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Review

Pheochromocytoma and Paraganglioma: From Treatment to Follow-up

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Abstract

Pheochromocytomas (PCC) and paragangliomas (PGL) are rare neuroendocrine tumors arising from chromaffin cells in the adrenal medulla, sympathetic or parasympathetic ganglia. Currently, the only curative treatment option of pheochromocytomas/paraganglioma (PPGL) is surgical resection. Surgery aims to eliminate both risks of hypersecretion and tumor growth. The consequences of hypersecretion should be carefully controlled with medical therapy before and during the surgery. Postoperative major complications are hypotension and rebound hypoglycemia, and patients should be followed closely for 24-48 hours. The choice of surgical approach is determined based on multiple factors, including germline genetic test results, the size of the tumor, body mass index, surgeon's experience, and the likelihood of malignancy. Primary tumor resection does not completely eliminate the risk of tumor persistence and recurrence. Therefore, all patients with PPGL who are surgically treated should be followed for at least 10 years for recurrent disease and new tumor formation. Although surgical resection is the only curative treatment for PPGLs, surgical treatment is palliative except for resectable locoregional metastases in metastatic disease or for isolated distant metastases. The purpose of palliative treatment is to reduce hormone secretion and prevent metastasis-related complications in a critical anatomical location Combined and alfa;- and beta- adrenergic blockade is usually applied in patients with PPGL preoperatively. Some patients may present with pheochromocytoma multisystem crisis, which is a life-threatening condition that can involve cardiovascular, pulmonary, neurological, gastrointestinal, renal, hepatic and metabolic systems. Pheochromocytoma crisis may be spontaneous or may present with the tumor manipulation, trauma, corticosteroids, beta-blockers, anesthetic drugs, and the stimulation of non-adrenal surgical stress. These patients should be considered as medical emergencies rather than surgical emergencies. In this review, it was aimed to evaluate the pre-, per and post-operative management, curative and palliative surgical management, and postoperative outcomes and follow-up of the patients with PPGLs.

Keywords: Follow up; pheochromocytoma; paraganglioma; palliative; surgical; systemic treatment.

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Pheochromocytomas (PCC) and paragangliomas (PGL) are rare neuroendocrine tumors arising from chromaffin cells in the adrenal medulla, sympathetic or parasympathetic ganglia.[1, 2] Currently, the only curative treatment option of pheochromocytomas/paraganglioma (PPGL) is surgical resection. Surgery aims to eliminate both risks of hypersecretion and tumor growth. The consequences of hypersecretion should be carefully controlled with medical therapy before and during the surgery. The choice of surgical approach is determined based on multiple factors, including germline genetic test results, the size of the tumor, body mass index, surgeon's experience, and the like-

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lihood of malignancy. Primary tumor resection does not completely eliminate the risk of tumor persistence and recurrence.[1-4] Therefore, all patients with PPGL who are surgically treated should be followed for at least 10 years for recurrent disease and new tumor formation.[5]

In this review, it was aimed to evaluate the pre-, per- and post-operative management, curative and palliative surgical management, and postoperative outcomes and follow-up of the patients with PPGLs.

Perioperative Treatment

Preoperative Treatment

Preoperative blockade is recommended in functional PPGLs to prevent perioperative cardiovascular complications.[4] There are no randomized controlled trials supporting the use of α-adrenergic blockade in preoperative patients.[6] In a recent multicentric retrospective study, tumor-specific complications associated with hemodynamic instability were found to be higher in patients receiving preoperative α-blockers (5.9% vs. 0.9%, respectively), and mortality rates were similar. Additional prospective randomized studies are needed to address which patients will benefit from α-blocker therapy.[7] Although the preoperative preparation of patients with PPGL using α-blocker has become highly dogmatic, it is recommended as guidelines or expert advice, and the α-receptor blockade is routine in the clinical practice of many centers.[4]

