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## Multiple nodal locoregional recurrence of pheochromocytoma



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## ABSTRACT

**INTRODUCTION:** Malignancy is present in 10% of pheochromocytomas (PCC) and is defined as local/vascular infiltration of surrounding tissues or the presence of chromaffin cells deposits in distant organs. The presence of isolated nodal recurrence is very rare and only 7 cases have been reported in the medical literature.

**PRESENTATION OF THE CASE:** The case of a 32-y male with a symptomatic recurrence of a previously operated (2-years ago) PCC is presented. Radiological and functional imaging studies confirmed the presence of multiple nodules in the surgical site. A radical left nephrectomy with extensive lymphatic clearance in order to get an R0 resection was performed. The pathologist confirmed the diagnosis of massive locoregional nodal invasion.

**DISCUSSION:** A detailed histological report and a thorough genetic study must be considered in every operated PCC in order to identify mutations and profiles of risk for malignancy. When recurrence or metastatic disease is suspected, imaging and functional exams are done in order to obtain a proper staging. Radical surgery for the metastatic disease is the only treatment that may provide prolonged survival. If an R0 resection is not possible, then a debulking surgery is a good option when the benefit/risk ratio is acceptable.

**CONCLUSION:** Isolated lymph nodal recurrence is very rare in malignant PCC, with only 7 cases previously published. The role of surgery is essential to get long-term survival because provides clinical and functional control of the disease.

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## 1. Introduction

Pheochromocytoma (PCC) is a catecholamine-secreting neuroendocrine tumor originating from chromaffin cells derived from the neural crest and arising from the adrenal medulla. Approximately 10% of PCC are malignant, being malignancy defined as infiltration of surrounding organs or presence of chromaffin cells deposits in locoregional lymph nodes (LN) and/or distant sites (specially liver, bones or lungs) [1].

We report the case of a patient with a malignant PCC (justified as locoregional recurrence) who underwent an extended left radical nephrectomy with regional lymphadenectomy to get a R0 resection. Diagnostic and therapeutic aspects of this unusual presentation are discussed.

## 2. Presentation of the case

An otherwise healthy 32-y male was admitted for headache and palpitation as clinical expression of an hypertensive crisis. As

background, a left laparoscopic adrenalectomy to treat a PCC was performed two years before, requiring an open immediate reoperation for acute bleeding. The resected tumor was 5.5 cm diameter and had neither necrosis nor vascular invasion, being its capsule macroscopically reported as “preserved” and having a mitotic rate of 1/10 high-power microscopic field (HPMF) with presence of some hyaline globules. The genetic panel screening showed no mutations for RET proto-oncogene. Analytical exams showed an elevated level of adrenalin in 24 h urine (150 µg, being normal value <90 µg/24 h).

Computed tomography (CT) scan described the presence of 6 nodules between 9 and 27 mm extending along the left renal hilum and downwards the para-aortic axis with compression of the left renal vein, being highly suggestive of PCC recurrent disease (Image 1). Functional imaging with metaiodobenzylguanidine (MIBG) was positive for pathologic deposits in left retroperitoneum (Image 2).

The patient underwent a left radical nephrectomy with extended retroperitoneal and para-aortic dissection and an R0 status was achieved (Image 3). Postoperative course was uneventful and the patient discharged on postoperative day +10. Pathology of the surgical specimen was reported as LN metastasis of PCC. No adjuvant treatment was indicated. Three years after the operation, the patient remains asymptomatic with normal analytical and radiological/functional exams.

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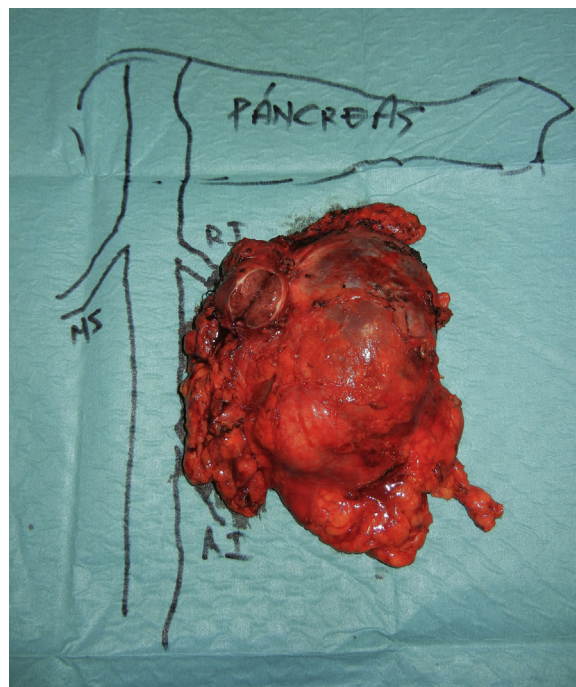


**Image 1.** CT scan. Three nodules can be seen in the para-aortic border and just anterior and posteriorly to the left renal vein, which is compressed and narrowed.

