



DOI: 10.14744/SEMB.2021.81598

Med Bull Sisli Etfal Hosp 2022;56(2):244–249

## Original Research

# Should We Hesitate to Perform Laparoscopic Adrenalectomy for Pheochromocytomas Larger Than 5 cm in Diameter with No Pre-Operative Suspicious Criteria for Malignancy?

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### Abstract

**Objectives:** We aimed to compare the outcomes of patients who underwent laparoscopic adrenalectomy (LA) for pheochromocytoma (PHE)  $\geq 5$  cm versus  $< 5$  cm in diameter.

**Methods:** Demographic variables, tumor characteristics, perioperative, and post-operative outcomes were evaluated retrospectively and compared between groups.

**Results:** Between February 2008 and August 2020, 54 patients (27 female and 27 male) enrolled to the study and divided into two groups according to the tumor size as group L  $\geq 5$  cm (28 patients) and group S as  $< 5$  cm (26 patients). Groups compared in the aspect of American Society of Anesthesiologists scores, body mass index, tumor locations, ratio of elder ( $\geq 60$ -years-old) patients, and gender ratio were similar between groups S and L ( $p=0.572$ ,  $p=0.516$ ,  $p=0.6$ ,  $p=0.331$ , and  $p=0.207$ , respectively). Mean duration of surgery ( $p=0.266$ ), mean estimated blood loss ( $p=0.587$ ), and mean length of hospital stay ( $p=0.374$ ) were similar between groups. Difference between maximum and pre-operative systolic pressure and the difference between maximum and pre-operative diastolic pressure were similar between S and L groups ( $p=0.852$  and  $p=0.526$ , respectively). Patients whose systolic blood pressure  $> 160$  mmHg, systolic blood pressure  $> 30\%$  of baseline, and heart rate  $> 110$  ( $p=0.307$ ,  $p=0.609$ , and  $p=0.296$ ) were similar. Diastolic blood pressure  $< 30\%$ , there is a difference between groups in favor of group L, but not statistically different ( $p=0.077$ ).

**Conclusion:** It is necessary to work in coordination with endocrinologists and anesthesiologists and LA for PHE should be performed in experienced medical centers regardless of tumor size with multidisciplinary approach.

**Keywords:** Adrenal mass, laparoscopic adrenalectomy, pheochromocytoma

Please cite this article as "Cicek MC, Gunseren KO, Ozmerdiven CG, Vuruskan H, Yavascaoglu I. Should We Hesitate to Perform Laparoscopic Adrenalectomy for Pheochromocytomas Larger Than 5 cm in Diameter with No Pre-Operative Suspicious Criteria for Malignancy? Med Bull Sisli Etfal Hosp 2022;56(2):244–249".

Laparoscopic techniques have become a standard approach for therapeutic and diagnostic procedure in urology. Laparoscopic adrenalectomy (LA) raises attention of urologists and general surgeons, because it provides

ease of dealing with the deep retroperitoneal placement of the adrenal gland and its minimal invasive nature. Open adrenalectomy requires a wide incision on the abdominal wall causes higher post-operative morbidity and longer

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**Submitted Date:** April 01, 2021 **Accepted Date:** June 02, 2021 **Available Online Date:** June 28, 2022

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hospitalization period.<sup>[1-3]</sup> LA first described by Gagner et al. with the experience with three patients in 1992.<sup>[4]</sup> Gagner described lateral decubitus transperitoneal approach also supine transperitoneal approach, prone retroperitoneal approach, and decubitus retroperitoneal approaches which are alternatives. Transperitoneal and retroperitoneal techniques are both seem to have similar effectiveness depends on the surgeons' experience.<sup>[5-7]</sup> LA for the treatment of adrenal pheochromocytoma (PHE) is reported more challenging than other adrenal pathologies.<sup>[8]</sup> Major challenging point of this pathology is maybe the hemodynamic instability (HDI) that occurs due to anesthesia or surgical intervention. Large adrenal tumors were considered as relative contraindication for minimal invasive surgery approximately 2 decades ago.<sup>[9-11]</sup> The reasons of this concerns were anatomic distortion of the gland due to large tumor, malignant potential of large adrenal tumor, and manipulating difficulties of large tumor during laparoscopic surgery. We aimed to evaluate 10 years' experience of LA for the treatment for PHE by comparing <5 cm and  $\geq$ 5 cm PHEs in diameter without suspicious of malignancy.

