EDITORIAL

International symposium on pheochromocytoma: an event of dedicated healthcare professionals and researchers striving for better patient outcomes

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Abstract

Pheochromocytomas and paragangliomas (PPGLs) are defined as neuroendocrine tumors that produce catecholamines. Many recent advances in their management, localization, treatment, as well as surveillance have significantly improved outcomes for patients with PPGLs or carriers of pathogenic genetic variants linked to the development of these tumors. At present, those advances mainly include the molecular stratification of PPGLs into seven clusters, the 2017 WHO revised definition of these tumors, the presence of specific clinical features pointing toward PPGL, the use of plasma metanephrines and 3-methoxytyramine with specific reference limits to assess the likelihood of having a PPGL (e.g. patients at high and low risk) including age-specific reference limits, nuclear medicine guidelines outlining cluster- and metastatic disease-specific functional (here mainly positron emission tomography and metaiodobenzylguanidine scintigraphy) imaging in the precise diagnostic localization of PPGLs, the guidelines for using radio- vs chemotherapy for patients with metastatic disease, and the international consensus on initial screening and follow-up of asymptomatic germline *SDHx* pathogenic variant carriers. Furthermore, new collaborative efforts particularly based on multi-institutional and worldwide initiatives are now considered key forces in improving our understanding and knowledge about these tumors and future successful treatments or even preventative interventions.

Key Words
- pheochromocytoma
- paraganglioma
- biochemistry genetics
- imaging
- pathology
- therapy

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Introduction

The International Symposium on Pheochromocytoma (ISP) became a tradition and a unique event gathering the best minds and experienced healthcare professionals and researchers in pathophysiology, genetics, diagnosis, and treatment of pheochromocytoma and paraganglioma. The ISP was originally established in 2005 under the auspices of the National Institutes of Health, Bethesda, USA in 2005. That year, the first meeting was held in the Holiday Inn hotel in Bethesda and brought together more than 100 participants from all over the

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world to outline the most important discoveries and achievements in these tumors as well as to discuss how to further advance the field and promote new international collaborative studies, grants, guidelines, consensuses, and position statements. The pioneer in pheochromocytoma and paraganglioma Dr William Manger gave the first plenary lecture. The mission of the first ISP was to support new professionals in the field as well as to foster the development of patient-oriented organizations focusing on these tumors with the ultimate goal of improving understanding, diagnosis, and outcomes for patients with pheochromocytomas and paragangliomas (PPGLs). Basic and clinical researchers were encouraged to engage in collaborations, most especially with young and promising individuals from various continents to fulfill the mission of the first ISP. To that aim, following this convention, several key pheochromocytoma–paraganglioma organizations have been established, including the PheoPara Alliance (2007), the Paradifference Foundation (2014) and the SDHB PheoPara Coalition (2016). In addition, several pheochromocytoma/paraganglioma patient-oriented conferences have been held and organized at the National Institutes of Health (e.g. *SDHB*-related pheochromocytoma /2005/; Pheochromocytoma 2007; International patient and healthcare professional conferences on pheochromocytoma and paraganglioma /2009/). The European Network for the Study of Adrenal Tumours (ENS@T) had been founded in 2002 to study adrenal tumors; in 2015, the American–Australian–-Asian Adrenal Alliance (A5) was established with one of its major missions to focus on PPGLs and promoting further collaborative efforts among many countries. Recently, A5 and ENS@T have joined forces, thus further extending its reach, and several future projects or initiatives between these two organizations are now ongoing or in the discussion. These endeavors demonstrate the spirit of moving toward a 'global initiative' to study these rare tumors. In 2014, several attendees of the first ISP under the auspices of the US Endocrine Society launched the first 'Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline' (Lenders *et al.* 2014). Soon after, the National Institutes of Health initiated the Cancer Genome Atlas beginning with 10 cancers which included pheochromocytoma and paraganglioma. This initiative included international experts on pheochromocytoma and paraganglioma from around the globe and resulted in a fundamental article which focused on the genetics of these tumors; for the first time, these tumors were divided into three main molecular clusters (pseudohypoxia (e.g. SDH, SDHAF2, FH, MDH2, SUCLG2, VHL, and EPAS1), Wnt-altered (CSDE1 and MAML3), and kinase signaling (RET, NF1, TMEM127, MAX, HRAS, FGFR1, and MET)) (Fishbein *et al.* 2017). Another initiative was undertaken by pathologists and other experts in these tumors, which resulted in the new 2017 WHO Classification of Tumours of Endocrine Organs, including a new definition and terminology of pheochromocytoma and paraganglioma that is now being considered. The initial motion replaced the term 'malignant' with the term 'metastatic' (Tischler *et al.* 2017). This and other initiatives continued with new international collaborations on cancer reporting that also included these tumors and their more detailed classification (Thompson *et al.* 2021). In 2019 (based on the previously published European Association of Nuclear Medicine 2012 Guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma), experts in these tumors put together the updated European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma (Taieb *et al.* 2019). This report became essential as it defined the stepwise approach to imaging/localization of these tumors using various functional modalities. Four important recent consensuses were published and incorporated into clinical practice: (a) 2016 Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary phaeochromocytomas and paragangliomas (NGS in PPGL (NGSnPPGL) Study Group *et al.* 2017); (b) 2019 Consensus of the Working Group on Endocrine Hypertension of the European Society of Hypertension outlines the most up-to-date clinical presentation, diagnosis, and treatment of these tumors (Lenders *et al.* 2020); (c) 2021 International consensus on initial screening and follow-up of asymptomatic *SDHx* mutation carriers outlining the most important considerations and diagnostic steps in the assessment of *SDHx* carriers (Amar *et al.* 2021); and (d) 2021 the North American Neuroendocrine Tumor Society consensus guidelines for surveillance and management of metastatic and/or unresectable PPGLs focusing on how to approach patients with hard-to-treat metastatic or locally advanced disease (Fishbein *et al.* 2021). Regarding efforts to establish and promote databases, for the last several years, both ENS@T and A5 have supported multinational PPGL databases. In 2022, the International initiative for a curated *SDHB* variant database improving the diagnosis of hereditary

