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ORIGINAL RESEARCH

Comparison of Perioperative Outcomes Between Laparoscopic and Robot-Assisted Adrenalectomy for Large Pheochromocytoma (≥ 5cm): A Retrospective Study

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Purpose: The objective of this study was to compare perioperative outcomes in patients with large (≥5cm) pheochromocytomas who underwent adrenalectomy.

Patients and Methods: We retrospectively reviewed patients who underwent laparoscopic adrenalectomy (LA) and robot-assisted adrenalectomy (RA) for large pheochromocytoma (≥ 5cm) at our center between January 2015 to February 2023. We compared the perioperative outcomes between the two groups and investigated impact of high Nor-Metanephrine (NMN) levels on perioperative outcomes by analyzing this subgroup.

Results: A total of 115 patients were included in the study, with 48 patients in the robotic group and 67 patients in the laparoscopic group. The following significant difference were identified in favor of RA: shorter operative (excluding docking time) time (190.0 vs 220.0 min, p=0.002), lower estimated blood loss (50.0 vs 120.0 mL, p=0.013), however, RA group has higher surgical expenses (37933.0 vs 7936.0 CNY, p< 0.001). This finding remained consistent when analyzing patients with high NMN levels.

Conclusion: Patients with large pheochromocytoma may experience reduced blood loss and shorter operative time when undergoing robot-assisted adrenalectomy. However, it is important to note that the RA approach is associated with significantly higher costs.

Keywords: large pheochromocytoma, adrenalectomy, laparoscopic, robotic, high nor-metanephrine

Introduction

Pheochromocytoma (PHEO) is a rare neuroendocrine tumor that primarily originates from the adrenal medulla.[1] PHEO has a significant impact on multiple systems, particularly the cardiovascular system, due to the excessive production and release of catecholamines.[2] Surgical resection is a standard treatment for patients with pheochromocytoma. Since the first report of laparoscopic adrenalectomy in 1992,[3] multiple studies have demonstrated the feasibility and safety of laparoscopic approaches for resecting pheochromocytoma.[4–9] However, laparoscopic approaches have certain limitations, such as limited instrument movement, a two-dimensional image, and tremor amplification.[10] As a result, laparoscopic surgery can be challenging for complex pheochromocytomas, such as those requiring reoperation, those compressing the inferior vena cava, or those with large tumor volumes.

In 2002, the preliminary Da Vinci Robot-assisted adrenalectomy was first reported.[11] Since then, this surgical procedure has rapidly advanced. It is now not only commonly used for treating smaller pheochromocytomas but also shows excellent therapeutic outcomes for larger ones.[12] In our previous study, Ma et al conducted a prospective study and identified robotic adrenalectomy had superior outcomes than laparoscopic adrenalectomy, including shorter operative time and lower estimated blood loss.[13] However, previous studies often focus on adrenal tumors in general or include all patients with pheochromocytoma, without specifically targeting larger cases.[12,14] It is important to note that large adrenal

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tumors are typically defined as those ranging in size from 5 to 10cm in diameter, with a consensus of approximately 5cm.[12,15] Therefore, pheochromocytomas that exceed 5cm in diameter serve as the primary focus of our present study.

The aim of this retrospective study is to compare the perioperative results for patients undergoing robotic adrenalectomy versus laparoscopic adrenalectomy for large pheochromocytoma. Additionally, we aim to identify subgroups of patients who would benefit more from robotic adrenalectomy or laparoscopic adrenalectomy.

Materials and Methods

Patients

A total of 115 patients with large pheochromocytoma who underwent laparoscopic adrenalectomy and robotic adrenalectomy were enrolled in this retrospective study after obtaining approval from the Ruijin Hospital Ethics Committee. The inclusion criteria were unilateral and adrenal-originated large pheochromocytoma, while the exclusion criterion was recurrence or distant metastatic pheochromocytoma.

Demographic, laboratory data, and disease characteristics were compared between the two groups: laparoscopic adrenalectomy (LA) and robotic adrenalectomy (RA). The choice of surgical approach (LA or RA) was determined collaboratively by the surgeons and patients. Surgeons offered recommendations based on the patients' medical condition, surgical complexity, and associated risks, while also taking into consideration the patients' financial circumstances. Ultimately, the decision-making process allowed patients to make informed choices that aligned with their individual medical needs and financial capabilities. Demographic factors included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, Charlson comorbidity index (CCI) score, history of smoking or alcohol use, presence of diabetes and hypertension, and history of abdominal surgery. Laboratory data, including hemoglobin, albumin, metanephrine (MN), and nor-metanephrine (NMN), were obtained from pre-surgery blood screening tests. If multiple preoperative blood tests were available for a patient, the value closest to the date of adrenalectomy was used. The normal range of metanephrine and nor-metanephrine in our center is 14–90 pg/mL and 19–121 pg/mL, respectively. NMN levels higher than 650 pg/mL were considered high. Disease characteristics such as tumor size and tumor side, were obtained from preoperative radiological imaging, including enhanced adrenal computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography-computed tomography (PET-CT), performed before surgery.

