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# 1

# Macro and Microscopic Aspects

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## 1. Introduction

In 1886, Fränkel first described pheochromocytoma at autopsy [1]. The term pheochromocytoma was coined by Poll in 1905 to describe the dusky (pheo) color (chromo) of the cut surface of the tumour when exposed to dichromate [2]. Not until 1926 did Mayo [3] at the Mayo Clinic and Roux [4] in Switzerland successfully remove these adrenal tumours. Interestingly, neither of these tumours was diagnosed preoperatively. Pheochromocytomas are rare catecholamine-producing neuroendocrine tumours arising from the chromaffin cells of the embryonic neural crest mainly of adrenal medulla or the extra-adrenal chromaffin tissue (paraganglia). Which synthesize, store, metabolize, and usually but not always secrete catecholamines.

### 1.1 Incidence

Population studies report an annual incidence of between 0.4 and 9.5 new cases per 100,000 adult persons each year [5,6,7], which constitute a curable form of hypertension in 0.1 to 1% of hypertension patients [8]. Of patients with pheochromocytoma discovered only at autopsy, 75% died suddenly from either myocardial infartion or a cerebrovascular catastrophe. Moreover, one third of the sudden deaths occurred during or immediately after unrelated minor operations [9,10]. Referrals for pheochromocytoma have been reported to be increasing, likely as a result of improved detection.

### 1.2 Clinical features

The majority of pheochromocytomas are sporadic in origin (80-90%) but may be associated with other diseases. Classically, pheochromocytomas has been termed a “10% tumour because roughly 10% of these tumours are malignant, multifocal, and bilateral, arise in extra-adrenal sites, and occur in children. However, recent evidence suggests the percentage of familial tumours is considerably higher [11].

### 1.3 Classic presentation

The classic triad of pheochromocytoma presentation is episodic headache, sweating, and palpitations. Manifestations of catecholamine excess form a wide spectrum of symptoms in

these patients, the foremost being hypertension. Persistent hypertension is frequently considered part of the presentation. Also is typically found with a diverse set of symptoms, which may include anxiety, chest and abdominal pain, visual blurring, papilledema, nausea and vomiting, orthostatic hypotension, transitory electrocardiographic changes, and psychiatric disorders. As to be expected, these symptoms are not always present and certainly do not always constitute a diagnosis. Nonfunctioning pheochromocytomas are distinctly uncommon; nearly all patients with these tumours, at least in retrospect, demonstrate some characteristic symptom or sign, especially accentuated at the time of operative tumour manipulation. Diagnosis of pheochromocytoma includes detection of catecholamines in urine and plasma and radiological tests such as computed axial tomography, nuclear magnetic resonance imaging and metaiodobenzylguanidine scintigraphy. Laparoscopic techniques have become standard for treatment of tumours of the adrenal glands [12].

## 2. Pathology features

### 2.1 Macroscopy findings

Nearly 90% of pheochromocytomas are usually confined to the adrenal gland, and may appear encapsulated. In sporadic pheochromocytomas, even though lobulated, the tumour is actually a single neoplasm. In contrast, familial tumours are often bilateral and usually multicentric [13]. Pheochromocytomas are of variable size, ranging from 3 cm to 5 cm in diameter but can be more than 10 cm [14]. The weight may range from < 5g to over 3,500g, the average in patients with hypertension being 100g [15]. The cut surface is usually soft, yellowish white to reddish brown. The larger tumours often have areas of necrosis, hemorrhage, central degenerative change, cystic change and calcification. The normal gland can be seen in most cases but is sometimes attenuated (Fig. 1).

