Review Article

Minimally invasive adrenalectomy for adrenocortical cancers: A systematic review

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ABSTRACT

Introduction: Adrenocortical cancer (ACC) is a rare malignancy with poor prognosis. Due to the widespread use of imaging, greater proportion of cases are being discovered at an early stage, and it is possible to surgically excise these tumors by minimally invasive (MIS) approaches, including pure laparoscopy and robotic assistance. However, due to the fear of capsular breach, tumor spill, and incomplete removal, open surgery (OS) is still the preferred option for managing ACC. The aim of this review is to compare the two approaches and assess where MIS can be option for the surgical management of ACC.

Methods: This review was performed as per the Preferred Reporting Items for Systematic Reviews statement. Studies comparing OS and MIS approaches for ACC were retrieved from the PubMed, Scopus, and Cochrane databases. The two approaches were compared for tumor characteristics and outcomes.

Results: A total of 22 studies comparing MIS with OS were included in this review. Out of the total 4639 patients, 1411 underwent surgery by MIS and 3228 by OS. Patients operated by MIS had smaller tumors, lower operative time and blood loss with higher positive surgical margin rate, and higher rate of local recurrence. However, the overall survival was comparable between the two approaches.

Conclusions: MIS can be used in localized Stage-I ACC but only at high-volume centers. Stage II ACC may be considered for MIS if there is no evidence of local invasion and the surgery can be performed without capsular perforation and conversion to OS.

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare malignancy with an incidence of 0.7–2 per million population.[1] The distribution is bimodal with the first peak in the first decade of life and the second peak in the fourth to fifth decades of life.[2] Most ACCs are sporadic and unilateral; however, 2% to 6% of the patients have bilateral disease with hereditary predisposition.[3] Surgical resection remains the cornerstone of management when the disease is localized and offers the highest chance of cure. When the disease is locally advanced, multimodal therapy including systemic chemotherapy and radiation therapy is often required. ACCs tend to be larger than benign adrenal tumors at presentation, with >90% of them being larger than 5 cm in size.[4]

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Laparoscopic adrenalectomy (LA) is the gold standard treatment for benign adrenal masses; however, for ACC, the laparoscopic approach remains controversial, particularly in regards to the oncological outcomes.[5,6] Some studies have shown comparable results between the laparoscopic and open approaches[7-17] while others have reported an increased risk of tumor capsule violation, tumor fragmentation, port-site or peritoneal carcinomatosis, greater chances of spillage if the tumour is cystic or necrotic, and incomplete resection with the laparoscopic approach.[18-28] We reviewed the

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existing literature comparing the minimally invasive (MIS; laparoscopic or robot-assisted laparoscopy) and open surgical (OS) approaches to assess the role of MIS in the management of ACC.

METHODS

This review was carried out as per the methodological criteria of the Preferred Reporting Items for Systematic Reviews statement. Literature search was performed in the PubMed, Scopus, and Cochrane databases using adrenocortical cancer, (adrenocortical cancer) AND (laparoscopy), (adrenocortical cancer) AND (Robotics), ([adrenocortical cancer] AND [laparoscopy]) AND (open surgery) as search options. Literature was searched for publication dates between 2005 and 2024. Only studies in the English language comparing MIS approaches with open surgery were included. Review articles, meta-analysis, case reports, case series, and studies reporting only on the open approach or the laparoscopic approach were excluded. For comparative analysis, weighted means of variables were used since the studies had differing number of cases.

RESULTS

A total of 22 studies were included in this review [Table 1]. These included 4639 patients, of which 1411 were operated by MIS approaches and 3228 by OS. Three studies[9,10,19] included patients operated by robot-assisted laparoscopy, laparoscopy, and OS while the remaining only compared laparoscopy with OS. Six studies included patients with European Network for the Study of Adrenal Tumors (ENSATs) Stage I-II disease, eight included stages I-III, and eight included stages I-IV tumors [Table 2].

