OPEN ACCESS
Global Journal of Research in Medical Sciences
ISSN: 2583-3960 (Online)
Volume 05 | Issue 03 | May-June | 2025
Journal homepage: https://gjrpublication.com/gjrms/

Research Article

Clinical Experience Over 10 Years with Pheochromocytoma in A Tertiary Center: The Endocrinology Department at Mohamed VI University Hospital Center, Marrakech, Morocco

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DOI: 10.5281/zenodo.15426441 **Submission Date: 10 April 2025 | Published Date: 15 May 2025**

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Abstract
Pheochromocytomas (PCCs) are rare but serious neuroendocrine tumors (NETs), arising from medullary chromaffin cells. It is a rare but curable cause of arterial hypertension, and early diagnosis can reduce its severity. The aim of this study is to demonstrate the clinical, biological and radiological features of pheochromocytoma, as well as the main therapeutic and follow-up methods. We report a retrospective study of 48 cases of pheochromocytoma, hospitalized and followed at the endocrinology department of Mohamed VI University Hospital Center Marrakech, Morocco, over a 10 years and 9 months period spanning from April 2014 to December 2024 with review of the literature. The clinical picture was variable, dominated by headache, palpitations sweats, weight loss and abdominal pain. Determination of the 24-hour urinary metanephrines confirmed the diagnosis in the majority of cases. Ultrasound, CT scan, adrenal MRI or MonoIodo Benzyl Guanidine (MIBG) scintigraphy localized the tumor. Genetic testing for RET gene mutation was performed on 5 patients. Short-term evolution was marked by normalization of Blood Pressure (80.49% of cases) and long-term by recurrence in 14.63%, metastasis in 24.39% and death in one patient. Only the presence of metastasis (chromaffin tissue of unusual location) at the time of diagnosis or during post-operative and long-term evolution can confirm the malignant nature of PCCs.

Keywords: *Neuroendocrine tumor -Medullary adrenal gland, Metanephrines -Surgery - Genetics.*

INTRODUCTION:
Pheochromocytoma is a neuroendocrine tumor which is developing from the chromaffines cells of the medulla of the adrenal gland. The prevalence varies between 1/2500 and 1/6500 (1). PCC usually develops sporadically, and about 30% of cases are due to germline mutations (2). PCC are characterized in their genetic variety by association with so-called genetic predisposition syndromes such as multiple endocrine neoplasia type 2 (MEN2), neurofibromatosis type 1 (NF1), Von Hippel Lindeau disease (VHL). SDHx mutations part of the pseudohypoxic group of genetic PCC are characerized by aggressiveness and high metastatic potential especially SDHB mutation.

Patients with PCCs, often present with very high arterial hypertension and symptoms associated with excess catecholamines (CA), particularly headache attacks, palpitations and sweating, but this clinical presentation can sometimes be non-typical, making diagnosis rather difficult (3).

Biological confirmation is based on plasma and/or 24-hour urinary metanephrines, and localized radiological imaging of the medulloadrenal tumor. The main treatment for PCC is surgery, after an essential phase of medical preparation.

The aim of this study is to anlyze epidemiological, clinical, paraclinical and therapeutic characteristics of patients diagnosed with PCCs.

MATERIALS AND METHODS:

This is a retrospective descriptive study of patients diagnosed with PCCs in the Endocrinology Department of the Mohamed VI University Hospital Center at Marrakech Morocco, from April 2014 to December 2024 (10 years and 9 months), a total of 48 patients.

Patients included in our study were those whose diagnosis of PCC was confirmed clinically, biologically and/or histologically. Epidemiological, clinical, biological, radiological and histological data were collected retrospectively from physical records and our hospital's computerized medical management system in compliance with international rules on the collection and protection of patient confidentiality.

RESULTS:

Our series consisted of 48 patients with PCCs, with a female predominance (68.7% women and 31.3% men), the mean age of our patients was 40.91±12.71 years, with extremes ranging from 19 to 70 years. The most frequent clinical manifestation was the Menard triad. Among our 48 patients, 39 (82.2%) consulted for headaches, 38 (79.16%) for palpitations, 34 (70.83%) for palpitations. Abdominal pain was noted in 25 (52%) patients (**Figure 1**).