Combined α- and β- adrenergic blockade is usually applied in patients with PPGL. An α-adrenergic blockade may be applied via non-selective or selective adrenergic receptor antagonists. Non-selective α-adrenergic blockade is started with an oral dose of 2x10 mg phenoxybenzamine and can be increased to a dose of 1 mg/kg/day, depending on the age of the patient, with blood pressure adjusted to the lower limit of normal limits.[4, 8] If the selective α-1 adrenergic blockade is to be performed, doxazosin can be started at a dose of 2 mg/day and can be increased up to 32 mg/day until the desired blood pressure is obtained.[4] In the recent prospective randomized study, although phenoxybenzamine was more effective in preventing intraoperative hemodynamic instability than doxazosin, it was not been established whether this was related to better clinical outcomes.[9] Patients who are administered adrenergic blockade should be accompanied by a high-dose sodium diet (5000 mg/day) and adequate daily fluid intake (2.5 L/day) to prevent severe hypotension after tumor removal.[8] Another option is to administer 1-2 L intravenous saline (0.9% NaCl) solution one day before the surgery.[6] The aim should be to keep the blood pressure below 130/80 mmHg while sitting and not lower than 80/45 mmHg while standing. The target in the heart rhythm is 60-70 bpm while sitting and 70-80 bpm while standing.[10] If the patient's blood pressure cannot be controlled with the α-adrenergic blockade, additional calcium channel blocker can be used. In addition, calcium channel blocker can be used alone in patients with normotensive or mild hypertension.[6] The tyrosine hydroxylase inhibitor metyrosine, which inhibits catecholamine synthesis, should be administered in patients who cannot tolerate α-blocker or in hypertension that cannot be controlled by α-blocker and/or calcium channel blocker.[2] However, recent data suggest that the use of metyrosine in combination with preoperative phenoxybenzamine may reduce intraoperative hemodynamic instability and postoperative cardiovascular problems.[11] If the patient is at home preoperatively, they should be recommended to check and record blood pressure and pulse at least twice a day.

If the pulse is above 100 bpm 3-4 days after α-blockade is started, β- adrenergic receptor blockade should be administered to control tachycardia. The use of beta-adrenergic receptor blockers without the initiation of an α-receptor blocker is not recommended due to the potential for hypertensive crisis with the unopposed stimulation of α-adrenergic receptors. Propranolol can be started up as 3x20 mg/day and can be increased up to 3x40 mg/day depending on heart rate. Or atenolol 25 mg/day can be started and the dose can be increased to 50 mg/day. Although there are no data regarding the optimal duration of preoperative treatment, blood pressure and heart rate can be normalized with 7-14 days of treatment.[4] Tachycardia is less common in those who use selective α-blockers, but especially in patients who use phenoxybenzamine, additional β-adrenergic receptor blockade is often required for tachycardia control. Even if the patient does not have hypertension, blockade should be initiated with low-dose α-blocker. Phenoxybenzamine, β-blockers, calcium channel blockers, doxazosin can be used safely in pregnant women.[2]

Pheochromocytoma Crisis

Some patients may present with pheochromocytoma multisystem crisis. Although this condition is rare, it is a life-threatening condition that can involve cardiovascular, pulmonary, neurological, gastrointestinal, renal, hepatic and metabolic systems and cause different symptoms related to these systems and can be difficult to diagnose.[12] The patient may present with hypertension or hypotension, hyperthermia, encephalopathy or multiorgan failure and it may be associated with high mortality.[13, 14] Pheochromocytoma crisis may be spontaneous or may present with the tumor manipulation, trauma, corticosteroids, β-blockers, anesthetic drugs, and the stimulation of non-adrenal surgical stress.[4, 12]

In these patients, immediate surgical intervention without stabilizing the patient is associated with high morbidity and mortality. These patients should be considered as medical emergencies rather than surgical emergencies. Many of these patients can be stabilized with α-blocker. However, such patients should be followed and stabilized with a multidisciplinary approach.[14] Rarely, intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) may be required to treat severe cardiogenic shock, which can contribute significantly to treatment and increase survival. Tumors can be resected within 1-2 weeks in patients who generally recover with medical and intensive care support. However, in very severe cases, immediate surgery may rarely be required.[14-16] In addition, immediate surgery may be required in case of tumor rupture or uncontrolled bleeding.[12]