Surgery

All patients included in our study underwent a minimum 3-week course of doxazosin before surgery.

All surgeries were performed by experienced surgeons. Even if some surgeries are performed by junior surgeons, they were under the supervision of senior surgeons. Calcium channel blockers were also used as preoperative medications.[16] Data regarding different surgical approaches (transperitoneal and retroperitoneal) were collected and compared between the two surgical groups. The selection of a retroperitoneal or transperitoneal approach is typically based on multiple factors, including tumor location, the preference of surgeons, as well as the specific characteristics and medical history of patients. Detailed descriptions of the surgical procedures can be found in other literature.[11]

Perioperative Outcomes and Follow-Up

Perioperative outcomes were compared between the two groups, including operative time (OT), estimated blood loss (EBL), intraoperative transfusion, intraoperative complications, conversion to open adrenalectomy, postoperative complications, postoperative transfusion, postoperative transfer to the Surgical Intensive Care Unit (SICU), and postoperative length of stay (PLOS). Moreover, surgical expenses were collected in our study and compared between the two groups.

Operative time was calculated from trocar insertion to abdominal closure, while estimated blood loss was evaluated by subtracting the amount of irrigation fluid used from the suction volume. Operative time (OT) was recorded from the skin incision to skin closure. Patients were followed up within 2–6 months after the operation in the outpatient clinic. Endocrine evaluation of MN, NMN, and enhanced CT was conducted during the first postoperative follow-up, and the levels of MN and NMN were recorded.

Statistical Analysis

Continuous variables were reported as median (interquartile range, IQR), and categorical variables were expressed as count (percentage). The Mann–Whitney *U*-test was used for analyzing continuous variables, while Chi-square tests or Fisher's exact tests were used for analyzing categorical variables. Statistical analyses were performed using SPSS version 26.0. All statistical tests were two-sided, and a p-value less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

From January 2015 to February 2023, a total of 115 patients were enrolled in this study. Among them, 48 patients underwent robotic adrenalectomies, and 67 patients underwent laparoscopic adrenalectomies. Table 1 provides an

Table 1 Baseline Characteristics of Patients

Preoperative Data	Total (n=115)	Robotic Group (n=48)	Laparoscopic Group (n=67)	*p*-value
Age, year	45.0 (33.0–60.0)	43.5 (32.5–58.0)	45.0 (33.0–60.0)	0.563
Gender, n%				0.789
Male	52 (45.2)	21 (43.8)	31 (46.3)	
Female	63 (54.8)	27 (56.3)	36 (53.7)	
BMI, kg/m^2	22.9 (21.1–25.2)	23.1 (21.9–24.5)	22.6 (20.9–25.4)	0.854
Hypertension, n%	86 (74.8)	40 (83.3)	46 (68.7)	0.074
Diabetes, n%	23 (20.0)	9 (18.8)	14 (20.9)	0.777
Smoking, n%	8 (7.0)	2 (4.2)	6 (9.0)	0.533
Alcohol, n%	5 (4.3)	1 (2.1)	4 (6.0)	0.586
ASA, n%				0.143
1–2	99 (86.1)	44 (91.7)	55 (82.1)	
3–4	16 (13.9)	4 (8.3)	12 (17.9)	
CCI, n%				0.457
0–1	87 (75.7)	38 (79.2)	49 (73.1)	
≥2	28 (24.3)	10 (20.8)	18 (26.9)	
Prior abdominal surgery, n%	21 (18.3)	7 (14.6)	14 (20.9)	0.388
Preoperative hemoglobin, g/L	131.0 (118.0–139.0)	130.5 (117.0–137.0)	132.0 (120.5–142.5)	0.240
Preoperative albumin, g/L	41.0 (39.0–43.0)	41.0 (39.0–43.0)	41.0 (38.0–42.0)	0.157
Metanephrine, pg/mL	103.4 (67.1–718.9)	90.6 (62.9–553.3)	112.6 (71.2–1027.6)	0.392
Nor-Metanephrine, pg/mL	1200.9 (577.4–2630.5)	1701.6 (824.5–3252.9)	927.0 (337.9–2430.0)	0.045*
Tumor size, cm	6.0 (5.5–7.0)	6.0 (5.5–7.3)	6.0 (5.5–7.0)	0.551
Tumor Laterility, n%				0.274
Left	65 (56.5)	30 (62.5)	35 (52.2)	
Right	50 (43.5)	18 (37.5)	32 (47.8)	
Surgical Technique, n%				0.250
Transperitoneal	77 (67.0)	35 (72.9)	42 (62.7)	
Retroperitoneal	38 (33.0)	13 (27.1)	25 (37.3)	