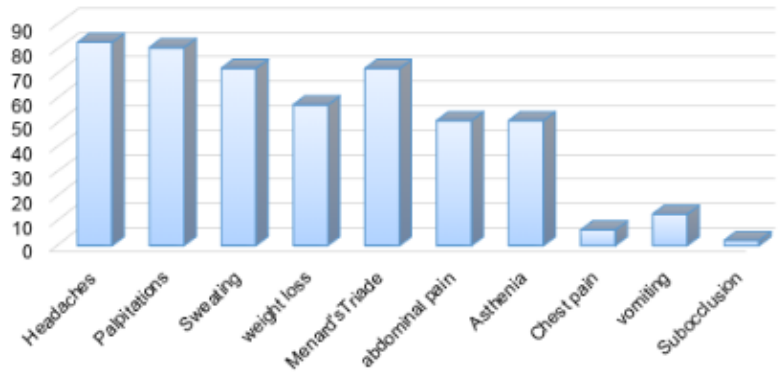

Figure 1 : Clinical manifestations of PCC in our patients (%)

Physical manifestations noted were increased blood pressure in 24 patients (50%), orthostatic hypotension in 5 patients (10.41%), mucocutaneous heat in 10 patients (20.83%), café-au-lait spots in 8 patients (16.67%)**.** Electrocardiogram performed in all our patients showed, left ventricular hypertrophy (LVH) in 9 patients (18.75%), including one with secondary repolarization disorders, one with sinus tachycardia and one with ST-segment elevation. Incomplete right branch block (RBB) was also noted in one patient.

Abdominal ultrasound was performed in 27 patients, allowing visualization of a mass in 23 cases (85.18%)

For diagnostic confirmation, 24-hour urinary metanephrines were measured in 44 patients: elevated in 42 cases and normal in 2. Among 42 patients, metanephrine was elevated in 27 cases with an average of 26.6 times normal, while normetanephrine was elevated in 41 cases with an average of 23.02 times normal. Urinary 3-ortho-methyl-dopamine was measured in 12 patients, returning elevated in 5 cases.

For the outcome evaluation, hyperglycemia was noted in 16 patients (33.33%), anemia was noted in 14 patients (27.16%), predominantly normocytic normochromic. As part of the MEN2 assessment, calcitonin was elevated in 4 patients with a mean level of 129.22 times normal, detected respectively 2 years, 4 years, 5 years and 7 years after PCC surgery on the occasion of MEN2 screening., while parathormone was non-significantly elevated in 5 patients with a mean level of 1.4 times normal.

Tumor localization assessment consisted of performing abdominal CT scans in 44 patients, 8 of whom had bilateral tumours (**Figure 2)**, and 36 unilateral tumours, 18 on the right and 18 on the left. Abdominal MRI was performed in 4 patients in view of the context of pregnancy (2 cases the mass was right and left in the other 2 cases) **(Figure 3).** Mean tumoral size on CT and MRI was 7.2±3.12 cm.

MIBG scintigraphy was performed in 8 patients, showing a focus of hyperfixation in the pathological adrenal gland with pulmonary lesion of secondary appearance **(Figue 4)**. Somatostatin receptor analog scintigraphy (Octreo Scan) was performed in 4 patients, showing hyperfixation opposite the adrenal lodge **(Figure 5).**

The tumor was familial in 2 patients (4.17%), MEN2 was present in 4 patients (8.33%). None of our patients showed clinical evidence of VHL.Only one case of association of NF1 and malignant PCC was noted in a 23-year-old patient, i.e.

