Surgical Management of Pheochromocytoma and Retroperitoneal Paraganglioma

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Foreword

Rare diseases generally refer to diseases with a very low incidence. According to the definition of the World Health Organization, rare diseases are diseases with 0.65‰ to 1‰ of the total population. At present, there are more than 7000 rare diseases known in the world, of which about 80% are hereditary diseases caused by gene defects, and there is no effective drug treatment for the vast majority of rare diseases. It is estimated that there are more than 20 million rare disease patients in my country, and more than 200,000 children with rare diseases are born every year. Compared with common diseases, the level of related medical research on rare diseases is obviously lagging. Due to the limited understanding of the pathogenesis of many rare diseases and insufficient diagnostic methods, 40% of rare disease patients have been misdiagnosed at least once, and many patients have been misdiagnosed for a long time. I searched for a doctor but couldn't get a clear diagnosis. In addition, there are still some patients who suffer from the lack of effective treatment, or the unaffordable cost of treatment despite being diagnosed. Rare disease patients often become socially disadvantaged groups due to their illness. In addition to scientific significance, the research on rare diseases also has great significance in sociology and ethics.

In recent years, the state has vigorously supported basic and clinical research on rare diseases, including rare diseases in the "13th Five-Year Plan" development plan, and related fields have gradually developed and expanded, fully reflecting the state's care for vulnerable groups and the principle of social equity. In 2018, five ministries and commissions jointly released the first batch of rare disease catalogs in my country, filling the gap in the identification standards of rare diseases in my country for many years. Peking Union Medical College Hospital has compiled and published my country's first batch of rare disease catalog definitions and rare disease diagnosis and treatment guidelines, and elaborated the clinical manifestations, differential

diagnosis, treatment methods, etc. Which clearly illustrates the diagnosis and treatment path for rare diseases with a clear flowchart.

Pheochromocytoma/retroperitoneal paraganglioma is a rare disease with variable tumor size and location and dangerous clinical symptoms. Peking Union Medical College Hospital has treated patients from all over the country, concentrated a wide variety of cases with complex manifestations, and accumulated a lot of experience in clinical diagnosis and treatment. In the multidisciplinary team consultation including urology, endocrinology, anesthesiology, ICU, respiratory medicine, neurology, dermatology, ophthalmology, stomatology, pathology, imaging, and other departments, we found that in the form of cases, according to the patient's medical history, clinical manifestations, imaging manifestations, MDT discussion, and the order of treatment methods can provide a relatively comprehensive understanding of the disease; and on this basis, the "Pheochromocytoma/Retroperitoneal Paraganglioma Surgery" was compiled. The book of "Surgical management of pheochromocytoma and retroperitoneal paraganglioma" was compiled on this basis. The cases in this book are all selected from the difficult cases in the Department of Urology of Peking Union Medical College Hospital. It is rich in content and has accurate data. It systematically shows the main points of analysis, diagnosis, and treatment of difficult diseases. Which can be used as a reference for doctors engaged in clinical work, as well as for medical students to consult and learn. It is my sincere hope that this book can enhance the medical staff's understanding of the disease and make a certain contribution to the progress of the diagnosis and treatment of rare diseases in my country.

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Nov 2022

Editorial Board

Preface

Pheochromocytoma/Retroperitoneal Paraganglioma Surgical Diagnosis and Treatment Strategy adopts a format that is different from textbooks. We select representative cases, show their diagnosis and treatment process, and describe the clinical thinking process in the diagnosis and treatment. In this way, we present the book to the readers. This unique form of arrangement can not only consolidate the theoretical knowledge of clinical medical students, urological graduate students, advanced physicians, and urologists who have a certain level of theory and clinical practice, but also reproduce the collection, testing, and analysis of case data for each disease. The process of analyzing imaging results and making diagnosis and treatment is very important for cultivating their clinical active thinking ability and creative ability.

The theoretical part of this book mainly refers to the papers and reviews written by the editors in recent years. The selected cases are also real cases of urological surgery in Peking Union Medical College Hospital after team discussion. This form can not only show the problems that junior doctors may encounter in disease diagnosis and treatment and may remind readers to avoid the same mistakes in future clinical work, but also reflect the scientific and careful clinical diagnosis and treatment thinking of senior doctors in disease diagnosis and treatment.

Due to the limitations of the author's diagnosis and treatment experiences or professional level, some cases may not be perfect, and the content of the book may have some deficiencies and omissions. I urge readers to criticize and correct them so that it can be revised and improved in the next edition.