## Methods

The data of the patients evaluated retrospectively after the study protocol was approved by the Bursa Uludag University Clinical Research Ethics Committee (10.06.2020. 2020-10/19). Patients younger than 18 years old and patients whose adrenal tumors have suspicious for the primary adrenal malignant neoplasm were excluded from the study. The term "Primary adrenal malignant neoplasm" is used for adrenocortical carcinoma or other malignant tumors originated from the adrenal gland. However, patients with metastatic mass (metastases from any tissue to the adrenal gland) in the adrenal gland were included in the study. Adrenal tumors have suspicious for the primary adrenal malignant neoplasms that were evaluated with contrast-enhanced computerized tomography (CT) scans or dynamic magnetic resonance scans by an experienced uro-radiologist. All the cases performed transperitoneally on decubitus position. Pre-operative preparation arranged in accordance with anesthesiology and endocrinology consultations. PHE evaluated with history, physical examination, laboratory tests, and CT/magnetic resonance imaging scans. Standard laboratory tests were ACTH, DHEAS, total testosterone, 17 alpha-OH progesterone, aldosterone, cortisol, plasma catecholamines, urinary free cortisol, plasma renin activity, plasma, and urine catecholamines' metabolites. All the patients underwent alpha-blocker therapy (doxazosin 20 mg/day) 2 weeks before surgery as recommended.<sup>[12-15]</sup> Beta-blocker therapy started in case of necessity. Normal saline solution used for loading intravascular volume.

Patients under 18 years old and having adrenal masses with suspicious of malignancy in diagnostic tests were excluded from the study. Patients divided into two groups according to adrenal tumor size (longest diameter in centimeters) in pathological examination reports as S group (<5 cm) and L groups ( $\geq$ 5 cm). Patients' demographics (age, gender, American Society of Anesthesiologists [ASA] score, and body mass index [BMI]), tumor size, tumor laterality (right/left), duration of surgery (minutes), estimated blood loss (EBL) (milliliters), length of hospital stay (days), and post-operative complications were compared between two groups. The duration of surgery was calculated as the time from the insertion of trocars till the closure of the specimen extracting incision.

## Anesthesia

Anesthesia was induced intravenously with 0.03–0.05 mg/kg<sup>-1</sup> midazolam, 1 mg/kg<sup>-1</sup> lidocaine HCL, 2.5–3 mg/kg<sup>-1</sup> propofol, 1–1.5 mg/kg<sup>-1</sup> fentanyl, and 0.6<sup>-1</sup> mg/kg<sup>-1</sup> rocuronium and was maintained with 2% sevoflurane in a mixture of 50/50 O<sub>2</sub>/NO<sub>2</sub>. Positive pressure ventilation parameters were adjusted to maintain end-tidal CO<sub>2</sub> at 35–45 mmHg. Intraoperative crystalloid fluid (lactated ringer's solution) was infused at the rate of 3–5 ml/kg/h. Hemodynamics parameters data were collected from anesthesiology perioperative patient follow-up charts.

## Surgical Technique

Central venous catheter and radial arterial line were prepared for infusion and continuous blood pressure monitoring. Nasogastric/orogastric tube and urethral catheter were inserted. LAs performed in general anesthesia with endotracheal intubation through lateral decubitus transperitoneal approach. Pneumoperitoneum was established with Veress needle at 1/3 lateral side between SIAS and umbilicus. Pneumoperitoneum pressure set to 20 mmHg. A zero – degree laparoscope is inserted into the peritoneal cavity. Two or three additional trocars are inserted on the subcostal space from midclavicular line to posterior axillar line. After insertion of all trocars, pressure set to 12 mmHg.

For the right-sided tumors, Toldt line incised and colon medialized. Duodenum taken down with Kocher maneuver. Vena cava inferior and right renal vein are identified. Dissection carried out cranially from the right renal vein to adrenal vein. It is identified and dissected than controlled with polymer clips. The inferior edge of the adrenal vein is identified and psoas muscle was seen. Adrenal gland dissected with ultrasonic scalpel from renal parenchyma and retroperitoneal attachments. Adrenal gland is removed in a 10 mm endobag from extended trocar incision.

For the left sided tumors, Toldt line incised and colon taken down. The left renal vein is identified. Adrenal vein is dissected and clipped. The same remaining steps are performed as the right-sided tumors.

