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Original article

Pathological and clinical outcomes of adrenalectomy: A multi-center experience in Saudi Arabia

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ABSTRACT

Objective: To determine the nature of adrenal pathology in patients undergoing adrenalectomy in Saudi Arabia over the last decade and compare it with the literature. We compared perioperative outcomes between minimally invasive adrenalectomy (MIA) and open adrenalectomy (OA).
Methods: This retrospective study included patients who underwent adrenalectomy at five tertiary care centers in Saudi Arabia from 2010 to 2020. We collected patients' baseline and perioperative characteristics and detailed hormonal evaluation of adrenal masses.
Results: Among 160 patients (mean age 44 ± 14.5 years; mean BMI 29.17 ± 5.96 kg/m^2), 84 (51.5 %) were men and 51.5 % had left-sided adrenal masses. The mean tumor size was 6.1 ± 4.2 (1.0–19.5) cm, including 60 (37.5 %) incidentalomas and 65 (40.6 %) functioning masses. Histopathology revealed 74 (46.2 %) adenomas and 24 (15 %) cancers or metastases from other primary organs; 20 %, 8.8 %, and 2.5 % of patients had pheochromocytoma, myelolipoma, and 2.5 % ganglioneuroblastoma, respectively. MIA and OA were performed in 135 (84.4 %) and 21 (15.6 %) patients, respectively. Adrenalectomy was increasingly performed over three equal periods in the last decade (17.5 % vs 34.4 % vs 48.1 %), with increasing numbers of MIAs to replace OAs. OA patients had larger tumors and needed blood transfusion more frequently (47.6 % vs 10.8 %, p< 0.001). MIA was significantly associated with shorter operative time, shorter length of stay, and less blood loss. Postoperative complications occurred in 10 (6.2 %) patients and were significantly higher for OA (24 % vs 3.0 %, p< 0.001).
Conclusions: The majority of adrenal masses are benign. Herein, the observed functional and perioperative outcomes were comparable to those of available *meta*-analyses.

1. Introduction

Adrenal gland pathology has a broad spectrum, ranging from benign pathology with no hormone secretion to secretory and highly aggressive tumors. This necessitates a thorough clinical and radiological assessment for selecting surgical candidates, including genetic evaluation when necessary and assessment of whether the tumor is functioning according to the guidelines (Zeiger et al., 2009). However, adrenal tumors may present a diagnostic and management dilemma and may be diagnosed incidentally during abdominal imaging performed for an unrelated reason (adrenal incidentaloma) (Zeiger et al., 2009). Although most adrenal incidentalomas can be managed conservatively, surgical

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resection is required for symptomatic or subclinically functioning tumors and malignant or potentially malignant tumors (Brunaud et al., 2003; Shen et al., 2005).

The relative inaccessibility of the adrenal gland and its proximity to vital structures represent a surgical challenge. Minimally invasive adrenalectomy (MIA) has been introduced over the last few decades as an alternative to conventional open adrenalectomy (OA) for malignant and hormonally active lesions (Al-Otaibi, 2012; Patel et al., 2019). This was secondary to advancements in minimally invasive surgery (MIS) and the availability of advanced biochemical workups and high-quality radiological imaging. Compared to open surgery, MIS allows easier access to the relatively small gland located in a critically high retroperitoneal location without large muscle incisions. Since its first description in 1992, laparoscopic adrenalectomy (LA) has become the preferred approach at most institutions due to its faster recovery, shorter hospital stay, lower incidence of complications, decreased postoperative analgesia, and lower morbidity and mortality rates (Assalia and Gagner, 2004; Coste et al., 2017; Schreinemakers et al., 2008). Outpatient adrenalectomy has been performed safely without an increased risk of postoperative complications or readmission in appropriately selected patients (Gartland et al., 2021). Therefore, laparoscopic and robotic approaches are currently considered the standard of care for adrenal lesions smaller than 8 cm (Germain et al., 2011). Nevertheless, OA offers the advantages of gentler handling of larger tumors with the ability to explore and resect adjacent organs in cases of local invasion (Mir et al., 2013).

