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Abstract

Purpose:
This study was designed to determine the role of laparoscopic adrenalectomy (LA) in the surgical management of adrenocortical carcinoma (ACC).
Methods:
A systematic literature review was performed on January 2, 2015 using PubMed. Article selection proceeded according to PRISMA criteria. Studies comparing open adrenalectomy (OA) to LA for ACC and including at least 10 cases per each surgical approach were included. Odds ratio (OR) was used for all binary variables, and weight mean difference (WMD) was used for the continuous parameters. Pooled estimates were calculated with the fixed-effect model, if no significant heterogeneity was identified; alternatively, the random-effect model was used when significant heterogeneity was detected. Main demographics, surgical outcomes, and oncological outcomes were analyzed.
Results:
Nine studies published between 2010 and 2014 were deemed eligible and included in the analysis, all of them being retrospective case–control studies. Overall, they included 240 LA and 557 OA cases. Tumors treated with laparoscopy were significantly smaller in size (WMD −3.41 cm; confidence interval [CI] −4.91, −1.91; $p < 0.001$), and a higher proportion of them (80.8 %) more at a localized (I–II) stage compared with open surgery (67.7 %) (odds ratio [OR] 2.8; CI 1.8, 4.2; $p < 0.001$). Hospitalization time was in favor of laparoscopy, with a WMD of −2.5 days (CI −3.3, −1.7; $p < 0.001$). There was no difference in the overall recurrence rate between LA and OA (relative risk [RR] 1.09; CI 0.83, 1.43; $p = 0.53$), whereas development of peritoneal carcinomatosis was higher for LA (RR 2.39; CI 1.41, 4.04; $p = 0.001$). No difference could be found for time to recurrence (WMD −8.2 months; CI −18.2, 1.7; $p = 0.11$), as well as for cancer specific mortality (OR 0.68; CI 0.44, 1.05; $p = 0.08$).
Conclusions:
OA should still be considered the standard surgical management of ACC. LA can offer a shorter hospital stay and possibly a faster recovery. Therefore, this minimally invasive approach can certainly play a role in

	this setting, but it should be only offered in carefully selected cases to avoid jeopardizing the oncological outcome.
Footnote Information	On the behalf of Italian Endourological Association (IEA) Research Office and International Translational Research in Uro-Sciences Team (ITRUST).

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REVIEW ARTICLE – ENDOCRINE TUMORS

Open Versus Laparoscopic Adrenalectomy for Adrenocortical Carcinoma: A Meta-analysis of Surgical and Oncological Outcomes

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ABSTRACT

Purpose. This study was designed to determine the role of laparoscopic adrenalectomy (LA) in the surgical management of adrenocortical carcinoma (ACC).

Methods. A systematic literature review was performed on January 2, 2015 using PubMed. Article selection proceeded according to PRISMA criteria. Studies comparing open adrenalectomy (OA) to LA for ACC and including at least 10 cases per each surgical approach were included. Odds ratio (OR) was used for all binary variables, and weight mean difference (WMD) was used for the continuous parameters. Pooled estimates were calculated with the fixed-effect model, if no significant heterogeneity was identified; alternatively, the random-effect model was used when significant heterogeneity was detected. Main demographics, surgical outcomes, and oncological outcomes were analyzed.

Results. Nine studies published between 2010 and 2014 were deemed eligible and included in the analysis, all of them being retrospective case–control studies. Overall, they included 240 LA and 557 OA cases. Tumors treated with laparoscopy were significantly smaller in size (WMD −3.41 cm; confidence interval [CI] −4.91, −1.91; $p < 0.001$), and a higher proportion of them (80.8 %) more at a localized (I–II) stage compared with open surgery (67.7 %) (odds ratio [OR] 2.8; CI 1.8, 4.2; $p < 0.001$). Hospitalization time was in favor of laparoscopy, with a WMD of −2.5 days (CI −3.3, −1.7; $p < 0.001$). There was no difference in the overall recurrence rate between LA and OA (relative risk [RR] 1.09; CI 0.83, 1.43; $p = 0.53$), whereas development of peritoneal carcinomatosis was higher for LA (RR 2.39; CI 1.41, 4.04; $p = 0.001$). No difference could be found for time to recurrence (WMD −8.2 months; CI −18.2, 1.7; $p = 0.11$), as well as for cancer specific mortality (OR 0.68; CI 0.44, 1.05; $p = 0.08$).

