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REVIEW

Minimally invasive versus open adrenalectomy for adrenocortical carcinoma: the keys surgical factors influencing the outcomes—a collective overview

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Abstract

Purpose Adrenocortical carcinoma (A.C.C.) is a rare tumour, often discovered at an advanced stage and associated with a poor prognosis. Surgery is the treatment of choice. We aimed to review the different surgical approaches trying to compare their outcome.

Methods This comprehensive review has been carried out according to the PRISMA statement. The literature search was performed in PubMed, Scopus, the Cochrane Library and Google Scholar.

Results Among all studies identified, 18 were selected for the review. A total of 14,600 patients were included in the studies, of whom 4421 were treated by mini-invasive surgery (M.I.S.). Ten studies reported 531 conversions from M.I.S. to an open approach (OA) (12%). Differences were reported for operative times as well as for postoperative complications more often in favour of OA, whereas differences for hospitalization time in favour of M.I.S.

Some studies showed an R0 resection rate from 77 to 89% for A.C.C. treated by OA and 67 to 85% for tumours treated by M.I.S. The overall recurrence rate ranged from 24 to 29% for A.C.C. treated by OA and from 26 to 36% for tumours treated by M.I.S.

Conclusions OA should still be considered the standard surgical management of A.C.C. Laparoscopic adrenalectomy has shown shorter hospital stays and faster recovery compared to open surgery. However, the laparoscopic approach resulted in the worst recurrence rate, time to recurrence and cancer-specific mortality in stages I–III ACC. The robotic approach had similar complications rate and hospital stays, but there are still scarce results about oncologic follow-up.

Keywords Adrenalcortical carcinoma · Open adrenalectomy · Laparoscopic adrenalectomy · Robotic adrenalectomy · Mininvasive surgery

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Introduction

Adrenocortical carcinoma (A.C.C.) is a rare and aggressive endocrine malignancy, with an annual incidence of approximately 1–2/1,000,000 people worldwide, accounting for 0.05–0.2% of all malignancies. In a recent Japanese nationwide survey, A.C.C.s accounted for 1.4% of many incidentalomas [1]. The age distribution is bimodal, with the first peak in childhood and a second higher peak in the fourth and fifth decade of life, with a slight female predominance [2]. Although most A.C.C.s are sporadic, many hereditary syndromes have been associated with this type of cancer, including Beckwith-Wideman syndrome, multiple endocrine neoplasia type 1, Li-Fraumeni, congenital adrenal

hyperplasia, familial adenomatous polyposis and Lynch syndrome [3].

The diagnosis of A.C.C. is often presumptive based on imaging (C.T. or M.R.I.) and hormonal workup and is confirmed postoperatively on surgical pathology. Malignancy must be suspected when the tumour size ranges from 4 to 6 cm, with an increased risk of malignancy for masses larger than 4 cm. The literature defines giant adrenal tumours (G.A.T.) as adrenal masses larger than 6 cm. G.A.T. are considered rare, with an incidence ranging from 8.6 to 38.6% of all adrenal tumours [3]. In the literature, the size criteria remain the main subject to establish the indication for surgery. The size is an essential variable in predicting malignancy. If the lesions are smaller than 4 cm, the risk of malignancy is approximately 2%, while for lesions of 4–6 cm, the risk of malignancy is 6%, and for lesions of 6 cm, the risk of malignancy is 25% (10–53%) [4]. Moreover, an adrenal nodule increasing in size by more than 1 cm per year must be considered potentially malignant.

At the time of the first diagnosis, A.C.C. is often at an advanced stage, with distant metastases found in 20% of patients, with the prevalent location in the lungs and liver (45% and 40%, respectively). Thus, the prognosis of A.C.C. is often poor, with overall survival (O.S.) of 3.21 years from diagnosis [5].