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists score; CCI, Charlson comorbidity index.

overview of the patients' characteristics. The two groups were comparable in terms of all baseline characteristics, including age (p=0.563), gender (p=0.789), BMI (p=0.854), presence of hypertension (p=0.074) and diabetes (p=0.777), alcohol use (p=0.586), smoking (p=0.533), ASA score (p=0.143), CCI (p=0.457), history of previous abdominal surgery (p=0.388), tumor size (p=0.551), tumor side (p=0.274), and surgical approach (p=0.250).

Comparison of Perioperative Outcomes

The perioperative outcomes were compared between the two groups, and the results are presented in Table 2. The RA group showed a significantly shorter operative time (190.0 vs 220.0 min, p=0.002) and lower estimated blood loss (50.0 vs 120.0 mL, p=0.013). However, the hospitalization cost in the RA group was higher than that in the LA group (37933.0 vs 7936.0 CNY, p< 0.001). Only three patients in laparoscopic surgery group required conversion to open surgery, while no patients in the robotic group required conversion to open surgery. However, there was no statistically significant difference between the two groups (0.0% vs 4.5%, p=0.372).

Table 2 Perioperative Outcomes

Variables	Total (n=115)	Robotic Group (n=48)	Laparoscopic Group (n=67)	*p*-value
Conversion to open	3 (2.6)	0 (0.0)	3 (4.5)	0.372
OT, min	210.0 (180.0–250.0)	190.0 (170.0–215.0)	220.0 (190.0–260.0)	0.002*
EBL, mL	100.0 (50.0–200.0)	50.0 (30.0–212.5)	120.0 (100.0–200.0)	0.013*
Intraoperative complications	19 (16.5)	6 (12.5)	13 (19.4)	0.326
Intraop. ventricular fibrillation	1 (0.9)	1 (0.0)	0 (0.0)	
Intraop. hypertension after removal of adrenal tumor, n%	10 (8.7)	2 (4.2)	8 (11.9)	
Intraop. tissue or organ injury, requiring suture, n%	3 (2.6)	1 (2.1)	2 (3.0)	
Cava vein damage with intracorporeal suture, n%	1 (0.9)	0 (0.0)	1 (1.5)	
Significant bleeding in the surgical field, n%	2 (1.7)	1 (2.1)	1 (1.5)	
Suspected spleen repture, requiring abdominal exploration, n%	1 (0.9)	0 (0.0)	1 (1.5)	
Diaphragmatic rupture, requiring intraoperative suture, n%	1 (0.9)	1 (2.1)	0 (0.0)	
Intraoperative transfusion	36 (31.3)	18 (37.5)	18 (26.9)	0.225
Postoperative complications	5 (4.3)	1 (2.1)	4 (6.0)	0.586
Postop. Electrolyte imbalance, n%	2 (1.7)	1 (2.1)	1 (1.5)	
Postop. fever management with broad spectrum antibiotics, n%	1 (0.9)	0 (0.0)	1 (1.5)	
Postop. pulmonary infection, n%	1 (0.9)	0 (0.0)	1 (1.5)	
Postop. heart failure, n%	1 (0.9)	0 (0.0)	1 (1.5)	
Postoperative transfusion, n%	27 (23.5)	13 (27.1)	14 (20.9)	0.440
Postoperative transfer to SICU	14 (12.2)	4 (8.3)	10 (14.9)	0.286
Postoperative hospital stay, day	13.0 (8.0–18.5)	12.5 (8.0–18.0)	13.0 (8.0–21.0)	0.980
Surgical expense (CNY)	9235.0 (7776.5–37323.3)	37933.0 (36725.0–38597.5)	7936.0 (6889.5–8829.0)	<0.001*
Postoperative MN, pg/mL	32.1 (17.3–50.3)	32.1 (23.7–41.5)	33.1 (16.0–50.9)	0.772
Postoperative NMN, pg/mL	72.5 (49.5–98.0)	75.6 (61.2–98.0)	69.3 (44.4–98.6)	0.234
Readmission, n%	2 (1.7)	0 (0.0)	2 (3.0)	0.509

Notes: *Statistically significant.
Abbreviations: OT, operative time (excluding docking); EBL, estimated blood loss; SICU, Surgical Intensive Care Unit; CNY, Chinese Yuan; MN, metanephrine; NMN, nor-metanephrine.