2.08% of cases. In this patient, NF1 was suspected on the basis of the presence of 6 coffee and milk spots, 2 neurofibromas, lenticular spots in the axillary fossa and 2 Lisch nodules **(Figure 6).**

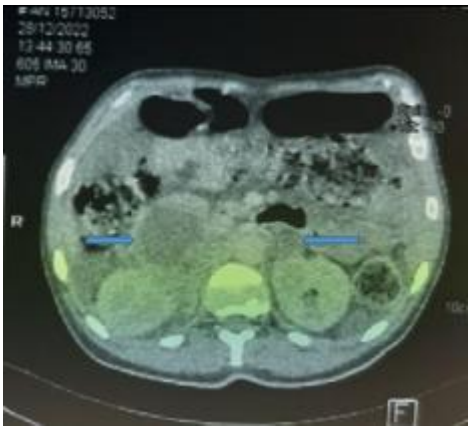

Figure 2: Abdominal CT scan: Bilateral adrenal masses (blue arrows)

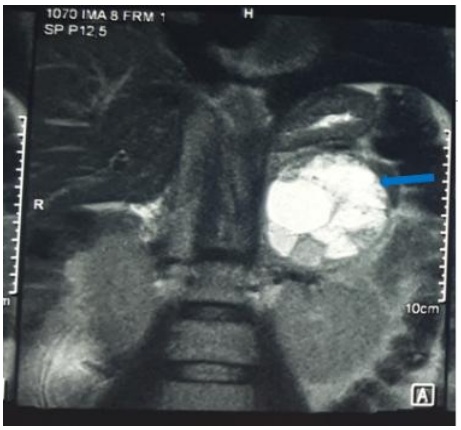

Figure 3: Abdominal MRI: Left Adrenal masse (blue arrow)

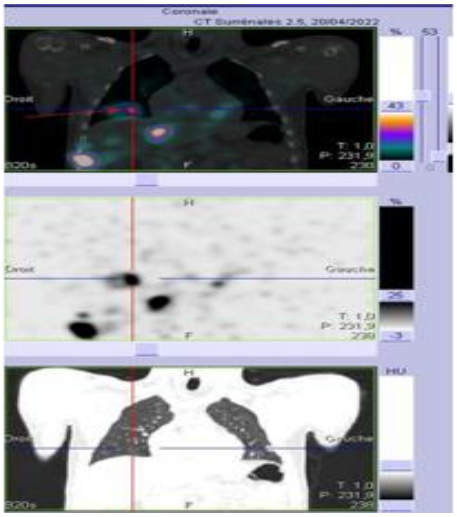

Figure 4: MIBG scintigraphy: pulmonary hyperfixation.

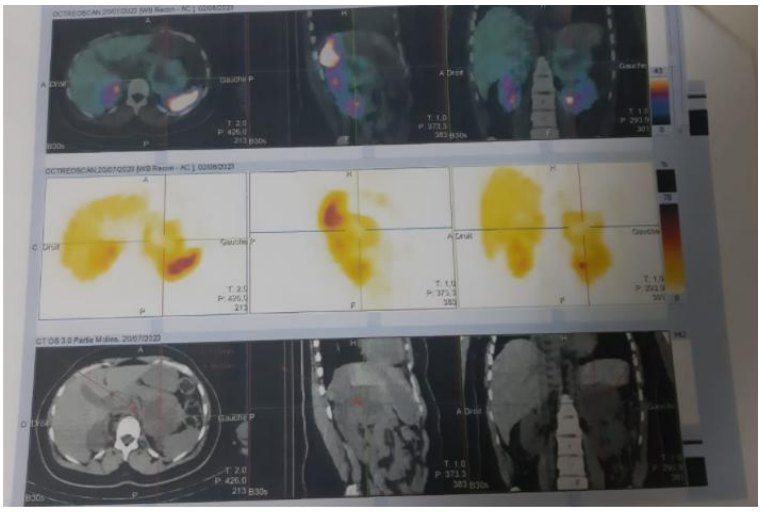

Figure 5: Octreo Scan: hyperfixation of adrenal lodge

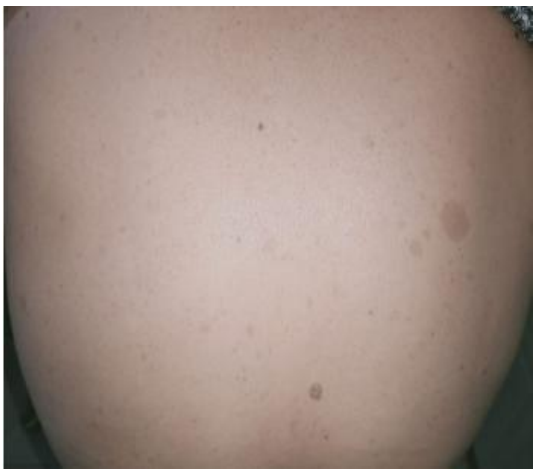

Figure 6: coffee and milk spots on the back

Genetic testing mutations was recently performed in 5 of our patients and results are still pending.

