Update on Pheochromocytoma (PHEO) and Paraganglioma (PGL): Implications for Clinical Practice

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Disclosure

Nothing to disclose
**Current important facts:**

- In about 70% of PHEOs/PGLs, a genetic defect is known (30% have germline and 40% have somatic mutations); 22 PHEO/PGL susceptibility genes are currently known.
- Biochemical dg. and localization is highly successful.
- New treatments using $^{177}$Lu-DOTATATE (Lutathera®) and $^{223}$Radium dichloride (Xofigo®) are on the horizon.

**PHEO/PGL: continuing progress**

*UBTF-MAML3*: upstream binding transcription factor-mastermind like transcriptional coactivator 3

*CSDE1*: cold shock domain-containing E1
New PHEO/PGL susceptibility genes

Family history or syndromic presentation?

- **HIF2A** (S) → Multiple PGLs/PHEOs, meta
- **PHD1** (G) → Multiple PGLs/PHEOs
- **FH** (G) → Multiple PGLs/PHEOs, meta
- **MDH2** (G) → Multiple PGLs, meta
- **H-RAS** (S) → Multiple PGLs/PHEOs
- **CSDE1** (S) → PGLs/PHEOs, meta
- **UBTF-MAML3** (S) → PGLs/PHEOs, meta

S: somatic; G: germline; meta: metastatic

Zhuang et al. NEJM 2012; 6:922
Crona et al. JCEM 2013; 98:E1266
Letistri et al. Cancer Cell 2013; 23:739
Oudijk et al. JCEM 2014; E1376
Cascon, JNCI 2015JNCI, in press
TCGA, 2016, in preparation

Current characteristics of **SDHB/D**-related PHEOs/PGLs

- Mostly extra-adrenal abdominal, some HNPGLs (SDHD), aggressive, multiple, metastatic (if from an abdominal PGL, 40% chance of **SDHB** mutation)
- Most mediastinal, organ of Zuckerkandl, cardiac (78%), and urinary bladder (50%) PGLs
- **Kidney cancer** (14%)
- Gastrointestinal stromal tumors & pituitary adenomas (PRL, GH) “3P syndrome?”
- Pancreatic neuroendocrine tumors

Martucci et al. Urol. Oncol. 2015; 33:167
Martucci et al. Am. J. Cardiol. 2015; 115:1753
Xekouki et al. JCEM 2015; 100:E710
Niemi & et al. JCEM 2015; 100:1386
132 patients were included (27 children, 105 adults), 73 had SDHB, 59 were sporadic metastatic PHEO/PGL

Only 16% of all primary tumors were smaller than 4.5 cm

In children, metastatic PHEO/PGL was mainly due to SDHB. In adults, tumors were equally distributed between SDHB and sporadic

23% of SDHB and 16% of sporadic PHEO/PGL had metastatic disease at initial diagnosis

Survival: 5 & 10 years: SDHB: 92%/76%; sporadic: 95%/86%

In all patients, polycythemia presents at birth or early childhood; EPO levels are always elevated

PGLs: Mostly extra-adrenal multiple abdominal, less commonly PHEOs, median age: 17 years, 29% metastatic, ALL NE-producing

Somatostatinoma: always in the 2nd portion of the duodenum, median age: 29 years, 40% multiple, 60% metastatic,

Cholelithiasis in almost all patients

Cysts in kidney, breast, lung, pancreas in 57% of patients

Various retinal changes

HIF2A: hypoxia-inducible factor 2α gene (also called EPAS1)
70% of patients were found to have ocular abnormalities. First successful laser surgery was performed in May 2016 at the NIH.

Pacak et al. Ophthalmology; 2014; 12:2291 & unpublished observations

Functional imaging in the localization of PGL/PHEO-related to HIF2A mutations

Därr et al., in preparation
Germline fumarate hydratase (FH) mutations

- PHEO/PGL: multiple, also head and neck
- Moderate rate of malignancy (2nd to SDHB)
- NE producing tumors
- Papillary renal cell carcinoma, uterine fibroids, leiomyomas

Letouze et al. Cancer Cell 2013; 23:739
Clark et al. JCEM 2014; 99:E2406
Namibua et al. Endocr. Pract.; in press

PHEO/PGL: continuing progress

Genetics

- NF1
- VHL
- MEN 2
- SDHD
- SDHC
- SDHB
- TMEM127
- PHD2
- DH1
- SDHA
- MAX
- HIF2A
- PHD1
- MDH2
- FH
- H-RAS
- PHD
- FB
- UBTM-MAML3
- CSDE1