Patients operated by the MIS had smaller mean tumor size of 70 mm (range: 40–90 mm) compared to 118.5 mm in the OS arm (range: 68–140 mm) [Table 3]. Around 21% of the cases performed by MIS had positive surgical margins compared to 15% in the OS group. Margin-free (R-0) resection was achieved in 75.8% of the cases in the MIS group compared to 80.8% in OS group. Operative time was reported in eight studies and the mean operative time was 142.5 (range: 120–297.5) min in the MIS and 160 (range: 75–272.5) min in the OS groups, respectively. A total of 174 patients (15.4%) required conversion to OS in the MIS group. Mean blood loss and hospital stay were lower in the MIS group (300 mL, 5.15 days vs. 950 mL, 7.65 days, respectively).

The overall recurrence rate was comparable in both the groups (49.3%, range: 13%–100% for MIS vs. 49.3%, range: 22%–80% in OS), while the local recurrence was higher in the MIS group (36.9% vs. 20.7%). The disease-free survival was superior in the MIS group in six studies[18,10,12-15] and the OS was superior in eight studies.[6,11,17,20,22-25] The disease-free interval ranged from 9.7 to 72 months in the MIS compared to 8.1–52.9 months in the OS group, respectively.

DISCUSSION

Laparoscopic adrenalectomy is the gold standard of treatment for the surgical management of benign adrenal masses and results in reduced blood loss, reduced postoperative pain, early ambulation, shorter hospital stay, and superior cosmesis as compared to the OS.[29,30] The deep-seated nature of the gland, coupled with its small size makes it ideally suited to a MIS approach, avoiding large incisions that are typically required to gain exposure in the open surgery. However, the rarity of ACC coupled with its relatively larger size at presentation has resulted in limited literature evaluating the role of MIS in the management of ACCs. There are no randomized trials and all the available data comes from retrospective case series.

Surgery plays a critical role in the management of ACC as alternative treatment options such as the chemotherapy and radiotherapy have limited efficacy. For surgery to be curative, resection of the tumor must be complete with negative margins and an intact capsule. ACCs tend to be friable with necrosis and require gentle dissection and precautions to avoid tumor rupture and spillage. Complete surgical resection is possible in Stage I–II ACC as they are confined to the adrenal gland, without invasion into the surrounding tissues.

Tumor size correlates with the risk of malignancy in adrenal masses. Lesions <4 cm have a 2% incidence of malignancy which rises to 25% (10%–53%) for lesions >6 cm.[31] Adrenal tumors larger than 6 cm are usually approached by OS for the fear of harboring malignancy. Laparoscopy has been used primarily in localized disease,[32] reserving OS for the locally advanced cases.[33,34] There is no consensus regarding the role of MIS in the management of adrenal tumors >6 cm in size. Hue *et al*. demonstrated that MIS can be performed for tumors of all sizes with an overall conversion rate of 16.5%.[35] Calcatera *et al*.[20] described that the tumor size was not an independent predictor of survival in ACC even though a larger size was associated with a greater likelihood of conversion. Kastelan *et al*.[9] showed that laparoscopic surgery is feasible and safe in patients with larger tumors if the principles of oncologic surgery are followed, but should be limited to specialized referral centers with large experience. Even though the utilization of laparoscopy for the management of ACC has increased over the years at high volume centers, proper case selection is a must and laparoscopy cannot be the default option for all the patients.[8] During laparoscopy, patients with local invasion, if converted to OS, have an increased likelihood of positive surgical margins and poor survival.[33] These patients also have higher incidence of both local and peritoneal carcinomatosis and earlier recurrence when