In 2004, the World Health Organization (WHO) and Union for International Cancer Control (UICC) introduced the first Tumor, Node and Metastasis (T.N.M.) staging system for A.C.C. based on the traditional McFarlane classification, modified by Sullivan. This classification system has been recently challenged due to the failure to discriminate between the prognosis of patients classified as stages II and III. Rather, the newly introduced European Network for the Study of Adrenal Tumors (ENSAT) system has become more widely adopted due to its reliable stratification of patient outcomes. The ENSAT staging system defines A.C.C. disease into four stages. Stage I (< 5 cm) and stage II (> 5 cm) tumours are confined to the adrenal gland. Stage III tumours extend into the surrounding tissue (para-adrenal adipose tissue or adjacent organs) or involve locoregional lymph nodes. Stage IV includes distant metastases, including lung (40–80%), liver (40–90%) and bone (5–20%) [6]. Although prognosis is certainly dependent on an accurate diagnosis, survival of patients with A.C.C. is mainly associated with intraoperative findings and a radical surgical approach, with the R0 margin being one of the most important prognostic factors. When surgical excision is deemed complete, the 5-year survival ranges from 32 to 58%, but when incomplete, the median survival is generally < 1 year (range, 2–16 months). Unfortunately, even after an apparent complete resection, local or distant relapse occurs in nearly 80% of patients. Complete surgical excision with microscopically negative margins is, therefore, the standard of care for localized/locally advanced disease (ENSAT I–III), leading to palliation of symptoms for patients with functional A.C.C.s and an increased disease-free (D.F.S.) and overall survival (O.S.) [7].

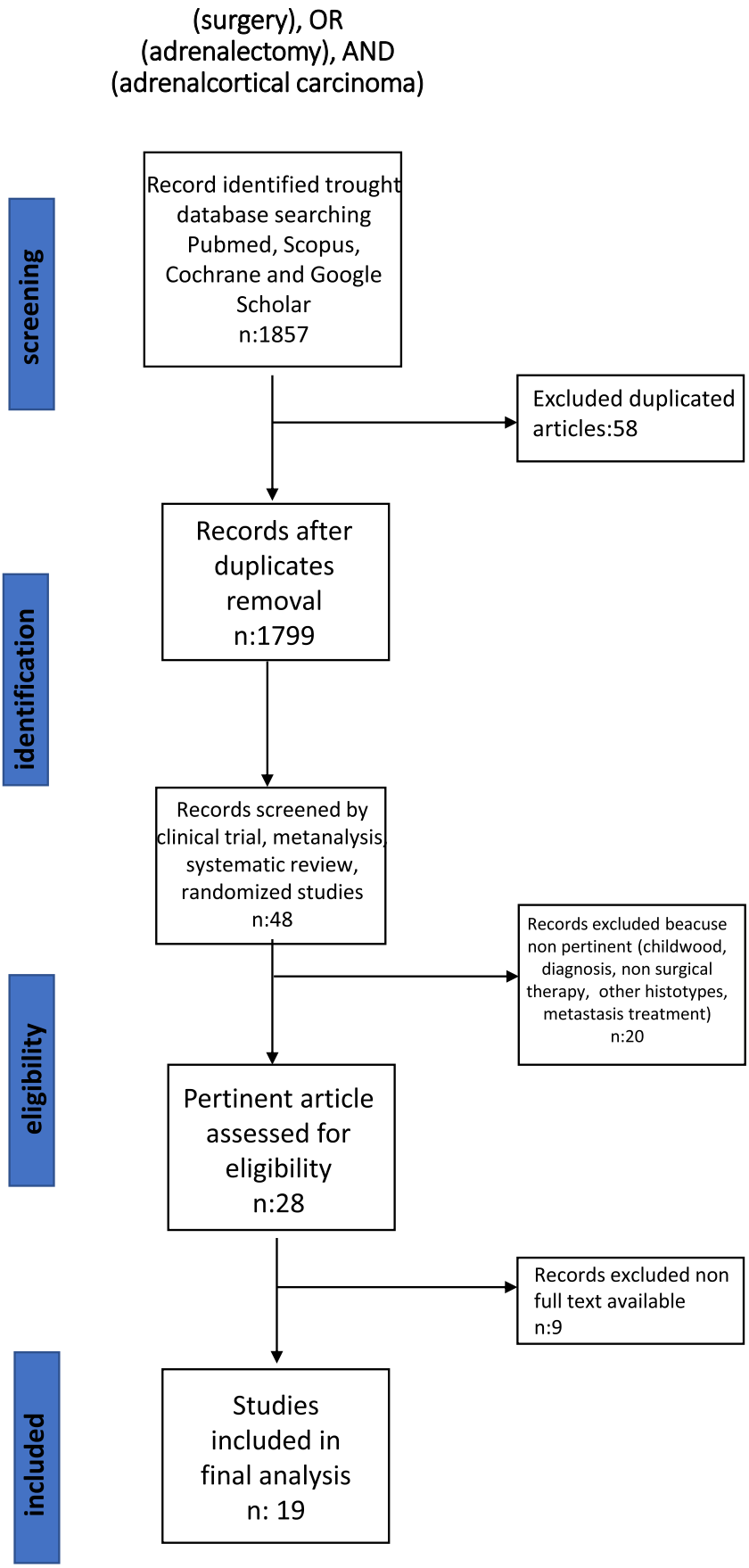
Open surgery has been recognized as the gold standard for A.C.C. because of the better achievement of R0 resection. Nevertheless, minimally invasive surgery (M.I.S.), which includes laparoscopic adrenalectomy (L.A.) and robotic adrenalectomy (R.A.), is increasingly considered a feasible approach for the resection of adrenal tumours. Indeed, in recent years, many studies in the literature have reported excellent results in terms of surgical and oncological outcomes with the minimally invasive approach to malignant adrenal tumours and G.A.T. [4].