Conclusions. OA should still be considered the standard surgical management of ACC. LA can offer a shorter hospital stay and possibly a faster recovery. Therefore, this minimally invasive approach can certainly play a role in this setting, but it should be only offered in carefully selected cases to avoid jeopardizing the oncological outcome.

Adrenocortical carcinoma (ACC) represents a rare but rather aggressive tumor,[1] often associated with poor prognosis, despite aggressive multimodality treatment.[2] Surgical resection has traditionally been paying a major role in the management of the disease, especially in its early stages, where there might still be a window for cure.[3]

On the behalf of Italian Endourological Association (IEA) Research Office and International Translational Research in Uro-Sciences Team (ITRUST).

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Laparoscopic adrenalectomy was first reported by Gagner et al. 1992 and since then rapidly implemented for the resection of functioning and non functioning adrenal masses, given the recognized advantages in terms of postoperative morbidity and hospital stay compared with open surgery.[4–6] More recently, the role of robot-assisted laparoscopy has been postulated for adrenal surgery.[7]

Laparoscopic surgery for malignant adrenal tumors also has been explored, but its role remains highly debated, given concerns regarding the quality of surgical resection and related oncological risks.[8–10] In case of ACC, several laparoscopic series have been reported, with conflicting results. According to contemporary guidelines open surgery should be regarded as the standard treatment of patients with localized (stage I–II)/locally advanced (stage III) ACC, whereas laparoscopic adrenalectomy can be pursued in selected patients with small ACCs (<8 cm) without preoperative evidence for invasiveness. Moreover, this technique should be ideally performed in centers with a consolidated experience in laparoscopic adrenal surgery.[11,12]

The goal of this study was to provide a systematic review and meta-analysis of available comparative studies assessing laparoscopic adrenalectomy (LA) versus open adrenalectomy (OA) for the surgical resection of ACC.

METHODS

Literature Search and Studies Selection

A computerized systematic literature search was performed by using the PubMed database to identify studies published as of January 2, 2015. The following search free text terms were used: "*laparoscopic adrenalectomy*" OR "*adrenocortical carcinoma.*" Only studies that meet the following eligibility criteria were included: original study, comparing OA to LA for the specific indication ACC, including at least 10 cases per study group, and allowing data extraction of relevant outcomes. Identification and selection of the studies was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria (www.prisma-statement.org). All titles were screened for manuscripts written in the English language, and only on adult patients. Titles of articles were first reviewed to ascertain whether they might potentially fit the inclusion criteria. After assessing the abstract, a more thorough subsequent assessment was performed by looking at full text.

Study Quality Assessment

Because none of them was a randomized controlled trial, the methodological quality of the studies was rated according the Newcastle–Ottawa Scale (NOS) for observational retrospective studies.[13] The level of evidence was reported as described by the Oxford Center for Evidence-Based Medicine.[14]

Outcomes of Interest

The following relevant parameters were assessed: demographics, including patients' age, tumor characteristics (clinical presentation, size, stage, Weiss score [15]); surgical outcomes (operative time, postoperative major (Clavien grade >2) complication rate, hospital stay, R0 surgical margins status, use of adjuvant therapy—defined as any form of adjuvant therapy, such as chemotherapy, mitotane, radiation therapy), and oncological outcomes (rate of recurrence—defined as clinical, laboratory, or radiologic evidence of disease recurrence; time to recurrence—defined as the time between surgery and occurrence of disease recurrence; rate of cancer specific mortality—defined as number of deaths, with cancer as the underlying cause of death, occurring in the study population during the follow-up period).

