are important parameters to determine response to chemotherapy and should be objectively monitored in every clinical visit. The value of FDG-PET scanning for follow-up is still to be determined.

Chemotherapy could be offered to patients with progressive disease, in particular to patients with very rapid progression. Additionally, chemotherapy should be considered in patients with unresectable tumors and overwhelming symptomatology related to tumor burden and hormone excess. Finally, chemotherapy should be considered when there is limited access to MIBG therapy or when patients have non-MIBG avid tumors.

Molecular Targeted Therapies

In our series, 47% of patients with progressive metastatic PHEO or SPGL who were treated with sunitinib experienced clinical benefit such

Figure 4: Patient with sporadic pheochromocytoma treated with sunitinib

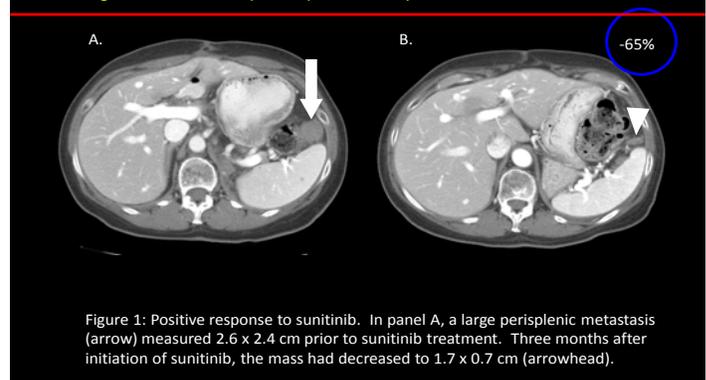
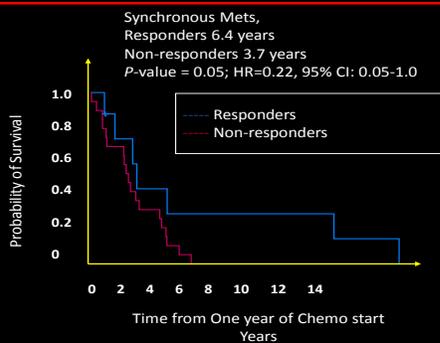


Figure 3: Overall Survival in Patients with metastatic disease (Responders Vs. Non-Responders)



Ayala Ramirez, Cancer, 2011

as tumor size reduction or disease stabilization. The blood pressure of responder patients with hypertension improved with discontinuation or dosage reduction of antihypertensive medications. The duration of these benefits varied among patients and lasted 6 to 35 months with use of sunitinib alone. In one patient who was treated with sunitinib and rapamycin, clinical benefits were still evident after 36 months.

Six of the eight patients who experienced clinical benefit carried germline-inactivating mutations in the *SDHB* (PGL4) or *VHL* (*VHL* disease) genes, and two had apparently sporadic tumors. *SDHB* mutations predispose patients to loss of electron transport chain activity and high intracellular concentrations of succinate that interfere with *VHL* protein activity and are associated with rapidly progressive disease and poor prognosis. Tumors associated with *SDHB* and *VHL* mutations display pseudohypoxic environments, with rich expression of angiogenesis and extracellular matrix elements,

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(Jimenez Vasquez, continued)

suppression of oxidoreductase enzymes, and increased intracellular hypoxia-inducible factor concentrations. Metastatic tumors have also been described in association with mutations in other succinate dehydrogenase subunit genes, including *SDHC* (PGL3) and *SDHD* (PGL1). *VHL*, *SDHB*, *SDHC*, and *SDHD* mutations are all reported to cause deregulation of hypoxia-inducible factor suggesting an overlapping common mechanism of tumorigenesis and a similar angiogenic profile. Since some sporadic PHEOs and SPGLs also share a similar pseudohypoxic and angiogenic profile with *VHL*-, *SDHB*-, *SDHC*-, and *SDHD*-related tumors, a considerable number of patients with metastatic tumors may benefit from therapies, such as sunitinib, that target angiogenic factors

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Conclusions

Patients with metastatic PHEO/PGLs could be treated with systemic chemotherapy, MIBG, or molecular targeted therapies. As there are no comparative studies amongst these therapies, it is currently difficult to determine which of these systemic therapies should be the first line of treatment for a particular patient with a malignant PHEO/PGL. Therefore, clinical trials in this field are urgently needed. These clinical trials will help to demonstrate survival benefits and clinical predictors of response; more important they will help us to discover new therapies for this rare and aggressive disease. Personalized cancer medicine will help us to determine more specific therapeutic approaches and combinations.

