Chapter

Surgical Approach in Pheochromocytoma

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Abstract

Pheochromocytomas are tumors composed of chromaffin cells that can produce, secrete and metabolise catecholamines. The surgical excision procedure of these tumors may present the risk of significant variations in blood pressure, as well as the chance of cardiovascular complications in the perioperative period. During surgery, patients may be at risk for cardiovascular events such as major variations in blood pressure, pulmonary edema, stroke, myocardial infraction and a long period of intubation. The surgical approach to pheochromocytomas must always be preceded by accurate imaging evaluation, endocrine screening and identification of associated genetic mutations. In addition, the surgical technique of choice consists in using minimally invasive surgical methods, with a transabdominal or retroperitoneal approach.

Keywords: pheochromocytomas, adrenalectomy, laparoscopic surgery, epinephrine, transabdominal approach

1. Introduction

Pheochromocytomas are rare tumors composed of chromaffin tissue that can secrete catecholamines in excess (epinephrine, norepinephrine, and dopamine) and their metabolites (metanephrine, normetanephrine, and 3-methoxytyramine). Pheochromocytomas can develop from the chromaffin cells inside the adrenal gland. Moreover, about 80–85% of these neuroendocrine tumors are localized inside the adrenal gland as pheochromocytomas and 15–20% can be extra-adrenal tumors that are named paragangliomas [1–4].

The USA has a pheochromocytoma's annual incidence of 500–1,600 cases per year with equality between genders and a peak incidence in the forth decade of life. The association with hypertension is well known; in the case of patients with hypertension, it is encountered with an incidence of 0.1–0.6% [5]. The classical mode of presentation of a pheochromocytomas case consists of headaches, diaphoresis, flushing and paroxistic hypertension [6].

The latest studies indicate a genetic cause for pheochromocytomas in about 40% of cases, from specific genetic syndromes or de novo mutation [7]. After the biochemical phenotype established, the genetic screening completed, and the imaging investigations performed, the patient has two surgery approaches: through minimally invasive surgical methods or through classical open surgery technique. The surgical method and grade of adrenalectomy can be decided depending on different factors: germline genetic test results, tumor size, body mass index, surgeon experience, and risk of malignancy [1].

The classic surgical methods approaching the adrenal pathology can be transabdominal, transthoracic and retroperitoneal. These include large incisions and extensive plans dissections to offer a reasonable control of vascular pedicles' maneuvers treatment. Usually, this is the critical point for surgical resection due to the difficulty of reaching the vascular branches and the rule of vein first, artery second (preventing releasing the catecholamine into the bloodstream). Postoperative morbidity can be influenced by the type of surgical approach to the adrenal gland. The development of minimally invasive surgery (MIS) techniques has ensured great changes for most surgical procedures. Adrenalectomy is an excellent example of this. This type of pathology fully benefits from the advantages of laparoscopy.

The first laparoscopic adrenalectomy was performed in 1991 by Dr. Lamar Snow, and in 1992 Dr. Joseph Petelin published the first description of the operation. The first laparoscopic adrenalectomy was performed on January 17th, 1992, by a Japanese surgical team led by Go H at Niigata University School of Medicine, Japan [16]. A significant moment in the evolution of laparoscopic adrenal surgery is the publication of the lateral transperitoneal procedure by Michel Gagner in 1992. This later became the most widely used laparoscopic adrenalectomy procedure. Similar to open procedures, the video-assisted approach recognizes three variants, depending on the patient's position and the access: first: anterior approach (transperitoneal), second: lateral approach (transperitoneal or retroperitoneal), and the third one is the posterior approach (retroperitoneal). Soon after it, the laparoscopic adrenalectomy became the second gold standard therapy (after cholecystectomy) in the field of surgery.

The accuracy of new imaging techniques for locating preoperative tumors is necessary because surgical exploration in the blind manner is unlikely to identify any unlocated tumor.

2. Preoperative management

The surgical approach of pheochromocytomas can include significant variations in blood pressure values and cardiovascular events such as arrhythmias and tachycardia can appear in the perioperative patient period.

Intraoperatively, patients undergoing surgical resection can have arrhythmias, sustained hypertension or hypotension and also postoperative myocardial infarction, stroke, pulmonary edema, and prolonged intubation.

