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Research Article

Comparative Outcomes Of Laparoscopic Versus Open Adrenalectomy For Adrenal Masses Larger Than 6 Centimeters: A Retrospective Cohort Study

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ABSTRACT

Background: The optimal surgical approach for large adrenal masses exceeding 6 centimeters remains controversial. While laparoscopic adrenalectomy has become the gold standard for smaller masses, concerns persist regarding its safety and oncological adequacy for larger lesions. This study compared perioperative and oncological outcomes between laparoscopic and open adrenalectomy for adrenal masses larger than 6 centimeters.

Methods: A multicentric retrospective analysis was conducted of 34 patients who underwent adrenalectomy for masses ≥6cm between January 2020 and December 2023. Patients were divided into laparoscopic (n=16) and open (n=18) groups. Primary outcomes included operative time, blood loss, conversion rate, complications, and length of hospital stay. Secondary outcomes encompassed ICU requirements and pathological diagnoses.

Results: Mean mass size was 7.6±1.8cm in the laparoscopic group and 8.2±2.1cm in the open group (p=0.385). Laparoscopic approach demonstrated significantly reduced blood loss (120±90mL vs 340±210mL, p<0.001) and shorter hospital stay (3.4±1.2 vs 6.2±2.1 days, p<0.001). One conversion occurred (6.3%) in a hemorrhagic cyst case due to dense adhesions and bleeding. Myelolipoma was the most common diagnosis (58.8%), followed by pheochromocytoma (17.6%). All pheochromocytoma patients required postoperative ICU monitoring. No mortality occurred in either group.

Conclusion: Laparoscopic adrenalectomy for carefully selected adrenal masses larger than 6 centimeters is feasible and safe, offering superior perioperative outcomes. The high prevalence of myelolipomas in our population warrants consideration in surgical planning.

Keywords*: Laparoscopic Versus, Adrenal Masses Larger.*

INTRODUCTION

The surgical management of adrenal masses has undergone substantial evolution over the past three decades, with laparoscopic adrenalectomy emerging as a transformative approach that has fundamentally altered the therapeutic landscape of adrenal surgery (1). Since Gagner and colleagues first described laparoscopic adrenalectomy in 1992, this minimally invasive technique has progressively gained acceptance and is now considered the gold standard for the surgical treatment of small to moderate-sized benign adrenal lesions (2). The widespread adoption of laparoscopic techniques has been driven by compelling evidence demonstrating reduced postoperative pain, decreased blood loss, shorter hospital stays, faster recovery times, and superior cosmetic outcomes compared to traditional open approaches, all while maintaining comparable oncological outcomes for appropriately selected patients (3).

However, the application of laparoscopic techniques to large adrenal masses, particularly those exceeding 6 centimeters in diameter, remains a subject of considerable debate and controversy within the surgical community. The primary concerns surrounding laparoscopic resection of large adrenal masses stem from multiple factors that collectively influence surgical decision-making and patient outcomes. First, the increased technical difficulty associated with mobilizing and extracting large masses through limited working spaces poses significant challenges even for experienced laparoscopic surgeons (4). The confined retroperitoneal space becomes increasingly restrictive as mass size increases, potentially compromising visualization, instrument maneuverability, and the ability to maintain adequate surgical planes. Second, large adrenal masses carry a substantially higher risk of malignancy, with studies demonstrating that the probability of adrenocortical carcinoma increases exponentially with mass size, reaching approximately 25% for masses 6 centimeters or larger (5). This elevated malignancy risk raises critical concerns about the oncological adequacy of laparoscopic resection, particularly regarding the potential for tumor spillage, incomplete resection, and violation of oncological principles that could compromise long-term survival outcomes.