Complications noted in our patients were represented by: hypertension in 50% of cases, left ventricular hypertrophy (LVH) in 18.75%, orthostatic hypotension in 10.41%, repolarization disorders and acute myocardial ischemia in 2.94% of cases each. Two patients presented with peripheral limb ischemia, one in the upper limbs and the other in the lower limbs, complicated in the latter case by dry gangrene and necrosis **(Figure 7).** Cerebrovascular accidents were noted in 3 patients.

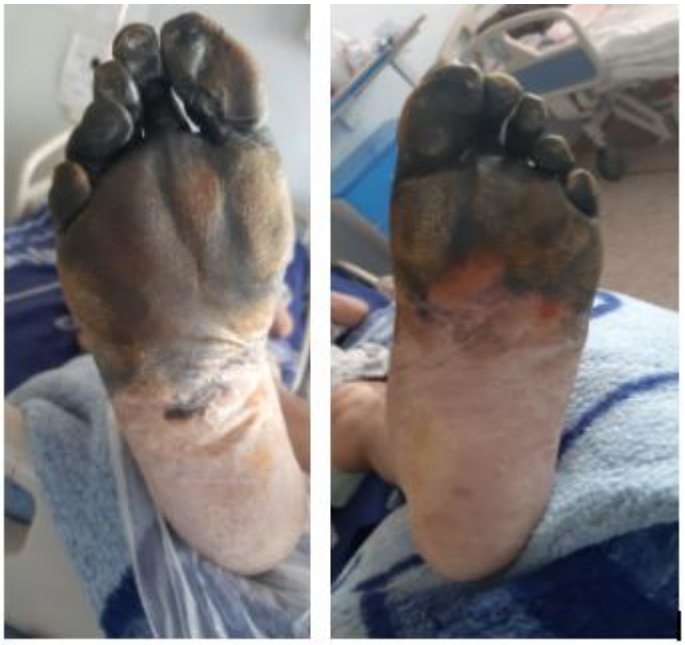

Figure 7 : Gangrene and necrosis of feet

Metastases were present in 10 patients (including 2 cases in lung, bone and liver, 3 cases in lung and bone, 2 cases in lung, 1 case in lung and liver, 1 case in bone and liver, 1 case in lung and another case in bone).

Therapeutic management initially consisted of medical preparation with antihypertensives (alpha-blockers, calcium channel blockers and beta-blockers) and rehydration (48 hours before surgery). Fourthy patients had unilateral pheochromocytoma, 33 of whom underwent unilateral adrenalectomy: 23 by laparoscopy and 10 by laparotomy. Eight patients had bilateral PCC; they underwent bilateral adrenalectomy, including 4 cases by laparoscopy, 3 cases by laparotomy and laparoscopy, and one case by laparotomy.

During the intra-operative period, one patient presented with cardiac rhythm disturbances, 25.8% of patients presented with arterial hypotension, one of which was severe, reaching 58/43 mmhg with collapse and recovered cardiac arrest; having necessitated filling with noradrenaline in self-push syringe. Postoperative hypoglycemia (4.87%) and hypotension were the two most common postoperative symptoms.

Pathological and immunohistochemical studies confirmed the diagnosis of PCC. Determination of the pheochromocytoma adrenal gland scaled score (PASS) showed a score of 3 in six patients, 4 in six patients, 5 in three patients, 9 in three patients, 8 in two patients, 18 in one patient, 12 in one patient, 6 in one patient, 2 in one patient and 1 in another patient. In terms of aggressiveness on pathology specimens, 6 PCCs were classified as possibly aggressive, 3 as potentially aggressive, 1 as mildly aggressive and one as non-aggressive. Of the patients with metastatic PCC, one died, 2 patients underwent revision surgery, and a total of 8 were referred to oncology departement (including 1 who had already undergone revision surgery). The 4 cases of CMT found were managed by surgical total thyroidectomy with cervical lymph node dissection.