However, adrenalectomy remains an infrequent procedure, where malignant disease and tumor size are independently associated with mortality (Patel et al., 2019). In addition, the effectiveness of the laparoscopic approach, which is the standard for benign adrenal lesions, remains controversial for large masses or adrenocortical carcinoma (Porpiglia et al., 2010). Therefore, this multicenter retrospective analysis was conducted to review the institutional experience of adrenalectomy in Saudi Arabia over the last decade and to compare the observed clinical and pathologic outcomes with existing literature.

2. Methods

2.1. Study design

Retrospectively collected data of all patients who underwent adrenalectomy, including OA and MIA, at five different academic and tertiary care centers in Saudi Arabia between 2010 and 2020 were prospectively reviewed. MIS included LA (either transabdominal or posterior retroperitoneal) and robotic transabdominal adrenalectomy**.** As per the pathology department's database and electronic health record systems, all cases of adrenalectomy that met our inclusion criteria were included. In total, 160 patients met the study criteria.

2.2. Preoperative workup

All patients underwent a preoperative complete laboratory workup, including complete urinalysis and culture, complete blood count, bleeding and electrolyte profiles, kidney and liver function tests, blood sugar analysis, electrocardiography, and chest X-ray, to assess comorbid conditions and fitness for anesthesia. Enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) was performed prior to surgery to identify the adrenal lesion and to ensure proper surgical planning. In addition, all patients were appropriately evaluated to identify possible endocrine dysfunction secondary to a functioning adrenal mass, for which an endocrinology team joined surgery. Cases of adrenal masses with suspected malignancy were discussed on a formal tumor board and were approached by a multidisciplinary team.

2.3. Data collection

Demographic data, including age, sex, body mass index (BMI), smoking history, concomitant medical comorbidity, and family history of cancer were recorded. Evaluated tumor characteristics included symptoms at presentation, whether the tumor was functioning or the patient had previous hypo- or hypertensive crises, laterality, and tumor size. Pathological assessment was carried out by examination of hematoxylin and eosin (H&E)-stained slides of the tumors, with the aid of immunohistochemical markers when needed. Perioperative parameters included institution, surgeon, total operative time (evaluated as the time from starting of the procedure or incision to closure or hands off), estimated blood loss (EBL), need for blood transfusion, conversion of MIS to open surgery, intraoperative adverse events, postoperative complications (classified according to the Clavien–Dindo classification), and length of hospital stay. Patients converted to open surgery were classified as the OA group, but to avoid bias, their operative times were not included in the analysis model. Recurrences, reoperations, or additional therapy provided to patients in addition to postoperative outpatient follow-up were assessed. Additionally, patient, tumor, and perioperative characteristics were compared between OA and MIA.

2.4. Data analysis

Data using the commercially available Statistical Package for the Social Sciences software (*SPSS Inc., Chicago, IL, USA*), version 22 were collected and analyzed. Categorical variables were presented as frequencies and percentages and then compared with Fisher's exact test. We present continuous variables as medians and quartiles or means and standard deviations and compared them with the Mann–Whitney *U* test or Student's *t test*, depending on the data distribution. Two-tailed p values< 0.05 were considered statistically significant.

3. Results

A total of 160 patients who underwent adrenalectomy between January 2010 and December 2020 were included in the study. The mean (range) age was 44 ± 14.5 (13–92) years, and BMI was 29.17 ± 5.96 (12.7–43.8) kg/m2; 84 patients (51.5 %) were males and had left-side adrenal masses. Adrenal masses were detected as incidentalomas in 60 patients (37.5 %), and 65 (40.6 %) had functioning masses. The mean tumor size was 6.1 ± 4.2 (1.0–19.5) cm: 73 patients (45.6 %) had tumors< 4.0 cm, 36 (22.5 %) had tumors between 4.0 and 6.0 cm, 51 (31.9 %) had tumors> 6.0 cm and 26 (16.2 %) had tumors> 10.0 cm (Table 1). The overall mean operative time was 209 ± 90 min, and the EBL was 259 ± 374 ml. EBL> 500 ml was detected in 17 patients (10.6 %), and 25 (15.6 %) required a perioperative blood transfusion. The overall mean length of hospital stay (LOS) was 7.6 ± 5.4 (1–30) days.