Heart failure risk can be influenced by high levels of metanephrines and normetanephrines associated with large tumor size and a longer duration of surgery due to technically difficult surgical excision [8].

Preoperative alpha-blockers ensure a significant decrease in the risk of major hypertensive crises intraoperatively. Patients with pheochromocytoma are systematically examined preoperatively by the cardiologist and anesthesiologist, and the latter will be provided at the time of surgery with all necessary material and drug support (invasive monitoring of BP, central venous catheter, sufficient doses of sodium nitroprusside, etc.) [9].

However, experienced medical specialists (surgeons and endocrinologists) agree that preoperative optimisation must include a seated blood preasure of 120–130/80 mmHg, a standing systolic blood pressure over 90 mmHg, a seated heart rate between 60–70 bpm and a heart rate 70–80 bpm in standing position. In addition, is important to encourage patients to supplement their water intake along with a high sodium diet before surgery [8, 10].

Regarding specific drugs utilized in the preoperative period, Phenoxybenzamine is a non-selective alpha receptor blocker that has been associated with better perioperative hemodynamics parameters, compared with other medication [9].

However, due to the slower onset than selective alpha-blockers such as doxazosin or prazosin it is preferably to be used for 10–14 days instead of 4–7 days. In addition, alpha adrenergic blockers side effects can consists of orthostatic hypotension with secondary tachycardia, palpitation, nasal congestion and headache. In terms of pharmacological actions, alpha adrenergic blockers control volume expansion, minimize the frequency of hypertensive peaks during surgery and control blood pressure values [11, 12].

Furthermore, calcium channel blockers represents a proper variant as a primary drug choice or as an alternative medication. In addition, they can counterbalance coronary vasospasm caused by catecholamines and may induce orthostatic hypotension less frequently than alpha blockers.

Methyrosine is a pharmacological blocking agent of the enzyme tyrosine hydroxylase that inhibits the conversion of tyrosine to dihydroxyphenylalanine, thus blocking the catecholamine synthesis pathway.

This drug can be used in patients who do not tolerate treatment with alpha blockers or is reserved for cases of hypertension refractory to the use of alpha-blockers, beta-blockers and calcium channel blockers [11].

Possible unpleasant side effects of this medication include drowsiness, neurological disorders, and intestinal transit disorders.

In addition, the main medical management approaches are: the expansion of intravascular volume with a saline solution together with the control of hypertension or other cardiovascular events, the correction of metabolic and electrolyte imbalance and the treatment of possible anemia.

Beta-adrenergic receptor blockade with propranolol is used in the treatment of catecholamine induced tachycardia after at least three to four days of alpha blockade administration; beta blockers usage is contraindicated until the alpha-adrenergic receptor blockade is done, in order to prevent severe hypertensive crisis caused by unopposed alpha vasoconstriction [12].

Appropriate and smooth venous access and arterial catheters for continuous blood pressure monitoring must be placed before surgery. Communication between the anesthesiologist and surgeon is essential to ensure safe results. Ideally, the anesthesia team should be prepared to use intravenous vasoactive drugs to manage hemodynamic variations and has to remain vigilant throughout the entire medical-surgical procedure [13].

More than that, the timing of surgical dissection should be coordinated with the anesthesiologist's maneuvers even from the time of pneumoperitoneum inflation – new recordings of blood pressure (BP) of the patient should be registered every minute, according to the gas amount already introduced (until the value of 12 mmHg); if the BP is too high, a lower intraperitoneal pressure should be taken into consideration during the all-time of the procedure. Another example of surgeon-anesthesiologist cooperation can be the proper time of dissection around the gland – touching the gland (with catecholamine release and rapid increase of BP). The surgeon requires rapid measures from the anesthesiologist to control the cardiac output and possible arrhythmias [14–16].

3. Surgical intervention approach

Surgery is the curative therapy for either benign or malignant pheochromocytoma. Morbidity in adrenalectomy operations is about 40% and can be associated

with cardiac events such as arrhythmia, myocardial dysfunction, pulmonary embolism and sepsis. Mortality for adrenalectomy has improved in the last decade, with an under 2% rate of death.

