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Is laparoscopic left adrenalectomy with the anterior submesocolic approach for Conn's or Cushing's syndrome equally safe and effective as the lateral and anterior ones?

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note finali coverage

(Article begins on next page)

Surgical Endoscopy

Is laparoscopic left adrenalectomy with the anterior submesocolic approach for Conn's or Cushing's syndrome equally safe and effective as the lateral and anterior ones?

--Manuscript Draft--

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Full Title:	Is laparoscopic left adrenalectomy with the anterior submesocolic approach for Conn's or Cushing's syndrome equally safe and effective as the lateral and anterior ones?
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Author Comments:	
Response to Reviewers:	<p>Professor George B. Hanna Editor-in-Chief Surgical Endoscopy</p> <p>Dear Professor Hanna,</p> <p>the manuscript entitled "Is laparoscopic left adrenalectomy with the anterior submesocolic approach for Conn's or Cushing's syndrome equally safe and effective as the lateral and anterior ones?" has been revised according to the valuable comments made by the reviewers. All comments have been addressed and changes have been made and highlighted in the manuscript, as follows:</p> <p>#Reviewer 1:</p> <p>1.Thank you for submitting your work. It is a very respectable experience in such a novel topic. Overall, the manuscript is very good. I do, however, advise to consider summarizing this part of the methodology that details the process of patient diagnosis and preparation since it is relevant to what is being evaluated which is the surgical technique.</p>

•The preoperative work up was summarized as follows:

“Hormonal assessment

In patients with hypertension or unexplained hypokalemia, aldosterone/renin ratio (ARR) was performed to exclude primary hyperaldosteronism [15-17]. Patients with a positive ARR (>3.8) underwent a saline infusion suppression test (infusion of 2 L of 0.9% intravenous saline solution) to definitely confirm or to exclude the diagnosis.

Baseline and after 4 hours blood samples for renin, aldosterone, cortisol and plasma potassium were taken, monitoring blood pressure and heart rate throughout the test.

Post-infusion plasma aldosterone levels higher than 10 ng/dl were diagnostic for Conn’s syndrome. In selected cases, adrenal vein sampling was used for distinguishing between unilateral and bilateral adrenal disease and to distinguish nonfunctioning incidentalomas from aldosterone-producing adenomas [15,18].

All patient with adrenal adenoma underwent overnight dexamethasone suppression test (1 mg-DST) receiving 1 mg of dexamethasone at 11 p.m. before taking the blood sample and having the blood test for serum cortisol taken between 8 and 9 a.m. the following morning. According to guidelines [19], diagnostic criteria that suggested Cushing’s syndrome was serum cortisol level greater than 1.8 g/dl (50 nmol/l) after 1 mg-DST.

Imaging

Adrenal Magnetic Resonance Imaging (MRI) with chemical shift or adrenal Computed Tomography (CT) scan were performed in all patients prior to surgery, to exclude large masses from adrenocortical carcinoma, to evaluate other unrelated diseases and to assist the surgeon during surgery.

Patient’s preoperative preparation and postoperative management

Conn’s syndrome

Before surgery, hypertension and hypokalemia were treated in all patients.

Hypertension may require the administration of several classes of antihypertensive drugs, always including a mineralocorticoid receptor (MR) antagonist, as spironolactone or eplerenone. MR antagonist is administered also for controlling hypokalemia, which in some cases requires potassium supplementation.

Cushing’s syndrome

Cushing’s syndrome patients are treated with 100 mg intravenous hydrocortisone at induction of anesthesia and then with 50 mg intravenous hydrocortisone every eight hours. The infusion therapy is then gradually reduced to oral hydrocortisone 10-20 mg/die [20].”

2.You mentioned the Ligasure device uses radiofrequency while it is bipolar diathermy.

•This sentence has been changed as follows: “The dissection is always carried out with a bipolar diathermy (LigaSure™ tissue fusion, Covidien, Mansfield, Massachusetts, USA) or...”.