Patients undergoing OA had significantly larger tumor sizes and a history of cancer. Otherwise, the baseline demographic and tumor characteristics of both groups were comparable (Table 2). OA was performed in a significantly higher percentage of patients who had pheochromocytomas (40 % vs 10.4 %, $p< 0.001$). MIS was associated with a significantly shorter operative time (120 vs 195 min, $p = 0.009$), a shorter LOS (6.0 vs 8.5 d, $p = 0.001$), and less EBL (60 vs 600 ml, $p< 0.001$). More patients in the OA group needed a blood transfusion (47.6 % vs 10.8 %, $p< 0.001$) (Table 3).

Table 1
Overall demographic and tumor characteristics of the study cohort.

Parameter*		N (%) or mean (range)
Age/years		44 (13–92)
Male sex, n (%)		84 (52.5)
Female sex, n (%)		76 (47.8)
Left sided, n (%)		84 (52.5)
BMI (kg/m^2)		29.17 (12.7–43.8)
Smoking	Current smoker	21 (13.1)
	Former smoker	3 (1.9)
	Nonsmoker	124 (77.5)
Comorbidities	Hypertension	81 (50.6)
	Diabetes	34 (21.3)
	Cardiovascular	10 (6.5)
	Others	49 (30.6)
History of cancer		12 (7.5)
Family history of cancer		5 (3.1)
Hypertensive crises (SBP> 180 mmHg)		19 (11.9)
Hypotensive crises (DBP< 90 mmHg)		2 (1.3)
Radiological tumor size	Mean size/cmMedian	6.1 ± 4.25.0
	(interquartile)	(2.6–8.0)
	< 4 cm	73 (45.6)
	4–6 cm	36 (22.5)
	> 6 cm	51 (31.9)
Incidentalomas		60 (37.5)
Functioning tumors	Cushing	9 (5.6)
	Pheochromocytoma	24 (15.0)
	Conn's disease	23 (14.4)
	Ganglioma	4 (2.5)
	Others	4 (2.5)

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 2
Comparison of patient demographic and tumor characteristics between minimally invasive and open adrenalectomy.

Parameter* N = 160		MIA n = 135	OA n = 25	*p value*
Median age/years (interquartile)		42 (33–51)	48 (40–66)	0.86
Male sex, n (%)		73 (52.5)	11 (52.4)	0.35
Left sided, n (%)		70 (51.8)	14 (56.0)	0.70
Median BMI (kg/m^2)		29.1 (25.2–34.4)	28.1 (20.1–31.2)	0.12
Smoking	Current smoker	17 (12.6)	4 (16.0)	0.71
	Former smoker	3 (2.2)	0 (0.0)	
	Nonsmoker	103 (76.3)	21 (84.0)	
Comorbidities	Hypertension	67 (49.6)	14 (56.0)	0.23
	Diabetes	27 (20.0)	7 (28.0)	
	Cardiovascular	7 (5.2)	3 (12.0)	
	Others	45 (33.3)	4 (16.0)	
History of cancer		7 (6.2)	7 (28.0)	< 0.001
Family history of cancer		3 (2.2)	2 (8.0)	0.13
Hypertensive crises (SBP> 180 mmHg)		18 (13.3)	1 (4.0)	0.18
Hypotensive crises (DBP< 90 mmHg)		2 (1.5)	0 (0.0)	0.54
Tumor size	Mean size/cmMedian	6.2 ± 4.15.0	9.5 ± 3.78.7	< 0.001
	(interquartile)	(2.6–8.0)	(7.1–10.0)	
	< 4 cm	67 (49.6)	6 (24)	0.01
	4–6 cm	31 (23.0)	5 (20.0)	
	> 6 cm	37 (27.4)	14 (56.0)	
Incidentalomas		52 (38.5)	8 (32.0)	0.54
Functioning tumors	Overall	48 (35.6)	12 (48.0)	0.24
	Cushing	8 (5.9)	1 (4.0)	< 0.001
	Pheochromocytoma	14 (10.4)	10 (40.0)	
	Conn's disease	23 (17.0)	0 (0.0)	
	Ganglioma	3 (2.2)	1 (4.0)	
	Others	3 (2.2)	2 (8.0 %)	