Table 1: Clinical details of the studies

Study	Patients (*n*)	Median age (years)	Gender (female/male)	Hormone secretion (LA/OA)	Surgical approach (LA/OA)	LND (LA/OA)	Operative time (min) (LA/OA)	Conversions	Blood loss	Hospital stay (LA/OA)	Complications
Gaillard *et al*., 2023[7]	49	45 (33.0–60.8)	37/12	8/11	19/30	8/19 (P=0.25)	120/150	1 (high tumor volume of 8 cm)	-	-	CD ≥3–3 (6%) Patients Adrenal insufficiency – 29 (59%)
Delman *et al*., 2022[8]	1483	56 (44–67)	903/580	-	501/982	-	-	79	-	3/6	-
Kastelan *et al*.[9]	46	48 (18–74)	32/14	10/11	23/23	-	NA	0	-	-	-
Zheng *et al*.[18]	42	46 (40–54)	23/19	11/13	20/22	-	130/175 (P=0.004)	0	70/800 (P=0.001)	7/9.5 (P=0.018)	CD 1–2=7/9 (P=0.18)
Wu *et al*.[19]	44	45 (2–74)	27/17	11/9	21/23	-	125/117 (P=0.362)	1	-	6/9	-
Calcatera *et al*.[20]	588	54	228/360	-	200/388	-	-	38		3.7/6.3 (P=0.02)	-
Maurice *et al*., 2017[10]	481	61 (50–69)/56 (43–67)	302/179	-	161/320	2/42 (P<0.01)	-	24	-	-	-
Lee *et al*., 2017[11]	201	52 (11–87)	131/70	11/58	47/154	63	180/236 (P=0.12)	9	-	-	-
Vanbrugghe *et al*., 2016[21]	25	47 (22–77)	15/10	4/3	16/9	-	-	0	-	-	-
Huynh *et al*., 2016[22]	423	58.6/53.3	259/164	-	137/286	4/88 (P<0.001)	-	-	-	-	-
Donatini *et al*., 2014[12]	34	45	26/8	3/8	13/21	-	-	-	-	5/6 (P<0.02)	1 Postoperative stroke in LA 3 tumor rupture, chylous fistula, wound infection in OA (P=0.387)
Mir *et al*., 2013[23]	44	49 (40–65)	22/22	-	18/26	6/14	297.5/272.5 (P=0.777)	5	1500/1100 (P=0.06)	4/6 (P=0.69)	1/5 (CD ≥3) 17/21 (CD 1–2); P=0.3
Fosså *et al*., 2013[13]	32	45/52	23/9	13/6	17/15	-	150/230 (P=0.005)	2	400/1700 (400–10 750) P<0.001	6/13 (P<0.001)	3/12 (CD ≥3) 14/3 (CD 1–2); P<0.001
Cooper *et al*., 2013[24]	302	45.8/45 (P=0.001)	196/106	-	46/256	-	-	-	-	-	-
Miller *et al*., 2012[25]	156	47 (18–80)	64/92	-	46/110	-	-	-	-	-	-
Lombardi *et al*., 2012[14]	156	47.7 (10–81)	100/56	4/58	30/126	1/23	135/129 (P=0.598)	0	-	5.3/9.3 (P<0.001)	1/7 (P=0.972)
Porpiglia *et al*., 2010[15]	43	47/41.3	26/17	11/14	18/25	-	-	-	-	-	-
Miller *et al*., 2010[26]	88	46.3 (18–81)	57/31	-	17/71	-	-	-	-	-	-
Brix *et al*., 2010[16]	152	50.7/52.3	108/44	34/63	35/117	-	-	12 4-bleeding 4-adhesions 1-bowl perf 2-technical 1-malign	-	-	-
Leboulleux *et al*., 2010[27]	64	54 (23–79)	36/28	35	6/58	16	-	-	-	-	-

Contd...

Table 1: Contd...