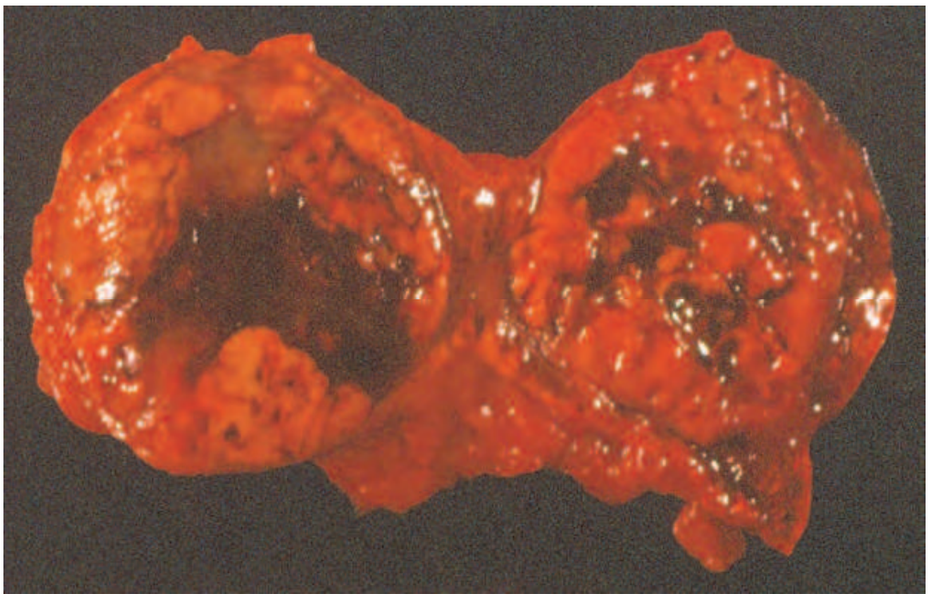


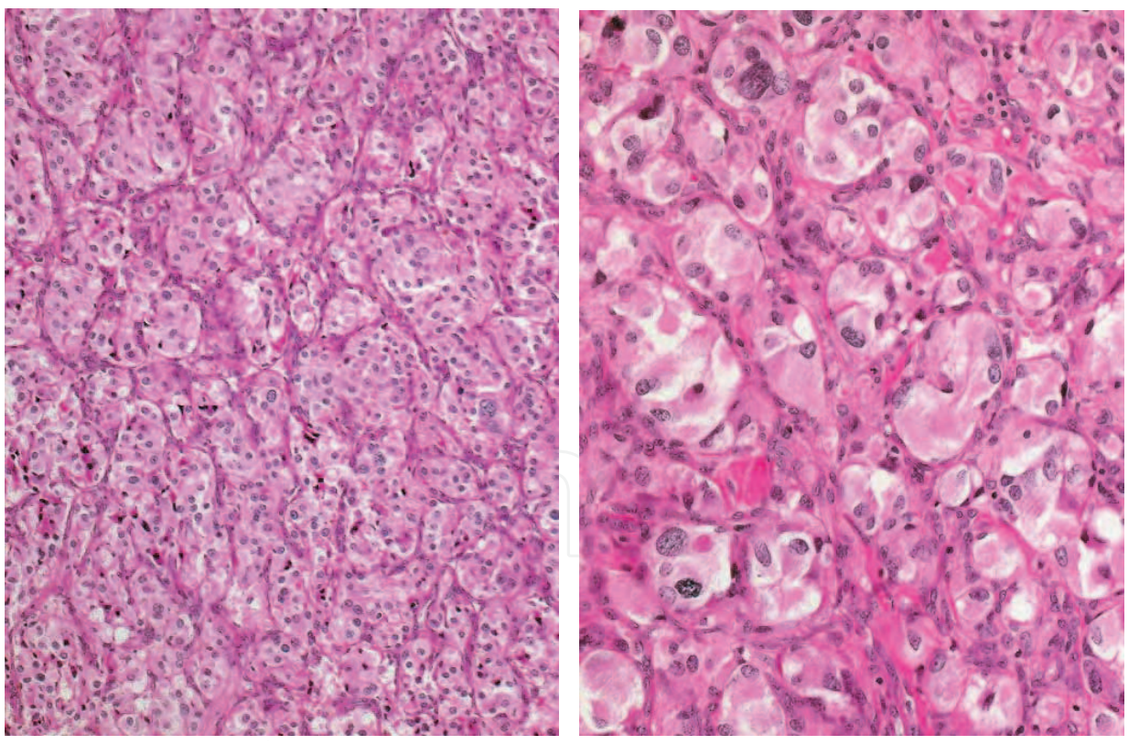
Fig. 1. Adrenal Pheochromocytoma. The round tumour extends torwards the adrenal cortex but is macroscopically well defined. Focal degenerative change and central hemorrhage is present. Attached adrenal remnant is also present.

