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EVALUATION OF THE CLINICAL INDICATIONS AND SURGICAL METHODS IN PATIENTS WHO UNDERWENT ADRENALECTOMY

ADRENALEKTOMİ YAPILAN HASTALARDA KLİNİK ENDİKASYON VE CERRAHİ YÖNTEMLERİN DEĞERLENDİRİLMESİ

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ABSTRACT

AIM: The aim of this study was to evaluate the clinical surgical indications, surgical method selection criteria, and histopathological results of patients who were operated on with the diagnosis of adrenal mass in our general surgery clinic.

MATERIAL AND METHOD: A retrospective analysis was made of the data retrieved from the hospital database of patients who underwent surgery for adrenal mass in our general surgery clinic between January 2016 and January 2021. The data examined included demographic characteristics, American Anesthesiologists Association (ASA) score, preoperative clinical diagnosis, surgical technique, perioperative complications, duration of hospital stay, and histopathological results.

RESULTS: A total of 16 patients underwent surgery for a diagnosis of adrenal mass in the specified study period. The patients comprised 13 (81.25%) females and 3 (18.75%) males with a mean age of 50.31 ± 15.06 years, and mean ASA score of 1.87 ± 0.61. Surgery was performed by open adrenalectomy (OA) in 3 (18.75%) cases and laparoscopic transperitoneal lateral adrenalectomy (LTLA) in 13 (81.25%) cases. The preoperative clinical diagnosis was functional tumour in 10 (62.5%) patients and non-functional mass in 6 (37.5%).

CONCLUSION: Although adrenal gland tumors are extremely rare, a multidisciplinary approach is very important at the stages of diagnosis, surgical method selection, and postoperative follow-up. Surgeons should select the surgical method in which they are most experienced and trained, to be able to obtain the best results considering the risk factors.

Keywords: *Adrenal tumor, laparoscopic adrenalectomy, open adrenalectomy*

ÖZET

AMAÇ: Bu çalışmada genel cerrahi kliniğimizde, adrenal kitle tanısı ile opere edilen hastaların klinik cerrahi endikasyonlarını, cerrahi yöntem seçim kriterlerini ve histopatolojik sonuçlarını değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: Ocak 2016 -Ocak 2021 tarihleri arasında, genel cerrahi kliniğimizde adrenal kitle nedeni ile opere edilen tüm olguların demografik özellikleri, American Anesthesiologists Association (ASA) skoru, preoperatif klinik tanı, cerrahi yöntem, perioperatif komplikasyonlar, hastanede kalış süresi ve histopatolojik sonuçları retrospektif olarak değerlendirildi.

BULGULAR: Adrenal kitle tanısı ile opere edilen toplam hasta sayısı 16 idi. Olguların 13 (%81.25)' ü kadın, 3 (%18.75)' ü ise erkekti. Yaş ortalaması 50,31±15,06, ASA skoru ortalaması: 1.87±0.61 idi. Olguların operasyon şekli 3 (%18.75)' ü açık adrenalektomi (AA), 13 (%81.25)' ü ise laparoskopik transperitoneal lateral adrenalektomi (LTLA) ile yapıldı. Preoperatif klinik tanı olarak 10 (%62.5) hastanın fonksiyonel tümörü, 6 (%37.5) hastanın ise nonfonksiyonel kitlesi vardı.

SONUÇ: Oldukça nadir görülen adrenal gland tümörlerinde gerek tanı aşamasında, gerek cerrahi yöntem seçiminde ve gerekse postoperatif takip sürecinde multidisipliner yaklaşımın çok önemli olduğu kanaatindeyiz. Cerrahlar risk faktörlerini de göz önüne alarak, eğitim aldıkları, en deneyimli oldukları ve en iyi sonucu alabileceği cerrahi yöntemi seçmelidir.

