

## Feasibility of laparoscopic approach in malignant and benign adrenal lesions

Feasibility of laparoscopic approach in malignant adrenal lesions

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### Abstract

**Aim:** The approach to adrenal lesions is still controversial, especially concerning the potentially malignant masses. This study aims to present the results of laparoscopic adrenalectomy of a tertiary referral center, and the laparoscopic management strategy of both benign and malignant lesions.

**Materials and Methods:** This retrospective study conducted in a single tertiary referral center was designed to evaluate the laparoscopic management strategy of both benign and malignant adrenal lesions. The demographic and clinical data were retrieved by reviewing electronic medical files yielding to 43 patients. The surgical outcomes were evaluated based on the postoperative complications and length of hospital stay. All patients were operated employing minimally invasive surgery techniques precisely via the lateral transperitoneal approach.

**Results:** Out of 43 patients, 35 had benign pathology, whereas eight had adrenocortical carcinoma (ACC). Regardless of the size of ACC, the National Comprehensive Cancer Network (NCCN), the American Association of Clinical Endocrinologists (AACE), and American Association of Endocrine Surgeons (AAES) recommend open surgery, however in selected cases of ACC, we do recommend the laparoscopic approach since the results are satisfactory and this recommendation is endorsed by the European Society of Endocrine Surgeons.

The mean duration of hospital stay was 2.96±0.9 days. The mean operative time was 124.8±45 minutes. The operative time was not affected by tumor sidedness, however, those operated for malignancy had statistically significant longer operative time than the benign lesions.

**Discussion:** Even though the posterior retroperitoneal approach is considered to be more comfortable for the patient, it is unfortunately restricted to selective non-obese cases with small, benign lesions, hence, benign and selected cases of malignant adrenal lesions could feasibly be treated through the transperitoneal approach.

### Keywords

Incidentaloma; Adrenal; Cushing; Aldosteronoma; ACC; Laparoscopy

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## Introduction

The first laparoscopic adrenalectomy was first described in 1992 by Michel Gagner [1], ever since the laparoscopic surgical approach to adrenal masses has increased exponentially. Nowadays adrenalectomy employing minimally invasive surgery has become a gold standard technique [2]. The type of laparoscopic adrenalectomy that is firstly described and mostly used all over the world is the transperitoneal approach. Over time and with the advance made in this field, other routes have been described and advised for the surgical management of adrenal masses, including posterior retroperitoneal, lateral retroperitoneal, transperitoneal, and transthoracic [3,4]. The minimally invasive technique is exclusively used for benign small lesions, however, malignant lesions and relatively larger lesions can still be managed laparoscopically. With the increase in the incidence of incidentalomas, which can be attributed mainly to the widespread use of radiodiagnostic tools, a parallel increase in the number of adrenalectomies due to benign pathologies, alongside there is an increase in postoperative complications too. This study aims to present the results of laparoscopic adrenalectomy of a tertiary referral center, and the laparoscopic management strategy of both benign and malignant lesions.

## Material and Methods

The study was designed as the evaluation of consecutive cases retrospectively collected in a single academic tertiary referral center. Ethics committee approval for this study was obtained from the Local Research Ethics Committee registered under the number 19-KAEK-231. The patients were recruited after the review of the electronic database using relevant ICD -10 codes. The search was limited to the period between January 2013 and January 2019. The demographic and clinical data including patient age, gender, location of the lesion, the diameter of the lesion, surgical technique, preoperative diagnosis, the postoperative pathology report, operation time, diagnostic tool, length of hospital stay, and morbidities were retrieved by reviewing patient electronic medical files. The data of this study were collected and analyzed in December 2019. The diagnosis of adrenal mass was made based on clinical presentation, physical examination, biochemical studies, or incidentally during radiological examinations for a different purpose on computed tomography CT, magnetic resonance imaging MRI or during PET-CT. The decision for the surgical approach was taken during a multidisciplinary meeting after meticulous biochemical and radiological investigations by the endocrinology, surgery, and radiology team. The surgical outcomes were evaluated based on the postoperative complications, length of hospital stay. All patients were evaluated monthly for the first three months postoperatively during routine clinical visits. Descriptive analyses were performed to provide information on the general characteristics of the study population. Quantitative data were obtained regarding the arithmetic mean, standard deviation. Qualitative data were expressed as count and percentages. The t-test was used to compare the performance between two groups; a p-value below 0.05 was considered statistically significant. Analyses were performed using SPSS 20 (IBM SPSS Statistics 20, SPSS inc., an IBM Co., Somers, NY). Preoperative patient Preparation

All patients, regardless of whether they applied directly to our clinics or not, were referred to the Endocrinology and Metabolism department for further assessment and evaluation of whether the adrenal mass was hormonally active or not, and, meanwhile, for adequate preparation of the hormone active ones for surgery.

