

Endocrinological Surgical and Pathological Evaluation of Large Adrenal Lesions: City Hospital and Tertiary Health Center Data

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ABSTRACT

Objective: We aimed to evaluate patients who presented to our clinic with large adrenal lesion and underwent surgical treatment through either a laparoscopic or open approach, focusing on endocrinological, surgical, and pathological aspects, in the context of existing literature.

Methods: In this retrospective study, the records of 757 patients admitted to our clinic for adrenal lesion between 2013 and 2024 were examined. Lesions larger than 5 cm were found in 38 of them. The data of 32 patients who met the study criteria and were operated with the surgical approach determined by an experienced surgeon were analyzed. Clinical, laboratory, surgical and pathological findings were evaluated comprehensively.

Results: Hormonal analysis of 32 patients included in the study revealed functional lesions in 23 patients (71.9%) (Group 1) and non-functional lesions in 9 patients (28.1%) (Group 2). The most common histopathological diagnosis after surgical resection was pheochromocytoma, which was observed in 12 patients (37.5%). The median volume of all large adrenal lesions was 118.3 cm³ (interquartile range [IQR] 51.9-296.3). The median volume of Group 1 lesions was 159.1 cm³ (IQR 46.8-436.8), while the median volume of Group 2 lesions was 100.1 cm³ (IQR 72.2-156.5) ($p>0.05$). When analysed according to surgical approach (laparoscopic vs. open), open surgery was performed more frequently in Group 1 compared to Group 2 ($p=0.035$). The median Ki-67 index values were 4 (IQR=1-20) for Group 1 and 6 (IQR=3.5-57.5) for Group 2 with no significant difference between the groups ($p>0.05$).

Conclusion: This study highlights the necessity of a multidisciplinary approach in managing large adrenal lesions, involving endocrinologists, skilled surgeons, and pathologists for optimal treatment. Tailored surgical decisions and preoperative preparation based on tumor functionality and size are essential for minimizing risks and ensuring successful outcomes.

INTRODUCTION

Large adrenal tumors are generally defined as those measuring ≥ 4 cm, though some systematic reviews and meta-analyses, which assess the safety and efficacy of laparoscopic versus open adrenalectomy, use a threshold of ≥ 5 cm. Large adrenal tumors, ranging in size from 4 to 6 cm, represent approximately 8.6% to 38.6% of all adrenal tumors.^[1]

The risk of malignancy in patients with adrenal masses increases with the size of the mass. However, there is no absolute size threshold that determines the need for adrenalectomy. Sensitivity for the risk of malignancy is re-

ported to be 80% to 93% for tumors larger than 4 cm, whereas specificity ranges only 34% to 61%. Guidelines recommend that adrenalectomy should be considered for masses exceeding 4 to 6 cm with an individualized approach, considering the characteristics of the tumors.^[2,3]

Among all adrenal lesions, non-functional benign lesions are the most common, with 82.5%, followed by cortisol-secreting adenomas (5.3%), pheochromocytomas (5.1%), adrenocortical carcinomas (4.7%), metastatic lesions (2.5%) and aldosteronomas (1%).^[4] Large adrenal tumors have a wide spectrum of pathology ranging from benign lesions to adrenocortical carcinoma and metastases.

Among 19 different histopathological diagnoses observed, adrenal carcinoma was the most common, followed by benign adenomas, pheochromocytomas and metastases.^[5] The prognosis varies significantly depending on the pathological type of the tumor; patients diagnosed with malignant tumors, especially adrenal metastases, have worse outcomes.^[6]

The decision to perform laparoscopic or open surgery for large adrenal masses depends on several factors, particularly the size and characteristics of the mass. Laparoscopic procedures are typically preferred for masses up to 6-10 cm in size. Larger tumors can also be resected laparoscopically by experienced surgeons; however, size alone may necessitate open adrenalectomy. Open surgery is generally preferred for masses larger than 10 cm, especially if malignancy is suspected, due to concerns about preventing rupture, achieving adequate surgical margins and the risk of tumor transplantation. Tumor characteristics such as irregular shape, invasion of surrounding tissues (e.g. vena cava or aorta), progressive growth, significant intra-abdominal adhesions from previous surgery and high risk of malignancy on imaging also influence the surgical approach. Patient-specific factors such as high risk for prolonged anesthesia and intraoperative findings such as excessive bleeding or difficult anatomy should also be considered. Ultimately, the choice of approach should be individualized based on the surgeon's expertise and these clinical considerations.^[7-9]

In large adrenal lesions, endocrinological evaluation, radiology and/or nuclear medicine studies, surgical operation planning, preoperative preparation, and correct management of anesthetic approaches during the intraoperative process are critical. Therefore, the best patient management is individualization of treatment with a multidisciplinary approach.^[10,11] This study aims to present the endocrinological, surgical, and pathological evaluation of large adrenal masses at a tertiary referral center.