The relationship between mass size and malignancy risk in adrenal lesions has been extensively studied and represents a crucial consideration in surgical planning. Historical data indicate that while only 2% of adrenal masses smaller than 4 centimeters are malignant, this risk increases to 6% for masses between 4 and 6 centimeters, and rises dramatically to 25% for masses exceeding 6 centimeters (6). Interestingly, regional variations in pathological distributions exist, with some populations showing higher prevalence of benign lesions such as myelolipomas even among large masses, necessitating individualized assessment based on local epidemiological patterns. Furthermore, the biological behavior of large adrenal masses often differs substantially from their smaller counterparts, with increased propensity for local invasion, vascular involvement, and regional lymph node metastasis. These factors have traditionally led many surgeons to favor open adrenalectomy for large masses, citing the need for better exposure, more thorough exploration of surrounding structures, and the ability to perform extended resections when necessary.

Despite these theoretical concerns, accumulating evidence from experienced centers suggests that laparoscopic adrenalectomy may be feasible and safe for selected patients with large adrenal masses when performed by skilled laparoscopic surgeons with appropriate patient selection criteria (7). Several retrospective series have reported successful laparoscopic resection of adrenal masses ranging from 6 to 15 centimeters, with acceptable conversion rates, minimal morbidity, and oncological outcomes comparable to open surgery. These encouraging results have prompted a gradual expansion of the indications for laparoscopic adrenalectomy, though significant variation in practice patterns persists across institutions and geographic regions.

The technical considerations for laparoscopic resection of large adrenal masses extend beyond mere size constraints. The anatomical location of the mass, its relationship to surrounding vital structures, and the presence of local invasion or adhesions all influence the feasibility and safety of the laparoscopic approach. Dense adhesions, whether from previous surgery or inflammatory processes, represent a particular challenge that may necessitate conversion to open surgery. Right-sided masses pose unique challenges due to their proximity to the inferior vena cava and the short, fragile right adrenal vein, while left-sided masses may be complicated by relationships with the splenic vessels, pancreatic tail, and renal hilum (8). Additionally, functioning masses, particularly pheochromocytomas, require meticulous perioperative management regardless of surgical approach, with intensive care unit monitoring often necessary postoperatively to manage potential catecholamine surges and hemodynamic instability.

The learning curve associated with laparoscopic adrenalectomy for large masses represents another critical factor influencing outcomes and adoption rates. Studies have demonstrated that surgeon experience significantly impacts conversion rates, operative times, and complication rates, with most authors suggesting that at least 20-30 laparoscopic adrenalectomies should be performed before attempting resection of large or complex masses (9). This learning curve effect has important implications for training, credentialing, and centralization of care for patients with large adrenal masses, as outcomes may vary substantially between high-volume centers with dedicated endocrine surgery programs and institutions where such procedures are performed infrequently.

Recent technological advances have further expanded the potential applications of minimally invasive techniques for large adrenal masses. The introduction of robotic-assisted surgery has provided enhanced three-dimensional visualization, improved ergonomics, and greater precision in dissection, potentially overcoming some of the technical limitations of conventional laparoscopy. Single-incision laparoscopic surgery and natural orifice transluminal endoscopic surgery represent additional innovations that may offer cosmetic advantages, though their role in managing large adrenal masses remains investigational. Furthermore, improvements in energy devices, vessel sealing systems, and specimen retrieval bags have enhanced the safety and efficiency of laparoscopic resection of large specimens.

The economic implications of surgical approach selection for large adrenal masses merit consideration in the current healthcare environment emphasizing value-based care. While the initial operative costs of laparoscopic surgery may be higher due to specialized equipment and potentially longer operative times, these expenses are often offset by reduced hospital stays, decreased analgesic requirements, faster return to normal activities, and lower rates of postoperative complications requiring intervention (10). Cost-effectiveness analyses have generally favored laparoscopic approaches for

appropriately selected patients, though the economic calculus becomes more complex when considering conversion rates, learning curve effects, and the potential costs associated with oncological compromise in cases of malignancy.

