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A Retrospective Study of 881 Lateral Transabdominal Laparoscopic Adrenalectomies Performed Between 1997 and 2017 at a Single Center in Poland to Determine Factors Associated with Surgery Time

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Laparoscopic adrenalectomy is acknowledged as a standard procedure in adrenal lesions management. This retrospective study of lateral transabdominal laparoscopic adrenalectomy performed between 1997 and 2017 in a single center in Poland aimed to determine the factors associated with surgery time.

Material/Methods: This retrospective study involved 881 patients. The factors identified as potentially affecting surgery time were age, sex, side of the lesion, histopathological type, hormonal activity, size of the lesion, history of previous abdominal operations, presence of intra-abdominal adhesions, and obesity. The following statistical tests were conducted: *t* test, Mann-Whitney U test, Kruskal-Wallis H test, Pearson correlation test, and multivariate regression modeling.

Results: The mean surgery time for all operations was 139 min (55-320 min). We observed statistically significant differences for surgery time in the following groups: sex, side of the lesion, presence of intra-abdominal adhesions, obesity, histopathological type, and hormonal activity ($P<0.05$). The multivariate regression model showed factors affecting surgery time were: sex, side of the lesion, size of the lesion, obesity, histopathological type (nodular hyperplasia and adenoma), and hormonal activity (non-functioning and aldosterone-secreting tumors) ($P<0.05$). There was no correlation between surgery time and patient age and tumor size ($P<0.05$). Mean tumor size was 42 mm (6-130 mm).

Conclusions: The 20-year experience of laparoscopic adrenalectomy performed at a single center showed that surgery duration was significantly longer in male patients, obese patients, left-sided adrenal tumors, tumors >6 cm in diameter, patients with a diagnosis of pheochromocytoma, and when intra-abdominal adhesions were present.

Keywords: Adrenal Gland Neoplasms • Adrenalectomy • Laparoscopy • Operative Time

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Background

Laparoscopic adrenalectomy is acknowledged as a standard procedure in management of adrenal lesions. The operation was first performed by Gagner in 1992 [1]. Compared to the open method, it is associated with better outcomes and reduction in morbidity, less postoperative pain, shorter length of hospital stay, lower complications rate, and less operative blood loss, as well as less hemodynamic instability in pheochromocytoma, faster recovery, and better cosmetic results [2-8]. Several methods of endoscopic adrenalectomy have been described: lateral transabdominal, posterior or lateral retroperitoneoscopic, and lateral robotic [7,8]. The most popular are lateral transabdominal and posterior retroperitoneoscopic approaches [7,8]. It is recommended that surgeons use the technique most familiar to them to reach maximal safety and effectiveness [7,8].

The surgery time of laparoscopic adrenalectomy can be influenced by various factors; the most widely discussed in the literature are the size of the lesion, histopathological type, and surgeon's experience [8-27]. The other important aspect is the volume of the center [8]. The European Society of Endocrine Surgeons published a consensus statement recommending that adrenal surgery should be performed only in centers performing at least 6 adrenalectomies per year [8]. The biggest series of patients operated on in a single institution and reported in the literature are 653 laparoscopic adrenalectomies over 24 years in the United States, 520 laparoscopic adrenalectomies over 20 years in France, 560 retroperitoneoscopic adrenalectomies over 12 years in Germany, and 245 laparoscopic adrenalectomies over 4 years in Poland [9-12].

Knowing the factors responsible for prolonged surgery can be useful in predicting difficult laparoscopic adrenalectomy. Therefore, this retrospective study from a single center in Poland included 881 patients who underwent lateral transabdominal laparoscopic adrenalectomy between 1997 and 2017 and aimed to determine the factors associated with surgery time.

Material and Methods

Study population and study design

The study was approved by the Bioethics Committee at the Medical University of Warsaw (approval no. AKBE/65/2019).

We conducted a retrospective study of the 991 laparoscopic adrenalectomies performed in the Department of General, Vascular and Transplant Surgery, Medical University of Warsaw from 1997 to 2017. This is a high-volume tertiary referral center. All operations were performed by 1 experienced surgeon, Prof. Maciej Otto, and his team specializing in endocrine and laparoscopic surgery.