Intraoperative Treatment

Communication and collaboration of the anesthesia and surgical team are important for the success of the operation. Before starting the surgery, a large vein or central venous catheter should be placed on the patient. Radial artery is cannulated for hemodynamic monitoring. Anesthesiologist should be prepared for the treatment of blood pressure changes. Esmolol is the most commonly used agent in intraoperative hypertension. Intravenous magnesium sulfate can be used in refractory hypertension. In surgery, blood pressure increase and arrhythmia can be seen with the manipulation of the tumor. In this case, the surgeon is warned by the anesthesiologist and the manipulation is stopped until the blood pressure decreases. If necessary, medication may be administered by the anesthesiologist to lower the blood pressure. Hypotension may occur after the tumor is removed. In this case, the patient is administered intravenous isotonic fluid (0.9% NaCl). Bolus or infusion ephedrine or phenylephrine can be administered if needed.[6]

Early Postoperative Follow-up and Treatment

Postoperative major complications are hypotension and rebound hypoglycemia, and patients should be followed closely for 24-48 hours.[4]

The patient's blood pressure, pulse, urine output and blood sugar should be closely monitored. Acute postoperative hypotension is generally related to the sudden fall of the catecholamines in the circulation and the expansion of the intravascular space due to the residual alpha-blocking effect. Intravenous fluid resuscitation is required. Vasopressor (ephedrine, phenylephrine, norepinephrine) can be administered, if necessary.[6] Reactive hypoglycemia may occur after PPGL resections, although not very often. High catecholamine levels suppress α and β cells in the pancreas. Rebound insulinemia may occur after surgery. Associated hypoglycemia typically occurs in the first four hours postoperatively. The patient's glucose level should be checked every six hours. The patient is administered intravenous dextrose 5% until tolerating oral intake, especially in diabetic patients, insulin requirement should be adjusted postoperatively.[4, 6]

Surgical Treatment

The main treatment of PPGL is surgery, and it offers the best chance for cure or remission. According to the patient's biochemical tests, genetic tests, anatomical and functional imaging results, the surgery is planned individually.[6] Adrenal surgery can be performed with the laparoscopic or open technique.[17, 18] Both methods can be applied transabdominally or retroperitoneally. Laparoscopic surgery can be applied conventionally or robotically.[18] The choice of surgery depends on the diameter and type of the lesion, the general characteristics of the patient, the surgeon's experience and preference.[17] Laparoscopic adrenalectomy has become the gold standard treatment in the treatment of selected patients.[18] Laparoscopic adrenalectomy should not be considered a contraindication even in patients with situs inversus.[19] Laparoscopic adrenalectomy is a minimally invasive surgical procedure, and intraoperative blood loss, postoperative pain, length of hospital stay, total 30-day postoperative complications and mortality rates are lower than open interventions.[18]

The basic principles in adrenal surgery for PCC include early identification and ligation of the adrenal vein, minimal manipulation of the tumor to prevent tumor rupture or the release of catecholamines that may cause blood pressure fluctuations.[18, 20]

Laparoscopic adrenalectomy is recommended for the treatment of many patients with PCC.[18] While laparoscopic adrenalectomy is recommended in PCCs up to 6 cm, open adrenalectomy is recommended to provide complete tumor resection, prevent tumor rupture and local recurrence in PCCs over 6 cm. Open surgery is recommended in PGLs because they have a higher risk of malignancy, and the tumor is often located in difficult anatomical regions for laparoscopic resection.[4] However, laparoscopic surgery can be performed in small non-invasive PGLs at appropriate localization that do not require adjacent organ resection.[4, 17, 21]

Larger tumors have a higher risk of both metastatic disease and tumor rupture.[22] Tumor rupture of primary PCC during surgical resection may result in tumor spillage and peritoneal and retroperitoneal dissemination. This can result in even an apparently benign process to become peritoneal

carcinomatosis and metastatic disease, which can potentially be fatal. Therefore, resection of the tumor completely and without rupture is very important for a good prognosis. In addition, in the case of tumor rupture, these patients must be carefully monitored because recurrence may occur after prolonged significant remission.[23] Preoperative knowledge of the type of preoperative germline mutation in PPGL affects the type of surgical approach and the extension of adrenalectomy.[24]