The other 10 to 15% of cases are found in the neck, mediastinum and heart, or along the course of the sympathetic chain. The most frequent extra-adrenal site is the aortic bifurcation, the so-called organ of Zuckerkandl [16].

### 2.2 Histopathology

Microscopically, the tumour cells are characteristically arranged in well-defined nest ("Zellballen") or trabecular pattern bound by a delicate fibrovascular stroma, or a mixture of the two (Fig. 2A). Diffuse or solid architecture can also be seen. A true capsule does not usually separate the tumour from the adjacent adrenal but a pseudocapsule may be present, or the tumour may extend to the adrenal capsule. The border with the adjacent cortex may be irregular, with intermingling of tumour cells with cortical cells.

The tumour cells vary considerably in size and shape and have a finely granular basophilic or amphophilic cytoplasm. The nuclei are usually round or oval with prominent nucleoli and may contain inclusion-like structure resulting from deep cytoplasmic invaginations. Cellular and nuclear pleomorphism is sometimes prominent (Fig. 2B) [17]. Spindle cells are present in about 2% of cases, usually as a minor component. Haemorrhage and haemosiderin deposits are common. Mitotic figures are rare, with an average of one per 30 high power fields reported in clinically benign lesions [18].

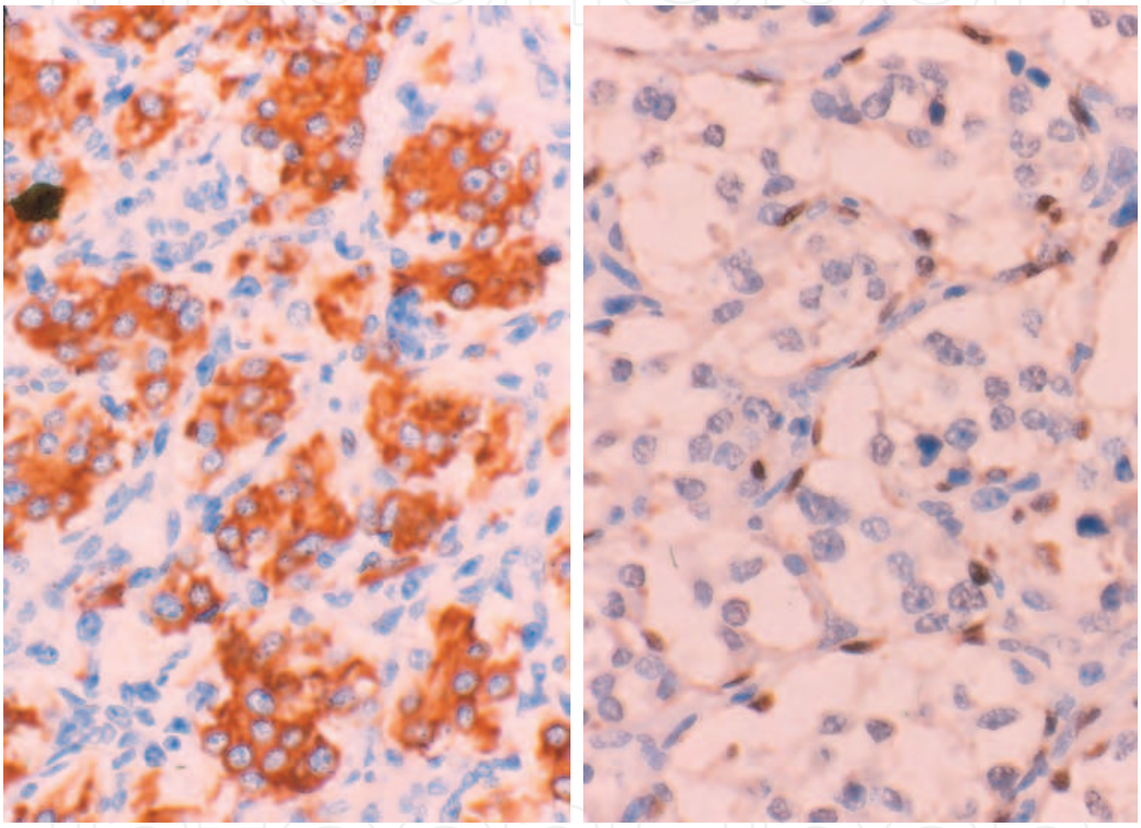


A B

Fig. 2. Benign pheochromocytoma. **A)** Well-defined nest of cuboidal cells are separated by highly vascularized fibrous septa ("zellballen"). A granular, basophilic cytoplasm is usually identified surrounding slightly irregular nuclei; **B)** nuclear pleomorphisms are sometimes prominent.

### 2.3 Immunohistochemistry

Specific diagnosis is usually based on morphology and confirmed by immunohistochemistry. Pheochromocytomas are positive for chromogranin A. Other neural markers such as synaptophysin have been reported to be variably positive in cortical tumours. The absence of positivity for epithelial membrane antigen helps distinguish pheochromocytoma from renal cell carcinoma. Immunostaining for S100 protein will demonstrate sustentacular cells [19] which are usually arranged around the periphery of the cell nests where there is an alveolar arrangement (Fig. 3).



A B

Fig. 3. Immunohistochemical staining. **A)** Positive cytoplasmic immunostain for chromogranin in the pheochromocytoma; **B)** Immunostain for S-100 protein shows intense dark staining of elongated nuclei of sustentacular cells. These are usually located near vascular channels.

## 3. Familial pheochromocytoma

Pheochromocytomas are considered to be unique neuroendocrine tumours since they can occur as part of several familial tumour syndromes. It is now recognized that the frequency of germline mutations in apparently sporadic presentations is as high as 15%–24% [11,20]. However, the genetic basis of the majority of sporadic pheochromocytomas remains largely uncharacterized.