#Reviewer 2:

1.The authors review their experience with laparoscopic adrenalectomy using several technical approaches. They found no difference in outcomes among the approaches, and recommend the submesocolic approach for left transabdominal laparoscopic adrenalectomy. however, their primary justification of this approach is because of early control of the adrenal vein, to avoid fluctuations in blood pressure. yet their cohort does not include any patients with pheochromocytomas, for whom intraoperative blood pressure fluctuations is typically present, not for patients with primary aldosteronism or cortisol excess. Why were pheochromocytoma patients not included in this cohort?

•Pheochromocytomas were not included in the present study because they were the object of a previously published article (Paganini AM et al. 2014. Laparoscopic transperitoneal anterior adrenalectomy in pheochromocytoma: experience in 62 patients. Surg Endosc. Sep;28(9):2683-9). In the previous article it was shown with two graphs that the intraoperative blood pressure and heart frequency remained stable during the operation.

In the Discussion the reason why pheochromocytomas were not included in the present study was explained as follows: “Moreover, data regarding pheochromocytoma and non-functional lesions have been previously reported [6-8].”

Other comments:

1.The authors may also consider including figures or intraoperative photos, to demonstrate this approach. without these data, it is difficult to truly state that the other approaches require more operative time and risk of complication, particularly since the authors found NO difference among the groups.

- Three figures regarding the submesocolic approach were added in the manuscript.

2.In the introduction, the authors state that there is debate among the best approach for adrenal surgery; laparoscopic adrenalectomy is truly the gold standard, except for those with concern for malignancy.

- The first sentence of the introduction has been changed as follows “Due to its position deep in the retroperitoneum and to the management complexities in case of secreting tumors, the open approach for adrenal surgery needs a wide abdominal incision and it is statistically associated with greater morbidity rate and longer postoperative stay [1].”

3.In addition to pheochromocytoma patients, why were not patients with nonfunctional tumors included?

- In the Discussion it was better explained why pheochromocytomas were not included in the present study: “Moreover, data regarding pheochromocytoma and non-functional lesions have been previously reported [6-8].”

4.It would be interesting to know if any patient had prior abdominal surgery, which may make the submesocolic approach more challenging?

- In the results section it was specified if patients who underwent conversion to open surgery during adrenalectomy with the submesocolic approach, underwent previous abdominal surgery as follows: “None of these patients had undergone previous abdominal surgery.”

Anyway, such as any abdominal procedure, also the adrenalectomy by submesocolic approach or by anterior or lateral transperitoneal ones could be more challenge in case of previous abdominal surgery.

The revised manuscript is now submitted again to your attention for review and possibly for publication in Surgical Endoscopy.

Looking forward to receiving your reply, I remain

Sincerely,

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Funding Information:

Abstract:

Background: The aim of the present study is to report and to compare the results of three different laparoscopic transperitoneal surgical approaches [lateral transperitoneal (LT), anterior transperitoneal (AT), and anterior transperitoneal submesocolic (ATS)] for the treatment of Conn's and Cushing's syndrome from left adrenal disease.

Methods: This study is a retrospective analysis of prospectively collected data. From 1994 to 2017, 535 laparoscopic adrenalectomies (LA) were performed. One-hundred-sixty-four patients with Conn's or Cushing's syndrome underwent left LA. Patients were divided in three groups based on the approach: LT (Group A), AT (Group B) and ATS (Group C).

Results: The diagnosis was Conn's and Cushing's syndrome in 99 and 65 patients, respectively. LT was used in 13 cases, AT in 55 and ATS in 96. No significant differences in patient's gender, age and BMI were observed. Mean operative time was 117.6±33.7, 107.6±40.3 and 96.2±47.5 minutes for Group A, B and C, respectively. Conversion to open surgery was observed in 4 Group C patients (4.1%). Morbidity

occurred in 2 Group B (2%) and in 5 Group C patients (5.2%).
Conclusions: In case of Conn's or Cushing's syndrome, left LA with ATS approach is equally safe and effective as compared to the LT and AT approaches. Early control of the adrenal vein with minimal gland manipulation and limited surgical dissection are the major advantages of the submesocolic approach. Even if statistically significant differences are not observed, postoperative results are the same as those reported in the literature with other approaches.

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Is laparoscopic left adrenalectomy with the anterior submesocolic approach for Conn's or Cushing's syndrome equally safe and effective as the lateral and anterior ones?