The incidence of intraoperative complications did not show a statistically significant difference between the robotic surgery group and laparoscopic surgery group (12.5% vs 19.4%, *p*=0.326). In the robotic surgery group, a total of 6 patients experienced intraoperative complications: one patient had ventricular fibrillation during the surgery, two patients experienced hypertension after tumor resection, one patient had damage to surrounding tissues or organs during the surgery and requiring suturing, one patient experience significant intraoperative bleeding, and one patient had diaphragmatic rupture during the surgery and required suturing. In the laparoscopic group, a total of 13 patients experienced intraoperative complications: eight patients experienced hypertension after tumor resection, two patients had damage to surrounding tissues or organs during the surgery and required suturing, one patient experienced cava vein damage and required suturing, one patient experience significant intraoperative bleeding, and one patient experienced suspected spleen rupture, requiring abdominal exploration.

No difference in terms of postoperative complication rate was found between the laparoscopic and the robotic group (2.1% vs 6.0%, *p*=0.586). In detail, in the robotic group, one patient underwent postoperative electrolyte imbalance. In the laparoscopic group, one patient experienced a postoperative fever treated with broad spectrum antibiotics, one patient underwent postoperative electrolyte imbalance, one patient had postoperative pulmonary infection, and one patient experienced heart failure.

There was no statistically significant difference between the two groups in terms of transfusion rate, both intraoperatively (37.5% vs 26.9%, *p*=0.225) and postoperatively (27.1% vs 20.9%, *p*=0.440). Similarly, there was no statistically significant difference between the two groups in terms of proportion of patients transferred to the intensive care unit after surgery (8.3% vs 14.9%, *p*=0.286) or the postoperative length of stay (12.5 vs 13.0 days, *p*=0.980). The robotic surgery group had no patients readmitted for further treatment after discharge, while the laparoscopic surgery group had two patients readmitted. However, there was no statistically significant difference between the two groups (0.0% vs 3.0%, *p*=0.509).

Patients with High NMN

Table 3 showed the baseline characteristics and perioperative outcomes for patients with high NMN. For these patients, the following significant differences were identified in favor of RA vs LA: shorter operative time (200.0 vs 220.0 min, *p*=0.024) and lower estimated blood loss (50.0 vs 150.0 mL, *p*=0.009). However, the hospitalization cost in RA group was higher than LA group (38052.5 vs 8005.0, *p*< 0.001). For patients with high NMN levels, the comparison of perioperative complications between different surgical approaches yielded the same result as those obtained for all patients.

Table 3 Patients with High Level of nor-Metanephrine (>650 Pg/Ml)

Variable	Total (n=82)	Robotic Group (n=41)	Laparoscopic Group (n=41)	*p*-value
Age, year	44.0 (32.0–57.0)	43.0 (32.0–55.0)	45.0 (32.0–60.0)	0.513
Gender, n%				0.654
Male	34 (41.5)	18 (43.9)	16 (39.0)	
Female	48 (58.5)	23 (56.1)	25 (61.0)	
BMI, kg/m^2	23.1 (20.3–25.3)	23.1 (21.8–24.4)	22.9 (20.3–25.4)	0.817
Hypertension, n%	61 (74.4)	34 (82.9)	27 (65.9)	0.077
Diabetes, n%	15 (18.3)	7 (17.1)	8 (19.5)	0.775
Smoking, n%	4 (4.9)	1 (2.4)	3 (7.3)	0.608
Alcohol, n%	2 (2.4)	0 (0.0)	2 (4.9)	0.474

(*Continued*)

Table 3 (Continued).