Exclusion criteria were: additional procedures performed together with adrenalectomy (cholecystectomy, hernia repair), bilateral adrenalectomy, conversion to open surgery, and adrenal-sparing procedure. The first 30 surgeries were included into the learning curve and were excluded from the analysis. Data of patients undergoing adrenalectomy from the open approach were not analyzed in this study.

Data Collection and Analyzed Parameters

The factors identified as potentially affecting surgery time were age, sex, side of the lesion, histopathological type, hormonal activity, size of the lesion, history of previous abdominal operations, presence of intra-abdominal adhesions, and obesity. Surgery time was counted from skin incision to skin closure. Histopathological results were divided into 5 groups: pheochromocytoma, adenoma, nodular hyperplasia, adrenocortical cancer and metastasis, and a group of other rarely occurring lesions. The hormonal activity was categorized as: lesions secreting glucocorticoids, lesions secreting mineralocorticoids, lesions secreting catecholamines, lesions secreting androgens, and hormonally inactive. The tumor size criterion used in our analysis was based on postoperative measurement performed by the pathologist during the histopathological examination. The previous abdominal operations category was split into 3 groups: no previous abdominal operations, 1 previous abdominal operation, and 2 and more previous abdominal operations. Intra-abdominal adhesions were defined as presence of strong adhesions requiring blunt and/or sharp dissection in the surgical area.

Perioperative Procedural Details

All patients underwent pre-operative endocrinological workup, including imaging and hormonal studies, as well as pharmacological preparation when needed. Prior to surgery, all patients signed a written patients' informed consent form for the operation. The lateral transabdominal approach was used as the surgical method of choice in all cases. The surgical method was previously described in the literature by the operating surgeon and our team [28,29].

Statistical Analysis

All data were collected and saved in an electronic spreadsheet (Microsoft Excel). Statistical analysis was performed using the SAS 9.4 program. In addition to standard descriptive statistics, we conducted a *t* test, a Mann-Whitney U test, and Kruskal-Wallis H test to test for significant differences in surgery time between the groups. Pearson's correlation test was used assess

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the association with univariate variables. The multivariate regression model was used to assess independent predictive factors affecting surgery time. In the case of tumor size, continuous variables were transformed into categorical variables with a cut-off point of 6 cm. A *P* value of <0.05 was considered statistically significant.

Results

Demographics and Clinical Patients' Characteristics

Data of 991 laparoscopic adrenalectomies were analyzed. After applying exclusion criteria, 110 operations were eliminated from statistical analysis (**Table 1**). A total of 881 operations were evaluated. Patient demographics are summarized in **Table 2**. There were 606 females and 275 males. Mean age was 53.6 years and standard deviation (SD) was 13.9 years. There were 397 left-sided tumors and 484 right-sided tumors. Histopathological diagnoses included pheochromocytomas (n=178), adenomas (n=391), nodular hyperplasia (n=177), malignancies (n=27 [9 adrenocortical cancer and 18 metastasis]), and other tumors (n=108). The group of other tumors is characterized in **Table 3**. Hormonal activity diagnoses included non-functioning lesions (n=410), aldosterone-secreting tumors (n=92), cortisol-secreting tumors (n=187), catecholamines-secreting tumors (n=179), and androgens-secreting tumors (n=13). Mean tumor size was 42 mm (6-130 mm), median=40 mm, SD=20 mm. There were 304 patients who underwent 1 abdominal operation prior to laparoscopic adrenalectomy and 89 patients who underwent at least 2 abdominal operations prior to laparoscopic adrenalectomy. Intra-abdominal adhesions were present in 204 operations and obesity in 202 patients.

Variables Associated with the Risk of Prolonged Surgery Time

Mean surgery time for all operations was 139 min (55-320 min), median=130 min, SD=42 min. Descriptive statistics for surgery time in particular groups are shown in **Table 2**. We observed statistically significant differences for surgery time in the following groups: sex, side of the lesion, presence of intra-abdominal adhesions, and obesity (*P*<0.05). Duration of surgery was longer in male patients, left-sided adrenal tumors, obese patients, and when intra-abdominal adhesions were present.