DISCUSSION:

The incidence of pheochromocytoma (PCC) is 2 to 8 per million per year, with a prevalence of between 1/2500 and 1/6500 (4). Four to eight percent of adrenal incidentalomas are PCCs (5). Approximately one quarter of suspected sporadic pheochromocytomas are associated with a germline mutation (6,7), making them part of a familial disease. In

our series, 4.17% of PCCs were familial (2 brothers). This percentage is close to that noted by KWANG.H in his series of 119 PCCs (6.7%), but it appears low compared with those of EL MAlKI, and EL MOKHTARI series, with respectively (20%, 27.7%). (Table 1).

Author	Number	Familial PCC	Prevalence
Our Series	48	02	04,17%
KWANG HYUN [8]	119	08	06,70%
KERCHER [9]	80	08	10,00%
GODEAU [10]	50	06	12,00%
EL MALKI [11]	10	02	20,00%
RAMBAUD [12]	20	04	20,00%
ULRICH [13]	152	35	23,00%
MOKHTARI [14]	44	12	27,27%

Table 1: percentage of familial pheochromocytoma

PCC is a tumor observed at any age, but predominantly in adult females, with peak incidence between the ages of 30 and 50 (15). In our series, the mean age at diagnosis was 40.91±12.71 years. There was a predominance of females (15 males vs 33 females), which is consistent with the literature.

PCCs may be revealed by a suggestive (symptomatic) clinical picture, an acute complication, pre-symptomatic family screening, palpation of a mass or incidentally on imaging performed for an unrelated reason (16). The headache-palpitation-sweating triad known as Menard's triad is the most common paroxysmal clinical manifestation of pheochromocytoma (17). In our series, Menard's triad was found in 70.83% of cases, while hypertension was present in 50%.

The positive diagnosis of PCC is based on the demonstration of excessive catecholamine production. Plasma free metanephrines or urinary fractionated metanephrines are the preferred assays, as they have a sensitivity and specificity of over 90% (18,19). The diagnostic specificity and sensitivity of urinary metanephrine are 93% and 61% respectively, while those of urinary normetanephrine are 68% and 94% respectively, reflecting the predominance of noradrenaline as the type of PCC secretion and making these 2 assays complementary (20). Their determination requires 24-hour urine collection on an acid medium, preceded by 8 days' withdrawal from any medication which might interfere with catecholamine metabolism (beta-blockers, methyl-dopa and levodopa, clonidine, tricyclic antidepressants, etc.).(21) To validate this assay, a 24-hour creatinuria must be performed, which must be normal. Among 44 of our patients in whom urinary metanephrines were tested, 42 were positive and 2 were normal; in the remaining 4 cases, PCC was diagnosed a posteriori on histological examination which is explained by the non-functional nature of the tumour.

Abdominal ultrasound remains an important diagnostic tool, especially in cases of abdominal symptoms. In our series, it guided the diagnosis in 23 patients, showing the existence of an adrenal-like mass. The reference radiological examination is the abdominal CT scan with adrenal slices, calculation of spontaneous density and washout. The suggestive appearance is a heterogeneous mass, generally exceeding 2 cm, with a spontaneous density greater than 10 HU, containing areas of necrosis.

MRI is comparable in accuracy to CT, but performs better in the case of multiple or metastatic forms, its non-irradiating nature makes it the method of choice for pregnant women and children. For PCC, MRI presents a T2 hypersignal (22). Its sensitivity ranges from 75 to 100%. It is superior to CT for bilateral or extra-adrenal tumors. Specificity ranges from 50 to 83% (20).

MIBG scintigraphy has a sensitivity of 83-100% and a specificity of 95-100% for the diagnosis of sporadic PCC (23). Somatostatin receptor scintigraphy (OctreoScan*) is of particular interest in PCC with negative MIBG scintigraphy and metastatic PCC. Its sensitivity is superior to that of MIBG for malignant forms (87% vs. 57%) and for supra-diaphragmatic PCC (paragangliomas), but inferior for adrenal localizations. PET Scan 18*F-FDG is more sensitive than MIBG scintigraphy in malignant forms.

