Outcome of adrenal sparing surgery in heritable pheochromocytoma

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Abstract (226 words)

The management of hereditary pheochromocytoma has drastically evolved in the last 20 years. Bilateral pheochromocytoma does not increase mortality in multiple endocrine neoplasia type 2 (MEN 2) or von Hippel-Lindau (VHL) mutation carriers who are followed regularly, but these mutations induce major morbidities if total bilateral adrenalectomy is performed. Cortical sparing adrenal surgery may be proposed to avoid definitive adrenal insufficiency. The surgical goal is to leave sufficient cortical tissue to avoid glucocorticoid replacement therapy. This approach was achieved by the progressive experience of minimally invasive surgery via the transperitoneal or retroperitoneal route. Cortical sparing adrenal surgery exhibits less than 5% significant recurrence after 10 years of follow-up and normal glucocorticoid function in more than 50% of cases. Therefore, cortical sparing adrenal surgery should be systematically considered in the management of all patients with MEN 2 or VHL hereditary pheochromocytoma. Hereditary pheochromocytoma is a rare disease, and a randomized trial comparing cortical sparing vs. classical adrenalectomy is probably not possible. This lack of data most likely explains why cortical sparing surgery has not been adopted in most expert centers that perform at least 20 procedures per year for the treatment of this disease. This review examined recent data to provide insight into the technique, its indications, and results and subsequent follow-up in the management of patients with hereditary pheochromocytoma with a special emphasis on MEN 2.
Introduction

Pheochromocytoma is a rare neuroendocrine tumor (estimated annual incidence of 2 to 8 per million) that arises from chromaffin cells in the adrenal medulla\(^1\)\(^-\)\(^2\). It is considered a sporadic disease in most cases\(^3\). The contribution of heredity increased to up to 25% with the discovery of new susceptibility genes, such as succinate dehydrogenase (SDH), MAX or TMEM127\(^4\)\(^-\)\(^6\). Overall, SDHB, SDHD, RET, VHL and NF1 germinal mutations represent most of all of the genetic etiologies of pheochromocytoma and paraganglioma\(^6\). SDHB and SDHD mutations primarily lead to unilateral pheochromocytoma and whole-body paraganglioma, with up to 40% malignity for SDHB mutations \(^7\). In contrast, bilateral pheochromocytoma is observed in syndromic diseases due to mutations of RET, which leads to multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Lindau syndrome (VHL) or neurofibromatosis type 1 (NF1) \(^3\). MEN 2 is an autosomal dominant disease in which medullary thyroid carcinoma (MTC) is present in 100% of cases, and pheochromocytoma occurs in approximately 50% of MTC cases either concurrently or after the diagnosis of MTC\(^8\). VHL is an autosomal dominant syndrome that primarily includes the central nervous system or retinal capillary hemangioblastoma, and pheochromocytoma occurs in approximately 20% of VHL cases (specifically in type 2) \(^9\). The mean age at first diagnosis of pheochromocytoma (unilateral or synchronous bilateral) is approximately 30 to 40 years in both genetic etiologies, and the risk of malignancy is low (less than 5%)\(^8\). The management and follow-up of medullary thyroid carcinoma in MEN 2-mutation carriers is well codified as early thyroidectomy\(^10\), which suggests that pheochromocytoma has progressively become the main determinant of the outcome in these patients.
However, the impact of pheochromocytoma in MEN 2-mutation carrier mortality in the 21st century is lower than expected. Only 2 deaths presumably due to pheochromocytoma were reported in 107 patients with the frequent germline 634-RET codon mutation, and these deaths were observed during surgery in the 1960s. We reported a similar result in a large international study of only 4 deaths out of 563 patients with MEN 2-associated pheochromocytoma. The results are similar for VHL mutation carriers. Bilateral pheochromocytoma exhibits a major functional impact following total bilateral adrenalectomy, which is still used in many centers. Approximately 50% of MEN 2 and 20% of VHL patients present bilateral pheochromocytoma by age 50, and these patients become adrenal insufficient following bilateral adrenalectomy. The commonly encountered adverse side effects with chronic steroid dependence are well defined, and insufficient steroid replacement may lead to Addisonian crisis and death. Excessive steroid replacement is associated with premature osteoporosis, hypertension and diabetes. Chronic steroid side effects also include an altered quality of life. Notably, even patients who receive appropriate information on the management of their chronic adrenal insufficiency are at risk of Addisonian crisis, which is a life-threatening emergency that may occur when the replacement dosage is not increased by the patient despite a major stress. A large recent study of 423 educated patients reported a risk of 8.3 Addisonian crises per 100 patient-years, and the occurrence of 0.5 Addisonian crisis-related deaths per 100 patient-years. Changing the functional prognosis of MEN 2 or VHL mutation carriers will require modifications in the treatment of patients with bilateral pheochromocytoma.