When comparing the surgery time in histopathological groups, we found statistically significant differences for pheochromocytoma, adenoma, and the group of other tumors (chi-square=24.17, *P*=0.0001). Pheochromocytoma resection was the longest procedure, while adenoma resection was the shortest procedure (**Figure 1**). In hormonal activity comparison, there were statistically significant differences in surgery time for all groups apart from androgens-secreting tumors (chi-square=27.84, *P*=0.0001). Resection of catecholamines-secreting tumors was the longest operation and resection of aldosterone-secreting tumors was the shortest operation (**Figure 2**). There were no statistically significant differences in surgery time in groups of patients who underwent previous operations (*P*=0.14) (**Figure 3**).

Table 1. Reasons for exclusion from the study.

Reason for exclusion from the study	Number
Learning curve	30
Additional procedure performed	
Cholecystectomy	25
Hernia repair	10
Bilateral adrenalectomies	17
Conversion to open surgery	11
Bilateral adrenalectomies and Conversion to open surgery	2
Adrenal-sparing procedure	21*

* Includes 6 cases which overlap with previous reasons for exclusion.

The multivariate regression model (F=31.06, *P*<0.0001) showed that the following factors were associated with surgery time: sex, side of the lesion, size of the lesion, obesity, histopathological type (nodular hyperplasia and adenoma), and hormonal activity (non-functioning and aldosterone-secreting tumors). The model confirmed that surgery time was longer in male patients, left-sided adrenal tumors, lesion size above 6 cm, and in obese patients. Surgery time was shorter in nodular hyperplasia lesions and adenoma, as well as non-functioning and aldosterone-secreting tumors (**Table 4**). Age, history of previous abdominal operations, and presence of intra-abdominal adhesions were not significantly associated with surgery time in the multivariate regression model.

There was no correlation between surgery time and patient age (correlation coefficient (r)=0.01; *P*=0.7), as well as surgery time and tumor size (r=0.2; *P*<0.05).

Discussion

In this study, we presented our extensive data on the unilateral laparoscopic adrenalectomy via lateral transabdominal approach, with all surgeries performed by a single surgeon. We evaluated factors possibly affecting surgery time, including age, sex, side of the lesion, histopathology, hormonal activity,

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Table 2. Patient demographics and statistical analysis of surgery time.

Factors	No.	Mean OT	SD OT	Median OT	Min OT	Max OT	Confidence interval OT		P value	Test
							-95%	+95%		
All operations	881	139	43	130	55	320	136	142		
Sex									<0.05	-5.58*
Female	606	133	40	125	55	320	130	137		
Male	275	151	45	150	60	300	146	157		
Side									<0.05	-10.46*
Right	484	126	39	120	55	320	122	129		
Left	397	155	42	150	70	300	151	159		
Histopathology									<0.05	24.17***
Pheochromocytoma	178	150	47	150	60	320	143	157		
Adenoma	391	132	39	125	55	300	128	136		
Nodular hyperplasia	177	137	41	135	70	300	131	144		
Malignancies	27	148	49	140	75	260	129	167		
Others	108	147	45	135	60	270	138	155		
Hormonal activity									<0.05	27.84***
Non-functioning	410	137	42	125	55	300	133	141		
Aldosterone-secreting	92	123	34	120	60	240	115	130		
Cortisol-secreting	187	140	41	135	60	280	134	146		
Catecholamines-secreting	179	150	47	150	60	320	143	157		
Androgens-secreting	13	158	51	150	90	240	127	189		
Previous surgeries									0.14	3.88***
0	488	138	42	130	55	320	134	142		
1	304	143	44	135	60	300	138	148		
2 or more	89	133	38	130	60	260	125	141		
Adhesions									<0.05	-2.43**
Absent	677	137	43	130	55	320	134	140		
Present	204	145	40	140	60	250	140	151		
Obesity									<0.05	-4.54*
Absent	679	136	43	125	60	320	133	139		
Present	202	149	40	150	55	280	144	155		

OT – surgery time; SD – standard deviation; * Mann-Whitney U test; ** *t* test; *** Kruskal-Wallis H test.

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Table 3. Characteristic of the group of other tumors.