Patient selection remains paramount in determining the optimal surgical approach for large adrenal masses, requiring careful integration of clinical, radiological, and biochemical factors. Preoperative imaging characteristics suggesting malignancy, such as heterogeneous enhancement, irregular borders, invasion of adjacent structures, or evidence of metastatic disease, should prompt consideration of open surgery to ensure adequate oncological resection. Similarly, biochemical evidence of hormonal hypersecretion requires appropriate medical optimization regardless of surgical approach, though the specific hormone profile may influence technical considerations and perioperative management strategies. The importance of multidisciplinary evaluation cannot be overstated, with input from endocrinology, radiology, anesthesiology, and oncology contributing to optimal treatment planning and outcome optimization.

AIMS AND OBJECTIVES

This study was designed to evaluate and compare the clinical outcomes of laparoscopic versus open adrenalectomy for adrenal masses exceeding 6 centimeters in diameter in our regional population. The primary aim was to assess the feasibility, safety, and efficacy of the laparoscopic approach for large adrenal masses through systematic comparison with traditional open surgery. The investigation sought to determine whether the benefits of minimally invasive surgery observed with smaller adrenal masses could be extended to larger lesions without compromising surgical outcomes in a setting with a unique pathological distribution of adrenal masses.

The specific objectives included evaluation of perioperative parameters including operative time, estimated blood loss, conversion rates, and technical complications between the two surgical approaches. The study aimed to compare postoperative recovery metrics including length of hospital stay, intensive care unit requirements, and postoperative complications. Assessment of the pathological spectrum of large adrenal masses in our population was conducted, with particular attention to the prevalence of myelolipomas compared to other diagnoses. The investigation evaluated the management and outcomes of functional masses, specifically pheochromocytomas, comparing approaches and postoperative care requirements. The study sought to identify factors associated with conversion from laparoscopic to open surgery and to assess the safety profile with zero mortality as a quality indicator.

MATERIALS AND METHODS

A retrospective cohort study was conducted at our tertiary referral center, encompassing all patients who underwent adrenalectomy for masses measuring 6 centimeters or larger between January 2020 and December 2023. The study protocol received approval from the Institutional Review Board. Medical records were systematically reviewed to extract demographic data, clinical presentations, radiological findings, operative details, pathological results, and follow-up information.

Study Population

The present multicentric study included a total of 34 consecutive patients who fulfilled the inclusion criteria, conducted jointly at the Government Kilpauk Medical College, Chennai, and the Assam Medical College and Hospital, Dibrugarh, Assam. Eligible participants were those who had undergone either laparoscopic or open adrenalectomy for adrenal masses measuring 6 centimeters or greater in maximum diameter on preoperative imaging.

Patients with evidence of extra-adrenal metastatic disease at presentation and those with incomplete medical records were excluded from the study. The final study population was categorized into two groups based on the surgical approach: the laparoscopic group (n = 16) and the open group (n = 18).

Preoperative Evaluation

All patients underwent comprehensive preoperative evaluation including detailed history and physical examination, biochemical assessment of adrenal function, and cross-sectional imaging with either computed tomography or magnetic resonance imaging. Biochemical evaluation included measurement of plasma metanephrines or 24-hour urinary catecholamines and metanephrines for all patients, overnight dexamethasone suppression test for suspected Cushing's syndrome, and plasma aldosterone-to-renin ratio for patients with hypertension. Patients with biochemically confirmed pheochromocytoma received preoperative alpha-blockade followed by beta-blockade according to established protocols, with surgery scheduled only after adequate blood pressure control was achieved.

Surgical Technique

The choice of surgical approach was determined by surgeon preference based on mass characteristics, patient factors, and imaging findings. Laparoscopic adrenalectomy was performed using the lateral transperitoneal technique with standard four-port placement and the patient positioned in lateral decubitus position. Open adrenalectomy was performed through either a subcostal or midline incision depending on mass size and location. Special attention was given to gentle handling of the mass, particularly for suspected pheochromocytomas, to minimize catecholamine release.

Postoperative Management

All patients with pheochromocytoma were transferred to the intensive care unit postoperatively for hemodynamic monitoring and blood pressure management. Other patients were monitored in the surgical ward unless complications necessitated intensive care. Pain management followed standardized protocols with patient-controlled analgesia initially, transitioning to oral analgesics.