This study aimed to review the current literature on the role of M.I.S. versus open technique in the surgical management of primary A.C.C. (ENSAT I–III) in adults. Since the oncological efficacy of surgery for A.C.C. is the most debated topic, this article has tried to critically evaluate which may be considered the best surgical approach depending on the ENSAT stage and to verify which are the most appropriate criteria for an oncologically adequate resection.

Method

This comprehensive review was performed according to the methodological criteria reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Fig. 1) [8]. The literature search was performed in PubMed, Scopus, Google Scholar and the Cochrane Library databases. The research was focused on the following issue: which kind of surgery should be proposed for which patients are affected by suspected/confirmed adrenocortical carcinoma, depending on the stage, size and other preoperative features? Which are the expected results of open, laparoscopic and/or robotic approaches? The search records were: ((surgery) OR (adrenalectomy)) AND (adrenocortical carcinoma). The research was limited to studies published after 2002, adult patients and papers written in English. The literature search was performed independently by two authors (AG and CB). Any discrepancies between the reviewers were discussed and solved by consensus. Quality studies were assessed for the level of evidence per the previously described methodology. Quality assessment of retrieved studies was performed with JADAD scores in the case of randomized clinical trials or MINORS scores for non-randomized studies. The risk of bias was assessed using the revised Cochrane risk-of-bias tool for non-randomized studies (ROBINS-I) [9].

Fig. 1 Prisma flowchart



Results

Studies included in our review article comparing minimally invasive surgical approaches to open adrenalectomy are reported in Table 1 [8, 10–26]. Surgical and oncological outcomes and the differences in terms of overall survival (O.S.) and disease-free survival (D.F.S.) between the open and laparoscopic approaches are shown in Table 2. In Fig. 2, the evaluation of the risk of bias in the review articles is evaluated according to the revised Cochrane risk-of-bias tool for non-randomized studies (ROBINS-I).

Among all studies identified, 18 were selected for entering the review [8, 10–26]. A total of 14600 patients were included in the selected studies, of whom 4421 were treated by mini-invasive approaches, and 10179 patients were treated by open surgery. In three studies, M.I.S. included both a laparoscopic and a robotic approach [8, 10, 15]. Some authors suggested that LA should be only performed in high-volume referral centres [25]. Ten studies reported 531 conversions from M.I.S. to an open approach (12%) [8, 11–19]. Among all included studies, A.C.C. staging was performed based on ENSAT stage: three studies involved stage I–II ACC [12, 14, 19], and two studies involved patients with stage I–III and stage I–IV disease, respectively [16, 21]. Patients treated with open adrenalectomy (OA) had a median tumour size of 8.6 to 11.9 cm, whereas those with LA were from 7.1 to 8.5 cm. Some studies showed that LA is effective for A.C.C. when the tumour size is < 10 cm and showed no local invasion, enlarged lymph nodes or distant metastases (ENSAT stage I–II) [15, 20–25]. Differences were reported for operative times as well as for postoperative complications more often in favour of OA [18, 19, 21–24], whereas differences for hospitalization time in favour of LA [13–19, 21–24]. In particular, the overall average complication rate reported after OA was 25% while after LA was 29%, conversely, the mean postoperative hospital stay after M.I.S. was 3.7 days vs 6 days after OA. Conversely, LA was mostly performed in many centers with a percentage of 74.5% for the treatment of ACC [15–25], while in other centers OA represents the standard operative technique in over 53% of the procedures [17–19].