Histopathological type	Number
Angiosarcoma	1
Adrenal gland (CDKN2Agene mutation)	1
Cyst	36
Ganglioneuroma	10
Gastrointestinal stromal tumor	1
Haemangioma	6
Hyaline-vascular variant of Castleman's disease	1
Lipoma	2
Lymphangioma	2
Myelolipoma	27
Neurofibroma	2
Oncocytic adenoma	4
Paraganglioma	1
Primary pigmented nodular adrenocortical disease	4
Pseudocyst	7
Schwannoma	2
Teratoma	1

size of the lesion, history of previous abdominal operations, presence of intra-abdominal adhesions, and obesity. All factors except for age and previous abdominal operations were found to have a significant association with surgery time. Our analysis showed that surgery time was longer in male patients, left-sided adrenal tumors, obese patients, presence of intra-abdominal adhesions, and tumor size above 6 cm. Surgery duration for pheochromocytoma resection was significantly longer than for other lesions.

Experience in laparoscopic adrenalectomy was reported by many authors, although none of the previous series is as large as ours. The mean surgery time in our series was 139 min (ranging from 55 to 320 min). It is consistent with published data, where mean surgery time ranges from 60 to 171 min (total surgery times reported in the literature were from 40 to 440 min) [10,13-20,30]. It is established in the literature that surgeon's experience can influence surgery time. However, in our series, all operations were done by the same surgeon. The literature does not show the exact learning curve endpoint for laparoscopic adrenalectomy, and it ranges from 20 to 40 operations [7,8,13,30,31]. We included 30 cases into the learning curve. The literature suggests that laparoscopic adrenalectomy should be done in high-volume centers to reduce the complication rate and achieve better outcomes [8]. Patient's age in our series as well as in other publications is not associated with surgery time [16,31].

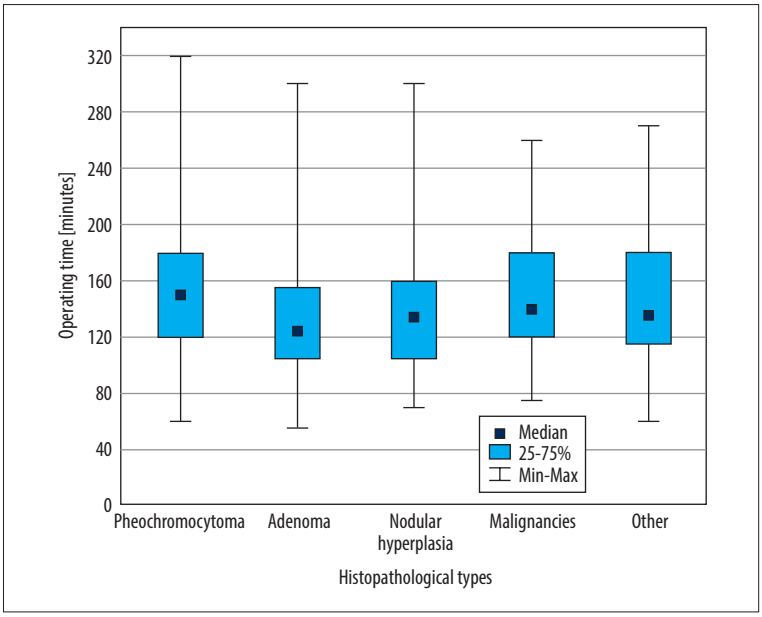

Figure 1. Box and whisker plot of surgery time in various histopathological types (Kruskal-Wallis H test) (Microsoft Office 2019).

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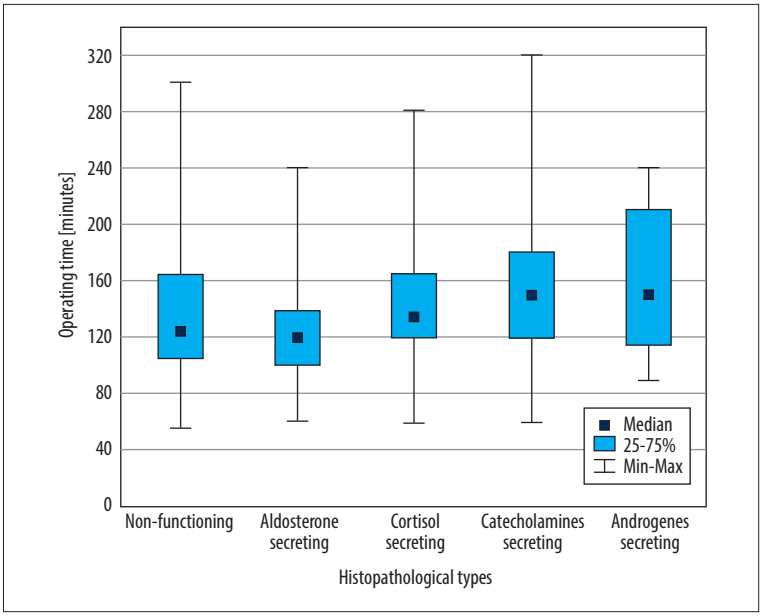

Figure 2. Box and whisker plot of surgery time in various hormonal activity groups (Kruskal-Wallis H test) (Microsoft Office 2019).