PCC is genetic in about 40% of cases, with mainly germline mutations (24). These tumors occur either in isolation or as part of a genetic syndrome, mainly MEN1, NF1, VHL disease. Mutations are divided into 3 groups known as molecular clusters; type 1: pseudohypoxic (mutation of genes: SDHx, FH, MDH2, VHL/EPAS1), type 2: abnormal kinase signaling (genes: RET, NF1, TMEM127, MAX) and type 3 (Wnt signaling anomaly). Cluster 1 is associated with metastatic PCC in around 50% of cases (25). In our series, the discovery of 4 cases of CMT during post-operative follow-up of PCC suggests a syndromic association in the context of MEN2.

Among the complications of PCC, hypertension is the most frequent (90%), either paroxysmal or sustained, whereas PCC is the cause of secondary hypertension in only 1% of cases. The continuous character is generally observed in norepinephrine-secreting PCCs, whereas it is usually paroxysmal in epinephrine-secreting PCCs or in MEN2 PCCs (26,27). Orthostatic hypotension is a widely reported complication in PCC (70%), its mechanism explained by an altered sympathetic vascular response secondary to preserved baroreceptor function, this alteration is linked to desensitization of peripheral alpha-adrenergic receptors in response to high levels of noradrenaline (26). In our series, hypertension was found in 50% of cases, and orthostatic hypotension in 10.41% which is less frequent than in the literature. Arrhythmias have also been described in these patients, secondary to overstimulation of beta-adrenergic receptors.

Coronary vasoconstriction and the positive chronotropic and inotropic effects of catecholamines are responsible for the myocardial ischemia observed in patients with this type of tumor. Catecholamines act on the myocardium through various mechanisms: the Beta1 adrenergic effect and oxidative stress with hyperproduction of free radicals, leading to myocardial histological lesions such as necrosis, neutrophilic infiltration and fibrosis (28). Peripheral ischemia is a rare manifestation of PCC, due to diffuse peripheral arterial damage secondary to activation of alpha1 adrenergic receptors, arterial occlusion by a thromboembolism mechanism favored by episodes of atrial fibrillation (3).

Catecholaminergic hypersecretion leads, via the alpha1 effect, to increased lipolysis with release of free fatty acids, thus stimulating gluconeogenesis and inhibiting insulin secretion. in parallel, activation of Beta2 receptors stimulates insulin secretion, leading to hypoglycemia, but given the predominance of the alpha1 effect, hyperglycemia is common in PCC (29).

In our series, moderate fasting hyperglycemia and diabetes were diagnosed in around 1/3 of cases, testifying to the frequency of this metabolic complication in PCC.

For the diagnosis of PCC malignancy, several parameters have been studied, such as secretory profile, tumor volume and Ki67 proliferation index, but none of them has been validated. The only universally validated criterion is the presence of metastases in tissues usually devoid of chromaffin cells.In our series, metastases were noted in 10 patients, with bone, lung and liver as preferred sites.

The treatment of PCC is mainly surgical, but an essentially cardiovascular preparation phase is essential to prevent the risk of catecholamine discharge during the operation. During this phase, the patient must be given medication to control blood pressure and block adrenergic receptors, in order to avoid the sometimes serious effects of catecholamines. The most commonly used molecules are alpha-blockers 7 to 14 days before surgery, including phenoxybenzamine, doxazosin and prazosin. Beta-blockers can also be used, especially in cases of tachycardia, provided they are introduced 2 to 3 days after alpha-blockers, to prevent serious hypotension and bradycardia. the recommended blood pressure targets are less than 130/85 mmHg in the sitting position and a systolic pressure greater than 90 mmHg, (30). Volcemic expansion is also indicated, generally starting 48 hours before surgery. In our series patients were started on doxazosin 7 to 15 days before the procedure with an initial dose of 1 mg/d, gradually increased according to blood pressure control, combined with rehydration 2 days before surgery.