### Statistical Analysis

Skewness and Kurtosis test were used to assess normality. The normally distributed data were presented as mean±standard deviation and non-normally distributed data were presented as median value (interquartile range). Baseline characteristics between <5 cm and >5 cm tumors were compared with an unpaired Student's t-test or the Mann-Whitney U-test for continuous variables and a  $\chi^2$  test or Fisher's exact test for categorical variables. All statistical procedures were performed with SPSS 23.0 (SPSS Inc, Chicago, Illinois).  $P < 0.05$  was considered as significant.

### Results

Three hundred and forty LAs performed between February 2008 and August 2020 with the initial diagnose of adrenal mass at our tertiary reference University hospital. Of these, 54 (27 female and 27 male) consecutive patients diagnosed PHE after pathologic evaluation. Mean age of the patients was  $47.6 \pm 13.6$  years (72.2% was 60 years and over). Twelve patients were ASA score 1, 33 were ASA score 2, 7 were ASA score 3, and 2 were ASA score 4. Twenty-nine (53.7%) tumors were located on the right adrenal and 25 (46.3%) were on the left side. Mean tumor size was  $47.2 \pm 17.04$  mm. There were 26 (48.1%) patients in S group and 28 (51.9%)

patients were in L group. Mean age of the patients were  $48 \pm 14$  and  $47 \pm 14$  years for group S and group L, respectively. Groups compared in the aspect of ASA scores, both groups were similar ( $p=0.572$ ). BMI of the groups S and L was  $28.9 \text{ kg/m}^2$  and  $26.1 \text{ kg/m}^2$ , respectively ( $p=0.516$ ). Furthermore, in the aspect of tumor side (location), the ratio of elder ( $\geq 60$ -years-old) patients, and gender ratio were similar between groups S and L ( $p=0.6$ ,  $p=0.331$ , and  $p=0.207$ , respectively).

When perioperative data were evaluated, mean duration of surgery for groups S and L was  $103 \pm 39$  min and  $115 \pm 39$  min, respectively ( $p=0.266$ ). Mean EBL was  $50 \pm 22$  ml and  $73 \pm 91$  ml, respectively ( $p=0.587$ ).

Perioperative records of patients' hemodynamics data were evaluated. Mean pre-operative systolic arterial pressure for S and L groups was  $155 \pm 25$  mmHg and  $155 \pm 26$  mmHg ( $p=0.992$ ), mean perioperative maximum systolic arterial pressure was  $170 \pm 33$  mmHg and  $173 \pm 29$  mmHg ( $p=0.768$ ), mean pre-operative diastolic pressure was  $95 \pm 18$  mmHg and  $94 \pm 16$  mmHg ( $p=0.741$ ), and mean perioperative maximum diastolic pressure was  $100 \pm 16$  mmHg and  $99 \pm 16$  mmHg ( $p=0.812$ ), all, respectively (Table 1).

Mean hospital stay between groups S and L was  $3 \pm 2$  days and  $3 \pm 1$  days, respectively ( $p=0.374$ ).

Only one complication in group S and one complication in group L was seen. The complication in group S was prolonged ileus and the complication in group L was perioperative blood transfusion due to venous bleeding. No conversion to open surgery was needed.

**Table 1.** Demographic and perioperative outcomes

	Group S (<5 cm) (n=26)	Group L ( $\geq 5$ cm) (n=28)	p
Age (years)	$48 \pm 14$	$47 \pm 14$	0.579
Gender	11 Male 15 Female	16 Male 12 Female	0.207
Laterality (Right/Left)	14 Right 12 Left	15 Right 13 Left	0.6
Number of elderly patients ( $\geq 60$ -years-old)	6/26	9/28	0.331
BMI ( $\text{kg/m}^2$ )	$28.9 \pm 5.9$	$26.1 \pm 5.9$	0.516
Tumor size (mm)	$32.79 (10-45)$	$60.07 (50-80)$	-
Operation time (minutes)	$103 \pm 39$	$115 \pm 39$	0.266
EBL (ml)	$50 \pm 22$	$73 \pm 91$	0.587
LoHS (days)	$3 \pm 2$	$3 \pm 1$	0.374
Systolic instability (mmHg)	$57 \pm 29$	$57 \pm 24$	0.852
Diastolic instability (mmHg)	$37 \pm 16$	$39 \pm 13$	0.526
Maximum systolic pressure (mmHg)	$170 \pm 33$	$173 \pm 29$	0.768
Maximum diastolic pressure (mmHg)	$100 \pm 16$	$99 \pm 16$	0.812

S: Small; L: Large; BMI: Body mass index; EBL: Estimated blood loss; LoHS: Length of hospital stay; P: P value.