MATERIALS AND METHODS

Study design

This retrospective study was conducted by analysing the medical records of patients admitted to the Endocrinology and Metabolic Diseases outpatient clinic of a tertiary care city hospital for adrenal lesions between 2013 and 2024. A total of 757 patient records with adrenal lesions were reviewed. As a result of detailed evaluations, 38 patients were diagnosed with large/giant adrenal mass. The laparoscopic or open adrenalectomy surgical approach of these patients was evaluated, and the postoperative pathology reports were examined. 6 patients were excluded from the study due to missing data. Ultimately, 32 patients who met the inclusion criteria were consecutively included in the study (Fig. 1). The clinical trial protocol was approved by the ethics committee of University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital (Date 28/06/2024; Number: 2020/514/182/12) and complied with the Declaration of Helsinki.

Eligibility

Study inclusion criteria: 1) Male and female patients aged 18 years or older, 2) Patients diagnosed with large adrenal masses (≥ 5 cm), 3) Patients who underwent laparoscopic or open adrenalectomy, 4) Patients with completed histopathological and immunohistochemical studies. Exclusion criteria: 1) Missing medical data, 2) Patients who were inoperable or refused surgery, 3) Patients who initially underwent laparoscopic surgery but were converted to open surgery.

Functional analysis

The diagnosis of Cushing syndrome (hypercortisolism) was confirmed through suppression of adrenocorticotropic hormone (ACTH) levels, an increase in free cortisol levels in urine, and failure to suppress cortisol in dexamethasone suppression tests. Primary hyperaldosteronism was diagnosed based on an elevated plasma aldosterone/

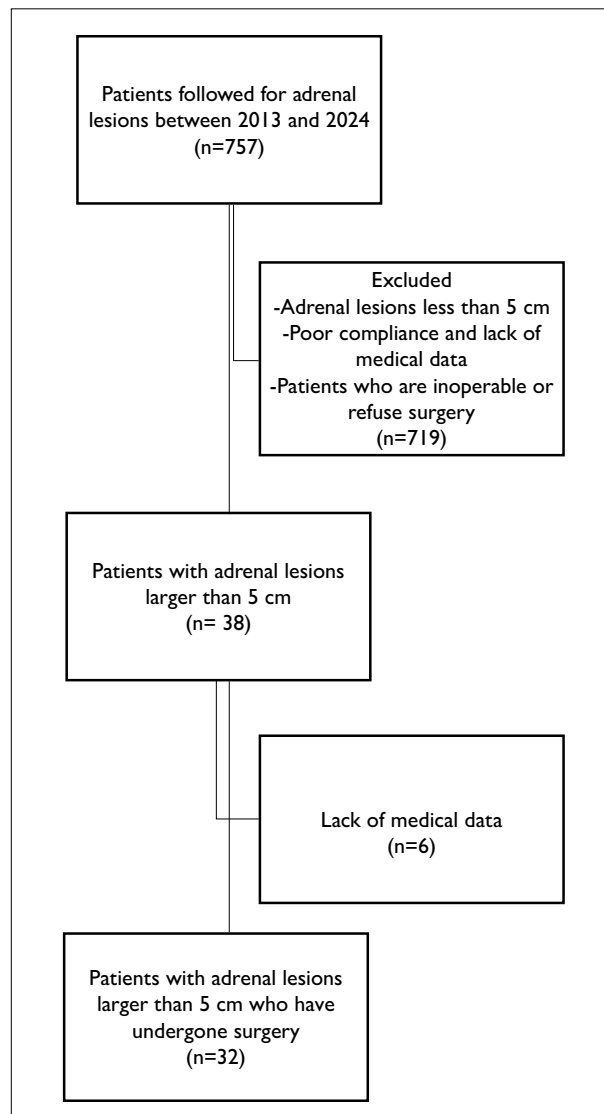


Figure 1. Flowchart diagram of the study.

plasma renin activity ratio and the inability to suppress aldosterone levels following dynamic testing. Pheochromocytoma was diagnosed in patients presenting with clinical symptoms and signs, supported by elevated urinary catecholamine and metabolite levels. For preoperative preparation, alpha receptor blockers were administered to pheochromocytoma patients two to three weeks prior to surgery, followed by beta receptor blockers after achieving adequate alpha-adrenergic blockade. A sex hormone-producing tumor was diagnosed based on elevated serum androgen and/or estrogen levels.