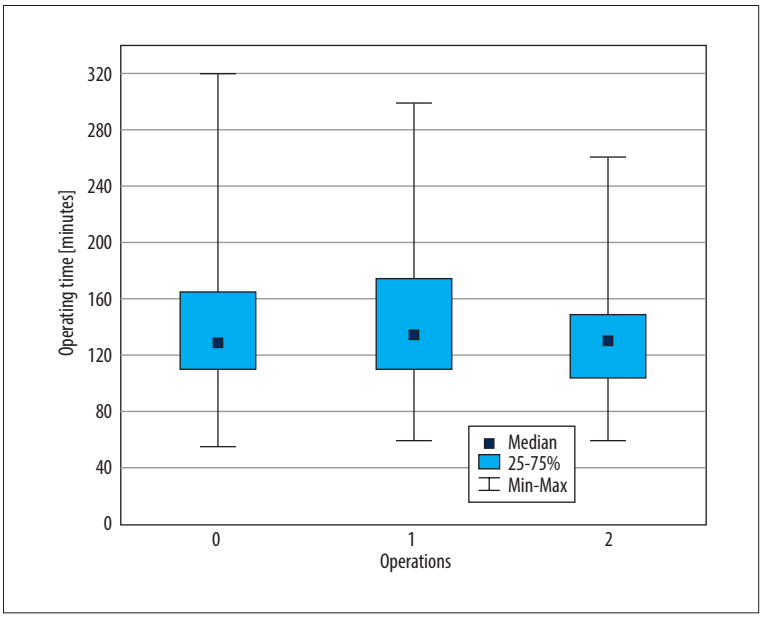

Figure 3. Box and whisker plot of surgery time in the number of previous operations (Kruskal-Wallis H test) (Microsoft Office 2019).

We observed a relationship between surgery time and sex. Operations in males were longer, and this finding is similar to those of other publications [16,31], perhaps because larger fat volume around adrenal glands in males than in females increases surgical difficulty and time [32]. The other fact, published by Alasina et al, is that malignant lesions and pheochromocytomas are more often diagnosed in males, and adrenalectomies for those tumors are more difficult and take more time [21]. In our series, the male-to-female ratio of malignancies was 20: 7, but in pheochromocytoma it was 83: 95.

Anatomical features of right- versus left-sided adrenalectomy can also influence the duration of surgery. In our series, left-sided adrenalectomy was significantly longer than right-sided, which is consistent with the majority of the presented literature. However, some authors did not observe differences in surgery time regarding the tumor's side [20,22,31]. On the right side, the surgical area is immediately exposed by elevating the right hepatic lobe and transection of the triangular ligament, the adrenal gland is seen through the translucent parietal peritoneum in its characteristic location. Dissection of the right suprarenal vein requires vigilance due to its close proximity to the vena cava. With left-sided adrenalectomy, locating the gland is more difficult due to the closeness of the spleen and tail of the pancreas, as well as the need for mobilization of the splenic flexure of the colon and division of the

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Table 4. Multivariate regression model on surgery time (F Value 31.06).

Model Fit Statistics: F=31.06			Pr <0.0001
Parameter	**Estimate**	**Wald chi-square**	**Pr >chi-square**
Sex	-17.66	-6.24	<0.0001
Side	-30.12	-11.57	<0.0001
Size >60 mm	18.46	5.14	<0.0001
Adenoma	-9.76	-3.13	0.002
Nodular hyperplasia	-14.94	-4.03	<0.0001
Non-functioning	-6.95	-2.51	0.01
Aldosterone-secreting	-17.57	-3.79	0.0002
Obesity	12.03	3.91	<0.0001
Adhesions	5.45	1.80	0.072

splenocolic and splenophrenic ligaments to mobilize the splenic-pancreatic block. The left renal vein needs to be reached to identify the left suprarenal vein.