Open adrenalectomy may be preferred in patients with SDHB, TMEM127 or FH germline mutations, as the risk of extra-adrenal disease, metastatic disease or recurrence risk is higher than in patients with NF1, RET or VHL germline mutations.[20, 24] Open surgery is preferred in patients with multifocal lesions where the laparoscopic approach is not possible.[6] Rarely, en bloc resection may require resection with the surrounding organs; open surgery should be preferred in this case.[25] In metastatic diseases, metastases occur primarily in lymph nodes; therefore, locoregional lymph node dissection should be performed together with primary tumor during laparotomy, in patients in whom lymph node metastasis is detected in preoperative imaging or during the intraoperative evaluation, or in patients with a high risk of lymph node metastasis, such as SDHB germline mutation.[6] Surgery may be curative in cases with metastases to regional lymph nodes.[26] Although PGLs are rarer than PCC, they are more likely to be malignant. Malignant PGLs often have a dense fibrous capsule and adhere to surrounding vascular structures, which can complicate complete resection. Preoperative preparation should be performed for possible vascular reconstructions with en bloc resection.[25] Multiple primary PGLs are often indistinguishable clinically from metastases to aortocaval lymph nodes, and in these cases, regional lymph node dissection should be performed.[6]

Partial adrenalectomy or cortical-sparing adrenalectomy can be performed in some selected patients with PCC to maintain adrenocortical function, to avoid lifelong steroid replacement, which has a negative effect on the quality of life.[18] Cortical-sparing surgery is preferred in patients with a high risk of bilateral disease and low probability of malignancy, such as MEN2 or VHL syndrome. Although the exact amount of adrenal gland remnant required is unknown, this approach has been shown to prevent postoperative adrenal insufficiency in up to 90% of patients.[20]

Head and Neck Paragangliomas

Head and neck PGLs are generally nonfunctional, and these are named according to the anatomical region they originate from, as carotid body PGL, jugulotympanic (middle ear) PGL, vagal PGL and laryngeal PGL. Carotid body PGLs constitute more than half of the head and neck PGLs. Less than 5% of all head and neck PGLs metastasize and the rate of metastasis is lower in carotid PGLs. Hereditary head and neck PGLs can be multiple and occur in association with sympathetic PGLs. Apparently, germline mutation is less than 20% in patients with sporadic tumors and much higher in patients with family history. The most commonly noted is the SDHx mutations. PGLs associated with SDHB mutations have a high risk of metastasis.[27] Traditionally, although first-line treatment of most of the carotid body PGLs is considered as surgical resection, recent evidence showing that many tumors have relatively low rates of malignancy increased interest in non-surgical treatments or follow-up. Surgical resection morbidity can be avoided by actively monitoring patients with the indolent disease, knowing the risk of metastasis, tumor biology, growth rate, tumor size, patient age, mutation status.[6]

Carotid body PGLs are often associated with germline mutations. SDHx mutations are the most common and are associated with paraganglioma syndromes from 1 to 4 (SDHD, SDHAF2, SDHC and SDHB mutations, respectively). While SDHB mutations cause more aggressive disease and metastasize more than SDHD mutations, SDHD mutations cause head and neck PGLs with higher rates and PCC with lower rates.[28] Ellis et al.[28] revealed that carotid body PGLs with SDHB mutation was associated with worse disease-free survival after resection despite early intervention, and a more aggressive surgical approach is required in these patients. However, in the carotid body PGLs without SDHB mutation, they reported that if the lesion is asymptomatic, its diameter is less than 2 cm and not biochemically hormone-active, the follow-up option can be considered.[28]

In carotid body PGLs, the risk of stroke and cranial nerve injuries are significantly increased as the tumor relates to the surrounding vessels and the difficulty of resection increases (Shamblin classification type 3> type 2> type 1). Total stroke rate after carotid body PGL resection is 3.5%, and cranial nerve injury rate persisting for more than 30 days is 11.5%. Neck haematoma rate requiring reexploration is 5.2%, and preoperative embolization does not decrease the rate of haematoma requiring reexploration.[29] In a patient presenting with multifocal disease, including diseases at the head and neck region and outside the neck region, extra-cervical lesions should be resected before approaching the head and neck PGLs.[6] PGLs outside the head and neck region are more likely to be hormone-active.[6]

Palliative Treatments

Although surgical resection is the only curative treatment for PPGLs, surgical treatment is palliative except for resectable locoregional metastases in metastatic disease or for

isolated distant metastases. The purpose of palliative treatment is to reduce hormone secretion and prevent metastasis-related complications in a critical anatomical location.[25] Primary tumor resection increases overall survival in metastatic PPGLs. It also contributes positively to the improvement of symptoms in hormone-active tumors.[30]