Anahtar kelimeler: *Adrenal tümör, laparoskopik adrenalektomi, açık adrenalektomi*

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INTRODUCTION

Adrenal glands are retroperitoneally located endocrine organs. If adrenal gland tumors are not functional due to the anatomic location, they may not be noticed until a large size is reached causing compression symptoms. With the current advances in radiological imaging methods and the widespread use of diagnostic laboratory tests, there has been an increase in the detection of adrenal masses. The prevalence of adrenal incidentaloma (AI) with the radiological diagnosis has been reported to be 4.4% (1). This rate increases in the presence of risk factors such as diabetes, hypertension, and obesity, and when the patient is of advanced age, the rate increases up to 7-10% (2,3).

Two main factors are considered for surgical indication in adrenal gland tumors. The first of these is the differentiation of hormonally functional and non-functional masses, and the second is the distinction between benign and malignant (4). If the tumor is functional or if there is a diagnosis or suspicion of malignancy as a result of radiological findings and fine-needle aspiration biopsy (FNAB), a direct surgical decision is made regardless of the diameter. The malignancy risk is 2% in non-functional tumors <4 cm, and if there is no suspicion of malignancy radiologically, the patient is followed up every 6 months. In non-functional adrenal gland masses with a tumor diameter of 4 - 6 cm, even if the FNAB result is benign, the indication for surgical treatment is decided according to the suspicion of malignancy with reference to the patient's age or clinical history. In non-functional tumors> 6 cm, the risk of malignancy increases to 25%, so a direct surgical decision is made. Since FNAB is contraindicated in pheochromocytoma (PCC), PCC must be excluded to perform a biopsy. (5). Adrenalectomy may also be indicated for resection of adrenal metastases (6).

The surgical treatment of adrenal gland tumors has evolved from open surgery to minimally invasive surgery with the development of technology over the years. This is because minimally invasive adrenalectomy results in less blood loss, postoperative pain, and lower complication rates compared to open surgery, resulting in early mobilization, shorter hospital stay, and similar long-term results (7). Different techniques have been proposed for minimally invasive surgery. After the first definition of laparoscopic adrenalectomy (LA) by Gagner in 1992, different surgical techniques such as the laparoscopic transperitoneal [anterior (LTAA), lateral (LTLA)] and retroperitoneal [posterior (LRPA), lateral (LRLA)] approach were developed (8, 9). With the advent of robotic surgery in recent years, robotic-assisted adrenalectomy (RA) has become an alternative to traditional LA (10).

The aim of this study was to evaluate the clinical surgical indications, choice of surgical method, and the histopathological results of patients who were operated on with the diagnosis of adrenal mass in our general surgery clinic.

MATERIAL AND METHOD

A retrospective analysis was made of the data retrieved from the hospital database of patients who underwent surgery for adrenal mass in our general surgery clinic between January 2016 and January 2021. The data examined included demographic characteristics, American Anesthesiologists Association (ASA) score, preoperative clinical diagnosis, surgical technique, perioperative complications, duration of hospital stay, and histopathological results. This study was approved by The Ethics Committee of Ankara Training and Research Hospital (approval date and number: 11.02.2021, 2021/21:597).

All cases were evaluated by the multidisciplinary endocrinology council consisting of endocrinology, general surgery, nuclear medicine, and radiology specialists. Function tests for all masses and tomography (CT) and/or magnetic resonance (MR) imaging of the adrenal gland were performed by the endocrinology clinic and general surgery clinic. Cases with a high malignancy risk were visualized by positron emission tomography (PET). The patients with preoperative clinical Cushing syndrome (CS) were prepared for surgery under the Addison protocol. For adrenal masses diagnosed with PCC, a detailed screening was performed for other organ diseases, due to the 10% familial risk of transmission. In the preoperative period, alpha blocker (doxazosin 2x4 mg) and beta blocker (propranolol 1x40 mg) were started. In addition, in order to prevent postoperative collapse, patients were given 2000 cc intravenous fluid preoperatively and phentolamine ampoule (alpha 1 + alpha 2 adrenergic blocker) was kept ready for possible hypertensive crisis during the operation. The operation was performed in all patients after obtaining informed consent. The surgical intervention was performed as a laparoscopic transperitoneal lateral approach or open (supra-umbilical median incision).