Familial pheochromocytomas are often multifocal or bilateral and generally present at an earlier age than sporadic pheochromocytoma. Germline mutations in six genes have been associated with familial pheochromocytoma, namely, the von Hippel-Lindau gene (*VHL*), which causes von Hippel-Lindau (VHL) syndrome, the *RET* gene, leading to multiple endocrine neoplasia type 2 (MEN 2), the neurofibromatosis type 1 gene (*NF1*), associated with neurofibromatosis type 1 (NF1) disease, and the genes encoding subunits B and D (and also rarely C) of mitochondrial succinate dehydrogenase (*SDHB, SDHD*, and *SDHC*), which are associated with familial paraganglioma/PPC. The recent description of mutations of the succinate dehydrogenase gene (*SDH*) has demonstrated a much stronger hereditary component than formerly thought. Currently, up to 24% of pheochromocytomas may have a genetic predisposition [11,20].

The genetic susceptibility of malignant and benign pheochromocytomas is similar. However, advances in molecular genetics continue to underscore the importance of hereditary factors in the development of pheochromocytoma and propensity to malignancy. Malignant tumours have been reported in patients with germline mutations of *RET*, *VHL*, *NF1* and the *SDH* genes [21,22]. On the other hand, malignant pheochromocytomas in the setting of MEN 2 occur less frequently than sporadic tumours [23,24,25,26]. Which suggesting certain groups are predisposed to malignant disease. For example, patients with *SDHB* mutations are more likely to develop malignant disease and nondiploid tumours have also been found to be associated with malignancy. Gene expression and protein profiling are beginning to identify the genetic characteristics of malignant pheochromocytoma. However, the genetic changes that induce malignant disease remain unclear.

## 4. Malignant disease

Most pheochromocytomas are benign and curable by surgical resection, but some are clinically malignant [27]. The pathologist cannot determine whether a tumour is benign or malignant based on histological features alone. Although extensive invasion of adjacent tissues can be considered an indicator of malignant potential, local invasiveness and malignant disease are not necessarily associated. Currently, there are no prognostic tests that can reliably predict which patients are at risk of developing metastatic disease. The World Health Organization tumour definition of a malignant pheochromocytoma is the presence of metastases, at site distant where chromaffin cells do not normally exist [28]. Metastases occur most frequently to bone, liver, lungs and regional lymph nodes, and can appear as many as 20 years after initial presentation, which implies that life-long follow-up of patients (Fig. 4) [29].