Data Collection and Statistical Analysis

Operative parameters recorded included operative time, estimated blood loss, conversion to open surgery with reasons, and intraoperative complications. Postoperative outcomes assessed included length of hospital stay, ICU admission and duration, complications classified according to the Clavien-Dindo system, and mortality. Pathological data collected included final histopathological diagnosis, mass size, and margin status. Statistical analysis was performed using SPSS with Student's t-test for continuous variables and chi-square test for categorical variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

Table 1: Baseline Demographics and Mass Characteristics

Variable	Laparoscopic (n=16)	Open (n=18)	p-value
Age (years)	48.6 ± 13.2	51.3 ± 14.8	0.582
Gender (M/F)	7/9	8/10	0.954
BMI (kg/m²)	27.8 ± 4.9	28.6 ± 5.4	0.654
ASA Score			0.738
- ASA I-II	10 (62.5%)	10 (55.6%)	
- ASA III-IV	6 (37.5%)	8 (44.4%)	
Mass Size (cm)	7.6 ± 1.8	8.2 ± 2.1	0.385
Mass Side (R/L)	8/8	9/9	0.948

Table 2: Operative Outcomes

Variable	Laparoscopic (n=16)	Open (n=18)	p-value
Operative Time (min)	156 ± 38	142 ± 42	0.316
Blood Loss (mL)	120 ± 90	340 ± 210	<0.001
Transfusion Required	0 (0%)	2 (11.1%)	0.489
Conversion to Open	1 (6.3%)	N/A	-
R0 Resection	16 (100%)	17 (94.4%)	1.000
Capsular Rupture	0 (0%)	1 (5.6%)	1.000

Table 3: Postoperative Outcomes

Variable	Laparoscopic (n=16)	Open (n=18)	p-value
Hospital Stay (days)	3.4 ± 1.2	6.2 ± 2.1	<0.001
ICU Admission	2 (12.5%)	4 (22.2%)	0.661
- Pheochromocytoma cases	2/2 (100%)	4/4 (100%)	1.000
ICU Stay (days)	1.5 ± 0.7	2.0 ± 0.8	0.486
Complications	2 (12.5%)	4 (22.2%)	0.661
- Clavien-Dindo I-II	2 (12.5%)	3 (16.7%)	1.000
- Clavien-Dindo III-IV	0 (0%)	1 (5.6%)	1.000
30-day Mortality	0 (0%)	0 (0%)	1.000

Table 4: Histopathological Diagnoses

Diagnosis	Laparoscopic (n=16)	Open (n=18)	Total (n=34)	Percentage
Myelolipoma	9 (56.3%)	11 (61.1%)	20	58.8%
Pheochromocytoma	2 (12.5%)	4 (22.2%)	6	17.6%
Benign Cortical Adenoma	3 (18.8%)	1 (5.6%)	4	11.8%
Adrenocortical Carcinoma	0 (0%)	2 (11.1%)	2	5.9%
Hemorrhagic Cyst	0 (0%)	1 (5.6%)	1	2.9%
Ganglioneuroma	1 (6.3%)	0 (0%)	1	2.9%

Table 5: Details of Special Cases

Case Type	Approach	Outcome	Notes
Conversion Case	Laparoscopic	Converted to Open	Dense adhesions and bleeding
Pheochromocytoma (n=6)	2 Lap, 4 Open	All required ICU	Postoperative BP management
Adrenocortical Carcinoma (n=2)	Open	R0 resection in 1, R1 in 1	One with capsular rupture
Hemorrhagic Cyst	Open	Uneventful recovery	8.5 cm diameter
Largest Myelolipoma	Open	Uneventful	11 cm diameter