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Genetics of Pheochromocytoma and Paraganglioma

Theresa Rich, MS, CGC, Genetic Counselor, Department of Clinical Cancer Genetics

Pheochromocytomas (PHEO) and paragangliomas (PGL) are rare tumors arising from the adrenal medulla and extra-adrenal sympathetic or parasympathetic paraganglia, respectively. At least 25-30% of PHEO/PGLs are caused by an underlying autosomal dominant hereditary disorder, up to half of which may have an "apparently sporadic" presentation while the other half may have a more classic syndromic or familial presentation.¹⁻⁴

Genetic evaluation should be considered in every patient with PHEO/PGL. Differentiation between patients who have a hereditary condition from those with sporadic disease may aid in the management of the patient as well as assessing risk for PHEO/PGL for their family members. Patients with hereditary PHEO/PGL syndromes are usually at risk for more than one primary tumor and may benefit from prospective surveillance for additional incident tumors, which may not be detected on routine follow-up of the existing PHEO/PGL. The underlying genetic basis can also, in some cases, aid in predicting the likelihood that the patient could develop metastatic disease.

If a patient is found to have a germline mutation in a hereditary PHEO/PGL susceptibility gene, their family members may be identified to be at risk for PHEO/PGL and may similarly benefit from prospective surveillance. Mutations in all of the hereditary PHEO/PGL genes identified to date are inherited in an autosomal dominant manner, meaning that a mutation carrier has a 50% risk to pass the mutation down to each of their children, irrespective of gender. However, some of the genes are associated with "parent of origin effects" such that the risk of developing the disease depends on whether the mutation was inherited from the mother or father.

Thirteen different genes have been implicated in hereditary PHEO/PGL (see Table on page 5). Additionally, the Carney triad is a non-hereditary syndromic form of PHEO/PGL with a yet unknown genetic basis. While many patients with PHEO/PGL may benefit for genetic testing, most do not need genetic testing for all 13 genes and some patients with PHEO/PGL may not need genetic testing at all. Several genetic testing algorithms have been proposed.⁵⁻⁸ While there is significant overlap in the clinical features between the hereditary PHEO/PGL syndromes, the following characteristics can be considered to help restrict the number of genetic tests needed and to target the genes most likely to be involved first so that genetic testing may be more cost-effective:

Age at diagnosis

Younger patients are much more likely to have an underlying hereditary syndrome than older patients. The prevalence of occult mutations in pa-

tients with seemingly sporadic benign PHEO/PGL ranges from approximately 50-70% for children diagnosed younger than age 18, 10-20% for adults diagnosed between 20-50 years, and less than 5% if the diagnosis is made older than age 50.^{1,4,9-12}

Number of independent tumors and presence/documented absence of other associated diseases

Patients with multiple primary PHEO/PGLs usually have an underlying genetic condition, whether a causative mutation is discovered or not. Additionally, consideration should be made on whether the patient has thyroid cancer or a thyroid nodule, signs of hyperparathyroidism, or mucosal neuromas in the case of MEN2/MEN2B, retinal or central nervous system tumors, cysts or tumors of the kidney and pancreas in the case of *VHL*, cutaneous features of NF1, and gastrointestinal stromal tumors (GIST) in the case of *SDHB*, *SDHD*, or *SDHC* mutations. The triad of GIST, pulmonary chondroma, and PHEO/PGL must all be present in order to diagnose Carney triad, and these patients typically do not benefit from genetic testing.¹³

Location(s) of PHEO/PGL

PHEO/PGL associated with *RET* mutations are virtually always intra-adrenal whereas those associated with *SDHAF2* have all been located in the head and neck.⁵ *VHL*, *NF1*, *TMEM127*, and *MAX*-related tumors are most often intra-adrenal. *SDHB*-associated tumors are most common in the sympathetic paraganglia whereas *SDHD* and *SDHC*-associated tumors are most common in the parasympathetic chain.