Variable	Total (n=82)	Robotic Group (n=41)	Laparoscopic Group (n=41)	*p*-value
ASA, n%				0.429
I–2	75 (91.5)	39 (95.1)	36 (87.8)	
3–4	7 (8.5)	2 (4.9)	5 (12.2)	
CCI, n%				0.594
0–1	64 (78.0)	33 (80.5)	31 (75.6)	
≥2	18 (22.0)	8 (19.5)	10 (24.4)	
Prior abdominal surgery, n%	10 (12.2)	5 (12.2)	5 (12.2)	1.000
Preoperative hemoglobin, g/L	129.0 (118.0–137.0)	130.0 (118.0–136.0)	128.0 (119.0–139.0)	0.926
Preoperative albumin, g/L	41.0 (39.0–43.0)	41.0 (39.0–43.0)	41.0 (38.0–42.0)	0.166
Metanephrine, pg/mL	112.7 (72.5–732.2)	168.3 (68.1–643.5)	95.5 (74.0–1072.0)	0.792
Nor-Metanephrine, pg/mL	2088.6 (1099.6–3717.3)	2067.2 (1076.1–3754.3)	2305.7 (1178.0–3224.6)	0.908
Tumor size, cm	6.0 (5.5–7.5)	6.0 (5.5–7.5)	6.0 (5.5–7.5)	0.888
Tumor Laterility, n%				0.075
Left	46 (56.1)	27 (65.9)	19 (46.3)	
Right	36 (43.9)	14 (34.1)	22 (53.7)	
Surgical Technique, n%				0.627
Transperitoneal	58 (70.7)	30 (73.2)	28 (68.3)	
Retroperitoneal	24 (29.3)	11 (26.8)	13 (31.7)	
Conversion to open	2 (2.4)	0 (0.0)	2 (4.9)	0.474
OT, min	210.0 (180.0–250.0)	200 (170.0–240.0)	220 (190.0–260.0)	0.024*
EBL, mL	100.0 (50.0–200.0)	50.0 (30.0–200.0)	150.0 (100.0–200.0)	0.009*
Intraoperative complications	14 (17.1)	6 (14.6)	8 (19.5)	0.557
Intraoperative transfusion, n%	28 (34.1)	16 (39.0)	12 (29.3)	0.352
Postoperative complications				
Postoperative transfusion, n%	21 (25.6)	12 (29.3)	9 (22.0)	0.448
Postoperative transfer to SICU	11 (13.4)	4 (9.8)	7 (17.1)	0.331
Postoperative hospital stay, day	13.0 (8.0–21.0)	13.0 (8.0–18.0)	14.0 (10.0–23.0)	0.518
Surgical expense (CNY)	22809.8 (8005.0–38075.0)	38052.5 (36780.0–38615.0)	8005 (6690.0–8828.0)	<0.001*
Postoperative MN, pg/mL	31.4 (17.3–50.0)	30.8 (20.9–46.5)	34.7 (16.6–49.7)	0.861
Postoperative NMN, pg/mL	72.2 (50.1–99.5)	75.6 (59.6–99.5)	68.8 (49.5–94.6)	0.394
Readmission, n%	1 (1.2)	0 (0.0)	1 (2.4)	1.000

Notes: *Statistically significant.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists score; CCI, Charlson comorbidity index; OT, operative time (excluding docking); EBL, estimated blood loss; SICU, Surgical Intensive Care Unit; CNY, Chinese Yuan; MN=metanephrine; NMN, nor-metanephrine.

Discussion

LA represents the gold standard for the treatment of most adrenal masses. However, in cases of large pheochromocytoma, LA can be extremely challenging surgery due to its limitations, such as a two-dimensional view, unstable camera platform, and rigid instrument.[14] To overcome these, in 1999 Piazza et al[17] and Hubens et al[18] performed the first robot-assisted adrenalectomy in Europe. Since then, with the progressive spread of robotic platform, RA has gradually adopted as an alternative to LA. However, large comparative series between LA and RA are lacking in current literature and evidence providing a real benefit of RA over LA have not been provided so far.

Most studies comparing the two surgical approaches did not specifically focus on a particular disease, but rather investigated adrenal masses as a whole.[19–24] However, different adrenal tumors have varying characteristics, and the probability of perioperative complications differs among them. For example, patients with primary hyperaldosteronism have smaller tumors than other pathologies, with no significant retroperitoneal fat and no significant hemodynamics, in contrast to pheochromocytoma.[25] Therefore, our study was limited to pheochromocytoma, aiming for a more specific and targeted investigation. Although open surgery is currently considered the standard approach for large pheochromocytoma, the increasing popularity of robotic surgery had led to more patients with large pheochromocytomas undergoing minimally invasive procedures. Hence, it is necessary to compare robotic surgery and laparoscopic surgery in patients with large pheochromocytoma.

Regarding operative time and estimated blood loss, our study found that the robotic group had shorter operative time (190.0 vs 220.0 min, p=0.002) and lower intraoperative blood loss (50.0 vs 120.0 mL, p=0.013). Aliyev et al[26] conducted a study including a total of 65 patients with pheochromocytoma, with 40 patients undergoing laparoscopic adrenalectomy and 25 patients undergoing robotic adrenalectomy. The Study found no significant differences in operative time (149.0 vs 178.0 min, p=0.132) and intraoperative blood loss (36.0 vs 43.0 mL, p=0.628) between the two groups. Fang et al compared the outcomes of open surgery, laparoscopic surgery, and robotic surgery for pheochromocytoma to determine which approach is superior.[8] In the comparison between laparoscopic adrenalectomy and robotic adrenalectomy, it was found that laparoscopic adrenalectomy had a shorter operative time (210.4 vs 157.9 min, p=0.004). There was no statistically significant difference in intraoperative blood loss between the two groups (173.0 vs 134.0 mL, p=0.584). The above-mentioned study focused on all patients with pheochromocytoma. Our study yielded different results compared to those studies, which could be attributed to several reasons. Firstly, our operative time did not include the docking time for robotic surgery. Secondly, it is possible that the advantages of robot-assisted adrenalectomy for larger pheochromocytomas can be better demonstrated, resulting in shorter operative time and less intraoperative blood loss.