Patients with the abdomen-limited disease are more likely to develop and maintain a postoperative biochemical response than those with the extra-abdominal disease. However, cytoreductive interventions are unlikely to cause a clinically significant persistent biochemical response.[30, 31] If curative surgical resection cannot be performed, cytoreductive surgery should be considered to decrease the volume of the target tumor tissue and increase the effectiveness of other therapeutic options, such as targeted radiotherapy.[6] In oligometastatic PPGLs, complete metastasectomy can be considered with a patient-based approach.[32]

Wedge resection or anatomical hepatectomies may be considered to reduce tumor burden in liver metastases. Resection of metastases can help reduce symptoms related to catecholamine excess. An additional option for liver lesions is radiofrequency ablation (RFA), which can be applied peroperatively or postoperatively percutaneously. Arterial embolization and transarterial chemoembolization (TACE) have also been shown to reduce metastatic foci.[6] Palliative options for metastatic PPGL other than cytoreductive surgery, such as RFA, cryoablation and percutaneous ethanol injection (PEI), can be effective in maintaining local control and relieving symptoms.[33]

Radiotherapy, RFA, radiosurgery (gamma knife/cyberknife) and cementoplasty are palliative treatment options in painful bone metastases. Antiresorptive treatments, such as bisphosphonate or denosumab, should be considered in bone metastases.[26] In epidural cord compression, patients with spinal instability can benefit from a combination of spinal surgery and external radiotherapy.[26] Before the aforementioned interventions in hormone-active metastases, patients should be stabilized cardiovascularly by treating with α-adrenergic blockade, and if necessary, β-blockers should be added.[26] Surgery should be considered in urinary tract obstructions.[25]

Systemic Treatments

Radiopharmaceuticals

Today, 131I-MIBG therapy is the most studied treatment in metastatic PPGL and is recommended as first-line therapy in patients with positive 123I-MIBG scintigraphy and slow-growing metastatic lesions.[26] In a multicentric phase II study in patients with advanced PPGL, partial radiological response and stable disease were obtained in 92% of the patients with 131I-MIBG (AZEDRA, Progenics Pharmaceuticals Inc) treatment with a high specific activity.[34] Biochemical and clinical responses can be obtained with advanced somatostatin analogs, such as 90 Y-DOTATATE or 177 Lu-DOTATATE in somatostatin receptor-positive metastases in advanced PPGLs.[20, 35]

Systemic Chemotherapy

Systemic chemotherapy regimens can be used to control tumor growth in fast progressive diseases. Cyclophosphamide, vincristine and dacarbazine are the standard treatment regimen in these patients. Information about signal paths and mutations in PPGL can guide targeted treatments. Targeted therapeutic agents, such as tyrosine kinase receptors associated with these signaling pathways, may be considered in therapy.[26]

Follow-up

Since all patients with PPGL have a risk of recurrence, they should be followed up after R0 resection. Existing pathological grading systems in determining whether PPGL is "malignant" or have "metastatic potential" have limited predictive strength.[36, 37] Therefore, pathologists cannot reliably identify metastatic disease from histological findings. Therefore, at least 10 years of follow-up is recommended for all patients with a history of PPGL to detect local or metastatic recurrences or new tumor formations.[4, 5] Lifelong follow-up is recommended for high-risk PCC patients (germline mutation, young age (<20 years), large tumor (>5–6 cm), SDHB carriers) and all PGL patients.[4, 5, 38] Of metanephrine, normetanephrine and 3-MT levels, whichever is higher preoperatively, the level of that metabolite in plasma or urine should be checked 2-6 weeks after surgery concerning the persistent disease. In patients with normal preoperative catecholamine metabolites and elevated chromogranin A levels, it is recommended to check for chromogranin A levels 2–6 weeks after surgery.[5]

In all patients who were operated due to high preoperative catecholamine values, or who were operated despite the normal catecholamine values, or patients operated without measuring catecholamine levels, control with imaging methods, and if possible, with functional imaging methods are recommended at postoperative 3rd month.[5]

The guideline recommends performing plasma or urine metanephrine and 3-MT tests annually in patients who are under follow up. Chromogranin A test should be performed annually in patients with negative metanephrine and 3-MT tests, and positive chromogranin A. Imaging tests are recommended every 1-2 years in patients with biochemically inactive PPGL.[5]