Standard dose analgesia was applied to all patients postoperatively, and maintenance doses were continued for patients in whom the Addison protocol was initiated in the preoperative period. PCC patients were followed up in the intensive care unit on the first postoperative day due to possible cardiopulmonary complications. Maintenance cortisol treatment was continued after discharge, following the endocrinology recommendations for the patients who were applied the Addison protocol. Follow-up examinations of the patients were carried out in the endocrinology and general surgery outpatient clinics in the first week after discharge.

Data obtained in the study were analyzed using statistical computer software. Descriptive statistics were stated as mean ± standard deviation values for

numerical variables, and as number (n) and percentage (%) for categorical variables.

RESULTS

A total of 16 patients were operated on with the diagnosis of adrenal mass, comprising 13 (81.25%) females and 3 (18.75%) males with a mean age of 50.31 ± 15.06 years and mean ASA score of 1.87 ± 0.61. The operation was performed as open adrenalectomy (OA) in 3 (18.75%) cases and as LTLA in 13 (81.25%) **(Figure 1).** The tumor localization was determined as right-side in 11 (68.75%) cases, left-side in 4 (25%) and bilaterally in 1 (6.25%) **(Table 1).**

Table 1. Demographic characteristics and clinical results of the patients.

Characteristics	PATIENTS (n=16) mean±SD
Age (years)	50.31±15.06
Gender n(%) *Female* *Male*	13 (81.25%) 3 (18.75%)
ASA score	1.87±0.61
Clinical diagnosis n(%) *Functional Tm* *Non-functional Tm,*	10 (62.50%) 6 (37.50%)
Tumor localization n(%) *Right* *Left* *Bilateral*	11 (68.75%) 4 (25%) 1 (6.25%)
Operation method n(%) *Laparoscopic* *Open*	13 (81.25%) 3 (18.75%)
Operation time (min) *Laparoscopic* *Open*	93.46±17.00 173.33±61.10
Perioperative bleeding amount (ml) *Laparoscopic* *Open*	65.76±21.97 250±132.28
Hospitalization time (day) *Laparoscopic* *Open*	3.61±0.86 5.66±0.57

The preoperative clinical diagnosis was functional tumor in 10 (62.5%) patients and non-functional mass in 6 (37.5%). Of the patients with functional tumor, 6 had CS and 4 had PCC. Of the patients with non-functional mass, 3 were operated on for recurrent adrenal cyst, 1 for recurrent MEN2A, 1 for non-functional tumor >4cm in size, and 1 for hepatocellular cancer (HCC) invasion of the right adrenal gland **(Table 2).**