Histopathological type of the tumor seems to be an important factor predicting surgery time. In our series, the longest were operations for pheochromocytoma removal, while adenoma resection had the shortest surgery time. Those 2 types of tumors were statistically significant for surgery time. Malignant tumors (metastases or adrenocortical carcinoma) were also associated with long surgery time, but the difference was not statistically significant when compared with other histopathological types. On the other hand, the multivariate regression model showed significance for nodular hyperplasia and adenoma, and those are associated with a shorter surgery time. When reviewing the literature, we found that the surgery time of laparoscopic adrenalectomy for pheochromocytoma was longer when compared with other histopathological types [22,23]. Pheochromocytomas are highly vascularized and surrounded by adhesions and fibrosis due to the local desmoplastic reaction [20]. Surgery in such a setting could increase dissection and hemostasis time. We also know from our own experience that in some cases during pheochromocytoma resection there is a need to stop surgery to stabilize the patient's blood pressure. The literature also widely discusses malignant tumors associated with prolonged surgery time [16,22]. However, some publications report no significant differences regarding surgery time in various histopathological types [15,20].

Type of hormonal activity can also influence surgery time. In our study, there were significant differences in surgery time for all groups apart from androgens-secreting tumors. Pheochromocytoma removal was the longest operation. The multivariate regression model showed that resections of nonfunctioning and aldosterone-secreting tumors were significantly shorter than for other operations. Alberici et al did not find an association between clinical diagnosis and surgery time [31].

There is an ongoing discussion in the literature regarding the definition of large adrenal tumor and tumor size cut-off point for laparoscopic adrenalectomy, indicating the procedure's safety and difficulty. In 2016, the European Society of Endocrinology Clinical Practice Guideline recommended an individualized decision process for each patient, and the low recommendation was to perform laparoscopic adrenalectomy for tumors size <6 cm and without local invasion [24]. Nowadays, laparoscopic adrenalectomy is commonly used in patients with tumor size >6 or 8 cm [11]. Many authors reported successful and safe laparoscopic adrenalectomies for tumors larger than 12 cm or even 18 cm [10,13,18,21,25]. The largest tumor removed in our department was 13 cm. The majority of publications show an association between tumor size and surgery time [7,9,10,15,16,25,31]. In our study, the multivariate regression model demonstrated that surgery time increases for tumors larger than 6 cm. However, there was no correlation between surgery time and tumor size. We also found publications where no relationship between surgery time and tumor size was found [19,26].

It is widely documented in the literature that previous abdominal operations were not associated with surgery time of laparoscopic adrenalectomy [16,33,34], in agreement with our series.

The presence of intra-abdominal adhesions was significantly associated with longer surgery time in our study. However, Pedziwiatr et al reported that surgery time of laparoscopic adrenalectomy is not influenced by the presence of abdominal adhesions [34].

The adrenal glands are anatomically surrounded by retroperitoneal fat regardless of the presence of obesity. Excess adipose tissue can increase time needed for locating and dissecting the adrenal tumor. We demonstrated a significant role for obesity as a predictor of longer surgery time, as did Kazaryan

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et al [35], but other series did not show that association [16,36]. There is also discussion in the literature regarding the superiority of measuring periadrenal fat volume versus body mass index (BMI) to predict surgical outcomes [32].

Study Limitations

We would also like to address some limitations of our study. Its retrospective character did not allow us to evaluate some factors which could be associated with surgery time due to lack of data in medical documentation. We could only isolate information regarding obesity, but not exact BMI. Periadrenal fat volume is another possibly significant factor that we could not evaluate. The last factor is the type of dissecting instrument used, as technology was improving and equipment was changing over time. The study would also have benefited from separately assessing the durations of specific parts of the operation, such as exposing the adrenal loggia, tumor dissection, and identification of the adrenal vein.

Conclusions

The 20-year experience of laparoscopic adrenalectomy performed at a single center showed that surgery time was significantly longer in male patients, obese patients, left-sided adrenal tumors, tumors >6 cm in diameter, patients with a diagnosis of pheochromocytoma, and when intra-abdominal adhesions were present.

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We would like to thank Prof. Maciej Otto for years of surgery and contribution to development of laparoscopic adrenalectomy in Poland.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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