Firstly, the main critical point in adrenalectomy in pheochromocytoma is the minimal manipulation of the tumor to avoid seeding the tumor in adjacent tissues and in order to prevent a hypertensive crisis during the operation (it is said that adrenalectomy should be performed by dissecting away the body from the gland, not the gland from the body). Secondly, another crucial step during the surgical procedure is the control of vascular supply together with the complete tumor resection. All of these can be provided by adequate surgical exposure in order to prevent other organs injuries.

Minimally invasive techniques can be done laparoscopically or robotically. The aim of minimally invasive procedures and open surgical approach is the minimal manipulation of the tumor, in order to prevent catecholamine release as mentioned above; if this is not respected, it can result in hemodynamic instability and tumor rupture.

Also, to diminish the risk of releasing large amounts of hormones, it is indicated to early ligature the adrenal vein. This step can be performed through the transabdominal or posterior surgical approaches.

Furthermore, the surgical approach is dependent on surgeon choise, experience and familiarity with the specific techniques. However, some factors may influence the decision of surgical approach: body mass index, tumor size and location, and patient's personal pathological history of abdominal or retroperitoneal surgical procedures [14].

Our paper will focus mainly on the minimally invasive laparoscopic approach, being the surgical procedure of choice for adrenal tumors, due to its advantages of surgical technique.

The laparoscopic approach includes normal anatomy and easy conversion to open surgery if necessary for exceptional cases [15].

Although the retroperitoneal approach can directly access the adrenal gland and would require less effort to dissect and mobilize nearby visceral organs, this technique is not easy for general surgeons due to lack of familiarity with it. In addition, the contraindications for the retroperitoneal surgical approach include tumors bigger than seven to eight cm due to the narrow working space and an increased body mass index with increased retroperitoneal fat. Simultaneously, a tumor lying around the inferior vena cava (on the right side) or close to the aorta (on the left side) can lead to a complex surgical resection by retroperitoneal access [13].

Retrospective studies from literature have shown that robotic and laparoscopic resection of pheochromocytomas are equivalent in terms of operative time, blood loss volumes, intraoperative hemodynamic events, rates of morbidity and mortality, and rates of conversion from minimally invasive approach to open surgery technique [9].

Furthermore, the main advantages of robotic adrenalectomy include: the three dimensional acces, improved wrist mobilization for the surgeon, and a stable camera port. Disadvantages of robotic adrenal surgery include increased cost, insufficient learning curve and lack of tactile feedback.

When invasive malignant pheochromocytoma is suspected or concerned clinically, open approach is the first choice. Open treatment may benefit from a greater risk of tumor rupture, which may lead to pheochromocytoma disease. For patients with confirmed SDHB mutations, that are associated with a higher metastatic disease rate, the open approach is prefered [16].

For patients with pheochromocytoma associated with different syndromes, minimally invasive or open surgical methods can also be used for cortical sparing

(partial) adrenalectomies. Patients with multiple endocrine tumor 2 (MEN2) or von Hippel–Lindau disease (VHL) syndrome can benefit from cortical-preserving adrenalectomy in order to preserve and to maximize the adrenal function and to avoid chronic glucocorticoids replacement. Furthermore, cortical sparing technique can reduce the risk of Addisonian disease [17].

4. Laparoscopic technique

4.1 Elements of surgical technique and tactics

The operating table must benefit from adequate mobility in order to allow an adequate angulation in order to optimally open the anatomical space from the costal rim to the iliac crest. The operating surgeon and the cameraman are positioned in front of the patient and the assistant on the opposite side. The patient can be placed on the operating table in a lateral decubitus with a 90-degree angle position to ensure the full retraction of the spleen and a partial retraction of the liver by the gravity force.

At the time of pneumoperitoneum installation, the patient is already lying on his side. The Veress needle will be inserted through the abdominal flank, being warned of the risk of visceral (liver or colon on the right side) or vascular (epigastric pedicle branches) injuries. Classic, there are three subcostal ports that can be positioned on the left and one epigastric port that is localized at the inferior margin of the liver. It is not unusual for the first trocar (corresponding to the left mid-clavicular line) to be inserted just a little bit slower than the other three subcostal trocars in order to offer a comprehensive view of the operative field and to identify the entire trajectory of the left colonic flexure (to facilitate the dissection of the colonic ligament for a lower positioning of the colon and to offer a better view over the left adrenal lodge).