Biochemical Diagnosis

- 1950: HPLC Assays
- 1990: LC-MS/MS (routine)
- 2011: Methoxytyramine
- 1950: Improved understanding of catecholamine metabolism
- 2000: Shift from catecholamines to metanephrines

Colorimetric Assays

- 1986
- 1990
- 2000
- 2012
- 2013
- 2015
- 2016

Colorimetric Assays

- 1990
- 2000
- 2011

Colorimetric Assays

- 1950
Methoxytyramine (MTY) as a new biomarker in the diagnosis of PHEO/PGL


MTY in various PHEOs/PGLs

Adapted from G. Eisenhofer & Neumann et al. Harrison's Principles of Internal Medicine
Biochemical-genetic phenotype

Krebs cycle (FH, MDH2) and hypoxia (HIF2A, PHD1/2) genes

Are patients with functional PHEO/PGL initially receiving a proper adrenoceptor blockade?

- 381 patients were included
- 69.3% were treated properly (93% received α-adrenoceptor blockade - phenoxybenzamine)

Of those not treated properly, 53% did not receive any form of medication

PHEO/PGL: continuing progress

Genetics
1886 NF1 MEN 2 VHL 1950 1990 2000 2011 SDHD SDHC SDHB SDHAF2 TMEM127 HIF2A PHD1 MAX SDHA VH L RET SDHB

Biochemical Diagnosis
1950 1990 2000 LC-MS/MS (routine) 2011 Colorimetric Assays Improved understanding of catecholamine metabolism Shift from catecholamines to metanephrines Methoxytyramine

Imaging
1950 1990 2000 PET New PET Ligands: 18F-FDG, 18F-FDOPA, 18F-FDA MRI & CT DOTA analogs (111In-DOTA-TATE/TOC/NOC)

PHEO/PGL and somatostatin receptors (SSTRs) imaging

- PHEO/PGLs express SSTRs (mainly type 2) allowing for the use of Octreoscan scintigraphy (relatively poor spatial resolution)

<table>
<thead>
<tr>
<th>SSTR1</th>
<th>SSTR2</th>
<th>SSTR3</th>
<th>SSTR4</th>
<th>SSTR5</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHEO</td>
<td>+++/++++ (15-20%)</td>
<td>+++/++++ (75-80%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PGL</td>
<td>+++ (20%)</td>
<td>+++ (80%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

+: level of expression; %: proportion of SSTRs-expressing PHEO/PGL

- SSTR imaging can be performed with PET/CT to improve spatial resolution and sensitivity; PET/CT also provides a more rapid whole-body tomographic imaging, therefore, obtaining a precise anatomic localization
**68Ga-DOTATATE PET/CT in SDHB-related metastatic PGL**

- [18F]-FDG
- [18F]-FDOPA
- [18F]-FDA
- Octreoscan
- [123I]-MIBG

**68Ga-DOTATATE PET/CT performance in patients with SDHB-related metastatic PHEO/PGL compared to other imaging modalities**

*SDHB*-related metastatic PHEO/PGL*

- CT
- 18F-FDG PET
- 18F-DOPA PET
- 18F-DOTA PET
- 18F-FDA PET

* Only patients in whom all imaging modalities were performed

17 patients with SDHB-related metastatic PHEO/PGL were included (imaging comparator: composite of functional and anatomical imaging)  
**68Ga-DOTATATE PET/CT performance in patients with SDHB-related metastatic PHEO/PGL compared to other imaging modalities**

<table>
<thead>
<tr>
<th>Detection rate</th>
<th>[68Ga]-DOTATATE</th>
<th>[18F]-FDG</th>
<th>[18F]-FDOPA</th>
<th>[18F]-FDA</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All compartments</td>
<td>285/289 98.6%</td>
<td>248/289 85.8%</td>
<td>175/285 61.4%</td>
<td>148/285 51.9%</td>
<td>245/289 84.8%</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>65/65 100%</td>
<td>57/65 87.7%</td>
<td>39/65 60.0%</td>
<td>39/65 60.0%</td>
<td>55/65 84.6%</td>
</tr>
<tr>
<td>Lungs</td>
<td>62/63 98.4%</td>
<td>45/63 71.4%</td>
<td>45/63 71.4%</td>
<td>18/63 28.6%</td>
<td>62/63 98.4%</td>
</tr>
<tr>
<td>Abdomen</td>
<td>43/43 100%</td>
<td>40/43 93.0%</td>
<td>31/43 72.1%</td>
<td>19/43 44.2%</td>
<td>33/43 76.7%</td>
</tr>
<tr>
<td>Liver</td>
<td>5/5 100%</td>
<td>3/5 60.0%</td>
<td>4/5 80.0%</td>
<td>0/5 0.0%</td>
<td>5/5 100%</td>
</tr>
<tr>
<td>Bone</td>
<td>95/98 96.9%</td>
<td>91/98 92.9%</td>
<td>41/94 43.6%</td>
<td>57/94 60.6%</td>
<td>82/98 83.7%</td>
</tr>
</tbody>
</table>