Before surgical intervention, all patients were discussed at multidisciplinary meetings, where the decision for surgical treatment is taken, thorough medical history and physical examinations were performed, followed by routine biochemical analysis, complete blood count, serum cortisol, aldosterone, dehydroepiandrosterone sulfate levels, and 24-hour urine free cortisol, vanilla mandelic acid, and metanephrine levels were studied too. For the radiological diagnosis of the mass in the adrenal gland, 26 patients underwent chemical shift magnetic resonance imaging, all patients underwent upper abdominal computed tomography.

For the hormone-active adrenal masses, alpha and beta-blocker treatments were commenced preoperatively. Besides, all patients underwent daily hydration. Cushing's protocol was initiated during the perioperative period with the administration of steroids requiring follow-up and tapering under the guidance of an endocrinologist. The pheochromocytoma protocol consists of the initiation of a preoperative alpha-adrenergic blockade to prevent hypertensive crisis during the operation. The phenoxybenzamine starting dose is 10 mg/day, and then titrated by increments of 10 mg until the patient reaches an orthostatic status. Metyrosine is often added to phenoxybenzamine. It takes at least 2 weeks to prepare the patient before surgery; on the night of the intervention, the dosage is increased according to the patient's condition. Written informed consent was obtained from all patients preoperatively.

## Results

All patients were operated using minimally invasive surgery with no case of conversion to open technique. The mean age of the patients was  $55.6 \pm 11.2$  (34–79) years. Eleven (26%) cases were male and 32 (74%) were female. The median BMI was 29.6 (23–50). Adrenal masses were active in 27 patients (62.8%). Based on CT scans, the mean tumor size was 2.87cm (1.8–7.2). Twenty-one patients (48.8 %) underwent right adrenalectomy and 22 (51.2%) underwent left adrenalectomy (Table 1). All patients were operated via a lateral transperitoneal approach. No major peroperative events took place except for self-limited minimal bleeding, that did not request any transfusion and which was controlled employing compression via a laparoscopic sponge, this patient remained hemodynamically stable thereafter. All specimens have been extracted from the abdomen by an individual endobag through a 10-12 mm port incision, which is enlarged when necessary.

Five patients (11.6%) had a history of abdominopelvic surgery as follows: cholecystectomy (2 patients), total abdominal hysterectomy (1 patient), appendectomy (1 patient), and one patient had a history umbilical hernia repair with graft. The definitive pathology reports revealed adrenal cortical adenoma in 27 cases, adrenal cortical carcinoma in eight cases, pheochromocytoma in five cases, adrenal myelolipoma in one case, adrenal cyst in one case, and one patient with

adrenal nodular hyperplasia (Table 2). In the case of benign adrenal cyst, myelolipoma and adrenal nodular hyperplasia, the indications for surgery were the enlargement of the lesion and their increased malignant suspicion during follow-up.

Patients with malignant pathology were categorized as modified Weiss criteria (Table 3).

The postoperative period was uneventful except for one patient who developed atalactesia and pneumonia requiring the administration of antibiotics and intensive respiratory therapy hence prolonging in-hospital stay. The mean duration of hospital stay was 2.96±0.9 (2–8) days. The mean operative time was 124.8±45 (60–240) minutes. The operative time was not affected by the tumor sidedness; however, in those were operated for malignancy, the operation time was statistically significantly longer than in the benign lesions. All patients with pre-operative hormonally active adrenal mass returned to normal hormonal status in the postoperative follow-up period.