Biochemical properties

RET and *NF1*-related PHEO/PGL are typically adrenergic (secrete epinephrine/metanephrine) whereas *VHL*, *SDHB*, and *SDHD*-associated tumors are typically noradrenergic (secrete mainly norepinephrine/normetanephrine).^{5,14,15} *SDHB*- and *SDHD*-associated tumors may also secrete dopamine. The typical biochemical profile for many of the other genes is not as well defined at this time.

Presence of metastases

The likelihood of malignant transformation of a PHEO/PGL is estimated at 10-30% in patients with mutations in *SDHB* or *MAX* and lower than 5% for patients with mutations in *RET*, *VHL*, *SDHD*, *SDHAF2*, or *TMEM127*.⁵

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More than half of all patients with a malignant extra-adrenal PGL have an underlying germline *SDHB* mutation, and patients commonly present with a single tumor and without a suggestive family history. *SDHB* mutations are also found in 5-10% of patients with malignant intra-adrenal PHEO.^{11,12,16} In one series, the rate of identifying *MAX* mutations in patients with malignant PHEO/PGL was 1.5%.¹⁷

Expression of the *SDHB* protein in PHEO/PGL tumor tissue

Recently, immunohistochemistry to detect expression of *SDHB* protein in PHEO/PGL tumor tissue has been demonstrated to have utility in predicting which patients are more or less likely to have an underlying germline *SDHB*, *SDHD*, or *SDHC* mutation.^{18,19} *SDHB* immunohistochemistry, while not yet widely available, may be a cost-effective first step in screening patients who are good candidates for the more expensive germline testing.

Family history

A negative family history cannot rule out the presence of an underlying hereditary condition. Many patients with hereditary PHEO/PGL have negative family histories due to a number of different factors including *de novo* mutations (common in *NF1*, *VHL*, and *MEN2B*), incomplete penetrance of disease in mutation carriers (common with *SDHB* mutations), and parent of origin effects in the case of *SDHD*, *SDHAF2*, and likely *MAX*. Since patients with mutations in these three genes only develop PHEO/PGL if the mutation was inherited from the father, close attention should be paid to the paternal family history if one of these syndromes is suspected. In some cases, one may not see a family history of PHEO/PGL if, for example, the mutation was inherited from the paternal grandmother, in which case one would not expect to see PHEO/PGL in any relative in the father's generation.

Additionally, the family history should be assessed for individuals with sud-

den unexplained death, difficult to control hypertension, neck masses, and any ill-defined abdominal cancers, which may suggest a family member could have had an undiagnosed PHEO/PGL.

Clinical Utility of Genetic Testing

Consideration should also be made with regard to the clinical utility of the proposed genetic test – in other words, what information would be gained from the test and how is that information useful to the patient. The highest priority should be given to genetic tests for which there is an actionable clinical intervention if the test is positive. For example, *RET* and *VHL* genetic testing have the highest clinical utility because there is demonstrated medical benefit to an early diagnosis of the syndrome and surveillance for the other manifestations of the syndrome. The medical utility of *NF1* testing, on the other hand, is very low as the diagnosis can usually be made by physical examination. However, *NF1* testing may be useful for some patients who may want to use genetic testing in reproductive decision making (for example, pursuing pre-implantation or prenatal genetic diagnosis). The clinical utility for testing for some genes is uncertain. For example, the little data on *SDHA*-related PHEO/PGL suggests that the penetrance of disease in mutation carriers is quite low, and so it is still unclear at this time if the risk is high enough to justify ongoing surveillance.^{20,21}

In some cases, there may be little to no benefit for genetic testing for the patient. However, consideration should be given to whether there are any close relatives (children, siblings etc.) who might benefit from a genetic diagnosis in the patient. Any genetic testing is most informative when initiated in the affected patient, as the affected patient is the most likely person in whom you will find the disease-causing mutation if one were present in the family.

Genetic Counseling Considerations

Genetic testing should be considered for all patients with PHEO/PGL as a high proportion may have an underlying hereditary disorder, and the diagnosis may benefit the patient and/or their relatives. However, genetic counseling for these cases can be quite complicated. The genetic basis of PHEO/PGL is highly complex and rapidly evolving with several new susceptibility genes discovered within the past two years. This results in complicated risk assessment and genetic testing algorithms, and the requirement to regularly review new literature to stay current. Genetic testing cannot always identify all cases of hereditary PHEO/PGL because of mutations missed by the technology used, or the possibility that additional genes could be discovered over time. Therefore, patients who test negative may still need to be re-assessed for the possibility of a hereditary condition from time to time. Additionally, it is not uncommon to encounter genetic variants of uncertain significance.

