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Cushing's Syndrome: What an Endocrine Surgeon Needs to Know

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IMPORTANCE Cushing's syndrome (CS) is pathological hypercortisolism with significant morbidity and mortality due to its structural and metabolic complications, delays in establishing the diagnosis and etiology, and complexity of its lifelong management. Advancement in surgical techniques especially laparoscopy have helped in reducing the treatment related morbidities and has become treatment of choice for majority adrenal causes of Cushing's syndrome, except carcinoma where still laparotomy is often needed. Non-surgical options such as medical therapy and/or radiotherapy are second line options when surgery is awaited or inadequate to control the disease. Diagnosis and management of such complex cases needs a team work by endocrinologist and endocrine surgeon. Patient education is an essential component for the successful handling of the case. We aimed to simplify the management with recent updates.

KEYWORDS Cushing's Syndrome, Medical Adrenalectomy, Surgical Adrenalectomy, Adrenal Lesions, Pituitary Microadenoma

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Cushing's syndrome is endogenous hypercortisolism with significant complications including infection, immunosuppression, obesity, osteoporosis, diabetes, hypertension, cardiovascular complications and significant increase in mortality [1]. The syndrome is often complicated by late diagnosis due to its variable presentations, difficulty in establishing the diagnosis due to limitations of available tests and complexities of the management. Also, even after correction of hypercortisolism, the established complications of the syndrome may take longer to resolve or need additional treatment [2].

CLINICAL PRESENTATION OF CUSHING'S SYNDROME:

Pathophysiological mechanism of most of the clinical manifestations due to high cortisol are: 1) proteolysis to release amino acids for gluconeogenesis, hence reducing proteins in the bones, muscles & subcutaneous collagen, but at the same time increasing glucose, 2) cortisol causes triglyceride breakdown in peripheral fat which lead to fat influx in blood and central body, 3) apoptosis of lymphocytes and eosinophil, demargination of neutrophils, and boosts erythropoiesis in bone marrow, 4) fluid retention by mineralocorticoid properties. Adrenal androgens produced by the adenoma or more likely by the carcinoma produces many of the androgenic features of Cushing syndrome [Table.1].

DIAGNOSIS OF CUSHING'S SYNDROME

Screening for Cushing's syndrome:

First thing is to document that the patient with suggestive clinical symptoms has hypercortisolism and that high level is pathological. High cortisol can be physiological due to any stress (physical or psychological), obesity, alcoholism, sleep disturbance, diabetes, pain, exercise and pregnancy. Many patients have Cushing syndrome due to exogenous corticosteroid replacement. Screening tests for hypercortisolism includes: 24-hour urinary free cortisol (UFC), mid night salivary cortisol or Dexamethasone suppression test (DST). Usually we need two of these tests to document pathological hypercortisolism as all of these tests have limitations [2]. UFC can be high if urine volume is high such as over drinking or can be falsely low if patient has low urine output such as those with reduced GFR (renal failure) [3]. Also, improper 24-hour collection of urine will affect UFC level. Similarly, DST can be affected by the factor affecting dexamethasone metabolism (drugs affecting cytochrome P450, pituitary disease-causing slow dexamethasone metabolism) or high cortisol binding proteins such as high estrogen level and OCPs. There are two types of assays for cortisol measurement, immunoassay such as radioimmunoassay (RIA) or structure-based assay such as mass spectrometry (MS), later is more specific for cortisol

and has lower reference range. However, immunoassays are more useful to detect milder cases. Also, the reference range varies even within the same type of assay. Hence, these tests should always be interpreted according to the reference range used [4].