Some studies have suggested that the presence of necrosis, vascular invasion, extensive local invasion, and high rate of mitotic figures may indicate a malignant behavior in pheochromocytoma. Indeed, a recent study by Thompson used clinical features, histologic findings, and immunophenotypic studies to indentify parameters that may help distinguish benign from malignant pheochromocytoma of the Adrenal Gland Scaled Score (PASS) as a scoring system to differentiate benign from malignant pheochromocytomas. PASS is weighted for 12 specific histologic features that are more frequently identified in malignant pheochromocytomas. Factors such as tumour necrosis, high mitotic rate, tumour cell spindling, and vascular invasion are included in this scoring system (Fig. 5). Thompson found that tumours with ≥4 were biologically more aggressive than tumours with a PASS <4, which behaved in a benign fashion (Table 1) [30].

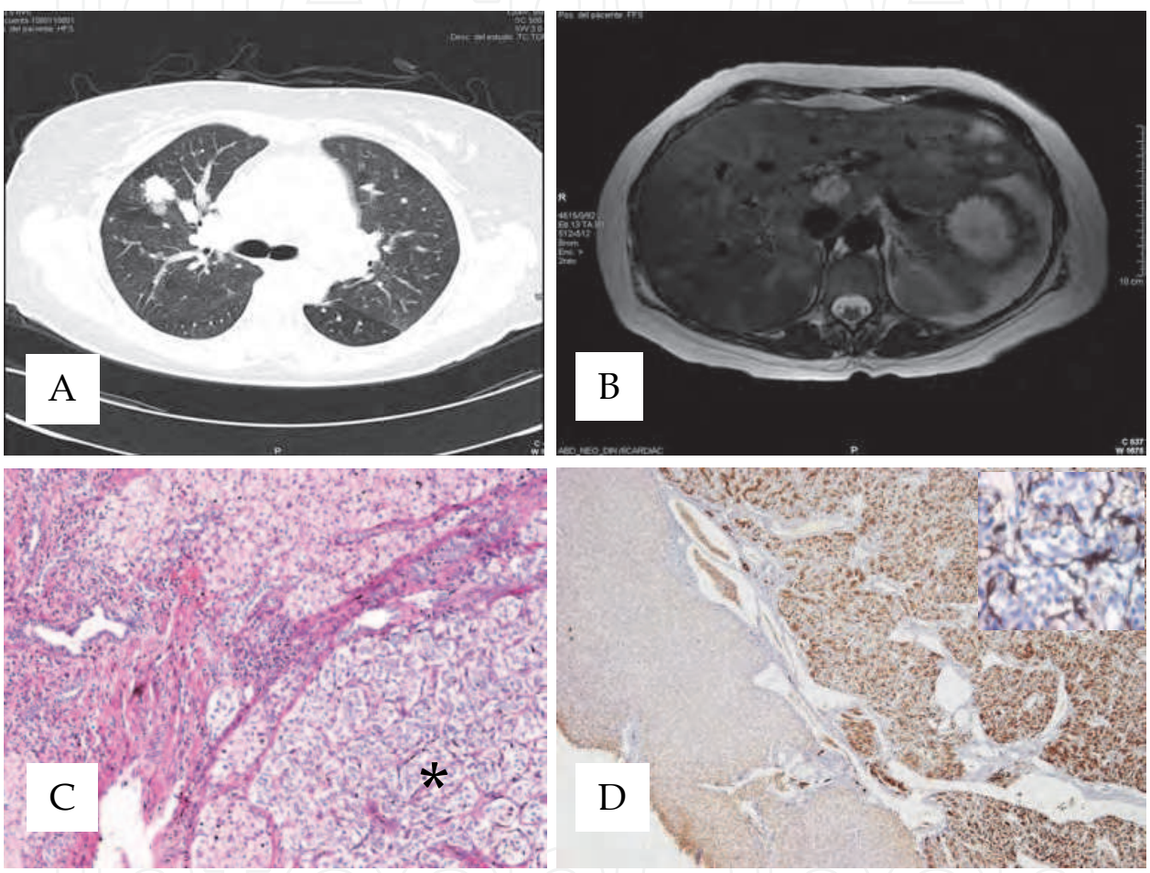
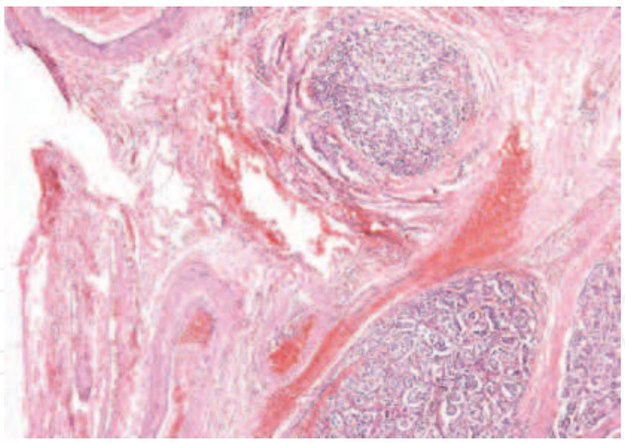
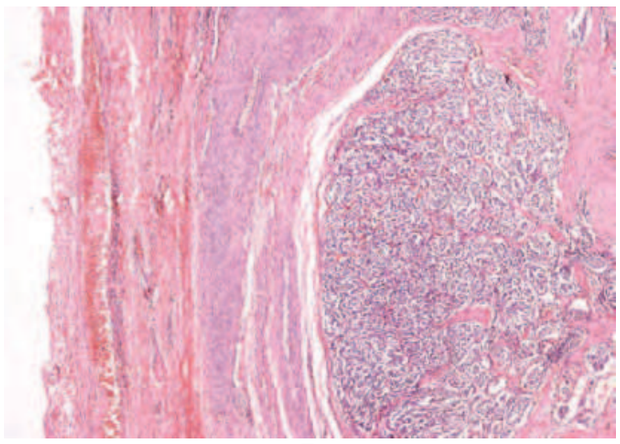