For the left adrenalectomy, the spleen can be mobilized till the gastric fundus appears in the visual field, this can allow the spleen to retract more medially. This maneuvers can develop the plane between the spleen and the pancreas' tail, up to the left adrenal gland. The first maneuver is the incision made at the later splenic peritoneum. Further dissection is performed in a relatively avascular plane that is located close to the retropancreatic and anterior to the adrenal and renal capsule. Through this conjunctive structure's transparency, the adrenal tissue specific aspect is easily distinguished as having a specific yellowish color.

Sometimes, it is mandatory to cut the conjunctive tissue between the left colonic flexure (at its highest point) to the abdominal wall and to re-positioning the colon down below the level of the inferior pole of the spleen. After that, a broad view of this area is noticed. More than that, an easy discovery of the kidney superior left pole is possible, and this should be the start to identify (especially on obese patients) the groove between the left kidney and the pancreas – the normal localization of the left adrenal gland. For a pheochromocytoma dissection, the surgical gestures should be delicate, precise, and firm – a proper instrument of dissection should be used (sealing-cutting device, ultrasound device – electrocautery hook is to be avoided by the beginners and is a time-consuming device for an experienced surgeon).

The essential vascular anatomical elements that will be treated in left adrenalectomy are the central vascular pedicle and the upper vascular pedicle. The left central vein (LCV) goes into the left renal vein, most commonly into the common trunk with the lower-left diaphragmatic vein (LLDV), from which it should be disected before injuring or clipping. The sectioning of this common

trunk interpreted as LCV will result in the cranial interception of LLDV; a vascular element misinterpreted as an accessory left central vein. The LCV must be double-clipped to the renal vein, for security reasons, and then sectioned with sharp surgical instrument – the latest surgical devices (like a sealing-cutting instrument with a computerized chip for measuring the impedance and secure the ligation) can be safely used with no clips (depending on surgeon's experience). The left middle adrenal artery comes from the aorta and will be highlighted later. It can be treated by titanium clip or bipolar electrosurgery. By following the upper margin of the adrenal gland, the upper adrenal pedicle branches will be highlighted and treated using an electrocoagulation procedure.

The complete disection of the entire adrenal gland is done by posterior dissection, in a very loose anatomical space, after witch is then separated from the upper renal pole and the muscular abdominal wall (up to the left quadratus lumborum muscle). The final steps of left laparoscopic adrenalectomy are made by the hemostasis, surgery gland extraction and local drainage.

Thoroughly attention should be given to the dissection of the superior part of the adrenal gland near the pancreas' inferior edge because important vessels are lying over there – including end-parts of the splenic vein and the veins' and arteries' network around the pancreatic tail. Finally, pancreatic parenchyma should be carefully avoided to be damaged during dissection to skip a postoperative pancreatic leakage.

For laparoscopic right adrenalectomy, four working trocars (3 of 10 mm and one of 5 mm) are required, arranged on a line parallel to the costal margin, developed between the sub-xiphoid region and the right anatomical flank (below the tip of the right tenth rib). Near the right kidney's upper pole covered by the right hepatic lobe can be found the the right adrenal gland, lying on the diaphragm, in close contact with the IVC. The right triangular ligament is disected, and the right liver lobe is then retracted with the instrument through the epigastric trocar. Displacemant of the right hepatic lobe depends a lot on obtaining a good and comfortable access in the adrenal gland's dissection space. The lifting of the hepatic love is performed by an atraumatic instument, of "snake" type or with atraumatic blades, inserted in the sub-xiphoid trocar. In the particular situation of a highly developed right hepatic lobe, additional maneuvers or additional tools are required to obtain a suitable elevation. A slightly reverse-Trendelenburg position also obtains a better position of the patient on the operating table. These exposure gestures are critical to prevent the application of excessive forces intended to widen the operating field. These traumatic maneuvers can lead to damage to the Glisson capsule and tears of the liver parenchyma. Consecutive bleeding significantly alters the dissection conditions, reducing the surgeon's ability to distinguish the specific appearance of the gland. The crimson-yellow specific gland color is easy to recognise under proper conditions of dissection. The anterior plane of the gland can be exposed by performing a blunt dissection or with the electrocautery. This can be performed in an extracapsular plane, anatomical space occupied by many loose and avascular lax fibrous tissue. The disection plane found between IVC and the right adrenal gland can be exposed. This will be the starting point of the surgical excision of a pheochromocytoma – the surgeon should prioritize the "attack" of the central vein expecially for the right adrenal gland. The arterial sources that approach the gland are anastomosing each other in the next presented way: first the central artery that arises from the aorta, second, the superior arterial pedicle that arises from the right inferior diaphragmatic artery and not the last, the inferior arterial pedicle from the right renal artery. Venous blood can be collected by the homonymous satellite veins, represented by the central vein that is collected directly into the IVC that should be well identified before any maneuver on the adrenal vessels. Any bloody source can