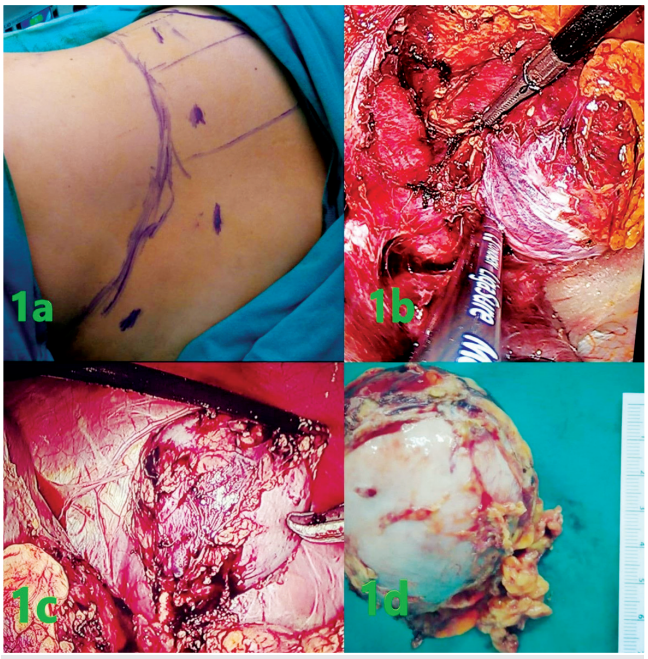

Figure 1. 1a: Trocars position for left laparoscopic transperitoneal lateral adrenalectomy (LTLA).
1b: Post-dissection view of adrenal mass in laparoscopic right adrenalectomy.
1c: Post-dissection view of adrenal mass in laparoscopic left adrenalectomy.
1d: Postoperative, specimen view of adrenal mass.

The mean operation time was 173.33 ± 61.10 min for OA and 93.46 ± 17.00 min for LA. The average amount of perioperative bleeding was 250 ± 132.28 ml for OA and 65.76 ± 21.97 ml for LA. Cardiac arrhythmia developed in a perioperative PCC patient, and the arrhythmia picture improved with pharmacological medication administered by the anesthesiologist. One patient who underwent LA had a serosal injury in the splenic flexure of the colon, and intracorporeal repair was performed. The mean duration of hospitalization was 5.66 ± 0.57 days for OA, and 3.61 ± 0.86 days for LA.

Table 2. Clinical and pathological diagnoses of the patients with functional and non-functional tumors.

	Patient n:16	Clinical diagnosis	Pathology
Functional tumors	6 (37.5%)	Cushing syndrome	Adrenocortical adenoma
	4 (25%)	Pheochromocytoma	Pheochromocytoma
Non-functional tumors	3 (18.75%)	Adrenal cyst	Adrenal cyst
	1 (6.25%)	Tumor invasion	Adrenocortical adenoma
	1 (6.25%)	Recurrent MEN2A	Adrenocortical adenoma
	1 (6.25%)	>4 cm mass	Adrenocortical adenoma

Multiple Endocrine Neoplasia (MEN)

Perioperative or postoperative blood transfusion was not required in any of the patients in this series who were operated on for primary adrenal tumor. Two units of erythrocyte suspension and 2 units of fresh frozen plasma replacement were applied perioperatively to the patient who was undergoing surgery for the diagnosis of HCC with the invasion of only the right adrenal gland. No postoperative morbidity or mortality was observed. All patients were discharged after consultation from the endocrinology clinic and following their recommendations before discharge.

In the histopathological results, the mean tumor diameter was 5.75 ± 1.96 (1-9) cm overall, with mean diameter of functional tumors: 4.15 ± 1.37 (2.5-6.5) cm, and non-functional tumors: 5,16 ± 3.06 (1-9) cm. When classified according to the pathology results, 9 (56.25%) of the cases were adrenocortical adenoma (ACA), 4 (25%) were PCC, and 3 (18.75%) were adrenal cyst (AC) **(Table 2).**

DISCUSSION

The two most important factors for adrenalectomy indication in adrenal gland masses are whether or not the mass is functional and whether the radiological appearance or size of the suspected malignancy creates a risk of malignancy. Functional tumors of the adrenal gland include CS caused by excessive secretion of glucocorticoids produced in the adrenal cortex, CS caused by excessive secretion of aldosterone produced by the adrenal cortex and PCC due to excessive catecholamine release from the adrenal medulla.

While 80% of patients diagnosed with AI are non-functional and benign, 15% are functional, 4% are adrenocortical carcinoma (ACC) and 1% are metastatic tumors (5). In some multicenter studies, it has been shown that the frequency of PCC in patients with incidentaloma can be 5-20% (11), the frequency of subclinical CS is 5-48%, and the frequency of subclinical hyperaldosteronism can be up to 32% (12, 13). In the current study, there were 10 (62.5%) patients with functional tumors, of which 6 (37.5%) had CS and 4 (25%) had PCC. Compared to the literature, the rate of functional tumors in this series was very high. The reason for this was that the masses found incidentally in our endocrinology and general surgery clinic were smaller than 4 cm in size and there was no suspicion of malignancy.