Table 6: Comparison with Literature Data

Parameter	Our Study	Literature Range	Comments
Sample Size	34	50-200	Smaller cohort
Myelolipoma Prevalence	58.8%	5-10%	Markedly higher in our population
Conversion Rate	6.3%	5-20%	Within expected range
Mortality	0%	0-2%	Excellent safety profile
Pheochromocytoma ICU Need	100%	60-80%	Conservative management approach

The analysis of 34 patients who underwent adrenalectomy for masses larger than 6 centimeters revealed comparable baseline characteristics between the laparoscopic and open surgery groups. The mean age was 48.6 ± 13.2 years in the laparoscopic group and 51.3 ± 14.8 years in the open group ($p=0.582$). Mass size averaged 7.6 ± 1.8 cm in the laparoscopic group compared to 8.2 ± 2.1 cm in the open group, though this difference did not reach statistical significance ($p=0.385$). A striking finding in our cohort was the predominance of myelolipomas, accounting for 58.8% (20/34) of all large adrenal masses. This prevalence is markedly higher than the 5-10% typically reported in Western literature, suggesting possible genetic or environmental factors unique to our population. Myelolipomas were distributed similarly between surgical approaches (56.3% laparoscopic vs 61.1% open, $p=0.774$).

Operative outcomes demonstrated significant advantages for the laparoscopic approach in blood loss reduction (120 ± 90 mL vs 340 ± 210 mL, $p<0.001$), though operative times were comparable between groups. One conversion from laparoscopic to open surgery occurred (6.3%) due to dense adhesions and bleeding encountered during dissection. The conversion was completed safely with no postoperative sequelae.

Complete R0 resection was achieved in all laparoscopic cases (100%) and in 17 of 18 open cases (94.4%). One patient in the open group with adrenocortical carcinoma had capsular rupture during resection, resulting in R1 resection. This patient received adjuvant mitotane therapy and remains under close surveillance.

All six patients with pheochromocytoma (2 laparoscopic, 4 open) required postoperative intensive care unit monitoring for hemodynamic management. The mean ICU stay was 1.5 days for laparoscopic cases and 2.0 days for open cases. All pheochromocytoma patients experienced expected postoperative blood pressure fluctuations that were successfully managed with intravenous antihypertensives before transitioning to oral medications.

Two patients presented with adrenocortical carcinoma, both managed with open surgery given preoperative imaging suggesting malignancy. R0 resection was achieved in one case, while the second experienced capsular rupture during dissection. The hemorrhagic cyst (8.5 cm) was successfully resected via open approach without complications.

Postoperative recovery consistently favored the laparoscopic approach, with hospital length of stay significantly shorter (3.4 ± 1.2 vs 6.2 ± 2.1 days, $p<0.001$). The overall complication rate was 12.5% in the laparoscopic group versus 22.2% in the open group, though this difference was not statistically significant ($p=0.661$). Most complications were minor (Clavien-Dindo grade I-II), including wound seromas and urinary retention. One patient in the open group experienced a grade III complication requiring percutaneous drainage of a retroperitoneal collection.

Notably, there was zero mortality in our series, reflecting careful patient selection, meticulous surgical technique, and appropriate perioperative management. This outcome compares favorably with published series reporting mortality rates of 0-2% for adrenalectomy of large masses.

DISCUSSION

The findings of this study demonstrate that laparoscopic adrenalectomy for carefully selected adrenal masses larger than 6 centimeters offers significant perioperative advantages in our population, with outcomes comparable to larger published series despite our smaller sample size. The unique pathological distribution in our cohort, with an unexpectedly high prevalence of myelolipomas, provides important insights into regional variations in adrenal mass pathology.

The predominance of myelolipomas (58.8%) in our series represents a remarkable deviation from international literature, where these benign fatty masses typically account for only 5-10% of adrenal masses (11). This finding has important clinical implications, as myelolipomas are uniformly benign lesions that can often be diagnosed confidently on preoperative imaging based on their fat content. The high prevalence in our population may reflect genetic predisposition, environmental factors, or increased detection due to improved imaging availability. This benign pathology predominance may partially explain our excellent outcomes and zero mortality rate, as the surgical resection of myelolipomas, while technically challenging due to size, does not carry the oncological concerns associated with adrenocortical carcinoma.