Surgical teams adopted different techniques to avoid the consequences of adrenal insufficiency in patients with bilateral pheochromocytoma. Adrenal
autotransplantation was performed with limited success, and sufficient autograft functioned in less than 30% cases. Therefore, this technique has been nearly abandoned. Cortical sparing adrenal surgery is increasingly performed. Cortical sparing is a surgical technique in which the surgeon leaves a small amount of vascularized unilateral or bilateral adrenal tissue that will be sufficient to maintain the normal function of the adrenal cortex for a prolonged period of time. This technique was successfully tested in pheochromocytoma and aldosterone–producing adenoma. The present review provides insight on the merits and pitfalls of cortical sparing adrenal surgery in the management of hereditary pheochromocytoma with a special emphasis on MEN 2 and VHL mutation carriers.

**Diagnosis of hereditary Pheochromocytoma**

Pheochromocytoma is detected concurrent with the genetic diagnosis or during the follow-up of mutation carriers who are diagnosed by familial screening. The steps of diagnosis are identical, but the option of cortical sparing adrenal surgery is more obvious in mutation carriers because the pheochromocytoma is generally smaller.

In the propositus (when pheochromocytoma is present at the genetic diagnosis)

The diagnosis of pheochromocytoma is biochemically based on increased levels of plasma or urinary free normetanephrines and metanephrines (sensitivity 97-100%, specificity 100%)\(^2\). VHL-associated pheochromocytoma usually secretes normetanephrines, and few of these tumors secrete metanephrines\(^19\). The profile of MEN 2-associated pheochromocytoma is the co-secretion of both biological markers \(^19\). Conventional imaging is performed using CT or MRI (with 1-2 mm slice thickness) because both of these techniques exhibit high sensitivity and specificity (90-100%
and 70-80%, respectively). CT or MRI will allow for the precise determination of the size of the pheochromocytoma, the number of lesions and the possibility of performing a partial adrenalectomy.

The role of metabolic imaging in sporadic pheochromocytoma is debatable, but it is important in hereditary pheochromocytoma. Metabolic imaging aids in the detection of additional smaller secreting lesions in the same or contralateral gland. Limited data are available in the current literature on functional imaging studies in MEN 2-associated pheochromocytoma. One special advantage of $^{18}$F-FDOPA (3,4-dihydroxy-6-(18)F-fluoro-l-phenylalanine) PET over metaiodobenzylguanidine (MIBG) stems from its lack of high uptake in normal adrenal glands. The recent European Association of Nuclear Medicine (EANM) guidelines state that $^{18}$F-FDOPA uptake should be considered pathological only in cases of asymmetrical adrenal uptake with a concordant enlarged gland or adrenal uptake that is more intense than the liver with a concordant enlarged gland. We consider that $^{18}$F-FDOPA should be the optimal metabolic imaging technique if it is performed during the decision process for cortical sparing surgery. The MIBG scan is another option for the evaluation of these tumors. $^{123}$I-MIBG scintigraphy is preferable to $^{131}$I-MIBG scintigraphy. However, the main drawback of MIBG scan is related to the high uptake by normal adrenal medulla. $^{18}$F-FDG PET is suboptimal in the diagnosis of MEN 2- and NF 1-associated pheochromocytoma, but some tumors may exhibit high tracer uptake. SDHx- and VHL-associated pheochromocytoma exhibit high avidity for $^{18}$F-FDG.