Running Head: Laparoscopic adrenalectomy by submesocolic approach

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18 The present study was accepted for ORAL presentation at the 26th International EAES Congress in
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20 London (UK), May 30th-June 1st 2018 and it was selected among the fifty best abstracts that
21
22 received a travel grant for the presenting author.
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ABSTRACT

Background: The aim of the present study is to report and to compare the results of three different laparoscopic transperitoneal surgical approaches [lateral transperitoneal (LT), anterior transperitoneal (AT), and anterior transperitoneal submesocolic (ATS)] for the treatment of Conn's and Cushing's syndrome from left adrenal disease.

Methods: This study is a retrospective analysis of prospectively collected data. From 1994 to 2017, 535 laparoscopic adrenalectomies (LA) were performed. One-hundred-sixty-four patients with Conn's or Cushing's syndrome underwent left LA. Patients were divided in three groups based on the approach: LT (Group A), AT (Group B) and ATS (Group C).

Results: The diagnosis was Conn's and Cushing's syndrome in 99 and 65 patients, respectively. LT was used in 13 cases, AT in 55 and ATS in 96. No significant differences in patient's gender, age and BMI were observed. Mean operative time was 117.6 ± 33.7 , 107.6 ± 40.3 and 96.2 ± 47.5 minutes for Group A, B and C, respectively. Conversion to open surgery was observed in 4 Group C patients (4.1%). Morbidity occurred in 2 Group B (2%) and in 5 Group C patients (5.2%).

Conclusions: In case of Conn's or Cushing's syndrome, left LA with ATS approach is equally safe and effective as compared to the LT and AT approaches. Early control of the adrenal vein with minimal gland manipulation and limited surgical dissection are the major advantages of the submesocolic approach. Even if statistically significant differences are not observed, postoperative results are the same as those reported in the literature with other approaches.

Key words: Conn's syndrome; Cushing's syndrome; Laparoscopic adrenalectomy; Transperitoneal anterior approach; Submesocolic approach; Lateral approach

INTRODUCTION

1
2 Due to its position deep in the retroperitoneum and to the management complexities in case
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4 of secreting tumors, the open approach for adrenal surgery needs a wide abdominal incision and it is
5
6 statistically associated with greater morbidity and longer hospital stay [1]. Laparoscopic surgery,
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8 instead, is associated with a low morbidity rate, reduced postoperative pain, shorter hospital stay
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10 and a quicker return to daily activities in comparison to open surgery [2]. After the first
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12 laparoscopic adrenalectomy (LA) by transperitoneal lateral approach reported by Gagner,
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14 laparoscopy has become the gold standard option for benign adrenal diseases and in selected
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16 patients with primary or metastatic adrenal cancer [3]. Other authors have reported LA with the
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18 same approach or, alternatively, the retroperitoneal one with the patient in the prone or in the lateral
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20 decubitus position, or the transperitoneal anterior one with the patient supine [4, 5]. In the last
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22 decade, the authors have proposed the anterior transperitoneal submesocolic approach in case of left
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24 LA [6-8].
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31 According to the literature, the most common pathologies setting the indication to perform
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33 LA are benign functioning adenomas such as primary hyperaldosteronism (Conn's syndrome) and
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35 primary hypercortisolism (Cushing's syndrome), which both have an incidence of 0,002%, or non-
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37 functioning adenomas [9-12]. During LA, hemodynamic instability is one of the major challenges
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39 to consider, especially in case of functioning adenomas [13, 14]. The aim of the present study is to
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41 report and to compare the results of three different laparoscopic transperitoneal surgical approaches
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43 [lateral transperitoneal (LT), anterior transperitoneal (AT), and anterior transperitoneal
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45 submesocolic (ATS)] for the treatment of Conn's and Cushing's syndrome from left adrenal
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47 adenoma.
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MATERIALS AND METHODS

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58 This study is a retrospective analysis of prospectively collected data. From January 1994 to
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60 July 2017, 535 laparoscopic adrenalectomies (LA) were performed in two centers (Department of
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General Surgery and Surgical Specialties, "Paride Stefanini", Sapienza University of Rome and Department of General Surgery, Università Politecnica delle Marche, Ancona, Italy) which follow the same treatment protocol and identical surgical approach [6-8]. Institutional review board (IRB) approval and informed consent from all individual participants included in the study were obtained. Out of 535 patients, 255 underwent right adrenalectomy, 259 underwent left adrenalectomy and 21 bilateral adrenalectomies. One-hundred-sixty-four out of 259 patients, who underwent left adrenalectomy, had Conn's or Cushing's syndrome and are the object of the present study.