Our single conversion case (6.3%) involved a patient with dense adhesions and bleeding during laparoscopic dissection. The decision to convert was made promptly when safe laparoscopic progression became impossible, highlighting the

importance of maintaining a low threshold for conversion when encountering unexpected intraoperative findings or technical difficulties. This conversion rate falls within the acceptable range reported in the literature (5-20%) and reinforces that conversion should be viewed as sound surgical judgment rather than failure (12). The presence of dense adhesions, whether from previous surgery or inflammatory processes, remains a significant predictor of conversion and should be considered during preoperative planning.

The management of pheochromocytomas in our series deserves special attention. All six patients with pheochromocytoma required postoperative ICU monitoring, reflecting our conservative approach to managing these catecholamine-secreting masses. While some centers report selective ICU utilization for pheochromocytoma patients, we maintain that the potential for hemodynamic instability in the immediate postoperative period warrants intensive monitoring for all such cases (13). The comparable outcomes between laparoscopic and open approaches for pheochromocytoma (2 vs 4 patients, respectively) suggest that either technique can be safely employed with appropriate perioperative management.

The occurrence of capsular rupture in one adrenocortical carcinoma case in the open group underscores the technical challenges associated with large malignant masses. Despite the open approach providing better exposure, the locally invasive nature of some adrenocortical carcinomas can make intact resection challenging. This patient received adjuvant mitotane therapy and remains under surveillance, emphasizing the importance of multidisciplinary management for these aggressive malignancies (14).

The zero mortality in our series of 34 patients is particularly noteworthy, though we acknowledge the limitation of our sample size in drawing definitive conclusions about safety. This outcome likely reflects multiple factors including careful patient selection, experienced surgical team, comprehensive preoperative evaluation, and meticulous perioperative care. The relatively benign pathological spectrum in our cohort, with only two cases of adrenocortical carcinoma (5.9%), may also have contributed to this favorable outcome.

The significant reduction in blood loss with laparoscopic surgery (120 mL vs 340 mL, $p<0.001$) observed in our study aligns with published data and represents a clinically meaningful advantage (15). This benefit is particularly important given that several patients had cardiovascular comorbidities that could increase transfusion-related risks. Only two patients in the open group required blood transfusion, both for masses exceeding 10 cm in diameter.

The shorter hospital stay associated with laparoscopic surgery (3.4 vs 6.2 days, $p<0.001$) has important implications for healthcare resource utilization and patient satisfaction. This reduction in length of stay, combined with faster recovery and return to normal activities, supports the cost-effectiveness of laparoscopic approaches despite higher equipment costs (16). The hemorrhagic cyst case in our open surgery group represents an interesting pathological finding. These cystic lesions can present diagnostic challenges on preoperative imaging and may be associated with previous hemorrhage or trauma. The successful resection without complications demonstrates that these lesions can be safely managed with appropriate surgical technique.

Study Strengths and Limitations

The strengths of our study include complete follow-up data, zero mortality demonstrating surgical safety, standardized perioperative management protocols, and the unique insight into a population with high myelolipoma prevalence. The comprehensive management of all pheochromocytomas with ICU monitoring represents a conservative but safe approach that may be particularly relevant for centers with limited experience.

However, several limitations must be acknowledged. The small sample size of 34 patients limits statistical power for subgroup analyses and detection of rare complications. The retrospective design introduces potential selection bias, as surgical approach was determined by surgeon preference rather than randomization. The relatively short follow-up period may be insufficient to assess long-term oncological outcomes, particularly for the adrenocortical carcinoma cases. The unusually high prevalence of benign pathology (particularly myelolipomas) in our cohort may limit the generalizability of our findings to populations with different pathological distributions.