Obesity: moon face, buffalo hump, central obesity with thinning of limbs.
Skin: Stria, thinning of skin, easy bruising, pigmentation of skin creases & buccal mucosa (if ACTH dependent Cushing), facial flushing, delayed wound healing, hyperandrogenic skin changes (acne, hirsutism, male pattern baldness).
Musculoskeletal: Proximal myopathy with normal CK level, osteoporosis, pathological fractures
Cardiovascular: hypertension, increased cardiovascular mortality, edema, hypercoagulability, VTE and pulmonary embolisms.
Metabolic: insulin resistance, hyperglycemia, diabetes, hyperlipidemia, electrolyte imbalance (low K, high Na, low serum Calcium, increased urinary calcium), increased urea level, increased ammonia level.
Reproductive: infertility, decreased libido, hypogonadism, hyperandrogenism, delayed puberty and short stature (in pediatric cases)
Psychiatric: depression, psychosis. insomnia, labile mood.
Infections and immunosuppression.
Hematological: Lymphopenia, eosinopenia, thrombocytosis, polycythemia, and neutrophilia.

Table 1: Common Signs & Symptoms of Cushing 's syndrome:

ACTH dependent pathological hypercortisolism:

These patients with pathological hypercortisolism have high or normal / unsuppressed ACTH despite high cortisol (1 1pm plasma ACTH > 20 pg./ml) and includes pituitary adenoma (almost 80% of adult cases of Cushing's syndrome or 85 % of pediatric cases above 7 years of age) or ectopic ACTH producing tumors (rare, 1-2% of total cases). Ectopic ACTH secreting tumor is not suppressible by high dose dexamethasone suppression test (high dose DST) whereas the pituitary adenoma is suppressible by high dose DST. High ACTH will also cause skin and mucosal pigmentation, so the patients are dark complexion with pigmentation affecting buccal mucosa and skin creases or scars. MRI of the hypo-thalamic pituitary axis may show adenoma but sometimes adenoma is too small to be seen by MRI and hence will need inferior petrosal venous sampling to demonstrate pituitary source of high ACTH. Rarely we need Corticotropin stimulation test when obtaining samples from inferior petrosal sinus [5]. Ectopic ACTH is commonly produced by small cell lung cancer and hence CT chest is often needed if we fail to demonstrate pituitary source of high ACTH [6].

ACTH independent pathological hypercortisolism:

These patients have high cortisol and suppressed (low) ACTH level (plasma ACTH < 10 pg./ml). This is either due to exogenous corticosteroid replacement or adrenal source of high cortisol. The term Cushing's Syndrome is commonly used when its adrenal gland causing hypercortisolism and is not suppressible by high dose DST. Low ACTH causes less melanin in skin and patients are often pale or white. CT Adrenal glands or MRI are often diagnostic, however rarely adrenal venous sampling may be needed to differentiate unilateral vs bilateral lesions as decision is important for unilateral or bilateral adrenalectomy [6]. Also, it's important to document that the lesion found on the CT /MRI adrenal is producing pathological amount of cortisol and is not just an incidentaloma as adults over 40 years of age have incidental findings of adrenal tumors (10%) or micronodular hyperplasia (36%) on autopsy [7].

Androgen production such as dehydroepiandrostenedione (DHEA) is predominantly seen in cases of adrenal carcinoma and is less common in benign lesions, hence androgenic issues such as hirsutism and virilization are sinister signs in patients having Cushing's syndrome. Cushing's syndrome is due to adrenal causes in 20% adults and 15% children above 7 years of age and almost 50% in children younger than 7 years of age. Most common adrenal lesions are isolated sporadic adenoma, whereas carcinoma and congenital adrenal hyperplasia (CAH) are rare. Adrenal adenoma is mostly unilateral and often due to abnormal cAMP signaling pathway, whereas hyperplasia is mostly bilateral and genetic. Hyperplasia has many sub varieties such as micronodular, pigmented nodular, macronodular varieties, ACTH independent macronodular or massive macronodular hyperplasia. Macronodular hyperplasia are less likely to be genetic and are rare in pediatric patients [8]. Adrenal carcinoma is an aberrant defect of growth factors and germ line or somatic mutation in tumor suppressor gene, P53.. Using the most commonly accepted radiological criteria of size more 5cm, adrenal carcinoma can be found in 7% of the adrenal lesions [9].