Statistical Analysis

A meta-analysis of extractable data was performed. Odds ratio (OR) was used for all binary variables, and weight mean difference (WMD) was used for the continuous parameters. For the studies presenting continuous data as means and range, estimated standard deviations were calculated using the methodology described by Hozo et al.[15] Pooled estimates were calculated with the fixed-effect model (Mantel–Haenszel method), if no significant heterogeneity was identified; alternatively, the random-effect model (DerSimonian–Laird method) was used when significant heterogeneity was detected.[16,17] The final pooled effects were reported by the z test, and $p < 0.05$ was considered as statistically significant. To assess the heterogeneity among the included studies, the Cochrane χ^2 test and inconsistency (I^2) were used. Evaluation of potential publication bias was done by funnel plots analysis for each outcome. The data analysis was performed using the Review Manager software (Revman v.5.2.8, Cochrane Collaboration, Oxford, UK).

RESULTS

The initial search yielded 2070 and 2566 records, whose titles were screened. After initial screening and removal of duplicates, 24 articles were considered and reviewed based on title and abstract. At the end of the process, nine studies were reviewed in full text and confirmed to meet eligibility criteria (Fig. 1).[18–26]

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AQ6 An overview of the studies, all published between 2010 and 2014, is provided in Table 1. Overall, the quality of studies was high, despite all being retrospective case–control studies with a low level of evidence.

Demographics

Patients undergoing OA were older than those submitted to LA (WMD 2.56 years; CI 0.78, 4.34; $p = 0.005$). In four studies the clinical presentation of the adrenal tumor was described, and a higher rate of incidentalomas was found in the LA group (43 %) versus the OA group (31.8 %) (OR 2.39; CI 1.39, 4.12; $p = 0.002$).[18,20,21,24] Tumors treated with laparoscopy were significantly smaller in size (WMD −3.41 cm; CI −4.91, −1.91; $p < 0.001$), and a higher proportion of them (80.8 %) more at a localized (I–II) stage compared to open surgery (67.7 %) (OR 2.8; CI 1.8, 4.2; $p < 0.001$). The Weiss score, which was available in four studies only, was similar between the two groups (WMD −0.01, CI −0.27, 0.25; $p = 0.95$).[18,20,23,26]

Surgical Outcomes

Data related to operative time were available for analysis in three studies, and no difference could be detected between the two techniques ($p = 0.85$).[21,23,24] EBL was reported in