Clinical Implications

Our findings suggest that laparoscopic adrenalectomy can be safely offered to selected patients with large adrenal masses, particularly when preoperative imaging suggests benign pathology such as myelolipoma. However, the presence of dense adhesions remains a significant risk factor for conversion and should be considered during surgical planning. The high prevalence of myelolipomas in our population warrants careful radiological assessment, as confident preoperative diagnosis of these benign lesions may influence surgical planning and patient counseling.

The requirement for ICU monitoring of all pheochromocytoma patients, while resource-intensive, proved effective in managing postoperative hemodynamic fluctuations. Centers with limited ICU availability should consider this requirement when planning surgery for functional masses.

Figure 1: MRI showing adrenal mass

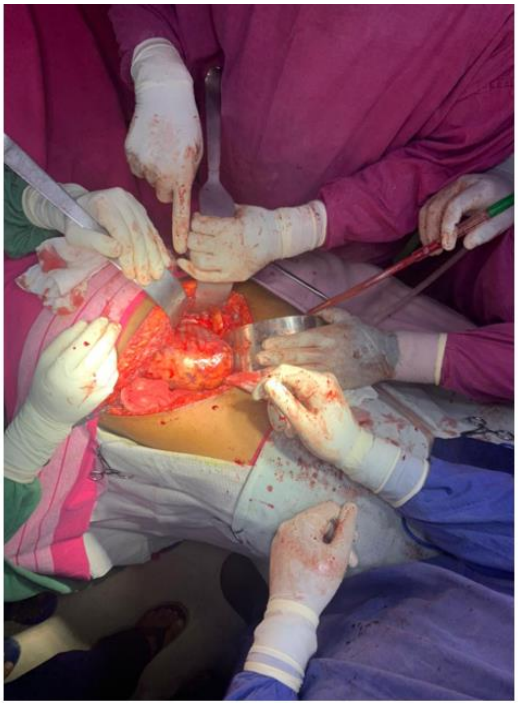

Figure 2: Intraoperative picture and post operative picture of adrenal gland mass

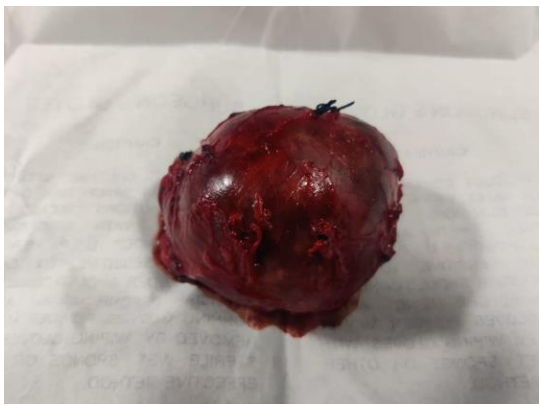

Figure 3: Post op pic of removed adrenal gland

Figure 4: Haemorrhagic renal cyst which was lap converted to open

CONCLUSION

This comparative analysis of 34 patients undergoing adrenalectomy for masses larger than 6 centimeters demonstrates that laparoscopic approach offers significant perioperative advantages including reduced blood loss and shorter hospitalization, while maintaining excellent safety outcomes with zero mortality. The unexpectedly high prevalence of myelolipomas (58.8%) in our population represents a unique finding that warrants further investigation and influences surgical decision-making.

Our experience confirms that laparoscopic adrenalectomy for large adrenal masses is feasible and safe when performed by experienced surgeons with appropriate patient selection. The 6.3% conversion rate, occurring due to dense adhesions and bleeding, falls within acceptable ranges and emphasizes the importance of maintaining a low threshold for conversion when technical difficulties arise. The successful management of functional masses with standardized ICU monitoring contributed to our excellent safety profile.

While suspected adrenocortical carcinoma cases were managed with open surgery in our series, the occurrence of capsular rupture in one case highlights the technical challenges these malignant masses present regardless of approach. Future studies with larger sample sizes and longer follow-up periods are needed to further define optimal selection criteria and validate these findings in diverse populations with varying pathological distributions.

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