**Table 1.** Patients Demographics and other parameters (n: 43)

Parameters	Values	Standard Deviation
Mean age, mean (range)	55.6 (34–79)	±11.2
Male/female (n)	11/32	-
BMI, median (range)	29.6(23-50)	±5.5
History of abdominal surgery (n)	5	-
Tumor size (cm)	2.87 (1.8–7.2)	±1.1
Operative time (min)	124.8 (60–240)	±45
Hospital stay (day)	2.96 (2–8)	±0.9
Morbidity (n)	1	-
Mortality (90 days) (n)	0	-
Malignant tumors (n)	8	-
Benign tumors (n)	35	-
Right-sided tumors (n)	21	-
Left-sided tumors (n)	22	-

**Table 2.** Histopathologic results and clinical diagnoses

Histopathologic Diagnosis	Clinical Diagnosis	N (%)
Functional Adrenal tumors (34)		
Cortical adenoma	Aldosteronoma (19 cases) Cushing syndrome (8 cases)	27 (62.8%)
Adrenal nodular hyperplasia	Adrenal nodular hyperplasia	1 (2.3%)
Pheochromocytoma	Pheochromocytoma	5 (11.7%)
Benign adrenal cyst	Benign adrenal cyst	1 (2.3%)
Non-functional adrenal tumors (9)		
Adrenal cortical carcinoma	Adrenal cortical carcinoma	8 (18.6%)
Myelolipoma	Myelolipoma	1 (2.3%)
Total		43(100%)

**Table 3.** Patients with malignant pathology categorized according to modified Weiss criteria

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Mitotic rate > 5/50 high power fields	-	-	1	1	-	1	1	1
Cytoplasm (clear cells 25% or less)	1	1	-	-	1	1	-	-
Abnormal mitoses	1	1	1	1	1	-	1	1
Necrosis	-	-	-	-	1	-	-	-
Capsular invasion	-	-	-	-	-	-	-	-
Modified Weiss score	3	3	3	3	4	4	3	3

Mitotic rate criterion x 2 + clear cytoplasm criterion x2 + abnormal mitoses + necrosis + capsular invasion (score of 3 or more suggests malignancy) each criterion is scored 0 when absent and 1 when present in the tumor.

## Discussion

This study presents a six-year experience of adrenal surgery at a tertiary center hospital. A total of 43 patients were operated by lateral transabdominal route, without conversion to open surgery in none of the cases; 27 patients (62.8%) had cortical adenoma and this ratio is much the same as in the study conducted by Ari et al., which was 65.5%. Eight patients (18,6%) had malignant masses diagnosed postoperatively but were suspected preoperatively. According to O’Neill et al.’s study, this ratio is estimated to be less than 10% [5], five patients had a history of previous abdominopelvic surgery, no postoperative mortality record, one patient developed pneumonia postoperatively, the mean hospital stay was less than three days and the mean operative time was around two hours.

Laparoscopic adrenalectomy is the gold standard approach for both functioning and non-functioning adrenal masses [6,7]. The probable limitation to this approach is the size and the potential malignant pathology of the lesion, furthermore, according to some authors, the size is directly proportional to the character of the lesion, and the larger the size (> 6cm), the higher the probability that the lesion will turn out to be a malignant adrenal tumor. However, this is not always the case, because in this study, out of eight malignant cases, five were less than 6 cm in diameter with stage I and II ACC disease. Many studies accept open adrenalectomy as the procedure of choice for ACC [8-13], however, this should not be a strict rule, as a matter of fact, a selective group of patients with early-stage ACC, those with no evident sign of invasion and relatively small masses still can be managed laparoscopically, this approach is supported by several authors and studies [14] who demonstrated that the oncologic outcomes of localized ACC following laparoscopic and open adrenalectomies had similar outcomes. A mass with a diameter greater than 10 cm would create difficulties not only during the dissection and resection but also during its extraction from the abdominal cavity.

Adrenalectomy can be performed using an open technique as it may be done laparoscopically, the laparoscopic approach can be either in a transabdominal or retroperitoneal fashion, and the transperitoneal route can be with an anterior or lateral approach whereas the posterior approach can be performed laterally or posteriorly. Open adrenalectomy is mainly preserved for large tumors (>10 cm) and malignant masses [7,14,15]. Minimally invasive surgery for adrenal masses with a size smaller than 10 cm and potentially benign is considered to be the gold standard technique.

Controversies exist concerning the more appropriate route for adrenalectomy. The lateral transabdominal approach provides the surgeon with a wide operative space, obvious anatomical landmarks, and more ease, especially for general surgeons who are more familiar with the abdominal cavity, moreover, it is safer, since one can more easily convert to open surgery in case of exigency situation such as abundant bleeding. If the laparoscopic approach is considered for a potentially malignant adrenal mass, but without any radiological sign of invasion, then the transabdominal lateral approach would be more appropriate, since it allows proper evaluation of the abdominal cavity for any metastatic lesions, meanwhile this approach thanks to the wide operative field allows also en-bloc resection of the tumor more unperturbed [13].