To minimize radiation exposure, magnetic resonance imaging (MRI) is the preferred imaging method for follow-up, but it should be noted that it may miss tumors in unusual places.[32] However, details of follow-up of patients who will be lifelong followed-up are uncertain, especially how often and when imaging should be performed. Accordingly, as patients are heterogeneous, a personalized follow-up program is proposed based on disease characteristics and underlying germline mutations.[32]

Clinical/biochemical control and MRI every two years are recommended for patients with high-risk mutations (especially SDHA, SDHB, SDHD (except head and neck PGLs), EPAS1 (HIF2A), PHD1/2). Computed tomography (CT) should be considered for suspected lung involvement.

For fully resected metastatic PPGL, MRI is recommended every six months, at postoperative six months and 12 months, and then annual control. CT can also be used, but since it has a radiation risk, it should be used with more caution and less frequently. An alternative approach using CT and MRI is also an option. Additional radionuclide imaging can be considered every two to three years, especially in the case of high risk mutations (SDHA/B). Functional imaging may also be considered in other risk factors.

Whole-body CT or MRI is recommended every four to six months for staging the metastatic disease. If peptide receptor radionuclide therapy is considered as the treatment option, radionuclide imaging is recommended every 1-2 years. The age of the patient and the growth rate/grade of the tumor are also important factors to be considered.[32]

Postoperative Results

PPGL increases cardiovascular morbidity and mortality. When the causes of death of patients with undiagnosed and untreated PCC were evaluated in an autopsy, it was detected that 71% of these patients died of cardiovascular causes, such as myocardial infarction, hypertensive heart failure, stroke or hemodynamic crises during unrelated interventions.[39]

In the study of Stolk et al., patients with PCC were found to have a 14-fold increased risk of cardiovascular complications such as myocardial infarction, stroke or angina pectoris, compared to patients with essential hypertension within five years before diagnosis. This is not related to differences in blood pressure or other cardiovascular risk factors, and the most likely explanation for this was stated to be the long-term exposure to toxic effects of tumoral catecholamines.[40]

In another retrospective study, 64% of patients with benign PCC had a significant reduction in blood pressure after surgery. Only one-third of the patients were shown to be drug-free normotensive. In the follow-up of these patients, life expectancy was similar in patients who did not develop metastasis compared to the paired population but lower in patients who developed metastatic disease. Therefore, lifelong follow-up for these patients is crucial concerning the metastatic disease.[41] In the series of Beninato et al., diabetes was detected in 23% of patients with PCC, 93% of patients had an improvement in diabetes after surgery, and 78.6% reported complete recovery.[42]

Results in Cortical-Sparing Surgery

In patients with the hereditary syndromes, such as MEN syndrome and VHL syndrome, cortex-sparing surgery, may be helpful to prevent steroid dependence.[20]

In one of the recent studies, the recurrence rate in hereditary PCC is 7%, acute adrenal insufficiency is 3% in the 3-year follow-up, and 78% of patients are steroid independent.[43]

In the median 9-year follow-up of patients with VHL syndrome who underwent cortex-sparing surgery, the metastatic disease did not develop, local recurrence was seen in 11%, and 11% of patients developed PCC that required cortical-sparing surgery in the contralateral adrenal gland, and the rate of steroid-dependent patients was 11%.[44]

In patients with MEN2A who underwent cortical-sparing adrenalectomy, the contralateral adrenal recurrence rate in the 7-year follow-up was 38%.[45]

Although there is a high risk of developing PCC in contralateral adrenal in patients with MEN syndrome, the risk of recurrence in operated adrenal is low in both VHL and MEN syndromes in patients who had cortical-sparing surgery. In the multicentric wide observational study, PCC recurrence occurred in 3% of patients undergoing cortical-sparing surgery and in 2% of patients undergoing adrenalectomy, after 6-13 years of follow-up in patients with MEN syndrome. While steroid dependence developed in 86% of patients undergoing bilateral adrenalectomy, 57% of patients undergoing bilateral cortical-sparing surgery were steroid independent.[46] As a result, cortical-sparing surgery in selected patients can reduce the need for steroids in a significant proportion of patients.

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