Some authors state that LA for A.C.C. is associated with a high recurrence rate, particularly in peritoneal carcinomatosis [8, 12–22]. Other studies showed an R0 resection rate from 77 to 89% for A.C.C. treated by OA and 67 to 85% for tumours treated by mini-invasive surgery [22–26]. Some studies compared M.I.S. vs open lymph node (L.N.D.) dissection [14]. Several studies reported detailed follow-ups. The local recurrence rate ranged from 34 to 54% for A.C.C. treated by OA, and 44 to 51% for tumours treated by mini-invasive surgery [8, 10–26]. The overall recurrence rate ranged from 24 to 29% for A.C.C. treated by OA and from 26 to 36% for tumours treated by mini-invasive surgery [8, 10–26]. The median disease-free survival (D.F.S.) ranged from 26 to 38 months for A.C.C. treated by OA and from 21 to 32 months for tumours treated by mini-invasive surgery

Table 1 Studies general features

Study	Year	Design	Gender (F-M)%	Patients N OA	LA	Median age (year)	Conversion, (%)	Median follow-up (months)
Machado et all. [10]	2015	Retrospective	57/43	638	206	58	24	25
Calcaterra et all. [11]	2017	Retrospective	70/30	388	200	48	0	52
Ball et all. [8]	2016	Retrospective	62/48	187	78	66	0	31
Sgourakis et all. [12]	2015	Retrospective	67/33	815	1118	46	0	36
Winoker et all. [13]	2018	Retrospective	27-17	803	206	45	1	34
Hendriks et all. [14]	2022	Retrospective	58/42	662	734	54	38	-
Cavallaro et all. [15]	2021	Retrospective	47/53	1764	871	52	9	60
Buller et all. [16]	2019	Retrospective	49/51	153	35	47	0	52
Maurice et all. [17]	2016	Retrospective	65/35	256	46	45	0	66
Kastelan et all. [18]	2020	Retrospective	62/38	286	128	49	5	26
Hue et all. [19]	2021	Retrospective	54/46	310	377	48	2	29
Mpaili et all. [20]	2018	Retrospective	55/45	353	163	45	-	34
Autorino et all. [21]	2015	Retrospective	46/54	2043	305	47	-	29
Deloizer et all. [22]	2020	Retrospective	68/32	1105	158	47	0	42
Gonzales et all. [23]	2005	Retrospective	55/45	465	47	43	-	35
Zheng et all. [24]	2018	Retrospective	57/43	105	20	46	-	36
Wu et all. [25]	2018	Retrospective	44/56	45	21	54	-	35
Lee et all. [26]	2016	Retrospective	61/39	154	17	51	11	39

Table 2 Surgical and oncological results

Study	Stage (ENSAT)	Tumour size (cm)	R0 Resection (OA-LA),n	LND (OA-LA) n(positive)	Local recurrence (OA-LA), n	Overall recurrence (OA-LA), n (%)	Disease-free survival (OA/LA), months	Overall survival (OA/LA), months
Machado all. [10]	II–III	9.7	110–0	–	129–6	100–100	0.02	(1–54) p.054
Calcaterra et all. [11]	I–III	12.7	22–33	–	2–1	5–3	0.55	0–76
Ball et all. [8]	I–III	10.1	22–20	–	5–8	13–11	0.02	–
Sgourakis et all. [12]	I–II	6.8	–	3–0	5–9	12–11	0.8	(2–66) p.0.63
Winoker et all. [13]	I–IV	12.4	289–141	–	–	–	–	–
Hendriks et all. [14]	I–IV	11.7	266–129	42–2	–	–	–	(1–65) p.0.42
Cavallaro et all. [15]	I–IV	10.9	114–36	63	–	82–22	0.2	(3–96) p.0.23
Buller et all. [16]	I–III	6.8	9–12	–	0–2	4–6	1	(2–77) p.0.36
Maurice et all. [17]	I–II	11.6	21–13	–	–	5–4	–	(4–88) p.0.63
Kastelan et all. [18]	I–IV	13.7	16–11	14–6	12–10	–	–	(4–69) p.0.6
Hue et all. [19]	I–III	13.8	12–12	-	1–1	5–3	–	(3–102) p.0.22
Mpaili et all. [20]	I–IV	12.8	134–25	-	-	73–76	–	(4–99) p.0.07
Autorino et all. [21]	I–III	12.7	72–26	-	-	40–86	–	(2–154) p.0.002
Deloizer et all. [22]	I–II	9.7	126–30	23–1	14–4	48–8	–	(3–93) p.0.2
Gonzales et all. [23]	I–II	10.5	25–18	-	6–6	16–9	–	–
Zheng et all. [24]	I–III	12.3	82–50	-	20–25	-	–	–
Wu et all. [25]	I–IV	14.7	37–5	-	72–34	-	–	–
Lee et all. [26]	I–III	8	64–24	-	38–50	81–27	–	–