**3. Discussion**

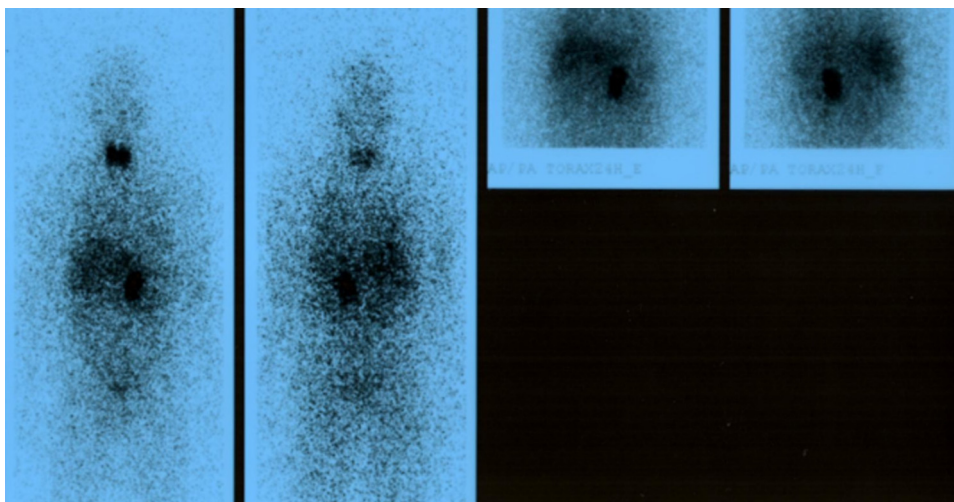
The last World Health Organization classification of endocrine tumors considers the concept of PCC exclusively for chromaffin tumors arising from the adrenal medulla [1]. Genetic research has identified up to 18 genes (both somatic and germ-line mutations) involved in the pathogenesis of familial and sporadic forms of PCC. Approximately 10–20% of PCC are associated with a specific genetic syndrome (MEN-2, von Hippel-Lindau, Neurofibromatosis type I and familial PCC syndromes) but the risk of associated malignancy in these cases is low. More recently, other causative genes have been related to PCC, as the ones codifying the subunit B of the succinate dehydrogenase B (SDHB), transmembrane protein 127 (TMP127) and MYC-associated factor X (MAX). Germline mutations of the SDHB and MAX have been associated with a higher rate of malignancy in cases of PCC (up to 90% and 25%, respectively) [2]. Thus, genetic study of these mutations may be useful in estimating the life-long risk for development of recurrent or contralateral disease and malignant differentiation, having an influence in follow-up protocols [2,3].

Although there are no clearly defined histologic characteristics for malignancy, some features are considered suggestive: tumor necrosis, mitotic rate greater than 3/30H.P.M.F., capsular and/or vascular invasion, presence of large nests with central degeneration, lack of hyaline globules, high nuclear/cytoplasmic ratio, monotony of cytological pattern and a spindle cell pattern [2,4].



**Image 3.** Reconstruction of the surgical field with the surgical specimen of left nephrectomy “en bloc” with the pathologic nodes (which can be seen opened in central axis “like an orange”).

Nearly all of them are included in the PASS (Pheochromocytoma of the Adrenal gland Scales Score) score, described by Thomson in 2002 and establishing that values <4, between 4 and 6 and >8 suggest, respectively, low, intermediate and high risk of malignancy PCC [5] (Fig. 1). Primary PCC larger than 5 cm have been associated with a higher risk of malignancy and this is the main argument to discuss the laparoscopic approach for big size PCC. Goffredo et al. reported a series of 287 malignant PCC, being 72.5% larger than 5 cm. Although a regional lymphadenectomy was only performed in 14% of the cases, an impressive rate of 67.8% metastatic involvement was found. Five years overall survival was significantly higher for patients with tumors measuring less than 5 cm (72.5% vs 27.5%) and the authors waked up the debate about the need to perform systematic staging lymphadenectomies in PCC larger than 5 cm [6].