MIA: minimally invasive adrenalectomy; OA: open adrenalectomy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure.
* Data presented as numbers (%) or medians (interquartile).

Both groups were significantly different in terms of the final histopathological assessment: there were 74 (46.2 %) patients with adrenal adenomas, 24 (15 %) with cancer or metastasis from another primary organ, 32 (20 %) with pheochromocytoma, 14 (8.8 %) with myelolipoma, 4 (2.5 %) with ganglioneuroblastoma, and 12 (7.5 %) with other varieties. MIA was used for a significantly higher percentage of patients with benign conditions (68.9 % vs 28 %, p< 0.001), whereas OA was used for a significantly higher percentage of patients with malignant diseases (72.0 % vs 31.1 %, p< 0.001), including pheochromocytoma, adrenal carcinoma, or secondary metastasis (Table 2).

Postoperative complications were observed in 10 (6.2 %) patients and were significantly more frequent in patients who underwent OA (24 % vs 3.0 %, p< 0.001). Two patients had Clavien–Dindo grade I complications, seven had grade II complications, and one had grade III complications (Table 4). Four MIA cases

Table 3
Comparison of perioperative parameters and histopathological assessments between minimally invasive and open adrenalectomy.

Parameter*		MIA n = 135	OA n = 25	*p value*
Median operation time (mins)		120 (52–211)	195 (128–302)	0.009
Estimated blood loss (mL)		60 (40–200)	600 (410–925)	< 0.001
Blood transfusion, n (%)		15 (10.8)	10 (47.6)	< 0.001
Length of hospital stay (days)		6.0 (4.0–8.0)	8.5 (7.2–14.0)	0.001
Histopathology	Adrenocortical adenoma	70 (51.8)	4 (16.0)	< 0.001
	Pheochromocytoma	23 (17.0)	9 (26.0)	
	Myolipoma	13 (9.6)	1(4.0)	
	Adrenal carcinoma	8 (5.9)	4 (16.0)	
	Metastatic	8 (5.9)	4 (16.0)	
	Ganglioneuroblastoma	3 (2.2)	1 (4.0)	
	Others	10 (7.4)	2 (8.0)	

MIA: Minimally invasive adrenalectomy; OA: Open adrenalectomy.
* Data presented as numbers (%) or medians (interquartile).

Table 4
Postoperative complications of the included cohort.

Complication*	Clavien–Dindo grade	MIA n = 135 (%)	OA n = 25 (%)	*p value*
Overall complications, n (%)		4 (3.0)	6 (24.0)	< 0.001
Surgical site infection (I)	I	0 (0.0)	2 (8.0)	< 0.001
Bleeding requiring transfusion (II)	II	2 (1.5)	3 (12.0)	
Urinary tract infection (II)	II	3 (2.2)	3 (12.0)	
Postoperative pneumonia (II)	II	0 (0)	2 (8.00)	
Incisional hernia (III)	III	0 (0)	1 (4.0)	

MIA: Minimally invasive adrenalectomy; OA: Open adrenalectomy.
* One patient may have many complications.