Beijing, China
Nov 2022

Jin Wen

Acknowledgments

I am indebted to all the authors who have contributed new chapters describing the novel topics covered in this book, *Surgical Strategies for Pheochromocytoma/Paraganglioma*. These researchers have lighted the candles of knowledge so that the entire community can tap into their light and break through knowledge barriers, especially through the participation of a group of eminent/prominent urologists, clinicians, and academicians. I express my special gratitude to the reviewers for offering help and valuable comments to improve chapter contents and enhance their scientific importance. This work would not have been possible without the acceptance of the publisher, Springer, and the entire technical team, which has taken diligent care during the different stages of writing, evaluation, and correction, in addition to the stages of preparation and publication. For this, I would like to express my sincere thanks to both the publishing house and the technical team. I would also like to extend my special thanks to the translators team, which spared no effort to ensure the success of this work, and to all the members of the editorial committee who mobilized all their technical and scientific efforts for the realization of this work.

Jin Wen

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Editor and Contributors

About the Editor

Jin Wen is an Assistant to the Chief of Urology Department of Peking Union Medical College Hospital, Chief Physician, Master Tutor, Senior Visiting Scholar of Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, USA. In 2004, he obtained a PhD in Urology. He has been engaged in clinical work related to urological diseases. He keeps improving his surgical techniques, especially in the minimally invasive treatment of adrenal diseases. He has accumulated rich experience and achieved good results.

He is currently the national youth committee member of the Urology Branch of the Chinese Medical Doctor Association, the deputy head of the Laser Collaboration Group, a member of the International Exchange Committee of the Urology Branch of the Chinese Medical Association, a youth member of the Beijing Medical Association Organ Transplantation Branch, a member of the Beijing Medical Award Foundation Urology Branch and Member of the second committee of Beijing Medical Association, Medical Science Branch.

With good scientific research ability and organization and coordination ability, he has successively received funding from Peking Union Medical College Hospital Youth Fund, Young Teacher Training Fund, and Chinese Academy of Medical Sciences Clinical Transformation Fund. In 2017, he was selected as the "Sino-French Outstanding Young Scientists Exchange Program" of the Ministry of Science and Technology and visited the Saint-Etienne University Hospital in France. He has published more than 30 research papers in domestic

core journals and foreign SCI journals, obtained 3 invention patents, and edited the medical monograph *Surgical Treatment Strategies for Pheochromocytoma/Paraganglioma*.

About the Honor Consultants

Han Z. Li is a Chief Physician, Professor, PhD tutor, and Doctoral Supervisor of Urology Department of Peking Union Medical College Hospital, Director of Department of Surgery, Peking Union Medical College Medical School, Academic Leader of Urology Department, recipient of Government Allowance of the State Council; Honorary Professor of the University of Hong Kong; Chairman of the Urology Branch of the Beijing Medical Association, Chairman of the Urology Branch of the Beijing Medical Association, Chairman of the Expert Committee, Deputy Head of the Minimally Invasive Group and Deputy Head of the Oncology Group of the Urology Branch of the Chinese Medical Association, Urology of the Chinese Medical Association Member of the Standing Committee of the Surgeon's Association, Deputy Editor-in-Chief of *Chinese Journal of Urology*, Deputy Editor-in-Chief of *Union Medical Journal*, editorial board member of *Chinese Journal of Surgery*, and Deputy Editor-in-Chief of *Beijing Medicine*.

He has won the China Medical Science and Technology Award, the Huaxia Medical Science and Technology Award, "Top Ten Health Guards in the Capital," "National Health System Advanced Worker," "Golden Cystoscopy Award," "Golden Lancet Award," "Chinese Physician Award," "Beijing University," , "Teaching Famous Teacher Award," "Peking Union Medical College Teacher Morality Pioneer." He has published more than 300 professional papers at home and abroad, including dozens of SCI papers and more than 10 monographs.