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PPGL was achieved based on international collaboration of several universities and medical centers focusing on PPGL studies (Ben Aim *et al.* 2022).

The great spirit and enthusiasm brought by the first ISP was soon transferred into subsequent and highly successful ISP meetings including the second ISP in Cambridge in 2008; third ISP in Paris in 2011, fourth in Kyoto in 2014, fifth in Sydney in 2017 and, after a delay due to the COVID-19 pandemic, the sixth ISP in Prague in 2022. Although each of these meetings had a unique atmosphere and purpose, each one has always attracted dedicated and knowledgeable healthcare professionals ushering in the next wave of innovation to improve patient care.

The sixth ISP in Prague, despite many difficulties and obstacles presented by the COVID-19 pandemic, brought together more than 120 participants. It was held in the Great Hall at the Carolinum of Charles University in Prague, Czech Republic. Charles University is one of the oldest universities in the world, founded in 1348 during the rule of the King of Bohemia and Holy Emperor Charles IV. The Carolinum, named after Charles IV, is a national cultural monument, the seat of the Rector (the President of the Charles University), and a symbol of Charles University and holds University ceremonies and festivities, including matriculation and graduation ceremonies. As the Rector's seat, the premises often hold lectures from significant national and foreign personalities and major social events. It is also within this Great Hall that the degree of professor is awarded by the President of the Czech Republic. The vibrant program of the sixth ISP included 3 plenary lectures, 1 historical lecture, 10 oral sessions with 54 regular lectures (including the Young Investigator Award symposium), a patient-oriented session, a symposium dedicated to high-specific-activity ^{131}MIBG (Azedra) use in clinical practice, and 30 posters. As for previous ISP meetings, the goal was to outline the most important advances in the pathogenesis, genetics, diagnosis, and treatment of these tumors and to determine the immediate priorities while strategically planning future steps toward advancing this field, often by outlining new collaborative initiatives. Participants felt that now, perhaps more than ever, there exists a need to create national and international collaborative programs. To this aim, it was felt that resources should be combined amongst Asia, Europe, South and North America, and Africa in order to fight PPGL and to improve patients' outcomes. These tumors are rare, and we all must, therefore, work together to foster a new era of innovation in the diagnosis and treatment of these tumors.