		Pre-intervention		At intervention	Post-intervention				Final Judgement
Authors	Study Type	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Low/ Moderate/ Serious
Machado all. [14]	retrospective	low	low	low	moderate	low	low	moderate	low
Calcaterra et all. [15]	retrospective	moderate	moderate	low	moderate	low	serious	moderate	moderate
Ball et all. [16]	retrospective	low	low	low	moderate	low	moderate	low	low
Sgourakis et all. [17]	retrospective	low	moderate	low	moderate	low	serious	moderate	moderate
Winoker et all. [18]	retrospective	moderate	serious	low	low	low	serious	moderate	moderate
Hendriks et all. [19]	retrospective	low	moderate	low	low	low	low	low	low
Cavallaro et all. [20]	retrospective	low	low	low	moderate	low	low	low	low
Buller et all. [21]	retrospective	low	moderate	low	moderate	low	moderate	moderate	moderate
Maurice et all. [22]	retrospective	low	low	low	low	low	moderate	moderate	low
Kastelan et all. [23]	retrospective	low	low	low	moderate	low	moderate	low	low
Hue et all. [24]	retrospective	moderate	moderate	low	moderate	moderate	moderate	low	moderate
Mpaili et all. [25]	retrospective	low	moderate	low	moderate	moderate	moderate	low	moderate
Autorino et all. [26]	retrospective	low	moderate	low	low	low	moderate	low	moderate
Deloizer et all. [27]	retrospective	low	low	low	moderate	moderate	moderate	moderate	moderate
Gonzales et all. [28]	retrospective	low	moderate	low	moderate	moderate	serious	moderate	moderate
Zheng et all. [29]	retrospective	low	low	low	moderate	moderate	serious	moderate	moderate
Wu et all. [30]	retrospective	moderate	moderate	low	low	low	moderate	low	low
Lee et all. [31]	retrospective	moderate	moderate	low	low	moderate	moderate	serious	moderate

Fig. 2 The risk of bias assessment of included papers using the ROBINS-I tool for non-randomized studies

[8, 10–26]. Time to recurrence and cancer-specific mortality were similar between LA and OA. The rates of positive margins in the LA group and OA were similar. In contrast, tumour spillage was demonstrated in 17% of patients in OA and 22% in LA. OA is considered the treatment of choice for A.C.C. according to most of the meta-analysis published [12, 14, 21]. They compared OA vs minimally invasive surgery (MIS). Although no significant differences were found for OS (HR 0.97, $p = 0.801$), cancer-specific survival (HR 1.4, $p = 0.869$) and recurrence/disease-free survival (HR 0.96, $p = 0.791$) between the two approaches, MIS was significantly associated with earlier recurrence (WMD 8.42, $p = 0.048$), positive surgical margin (RR 1.56, $p = 0.018$) and peritoneal recurrence (RR 2.63, $p < 0.001$).

Regardless of the surgical approach used, there is a general agreement about the rules of oncologic surgery: "R0 resection en bloc", "complete excision", "no tumour grasping or fragmentation or tumour capsule effraction". The 5-year overall survival for R0 versus R1 resection was 33–68% ($p <$ 0,001), and the 5-year recurrence-free survival for R0 and R1 resection was 28–34%. ($p = 0,60$), respectively [8, 10–26].

The potential role of the robotic approach (RA) has been shown to have several theoretical advantages compared to LA [8, 11, 15]. To our knowledge, no specific or dedicated studies about RA performed for A.C.C. have been published. Data regarding adrenalectomy performed for A.C.C. with minimally invasive robotic techniques are extracted from more general studies and only a few articles report and compare RA to LA or OA in the management of A.C.C. Recent evidence suggests that robotic adrenalectomy can be performed safely and effectively with the potential advantages of a shorter hospital stay, less blood loss and lower postoperative complications [27] Different technical approaches are available such as robotic-assisted lateral or anterior transabdominal adrenalectomy and robotic-assisted posterior retroperitoneoscopic adrenalectomy. The transperitoneal approach is advisable for the larger working space, the easier orientation and the magnification of surrounding anatomical structures. The retroperitoneal approach mimics OA and should be preferred in the case of bilateral tumours or previous abdominal surgeries [28, 29].