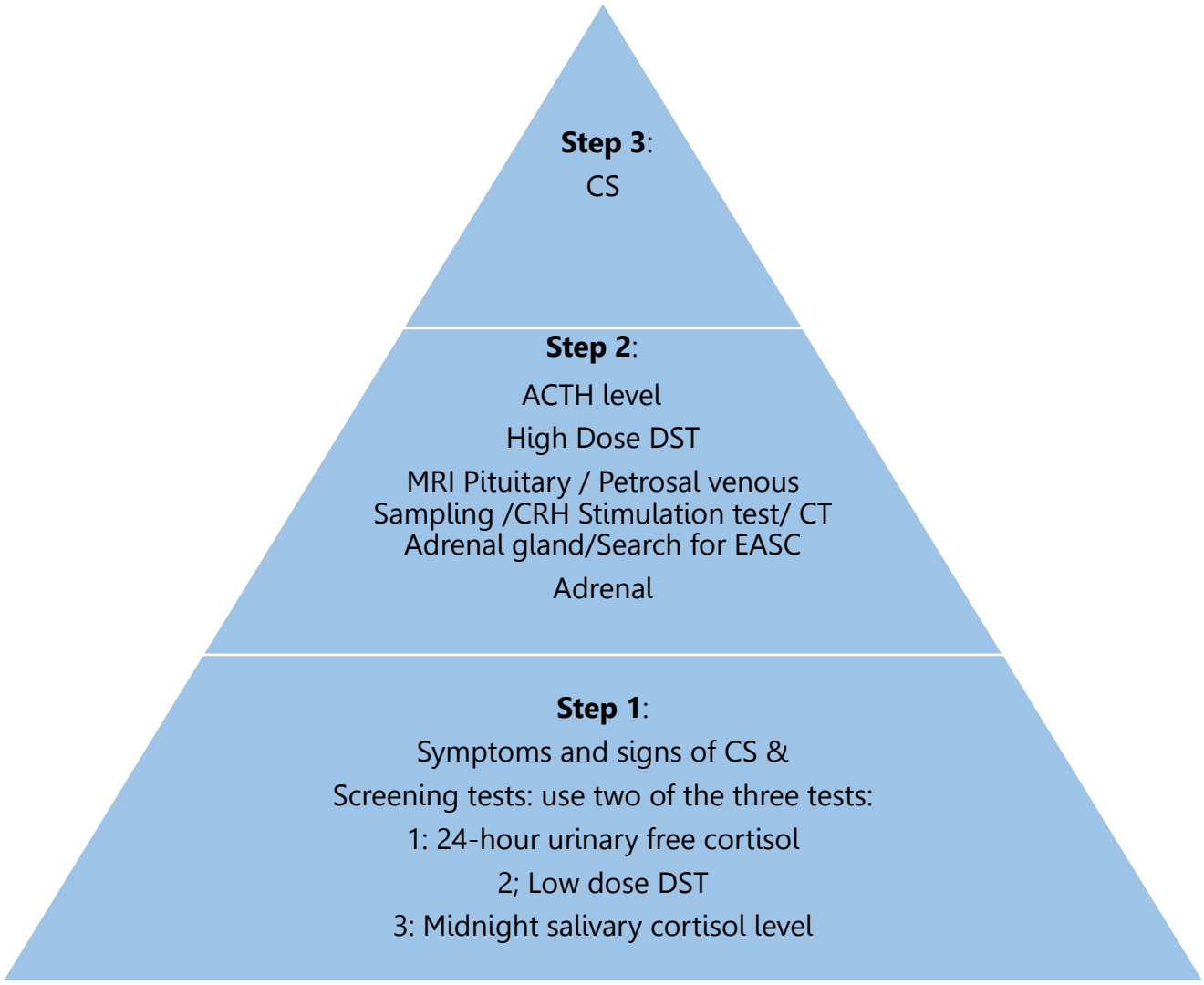

Fig.1: Stepwise approach to diagnose Cushing's Syndrome: CS: Cushing's Syndrome, DST: Dexamethasone Suppression Test, ACTH: Adrenocotropic Hormone, CRH: Corticotropin Releasing Hormone, EASC: Ectopic ACTH Secreting Cancers.