Tumor Volume Calculation and Pathological Evaluation

All patients were evaluated radiologically before surgery using contrast-enhanced abdominal and/or adrenal computed tomography (CT) and/or contrast-enhanced magnetic resonance imaging (MRI). Tumor characteristics including lesion location, maximum tumor diameter measured in all planes (craniocaudal, transverse, and anteroposterior), and histopathological findings were described. Adrenal mass volume was calculated postoperatively using the ellipsoid model formula (length x thickness x width x 0.52).^[12] Given the subjectivity of the Ki-67 index, all pathology samples were reviewed by pathologists specialized in adrenal to address potential heterogeneity in results.

Surgical Procedure Selection

The decision to perform laparoscopic or open surgery for adrenal masses is influenced by several factors, including the size and characteristics of the mass (irregular shape, invasion of surrounding tissues such as the vena cava or aorta, and intra-abdominal adhesions due to previous surgery, high risk of malignancy). Patient-specific considerations, such as the high risk of prolonged anesthesia, also play a crucial role, especially regarding whether an adequate and safe surgical margin can be achieved. Ultimately, the choice of surgical approach is determined by the experienced surgeon, considering the patient's risk factors and intraoperative findings such as excessive bleeding and complex anatomy.

Statistical analysis

Descriptive statistical methods, including frequency (n), percentage (%), mean \pm standard deviation (SD), and median (interquartile range [IQR]), were used to summarize the main characteristics of the data, depending on the normality of the distribution. The normality of the data distribution was assessed using the Shapiro-Wilk test. Data from all patients meeting the inclusion criteria were obtained from the institution's database. Group 1 (functional adrenal masses) and Group 2 (non-functional adrenal masses) were compared using the Independent Samples T-test for normally distributed data, the Mann-Whitney U test for non-normally distributed data, and Fisher's exact test for categorical variables. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using SPSS version 17.0 (SPSS for Windows, Inc., Chicago, Illinois, USA).

RESULTS

A total of 32 patients were included in the study, of which 14 (43.8%) were male and 18 (56.3%) were female, with a mean age of 47.9 ± 11.8 years. The detailed functional analyses, histopathological types of the adrenal masses, tumor sizes (cm), tumor volumes (cm³), and Ki-67 (%) indices for each patient are presented separately in Table 1.

Postoperative histopathological diagnoses revealed pheochromocytoma in 12 (37.5%) patients, cortical adenoma in 7 (21.9%), cortical carcinoma in 5 (15.6%), myelolipoma in 2 (6.2%), and schwannoma, angiomyolipoma, ganglioneuroma, cortical neoplasm, metastasis, and leiomyosarcoma in 1 (3.1%) patient each (Table 2).

Hormonal analysis revealed functional tumors in 23 patients (71.9%) (Group 1) and non-functional tumors in 9 patients (28.1%) (Group 2). The distribution of adrenal lesions was 16 (50%) right-sided, 15 (46.9%) left-sided and 1 (3.1%) bilateral with no statistically significant difference ($p > 0.05$). The median volume of all adrenal lesions was 118.3 cm³ (IQR 51.9-296.3), while the median volumes for Group 1 and Group 2 were 159.1 cm³ (IQR 46.8-436.8) and 100.1 cm³ (IQR 72.2-156.5), respectively ($p > 0.05$). When comparing the surgical approach (laparoscopic versus open surgery) for functional and non-functional large lesions, the rate of open surgery was significantly higher in Group 1 ($p = 0.035$). The median Ki-67 index for the 17 patients with available data was 5 [IQR 2-20], while the median Ki-67 indices for the functional and non-functional groups were 4 [IQR 1-20] and 6 [IQR 3.5-57.5], respectively ($p > 0.05$) (Table 3).

DISCUSSION

In this study, we presented the endocrinological, surgical, and pathological experiences related to large adrenal lesions (≥ 5 cm) at a tertiary referral center and a city hospital. Given the limited data available regarding the management of large adrenal lesions, we believe that a multidisciplinary approach involving an endocrinologist, pathologist, and experienced adrenal surgeon is the most appropriate method for individualized assessment and management of these patients.