For many of the syndromes, consensus management recommendations are not available making it difficult to know how to follow a given mutation carrier and difficult to predict whether suggested screening studies are reimbursable by insurance. Additionally, the counseling provided regarding risk to family members and recommending an appropriate age to begin genetic testing in at-risk individuals should be carefully considered, particularly for those syndromes that are still not well characterized and for those with parent of origin effects. In some cases, testing an at-risk child as a minor is appropriate if it will alter medical surveillance; however in some cases, testing children is not recommended. For example, a minor child at risk to inherit a *SDHD* mutation from their mother is not an appropriate candidate for genetic testing since the result would not affect their management. Rather it would only impact their risk to have a child with the mutation, so the decision about undergoing genetic testing should be made by the child after reaching the age of majority. For a complete list of references, please email Charles Stava at cstava@mdanderson.org.

Overview of Pheochromocytoma/Paraganglioma Susceptibility Syndromes						
Syndrome (Gene)	Proportion of all PHEO/PGL	Penetrance of PHEO/PGL	Mean Age at Presentation (years;range)	Most Common Tumor Location	Risk of Malignancy	Most Common Other Clinical Manifestations
<i>MEN2 (RET)</i>	5.3%	Up to 50% (varies by genotype)	35.3 (4-73)	Adrenal (~100%)	2.9%	MTC, PHPT, mucosal neuromas and ganglioneuromatosis of the GI tract (<i>MEN2B</i>)
<i>VHL (VHL)</i>	9.0%	10-26% (varies by genotype)	28.6 (5-67)	Adrenal (90%)	3.4%	Hemangioblastomas of the CNS and retina Renal cysts and RCC Pancreatic cysts and NETs
<i>NF1 (NF1)</i>	2.9%	0.1-5.7%	41.6 (1-74)	Adrenal (95%)	9.3%	Café-au-lait macules, axillary/inguinal freckling, neurofibromas, Lisch nodules
<i>PGL1 (SDHD)</i>	7.1%	86% by age 50 for paternally inherited mutations	35.0 (10-96)	Extra-adrenal, parasympathetic	3.5%	GIST
<i>PGL2 (SDHAF2)</i>	<1%	100% for paternally inherited mutations	32.2 (20-59)	Extra-adrenal, parasympathetic (100%)	Not reported	None reported
<i>PGL3 (SDHC)</i>	0.5%	Unknown	42.7 (13-73)	Extra-adrenal, parasympathetic	Reported in a few cases	GIST
<i>PGL4 (SDHB)</i>	5.5% (up to 50% of malignant PGL)	30-77% ²²	32.7 (6-77)	Extra-adrenal, sympathetic	30.7%	GIST, renal tumors
- (<i>SDHA</i>)	<3%	Unknown	40.0 (27-55)	Extra-adrenal	0-14.3%	Unknown
- (<i>TMEM127</i>)	<2%	Unknown	42.8 (21-71)	Adrenal	4.3%	Unknown
- (<i>MAX</i>)	~1%	Unknown	32.2 (17-47)	Adrenal	10-25%	Unknown
Carney Triad (unknown)	<1%	N/A	27.5 (12-48)	Extra-adrenal	10.8%	GIST, pulmonary chondroma, primarily identified in young women, not hereditary

Mutations in *MEN1*, *KIF1Bβ*, and *EGLN1* have also been reported in PHEO/PGL patients in a few cases²³⁻²⁵

Adapted from Welander et al 2011 and Waguespack et al 2010^{5,6}

Abbreviations: GIST=Gastrointestinal Stromal Tumor; MEN =Multiple Endocrine Neoplasia; MTC=Medullary Thyroid Carcinoma; PHPT= primary hyperparathyroidism; GI = Gastrointestinal; NET=Neuroendocrine Tumor; NF=Neurofibromatosis; PGL=Familial Paraganglioma Syndrome or paraganglioma; PHEO=Pheochromocytoma; RCC=Renal Cell Carcinoma; VHL= von Hippel-Lindau Disease

The Thyroid Cancer Survivorship Clinic



The Department of Endocrine Neoplasia and Hormonal Disorders is proud to feature the Thyroid Cancer Survivorship Clinic at The University of Texas MD Anderson Cancer Center. The mission of the Thyroid Cancer Survivorship Program is to address the outcomes of thyroid cancer and its therapy, and improve survivors' health and quality of life through integrated programs in patient care, research, prevention and education.