MANAGEMENT OF CUSHING'S SYNDROME

Surgical treatment for Cushing's syndrome is first choice:

Recommended treatment for Cushing's syndrome is normalizing cortisol level and/or its actions in all patients except those where there are only mild biochemical abnormalities due to pituitary diseases without any clinical manifestations. The gold standard treatment for such patients is surgical resection of the underlying lesions unless the patient is unfit for surgery or surgery is not possible for other reasons, failed resection or recurrence of the disease [10].

Pre-operative adjuvant management includes optimizing treatment of Cushing's related complications such as hypertension, diabetes, infections, hyperlipidemia, osteoporosis and electrolyte abnormalities. Also, treatment should be provided by a multi-disciplinary team including an experienced endocrine physician and an endocrine surgeon. Patients and their families should be educated about surgery and possible outcomes and also about other treatment options. In addition, age appropriate vaccinations should be provided such as influenza, herpes zoster and pneumococcal vaccine as these patients are often immunocompromised. Venous thromboembolic prophylaxis should be used perioperatively to reduce such complications. Patients with severe complications of hypercortisolism such as psychosis, pulmonary embolism, infections or cardiovascular complications should be treated urgently as soon as they are stable for surgery.

Preoperatively normalization of cortisol is important by using the drug therapy [9].

Surgical resection of adrenal adenoma (unilateral) or bilateral macronodular disease or surgically resectable adrenal tumor by an experienced adrenal surgeon should be first option for all adrenal lesions. If adrenal cancer is not resectable, then medical treatment is an option. Adenomas are usually resected laparoscopically but carcinoma may need laparotomy. Laparoscopic surgery has reduced morbidity especially for those who have complications of Cushing's syndrome such as diabetes or hypertension. Surgery is often not curative for carcinoma due to metastatic disease or locally advance disease and needs medical treatment and radiotherapy [11]. For adrenal carcinoma patients, surgery is either curative (for limited disease) or debulking for locally advance or metastatic disease. Also, when possible, resection of metastasis helps improve the survival. Mitotane is used as adjuvant therapy or monotherapy in inoperable cases [12].

Ectopic ACTH secreting surgically resectable cancers should be removed along with the regional lymph nodes when possible. Occult or metastatic ACTH secreting tumor or medically resistant ectopic ACTH related Cushing's patients may benefit from bilateral adrenalectomy. Patients who undergo bilateral adrenalectomy should be monitored regularly with MRI pituitary-hypothalamic axis and ACTH for Nelson Syndrome (ACTH producing pituitary tumor). Similarly, resection of pituitary adenoma by trans-sphenoidal approach by an experienced pituitary surgeon is recommended as first line options. However, if the first resection was not successful, then either repeat resection or radiation therapy or medical treatment is an option [7]. Recurrence rates are higher in patients with pituitary macroadenoma and remission rates are higher in patients who have microadenoma of the pituitary. Recurrence depends on size and aggressiveness of the tumor, experience of the surgeon and type of the hormonal assay used to assess the recurrence [10,13]. Remission after pituitary resection ranges from 70-85% but can be as high as above 90% in centers where the procedures are done more often [14]. Those who fail the first TSS pituitary adenoma resection, repeat surgery is often preferred if feasible before recommending other options including radiotherapy, medical treatment &/or bilateral adrenalectomy [15].

Immediate life-threatening complication of surgery is acute Addison's disease which needs to be identified and treated with IV cortisol replacement unless oral replacement is possible. Unilateral adrenalectomy done for cases having adrenal adenoma may eventually recover from Addison's disease when contralateral adrenal gland gradually recovers from atrophic effect and it may take a few months to a year. Bilateral adrenalectomy cases will require lifelong cortisol replacement. Generally, patients with unilateral adrenalectomy needs glucocorticoid replacement for 6-12 months and those with bilateral adrenalectomies need lifelong replacement of both glucocorticoid and mineralocorticoid. Post operatively, monitoring for electrolytes especially Na, K, Calcium and blood glucose levels are important. For pituitary resection, monitoring for prolactin, thyroid hormones and sex hormone is also important and should be replaced if low. Post-operative MRI should be done within 1-3 months to assess the remaining pituitary gland. It's important to monitor for cortisol values as patients may still be having hypercortisolism which may need further medical treatment or patients may be hypocortisolism which will need cortisol replacement. Patient education about Addison's disease and stress dose adjustment for cortisol is prudent. Those who had pituitary surgery should be assessed for remaining adrenal reserve by ACTH-stimulation test and if its normal, they may not need cortisol replacement [16].