Adrenal lesions are often incidentally discovered during radiological examinations, and the prevalence of such findings increases with age.^[13] Generally, the larger the lesion, the higher the likelihood of adrenal carcinoma. In patients with adrenal masses, the risk of malignancy is directly proportional to the size of the mass. Numerous studies have reported 80-93% sensitivities for the risk of malignancy at a lesion size threshold of 4 cm, although specificity has been recorded at only 34-61%.^[14,15] Given this risk, Bednarczuk et al.^[16] suggested that tumors larger than 5 cm should be considered an additional indication for surgery in cases of adrenal incidentalomas. In the study of Zhang et al.,^[1] benign large adrenal lesions accounted for 68.13%, while malignant lesions comprised 28.69%. In our study,

Table 1. Pathological and clinical evaluation of large adrenal lesions

Case No	Age	Sex	Type of Pathology	Tumor Size (cm)	Tumor Volume (cm ³)	Function	Ki-67 (%)
1	46	F	Cortical carcinoma	8x7x7	203.84	Cortisol+ androgen	%5
2	39	F	Cortical carcinoma	5X4.5X4	46.8	Cortisol	%16
3	67	F	Cortical carcinoma	9X8.5X4	159.12	Cortisol+ androgen	%24
4	56	F	Cortical adenoma	5x3x3.5	27.3	Cortisol	-
5	49	F	Myelolipoma	9x6x3	84.24	Non-functional	-
6	56	F	Cortical neoplasm*	8.5x7x6	185.64	Cortisol	%4
7	44	M	Cortical adenoma	5.7x4.5x2.5	33.34	Cortisol+ aldosterone	-
8	47	M	Cortical adenoma	7x4x3.5	50.96	Cortisol	-
9	53	M	Malign epithelial tm.	6.8x4.0x6.6	93.35	Non-functional	%90
10	64	F	Schwannoma	5x5x4.5	58.5	Non-functional	-
11	54	F	Pheochromocytoma	12x11x10	686.4	Catecholamine	%18
12	33	M	Pheochromocytoma	15x11x7	600.6	Catecholamine	-
13	50	M	Cortical adenoma	6x5.5x3.5	60.06	Non-functional	-
14	49	F	Leiomyosarcoma	10.5x7.5x7	286.65	Non-functional	%25
15	38	M	Pheochromocytoma	6x4x3	37.44	Catecholamine	%3
16	49	M	Myelolipoma	8x6.5x5	135.2	Non-functional	-
17	62	M	Pheochromocytoma	5x4.5x4	46.8	Catecholamine	%25
18	50	F	Cortical adenoma	12x10x5.5	343.2	Cortisol	%20
19	41	F	Pheochromocytoma	8x5x2	41.6	Catecholamine	%5
20	25	M	Pheochromocytoma	5x3x1	7.8	Catecholamine	%1
21	45	F	Pheochromocytoma	12x10.5x9.3	609.33	Catecholamine	-
22	25	M	Pheochromocytoma	10.8x7x3.8	149.38	Catecholamine	-
23	43	F	Pheochromocytoma	6x5x3.8	59.28	Catecholamine	%1
24	55	F	Cortical carcinoma	20x13x11	1487.2	Cortisol	-
25	41	M	Pheochromocytoma	12x8x6	299.52	Catecholamine	-
26	59	M	Pheochromocytoma	9x7.5x7	245.7	Catecholamine	-
27	61	F	Angiomyolipoma	7x5.5x5	100.1	Non-functional	-
28	55	F	Cortical adenoma	7x5x3	54.6	Cortisol	%1
29	55	M	Cortical adenoma	9.5x9x4	177.84	Non-functional	-
30	68	M	Pheochromocytoma	14x10x8	582.4	Catecholamine	%1
31	32	M	Cortical carcinoma	14x12x5	436.8	Cortisol	%20
32	23	F	Ganglioneuroma	7.5x6.5x4	101.4	Non-functional	%5

*Adrenocortical neoplasm of uncertain malignant potential.

malignant lesions were found in 21.9% and benign masses in 37.5%. However, when indeterminate lesions, such as pheochromocytomas and adrenocortical neoplasms of uncertain malignant potential, were categorized as a separate group, these masses represented 40.6% of the total. Due to the metropolitan structure of the city where our tertiary referral hospital is located, rare (2-8 per million) pheochromocytoma cases are frequently referred to our center. In conclusion, the higher incidence of pheochromocytoma in our series leads to findings different from those reported in the current literature.