be solved by IVC partial clamping only if it is exposed and have a good control. It is mandatory for a safe treatment of the vascular pedicles and for the achievement of complete glandular removal to have a complete exposure of the entire medial and superior margin of the gland [4, 5].

The central vein can be clipped twice at the inferior vena cava margin and with a single clip to the margin of the gland. In approximately 20% of patients, there can be found a central accessory vein, sometimes this is the cause of difficult to control hemorrhage. Due to the lateral decubitus position, after dissecting the central vein, the IVC is mobilized to the medial, and the retro-IVC extension of the gland can be much easily dissected. The central artery can be dissected and sectioned by the branches with electrocautery. Modern means of electrosurgery (sealing-cutting devices or ultrasonic scalpel) offers additional operating comfort and efficiency, but the need to continuously follow the correct anatomical plans must be emphasized.

A complete mobilization of the gland is achieved by posterior dissection, to or from the side, in a loose fibrous anatomical space which is interposed between the renal upper pole and diaphragm until the aspect of the right quadratus lumborum muscle appears in the operating field. It is mandatory not to touch the adrenal tissue, especially the pheochromocytoma tumor, to avoid spillage the tumor cells in the peritoneal cavity. The piece will be placed in a bag and is extracted by widening one of the access wall brackets (usually the one on the right anterior axillary line). After a thorough control of the hemostasis, a drainage tube beneath the right hepatic lobe is placed for 24–48 hours [4].

For situations in which bilateral excision is required in the same operating session, the patient's position will be changed after removing one of the glands, the entire device is reset to perform the contralateral adrenalectomy.

Although this direction is time-consuming, involves the anesthetic-surgical team's synchronized effort, determines an increased consumption of materials by reorganizing the operating field, the benefit offered by the advantages of the transperitoneal lateral approach is entirely found in operating comfort [6, 7].

For cortical sparing/preservation technique, once the supraadrenal glands are exposed by the mobilization and dissection of the triangular hepatic ligament on the right side and the spleen on the left side, a mass can be seen in the retroperitoneum. Using the best imaging by ultrasound technique to identify the necessary anatomy, surgeons should try to preserve the adrenal veins to allow proper function of the adrenal remnants. It is recomanded to perform an ultrasound examination to assess relationship between the tumor and the adrenal veins and determin whether there are more nodules in patients with genetic predisposition. If there is only one nodule, a harmonic scalpel can be used to remove the nodule. Since the blood vessels of the adrenal gland are highly vigorous, harmonic activation is performed while the jaws are opened, and the adrenal tissue is slowly compressed to provide excellent hemostasis [4].

Do not use any device to grab the nodule or adrenal gland in any position. Grasping the nodule or the adrenal glands with any device may cause a rupture that lead to pheochromocytomatosis. Grasping a portion of adipose tissue located near the adrenal glands or attached to it, or using gentle retraction will give enucleation appropriate exposure. After the nodule is removed, the remaining adrenal glands should be checked for hemostasis. For multiple nodules suitable for removal, the surgeon should consider proceed as before. However, if there are multiple nodules and the restant gland is less than 30% of the total gland, the surgeon should consider total adrenalectomy. The remaining glands may lose function, and the patient may benefit from total adrenalectomy to avoid the need for reoperation of relapse. After the tumor is removed, put the specimen in the bag and take it out [4–7].

Laparoscopic adrenalectomy has been found to reduce the need for hospitalization, blood transfusion, postoperative analgesia and recovery. Laparoscopic adrenalectomy is more difficult to perform on the right side because of the exposure problems, the proximity of the gland to the IVC and the short right adrenal vein. Although there are more and more reports of laparoscopic resection of pheochromocytoma, but it should not be considered for malignant pheochromocytomas or tumors greater than 8 cm [2].

