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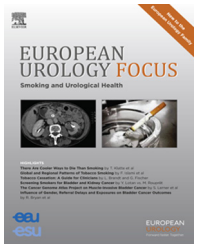

Review – Adrenal Glands

Pheochromocytoma in Urologic Practice

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Abstract

Context: Pheochromocytoma is regularly encountered in urologic practice and requires a thoughtful and careful clinical approach.
Objective: To review clinical aspects of the management of pheochromocytoma in urologic practice.
Evidence acquisition: A systematic review of English-language literature was performed through 2015 using the Medline database. Manuscripts were selected with consensus of the coauthors and evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria.
Evidence synthesis: Findings and recommendations of the evaluated manuscripts were discussed with an emphasis on the description of presentation, diagnosis, evaluation, and perioperative care.
Conclusions: In addition to surgical expertise, appropriate management of pheochromocytoma in urologic practice requires a nuanced understanding of pathophysiology, genetics, and endocrinologic principles. When skillfully managed, the vast majority of patients with pheochromocytoma can expect an excellent prognosis.
Patient summary: We review the clinical approach to patients with pheochromocytoma, a tumor that stems from the innermost part of the adrenal gland and often secretes excessive amounts of powerful hormones such as noradrenaline and adrenaline. Significant expertise is required to appropriately manage patients with these tumors.

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1. Introduction

Urologic surgeons' intimate knowledge of retroperitoneal anatomy and advanced skill set in both open and minimally invasive retroperitoneal surgery ideally positions them to be key members of the multidisciplinary team that cares for patients with pheochromocytoma. Nevertheless, beyond technical skill, care of patients with this complex condition requires nuanced expertise in patient evaluation, selection, and medical management. This article reviews the perioperative care of patients with pheochromocytoma.

2. Evidence acquisition

A comprehensive review of the English-language literature was performed to review the modern management of pheochromocytoma. This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria [1]. The terms *pheochromocytoma* in combination with *adrenal, diagnosis*, *imaging*, *perioperative*, *malignant*, or *hereditary* were used to perform a Medline database search through June 2015. Citations from appropriate manuscripts, prior book chapters written by the

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authors, and prior reviews were gathered to identify seminal articles. After exclusion of duplicates, the final list of references was identified with coauthor consensus.

3. Evidence synthesis

The annual incidence of pheochromocytoma ranges from 2 to 8 cases per 1 million persons [2,3]. Among those with nonessential hypertension, pheochromocytoma is found in 0.1–0.6% of patients [4,5]. Patients with an incidentally discovered adrenal lesion >1 cm in diameter are diagnosed with pheochromocytoma in approximately 4–5% of cases [6,7]. The average age of diagnosis in nonhereditary cases is approximately 45 yr and occurs in equal proportion in men and women [2,3,8].

Historically, pheochromocytoma was labeled as the "10% tumor" because it was thought to be 10% bilateral, 10% extra-adrenal, 10% hereditary, 10% pediatric, and 10% malignant [9]. Nevertheless, this axiom of medical education has been challenged as the literature on the subject has matured. For instance, some 25% of cases of pheochromocytoma stem from extra-adrenal tissue [10], and as many as 30% are hereditary [11,12]. Although it is the most common endocrine-secreting tumor in children, pheochromocytoma remains rare in this population, with only approximately 2% of those screened for hypertension harboring this pathology [13].

Finally, malignant pheochromocytoma is rare. Malignant disease is estimated to have an incidence of 93 cases per 400 million persons and thus occurring in approximately 5% of patients with sporadic disease originating in the adrenal gland [14]. Malignancy, however, is reported in up to 70% among those with extra-adrenal tumors, and up to 50% of those with *SDHB* mutations [15–17].

3.1. Pathophysiology

Pheochromocytoma and paragangliomas are tumors that stem from cells of the neural crest. The neural crest ultimately develops into the sympathetic paraganglia (including the adrenal medulla and organ of Zuckerkandl) and parasympathetic paraganglia (including the carotid body). Pheochromocytomas and paragangliomas can thus develop at any of these locations extending from the head to the pelvic floor. The vast majority of these tumors stem from the adrenal gland; however, up to 25% occur at extra-adrenal sites and are termed *paragangliomas* [10,18].

Chromaffin cells lie in the adrenal medulla and are innervated by preganglionic neurons from T11 to L2 sympathetic fibers. The enzyme phenylethanolamine-N-methyl transferase (PNMT) is responsible for the conversion of norepinephrine to epinephrine within the adrenal. PNMT is unique to the adrenal gland, the brain, and the organ of Zuckerkandl. As such, the adrenal medulla secretes the catecholamines norepinephrine (80%), epinephrine (19%), and dopamine (1%) [19].

Catecholamines are metabolized by the enzyme catechol-O-methyl transferase (COMT) that catalyzes the conversion of norepinephrine to normetanephrine, and epinephrine to metanephrine. Thus these inactive metabolites of catecholamines, collectively known as metanephrines, are also secreted by the gland [20]. Vanillylmandelic acid (VMA) is a degradation product formed by the deamination and subsequent O-methylation and oxidation of norepinephrine and epinephrine via the COMT and monoamine oxidase (MAO) pathways [21].

In response to sympathetic nerve activity, catecholamines stored in presynaptic terminal vesicles are released into circulation for travel to end organs [21]. The ultimate pathophysiologic effects of pheochromocytomas vary based on the proportion of each type of catecholamine released, the effector organ, and the target receptor type (α vs β) and subtype. Thus pheochromocytomas have a wide range of clinical symptoms. For example, the rare tumors that exhibit a predominance of epinephrine release have a primary effect on the β-2 receptor, resulting in systemic vasodilation and the clinical manifestation of orthostatic hypotension. More commonly, tumors with a predominance of norepinephrine release demonstrate primary activity against the α-receptor, resulting in vasoconstriction and hypertension [22].

3.2. Signs and symptoms

Signs and symptoms of pheochromocytoma are due to excess catecholamine secretion by the tumor. Patients may present with the triad of episodic headache, sweating, and tachycardia [23,24], although these symptoms are concomitantly present in only 24% of cases [25]. Approximately half of patients have paroxysmal hypertension, of which 50–60% have sustained hypertension in between episodes. Nevertheless, it is important to note that 5–40% of patients with pheochromocytoma never exhibit episodes of blood pressure elevation [26]. As many as 50% of patients are asymptomatic and are diagnosed incidentally during abdominal imaging [15,25].

Other possible presenting symptoms of pheochromocytoma include angina pectoris, tremor, blurred vision, constipation, nausea, early satiety, weight loss, and anxiety. Less common signs include facial pallor, hypotension (epinephrine-secreting tumor or reflective of low plasma volume), and hyperglycemia [15,27]. Rarely, a patient can present with catecholamine-induced cardiac stress resulting in so-called Takotsubo cardiomyopathy; although it is generally transient and reversed by elimination of the catecholamine source, permanent histologic and pathophysiologic changes can occur in some patients [28]. Hyperglycemia is due to the direct effects of catecholamines both on α-2 receptors of pancreatic islet cells (resulting in decreased insulin secretion), and on β-2 receptors of skeletal muscle (resulting in increased contractility and glycogenolysis). As a rule, signs and symptoms of pheochromocytoma can be fully reversed by catecholamine blockade and surgical extirpation [29].

3.3. Diagnosis

The work-up for pheochromocytoma is generally prompted by the presence of any of the signs or symptoms just described or by the incidental finding of an adrenal mass on