Increased research on familial syndromes in recent years has resulted in an increasing number of diagnosed PCC patients (14). There is a "rule of 10" in PCC disease, which mostly has a sporadic tumor form. Accordingly, it is 1/10 bilateral, 1/10 malignant, 1/10 extradrenal localized, and 1/10 familial. (15). PCC can coexist with hereditary inherited diseases such as Multiple endocrine neoplasia 2 (MEN 2), von Hippel-Landau disease (VHL), and neurofibromatosis. It is seen in 30-50% of MEN 2 cases and 15-20% of VHL cases (16). Partial adrenalectomy is performed for the treatment of hereditary and sporadic bilateral tumors, especially in young patients to reduce the risk of adrenal insufficiency and the need for lifelong steroid use. In a recent meta-analysis, it was observed that the risk of recurrence is low and the need for steroids is quite low in this patient group. However, it was stated that the highest recurrence rate in this patient group was in those who underwent surgery due to bilateral PCC disease and therefore, patient selection and close follow-up are important in terms of recurrence (17). In the current study, PCC cases were also investigated in terms of other possible organ diseases due to the risk of hereditary transmission in the preoperative period, and no adrenal gland disease was detected. In a patient who had undergone bilateral adrenalectomy with a diagnosis of MEN2A syndrome and PCC in another center, the bilateral recurrent adrenal mass was detected in the follow-up examinations. OA was performed in this patient with the diagnosis of subclinical PCC.

There are many studies related to the selection of OA or LA in adrenal gland tumors and this remains a matter of current debate. The basis of the dilemma is that the risk of ACC increases as the tumor size increases and that R0 resection cannot be performed in LA. The frequency of ACC reported in patients operated on for adrenal incidentaloma has been reported to reach 10% in some series (18). Since the risk of ACC increases as the tumor size increases, this should be taken into consideration when planning a surgery, but it is not an absolute contraindication to laparoscopic resection. In the past, tumors> 6 cm were considered a contraindication for laparoscopy, but actually tumor size > 6 cm is not an absolute contraindication for laparoscopy (19). In recent years, several serial studies conducted in the USA have not recommended LA for patients with known or suspected ACC (20-22), while some reports from Europe have shown that LA does not compromise the oncological outcome of selected ACC cases (23-25).

LA is considered the gold standard treatment for adrenal lesions (26). All functional and non-functional tumors, including PCC, are candidates for the laparoscopic approach in the absence of other contraindications. While coagulopathy, malignancy, tumors >12 cm, and cardiopulmonary high-risk patients are the absolute contraindications criteria for LA, previous abdominal surgery, obesity, and relatively large tumors are the relative contraindication criteria. It has been stated that in the presence of local invasion of neighboring structures in preoperative imaging examinations in malignancy diseases, lymph node dissection for R0 resection and en bloc resection of adjacent structures will be easier in OA (5). In the light of this information, it can be considered that a multidisciplinary approach is of great importance in the decision-making process, taking into account the surgeon's experience, anesthesia, endocrinology, nuclear medicine, and radiology, as well as the choice of OA or LA. In the current study,

the average histopathological tumor diameter of the patients was 5.75 ± 1.96 cm. OA was applied to only 3 of this series of patients. The reasons for open surgery were that 2 cases had a history of previous abdominal surgery. In one case, right hepatectomy and open surgery for right adrenalectomy were performed in the patient with HCC invading the right adrenal gland. There were no patients who were operated on with the suspicion or diagnosis of ACC, or with a postoperative diagnosis of ACC.