Agcaoglu et al. [30] performed 62 adrenalectomies for tumours larger than 5 cm (24 robotic vs. 38 laparoscopic) showing significant shorter operative time (159.4 13.4 vs 187.2 8.3 min, $p = 0.043$), less conversion rate (4% vs. 11%, $p = 0.43$) and shorter hospital stay (1.4 0.2 vs. 1.9 0.1 days, $p = 0.009$), respectively, concluding that in large masses (> 6 cm), RA allowed one to shorten operative time providing less conversion rate compared to LA. Also, Nordenström et al. [31], in a series of 100 robotic-assisted laparoscopies, showed a conversion rate of 7%, but all converted cases were during the initial stage of the robotic approach. Although RA and LA showed similar operating times ($p = 0.18$), hospital stays were significantly lower for the RA group (W.M.D.: 0.52, $p = 0.001$). No significant differences in oncological efficacy ($p = 0.81$) and morbidity profile ($p = 0.94$) were reported, and the perioperative mortality rate was similar among the groups ($p = 0.45$). The above-mentioned pooled analysis showed the superiority of RA regarding conversion rate and hospital stay compared to LA. However, comparable results are provided for operating time, positive margin rate and postoperative morbidity and mortality.

In a recent study, Selvaraj et al. [32] analyzed peri- and postoperative data of 235 patients who underwent adrenalectomy (OA ($n = 29$), LA ($n = 146$) and RA ($n = 60$)) at three Institutions over a 7-year period. OA ($n = 29$) versus MIS ($n = 206$) showed significant differences in larger tumour size, cm (9.4 vs 5, ($p = 0.0001$)), longer operative time, mins (240 vs 100, ($p = 0.0001$)), longer hospital stay (8 vs 3 days,($p = .0001$)), higher readmission rates (14% vs 1.9%), higher blood loss (400 vs 100 ml, ($p = 0.0001$)) requiring blood transfusion (14% vs 4.3%) ($p = 0.03$), higher intraoperative complication (21% vs 6%) ($p = 0.0004$) and post operative complications (17% vs 5.3%) ($p = 0.01$). Amongst the MIS (RA vs LA), RA appeared to have better outcomes in terms of shorter operative time, less blood loss and less intra operative complications with a p value <0.05. The postoperative complication rates were lowest with RA (3.3%) compared to OA (17%) and LA (6.1%).

Discussion

An appropriate surgical resection is a mandatory step in the therapeutic management of A.C.C.: a complete resection with negative margins and an intact adrenal capsule is necessary for curative intent [33]. Considering the fragility of A.C.C., surgeons must choose an appropriate approach that provides adequate exposure and access to the surrounding tissues and structures.

Although surgery remains the treatment of choice for A.C.C., the role of M.I.S. is still debated regarding oncological outcomes. In early 2000, the First International Adrenal Cancer Symposium defined open adrenalectomy (OA) as the gold standard for A.C.C. [34]. According to these recommendations, OA represents the treatment of choice to secure oncological principles, such as complete R0 "en bloc" resection and lymphadenectomy, as also confirmed by the last guidelines [35].

LA is today considered the gold standard treatment for benign adrenal tumours. Over the decades, there has been a radical change in the management of adrenal masses because minimally invasive adrenalectomy has been shown to decrease the length of hospital stay, reduce healthcare costs, reduce wound complications and blood loss and improve the patient's outcome with earlier patient mobility and faster return to regular activity [30]. The basic principle of LA is to perform gentle and elegant dissection of the surrounding

tissues away from the adrenal mass, avoiding tumour rupture or excessive manipulation. Even so, the main concern in LA is the risk of capsule rupture and intraperitoneal tumour spread. Current guidelines from ESMO-EURACAN [35] suggest performing LA in patients with unilateral adrenal masses with radiological findings suspicious of malignancy and a diameter ≤ 6 cm but with no evidence of local invasion (ENSAT stage I/II). Due to the lack of literature concerning the approach for ENSAT stage III, OA remains recommended for unilateral adrenal masses with radiological findings suspicious of malignancy, including signs of local invasion [31].