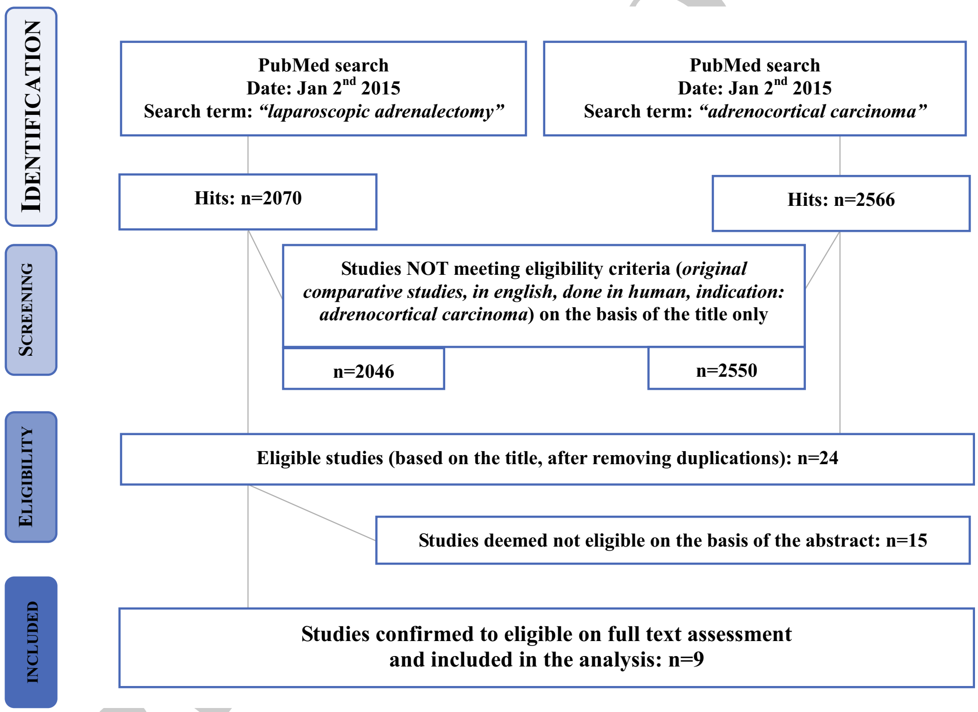

FIG. 1 PRISMA flow diagram illustrating the study selection process

TABLE 1 Characteristics and quality assessment of the included studies

Study	Study period	No. of cases (OA:LA)	Tumor stage	Study design	Level of evidence[a]	Quality score[b]
Porpiglia [18]	2002–2008	25:18	I/II only	Retrospective case control	4	8/9
Miller [19]	2003–2008	71:17	I–III	Retrospective case control	4	8/9
Brix [20]	1996–2009	117:35	I–III	Retrospective case control	4	9/9
Lombardi [21]	2003–2010	126:30	I–II	Retrospective case control	4	8/9
Miller [22]	2005–2011	110:46	I–III	Retrospective case control	4	8/9
Mir [23]	1993–2011	26:18	I–IV	Retrospective case control	4	8/9
Fossa [24]	1998–2011	15:17	I–III	Retrospective case control	4	8/9
Cooper [25]	1993–2012	46:46	I–IV	Retrospective case control	4	8/9
Donatini [26]	1985–2011	21:13	I/II only	Retrospective case control	4	8/9

OA open adrenalectomy, *LA* laparosocpic adrenalectomy

[a] Oxford criteria

[b] Newcastle–Ottawa scale

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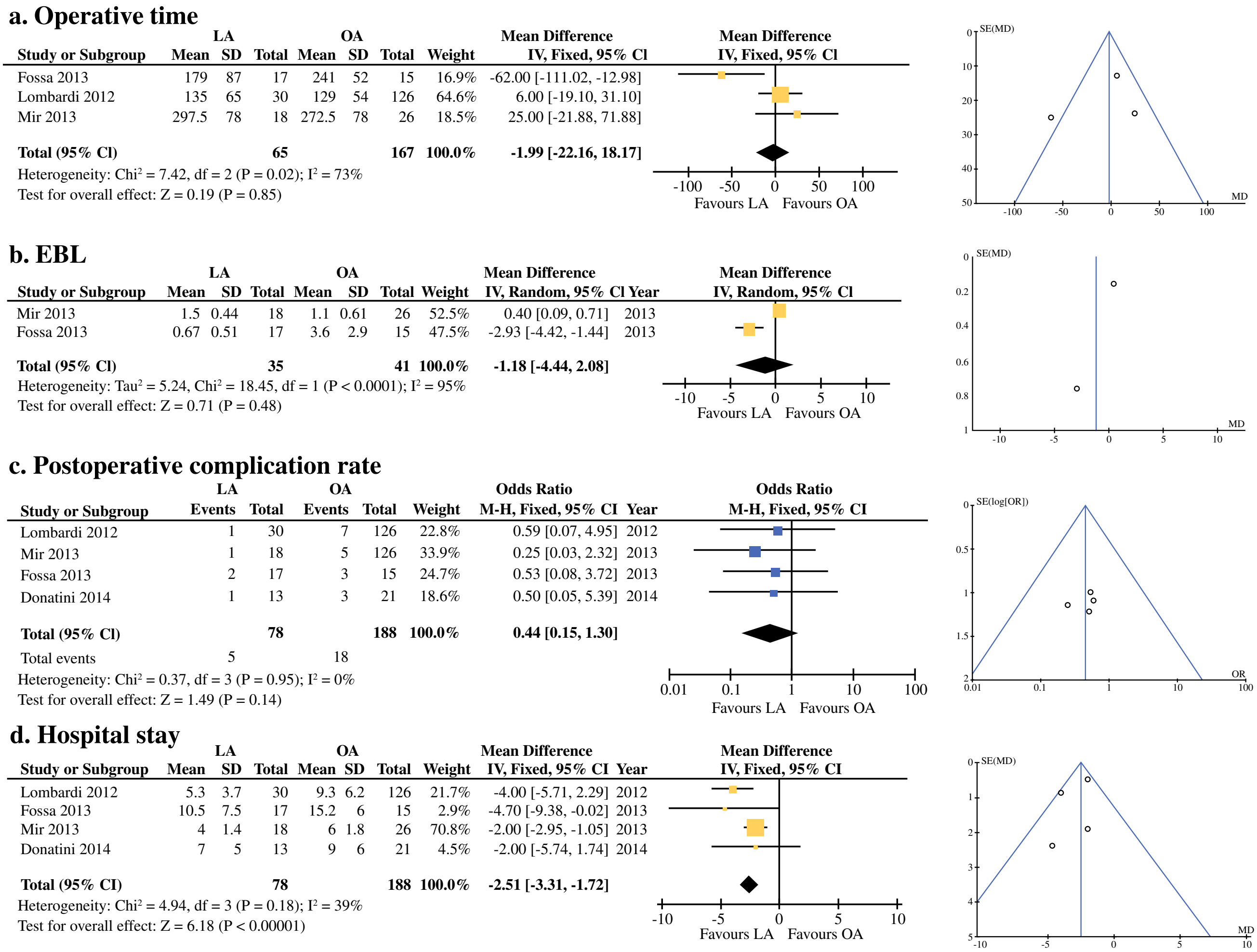