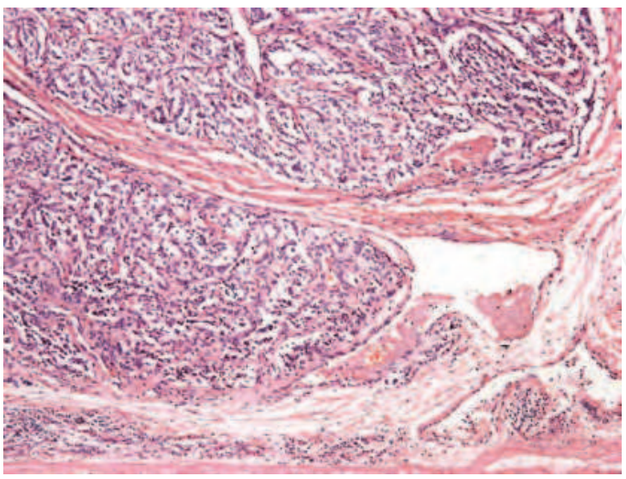

Fig. 4. Malignant pheochromocytoma. **A** and **B)** Multiple liver and lungs metastatic lesions were shown by computed tomography; **C)** Transition from the metastatic pheochromocytoma component (*) to the liver within the same section; **D)** By immunohistochemical was confirmed the presence of a metastatic pheochromocytoma with the characteristic chromogranin immunoreactivity in the pheochromocytos and the S-100 protein immunoreactivity of the sustentacular cells which contrasted with negative liver tissue.