A Specialty-trained dedicated nurse practitioner and Endocrinologist are here to monitor cancer survivors for recurrence of thyroid cancer. Additionally, our team works closely with other specialized physicians and nurses to look for and manage late effects related to thyroid cancer and its therapies. We are uniquely able to coordinate care related to speech and swallowing problems, bone and heart health, dry mouth, tearing, and dental complications, as well as fatigue.

Finally, an important mission of our Thyroid Cancer Survivorship Program is to ensure that all of our patients are receiving adequate cancer prevention screening for all malignancies, whether at MD Anderson or in the community.

To refer a patient, please call our New Patient Referral Coordinators at 713-563-4400.

For physician to physician referrals, please call 713-792-2841.



Case Files From The Department: The Carney Triad

Steven G. Waguespack, MD, F.A.AP., F.A.C.E., Associate Professor and Deputy Department Chair, Department of Endocrine Neoplasia and Hormonal Disorders

A 26-year-old female presented to the endocrinology clinic for further management of a paraganglioma (PGL). She first came to medical attention at the age of 22 when she was diagnosed with a multifocal gastrointestinal stromal tumor (GIST) after an episode of hematemesis. The patient was subsequently identified to have calcified pulmonary masses (small white arrows on Figure 1) and the diagnosis of Carney triad was made. Ultimately, she was found to have an FDG-avid mass in the mediastinum (large black arrows on Figure 2, 3) suspected to be a PGL. At the time of endocrine evaluation, she was asymptomatic with no evidence of catecholamine hypersecretion. Plasma normetanephrines were minimally elevated to 1.5 times the upper limit of normal. She underwent a successful surgical resection and pathology confirmed a PGL.

The Carney triad was originally described in 1977 by the Mayo pathologist J. Aidan Carney as the association of gastric epithelioid leiomyosarcoma (later renamed GIST), PGL, and pulmonary chondroma. Over time, the phenotype has expanded to include clinically nonfunctioning adrenocortical tumors and esophageal leiomyomas. The Carney triad affects primarily young women (85%) with a mean age of onset of 20 years (7-48). Although it has been accepted to be a genetic disorder, the responsible gene(s) remains unknown. Due to incomplete expression of

the phenotype, PGL is not present in all patients suspected to have the Carney triad. When it occurs, PGL generally presents with catecholamine excess and/or due to tumor mass effects. PHEO can occur in a minority of patients. As seen in this patient, the aortopulmonary body is a common site for development of PGL, although PGL occur equally in the head and neck, thorax, and abdomen.

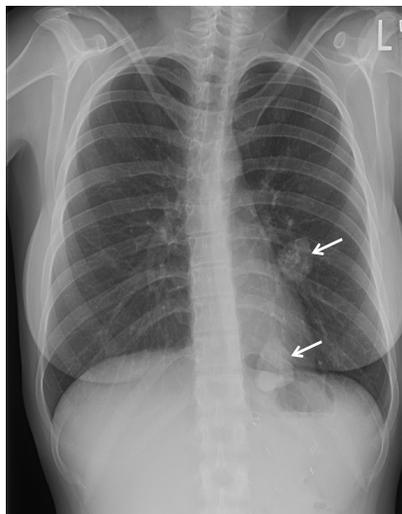


Figure 1



Figure 2



Figure 3

Notes from the Endocrine Faculty Team

Recognitions:

• We are proud to announce four new additions to our faculty team: Marie-Claude Hofmann, Ph.D., Professor, Sonali Thosani, M.D., Assistant Professor, Krishna M. Sinha, Ph.D., Assistant Professor, and Stephen P. Henry, Ph.D., Instructor.

Dr. Hofmann's current research focuses on basic mechanisms regulating adult stem cell self-renewal and differentiation within their micro-environment, or niche. Testis and thyroid are used as model systems because the stem cells of both organs utilize similar signaling pathways, in particular RET signaling. Through biochemical, cell biological, and mouse genetic approaches, her team seeks to understand how these stem cells normally develop and how they transform into cancer stem cells.