An alternative access road is a retroperitoneal approach which is favored by urologists because of their familiarity with the retroperitoneum, its only evident advantage that may provide over the transperitoneal approach is the unnecessary retraction of adjacent organs such as the colon, spleen, and pancreas, moreover, a systematic review for the minimally invasive surgical approach of adrenal tumors showed that the posterior approach was more effective than the transperitoneal one in the sense of operative time and hospital stay [16], on the other hand, the retroperitoneal route constitutes several limitations. Obese patients with a body mass index  $\geq 30$  have been assessed to be at risk of complications during laparoscopic adrenalectomy [17], this risk is even higher in the case of the posterior approach. Larger masses and potentially malignant lesions are also other limitations to the posterior approach [18]. The operative time was not affected by tumor sidedness ( $p > 0.17$ ), however, those operated for malignancy had statistically significant longer operative time than the benign lesions ( $p < 0.001$ ), and this may be explained by the meticulous dissection to prevent tumor rupture or spillage, and the relatively larger lesions in case of malignancy which are often accompanied by adhesions. The modified Weiss score of 3-4 corresponds to malignant criteria of ACC, meanwhile these patients had less aggressive findings during surgery, there were no major vessel or organ invasions that would necessitate more radical surgery, adrenalectomy accompanied by lymphadenectomy and perirenal soft tissue excision were sufficient to achieve negative resection margins.

It is believed that analgesic use is higher in patients treated with transperitoneal approach compared to the posterior one [19], however, other studies proved that there was no difference in analgesic use between the two approaches [7], therefore, postoperative pain relief should not be assessed as an advantage in favor of posterior approach. A complication that is uniquely related to the posterior approach is pain due to subcostal nerve injury [20]. Fortunately, this complication is only found in  $< 10\%$  of the patients and is self-limited [18]. Operative time is surgeon dependent, so it is really difficult to compare operative time between the two approaches.

The routine use of CT scan is not only for the evaluation of adrenal mass and its relationship with neighboring structures for signs of invasion, but also to obtain more information about the periadrenal lymph nodes, any anatomic vascular variations, especially concerning the right adrenal vein drainage and it

is entourage, finally, unexpected abdominal findings can be detected, likewise in this study, various unexpected findings were encountered such as Meckel diverticulum in one patient, extensive sigmoidal diverticular disease in one case, one case of adnexal mass and ovarian cyst in another patient. These findings may not be life-threatening, but are worthy noting and might necessitate close medical follow-up.

Adhesions, which are fibrous bands of scar tissue that can form between any internal organs of the abdominal cavity, these adhesions can be congenital or acquired in origin and are classified as filmy, localized, or dense. They constitute a troublesome situation for the surgeon, adhesions are associated with severe morbidities and a higher risk of conversion to open surgery [21,22], nevertheless, they are not contraindications for the laparoscopic approach, namely, in this study, five patients had a history of previous surgery (appendectomy, umbilical hernia repair, total abdominal hysterectomy, laparoscopic cholecystectomy), and none of them posed any problem during abdominal access or dissection [23]. Thus, claiming that previous surgery is a disadvantage for transperitoneal adrenalectomy is not the case.

A Cochrane systematic review and meta-analysis has documented that the posterior approach may show a shorter time to oral fluid or food intake and time to ambulation than the transperitoneal approach [24], however, in the current study, postoperative follow-up posed no impact on bowel movements, and all patients tolerated oral fluid intake at the 6th hour postoperatively, and normal diet on the first postoperative day. Mobilization and respiratory therapy using the tri-flow instrument are also initiated on the first postoperative day.

Whatever the route access, minimally invasive adrenalectomy results in less blood loss, earlier ambulation, less pain, better cosmetic results shorter hospital stay, and faster return to normal activity [25], thus laparoscopy and specifically transperitoneal approach should be recommended as a universal approach, whereas the posterior approach is for selective non-obese cases with small benign lesions.

Limitation of this study is the lack of a retroperitoneally approached group for comparison, and the type of the study was retrospective in profile, a randomized control study with a higher number of patients would contribute to higher evidence of knowledge.

### Conclusion

Minimally invasive surgery and specifically transperitoneal approach for adrenal masses should be recommended as the universal access route, whereas the posterior one should be advised for selective non-obese cases with small benign lesions.

### Scientific Responsibility Statement

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

### Animal and human rights statement

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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**Conflict of interest**

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