Study	Patients (*n*)	Median age (years)	Gender (female/male)	Hormone secretion (LA/OA)	Surgical approach (LA/OA)	LND (LA/OA)	Operative time (min) (LA/OA)	Conversions	Blood loss	Hospital stay (LA/OA)	Complications
Kirshtein *et al*., 2008[17]	26	56/40	19/7	3	14/12	-	153/170 (P=0.01)	1 (adhesions)	200/550 (P=0.01)	-	0/2 (P=0.12)
Gonzalez *et al*., 2005[28]	160	46	109/51	62	6/154	-	-	2 Tumor fracture Bleeding	-	-	1
Total	4639	49.9	2743/1896	294	1411/3228	100/209	161/185	174	542.5/1037.5 mL	5/8	

LA=Laparoscopic adrenalectomy, OA=Open adrenalectomy, LND=Lymph node dissection, CD=Clavien–Dindo, NA=Not available

compared to the OS. The conversion rates are lower if the tumor is on the left side.

There is data that suggests an increasing use of MIS for the management of ACC. While reviewing data of 588 patients who underwent adrenalectomy for ACC, Calcatera *et al.*[20] reported that the use of MIS has increased from 26% to 44% in 2010–2014. Further, with increasing penetration of the robotic systems, robotic-assisted surgeries have also increased from 5% to 16% during this period. Larger tumors (average: 10.2 cm) were more likely to require conversion to OS but comparative data between LA and robot-assisted procedures was not available.

In most of the studies, the OS is preferred over laparoscopy for larger tumors.[18,19,22] OS for ACC has been shown to be superior than MIS in terms of disease-free survival despite the larger size of the tumors in the OA group.[18] Pooled results from 9 studies, which directly compared LA (240 cases) to OS (557 cases), showed significantly higher rates of peritoneal carcinomatosis in the LA group despite a larger tumor size in the OS group.[36] Wu *et al.*[19] described a local and peritoneal recurrence rate of 42% for LA and 22% for the OS group (P = 0.035). Recurrence appeared earlier in the LA than in the OS group (P = 0.048).

This data suggests that the size, rather than the pathology, may be a better predictor of the ideal surgical approach. In contrast, Hue *et al.*[35] demonstrated that the tumor size is independently associated with an increased likelihood of conversion to open surgery but is not associated with margin positivity or overall survival. Conversely, local invasion is independent of tumor size and is associated with margin positivity and survival. Positive margins, positive nodes, tumor extension, and more advanced ENSAT stage increased mortality.[22] Existing data shows a trend toward a higher likelihood of margin positivity among tumors ≥10 cm when resected via MIS approaches.[37] Laparoscopy was associated with a poorer overall survival (P = 0.04) in patients with Stage II disease, and it continued to be an independent risk factor for mortality on the multivariate analysis as well.[21]

There is always a risk of upstaging in ACC, whether operated by open or laparoscopic approach. This upstaging is mostly seen in Stage II and III disease, and can be as high as 30%. This upstaging may also be responsible for the high positive surgical margin rates. Miller *et al.*[25] noted that 13 of the 40 patients (30%) with ACC operated by the laparoscopic approach and 22 of the 71 patients (31%) with ACC operated by the open approach, considered preoperatively to be Stage II, were upstaged post-surgery to Stage III. This translated to a 75% positive margin rate with laparoscopy compared to 36% with OS. Hence, the application of the MIS approach in Stage II ACC should be guarded.