In mutation carriers (without pheochromocytoma at the time of genetic diagnosis)

The way to follow mutation carriers is debatable. However, the follow-up is crucial for the option of cortical sparing surgery. Symptoms and signs of catecholamine
oversecretion (e.g., palpitations, hypertension, sweating) must be considered, but these symptoms are frequently absent in mutation carriers, who show a progressive increase of metanephrines. Therefore, plasma or urinary free normetanephrines and metanephrines should be monitored annually. The age to begin screening is well codified for MEN 2-associated pheochromocytoma, depending on RET mutation, but VHL-associated pheochromocytoma can occur during early childhood. This biological screening should be ideally maintained throughout the patient’s lifetime. Questions remain for the need to perform regular imaging in asymptomatic patients with negative biology. In our large cohort, 75/460 (16%) at-risk MEN 2 patients underwent CT or MIBG scans every 2-5 years despite negative biology. The theoretical risk of not being able to perform partial adrenalectomy because of the size of the pheochromocytoma is rather low because a large MEN 2- or VHL-associated pheochromocytoma would be secreting and detected using biological testing. However, the performance of regular imaging (with 1-mm slices) could aid in the detection of a small (< 1 cm) and not secreting pheochromocytoma. This screening would help define the intervals of further imaging surveillance or impact the decision for an early surgery, and cortical sparing surgery would be technically available at this stage. Radiation toxicity should also be considered, which supports the use of MRI rather than CT in cases who are willing to undergo imaging surveillance. In summary, whether imaging should play a role during the follow-up of these patients is not known, but it seems obvious that if it is performed, then it should not be performed too frequently. We suggest the performance of adrenal MRI every 3-5 years, and there is likely no place for nuclear imaging in this setting of surveillance.

Technique of Cortical Sparing Surgery
The performance of classical adrenalectomy or cortical sparing adrenal surgery does not modify the pre-surgical management of patients. The Endocrine Society guidelines recommend the maintenance of normal blood pressure levels using alpha blockers followed by beta-blockers before surgery. We consider that most patients are controlled with calcium blockers, but one major factor in the treatment is the experience of the surgeon and the anesthesiologist in the management of pheochromocytoma.

**When to perform cortical sparing surgery**

The possibility of cortical sparing surgery is evoked based on 3 assumptions:

- A very low risk of malignancy;
- A reasonable risk of recurrence that is easily followed, diagnosed and cured; and
- A high chance of maintaining normal adrenal cortical function.

The use of this technique in unilateral pheochromocytoma is highly debated, which is why the literature data on partial adrenalectomy only focus on patients with RET or VHL mutations. The low risk of malignancy and high risk of bilateral pheochromocytoma are obvious in these genetic cases, especially in MEN 2.

The main difficulty in cortical sparing surgery for the risk of recurrence is that it is impossible to ensure that there is no remaining medullar tissue. The predisposing mutation in MEN 2 involves all of the medullar cells, with hyperplasia preceding pheochromocytoma. The macroscopic difference between the cortex and the medulla is easy to see (figure 1), but expert surgeons report that the possibility of having a clear post-surgical cortex without any medullar cells is a myth. The remaining medullar tissue will systematically lead to a recurrence of
pheochromocytoma, but not for a prolonged period of time (as described in detail in the next chapter).

Conventional imaging (with 1-mm slices) will provide clues to determine whether the surgeon can safely maintain any adrenal tissue. The assumption will be based on the maximum size of the pheochromocytoma and the presence of other pheochromocytoma in the gland. A pheochromocytoma larger than 5 cm could make it difficult to perform partial adrenalectomy because a specific anatomical position of the tumor would be necessary. At least ¼ to 1/3 of the gland is needed to maintain normal cortical function. This minimal amount is sometimes impossible to obtain because of the large size of the pheochromocytoma and the presence of several smaller associated pheochromocytoma in the same gland. The decision of the appropriateness of cortical sparing adrenal surgery in these cases depends on the surgeon’s experience, which may be aided with intraoperative sonography.