A



B



C

Fig. 5. Invasive malignant pheochromocytoma. **A)** A thick fibrous capsule is transgressed by the neoplastic cells with extension into surrounding addipose connective tissue in malignant pheochromocytoma; **B)** Extension into a vascular spaces is noted in a malignant pheochromocytoma.

| Microscopic feature | Score |
|---|---|
| Extension into peri-adrenal adipose tissue | 2 |
| Presence of large nests or diffuse growth (>10% of tumour volume)† | 2 |
| Central tumour necrosis (in the middle of large nests or confluent necrosis) | 2 |
| High cellularity | 2 |
| Tumour cell spindling even when focal | 2 |
| Cellular monotony | 2 |
| Mitotic figures >3/10 high-power field | 2 |
| Atypical mitotic figures | 2 |
| Vascular invasion* | 1 |
| Capsular invasion | 1 |
| Profound nuclear pleomorphism | 1 |
| Nuclear hyperchromasia | 1 |
| Total | 20 |

*Defined by direct extension into vessel lumen, intravascular attached tumour thrombi, and/ or tumour nests convered by endothelium identified in a capsular or extracapsular vessel.
†Defined as 3-4 times the size of a zellballen or the normal size of the medullary paraganglia nest.

Table 1. Pheochromocytoma of the Adrenal Gland Scoring Scale (PASS) [30].

Additional markers that might be useful prognostic indicators in the pathological assessment of these tumours are sought. However, some studies with markers for important events in the cell cycle showed that less p21/WAF1 expression and aneuploidy correlated with malignant pheochromocytomas [31,32,33].

### 4.1 Prognosis and predictive factors

The rarity of this tumours and the resulting fragmented nature of studies, typically involving small numbers of patients, represent limiting factors to the development of effective treatments and diagnostic or prognostic markers for malignant disease. The prognosis for patients with benign pheochromocytoma is primarily dependent upon a successful surgical resection and extend of preoperative complications related to hypertension. The usual prognosis of malignant pheochromocytoma is poor, with a 45-55% 5-year survival [30,34,35,36,37,38]. However, some patients may have indolent disease, with life expectancy of more than 20 years [39]. Until further studies identify precise biological markers that can accurately predict the clinical behaviour of catecholamine-secreting tumours, it may be advisable for all pheochromocytoma patients to undergo lifelong hormonal monitoring and imaging studies to detect recurrence and metastases [40].

## 5. Composite pheochromocytoma

Ordinary pheochromocytoma is composed of polygonal to spindled cells arranged in an alveolar, trabecular, or solid pattern, often with a typical Zellballen appearance. Composite pheochromocytomas account for only 3% of both adrenal and extra-adrenal pheochromocytomas and can be associated with MEN 2A and phakomatoses [41,42]. Composite pheochromocytoma is a rare tumour composed of typical pheochromocytoma and other components, most often neuroblastoma [43], ganglioneuroblastoma, or

ganglioneuroma in adult cases, and pediatric were very rare. Rare cases have displayed pheochromocytoma with other coexisting neural or neural crest–derived tumours such as malignant peripheral nerve sheath tumour. Little is known about the biologic potential, outcome, or molecular genetic profile.
Because composite pheochromocytoma clinically resembles a typical pheochromocytoma, diagnosis is frequently made by the pathologist. The median age is 16 yr (9 to 24 yr) [43]. The pathologic diagnosis of composite pheochromocytomas creates a clinical dilemma because it is not known whether the neuroblastic component results in therapeutic and prognostic implications different from those in ordinary pheochromocytoma. Neuroblastoma is the most immature of the neuroblastic tumours; the others are ganglioneuroblastoma and ganglioglioma (Table 2). These tumours are differentiated based on the amount of schwannian stroma and the presence or absence of ganglion cell differentiation. This dual phenotype is supported by light microscopy and corroborated by immunohistochemistry and ultrastructural findings. Prognosis of coexistence with pheochromocytoma and ganglioneuroblastoma or neuroblastoma is variable.

| **Coexistence with** | **No. of cases** | % |
|---|---|---|
| Ganglioneuroma | 41 | 70 |
| Ganglioneuroblastoma | 7 | 11 |
| Neuroblastoma | 4 | 9 |
| Schwannoma | 4 | 7 |
| Neuroendocrine carcinoma | 1 | 2 |
| Total | 57 | 100 |

Table 2. Cases of composite pheochromocytoma of adrenal gland [43].