Number of identified lesions and detection rate (%) in 17 patients with SDHB-related PHEOs/PGLs
(imaging comparator: composite of functional and anatomical imaging)


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**68Ga-DOTATATE PET/CT in sporadic metastatic PHEO/PGL compared to other imaging modalities**

**Sporadic metastatic PHEO/PGL**

* Only patients in whom all imaging modalities were performed

22 patients with sporadic metastatic PHEO/PGL were included
(imaging comparator: composite of functional and anatomical imaging)

### 68Ga-DOTATATE PET/CT performance in sporadic metastatic PHEO/PGL compared to other imaging studies

<table>
<thead>
<tr>
<th>Detection rate</th>
<th>68Ga-DOTATATE</th>
<th>18F-FDG</th>
<th>18F-FDOPA</th>
<th>18F-FDA</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All compartments</strong></td>
<td>450/461</td>
<td>226/461</td>
<td>181/242</td>
<td>160/206</td>
<td>276/461</td>
</tr>
<tr>
<td>Detection rate</td>
<td>97.6%</td>
<td>49.2%</td>
<td>74.8%</td>
<td>77.7%</td>
<td>81.6%</td>
</tr>
<tr>
<td><strong>Mediastinum</strong></td>
<td>46/46</td>
<td>26/46</td>
<td>17/24</td>
<td>21/21</td>
<td>27/46</td>
</tr>
<tr>
<td>Detection rate</td>
<td>100%</td>
<td>56.5%</td>
<td>70.8%</td>
<td>100%</td>
<td>58.7%</td>
</tr>
<tr>
<td><strong>Lungs</strong></td>
<td>89/94</td>
<td>52/94</td>
<td>52/53</td>
<td>26/38</td>
<td>89/94</td>
</tr>
<tr>
<td>Detection rate</td>
<td>94.7%</td>
<td>55.3%</td>
<td>98.1%</td>
<td>68.4%</td>
<td>94.7%</td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td>74/74</td>
<td>42/74</td>
<td>30/41</td>
<td>35/38</td>
<td>57/74</td>
</tr>
<tr>
<td>Detection rate</td>
<td>100%</td>
<td>56.8%</td>
<td>73.2%</td>
<td>92.1%</td>
<td>77.0%</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>42/48</td>
<td>6/48</td>
<td>11/13</td>
<td>9/13</td>
<td>45/48</td>
</tr>
<tr>
<td>Detection rate</td>
<td>100%</td>
<td>12.5%</td>
<td>84.5%</td>
<td>69.2%</td>
<td>93.8%</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>199/199</td>
<td>100/199</td>
<td>71/111</td>
<td>69/96</td>
<td>158/199</td>
</tr>
<tr>
<td>Detection rate</td>
<td>100%</td>
<td>50.3%</td>
<td>64.0%</td>
<td>71.2%</td>
<td>79.4%</td>
</tr>
</tbody>
</table>

Number of identified lesions and detection rate (%) in 22 patients with sporadic metastatic PHEOs/PGLs (imaging comparator: composite of functional and anatomical imaging)  

### 68Ga-DOTATATE performance in patients with HNPGLs compared to other imaging modalities

**SDHx-related and sporadic HNPGLs**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/scan</td>
<td>14</td>
</tr>
<tr>
<td>68Ga-DOTATATE</td>
<td>34</td>
</tr>
<tr>
<td>18F-FDG</td>
<td>33</td>
</tr>
<tr>
<td>18F-FDA</td>
<td>10</td>
</tr>
</tbody>
</table>

* Only patients in whom all imaging modalities were performed

20 patients with SDHx-related or sporadic HNPGLs were included (imaging comparator: composite of functional and anatomical imaging)  
68Ga-DOTATATE performance in patients with HNPGLs compared to other imaging modalities