How to perform cortical sparing surgery

Surgery for pheochromocytoma has progressively evolved in the last 20 years from open to minimally invasive surgery. Surgery of these tumors has always been risky because of the possible delivery of catecholamines during the surgery, even in normotensive patients. Operative risks were progressively reduced by medical pretreatment, improvement of the techniques, and experience acquired in specialized surgical centers. Preservation of the main adrenal vein is not necessary to gain sufficient cortical function because the gland has many blood supplies. Minimally invasive adrenalectomy was first described in 1992, and it is now the standard treatment for benign pheochromocytoma via the transperitoneal or the retroperitoneal approach. These procedures have many advantages compared to open
adrenalectomy, such as very rare mortality, lower blood loss, better hemodynamic stability, decreased morbidity, including decreased post-surgical pain and ileus, shorter hospital stay, better esthetic results and faster return to daily life activities. Questions on minimally invasive surgery remain for malignant or very large tumors, which are not crucial in patients who should benefit from cortical sparing adrenal surgery. Minimally invasive surgery is likely the best surgical approach for candidates of partial adrenalectomy because it provides an optimal view and light on the gland, which is deeply located in the abdomen, and it is less traumatic. This surgery makes a 2nd surgery easier even with minimally invasive surgery or using another cortical sparing approach in case of recurrence. Cortical sparing adrenal surgery has been made easier as soon as the endoscopic approach became the gold standard. Our recent study reported a progressive increase in the number of cortical sparing procedures following a progressive increase in the number of endoscopic procedures (33 vs. 8% and 64 vs. 8% using both techniques before 1999 and after 2009, respectively).

The transperitoneal approach has the advantage of having a large operative field, which provides a well known anatomical view for the surgeon, and it is frequently used for adrenal surgery. However, the adrenals are located in the upper retroperitoneal space, and a retroperitoneal approach for total adrenalectomy was developed 20 years ago. A retroperitoneoscopic approach allows direct, rapid access to the adrenal gland without incursion into intra-abdominal viscera and provides a detailed view of the adrenal gland and its surrounding region. This approach is performed in a prone position, and it requires dilatation of the retroperitoneum. The primary contra-indication to this approach is a large-sized tumor (> 8 cm) due to the limited operative field. Severe obesity is another relative
contra-indication because it also reduces the operative field, and thick fat retroperitoneal tissue makes the surgery more difficult. Opponents to this technique also mention that the small operative field and the inability to explore the abdominal cavity may represent strong limitations to this approach. Anesthesiology analyses reported hemodynamic changes, such as significant increases in cardiac output, stroke volume, mean arterial pressure, mean pulmonary arterial pressure, and central venous pressure, without apparent adverse effects. The same approach was used for cortical sparing adrenal surgery in 22 patients, including 2 patients with MEN 2. This study was followed by several other studies by different teams, which suggests a better outcome for patients in terms of postoperative pain. This technique has the advantage of allowing the performance of bilateral adrenalectomy without patient repositioning, which decreases the duration of surgery. A recent study compared transperitoneal (n=26) and retroperitoneal (n=17) approaches for unilateral endoscopic procedures in adrenal tumors. No patient had hereditary pheochromocytoma. Blood loss was similar in both groups, but the mean operative time, the mean time to first oral intake, the global consumption of painkillers and the mean time of hospital stay were reduced in the retroperitoneal group.

In summary, minimally invasive surgery should be the preferred surgical procedure when performing cortical sparing adrenal surgery. The endocrine surgeon should decide the transperitoneal or retroperitoneal route because neither approach is better from a functional viewpoint. The post-surgical comfort of the patient may be improved with the latter approach, but the necessity of a learning curve due to an unusual anatomical view could make it more difficult to obtain effective results initially. Notably, the low morbidity of cortical sparing adrenal surgery and the similar duration
of the intervention do not exhibit evidence in favor of total adrenalectomy from a technical viewpoint.\footnote{52}

**Adrenal Function and Recurrence after Cortical Sparing Surgery**

The efficacy of cortical sparing adrenal surgery can be evaluated using 2 parameters:

- The rate of recurrence, and
- The rate of normal adrenal function when adrenal sparing surgery is performed in at least one adrenal in patients with bilateral pheochromocytoma.