Hormonal assessment

In patients with hypertension or unexplained hypokalemia, aldosterone/renin ratio (ARR) was performed to exclude primary hyperaldosteronism [15-17]. Patients with a positive ARR (>3.8) underwent a saline infusion suppression test (infusion of 2 L of 0.9% intravenous saline solution) to definitively confirm or exclude the diagnosis. Baseline and after 4 hours blood samples for renin, aldosterone, cortisol and plasma potassium were taken, monitoring blood pressure and heart rate throughout the test. Post-infusion plasma aldosterone levels higher than 10 ng/dl were diagnostic for Conn's syndrome. In selected cases, adrenal vein sampling was used for distinguishing between unilateral and bilateral adrenal disease and to distinguish nonfunctioning incidentalomas from aldosterone-producing adenomas [15,18].

All patient with adrenal adenoma underwent overnight dexamethasone suppression test (1 mg-DST) receiving 1 mg of dexametasone at 11 p.m. before taking the blood sample and having the blood test for serum cortisol taken between 8 and 9 a.m. the following morning. According to guidelines [19], diagnostic criteria that suggested Cushing's syndrome was serum cortisol level greater than 1.8 g/dl (50 nmol/l) after 1 mg-DST.

Imaging

Adrenal Magnetic Resonance Imaging (MRI) with chemical shift or adrenal Computed

1 Tomography (CT) scan were performed in all patients prior to surgery, to exclude large masses
2 from adrenocortical carcinoma, to evaluate other unrelated diseases and to assist the surgeon during
3 surgery.
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9 **Patient's preoperative preparation and postoperative management**

10 ***Conn's syndrome***

11
12 Before surgery, hypertension and hypokalemia were treated in all patients. Hypertension
13 may require the administration of several classes of antihypertensive drugs, always including a
14 mineralocorticoid receptor (MR) antagonist, as spironolactone or eplerenone. MR antagonist is
15 administered also for controlling hypokalemia, which in some cases requires potassium
16 supplementation.
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28 ***Cushing's syndrome***

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30 Cushing's syndrome patients are treated with 100 mg intravenous hydrocortisone at
31 induction of anesthesia and then with 50 mg intravenous hydrocortisone every eight hours. The
32 infusion therapy is then gradually reduced to oral hydrocortisone 10-20 mg/die [20].
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41 **Surgical Techniques**

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43 In the first part of the authors' experience LA was performed by AT approach.
44 Subsequently, the authors opted for the ATS and then, for a period of time, the LT
45 approaches. Surgical techniques for left LA have been previously described [7,8,21,22]. A
46 brief description of the technique is presented below.
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53 Under general anesthesia, urinary catheter, oro-gastric tube, intra-arterial radial catheter and
54 a central venous catheter are positioned. Pneumoperitoneum at a pressure of 12-13 mmHg is
55 established with a Veress needle or with an open technique and Hasson cannula or with an optical
56 trocar at the umbilicus. A 30° or 45° forward oblique optic is used, as previously reported [6-8].
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Lateral transperitoneal approach: The patient is turned on the operative table in right lateral decubitus position. Three or four trocars are employed. After division of the phreno-colic and phreno-splenic ligaments, followed by mobilization of the spleen and pancreatic tail, the adrenal gland is identified. The dissection of the adrenal gland begins from the peri-adrenal fat in a counter-clockwise direction until the adrenal vein is identified, that is divided between clips [21].

Anterior transperitoneal approach: The patient is on the operative table in supine position. Four trocars are employed. After division of the left parieto-colic peritoneum and of the spleno-colic ligament, the splenic flexure and descending colon are mobilized. Gerota's fascia is then opened and the adrenal gland is identified. Following the upper margin of the left renal vein medially, the inferior adrenal vein is identified, closed with clips and divided. The gland is then mobilized and removed [6-8].