The anaesthetic technique will depend on the risk of stimulating medullo-adrenal secretion and/or the possibility of rhythm disorders. General anesthesia is widely recommended, but sympathomimetic agonists, anticholinergics and histamine-releasing stimulants should be avoided (31). The induction stage is usually performed with propofol, thiopental or etomidate. In the maintenance phase, isoflurane was widely used, but sevoflurane is now beginning to occupy an important place, given its low solubility in blood and faster elimination kinetics, enabling it to better control intraoperative blood pressure fluctuations simply by adjusting its expired fraction (32). In addition to routine monitoring, invasive blood pressure monitoring is essential to assess any significant and rapid variations.

The management of intraoperative complications is a delicate stage in the management of a surgical procedure. Hypertension is usually managed with: sodium nitroprusside (0.3 and 10 microgram /kg/min), Urapidil (25 to 50 mg.), Nicardipine (0.5 to 2.0 µg.kg-1.min-1). In our context, management was based on stopping tumor manipulation, administering nicardipine and deepening anesthesia.

Surgical approaches are based on laparoscopy or laparotomy; in the case of tumors smaller than 6 cm in size with no scanographic signs of locoregional infiltration, laparoscopic adrenalectomy is preferred, while in the case of infiltrating PCCs larger than 6 cm in size with suspected metastases, laparotomy is the preferred approach. When laparoscopic

surgery becomes difficult and hemodynamic disturbances difficult to control, conversion to laparotomy will be justified (33). In our series, 73.17% of patients underwent laparoscopic adrenalectomy, with only one case of conversion to laparotomy, in the event of severe bleeding with hypotension, to better ensure hemostasis and hemodynamic stabilization.

In the case of malignant PCC, even at the metastatic stage, surgical resection brings considerable benefit by improving survival. Indications for chemotherapy, radiotherapy and metabolic radiotherapy (*131 Iodine-MIBG) require multidisciplinary consultation between surgeons, oncologists, endocrinologists, pathologists and geneticists. If the tumor is initially resectable: after medical preparation (RHD and aplha-blocker), we perform an adrenalectomy and check metanephrines in 2 to 6 weeks post-op. If elevated (in favor of residual or recurrent disease), we reprogram the patient for repeat surgery. If the tumour is initially unresectable: disease progression is assessed; if it is symptomatic and/or rapidly progressive, we opt for either metabolic radiotherapy (MIBG or DOTATOC), chemotherapy (cyclophosphamide, vincristine and dacabarzine : its tumor response rate is only 57% and its secretory response rate is 79% during an average of 21 months after 4 cycles) or local therapies and re-evaluate after 2 to 5 months, if progression is still active we repeat the same treatment and if the response is stable we keep the patient under surveillance (34).

Post-operative analgesia is based on morphinics and/or non-morphinics. Antibiotic prophylaxis (from induction) and thromboembolism prevention are systematic for this type of surgery. Hypoglycemia is a major postoperative risk, its frequency, reported in the literature, is of the order of 15-20%; this hypoglycemia is explained by the high production of insulin, the release of which is no longer inhibited by catecholamines. In our series, hypoglycemia was noted in 4.86% of cases, and management was based on infusion of serum glucose with close monitoring of capillary blood glucose levels.

In the event of bilateral adrenalectomy, prevent acute adrenal insufficiency by starting hormone replacement therapy with hydrocortisone hemisuccinate.

Five-year survival is estimated at 97% in initially benign cases and 23% in initially malignant cases. In benign cases, the recurrence rate is 8% at 5 years and 20% at 10 years, and recurrences can occur up to 20 years after the initial surgery. For this reason, the risk of recurrence and the need for long-term monitoring must be explained to the patient. Monitoring is clinico-biological and radiological, with the frequency and parameters to be monitored varying according to whether the PCC is functional, non-functional, of uncertain malignancy potential or syndromic (Table 2) (35). In our series, monitoring was based on clinical examination, 24-hour urinary methoxylate determinations, adrenal CT and, if necessary, functional imaging. Cure was achieved in more than 2/3 of patients, demonstrating the effectiveness of surgical treatment in the management of pheochromocytoma. Recurrences were observed mainly in cases of initially malignant and familial pheochromocytomas. The risk of mortality varies according to the potential malignancy of the PCC. Only one patient died after approximately two years' follow-up.