4.2 Posterior retroperitoneal laparoscopic approach

Place the patient in a jack-knife position and place a 1.5–2 cm transverse incision under the terlfth rib to access the retroperitoneum space. Digital palpation can be used to develop and disecting spaces. Guided by the surgeon's index finger, place another trocar along the lateral border of the paraspinous muscle. Similarly, place a side needle under the eleventh rib. Insert another 12 mm blunt balloon trocar into the first incision. When pneumoperitoneum is established, carbon dioxide needs to be injected and kept at 20–24 mmHg. The working space of superior border of the kidney is developed by dissecting the retroperitoneal areolar tissue and Gerota's fascia. After identifying the adrenal veins, dissect the upper adrenal glands laterally and inferiorly, and finally dissect the upper and mid-medial glands. Identify, dissect and remove the adrenal veins between the clamps. The adrenal gland is firstly dissected laterally and inferiorly and secondly the superior and medial adesions are dissected with the evidentiation of the adrenal vein. The adrenal vein is identified, dissected, and resected between clips. The next step is the dissection of the upper attachment, and then put the specimen into the Endo bag device and removed it from the abdomen [2].

4.3 Open techniques

Multiple incisions can be used to exposure the anatomy, including subcostal, midline, and the Makuuchi incision. The aim is to use subcostal incision two to three cm below the costal margin. This incision provides excellent liver and adrenal bed exposure. If a lymph node dissection is planned, the subcostal incision will provide the space betwen aorta and inferior vena cava and between the lymph nodes around the hilum. As with the laparoscopic technique, the triangular ligament on the right is also cut, and the spleen on the left is moved into the retroperitoneal cavity. Very important anatomical landmarks such as inferior vena cava, must be marked on the right, and the tail of the pancreas and the loose plane between the tail and the left adrenal gland on the left must be visualized. For boths sides, the adrenal veins must be identified and cut. Split all remaining attachments and remove the gland. The open transabdominal or thoracoabdominal approaches give the best exposure for resecting extensive tumors, for bilateral adrenalectomy or for metastatic disease [3].

5. Perioperative/postoperative management

Following surgical approach of pheochromocytoma, 80% of patients are suspected to be again normotensive. Persistent postoperative hypertension can be caused by the residual tumor, intraoperative injury to the kidney's renal artery or metastatic disease.

Intraoperative hypotension may be caused by (1) hemorrhage during surgery (2) insufficient hormone replacement after left and right adrenal excision (3) vascular

compliance changes and immediate reduction of catecholamine levels after tumor removal, (4) myocardial infarction (5) long-term residual effects of prolonged α-blockers before surgery. As shown, hypotension can be effectively controlled by replacing volume and blood transfusion. Use vasopressors only when hypotension fails to respond to sufficient volume replacement [16].

Postoperatively, the majority of patients that had an uneventful intraoperative course with or without hemodynamic instability do not necessitate intensive care supervision. In the first postoperative period, the patients that have pheochromocytoma have also a greater risk of hypoglycemia and hypotension [5]. After catecholamines are suddenly stopped, due to the relative increase in insulin sensitivity, hypoglecemia may occur. Therefore, blood glucose must be supervised every hour for the first three or four hours postoerative. When a total adrenalectomy is planned, glucocorticoid preparations can be taken before surgery, specifically for the patients that have bilateral tumors or a familial pheochromocytoma syndrome. After surgery,incidence of hypoglycemia droped from 15% to 4.2%. Independent predictors related to postoperative hypoglycemia include prolonged operation time and increased urine adrenaline in 24-hour period before surgery. Therefore, glicemia must be checked regularly in the first day after surgery. Isolated episodes of hypotension are very common and can be attribueted to the preoperative alpha blockade residual values, hypovolemia that can be due to intraoperative blood loss or/and preoperative volume contract,. Treatment must be aggressive in terms of IV perfusions and vasopressors [3].

5.1 Postoperative outcomes

The rate of morbidity in untreated pheochromocytoma is very high and difficult to determin. 71% of patients can die from cardiovascular causes: myocardial infarction, hypertensive heart insuiciency, or hemodynamic instability occurring during different procedures [18].