FIG. 2 Forrest and funnel plots for surgical outcomes

two studies only, and no difference could be detected ($p = 0.48$; Fig. 2).[23,24] Postoperative complication rate was available in four studies, and, again, there was no difference between laparoscopy and open surgery ($p = 0.14$).[21,23,24,26] In the same four studies, the hospitalization time was reported, and this was consistently in favor of laparoscopy, with a WMD of −2.5 days (CI −3.3, −1.7; $p < 0.001$).[21,23,24,26] There was no difference in the rate of negative surgical margins (R0), which was reported in seven of the studies (61.9 % for LA, 57.6 % for OA; $p = 0.98$).[19,20,22–26] Adjuvant therapy was used in a similar proportion of cases for LA and OA (32.5 and 29.8 %, respectively; $p = 0.91$).[20,21,23,25] The funnel plots suggested no publication bias, so that heterogeneity is most likely explained by other differences between the studies, such as study design, patient selection, and outcome assessment.

Oncological Outcomes

There was no difference in the overall recurrence rate between LA and OA (RR 1.09; CI 0.83, 1.43; $p = 0.53$; Fig. 3).[18–26] In five studies, investigators looked at the development of peritoneal carcinomatosis at the time of recurrence, and there was an overall higher risk for LA versus OA (RR 2.39; CI 1.41, 4.04; $p = 0.001$).[19,20,23–25]

Time to recurrence was reported in four studies only, and, also for this outcome, no significant difference could be detected between LA and OA (WMD −8.2 months; CI −18.2, 1.7; $p = 0.11$).[19,21–23] Cancer-specific mortality was available for analysis in six of the studies, and, again, no significant difference was found (OR 0.68; CI 0.44, 1.05; $p = 0.08$).[18,20,21,23,25], [26] Also for these outcomes, the funnel plots suggested no publication bias, but rather heterogeneity related to other confounders related to study design.

DISCUSSION

An appropriate surgical resection is a mandatory step in the therapeutic management of ACC. Thus, the role of minimally invasive surgery for this specific indication is still under scrutiny, as data supporting its implementation

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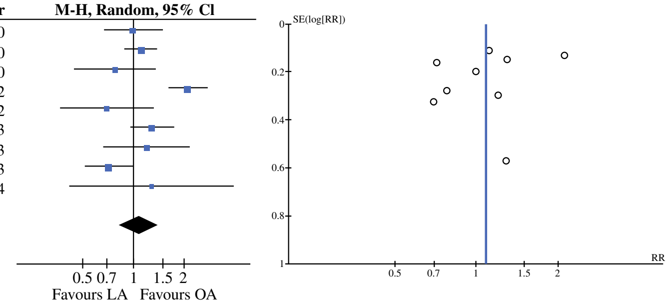
a. Overall recurrence rate