Dr. Thosani's research interests include improving the quality of health-care administered in the outpatient and inpatient setting, optimizing the management of steroid induced hyperglycemia and Type 2 Diabetes in the setting of cancer, and studying the endocrine side effects of chemotherapeutic agents. As a member of the clinical faculty, her contribution to the department is focused on providing care for outpatients with steroid induced hyperglycemia, Type 2 DM, and general endocrine diseases, and participating on the inpatient diabetes and general endocrine service. She strives to help build a state-of-the-art Diabetes program at our institution and collaborate with various departments to improve the quality of care that is administered to our patients.

Dr. Sinha's goal is to understand the molecular mechanism of Osterix function in activation of osteoblast target genes during the process of osteoblast differentiation and bone formation. Using a proteomic approach, his team identified a JumonjC-domain containing histone demethylase NO66 which interacts with Osx and inhibits Osx-dependent gene expression in osteoblasts. The epigenetic control of osteoblast genes and the physiological role of NO66 in osteoblast differentiation are currently being investigated.

Dr. Henry's research interest lies with the biology of the skeleton. Although his previous training focused on genetically engineered mouse models that recapitulate some aspects of the human diseases, osteoarthritis and degenerative intervertebral disk disease; currently, he is forging into the study of hormonal control over bone. In the distant future, Dr. Henry aspires to understand how cells in bone respond to mechanical forces impinging upon bone during periods of bone loss such as osteoporosis.

• Congratulations to Dr. Anita Ying for beginning her new tenure as the Center Medical Director of the Endocrine Center, starting in December of 2102.

• Kudos to Dr. Steven Sherman and Dr. Victor Lavis for being chosen for the Annual Best Boss Award.

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Vemurafenib in the Neoadjuvant Setting

Maria E Cabanillas, MD, Assistant Professor, Department of Endocrine Neoplasia and Hormonal Disorders

"Pharmacodynamic study of vemurafenib in the neoadjuvant setting in patients with locally advanced and metastatic papillary thyroid cancer" is an investigator-initiated clinical trial designed to explore biomarkers for response to vemurafenib (a selective BRAF inhibitor), mechanisms of resistance to the drug, safety, and efficacy of neoadjuvant vemurafenib.

The concept of treating patients in the neoadjuvant setting stems from the fact that over 80% of patients with advanced stage, high risk papillary thyroid cancer will develop recurrent disease and will require further surgery, which could lead to surgical complications such as permanent vocal cord paralysis, hypoparathyroidism and tracheal resections/laryngectomy. BRAF mutations are very common among patients with high risk papillary thyroid cancer. Thus, vemurafenib (trade name Zelboraf), an orally available, selective BRAF inhibitor was chosen for

this study. Vemurafenib has no antiangiogenic properties which could impair wound healing.

Main eligibility criteria include: 1. Adult patients with primary or recurrent papillary thyroid cancer, 2. T3, T4, or macroscopic lymph node involvement requiring surgery, 3. BRAF V600E mutation

Trial design: A core biopsy will be obtained at baseline for confirmation of BRAF status and for correlative, pre-treatment study specimens. Eligible patients will receive vemurafenib for 56 days prior to surgery. Pathologic specimen from surgery will be routinely collected for diagnostic purposes and will also serve as their post-treatment tissue sample for correlative studies. Patients with widely metastatic disease may continue vemurafenib after surgery as long as they are benefiting from treatment. We plan to enroll 22 patients. For more information please visit www.clinicaltrials.gov, Identifier: NCT01709292

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How to refer a patient to MD Anderson

Online Referrals:

MD Anderson has created an online referral process, myMDAnderson, to help you get your patient into MD Anderson as quickly as possible. You can use myMDAnderson to follow your patient's treatment regimen by viewing transcribed reports and accessing your patient's schedules. To qualify for this free service, you must be a licensed, practicing physician. To start a referral through myMDAnderson, please access this portal: <https://my.mdanderson.org/public/physicians/user/>



Telephone Referrals:

- Physician to Physician referrals, please call 713-792-2841.
- To speak with a New Patient Referral Coordinator, please call 713-563-4400.
- For Pediatric Referrals (patients less than 18 years of age), please call 713-792-5410.

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