Large adrenal lesions include a variety of pathological conditions. In our study, the three most common histological types—pheochromocytoma, adenoma, and carcinoma—account for 75% of the cases among the ten different diagnoses. We also identified some rare and unexpected lesions, such as schwannoma, ganglioneuroma, adreno-

Table 2. Histopathology of postoperative large adrenal masses

Histopathological diagnosis	n	%
Pheochromocytoma	12	37.5
Cortical adenoma	7	21.9
Cortical carcinoma	5	15.6
Myelolipoma	2	6.2
Schwannoma	1	3.1
Angiomyolipoma	1	3.1
Ganglioneuroma	1	3.1
Cortical neoplasm*	1	3.1
Metastasis**	1	3.1
Leiomyosarcoma	1	3.1

*Adrenocortical neoplasm of uncertain malignant potential. **Malign epithelial tumor.

Table 3. Comparison of functional and non-functional adrenal lesions

	Total (n=32)	Functional (Group 1) (n=23)	Non-functional (Group 2) (n=9)	p
Age	47.9±11.8	47±12.1	50.3±11.6	0.483
Gender				
Male n (%)	14 (43.8%)	10 (43.5%)	4 (44.4%)	1.0
Female n (%)	18 (56.3%)	13 (56.5%)	5 (55.6%)	
Lesion				
Localization*				
Right	16 (50%)	10 (43.5%)	6 (66.7%)	0.433
Left	15 (46.9%)	12 (52.2%)	3 (33.3%)	
Bilateral	1 (3.1%)	1 (4.3%)	0	
Lesion volume	118.3 (51.9-296.3)	159.1 (46.8-436.8)	100.1 (72.2-156.5)	0.753
Surgical procedure**				
Laparoscopic (n %)	14 (43.8%)	8 (36.4%)	6 (85.7%)	0.035
open (n %)	15 (46.9%)	14 (63.6%)	1 (14.3%)	
Ki-67 (%)	5 (2-20)	4 (1-20)	6 (3.5-57.5)	0.198

*As only one adrenal lesion was bilateral, it was not statistically analyzed. **The surgical procedure for three adrenal lesions (two nonfunctional and one functional) is unknown. Values are means ± SD, median (interquartile range [IQR]), or n (percent), and p-values are from the Independent Samples T-test, Mann Whitney U test or Fisher's exact test. Statistical significance p<0.05.

cortical neoplasm of uncertain malignant potential, and leiomyosarcoma, with each represented by a single case. These rare lesions make up 12.4% of all tumors resected in our investigation. Notably, primary adrenal leiomyosarcoma is extremely rare, with only about 30 cases documented in the literature.^[17] In this study, both tumor diameter and volume were calculated, with histopathological analysis indicating that pheochromocytomas and adrenal carcinomas exhibited the highest mean tumor volumes. The overall mean tumor volume for all lesions was 118.3 cm³, with functional lesions having a mean volume of 159.1 cm³, while non-functional lesions had a mean volume of 100.1 cm³. This observed difference can be attributed to the relatively high prevalence of pheochromocytomas (37.5%) and cortisol-secreting adrenal carcinomas (15.6%) within the cohort. It was also noted that 10 adrenal lesions in this review were more extensive than 10 cm in diameter, representing a significant proportion of the total patient cohort, approximately one third.

Following the first laparoscopic adrenalectomy performed by Gagner et al.^[18] in 1992, minimally invasive surgical techniques have become increasingly popular. Prior to the adoption of these techniques, open adrenalectomy was the standard procedure for adrenal lesions.^[19] Today, laparoscopic adrenalectomy is considered the gold standard for the resection of adrenal lesions.^[20] The optimal surgical approach for large adrenal lesions remains a subject of ongoing debate, and careful consideration of each case is required to determine the most appropriate option after thorough planning. Various surgical techniques are available, including open transperitoneal, transthoracic, retroperitoneal, laparoscopic transperitoneal, retro-peri-

toneoscopic, and robotic adrenalectomy.^[10] Castillo et al.^[21] demonstrated that in patients with large adrenal lesions (>8 cm), laparoscopic adrenalectomy is associated with prolonged operative time, increased blood loss, and more extended hospital stays without affecting perioperative morbidity.^[21] While tumor size greater than 12 cm is generally considered a contraindication for laparoscopic adrenalectomy, several recent studies have shown that laparoscopic adrenalectomy can be safely performed even in cases with masses up to 15 cm.^[22] Laparoscopic adrenalectomy for pheochromocytomas has been shown to be safe and effective even for tumors larger than 6 cm. However, larger pheochromocytomas are associated with higher conversion rates and an increased risk of intraoperative hypertensive crises.^[23] In our study, due to the high incidence of pheochromocytoma and the substantial proportion of tumors exceeding 10 cm, an open surgical approach was performed in nearly half of the cases (46.9%).