One of the primary issues when trying to determine the outcome of patients treated by this specific surgical approach is the low number of studies in the literature. An exhaustive search in PubMed using the words “partial adrenalectomy”, “cortical sparing”, “adrenal sparing” or “adrenalectomy” for the first published report on cortical sparing adrenal surgery revealed 69 original studies/case reports, with only 25 studies that dealt with more than 10 patients. Narrowing the search to hereditary pheochromocytoma led to 10 studies of at least 10 MEN 2 or VHL patients. The length of follow-up is also an issue because 3/10 studies had a follow-up that was less than 5 years, which likely under-evaluates the risk of significant recurrence in patients treated with this type of approach. Precise definitions of the recurrence (e.g., symptomatic, biological or identified by imaging) was not always clearly mentioned.

Table 1 summarizes these studies\footnote{12, 26-33, 53}.

The overall risk of recurrence in pheochromocytoma following cortical sparing adrenal surgery is estimated as 0 to 21\%. One study reported an estimated risk of recurrence greater than 50\%, but the number of patients having a follow-up greater than 5 years was low, and the risk was extrapolated\footnote{27}. The risk of recurrence seems lower in most recent studies, which primarily used endoscopic approaches, and risk
is higher in older studies, which were based only on open adrenalectomy as shown in table 1. These results confirm that endoscopy induced better functional results because of the magnification that is achieved using endoscopic equipment. Notably, the risk is not necessarily higher in studies with a longer follow-up. However, these studies rarely report follow-ups of more than 10 years, which is likely not sufficient. We recently reported the largest investigation of cortical sparing adrenal surgery in 114 MEN 2 patients. Notably, our study was based on 533 patients operated for MEN 2-associated pheochromocytoma, and it did not find any significant difference in the rate of recurrence between patients treated by total or partial adrenalectomy. Four of 153 (2.6%) operated glands presented recurrence after a mean follow-up of 10 years in the “cortical sparing” group, and 11 of 717 (1.5%) presented recurrence after a mean follow-up of 13 years in the “adrenalectomy” group. The mean time to recurrence in the entire cohort was 9.5 years, but 2 patients with cortical sparing adrenal surgery presented recurrence 11 and 13 years after surgery, which clearly indicates that a longer follow-up is required to develop a better idea of long-term recurrence risk. This longer follow-up is also needed for classical adrenalectomy because the risk of recurrence after total laparoscopic adrenalectomy for pheochromocytoma is very low, but the follow-up is generally less than 5 years.

Glucocorticoid function was normal in 57-100% of patients treated for bilateral pheochromocytoma with at least 1 adrenal sparing surgery. The diagnosis of adrenal insufficiency was based on a low 08:00 h cortisol level and an insufficient cortisol response to ACTH test. Two studies reported normal 08:00 h plasma cortisol levels but subnormal cortisol response to the ACTH test, and these patients did not require glucocorticoid substitution. No occurrence of Addisonian crisis was reported.
during the follow-up in these patients. The definition of normal cortical function should be more clearly determined when there is no need for substitutive treatment or a normal response to the ACTH test. A subsequent repetition of the test may lead to a normal response to ACTH in patients with normal basal cortisol levels. The 2 most recent studies reported the lowest rates of normal adrenal function\textsuperscript{12,31} in primarily MEN 2 patients who underwent minimally invasive surgery. These results may be observed because several smaller pheochromocytomas were detected during the surgery, and it was not possible to maintain a sufficient adrenal remnant to avoid glucocorticoid substitution. The only study that compared cortical sparing adrenal surgery with total adrenalectomy demonstrated a significant difference between groups (43\% vs. 100\% patients with adrenal insufficiency, respectively)\textsuperscript{12}. Cortical sparing adrenal surgery is likely an effective procedure to maintain normal adrenal function.

The results of cortical sparing adrenal surgery in MEN 2 strongly suggest that surgeons should perform cortical sparing surgery in patients with a history of renal/adrenal trauma (with only 1 remaining gland) when technically feasible. We consider that cortical sparing surgery should be the preferred method in cases of MEN 2- or VHL-associated unilateral pheochromocytoma because of the high risk of contralateral metachronous pheochromocytoma. Some authors suggest that the low risk of malignity of MEN2-associated pheochromocytoma support a waiting attitude in cases of unilateral non-symptomatic pheochromocytoma. However, the possible occurrence of several pheochromocytoma on the contralateral gland, which complicates cortical sparing surgery, is strong evidence for the performance of partial adrenalectomy at the first diagnosis of pheochromocytoma when possible. We encourage surgeons to perform bilateral adrenal sparing surgery in patients with
bilateral pheochromocytoma at diagnosis. The risk of recurrence will obviously be higher, but performing unilateral total adrenalectomy at the time of recurrence will allow patients to maintain normal cortical function via the spared contralateral gland for a prolonged period of time. It is also obvious that the second surgery will likely be more difficult in these patients, but the final aim of preserving cortical function for the longest period of time is obtained.