Study or Subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Miller 2010	11	17	46	71	12.2%	1.00 [0.68, 1.48]	2010
Brix 2010	27	35	81	117	14.8%	1.11 [0.90, 1.38]	2010
Porpiglia 2010	9	18	16	25	9.8%	0.78 [0.45, 1.35]	2010
Miller 2012	39	46	44	110	14.2%	2.12 [1.64, 2.75]	2012
Lombardi 2012	8	30	48	126	8.6%	0.70 [0.37, 1.32]	2012
Cooper 2013	35	46	27	46	13.7%	1.30 [0.97, 1.74]	2013
Mir 2013	10	18	12	26	9.2%	1.20 [0.67, 2.16]	2013
Fossa 2013	12	17	15	15	13.3%	0.72 [0.52, 0.99]	2013
Donatini 2014	4	13	5	21	4.3%	1.29 [0.42, 3.95]	2014
Total (95% CI)		**240**		**557**	**100.0%**	**1.09 [0.83, 1.43]**	
Total events	155		294				

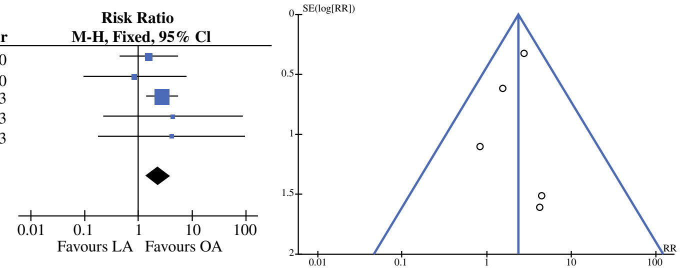
Heterogeneity: Tau^2 = 0.12; Chi^2 = 35.13, df = 8 (P < 0.0001); I^2 = 77%
Test for voerall effect: Z = 0.63 (P = 0.53)



b. Peritoneal carcinomatosis at recurrence

Study or Subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Miller 2010	3	17	8	71	20.8%	1.57 [0.46, 5.29]	2010
Brix 2010	1	35	4	117	12.4%	0.84 [0.10, 7.24]	2010
Cooper 2013	25	46	9	46	60.5%	2.78 [1.46, 5.28]	2013
Fossa 2013	2	17	0	15	3.6%	4.44 [0.23, 85.83]	2013
Mir 2013	1	18	0	26	2.8%	4.26 [0.18, 99.12]	2013
Total (95% CI)		**133**		**275**	**100.0%**	**2.39 [1.41, 4.04]**	
Total events	32		21				

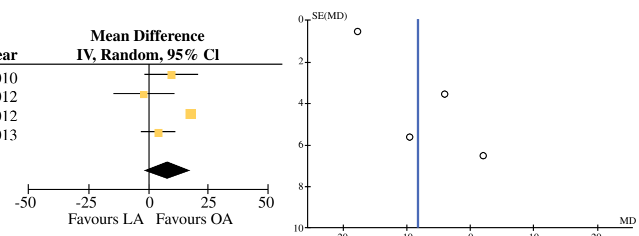
Heterogeneity: Chi^2 = 1.88, df = 4 (P = 0.76); I^2 = 0%
Test for voerall effect: Z = 3.24 (P = 0.001)



c. Time to recurrence

Study or Subgroup	OA Mean	OA SD	OA Total	LA Mean	LA SD	LA Total	Weight	Mean Difference IV, Random, 95% CI	Year
Miller 2010	19.2	37.5	71	9.6	14	17	22.4%	9.60 [-1.37, 20.57]	2010
Lombardi 2012	27	27	126	29	33	30	20.5%	-2.00 [-14.71, 10.71]	2012
Miller 2012	29.5	5.2	110	117	2.1	46	30.5%	17.80 [16.65, 18.95]	2012
Mir 2013	13.8	13.8	26	9.7	9.6	18	26.7%	4.10 [-2.81, 11.01]	2013
Total (95% CI)			**333**			**111**	**100.0%**	**8.25 [-1.75, 18.26]**	