Zhi Gang Ji is a chief physician, professor, PhD tutor, director of the Department of Urology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences; academic leader; member of the Standing Committee of the Urology Branch of the Chinese Medical Association, Vice President of the Urology Branch of the Chinese Medical Doctor Association, and Vice President of the Chinese Medical Association Andrology Branch President, President-designate of the Andrology Branch of the World Chinese Physician Association, Vice Chairman of the Urology Branch of the Beijing Medical Association, Chairman of the Urology Expert Committee of the Beijing Medical Award Foundation, and Deputy Head of the Oncology Group of the Urology Branch of the Chinese Medical Association, Deputy Head of Robotics Group of Urology Branch of Beijing Medical Association, Review Expert of Drug Evaluation Center of State Food and Drug Administration, Health Care Consultation Expert of Central Health Bureau; Editorial Board Member of *Chinese Journal of Urology*, *Chinese Journal of Medicine*, *Journal of Clinical Urology*, *Modern Journal of Urogenital Oncology*, *Chinese Journal of Surgery* correspondent editor, *International Journal of Surgery* correspondent editor.

He has won the China Medical Science and Technology Award. He has presided over and completed a number of clinical scientific research work. He has published more than 200 professional articles and written 6 monographs.

1 Principles of Diagnosis and Treatment of Pheochromocytoma and Retroperitoneal Paraganglioma

Han Zhong Li, Jian Hua Deng, Jin Wen, He Xiao, Yong Qiang Li, Xing Cheng Wu, Xue Bin Zhang, Peng Hu Lian, and Yin Sheng Zhang

Pheochromocytoma and retroperitoneal paraganglioma (PPGL) are neuroendocrine tumors derived from the neural crest cells of sympathetic and parasympathetic chain, including PPGL located in the adrenal medulla (85–90%) and PPGL located outside the adrenal gland (10–15%), the most common parts of which are located along with the abdominal aorta, bladder, chest, head, neck, and so on (Fig. 1.1). PPGL accounts for about 0.2–0.6% of hypertensive patients, with an annual incidence of about 0.8/100,000.

Han Zhong Li and Jian Hua Deng contributed equally to this work.

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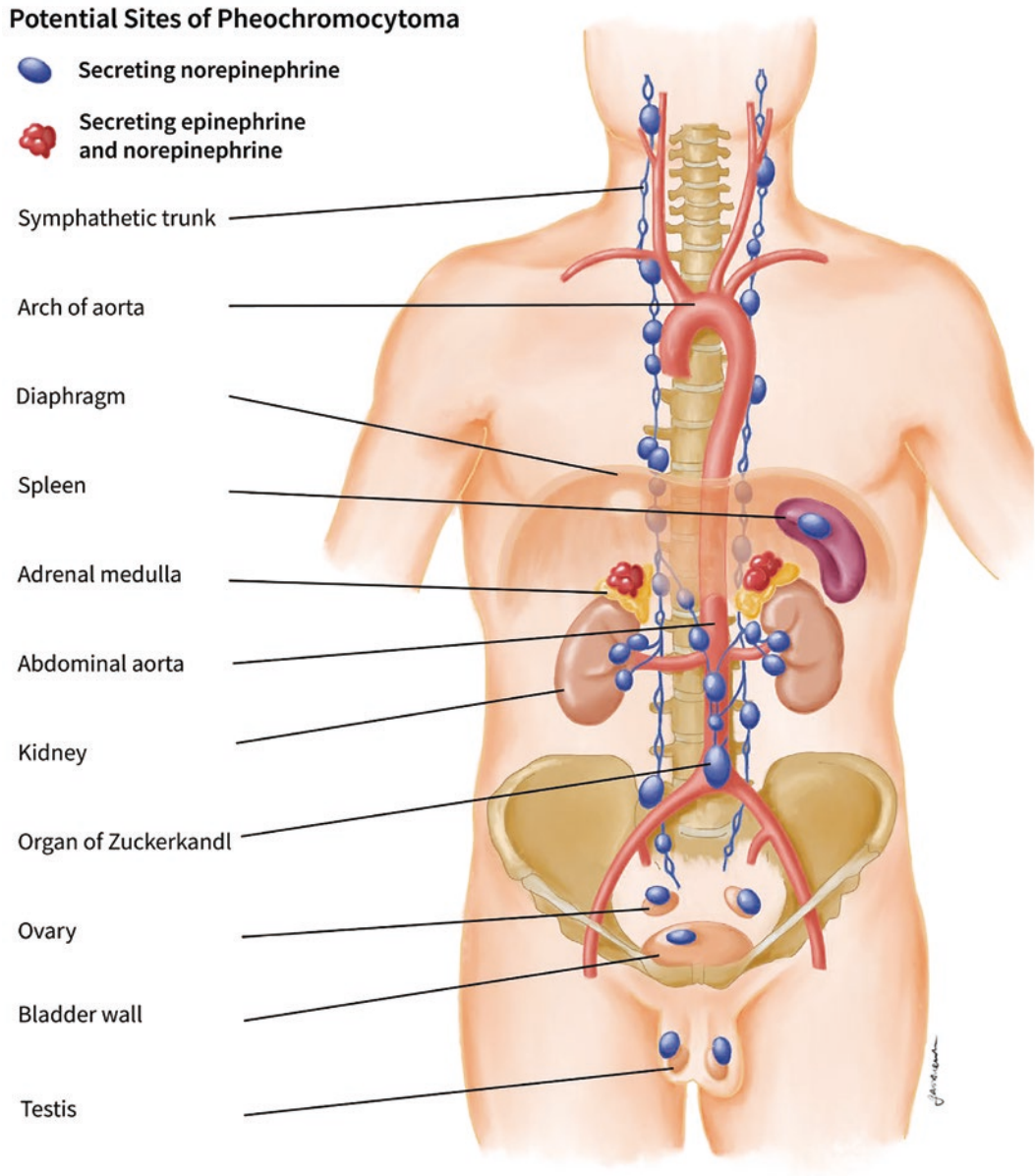