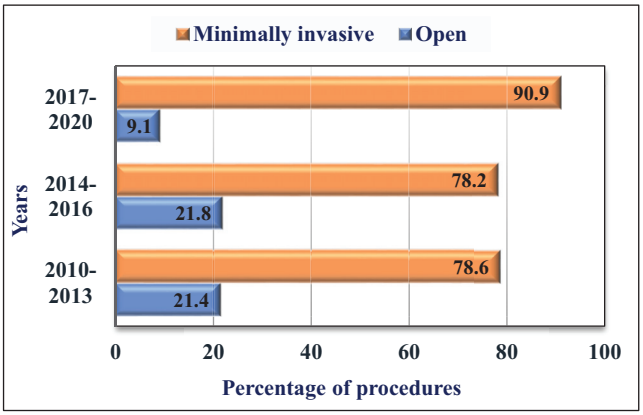

Fig. 1. The use of minimally invasive radical adrenalectomy is increasing in Saudi Arabia, and this technique is gradually replacing open procedures.

(3.0 %), including three cases of pheochromocytoma and one case of adrenal mass secondary to radical nephrectomy for renal cell carcinoma, were converted to open surgery due to uncontrolled intraoperative bleeding.

Among the four converted cases, three had a mass on the right side, two masses were< 4 cm, two masses measured 4–6 cm, two patients had a history of cancer, two patients had adjuvant chemotherapy, and one patient experienced a recurrence of the mass. Overall, six patients (3.8 %) experienced tumor recurrence, and this rate was comparable between MIA and OA patients (4 [2.9 %] vs 2 [9.5 %], respectively; p = 0.13). Nine patients received adjuvant chemotherapy, and two patients received adjuvant radiotherapy. Of the patients who underwent MIA and OA, five (3.6 %) and two (9.5 %), respectively, missed follow-up (p = 0.21), while three (2.1 %) and three (14.3 %) patients in each group, respectively, died (p = 0.006).

MIA and OA were performed in 135 (84.4 %) and 21 (15.6 %) patients, respectively. Of the 160 cases included, 28 (17.5 %) were performed between 2010 and 2013, 55 (34.4 %) were performed between 2014 and 2016, and 77 (48.1 %) were performed between 2017 and 2020. The number of MIAs increased over time and replaced OAs: 22 (78.6 %) vs 6 (21.4 %) between 2014 and 2016, 43 (78.2 %) vs 12 (21.8 %) between 2017 and 2020, and 70 (90.9 %) vs 7 (9.1 %) between 2017 and 2020 (p = 0.09) (Fig. 1).

4. Discussion

MIS has been evolving globally, and Saudi Arabia has been well adapted to such rapid advancements. This approach has replaced OA and has become the standard for surgical removal of the adrenal gland. The superiority of the laparoscopic approach compared with OA has been effectively proven, especially in terms of safety, faster recovery, less postoperative pain, and shorter LOS. Recently, Gartland et al. reported the safety of outpatient MIA without an increased risk of postoperative complications or readmission in appropriately selected patients (Gartland et al., 2021). Dworak et al. found that supervised residents could perform transperitoneal LA safely, with outcomes comparable to those of attending surgeons in terms of operative time, EBL, LOS, perioperative complications, and operator conversion (Dworak et al., 2019).

In the present study, adenoma and pheochromocytoma were the most prevalent pathological patterns, where MIA was mostly used. This was consistent with the findings of *Germain and colleagues*, where adrenalectomy is mostly performed, in decreasing order, for adenoma, pheochromocytoma, Cushing adenoma, nonsecreting incidentaloma, and adrenal metastases (Germain et al., 2011). Furthermore, MIA is increasingly performed in low-volume centers and replacing OA over time in Saudi Arabia, which may reflect the successful spread of MIS and support the availability of skilled technical staff in these centers. Despite being clinically clear, the small number of included OA cases precluded any statistical significance in the difference between procedures over subsequent time periods. The outcomes can be further improved in the future by including more cases and increasing the diversity of operating cases.