## 6. New insights on pheochromocytoma

The molecular events involved in the malignant transformation of pheochromocytoma are poorly understood. There are also no reliable and uniformly accepted histopathologic criteria to distinguish benign from malignant pheochromocytoma. Unsupervised cluster analysis showed 3 main clusters of tumors that did not have complete concordance with the clinical and pathologic groupings of pheochromocytomas. Supervised cluster analysis showed almost completely separate clustering between benign and malignant tumours. The differentially expressed genes with known function belonged to 8 biologic process categories; signal transduction, transcription, protein transport, protein synthesis, smooth muscle contraction, ion transport, chemotaxis, and electron transport. Gene set enrichment analysis revealed significant correlation between the microarray profiles of malignant pheochromocytomas and several known molecular pathways associated with carcinogenesis and dedifferentiation. Ten differentially expressed genes had high diagnostic accuracy, and 5 of these genes (CFC1, FAM62B, HOMER1, LRRN3, TBX3, ADAMTS) in combination distinguishing benign versus malignant tumours. Differentially expressed genes between benign and malignant pheochromocytomas distinguish between these tumours with high diagnostic accuracy. These findings provide new insight into the genes and molecular pathways that may be involved in malignant pheochromocytomas [44].

## 7. Future directions

Much attention has recently been devoted to pheochromocytoma as the understanding of this disease continues to improve. If it becomes widely available, it would greatly aid in the staging and management of malignant disease. Continually improving detection methods, especially screening of high-risk populations, will only contribute to the treatment and knowledge of these conditions in the future. It has become clear that many apparently sporadic pheochromocytomas have a genetic component. Not only has there been a great deal of attention directed toward the hereditary components, but better predictive molecular factors have been identified for malignant pheochromocytoma, which could lead to more effective genetic testing. In addition, microarray studies have identified a set of genes preferentially expressed in malignant pheochromocytoma. The combination of an identifiable hereditary component along with an understanding of the genetic and molecular defects in sporadic pheochromocytoma makes this a promising model and approach for insights into other cancers. The future is wide open for improvements in the understanding and treatment of this disease.

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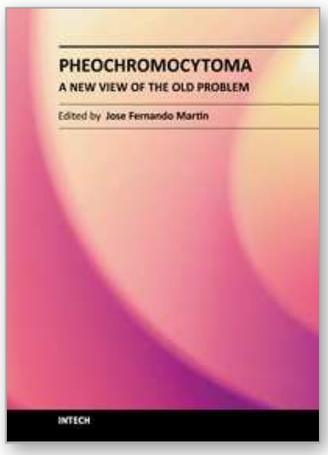
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**Pheochromocytoma - A New View of the Old Problem**

Edited by Dr. Jose Fernando Martin

ISBN 978-953-307-822-9
Hard cover, 164 pages
**Publisher** InTech
**Published online** 16, December, 2011
**Published in print edition** December, 2011

The book is divided into six sections. The first three sections focus on the pathophysiology of the disease, showing anatomo- and histopathological aspects, experimental models and signaling pathways and programmed cell death related to pheochromocytoma. The fourth discusses some specific aspects of clinical presentation, with emphasis on clinical manifestations of headache and heart. The fifth section focuses on clinical diagnosis, laboratory and imaging, including differential diagnosis. Finally, the last section discusses the treatment of pheochromocytoma showing clinical cases, a case about undiagnosed pheochromocytoma complicated with multiple organ failure and other cases about catecholamine-secreting hereditary tumors. Thus, this book shows the disease "pheochromocytoma" in a different perspective from the traditional approach. Enjoy your reading.

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Fernando Candanedo-Gonzalez, Leslie Camacho-Rebollar and Candelaria Cordova-Uscanga (2011). Macro and Microscopic Aspects, Pheochromocytoma - A New View of the Old Problem, Dr. Jose Fernando Martin (Ed.), ISBN: 978-953-307-822-9, InTech, Available from: http://www.intechopen.com/books/pheochromocytoma-a-new-view-of-the-old-problem/macro-and-microscopic-aspects

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