Another issue discussed in OA and LA selection is for PCC patients with large tumor volume. Surgery for PCC can cause major complications such as intraoperative hypertensive crises, perioperative or postoperative myocardial infarction, cardiac arrhythmia, or pulmonary or cerebral edema due to excessive secretion of catecholamines. In the PCC clinical status, as the tumor size increases, the hypervascularization of the tumor and the increase in adhesion to adjacent organs, large vessels such as the renal vein and vena cava cause difficulties in mobilization and dissection of the adrenal gland (27). In PCC, as damage to the tumor capsule during surgery may trigger iatrogenic pheochromatosis, some researchers have stated that dissection may be difficult in large tumors during LA, causing greater capsular injury because there is no sense of touch as in open surgery (14). The role of the laparoscopic approach for tumors> 6 cm in PCC patients is still controversial, as is the risk of ACC. Some studies have stated that it prolongs the perioperative cancer and surgery time in tumors> 6 cm, but does not affect the surgical outcome (28, 29). The risk of malignancy has been reported to increase in tumors larger than 6 cm (30).

Recent studies have emphasized that in high-volume centers experienced in LA, experienced multidisciplinary teams can prevent cardiopulmonary major complications and achieve the best results in the treatment of the disease, even if there are perioperative hypertensive or hypotensive crises treated with pharmacologically good medication in the preoperative and perioperative period (27, 28). In the current study, LA was performed in 3 PCC patients and OA was performed in only 1 patient because of abdominal surgery. Perioperative cardiac arrhythmia developed in only one patient who underwent LA. Due to the experienced anesthesia team, this was taken under control with pharmacological medication. Postoperative cardiopulmonary complications did not occur in any of the current study patients. The bleeding amount was less (LA: 60ml, OA: 100ml) and operation time (LA: 80 min, OA: 120 min) was shorter in the PCC patients who underwent LA than in those who underwent OA. Given the challenges associated with dissection of the adrenal glands and the risk of perioperative adverse cardiovascular events, LA remains a complex procedure for PCC patients and requires extreme caution, especially in large tumors.
After the first LA was defined in 1992, different surgical techniques such as LTAA, LTLA, and LRPA, and LRLA approach were developed (8, 9). With the advent of robotic surgery in recent years, RA has become an alternative to traditional LA (10). There are advantages and disadvantages of the 4 different approaches defined for LA.

In general, the advantages of the transperitoneal approach are that it offers a wider surgical working area, the best view of the operation area and surrounding structures, and unlike LTLA, the LTAA approach also provides the opportunity for bilateral LA without the need for repositioning and provides a better view in larger adrenal tumors. However, there are also disadvantages such as the risk factors of access to the peritoneal cavity, adhesions caused by previous procedures and the possibility of being affected by intraperitoneal diseases, hemodynamic and respiratory instability caused by CO2 pneumoperitoneum. The advantage of the retroperitoneal approach is that the peritoneal cavity is not entered, so it is not affected by adhesions or intraperitoneal diseases of previous operations, it is beneficial in obese patients in terms of preventing hemodynamic and respiratory effects caused by pneumoperitoneum, and unlike the LRLA approach, it offers bilateral LA opportunity without the need for repositioning in the LRPA approach. The disadvantages of this method are that the learning process is difficult, the surgeon orientation is likely to be disrupted, and manipulation becomes more difficult in limited study areas and large tumors (5, 9).

In our general surgery clinic, considering the contraindication criteria, LA is predominantly preferred because of less blood loss, postoperative pain, low complication rates and consequently early mobilization, shorter hospital stay, and similar long-term results. The transperitoneal approach can be considered better for anatomic control and is more comfortable for manipulation, and with a lateral (LTLA) approach requires fewer trocars.

CONCLUSION

In conclusion a multidisciplinary approach is of great importance at the stages of diagnosis, surgical method selection, and postoperative follow-up in adrenal gland tumors, which are extremely rare. As suggested by the Society of Gastrointestinal and Endoscopic Surgeons (SAGES) Guidelines (31), surgeons should select the surgical method in which they are trained and most experienced, and can obtain the best results, considering the risk factors.

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