Heterogeneity: Tau^2 = 85.22; Chi^2 = 25.45, df = 3 (P < 0.0001); I^2 = 88%
Test for voerall effect: Z = 1.62 (P = 0.11)



d. Cancer specific mortality rate

Study or Subgroup	LA Events	LA Total	OA Events	OA Total	Weight	Risk Difference M-H, Fixed, 95% CI	Year
Porpiglia 2010	1	18	7	25	10.6%	-0.22 [-0.43, -0.02]	2010
Brix 2010	13	35	48	117	27.3%	-0.04 [-0.22, 0.14]	2010
Lombardi 2012	5	24	41	110	19.9%	-0.16 [-0.35, 0.02]	2012
Mir 2013	10	18	20	26	10.8%	-0.21 [-0.49, 0.07]	2013
Cooper 2013	22	46	20	46	23.3%	0.04 [-0.16, 0.25]	2013
Donatini 2014	2	13	4	21	8.1%	-0.04 [-0.29, 0.22]	2014
Total (95% CI)		**154**		**345**	**100.0%**	**-0.08 [-0.17, 0.01]**	
Total events	53		140				

Heterogeneity: Chi^2 = 5.22, df = 5 (P = 0.39); I^2 = 4%
Test for voerall effect: Z = 1.83 (P = 0.07)

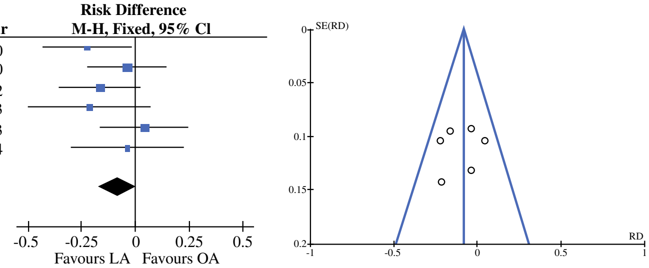


FIG. 3 **a**, **b** Forrest and funnel plots for oncological outcomes

remain scanty and controversial outcomes have been reported.[12] A recent analysis of the large National Inpatient Sample database has suggested that the use of laparoscopic techniques to perform adrenalectomy has increased at a slower rate over the last decade when compared with other procedures.[27]

The present systematic review and meta-analysis provides the best currently available evidence on the comparative outcomes of laparoscopy versus open surgery for the surgical resection of ACC with the aim of determining to what extent a minimally invasive approach should be considered in this setting.

Few findings of our analysis are of worth of consideration. First and foremost, the fact that a limited number of comparative studies are available, most of them with a limited number of cases, especially for the laparoscopic cohorts, which reflects the rarity of the disease. Moreover, despite being of good quality, all of these studies are retrospective case–control series, implying a patient selection bias and other intrinsic limitations related to their design.

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Nevertheless, the lack of randomized trial is recognized as a common drawback of clinical investigation for any surgical specialty. The two largest studies comparing LA to OA are based on multi-institutional analyses, namely the one reported by the German Adrenocortical Carcinoma Registry Group and the one based on an Italian multi-institutional survey.[20,21] In both studies, the ratio open:laparoscopic cases was approximately 3:1, which suggest that in these specialized centers there has been a selective implementation of laparoscopy. Both studies concluded that oncologic outcomes are not jeopardized if proper patient selection is embraced and principles of oncological radicality are respected.

Not surprisingly, we found that patients undergoing OA were on approximately 2.5 years older than those submitted to LA ($p = 0.005$). Moreover, tumors treated with LA are more likely to represent incidental diagnosis ($p = 0.002$), smaller in size ($p < 0.001$), and a localized (I–II) stage compared with OA ($p < 0.001$). On the other hand, in six of the nine comparative studies, cases of nonlocalized ACC (stage III–IV) were included,[19,20,22–25] which can reflect the status of referral centers reporting the studies. Center volume and surgical experience play a crucial role in the oncologic outcome of patients with adrenal malignancies; it has been suggested that adrenal cancer surgery should be performed only in centers with >10 cases per year.[28]

No significant differences could be found in terms of main surgical parameters (operative time, EBL, and complication rate) between LA and OA. The lack of significant difference in terms of operative time can be regarded as an unexpected finding especially considering the need for adjacent organ removal that is very time consuming step, and it was probably more extensive in the open surgery cases. To note, the surgical outcome "operative time" could be retrieved only in one third of the studies included in the meta-analysis. Thus, there might have certainly been a case selection bias. In addition, we could not assess in this setting the impact of the "learning curve" factor. In other words, the surgical experience of the different surgeons from the different studies might have played a role. Also, when considering that most of these are academic institutions, one can speculate that residents/fellows were involved in portions of the cases, thus impacting the duration of surgery.