According to our research, robotic approach did not reduce intraoperative and postoperative outcomes or shorten postoperative hospitalization stays. Although many studies have compared the occurrence of intraoperative and postoperative complications between laparoscopic adrenalectomy and robot-assisted laparoscopic adrenalectomy for pheochromocytoma, the results of these studies are controversial. Brandao et al[27] pooled 9 studies including 323 laparoscopic adrenalectomies and 277 robotic adrenalectomies into their meta-analysis. They found no statistical difference in surgical complication rate between the two groups, which is similar with our result. However, they found that RA group had a significantly longer length of hospitalization, which is converse to our result.

The cost associated with using robotic systems has been a concern examined in several studies. In our research, the total hospitalization cost was significantly higher in the RA group compared to the LA group (37933 vs 7936 CNY, $p<0.001$). Agcaoglu et al estimated that the expenses associated with RA were higher than those of LA, primarily due to the fees for annual maintenance and additional instruments.[28] Moreover, our finding is similar to the study conducted by Higgins et al, who noted a substantial increase in the cost of general surgery procedures when performed robotically instead of laparoscopically.[29] It is worth noting that costs and charges may vary depending on the institution and country. Nonetheless, it is clear that as the number of robotic procedures performed increases and the price of robotic systems decreases, the cost of robotic surgery is expected to decrease.

The clinical presentation of pheochromocytoma varies depending on the tumor's catecholamine secretion, which differ among patients. A high plasma nor-metanephrine concentration is a risk factor for hemodynamic instability during pheochromocytoma surgery. Careful manipulation is necessary to prevent a massive release of NMN into the bloodstream, which can prolong the operative time.[30] Furthermore, catecholamines may play a significant role in the angiogenesis of pheochromocytoma. Xia Y et al have stated that catecholamine promotes tumor angiogenesis by triggering the M2 polarization of macrophages and enhancing the VEGF expression.[31] Therefore, hyper-vascular pheochromocytoma may be associated with higher NMN levels. In our study, subgroup analysis was performed to determine whether patients with high NMN levels should benefit more from RA surgery or laparoscopic surgery.

However, in our study, no additional findings were discovered when comparing the perioperative outcomes of the two surgical approaches for patients with high NMN levels. Although no differences were found between the two surgical approaches, our study is the first to attempt to compare them for large pheochromocytoma through patient stratification.

It is acknowledged that the surgical experience of the surgeon plays an important role in the occurrence of perioperative complications. A study conducted by Park et al[32] demonstrated that surgeons with low surgical volume had a 1.5 times higher risk of complications in adrenal resection compared to surgeons with high surgical volume. In our study, both laparoscopic and robotic surgeries for large pheochromocytomas were typically performed by experienced surgeons due to the high surgical risk involved. Even if some surgeries are performed by junior doctors, they were under the supervision of senior doctors. Pedziwiatr et al found that[33] in certain large-scale hospitals, junior doctors performed many surgeries, but the incidence of perioperative complications did not increase due to the supervision and guidance provided by experienced senior doctors within the surgical team. Therefore, we consider the difference in surgical experience between the two groups (RA and LA) in our study to be minimal. We found that the robotic group achieved better perioperative outcomes, independence of the difference in surgical experience between the two groups of surgeons.

Although our study demonstrated that robot-assisted laparoscopic adrenalectomy had better perioperative outcomes for large pheochromocytomas. Despite the many advantages of the da Vinci robotic system, such as precise operation, improved visualization, and enhanced instrument flexibility, it may face technical challenges in specific anatomical structures and surgical situations. For example, the retroperitoneal approach may have limitations in terms of anatomical structure, which could restrict the operating space of the da Vinci system. Additionally, using the da Vinci robotic system for retroperitoneal or laparoscopic resection requires surgeons to have specialized skills and experience to ensure the safety and effectiveness of the surgery. Moreover, robot-assisted surgery incurs high costs, approximately 4–5 times higher than laparoscopic surgery. Whether it can provide corresponding multiples of better prognosis is worth exploring. Therefore, the choice of surgical approach should be based on multiple factors, including the characteristics of the tumor, the feasibility of the surgery, and the patient's financial capability, and should be considered comprehensively.

The present study has several limitations that should be acknowledged. Firstly, being a retrospective single-center study, our research is susceptible to selection bias. Secondly, due to the low incidence rate of pheochromocytoma and the further screening of the population to specifically select individuals with large pheochromocytomas, our study had a relatively small cohort. The number of cases included in our study was not large enough to draw definitive conclusions. To further validate the conclusions of our study, subsequent randomized controlled trials will be necessary for further verification. Thirdly, the postoperative follow-up period for some cases was not sufficiently long to evaluate important oncologic outcomes, such as tumor recurrence or metastasis.