Medical Treatment for Cushing's Syndrome:

Medical treatment is often a second line choice when surgical cure is not possible such as patients who are unfit for surgery, who have failed / inadequate surgical resection or recurrence of the tumors, occult or metastatic ectopic ACTH producing tumor, or in adjuvant adrenal carcinoma patients where complete resection is often not possible. Pituitary causes of Cushing's requiring medical treatment are managed by using somatostatin or dopamine analogues to reduce ACTH production with or without radiotherapy.

Corticosteroid synthesis inhibition by adrenal enzymes blocking drugs such as metyrapone (11 Hydroxylase blocker) or ketoconazole (17 Hydroxylase blocker) or aminoglutethimide or mitotane (11 Hydroxylase inhibitor) are options. As a monotherapy they are effective controlling hypercortisolism in 65% cases [8]. These drugs can also be used in combination for severe cases. In addition, corticosteroid receptor blockers such as mifepristone, RU 486 has been FDA approved treatment for hyperglycemia in Cushing's syndrome patients [13]. Chemotherapy for non-resectable adrenal cancer or ectopic ACTH producing tumor is an additional option which may also help [2]. Mitotane is adrenocytolytic chemotherapeutic agent which helps control the disease in half to two third patients, and control disease progression in a third of adrenal carcinoma cases [17].

Follow up Monitoring:

Lifelong monitoring for recurrence of hypercortisolism or underlying malignancy or Addison's disease should be done by hormone testing and imaging. Patients and families should be educated about cure, recurrence and hormonal deficiency / excess. Comorbidities such as diabetes, blood pressure, osteoporosis etc. should be treated adequately [9]. Quality of life is closer to normal after adequate treatment of Cushing's syndrome with clinical and biochemical remission. 75-90% of patients improve with regards to complications such as diabetes, hypertension, psychiatric issues, proximal myopathy and other symptoms. However

chronic fatigue and psychiatric symptoms are often persistent [18].

DISCUSSION:

Cushing's syndrome has significant morbidity and mortality due to its complications, late detection due to variable presentations, complex diagnostic approach and need for multi-modality treatment with lifelong follow up issues. High degree of clinical suspicion for Cushing's syndrome, proper clinical assessment, careful selection and interpretation of the biochemical tests followed by appropriate radiological imaging is essential to minimize these delays and complications. Rarely interventional testing is also needed to confirm the diagnosis. Confirmation of the diagnosis and identification of the underlying cause is imperative for its treatment as each cause has different treatment guidelines.

Once confirmed, patient needs to be assessed and stabilized for the surgical removal of the underlying lesion as it is first line treatment option in suitable candidates. Pre-operative treatment of comorbidities and complications, normalization of cortisol with medical therapy and patient education are essential. An experienced endocrine surgical team can have higher success rate. Immediate and long-term post op complications such as Addison's disease, recurrence of the underlying lesion, management of the ongoing complications of Cushing such as diabetes and hypertension, inadequacy/failure of surgical option make the post-operative course complex and laborious. Medical therapy is a second line option mainly for those where surgical therapy is not an option or inadequate. Lifelong follow up is essential.

CONCLUSIONS

Diagnosis and management of Cushing's syndrome is complex and needs a vigilant team approach including experienced endocrinologist and endocrine surgical team with efficient diagnostic approach, perioperative and postoperative care, and patient involvement is of utmost important. Surgical resection is first line treatment whereas medical / radiotherapy ae used when surgery is contraindicated or is inadequate.