Hospitalization time was clearly in favor of laparoscopy, with a statistical ($p < 0.001$) but also clinically significant difference (WMD of −2.5 days). The concept that laparoscopic surgery shortens hospital stay and likely enables a faster return to normal daily activities has been largely demonstrated for a variety of urologic diseases.[29]

The importance of complete, en bloc, margin-negative resection of ACC in patients who are fit to undergo surgery is a consolidated principle. In a large analysis from the national cancer database, Bilimoria et al. showed that median survival for patients with margin-negative resection was 51.2 months, whereas it was only 7 months for those who underwent margin positive resection.[30] We found no difference in the rate of negative surgical margins, which was reported in seven of the studies (61.9 % for LA, 57.6 % for OA; $p = 0.98$).[19,20,22–26]

The aggressive behavior of ACC provided the rationale for the use of adjuvant therapy, either radiotherapy to the tumor bed or mitotane.[31] We found that adjuvant therapy (any form) was used in a similar proportion of cases for LA and OA (32.5 and 29.8 %, respectively; $p = 0.91$) [20,21,23,25]; however, this finding is difficult to interpreter as different Centers might have adopted different therapeutic criteria.

In the only available meta-analysis of studies comparing LA versus OA for ACC, Sgourakis et al. looked at the oncological outcomes for stage I/II disease.[32] They included four comparative studies, all of them also included in our meta-analysis.[18,21,24,26] The authors found that OA seems to provide better survival rates at 5 years. This finding resembles those reported by Miller et al., who reviewed the single-institution experience with the surgical treatment of 217 cases of ACC (stage I–III).[19] Overall survival for patients with stage II cancer was longer in those undergoing OA. Moreover, time to local or peritoneal recurrence was shorter in those treated laparoscopically.

We could not find differences for 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., who found the surgical approach to be related to the risk of peritoneal carcinomatosis,[33] as well as data reported by Gonzalez et al. who observed peritoneal carcinomatosis in 5 of the 6 patients (83 %) who underwent laparoscopic resection of ACC in their series.[10] Considering that patients with ACC 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 remains the key factor, and it should not be compromised by the implementation of a minimally invasive approach.

The major limitation of this meta-analysis is related to the retrospective design of included studies, which allowed the analysis to be necessarily limited to certain parameters. Thus, it was not possible to perform a more detailed separate analysis of oncological outcomes (local recurrence only versus distant recurrence only versus peritoneal carcinomatosis only versus a combination of these events).

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Similarly, it was not possible to weight the impact of the different forms of adjuvant therapy used in the different studies. Moreover, it is not possible to account for existing differences among centers in terms of surgical techniques, as well as protocols of perioperative management and oncological follow-up. Despite these limitations, we are able to provide the best available evidence in the field, as nine studies with more than 700 ACC cases were included in the analysis. Thus, our findings can be used as reference for further clinical investigation.

Last, the role of robot-assisted laparoscopy in this setting remains to be determined. Robot-assisted laparoscopy is being implemented for adrenal surgery and recent evidence suggests that robotic adrenalectomy can be performed safely and effectively with potential advantages of a shorter hospital stay, less blood loss, and lower occurrence of postoperative complications.[7] Data on the use of robotics for large adrenal masses remain scanty, but early series are encouraging.[34]

CONCLUSIONS

OA should be still considered the standard for the surgical management of ACC, as it allows proper radical extirpation of the disease. LA can offer a shorter hospital stay, possibly allowing a quicker postoperative recovery, and it can certainly have a complementary role in this setting. However, this minimally invasive approach should be only offered in carefully selected ACC cases and by centers with appropriate laparoscopic expertise in order to avoid jeopardizing the oncological outcome.

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