CHAPTER 1
Introduction

Pheochromocytomas are rare but treacherous *catecholamine-producing tumors*, which if missed or not properly treated, will almost invariably prove fatal [1–6]. Prompt diagnosis is, therefore, essential for effective treatment, usually by surgical resection. The manifestations are diverse and the tumor can mimic a variety of conditions, often resulting in erroneous and delayed diagnosis [1, 7]. Therefore, not surprisingly pheochromocytoma earned the title "*great mimic*" [8].

The incidence of pheochromocytoma in autopsy studies is about 0.05–0.1% [9–14]. Autopsy studies have also shown that up to 50% of pheochromocytomas are unrecognized [12, 14]. Recent advances in biochemical diagnosis (the measurement of plasma free metanephrines), tumor localization (the use of positron emission tomography), surgical approaches (the use of laparoscopic adrenal-sparing surgery), and improved understanding of the pathophysiology and genetics of pheochromocytoma (the role of succinate dehydrogenase gene family or hypoxia and apoptosis pathways) are leading to earlier diagnosis and changes in management strategies and therapeutic options [1, 2, 5, 15–29].

Pheochromocytomas are most frequent in individuals between 40 and 50 years, with very slight predilection in females. The tumors occur in all races, but have been predominantly reported in caucasians [30]. Pheochromocytomas typically derive in about 85% of cases from adrenal medullary chromaffin tissue and in about 15% of cases from extra-adrenal chromaffin tissue [31]. Those arising from extra-adrenal tissue are commonly known as *paragangliomas*. The 2004 WHO classification of endocrine tumors defines pheochromocytoma as a tumor arising from catecholamine-producing chromaffin cells in the adrenal medulla – an intra-adrenal paraganglioma. Paragangliomas are divided into two groups: those that arise from parasympathetic-associated tissues (most commonly along cranial and vagus nerves; e.g. glomus or carotid body tumors) and those that arise from sympathetic-associated chromaffin tissue (often designated *extra-adrenal pheochromocytomas*).

Extra-adrenal pheochromocytomas arise mainly from chromaffin tissue of sympathetic ganglia in the abdomen (in about 75%) [32, 33]. Extra-adrenal pheochromocytomas in the abdomen most commonly arise from a collection

of chromaffin tissue around the origin of the inferior mesenteric artery (the organ of Zuckerkandl) or aortic bifurcation [1]. Both adrenal and extra-adrenal paragangliomas display similar histopathological characteristics. Less frequent sites of pheochromocytoma include kidney, urethra, prostate, spermatic cord, genital tract, and liver.

Most pheochromocytomas arise sporadically, but based on recent reports up to 24% are familial [25, 34]. Up to 25% of patients with pheochromocytoma present with adrenal incidentaloma, whereas approximately 5% are diagnosed at surgery [22, 35–39]. In contrast to sporadic pheochromocytomas that are usually unifocal and unilateral, familial pheochromocytomas are often multifocal and bilateral [1, 4, 7, 15, 40]. Although metastases may be rare for adrenal (about 10%) and familial (less than 5%; except succinate dehydrogenase subunit B SDHB pheochromocytomas [32, 41], the prevalence is up to 36% for extra-adrenal abdominal pheochromocytomas [38, 40, 42–44]. Finally, up to 14% of intra-adrenal pheochromocytomas show local recurrence [22, 30, 45]. One study also showed that patients with mainly adrenal pheochromocytoma have an increased risk for developing other cancers (e.g. liver and biliary tract cancers, malignant melanoma, cervix carcinoma, and central nervous tumors) [46].

According to different reviews and statistics, pheochromocytomas account for approximately 0.05–0.6% of patients with any degree of sustained hypertension [1, 15, 47–49]. However, this probably accounts for only 50% of persons harboring the tumor, when it is considered that about half the patients with pheochromocytoma have only paroxysmal hypertension or are normotensive. Also, despite the low incidence of pheochromocytoma among patients with sustained hypertension, it must also be considered that the current prevalence of sustained hypertension in the adult population of Western countries is up to 30% [50–52]. Thus, the prevalence of pheochromocytoma can be estimated to lie between 1:4500 and 1:1700, with an annual incidence of detection three to eight cases per 1 million per year in the general population [53].