First control at 2 - 6 weeks post-op is indicated for categories (functional PCC, PCC of uncertain malignant potential and syndromic PCC): BP, CG, BF, HR, FBG, AIC, ECG, Metanephrines.

	Three (03) months control				**Follow-up frequency**
	Clinical	Paraclinical	Conventional imaging	Functional imaging	
Functional PCC	BP, CG, BF, HR	FBG, AIC, ECG, AMAP,	TAP CT*/MRI**	MIBG***	Lifetime annual: BP, CG, HR, Metanephrines, TAP-CT.
Non Functional PCC	BP, CG, RT, HR	_____	TAP CT*/MRI**	_____	Imaging every 2 years and then at intervals
PCC with uncertain malignant potential	BP, CG, RT, HR	FBG, AIC, ECG, AMAP,	TAP CT*/MRI**	_____	Lifetime annual: Metanephrines, FBG, AIC, ECG, AMAP, TAP CT*/MRI**

	Clinical	Biology	Imaging
PCC-VHL	Annually: BP and symptoms	Annually: Metanephrines	Annualy: Fundus. Every 2 years: Abdominal Ultrsound, Abdominal MRI, Cerebromedullar MRI.
PCC-MEN 2	Annually: BP and symptoms	Annually: Metanephrines, Calcemia, PTH, Calcitonine.	Cervical Ultrasound+/-
PCC-NF 1	Annually: BP/AMAP	No systematic examination	No systematic examination

Table 2: Parameters and frequency of postoperative monitoring of PCCs

BP: Blood pressure, BF: Breathing frequency, Capillary Glycemia, Rate heart, ReFBG : Fasting blood glucose, ECG: Electrocardiogram, AMAP: Ambulatory Measurement Arterial Pressure, MIBG: MIBG-Scintigraphy* if metanephrines are elevated postoperatively. ** child or pregnant woman ***high risk of metastasis or recurrence.

CONCLUSION:

Pheochromocytoma is a rare but serious neuroendocrine tumor, caused by tumor-induced hypersecretion of catecholamines by chromaffin cells. Its positive diagnosis requires clinical orientation, biological confirmation based on plasma and/or urinary metanephrines, tumor localization by adrenal CT and/or MRI and, in some cases, functional imaging (MIBG, Octreoscan, PET SCAN), the search for other genetic syndromes (MEN2, NF1, VHL, etc.), drug preparation and surgery, which plays a key role in management. PCC is a type of tumour which requires well-coordinated multidisciplinary management by all the teams involved.

Despite its rarity, PCC should be systematically evoked in the presence of any young-onset hypertension, severe hypertension and/or hypertension resistant to antihypertensive treatment, the existence of suggestive symptoms (Menard's triad) and, above all, a family history of PCC or a syndrome of genetic predisposition to PCC.

Our case series enabled us to compare a number of clinical situations with diverse biological and radiological pictures, urgent surgical interventions and intensive care management, testifying to the atypical and serious nature of this rare type of tumour.

Compliance with Ethical Standards Acknowledgments: We would like to thank the teams of endocrinology, urology, anatomic pathology, radiology, intensive care departments of Mohammed VI University hospital of Marrakech.

Disclosure of Conflict of Interest: The authors declare no conflict of interests.

Statement of Ethical Approval: The present research work does not contain any studies performed on animals/humans subject by any of the authors.

Statement of Informed Consent: Informed consent was obtained from all individual participants included in the study.

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CITATION
Boukhalfa A., Sana R., Ijdda S., Ghizlane El M., & Nawal El A. (2025). Clinical Experience Over 10 Years with Pheochromocytoma in A Tertiary Center: The Endocrinology Department at Mohamed VI University Hospital Center, Marrakech, Morocco. In Global Journal of Research in Medical Sciences (Vol. 5, Number 3, pp. 3–38). https://doi.org/10.5281/zenodo.15426441