Furthermore, there is no consensus on the role of LAfor tumours > 6 cm and local invasion. The size is an essential variable in predicting malignancy, if the lesions are smaller than 4 cm, the risk of malignancy is approximately 2%, while for lesions of 4–6 cm, the risk of malignancy is 6%, and for lesions of 6 cm, the risk of malignancy is 25% (10–53%) [3]. No evidence suggests that a laparoscopic approach is contraindicated for G.A.T. because the size is only a predictor factor of malignancy [4]. In a recent metanalysis, Hue et al. [36] demonstrate that minimally invasive resections are being performed for tumours of all sizes. The authors performed an analysis stratified by tumour size and highlighted several important points. First, increasing tumour size and right-sided tumours were associated with an increased likelihood of conversion from M.I.S. to OA. Second, operations that required conversion to open and tumours with evidence of local invasion were associated with an increased likelihood of a positive surgical margin, however, tumour size was not an independent predictor of margin status. Third, positive margins, local invasion and operations that required conversion to open were all associated with poor survival, however, tumour size was not an independent predictor of survival. These collective data suggest that evidence of local invasion and operative technique play a significant role in treating patients with A.C.C. However, tumour size by itself may not be the most critical metric. This analysis adds granularity to the existing literature regarding the most important factors when determining the operative approach. M.I.S. may be cautiously considered in tumours with a relatively low risk of conversion (small size left-sided) and with no evidence of local invasion preoperatively. Otherwise, OA should remain the standard of care.

It is mandatory to consider the surgeon's experience and hospital volume. The last guidelines stated that adrenal cancer surgery should be performed only in centres performing at least six adrenalectomies per year (but with a preference for > 20 surgeries per year) [35] and by surgeons with expertise in both open and laparoscopic surgery [19].

In their meta-analysis, Autorino et al. [21] have not found differences in most relevant oncological outcomes between LA and OA, namely the overall recurrence rate ($p = 0.53$), time to recurrence ($p = 0.11$) and cancer-specific mortality ($p = 0.08$). However, there was a higher risk of development of peritoneal carcinomatosis at the time of recurrence for LA (RR 2.39, CI 1.41, 4.04, $p = 0.001$). This finding is in line with the study by Leboulleux et al. [37], who found the surgical approach to be related to the risk of peritoneal carcinomatosis observed in 5 of the 6 patients (83%) who underwent laparoscopic resection of A.C.C. in their series. Considering that patients with A.C.C. recurrence seem to have higher survival rates if amenable to complete surgical resection and the presence of peritoneal recurrence is likely to compromise a salvage surgery, these findings support the concept that a complete oncological resection, possibly involving adjacent organs and avoiding the rupture of the adrenal capsule, remains the key factor and it should not be compromised by the implementation of M.I.S.

Beyond the surgical approach, resection should be extended, in the case of extra-adrenal invasion, to include en bloc resection of macroscopically invaded surrounding organs [25]. In the early 1990s, Icard et al. [38] advocated for en bloc removal of the ipsilateral kidney, including peri-hilar lymph nodes and other adjacent structures, to obtain wide operative margins with a low risk of surgical tumour infringement. Thirteen patients (32%) underwent extensive resections over 12 years, including one partial pancreatectomy, four nephrectomies, three right hepatectomies and three bowel resections, all for apparent invasion. Additionally, 11 patients underwent en-bloc nephrectomy without evident tumour invasion. No improvement in the outcome was observed. However, the authors argued that an "en bloc resection" allowed R0 surgery. Kidney involvement is rare, and there is no evidence that nephrectomy may positively influence the oncologic outcome. It is suggested to remove an adjacent organ case-by-case basis, considering preoperative imaging and overall inspection during surgery.

There is no consensus on the role of lymph-node dissection (L.N.D.) in adrenal tumours. The adrenal gland has two main lymphatic drain flows: the first to the inferior vena cava and right/left edge of the aorta and the second one to the lomboaortic nodes and interaorticocaval space. Adrenal lymphatic drainage patterns are complex, so the extent of lymphadenectomy in A.C.C. resection remains unclear [27]. Last ESMO-EURACAN guidelines [35] advise that locoregional lymphadenectomy improved tumour staging leading to a better oncological outcome. Moreover, the E.S.E. guidelines suggest performing a locoregional lymphadenectomy in highly suspected or proven A.C.C cases. In the studies regarding L.N.D. in A.C.C., the German A.C.C. Registry analyzed 283 patients: 47 cases underwent adrenalectomy with L.N.D., and 236 patients underwent adrenalectomy with no L.N.D. [39]. Multivariate analysis indicated a reduced risk of tumour recurrence (hazard ratio [H.R.] 50.65, P5.42) and disease-related death (HR 50.54,

P5.049) for the L.N.D. group 2. In a recent study, Deschner et al. demonstrated that L.N.D. is not associated with an increased survival rate [40]. Lymph node metastasis is associated with advanced tumours ($p = 0.4$). Median overall survival was incrementally worse with an increasing number of positive lymph nodes (88.2 months for N0, 34.9 months for 1–3 positive nodes and 15.6 months for ≥ 4 positive nodes, $p < 0.001$). The optimal extent of lymphadenectomy in A.C.C. is still not known.