**Managing the Follow-Up after Cortical Sparing Adrenal Surgery**

The follow-up determines glucocorticoid function and identifies a potential recurrence. There are no guidelines for patient follow-up after bilateral adrenalectomy with at least 1 cortical sparing adrenal surgery to detect the need for substitutive treatments. One reasonable approach would be to treat the patients systematically with glucocorticoids (supplemental dose) after surgery and evaluate before glucocorticoid intake 08:00 h plasma ACTH and cortisol at 1, 3, 6 and 12 months (if still less than normal) after surgery. A cortisol value greater than 140 nmol/l should lead to an ACTH stimulation test, which will allow the withdrawal of glucocorticoids if cortisol > 550 nmol/l. This approach is similar to the guidelines for the follow-up of classical adrenal insufficiency patients\(^\text{15}\). The probability of recovering a normal adrenal function for more than one year after surgery seems highly unlikely.

The symptoms and signs of catecholamine oversecretion are rarely effective markers to detect recurrence. The follow-up is identical to the follow-up for mutation carriers based on annual plasma and/or urinary metanephrines and normetanephrines assessments. A negative biology does not exclude a small pheochromocytoma, which is not a fatal event in regularly followed patients. Notably, the genotype *per se* does not modify the risk of recurrence, but it might shorten the period between
surgery and recurrence. This result is supported by the fact that patients with germline mutations of exon 11 of the RET gene exhibit pheochromocytoma at a younger age than patients carrying exon 10 mutations \(^{12}\). The role of systematic conventional imaging during the follow-up is controversial, and it should not be more frequent than for mutation carriers before the first diagnosis of pheochromocytoma. However, there is a larger place for high-resolution nuclear imaging in cases of positive biology because CT and MRI are less effective in detecting small local recurrence. 18F-FDOPA PET/CT may provide further information to distinguish between compensatory adrenal cortex remnant hyperplasia and recurrent pheochromocytoma. Obviously, the follow-up is also aimed at the detection of contralateral pheochromocytoma in cases of unilateral adrenalectomy. Management of recurrence is currently based on total adrenalectomy, but one study reported the possibility of performing another partial procedure, similarly to the multi-surgical management of hyperparathyroidism in multiple endocrine neoplasia\(^{44}\).

**Conclusions and Future Directions**

Pheochromocytoma patients need highly individualized interdisciplinary evaluation and treatment.

Cortical sparing endoscopic surgery is a safe and effective procedure for the management of hereditary bilateral pheochromocytoma in referral centers. In this context, the knowledge of genetic status before surgery may be useful (phenotypically for VHL, using calcitonin measurement for MEN 2, and genetically for SDHB) to create a tailored optimal management strategy. The 10-year risk of recurrence is low, and more than 50% of patients will maintain normal glucocorticoid function for 10 years. However, this approach is not systematically proposed. Only
33% of the patients in our international study were treated using cortical sparing adrenal surgery between 2009 and 2014. This low frequency should be considered an anomaly because this approach can alter the functional outcome of primarily young patients for a prolonged period of time. Cortical sparing adrenal surgery should now be considered the preferred method, even at the first diagnosis of metachronous pheochromocytoma, and these data emphasize the need for optimal management in expert centers.

Further studies should determine the long-term risk of recurrence after cortical sparing adrenal surgery because this rate likely dramatically increases after 10 years of follow-up. Finally, future studies should also help determine whether cortical sparing adrenal surgery should be proposed to patients with sporadic unilateral pheochromocytoma. Cortical sparing adrenal surgery may be a valuable option because of the monoclonal nature of sporadic unilateral pheochromocytoma, and the lack of hyperplasia that surrounds the tissue. This technique was successfully performed in aldosterone-producing adenoma, and this technique is already an option in patients with unilateral pheochromocytoma and loss of the contralateral adrenal gland due to previous surgery or trauma. Optimal management performed by experts in cortical sparing surgery may also aid in the repeating of partial adrenalectomy in case of recurrence to delay the development of adrenal insufficient.