Table 2: Surgical and oncological outcomes between the two approaches

Study	Size (LA/OA) (mm)	ENSAT stage	PSM (LA/OA)	R0 resection (LA/OA)	Overall recurrence (LA/OA)	Local recurrence (LA/OA)	DFS (months) (LA/OA)	Overall survival	Follow-up (months)
Gaillard *et al*., 2023[7]	54/70 (*P*=0.01)	I–II	2/0 (*P*=0.28)	17/30	-	8/5	3 years DFS 73.3/89.7w (*P*=0.02)	83.5/89.4^{w} (*P*=0.16) (5 years OS)	60
Delman *et al*., 2022[8]	75/120 (*P*<0.01)	I–IV	100/180	401/802	-	-	-	53/55^{w} (5 years OS)	60
Kastelan *et al*.[9]	75/120 (*P*<0.001)	I–III	0	23/23	3/5 (*n*=8)	1/2 (*n*=3)	-	109/149^{x} (*P*=0.767)	52
Zheng *et al*.[18]	63/101 (*P*<0.01)	I–III	0	20/22	11/13 (*n*=24)	8/5 (*n*=13)	17:45 (*P*=0.02)	-	36
Wu *et al*.[19]	58.0/68.7 (*P*=0.07)	I–II	7/6	14/17	11/12 (*n*=23) (52:52)	9/5 (*n*=14) (43:22)	25/22 (*P*=0.8) 39/36w (5 years)	47:43^{w} (5 years), *P*=0.63	34
Calcatera *et al*.[20]	89/124 (*P*<0.001)	I–IV	36/58	141/289 23/41	-	-	-	-	-
Maurice *et al*., 2017[10]	75/117 (*P*<0.01)	I–II	32/54 (*P*=0.42)	129/266	-	-	-	58.0/62.1^{w} (3 years OS), *P*=0.42	23.6/25 (LA/OA)
Lee *et al*., 2017[11]	55/109 (*P*<0.001)	I–IV	11/40 (*P*=0.953)	36/114	22/82 (*P*=0.074)	-	14.26/9.79 (*P*=0.285)	90.97/53.88^{x} 68/49^{w} (*P*=0.239)	60
Vanbrugghe *et al*., 2016[21]	62.5/116.3 (*P*=0.09)	I–III	4/0 (*P*=0.260)	12/9	6/4 (*P*=0.9)	2/0 (*P*=0.74)	55.6/62.5w (*P*=1.000)	88.9/68.8^{w} (*P*=0.36)	36.4/52.9
Huynh *et al*., 2016[22]	80/127 (*P*<0.001)	I–III	25/43 (*P*=0.58)	98/218 30/58	-	-	-	-	21.9/22
Donatini *et al*., 2014[12]	55/68 (*P*=0.112)	I–II	6/4	7/17	4/5 (*P*=0.655)	1/2 (*P*=0.655)	46/47 (*P*=0.893)	85/81^{w} (*P*=0.634)	80/57
Mir *et al*., 2013[23]	70/130 (*P*=0.001)	I–IV	7/10 (*P*=0.5)	11/16	21/27	10/12	9.7/13.8	58/54^{w} (*P*=0.7)	26
Fosså *et al*., 2013[13]	80/130 (*P*=0.002)	I–III	5/3 (*P*=1)	12/12	3/5	1/1	15.2/8.1 (*P*=0.057)	103/36^{x} (*P*=0.22)	29.1
Cooper *et al*., 2013[24]	80/120 (*P*<0.0001)	I–IV	13/41 (*P*=0.01)	25/131 8/80	35/205	-	10.9/16.7	54/110^{x} (*P*=0.07)	34.4
Miller *et al*., 2012[25]	74/120	I–III	20/38	26/72	18/45	17/26	Stage II: 17.6/52.9 (*P*=0.001) Stage III: 5.0/10.7 (*P*=0.12)	Stage II: 50.9/103.1 (*P*=0.002) Stage III: 27.5/43.7 (*P*=0.77)	19/29.5
Lombardi *et al*., 2012[14]	77.3/90.4 (*P*=0.147)	I–II	0/0	30/126	8/48 (*P*=0.48)	4/14 (*P*=0.48)	72/48 (*P*=0.12)	108/60^{x} (*P*=0.20)	50/40
Porpiglia *et al*., 2010[15]	90/105 (*P*=0.39)	I–II	0/0	18/25	6/6	9/16	23/18	95/72^{w}	35
Miller *et al*., 2010[26]	70/123	I–III	8/8	9/63	10.71/46.15 (63:65)	4.25/14.2 (25:20)	9.6/19.2 (*P*<0.005)	-	36
Brix *et al*., 2010[16]	62/80 (*P*=0.6)	I–III	2/13	24/64 9/40	27/81 (*P*=0.36)	17.5/44.66 (50:38)	24.2/21.5	-	39.3
Leboulleux *et al*., 2010[27]	70/140 (*P*=0.006)	I–IV	3/10	3/48	5.7/27.26	1.5/11.6	-	5/38^{x}	35
Kirshtein *et al*., 2008[17]	40/80 (*P*=0.009)	I–IV	-	-	-	-	-	-	-
Gonzalez *et al*., 2005[28]	60/130 (*P*=0.003)	I–IV	-	-	6/115	3/51	-/13	-/43^{w}	28
Total	68.8/108.6	-	276/491	1064/2377	373.7/843.15	229.2/305.2	-	-	-