Anterior transperitoneal submesocolic approach: The patient is on the operative table in supine position. Four trocars are employed. After lifting the transverse mesocolon followed by positive identification of the Treitz ligament, the posterior peritoneum is opened between the first jejunal loop and the arch of the inferior mesenteric vein or immediately lateral to this vessel, based on its distance from the first jejunal loop (Figure 1). The dissection proceeds by opening the Toldt's and Gerota's fascia at the level of the inferior pancreatic margin. The left renal vein is readily identified and it is followed medially up to its junction with the inferior adrenal vein, that it is closed with clips and divided (Figure 2). The gland is then mobilized and removed [6-8].

The dissection is always carried out with a bipolar diathermy (LigaSure™ tissue fusion, Covidien, Mansfield, Massachusetts, USA) or ultrasonic (Ultracision, Harmonic Scalpel, Ethicon Endo Surgery, Cincinnati, Ohio, USA) device. The gland is extracted inside an extraction bag and the residual cavity (Figure 3) is filled with hemostatic material (FloSeal, Baxter Healthcare Corporation, Deerfield, Illinois, USA or Surgiflo Hemostatic Matrix Kit, Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, Ohio, USA). A drainage is left in place according to the surgeon's preference.

Study design

The patients were divided in three groups based on the surgical approach: LT (Group A), AT (Group B) and ATS (Group C). Patients data including gender, age, Body Mass Index (BMI), previous abdominal surgery, approach, lesion size, operative time, conversions, postoperative complications (graded according to the Clavien Classification [23]), blood transfusions, associated procedures, hospital stay and definitive histology were collected in a Microsoft Excel program (Microsoft Corporation, Redmond, Washington, USA).

Statistical Analysis

Results are expressed as mean \pm Standard Deviation (SD) for continuous variables and percentages for categorical variables. Statistical analysis was performed using the t-test and Fisher's exact test. A probability (p) value lower than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the patients' characteristics. There were 13 cases in Group A, 55 cases in Group B and 96 cases in Group C. There were no statistically significant differences among the three Groups in terms of gender, mean age and Body Mass Index (BMI) (Table 1). The number of previous abdominal surgical procedures was significantly different in Group A versus C ($p=0.0229$) (Table 1).

Regarding operative data, no significant differences were observed (Table 2). After stratifying patients based on the lesion size (0-3 cm, 3.1-6 cm and 6.1-10 cm), subgroup analysis of the operative time showed a statistically significant difference between Group A and Group C for lesions up to 3 cm in diameter (Table 3). Conversion to open surgery was not observed in Groups A and B. In Group C, the procedure was converted to open surgery for hemorrhage (2), adhesions to the left diaphragmatic crus (1) or to the pancreatic tail (1). **None of these patients had undergone previous abdominal surgery.**

1 Complications were not observed in Group A. In Group B, two postoperative complications
2 were observed (3.6%): pneumonia (1) and colon fistula (1), grade II and III-b according to Clavien
3 Classification, respectively. In Group C, five complications were observed (5.2%): trocar
4 hematoma (1, I), fever (1, II), wound infection (1, II), pneumonia (1, II) and hemoperitoneum (1,
5 III-b) (Table 2). In one Group B patient and in 4 Group C patients, cholecystectomy was associated
6 to LA (Table 2). Postoperative blood transfusions were not required in Group A and B, but were
7 required in 2 Group C patients (2%). Oral intake occurred on the first postoperative day in all
8 patients without surgical complications. Mortality was nil. The distribution of BMI, lesion size,
9 operative time and hospital stay based on type of approach is shown in **Figure 4**.
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22 Definitive histopathological assessment was adrenal adenoma in 125 cases [(76.2%), 11 in
23 Group A, 49 in Group B and 65 in Group C] and adrenal hyperplasia in 39 cases [(23.8%), 2 in
24 Group A, 6 in Group B and 31 in Group C)].
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31 **DISCUSSION**