The study's limitations include its single-center design, potential selection bias, retrospective nature, and relatively small number of tumors with rare pathologies. Considering that large adrenal lesions are rare and frequently reported as case studies in the literature, the sample size in the current series may be considered a relative limitation.

Conclusion

This study emphasizes the importance of a multidisciplinary approach to managing large adrenal masses. Collaboration between endocrinologists, pathologists, and experienced surgeons allows for the individual assessment of each patient, allowing for optimal treatment strategies. Appropriate surgical method selection by experienced

surgeons in the treatment of large adrenal lesions and comprehensive preoperative preparation for pheochromocytomas are also crucial to minimizing intraoperative risks and achieving successful outcomes.

Ethics Committee Approval

The study was approved by the University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital Ethics Committee (Date: 28.06.2024, Decision No: 2020/514/182/12).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: N.G., S.Ö.; Design: N.G., S.Ö., K.A.; Supervision: A.E.G., H.F.K., S.Ö.; Fundings: N.G., S.Ö., M.B., K.A., S.B.A., A.E.G., H.F.K.; Materials: N.G., S.Ö., M.B., K.A., S.B.A.; Data: N.G., S.Ö., K.A., M.B., S.B.A., A.E.G., H.F.K.; Analysis: N.G., S.Ö., K.A.; Literature search: N.G., S.Ö., M.B., S.B.A.; Writing: N.G., S.Ö.; Critical revision: N.G., S.Ö., K.A.

Conflict of Interest

None declared.

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Büyük Adrenal Lezyonların Endokrinolojik Cerrahi ve Patolojik Değerlendirilmesi: Şehir Hastanesi ve Üçüncü Basamak Sağlık Merkezi Verileri

Amaç: Kliniğimize büyük adrenal lezyon ile başvuran ve laparoskopik veya açık yaklaşımla cerrahi tedavi uygulanan hastaları, endokrinolojik, cerrahi ve patolojik yönlerine odaklanarak mevcut literatür eşliğinde değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmada, 2013-2024 yılları arasında adrenal lezyon nedeniyle kliniğimize başvuran 757 hastanın kayıtları incelendi. Bunların 38'inde 5 cm'den büyük lezyonlar saptandı. Çalışma kriterlerini karşılayan ve deneyimli bir cerrah tarafından belirlenen cerrahi yaklaşımla ameliyat edilen 32 hastanın verileri analiz edildi. Klinik, laboratuvar, cerrahi ve patolojik bulgular kapsamlı bir şekilde değerlendirildi.

Bulgular: Çalışmaya dahil edilen 32 hastanın hormonal analizinde 23 hastada (%71.9) fonksiyonel lezyonlar (Grup 1) ve 9 hastada (%28.1) fonksiyonel olmayan lezyonlar (Grup 2) saptandı. Cerrahi rezeksiyon sonrası en yaygın histopatolojik tanı 12 hastada (% 37.5) gözlenen feokromositoma idi. Tüm büyük adrenal lezyonların medyan hacmi 118.3 cm³ (IQR; 51.9-296.3) idi. Grup 1 lezyonların medyan hacmi 159.1 cm³ (IQR 46.8-436.8) iken, Grup 2 lezyonların medyan hacmi 100.1 cm³ (IQR 72.2-156.5) idi (p>0.05). Cerrahi yaklaşıma (laparoskopik vs. açık) göre analiz edildiğinde, Grup 1'de Grup 2'ye kıyasla açık cerrahi daha sık uygulanmıştır (p=0.035). Ki-67 indeks değerleri Grup 1 için 4 (IQR=1-20) ve Grup 2 için 6 (IQR=3.5-57.5) olup gruplar arasında anlamlı fark yoktu (p>0.05).

Sonuç: Bu çalışma, büyük adrenal lezyonların yönetiminde, optimal tedavi için endokrinologları, yetenekli cerrahları ve patoloğları içeren multidisipliner bir yaklaşımın gerekliliğini vurgulamaktadır. Tümör işlevselliği ve boyutuna göre özel cerrahi kararlar ve ameliyat öncesi hazırlık, riskleri en aza indirmek ve başarılı sonuçlar elde etmek için esastır.

Anahtar Sözcükler: Büyük adrenal lezyonlar; dev adrenal kitle; fonksiyonel tümörler; laparoskopik cerrahi.