Fig. 1.1 Occurrence sites of pheochromocytoma/paraganglioma

1.1 Clinical Manifestations

Pheochromocytoma and retroperitoneal paraganglioma (PPGL) secrete catecholamines. The main clinical manifestations are persistent or intermittent hypertension, palpitations, headache, and other symptoms (nausea, fatigue, sweating, abdominal pain, chest pain, arrhythmia, etc.) Life-threatening symptoms such as heart failure and myocardial infarction may occur. The currently recommended laboratory test method is the determination of plasma/urine catecholamine or intermediate metabolites methoxyephrine or methoxyphenylephrine. The latest evidence shows that the sensitivity and specificity of plasma testing are better than urine testing and

the detection of epinephrine in plasma has a lower false-positive probability than epinephrine in urine. Free epinephrine, norepinephrine and 3-Determination of methoxytyramine are the preferred plasma test. Increased concentrations of two or more catecholamine metabolites are highly suggestive of PPGL.

CT (computed tomography) and MRI (magnetic resonance imaging) are commonly used imaging localization methods for clinical diagnosis of PPGL. On contrast-enhanced CT, tumor enhancement is obvious, and cystic degeneration, calcification, and hemorrhage may be found in the tumor. If the above imaging tests have no positive findings, 131I-m-iodobenzylguanidine (etaiodobenzylguanidine, 131I-MIBG) and somatostatin receptor imaging can be performed. The sensitivity and specificity of 131I-MIBG imaging in the diagnosis of pheochromocytoma were 82.41% and 100%, respectively. According to literature reports, the reason for the false negative may be related to, in some cases, insufficient uptake of the tracer by the tumor or by the patient taking reserpine, cocaine, amphetamine, and other drugs that affect the body's uptake of MIBG. Extensive necrosis and bleeding in tumors with a diameter of less than 2.0 cm or large tumors can easily lead to false negatives.

Fluorodeoxyglucose (18F-FDG) PET-MRI or 18F-FDG PET-CT can accurately visualize tumor histology, further assess the extent of disease, and is more sensitive than MIBG and CT/MRI in detecting metastatic disease. The latest data show that 68Ga-DOTATATE PET/CT is significantly better than the abovementioned examinations in the detection of metastatic PPGL lesions and has gradually become the preferred method of examination for metastatic PPGL.

PPGL is a highly hereditary tumor that is inherited in approximately 40% of patients. So far, more than 20 pathogenic genes have been identified, mainly including SDHB, SDHD, VHL, RET, TMEM127, and so on. The patient's genotype is related to clinical phenotype, such as tumor location, type of catecholamine secretion, tumor metastasis, and prognosis. Compared with sporadic tumors, patients with hereditary catecholamine-secreting tumors are generally younger, and their incidence is higher in patients with family history, bulky tumors, and multiple tumors. SDHB gene mutation carriers during diagnosis or follow-up indicate a high risk of malignant PPGL. Because the genetic data of patients are closely related to the clinic, genetic screening and enhanced follow-up should be carried out for families carrying PPGL-related gene mutations to facilitate early diagnosis of the disease and timely intervention.

At present, there are still many basic research issues that need to be discussed. It is necessary to establish a clinical data database of PPGL, as well as a database of patients' blood and tissue specimens, to lay a good foundation for further clinical and basic research of PPGL. To use the research results on VEGF, HIF, mTOR, and other signaling pathways to apply targeted drug therapy to clinical practice, extensive and in-depth basic research on the pathogenesis of PPGL is also required. In addition to the establishment of primary cultures of human PPGL, systematic studies should also be carried out in terms of genetics, epigenetics, signaling pathways, and targeted drugs.