The sixth ISP began with short opening remarks from Drs Pacak, Clifton-Bligh, and Widimsky. Those opening remarks were followed by honoring Dr Lenders with the Lifetime Achievement Award from the Pheochromocytoma research and Support Organization for his contribution and tireless commitment to advancing the understanding and treatment of patients afflicted with this disease. The historical lecture was presented by Dr Nanka, and it was dedicated to Dr Alfred Kohn who served as professor of histology between 1911 and 1937 at Charles University. Dr Kohn introduced the terms 'chromaffin', 'chromaffin system', 'paraganglion', and 'paraganglionic cell'. He also defined chromaffin cells as a part of the sympathetic nervous system. Finally, he also discovered that the organ of Zuckerkandl is a parganglion. Three plenary speakers included Dr Robledo ('Pheochromocytoma and paraganglioma: dialogue between genetic and epigenetics'), Dr Eisenhofer ('Catecholamine system biology and biochemical diagnosis of pheochromocytoma and paraganglioma') and Dr Taieb ('Nuclear medicine in pheochromocytoma and paraganglioma: at the crossroad of precision medicine). Fifty-four regular lectures were presented outlining new discoveries and novel insights gained from the study of the pathophysiology, genetics, biochemistry, and imaging of these tumors, animal models, cell cultures, and organoids, new biomarkers, and new collaborative efforts. Some examples included new collaborative efforts with the PheoPara Alliance together with the establishment of the PheoPara Centers of Excellence worldwide to improve patient care; the role of surveillance in *SDHB* pathogenic variants carriers (Davidoff *et al.* 2022); and the role of single-nuclei and bulk-tissue gene-expression analysis of PPGL with new findings of seven PPGL gene-expression subtypes with significant genotype and clinical associations (Zethoven *et al.* 2022). *EPAS1*, encoding HIF-2a, was a focus of several presentations, including new findings regarding somatic mutations occurring in PPGL patients with hemoglobinopathies, its role in PPGL proliferation and outcome, and its particular role in the development of the carotid body (Eckardt *et al.* 2021). Other presentations highlighted the role of succinate in bioenergetic sensing and the aggressive behavior of *SDHB*-mutated PPGLs; metabolic and proteomic assessment including targeting the polyamine pathway or new previously undiscovered biomarkers (e.g. adenosine receptor A2A) and cell surface targets in these tumors were presented (Rai *et al.* 2020, Vit *et al.* 2021, Gupta *et al.* 2022). Novel data related to the use of PPGL organoids, immune microenvironment,

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with immunogenomics or intratumoral immunotherapy outlined as novel therapeutic approaches, some of them having been successfully used on animal models (Uher *et al.* 2019). Regarding animal models and PC12 cells, data related to newly developed *SDHB* animal models as well as the role of PC12 in chromaffin cell fate and vulnerability to drugs were presented and discussed (Powers *et al.* 2020). Functional imaging of these tumors focused on the role of precision medicine, comparison with anatomic imaging, and the role of ^{18}F-fluorodeoxyglucose PET/CT in the assessment of metastatic PPGL (Noortman *et al.* 2022). Detailed clinical presentations, genomic alterations, predictions, outcomes, and treatment options (including clinical trials) for patients with metastatic PPGL were also presented and discussed and brought some new, although still limited, options for patients, particularly Food and Drug Administration (FDA)- or European Medicines Agency (EMA)-approved radiotherapeutic modalities using ^{177}Lu-DOTATATE (Lutathera) and high-specific-activity ^{131}metaiodobenzylguanidine (Azedra) (Jimenez *et al.* 2019, Jha *et al.* 2021). Finally, some clinical approaches using adrenoceptor blockade, including management of tachyarrhythmias and hypertensive crisis (Lenders *et al.* 2020, Nazari *et al.* 2020), the management of pregnant patients with PPGL (Bancos *et al.* 2021, Langton *et al.* 2021), and the use of machine learning applications for diagnosis and stratification of patients with these tumors (Reel *et al.* 2022) were discussed. The Young Investigator Award session included seven oral presentations, all of outstanding quality: the Manger Prize was awarded to Dr Rosenblum who presented some novel findings related to the syndrome of PPGL and polycythemia (Rosenblum *et al.* 2021).

In summary, the sixth ISP furthered and successfully expanded our current knowledge related to PPGL and paved new and promising venues to discover more about the pathogenesis, genetics, and tumor microenvironment with particular focus on immune cells, metabolomics, and proteomics of these tumors and linked nicely those discoveries to current and future treatment modalities as well as clinical trials. Undoubtedly, novel biomarkers, especially those presented upon the cell membrane or PPGLs, will be of great interest in the near future since they could serve as new theranostic targets, now more than ever, in the ear of new radiopharmaceuticals that include very promising alpha emitters and somatostatin receptor antagonists (Goldsmith, 2020, Vit *et al.* 2021, Zethoven *et al.* 2022). Immune microenvironment will also become a prime target in understanding the clinical behavior of these tumors as well as a treatment modality of choice for some patients with metastatic PPGL. Moreover, it will be interesting to see the new immunotherapeutic options that can be applied to patients with these tumors, e.g. intratumoral immunotherapy including neoadjuvant approaches (Hong *et al.* 2022). Nevertheless, these treatments should be approached very cautiously and with appropriate pre-treatment and cardiovascular monitoring, given that any tumor manipulations can result in significant catecholamine release. As outlined during some discussions at the symposium, we are eagerly awaiting new guidelines related to management of patients with *SDH* as well as pediatric PPGLs. New animal models as well as 3D organoid PPGL cultures will bring yet unrecognized and long-awaited results related to the potential and promising use of new drugs in the treatment of these tumors. Ongoing support of clinical trials related to these tumors, which are currently rather very limited, together with the support of professional organizations, academia, and other entities worldwide, brings new hopes to beat this rare cancer and improved outcomes of many patients as well as those individuals who carry PPGL-susceptibility genes. The future is bright if we unite our efforts in the mutual pursuit of caring for these patients.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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