The difference between maximum and pre-operative systolic pressure (MaxMinSys) and the difference between maximum and pre-operative diastolic pressure (MaxMinDia) as HDI parameters were similar between S and L groups ( $p=0.852$  and  $p=0.526$ , respectively).

When we examine other HDI parameters, there were not any patient who has mean arterial pressure (MAP)  $<60$  mmHg. In our cohort. In statistical analyze, there was not significant difference between group L and group S in the aspect of systolic blood pressure (SBP)  $>160$  mmHg, at least 10 episodes of SBP  $>30\%$  of baseline and HR  $>110$  ( $p=0.307$ ,  $p=0.609$ ,  $p=0.296$ ). In terms of diastolic blood pressure (DBP)  $<30\%$  (at least ten episodes), there is a difference between groups in favor of group L, but not statistically different ( $p=0.077$ ).

There was no difference between the groups in terms of complications. Only 2 (3.7%) complications were seen in our series. Complication of group L was Clavien Dindo Classification (CDC) grade 2 and one CDC grade 1 patient in group S ( $p=0.755$ ).

Pathology reports of total 340 LAs were; 172 adrenocortical adenoma, 53 PHE, only one malign PHE, 52 metastatic tumors, and 62 other benign pathologies (myelolipomas, nodular hyperplasia, benign adrenal cysts, ganglioneuromas, etc.).

## Discussion

This study shows that LA for PHE needs extra care because its potential risk to create HDI, especially in larger tumors and in elderly patients.

PHE is a catecholamine secreting tumor originates from chromaffin cells in the adrenal medulla.<sup>[16]</sup> Endotracheal intubation, manipulating the gland during the dissection or due to pneumoperitoneum pressure, tumor may secrete excessive amount of catecholamines as a result of this hypertension attacks could occur or by the effect of tumor resection hypotension attacks, may occur due to catecholamine withdrawal.<sup>[17-20]</sup> All these HDIs may cause severe fluctuations in blood pressure.<sup>[17-19]</sup>

Surgery is the unique successful treatment option for PHE.<sup>[21]</sup> Laparoscopy become gold standard for benign tumors of adrenal gland such as Cushing's disease, Conn's syndrome, incidentalomas, and also adrenal metastases.<sup>[22-25]</sup> In recent years with the gaining attention of minimally invasive techniques, laparoscopy took its place in the surgical treatment of PHE.<sup>[26]</sup> Transperitoneal lateral approach which provides excellent exposure and wide working space described first by Gagner is the most preferred technic, but also lateral retroperitoneal or anterior approaches are commonly used by several surgeons.<sup>[4,25]</sup> We preferred lateral transperitoneal

approach, because urologic surgeons are familiar with this technic from laparoscopic kidney surgeries. In the literature, cut-off tumor size for laparoscopic surgery provided as 5–6 cm in accordance with this we took the value of 5 cm as a cut-off size while forming our groups (group L and group S).<sup>[27-29]</sup> The size of an adrenal tumor is thought to have malignancy potential in PHE and it is purported that open surgery is the best choice for malign adrenal tumors.<sup>[11]</sup>

There are studies in the literature indicating that large adrenal masses prolong the operation time or do not affect it. In some studies, duration of surgery found to be longer in PHE patients.<sup>[8,30,31]</sup> In our former study, we analyzed similar operation time for PHE and other adrenal pathologies.<sup>[28]</sup> Interestingly Rao et al. found longer operation time for  $>4$  cm PHE, but it was not statistically significant.<sup>[32]</sup> In our study, operation time was similar between group S and group L ( $p=0.266$ ) and this may be because all operations were performed by the same three surgeons using the same technique.

By the fact that, the adrenal gland's anatomically deep localization dissection of the gland is arduous and may lead to unwanted bleeding that may even require conversion to open surgery. A study comparing LA for  $\geq 6$  cm and  $<6$  cm PHEs reported significantly higher EBL for large tumors (150 mL vs. 100 mL).<sup>[27]</sup> Similarly Bai et al. reported 100 mL EBL for large adrenal tumors that underwent LA for PHE.<sup>[33]</sup> In accordance with the literature, our EBL is  $50\pm 22$  mL and  $73\pm 91$  mL for group S and group L, respectively. Although EBL was higher in group L than in group S, this difference was not statistically significant ( $p=0.587$ ). In our opinion, larger PHEs tend to have more bleeding, but careful dissection and new technology sealing devices limit this problem.