^{w}%, ^{x}Months. LA=Laparoscopic adrenalectomy, OS=Open surgery, ENSAT=European Network for the Study of Adrenal Tumors, PSM=Positive surgical margins, OA=Open adrenalectomy, DFS=Disease-free survival

Table 3: Weighted mean values in the two approaches

Variable	MIS	OS
Total number of patients	1411	3228
Operative time (min), *n*=8 studies	142.5 (120–297.5)	160 (75–272.5)
LND (%), *n*=5 studies	3.3 (1–42.11)	30.77 (13–63.3)
Blood loss (mL), *n*=4 studies	300 (70–1500)	950 (550–1700)
Hospital stay (days), *n*=8 studies	5.15 (3–7)	7.65 (6–13)
Size (mm), *n*=22 studies	70 (40–90)	118.5 (68–140)
PSM (%), *n*=20 studies	21.68 (0–53.4)	14.99 (0–38.6)
R0 resection (%), *n*=20 studies	75.80 (53–100)	80.84 (52–100)
Local recurrence (%), *n*=15 studies	36.9 (4–55.56)	20.7 (0–64)
Overall recurrence (%), *n*=16 studies	49.36 (13–100)	49.36 (22–80)
DFS (months), *n*=12 studies	22.73 (9.6–72)	25.76 (8.1–52.9)
Overall survival (5 years) (%), *n*=8 studies	57.03 (47–95)	57.85 (43–89.4)

The mean values are weighted averages based on the number of subjects and their mean reported in each reviewed study. OS=Open surgery, MIS=Minimally invasive surgery, LND=Lymph node dissection, PSM=Positive surgical margins, DFS=Disease-free survival

It is difficult to draw definitive conclusion from the available literature as all the studies are retrospective, prone to the confounding errors inherent to the retrospective studies, with factors other than the intervention in question affecting the outcome. Irrespective of the degree of control employed in these studies, many had results whose generalizability was limited by a small or unbalanced patient population or limited long-term follow-up. Ten studies had patient sample of ≤10 in either of the arms. In addition, these studies possibly had a selection bias as smaller tumors were operated by the MIS and larger were offered OS.

Centre volume and surgeon experience are of key importance to optimize the oncologic outcomes in patients with localized ACC.[7] Surgery for ACC should be carried out at high-volume centers by experienced surgeons. Data reporting equivalent oncological outcomes for MIS and OS for Stage I–II ACC are from reference centers with stringent patient selection and are operated upon by expert surgeons.[12,14,15,19] MIS is an option for the management of suspected cases of ACC ≤6 cm without evidence of local or nodal invasion, at high-volume centers in experienced hands only.[33,34,38] Preoperative tumor size along with surgeon experience, laterality, cross-sectional imaging characteristics should help the surgeon choose patients for MIS with the goal to minimize conversion to OS.

CONCLUSION

Localized ACC (Stage 1) can be operated using minimal invasive approaches at high-volume centers. Stage 2 ACC may be considered for MIS if there is no evidence of local invasion and the surgery can be performed without capsular perforation and conversion to OS.

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