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REFERENCES


**LEGEND TO TABLE AND FIGURES**

**Table 1**: Literature search on cortical-sparing adrenal surgery. Studies were selected if at least 10 patients were treated in the indication of hereditary pheochromocytoma. The criteria used to define normal adrenal function were normal cortisol response (between 18 and 20 µg/dl 30-60 minutes after cosyntropin stimulation test) for all studies except for Benhammou et al. (need for corticosteroid replacement) and Alesina et al. (Follow-up data were obtained by contacting the general physician or the referral endocrinologist). Recurrence was defined as biochemical and/or radiological evidence of pheochromocytoma. *Only 1 bilateral adrenalectomy; only 3 operated patients had a follow-up > 5 years.

**Figure 1**: The history of adrenalectomy and cortical sparing adrenal surgery for hereditary (MEN 2 and VHL) pheochromocytoma.

**Figure 2**: Operated adrenal glands from MEN 2 patients. A, Two pheochromocytoma in the same gland (depicted by arrows), which impedes adrenal sparing surgery. Note the cortex in yellow and the medulla in pink. B, Single pheochromocytoma that could have led to successful adrenal sparing surgery.

**Figure 3**: Disease-free survival after cortical-sparing surgery and total adrenalectomy based on 563 patients carrying MEN 2-associated pheochromocytoma (adapted from Castinetti et al., Lancet oncology, 2014)\(^2\). Plain line, total adrenalectomy; Dotted line, cortical sparing adrenal surgery.
<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Genetics</th>
<th>Surgical approach</th>
<th>Recurrence</th>
<th>Normal glucocorticoid function</th>
<th>Mean follow-up</th>
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<tr>
<td>Lee et al., 1996</td>
<td>14</td>
<td>MEN2 and VHL</td>
<td>Open</td>
<td>21%</td>
<td>93%</td>
<td>138 months</td>
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<td>Neumann et al., 1999</td>
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<td>3%</td>
<td>100% (subnormal response to ACTH test in 20%, not requiring supplementation)</td>
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<td>12</td>
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<td>0%</td>
<td>100% (subnormal response to ACTH test in 50%, not requiring supplementation)</td>
<td>37 months</td>
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<td>Yip et al., 2004</td>
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<td>Open or laparoscopic</td>
<td>10%</td>
<td>65%</td>
<td>71 months</td>
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<td>0%</td>
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<td>11%</td>
<td>89%</td>
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<td>57</td>
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<td>0% (1 persistent disease)</td>
<td>91%</td>
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<td>Grubbs et al., 2013</td>
<td>33</td>
<td>MEN2, VHL</td>
<td>Open or laparoscopic</td>
<td>7%</td>
<td>58%</td>
<td>96 months</td>
</tr>
<tr>
<td>Castinetti et al., 2014</td>
<td>114</td>
<td>MEN2</td>
<td>Open or laparoscopic</td>
<td>3%</td>
<td>57%</td>
<td>120 months</td>
</tr>
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</table>
• **1953**: Classical bilateral adrenalectomy for Cushing’s syndrome. Open transperitoneal approach as the gold standard.

• **1992**: Laparoscopic adrenalectomy

• **1993**: Initial bilateral adrenalectomy should not be systematic in metachronous hereditary PHEO
  - First RET and VHL mutations identified

• **1996**: Open cortical sparing adrenalectomy
  - Retroperitoneal approach for total adrenalectomy

• **1998**: Laparoscopic cortical sparing adrenalectomy

• **2014**: Only 300 patients with hereditary pheochromocytoma reported in the literature as treated by cortical sparing adrenalectomy
<table>
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<th>Initial</th>
<th>5</th>
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<tr>
<td>Adrenalectomy</td>
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<td>347</td>
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<tr>
<td>Adrenal sparing surgery</td>
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