In the absence of clear-cut evidence of any benefits in the oncologic outcome, extended resection should be performed in selected cases when lymph node involvement is detected on preoperative imaging or intraoperatively. It remains controversial as an essential part of the surgical management for A.C.C. and deserves further investigation in a more extensive, prospective study. However, regional L.N.D. should still be considered for staging and prognostic purposes and to standardize surgical care [41, 42].

Therefore, from all the studies that we have cited, M.I.S. approaches might have a comparable oncologic outcome compared with OA for patients with localized (ENSAT I–II) or resectable A.C.C. (ENSAT I–III) if the principle of surgical oncology was respected. However, most studies were retrospective and involved a small number of patients. Hence, bias may exist. As a result, surgeons should carefully evaluate the condition of the patients and choose the surgical approach conducted in an oncologically appropriate manner to minimize the risk of recurrence and improve survival. Furthermore, more well-conducted studies with a large sample size are required to verify our findings.

The limitations of this study and the difficulty in concluding the evaluated studies are due to multiple confounding factors. First, all the studies analyzed were retrospective. They included a few cases due to the overall rarity of A.C.C. with inherent bias, which may affect our results and partially explain the heterogeneity among studies. Additionally, several factors may impact the results, such as adjuvant therapies, surgical volume, duration of follow-up and others. Over the years, radiological imaging techniques have improved and changed as well as surgical approaches with an increase in minimally invasive surgery, which may affect patient outcomes. L.N.D. and complete resection confer better oncologic outcomes, but they are not standardized and depend on the presentation stage and surgeons' expertise.

On the other hand, many patients included in the previous studies were operated at low-volume centres. Furthermore, it would have been helpful to compare surgical management by grouping tumours by size, hormonal profile or other clinical characteristics. However, these data are poorly available and inhomogeneous among the studies. Lastly, to our knowledge, no studies about RA performed for only A.C.C. have been published yet. Thus, clear indications and unambiguous management of A.C.C. patients are still lacking. Further investigations, with patient randomization according to staging and surgical treatment, are needed.

Conclusion

A.C.C. is a highly malignant tumour of the adrenal cortex necessitating complete surgical excision with microscopically negative margins. The suspicions of A.C.C. for an adrenal lesion are driven by tumour size (> 6 cm), radiological signs of malignancy, presence of local invasion or distant metastases and typical hormonal secretions. Surgery is the treatment of choice for A.C.C. (Stage I–III), whereas, for stage IV, ACC surgery may be of more palliative intent. During the last years, surgical approaches have changed. Initially, OA has defined as the gold standard for confirmed or suspicious A.C.C. LA has gained more consensus for its indications and efficacy. LA appears to be equivalent to the open method for localized/locally advanced primary A.C.C. (ENSAT I–III) in terms of R0 resection rate, overall recurrence rate, time to recurrence and cancer-specific mortality, therefore, suggesting that the extent of surgery with adequate tumour resection is the predominant endpoint, rather than the surgical approach itself. Theoretically, robotic adrenalectomy has been shown to have several advantages compared to L.A., but there is still a lack of documentation of RA on malignant adrenal lesions. Thus, no direct conclusion about RA in A.C.C. can be inferred. The importance of R0 resection is emphasized by several studies, with en bloc removal of adjacent involved tissues or organs for locally advanced lesions. Current guidelines state that locoregional lymphadenectomy improves tumour staging and a better oncological outcome can be reached, while there is no consensus about the extent of lymphadenectomy. An appropriate surgical resection is a mandatory step in the therapeutic management of A.C.C. Although RA represents the future perspective, the role of minimally invasive surgery still needs further investigation. Multicenter randomized controlled trials with long follow-up periods exploring the long-term oncological outcomes are required to determine the benefits of the laparoscopic over the open approach in A.C.C.

Author's contribution All authors contributed equally to this work. Alessio Giordano and Carlo Bergamini collected all the records and supervised the drafting of the article.

Declarations

Authors state that the work described has not been published previously, that it is not under consideration for publication elsewhere and that all authors approve its publication.

Conflict of interest The authors declare no competing interests.

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