1.2 Treatment

1.2.1 Preoperative Management

The impact of hypercatecholamineremia produced by PPGL on patients includes the following aspects: firstly, the greatest impact on blood pressure, serious cardiovascular, and cerebrovascular accidents is not uncommon; secondly, there is damage to cardiac function and structure caused by catecholamine cardiomyopathy; thirdly, it is the mass effect of the huge tumor that squeezes the surrounding organs and the possibility of invasion and metastasis of some PPGLs.

The incidence of paroxysmal hypertension in patients is 25–40%. The incidence of persistent hypertension is about 50%, of which 50% have paroxysmal exacerbation. About 70% of patients have orthostatic hypotension. For a small number of patients, blood pressure is normal. Surgery to remove the tumor is one of the most effective

treatments, but it is risky. Perioperative mortality can be as high as 45% in patients with complex PPGL without systemic preoperative adjustment and treatment of concurrent disease. Some tumors appear to be in a "quiescent state" without secreting hormones, but under stress conditions such as anesthesia and other organ surgery, they can induce hypertensive crisis or shock state. Enough attention should be paid to these tumors.

Alpha-blockers are usually prescribed for 2–4 weeks, depending on symptom severity, cardiac function status, and catecholamine levels. The criteria for adequate drug preparation are:

1. Blood pressure is controlled at about 130/80 mmHg; blood pressure is stable, and the original orthostatic hypotension is reduced.
2. Heart rate is less than 80 beats/min, with no palpitations, sweating, etc.
3. Hypermetabolic symptoms are improved or disappear.
4. Recovery of blood volume and improvement of peripheral circulation.

Alpha-blockers can reduce blood pressure, dilate the vascular bed, and gradually increase blood volume. The commonly used drug is phenoxybenzamine, which is usually taken for 2–4 weeks. After the patient has normal blood pressure control, blood volume recovery, weight gain, warm extremity skin, improved microcirculation, and improvement of hypermetabolic syndrome and abnormal glucose metabolism, surgery can be considered.

Catecholamine cardiomyopathy caused by high concentrations of catecholamines on myocardial damage can usually be relieved after the use of alpha-blockers and cardioprotective therapy. Arrhythmias, heart failure with pulmonary edema, myocardial infarction, and generalized or focal ventricular wall motion abnormalities may be improved. Such patients should be prepared for 3–6 months before surgery and then undergo surgery after the myocardial damage has recovered to a better state. Life-threatening cases of PPGL with a high level of catecholamine secretion are common during the onset of catecholamine cardiomyopathy, during interventional therapy, during induction of surgical anesthesia, and in the case of circulatory instability due to insufficient volume after surgery. These patients should be treated with caution.

In addition, a multidisciplinary discussion of mechanism needs to be established before surgery. A multidisciplinary collaborative team including urology, endocrinology, basic surgery, anesthesiology, ICU, radiology, pathology, etc., through careful preoperative discussion, repeatedly deduces intraoperative and postoperative possibility of complex PPGL. Various situations that may occur during and after PPGL surgery can be successfully handled for treating difficult and high-risk patients with PPGL tumors. Preoperative fingernail fold microcirculation detection, adequate preoperative drug preparation, and proper perioperative management are the keys to reducing surgical risks and making the surgery successful.

1.2.2 Surgical Management

Surgical resection is a radical cure for PPGL, but surgery and anesthesia are of high risk. Adequate preoperative preparation can effectively reduce the occurrence of various perioperative complications. Since the 1990s, the Department of Urology of Peking Union Medical College Hospital has taken the lead in carrying out laparoscopic adrenal tumor resection in China. Since 2003, Peking Union Medical College Hospital has focused on the clinical practice of laparoscopic surgery to remove adrenal PPGL with a sum of successful experience of 211 cases of laparoscopic surgery to remove PPGL. We focus on the safety and feasibility of this technology to lay a foundation for further work. Since December 2012, Peking Union Medical College Hospital has successively introduced 3D laparoscopic and da Vinci robotic surgery systems, which have advantages in the identification and dissection of blood vessels and organs around PPGL and have achieved satisfactory results.

PPGL is rich in blood supply, and larger tumors are more prone to hemodynamic instabil-