A study from USA reported very short ( $1.3\pm 0.2$  days) mean hospital stay for LA for PHE.<sup>[27]</sup> Another study from USA declared a bit longer (4.8 days) mean hospital stay.<sup>[21]</sup> Nguyen et al. stated that the mean hospital stay of PHE patients is  $3.4\pm 1.9$  days.<sup>[8]</sup> In accordance with the literature, our mean hospital stay were group S and group L were  $3\pm 2$  days and  $3\pm 1$  days, respectively, and the difference was not statistically significant. It is well known that perioperative complications prolong hospitalization; we associated the lack of difference in length of hospital stay between the groups with low complication rates in both groups.

HDI during surgery is a major challenging factor and may be the most important point that distinguishes PHE surgery from surgery of other adrenal pathologies and has a potential risk for end organ damage. There is no agreed quantitative definition on HDI. In different studies, HDI was defined by different methods. In a very recent study from China,

HDI is defined as intraoperative SBP >160 mmHg or to be 30% above the baseline (at least ten episodes) measurement (baseline blood pressure was defined as blood pressure after blockade and within 1 week before the operation) (SBP >30%) or DBP 30% less than baseline (at least ten episodes) measurement (DBP <30%).<sup>[34]</sup> In another recent study comparing HDI between transperitoneal and retroperitoneal approach SBP >200 mmHg, MAP <60 mmHg, combinations of these and need of intravenous vasopressor or vasodilator medication, were taken as HDI criteria.<sup>[35]</sup> In our study, we evaluated these parameters (SBP >160, SBP >30%, DBP <30%, MAP <60,) and patients whose heart (pulse) rate >110 beat per minute. In addition, we defined HDI as the difference between maximum and minimum systolic blood pressure (MaxMinSys) and the difference between maximum and minimum diastolic blood pressure (MaxMinDia) and diastolic blood pressure measurements.

Vorselaars et al. found greater risk on retroperitoneal adrenalectomy compared with transperitoneal approach, and interestingly, they reported medical center was a significant independent influencing factor for HDI.<sup>[35]</sup> According to Paganini et al., LA for PHE should be performed only in centers with a well-established, multidisciplinary experience in the diagnosis, and treatment of adrenal gland pathology, due to the complexity of the disease.<sup>[21]</sup> The recent study from China showed that tumor size (>5 cm) and five-fold increases of urine epinephrine levels as risk factors for HDI.<sup>[34]</sup> Similarly to this, in our study, DBP <30% as a HDI criteria was higher in group L compared to group S but not statistically significant. We also think like Paganini et al. that HDI is a challenging point and LA for PHE should be done in experienced centers with a multidisciplinary approach.

Surgical complications are perhaps the most disturbing point that keeps surgeons sleepless for PHE, because managing complications are really difficult and need multidisciplinary approach. Carter et al. reported 12% complication rate for 26 LAs for PHE. A French study decelerated 6.94% complication rate for PHE with retroperitoneal approach.<sup>[27]</sup> Prudhomme et al. reported 3.5% complication rate for transperitoneal or retroperitoneal LA. Similarly, in our study, we had a 3% complication rate compatible with the literature. The complication in group L was transfusion need due to a small vascular injury and it was CDC 2. Complication of groups S was prolonged ileus and it was CDC 1. Although our study has some points of limitations, the main one is the retrospective nature of the study. However, in our series, all patients underwent transperitoneal LA, we do not have retroperitoneal experience and another limitation of our study is lack of an agreed definition of HDI in the English literature.

## Conclusion

LA for PHE is more challenging than LA for other benign pathologies of adrenal gland in some aspects as HDI; therefore, by the nature of the PHE, these kind of tumors, regardless of tumor size, deserves more attention when compared with other benign pathologies of adrenal gland. In the authors' opinion, while planning treatment of such patients, it is necessary to work in coordination with endocrinologists and anesthesiologists and, if possible, LAs for PHE patients should be performed in experienced medical centers.

## Disclosures

**Ethics Committee Approval:** Uludag University medical faculty clinical research Ethics Committee 2011-KAEK-26/346.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – M.C.C., K.O.G.; Design – M.C.C., K.O.G.; Supervision – I.Y., H.V.; Materials – C.G.O.; Data collection &/or processing – M.C.C., C.G.Ö.; Analysis and/or interpretation – M.C.C., K.O.G.; Literature search – M.C.C., C.G.O.; Writing – M.C.C., K.O.G.; Critical review – I.Y., H.V.

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