Postoperative good outcomes for cortical-sparing adrenalectomy is focused on preventing a steroid dependency. The benefit of not having a steroid necesity must be compared to the risk of recurrence in time. The necessity of extensive adrenalectomy depends on the genetic or familial predisposition. The patients that have familial syndromes such as MEN 2B, VHL or/and MEN 2A are the ideal candidates for cortical sparing adrenalectomies. Patients with MEN 2A or 2B syndroms who suffered cortical sparing adrenalectomy have a recurrence risk about 51.8% at ten years. The steroid dependency rate of patients who underwent unilateral or/and bilateral cortical sparing technique was 43%. Cortical sparing adrenalectomy is the elective method for patients with VHL syndrome [19].

Patients with different type of pheochromocytomas should have a whole life follow-up program to avoid possible recurrence or the development of metastatic disease, which can occur up to 40 years after resectioning the tumor [17].

6. Particular situations

6.1 Malignant pheochromocytoma

As we all know, about 10% of adrenal pheochromocytomas tumors are malignant, and about 30% of any extra-adrenal tumors are are more commonly malignant. Malignant pheochromocytoma is less frequent in children than in elderly and is mainly at extra-adrenal glands. Pheochromocytomas that are associated with some familial syndromes usually have an early diagnoses and are less malignant than

the sporadic forms. The histological criteria that are used to distinguish benign and malignant forms of the tumors are not very accurate, as it happens in others endocrine or glandular tumors. Malignant tumors depend on the clinical tumoral manifestations and are accurantly diagnosed when there is infiltration of adjacent organs, distant metastasis or recurrence. The most common metastasis occur in bones, local LN, peritoneum, lungs and liver. Malignant tumors are commonly much bigger, with a higher frequency of vascular and capsule infiltration. They are usually characterized by DNA tetraploidy or aneuploidy, increased mitosis, angiogenesis, higher serum levels of neuropeptide Y, tumor necrosis, c-myc expression and higher neuron-specific enolase levels. Most malignant pheochromocytomas show increased uptake of metaiodo-benzylguanidine (MIBG). The survival rate at 5 years, for malignant pheochromocytomas is about 44%. In cases of extra-adrenal localization of pheochromocytomas the prognosis is worse than in adrenal tumors. Patients that have associated pulmonary metastasis have a much worse prognosis [18].

6.2 Pheochromocytoma in pregnancy

There are very common undiagnosed pheochromocytomas during pregnancy, and their maternal and infant mortality rates are very high, up to 58% and 56%. If the diagnosis is madein time, during the pregnancy period, the mortality and morbidity rate can reach below 11%. When the diagnosis is made at the time of delivery, the maternal mortality rate is still high, about 40%. In case of pregnant women the diagnosis of pheochromocytoma can be suspected in case of severe forms of hypertension in the first two months of pregnancy. If hypertension is not controlled in the second trimester, or is related to orthostatic hypotension, or if unexplainable shock occurs suddenly befor delivery, the diagnosis should be focused. The diagnosis as been confirmed by biochemical testing. MRI is the preferred local imaging tehnique to avoid radiation risk. In these cases, the freguently used irritation test is contraindicated, but in some specific cases, the clonidine inhibition test can be used. If the diagnosis is made in first trimester of pregnancy, it is recommended to remove the tumor after proper control of hypertension. In the last trimester of pregnancy, it is recommended to combine pregnancy with selective cesarean C-section intervention and immediate tumor removal under the same anesthesia through medical management. Due to the increased risk of fetal complication and hypertension, spontaneous and vaginal natural delivery methods should be avoided [19].

7. Conclusions/summary

The surgical methods for pheochromocytomas approach must have in priority list the assesment of the best imaging, the identifying any germline genetic mutations, and of course the utilization of any minimally invasive techniques when feasible and indicated. Biochemical diagnosis and precise tumor localization are necessary.

The minimally invasive technique of the abdominal or retroperitoneal approach is the standard surgical method. For large tumors with risk of rupture and potential malignancy, open surgery is recomanded. The results after surgical resection have a real potential to reduce the incidence of cardiovascular disease. Complete surgical resection is the ultimate treatment for benign and malignant pheochromocytoma that have low morbidity and mortality rates.

Special cases of malignant pheochromocytoma or this pathology's occurrence in pregnancy must be suppervised and treated with the utmost care. There are not any very accurate of uniform histological criteria so far, to distinguish malignancy in these cases, which depends on the tumor's clinical behavior.

Conflict of interest

The authors declare no conflict of interest.

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