**Image 2.** Nuclear scintigraphy with MIBG. An abnormal uptake can be observed in the left retroperitoneum just in the anatomical area of the previously resected adrenal gland.

Parameters	Score
High cellularity	2
Spindle cells (> 10% of tumor volume)	2
Atypical mitotic figure	2
Periadrenal adipose tissue invasion	2
Mitotic figures (> 3/10 HPF)	2
Cellular monotony	2
Capsular invasion	1
Vascular invasion	1
Central or confluent tumor necrosis	2
Large nests	2
Profound nuclear pleomorphism	1
Nuclear hyperchromasia	1

HPF, high power field.

Fig. 1. Parameters of the PASS Score as it was originally described by Thomson.

Tumor recurrence or persistence present, respectively, in the 6–23% and 3–13% of the PCC operated and is related to distant site or LN metastasis, which may appear even 20 years after the primary tumor [7]. Patients with liver or lung metastases tend to have a worse prognosis than patients with isolated bone lesions. Surgery is indicated as the best treatment when R0 resection or a proper debulking operation can be obtained. Kim et al. reported 8 malignant PCC (out of a series of 119 in Korea) with one survivor (the only patient undergoing surgery for LN and bone metastasis) and the other 7 in this series (none of them had surgical treatment) dying from progression of the disease [8]. In addition, Huang et al. reported an overall disease-specific survival of 80% in a group of 5 patients having only LN metastases as distant disease when a R0 resection was performed, concluding that complete excision of the metastatic disease is related to an excellent prognosis, with survival for more than 20 years being possible [9]. Rabi et al. reported in 2001 the only case published of a laparoscopic approach for resection of two para-aortic LN metastases (lower than 2 cm) of a previously operated PCC [10]. In our case, we did not consider performing laparoscopy because of the two previous operations, compression of the vessels of the renal hilum and the need of nephrectomy to achieve a R0 resection.

A mechanism of persistent or short term recurrent disease because of non-oncological surgery of primary PCC has been described by Rafat et al., who reported 5 cases in which the rupture of the capsule or an incomplete tumoral resection led to local recurrence in the retroperitoneum because of spillage of tumoral cells. Even when radical or debulking surgery was performed, only one patient was free of disease and 3 died of tumoral progression. Radiological findings related to this mechanism are not easy to differentiate preoperatively from regional LN metastases [11]. In our case, the CT images showed some nodules located in the left renal hilum and para-aortic margin and the report of the primary PCC operated informed of an “entire capsule”. Then, we considered the LN recurrence as the first possibility although the diagnosis of retroperitoneal “pheochromocytomatosis” was also in our mind. Anyway we indicated surgery in order to obtain a R0 resection as the only possibility of cure for the patient.

When complete resection of recurrent PCC can not be accomplished, surgical debulking and local therapies like ablation or stereotaxic radiotherapy can provide palliation. A lower tumor burden leads to a decrease in catecholamine secretion and means less risk of future cardio-vascular damage. Radiolabelled MIBG (<sup>131</sup>I) or

somatostatin analogues, separated or in synergistic combination, may achieve control of the volume tumor and partial hormonal response in 50% of the patients with metastatic PCC. Classical chemotherapeutic drugs have very low effectiveness and nowadays efforts are in the way of investigating the role of molecular targeted therapies (sunitinib/imatinib, everolimus or thalidomide).

#### 4. Conclusion

Isolated metachronic LN involvement is a very rare presentation of malignant PCC. Proper staging with radiological and functional studies must be performed in order to evaluate the best therapeutic option. Radical surgery must always be considered when a R0 status or a proper debulking can be achieved because it offers the best chance for long term survival.

#### Conflicts of interest

The author and co-authors reveal that we don't have financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated.

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#### Patient's consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

#### Consent

The ethics committee of the Hospital approved the reporting of this case, with the previous informed consent of the patient.

#### Author contribution

César Pablo Ramírez-Plaza is the main author of the paper. He had the idea or reporting the case and elaborated the discussion.

Elena Margarita Sanchiz-Cárdenas is the surgeon who assisted me in the operation and helped me to collect the bibliography.

Rocío Soler Humanes is the motivated surgeon of our team who wrote the case-report and collaborated in the discussion.

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