<table>
<thead>
<tr>
<th>Detection rate</th>
<th>[68Ga]-DOTATATE</th>
<th>[18F]-FDOPA</th>
<th>[18F]-FDG</th>
<th>[18F]-FDA</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>38/38 100%</td>
<td>37/38 97.4%</td>
<td>27/38 71.1%</td>
<td>10/34 29.4%</td>
<td>23/38 60.5%</td>
</tr>
<tr>
<td>Jugulotympanic</td>
<td>12/12 100%</td>
<td>11/12 91.7%</td>
<td>8/12 66.7%</td>
<td>4/10 40.0%</td>
<td>5/12 41.7%</td>
</tr>
<tr>
<td>Glomus vagale</td>
<td>10/10 100%</td>
<td>10/10 100%</td>
<td>9/10 90.0%</td>
<td>0/10 0.0%</td>
<td>8/10 80.0%</td>
</tr>
<tr>
<td>Carotid body</td>
<td>8/8 100%</td>
<td>8/8 100%</td>
<td>6/8 75.0%</td>
<td>3/7 42.9%</td>
<td>7/8 87.5%</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>8/8 100%</td>
<td>8/8 100%</td>
<td>4/8 50.0%</td>
<td>3/7 42.9%</td>
<td>3/8 37.5%</td>
</tr>
</tbody>
</table>

Number of identified head and neck lesions and detection rate (%) in 20 patients with HNPGLs (imaging comparator: composite of functional and anatomical imaging)


Overall performance of 68Ga-DOTATATE PET/CT compared to other imaging modalities

<table>
<thead>
<tr>
<th>Detection rate</th>
<th>[68Ga]-DOTATATE</th>
<th>[18F]-FDOPA</th>
<th>[18F]-FDG</th>
<th>[18F]-FDA</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lesions</td>
<td>513/525 98%</td>
<td>392/525 75%</td>
<td>325/525 68%</td>
<td>318/525 61%</td>
<td>435/525 83%</td>
</tr>
</tbody>
</table>

Immediate clinical outcome:

- These results suggest modifications in imaging guidelines for metastatic PHEOs/PGLs & HNPGLs
- These results also suggest that metastatic PHEOs/PGLs & HNPGLs may be targeted by 177Lu– or 90Y-DOTA analogs
- These findings resulted in the use of a gamma probe being used for hidden metastatic PHEOs/PGLs
**New European Soc. of Endocrinology guidelines**

- All patients with PHEO/PGL should be considered for genetic testing
- Plasma or urine metanephrines to be used for screening
- Follow-up for at least 10 years; high-risk patients (children, genetic disease, large tumors) should have lifelong follow up
“A5 PHEO/PGL Genomic Alliance”

“Together we have a chance, separately we fail”

Aim: To develop a precision medicine approach for improved treatment of metastatic PHEO/PGL

Large-scale international study

Multidisciplinary approach

Excellent clinical assessment

Comprehensive molecular analysis of metastatic PHEO/PGL

“A5 PHEO/PGL Genomic Alliance”

“Together we have a chance, separately we fail”

Aim: To develop a precision medicine approach for improved treatment of metastatic PHEO/PGL

Current precision medicine card for SDHB-related PHEO/PGL

Landmark findings

Screening:
• Metanephrines/methoxytryramine, chromogranin A
• MRI or CT from skull base to pelvic floor

Localization:
• MRI or CT, 18F-DOTATATE PET

Disease free

Management:
• Genetic screening from age 5
• No prior/current disease • Annual biochemistry, familial and genetic imaging

Staging: 18F-DOTATATE or 18F-FDG PET

Treatment:
• Localized stage • Surgery, external beam radiation or laparoscopic therapy
• Malignant stage • 18F-FDG PET scan and 18F-DOTATATE PET to predict success of interventional therapy
• Chemotherapy with CVDimedrazole or in rapidly progressing tumors

Future precision treatments

“Transforming hope to better lives through precision medicine”

Crona & Pacak, in preparation
Many thanks to all the members of my laboratory, scientists, attendings, and the endocrine, oncology, and surgery fellows for their dedication, passion, and long hours of effort towards those who suffer.

Many thanks to outside co-investigators: D. Taieb, L. Mercado-Asis, G. Eisenhofer, S. Fliedner, R. Lechan, A. Tischler, A. Grossman, H. Ghayee, J. Crona, Z. Frysak, TCGA and A5 members and many others

“Patients are our passion and we are their hope”