The current cohort showed that OA was significantly associated with significantly larger EBL, longer LOS, and higher requirements for transfusion than MIA. These outcomes are comparable with the findings of a recent *meta*-analyses, which included 1710 patients and found that although OA was associated with a shorter operative time than MIS, it was significantly associated with increased blood loss and longer LOS (Heger et al., 2017). In the latter study, pairwise *meta*-analysis of controlled clinical trials (CCTs) showed comparable complication rates between LA and OA [(OR: 95 % confidence interval): 0.22 (0.02–2.82); p = 0.24], with no significant advantage for any of the approaches in terms of operative time. LA was associated with significantly lower blood loss, which was confirmed by the included CCTs (Heger et al., 2017). The included single RCT comparing both techniques precluded *meta*-analyses but reported a significantly lower LOS for LA, which has been confirmed in CCTs (Heger et al., 2017). However, the current cohort showed that patients undergoing OA had significantly longer operative times because they had larger tumor sizes, which is different from that of *Heger*'s *meta*-analysis (Heger et al., 2017). This difference in operative time may be expected if considering the severe risk of bias exhibited by most of the trials included in the *meta*-analysis and the widely variable quality of the reported outcomes among the included trials, especially the perioperative complications, which were of very poor quality. Furthermore, the limited number of RCTs comparing LA and OA did not show significant differences in the operative time. Most surgeons may be biased by choosing a specific approach for only small tumors, which may influence the operative times. The observed perioperative complications in the present study were not better reported than those of the *meta*-analyses and their included studies.

In the present study, most adrenal adenomas were treated with MIA and had almost no complications or conversion to open surgery. This favorable outcome of MIA for benign diseases is consistent with that previously reported (Hazzan et al., 2001). Herein, most adrenal cortical carcinomas, which are rare malignant diseases or adrenal metastases, were treated by an open approach, which is the gold standard approach in suspicious cases (Moreno et al., 2013). This is specifically true for adrenal masses>6 cm, as it minimizes manipulation and ensures complete resection (Brunt et al., 1996). Several other studies proved the superiority of OA in such malignant cases (Cobb et al., 2005; Miller et al., 2012). However, the choice of surgical approach in adrenal carcinoma is still controversial, as the oncological outcomes are not dependent on the approach but on the appropriate surgical technique, including recurrence and disease-free survival (Pędziwiatr et al., 2015). Six patients (3.8 %) in the present cohort experienced tumor recurrence, and this was comparable between groups. *Zheng* et al. reported a higher incidence of local recurrence and a lower disease-free survival rate after radical adrenalectomy than the open approach and recommended OA for malignant adrenal disease. The author reported that LA should be considered only in carefully selected cases of adrenocortical carcinoma (Zheng et al., 2018). This finding is consistent with our observation of a lower recurrence rate, where most suspicious cases were managed by open surgery. However, others reported that a minimally invasive approach for pheochromocytoma has the advantages of less intraoperative fluctuations in blood pressure, less intraoperative blood loss, and shorter OR time, with fewer requirements of postoperative analgesics (Sprung et al., 2000; Wang et al., 2009). Considering that three of our four conversions to open surgery were pheochromocytomas, this would further support the idea that an appropriate surgical technique is crucial to the outcomes rather than the approach.

This study is limited by its retrospective nature, including recall bias and the relatively small number of patients undergoing OA. The comparative outcomes between the open and MIA groups may be biased by the significant difference in tumor size and subtypes of the functional masses. However, most reported data in the literature represent single-center experiences with small sample sizes, while the current study represents the first multicenter comparison of both approaches in low-volume centers in Saudi Arabia.

In conclusion, most adrenal masses are benign. The use of adrenalectomy has increased in Saudi Arabia over the last decade, with a progressive trend toward a minimally invasive approach rather than open surgery. The functional and perioperative outcomes from institutional low-volume centers in Saudi Arabia were comparable to the international data reported in recent *meta*-analyses.

5. Authors' contribution

R.A. contributed substantially to the study design, performed the surgery, interpreted data, drafted the article, and supervised the entire study. O.B. collected the data and participated in drafting the article. M.A.A contributed to data interpretation and participated in drafting the article. W.T. performed the surgery and participated in drafting the article. M.S.S. collected the data and participated in drafting the article. A.M.B. contributed to the study design and dafting the article. S.S.A. performed the surgery and participated in drafting the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Compliance with ethical standards

This is a retrospective study, and the data were collected from patients' records and files. Nevertheless, all participants gave written informed consent. We performed all procedures in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2023.103575.

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