Conclusion

In conclusion, our study offers valuable insights into the outcomes of laparoscopic adrenalectomy and robotic adrenalectomy for patients with large pheochromocytoma. The robotic approach showed advantages in terms of shorter operative time and lower estimated blood loss. However, it is crucial to consider the higher hospitalization cost associated with the robotic approach. Further studies with large sample sizes and longer follow-up periods are needed to validate these findings and provide more comprehensive evidence, which will help further establish the optimal surgical approach for patients with large pheochromocytoma, considering both clinical outcomes and cost-effectiveness.

Ethics Approval and Informed Consent

This study was conducted following the principles of the Helsinki declaration. It was approved by the Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Our ethics committee waived the requirement for informed consent due to the retrospective nature. Identifying information was removed to protect patient confidentiality.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. *Lancet*. 2005;366(9486):665–675. doi:10.1016/S0140-6736(05)67139-5
2. Pacak K, Linehan WM, Eisenhofer G, et al. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. *Ann Intern Med*. 2001;134(4):315–329. doi:10.7326/0003-4819-134-4-200102200-00016
3. Gagner M, Lacroix A, Bolté E. Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma. *N Engl J Med*. 1992;327:1033.
4. Agarwal G, Sadacharan D, Aggarwal V, et al. Surgical management of organ-contained unilateral pheochromocytoma: comparative outcomes of laparoscopic and conventional open surgical procedures in a large single-institution series. *Langenbecks Arch Surg*. 2012;397(7):1109–1116. doi:10.1007/s00423-011-0879-3
5. Wang W, Li P, Wang Y, et al. Effectiveness and safety of laparoscopic adrenalectomy of large pheochromocytoma: a prospective, nonrandomized, controlled study. *Am J Surg*. 2015;210(2):230–235. doi:10.1016/j.amjsurg.2014.11.012
6. Zhu W, Wang S, Du G, et al. Comparison of retroperitoneal laparoscopic versus open adrenalectomy for large pheochromocytoma: a single-center retrospective study. *World J Surg Oncol*. 2019;17(1):111. doi:10.1186/s12957-019-1649-x
7. Bai S, Yao Z, Zhu X, et al. Comparison of transperitoneal laparoscopic versus open adrenalectomy for large pheochromocytoma: a retrospective propensity score-matched cohort study. *Int J Surg*. 2019;61:26–32. doi:10.1016/j.ijsu.2018.11.018
8. Fang AM, Rosen J, Saidian A, et al. Perioperative outcomes of laparoscopic, robotic, and open approaches to pheochromocytoma. *J Robot Surg*. 2020;14(6):849–854. doi:10.1007/s11701-020-01056-9
9. Zhao J, Ma W, Xie J, et al. Laparoscopic treatment of large adrenal tumor is safe and effective? A single center experiences. *J Invest Surg*. 2021;34 (9):957–962. doi:10.1080/08941939.2020.1719243
10. Park JM, Kim HI, Han SU, et al. Who may benefit from robotic gastrectomy?: a subgroup analysis of multicenter prospective comparative study data on robotic versus laparoscopic gastrectomy. *Eur J Surg Oncol*. 2016;42(12):1944–1949. doi:10.1016/j.ejso.2016.07.012
11. Desai MM, Gill IS, Kaouk JH, et al. Robotic-assisted laparoscopic adrenalectomy. *Urology*. 2002;60(6):1104–1107. doi:10.1016/S0090-4295(02) 02011-3
12. Gan L, Meng C, Li K, et al. Safety and effectiveness of minimally invasive adrenalectomy versus open adrenalectomy in patients with large adrenal tumors (≥5 cm): a meta-analysis and systematic review. *Int J Surg*. 2022;104:106779. doi:10.1016/j.ijsu.2022.106779
13. Ma W, Mao Y, Zhuo R, et al. Surgical outcomes of a randomized controlled trial compared robotic versus laparoscopic adrenalectomy for pheochromocytoma. *Eur J Surg Oncol*. 2020;46(10):1843–1847. doi:10.1016/j.ejso.2020.04.001
14. Gan L, Peng L, Li J, et al. Comparison of the effectiveness and safety of robotic-assisted and laparoscopic in adrenalectomy: a systematic review and meta-analysis. *Int J Surg*. 2022;105:106853. doi:10.1016/j.ijsu.2022.106853