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REFERENCES

1. Clayton RN, Jones PW, Reulen RC, et al. Mortality in patients with Cushing's disease more than 10 years after remission: A multicentre, multinational, retrospective cohort study. *The Lancet Diabetes and Endocrinology*. 2016;4(7):569-576. doi:10.1016/S2213-8587(16)30005-5
2. Nieman LK, Biller BMK, Findling JW, et al. The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(5):1526-1540. doi:10.1210/jc.2008-0125
3. Chan KC, Lit LC, Tai MH, et.al: Diminished UFC in... - Google Scholar. Accessed September 10, 2020. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Chan+KC%2C+Lit+LC%2C+Tai+MH%2C+et.al%3A+Diminished+UFC+in+moderate+to+severe+renal+disease.+Clin+Chem.2004+Apr%3B+50%284%29%3A757-759.&btnG=
4. Kidambi S, Raff H, Findling JW. Limitations of nocturnal salivary cortisol and urine free cortisol in the diagnosis of mild Cushing's syndrome. doi:10.1530/EJE-07-0424
5. Lacroix A, Feelders RA, Stratakis CA, et al. Cushing's syndrome. *The Lancet*. 2015;386(9996):913-927. doi:10.1016/S0140-6736(14)61375-1
6. Nieman LK. Approach to the Patient with an Adrenal Incidentaloma. *The Journal of Clinical Endocrinology & Metabolism*. 2010;95(9):4106-4113. doi:10.1210/jc.2010-0457
7. Saeger W, Reinhard K, Reinhard C. Hyperplastic and tumorous lesions of the adrenals in an unselected autopsy series. *Endocrine Pathology*. 1998;9(3):235-239. doi:10.1007/BF02739963
8. Stratakis CA. Cushing Syndrome Caused by Adrenocortical Tumors and Hyperplasias (Corticotropin- Independent Cushing Syndrome). In: *Disorders of the Human Adrenal Cortex*. Vol 13. KARGER; 2008:117-132. doi:10.1159/000134829
9. Grumbach MM, Biller BMK, Braunstein GD, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). In: *Annals of Internal Medicine*. Vol 138. American College of Physicians; 2003:424-429. doi:10.7326/0003-4819-138-5-200303040-00013
10. Biller BMK, Grossman AB, Stewart PM, et al. Treatment of Adrenocorticotropin-Dependent Cushing's Syndrome: A Consensus Statement. *The Journal of Clinical Endocrinology & Metabolism*. 2008;93(7):2454-2462. doi:10.1210/jc.2007-2734
11. Gallagher SF, Wahi M, Haines KL, et al. Trends in adrenalectomy rates, indications, and physician volume: A statewide analysis of 1816 adrenalectomies. *Surgery*. 2007;142(6):1011-1021. doi:10.1016/j.surg.2007.09.024.

12. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant Mitotane Treatment for Adrenocortical Carcinoma. *New England Journal of Medicine*. 2007;356(23):2372-2380. doi:10.1056/NEJMoa063360
13. Fleseriu M, Biller BMK, Findling JW, et al. Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome. *The Journal of Clinical Endocrinology & Metabolism*. 2012;97(6):2039-2049. doi:10.1210/jc.2011-3350
14. Tanagho E, McAninch J. Smith s general urology. Published online 2004.
15. Locatelli M, Vance ML, Laws ER. CLINICAL REVIEW: The Strategy of Immediate Reoperation for Transsphenoidal Surgery for Cushing's Disease. *The Journal of Clinical Endocrinology & Metabolism*. 2005;90(9):5478-5482. doi:10.1210/jc.2004-2436
16. .Poiană C, Chirită C, Carsote M, et al. Adrenal and pituitary incidentalomas in a case of cushing's syndrome. *Chirurgia (Romania)*. 2013;108(6):886-891. Accessed September 10, 2020. https://europepmc.org/article/med/24331331
17. Schteingart DE. Adjuvant mitotane therapy of adrenal cancer - Use and controversy. *New England Journal of Medicine*. 2007;356(23):2415-2418. doi:10.1056/NEJMe078087
18. Alberda WJ, van Eijck CHJ, Feelders RA, et al. Endoscopic bilateral adrenalectomy in patients with ectopic Cushing's syndrome. *Surgical Endoscopy*. 2012;26(4):1140-1145. doi:10.1007/s00464-011-2020-7