15. Zhang Z, Wang L, Chen J, et al. Clinical analysis of adrenal lesions larger than 5 cm in diameter (an analysis of 251 cases). *World J Surg Oncol*. 2019;17(1):220. doi:10.1186/s12957-019-1765-7
16. Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab*. 2007;92(11):4069–4079. doi:10.1210/jc.2007-1720
17. Piazza L, Caragliano P, Scardilli M, et al. Laparoscopic robot-assisted right adrenalectomy and left ovariectomy (case reports). *Chir Ital*. 1999;51:465–466.
18. Hubens G, Ysebaert D, Vaneerdeweg W, et al. Laparoscopic adrenalectomy with the aid of the AESOP 2000 robot. *Acta Chir Belg*. 1999;99 (3):125–7; discussion 127–9. doi:10.1080/00015458.1999.12098462
19. Kim WW, Lee YM, Chung KW, et al. Comparison of robotic posterior retroperitoneal adrenalectomy over laparoscopic posterior retroperitoneal adrenalectomy: a single tertiary center experience. *Int J Endocrinol*. 2019;2019. doi:10.1155/2019/9012910
20. Ji C, Lu Q, Chen W, et al. Retrospective comparison of three minimally invasive approaches for adrenal tumors: perioperative outcomes of transperitoneal laparoscopic, retroperitoneal laparoscopic and robot-assisted laparoscopic adrenalectomy. *BMC Urol*. 2020;20(1):66. doi:10.1186/s12894-020-00637-y
21. Niglio A, Grasso M, Costigliola L, et al. Laparoscopic and robot-assisted transperitoneal lateral adrenalectomy: a large clinical series from a single center. *Updates Surg*. 2020;72(1):193–198. doi:10.1007/s13304-019-00675-8
22. Ma W, Mao Y, Dai J, et al. Propensity score matched analysis comparing robotic-assisted with laparoscopic posterior retroperitoneal adrenalectomy. *J Invest Surg*. 2021;34(11):1248–1253. doi:10.1080/08941939.2020.1770377
23. Piccoli M, Pecchini F, Serra F, et al. Robotic versus laparoscopic adrenalectomy: pluriannual experience in a high-volume center evaluating indications and results. *J Laparoendosc Adv Surg Tech A*. 2021;31(4):375–381. doi:10.1089/lap.2020.0839
24. Sforza S, Minervini A, Tellini R, et al. Perioperative outcomes of robotic and laparoscopic adrenalectomy: a large international multicenter experience. *Surg Endosc*. 2021;35(4):1801–1807. doi:10.1007/s00464-020-07578-5
25. Colvin J, Krishnamurthy V, Jin J, et al. A comparison of robotic versus laparoscopic adrenalectomy in patients with primary hyperaldosteronism. *Surg Laparosc Endosc Percutan Tech*. 2017;27(5):391–393. doi:10.1097/SLE.0000000000000455
26. Aliyev S, Karabulut K, Agcaoglu O, et al. Robotic versus laparoscopic adrenalectomy for pheochromocytoma. *Ann Surg Oncol*. 2013;20 (13):4190–4194. doi:10.1245/s10434-013-3134-z
27. Brandao LF, Autorino R, Laydner H, et al. Robotic versus laparoscopic adrenalectomy: a systematic review and meta-analysis. *Eur Urol*. 2014;65 (6):1154–1161. doi:10.1016/j.eururo.2013.09.021
28. Agcaoglu O, Aliyev S, Karabulut K, et al. Robotic versus laparoscopic resection of large adrenal tumors. *Ann Surg Oncol*. 2012;19(7):2288–2294. doi:10.1245/s10434-012-2296-4
29. Higgins RM, Frelich MJ, Bosler ME, et al. Cost analysis of robotic versus laparoscopic general surgery procedures. *Surg Endosc*. 2017;31 (1):185–192. doi:10.1007/s00464-016-4954-2
30. van Berkel A, Lenders JW, Timmers HJ. Diagnosis of endocrine disease: biochemical diagnosis of phaeochromocytoma and paraganglioma. *Eur J Endocrinol*. 2014;170(3):R109–19. doi:10.1530/EJE-13-0882

31. Xia Y, Wei Y, Li ZY, et al. Catecholamines contribute to the neovascularization of lung cancer via tumor-associated macrophages. *Brain Behav Immun*. 2019;81:111–121. doi:10.1016/j.bbi.2019.06.004
32. Park HS, Roman SA, Sosa JA. Outcomes from 3144 adrenalectomies in the United States: which matters more, surgeon volume or specialty? *Arch Surg*. 2009;144(11):1060–1067. doi:10.1001/archsurg.2009.191
33. Pędziwiatr M, Wierdak M, Ostachowski M, et al. Single center outcomes of laparoscopic transperitoneal lateral adrenalectomy--Lessons learned after 500 cases: a retrospective cohort study. *Int J Surg*. 2015;20:88–94. doi:10.1016/j.ijsu.2015.06.020