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33 The authors analyzed and compared the pre and postoperative outcomes after left
34 laparoscopic adrenalectomy for Conn's or Cushing's syndrome, hypothesizing to observe different
35 results among the three different approaches that were employed: lateral transperitoneal, anterior
36 transperitoneal and anterior transperitoneal submesocolic. To evaluate the results of the
37 submesocolic approach, which is not widely reported in the literature [10, 24], as compared to the
38 other two approaches, and to obtain a homogeneous patient sample only left adrenocortical lesions
39 were included in the study. **Moreover, the data regarding pheochromocytomas and non-functional**
40 **lesions have been previously reported [6-8].** No relevant differences were observed comparing the
41 three groups of patients. The only significant differences were observed between Groups A and C
42 concerning previous abdominal surgery and operative time in case of lesions up to 3 cm in
43 diameter. The present study confirms the safety and efficacy of LA by the ATS versus the LT and
44 AT approaches.
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1 Since its introduction, LA quickly became the gold standard for the surgical treatment of
2 benign adrenal diseases [25,26], due to several advantages such as less postoperative pain, reduced
3 blood loss and shorter hospital stay, decreased overall morbidity and faster return to daily habits in
4 comparison to open surgery [27,28].
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9 Despite several approaches for left LA are described in the literature, a widely accepted
10 consensus regarding the gold standard laparoscopic approach for adrenal gland surgery has not been
11 achieved [24]. This is related to the fact that every approach has specific advantages and
12 disadvantages, since definitive data regarding the superiority of one approach over the other are
13 missing. Guidelines strongly recommend to choose the approach that one is most familiar with
14 according to the surgeon's specific training [24].
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24 During the more than twenty-years authors' experience with LA, the approaches that were
25 employed were the anterior transperitoneal, the submesocolic and the lateral tranperitoneal, without
26 experience with the retroperitoneal one [6-8,21,22]. For left LA, the authors prefer the
27 submesocolic approach for several reasons. First of all, although early ligation of the adrenal vein
28 during LA is not considered mandatory, unlike in open surgery, due to gentle mobilization of the
29 gland that may be achieved during laparoscopy [24], in the authors' opinion adrenal vein ligation
30 prior to any gland manipulation is an important step of the procedure, to avoid catecholamines'
31 spread in case of pheochromocytoma and hormones' or neoplastic cells' spread in case of cortical
32 adenoma, adrenal carcinoma or metastasis, respectively [6-8,29,30]. With the patient positioned
33 supine on the operative table, it is possible to perform a rapid conversion to open surgery, if
34 required, and to perform bilateral adrenalectomy or any other procedure, which instead are not
35 possible with the flank approach without changing the patient's position [6-8,24,31]. Moreover, in
36 comparison with the anterior transperitoneal and the lateral transperitoneal approaches, the
37 submesocolic one does not require mobilization of the left colonic flexure or of the spleno-
38 pancreatic complex, reducing the extent of dissection, the risk of complications and the operative
39 time [6-8, 24, 32].
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In the present study, a clear superiority of one approach over the other has not been demonstrated. The operative time and hospital stay of the submesocolic approach were lower as compared to other approaches, but the differences were not statistically significant (Table 2). A higher conversion and morbidity rates after ATS were observed (Table 2), due to larger patients sample included in Group C, but again, the difference is not statistically significant. However, the outcomes of LA by ATS in this study in terms of mean operative time, conversion and complications rates are not different from those reported in the literature [33]. In fact, with the lateral approach mean operative time ranging from 77.5 to 423 minutes, a conversion rate of 4% and a complications rate of 6.4% are reported [33]. With the anterior approach the reported operative time ranges from 116 to 221 minutes, the conversion rate is 5.5% and the complications rate is 3.9% [29,34].

With each approach, it was possible to perform LA also for adrenal glands larger than 6 cm in diameter, that is considered by some authors as a contraindication to laparoscopy [22,35]. Although not statistically significant, most of the larger adrenal glands were removed with the ATS approach (2 in Group A, 7 in Group B, 9 in Group C).

The limitations of the present study are its retrospective nature, the fact that numerically the three groups are very heterogeneous, and that the widest authors' experience with the submesocolic approach could influence the results, but on the other hand, these biases are common to most comparative series reported in the literature.

Left LA in case of Conn's or Cushing's syndrome with ATS approach is equally safe and effective as compared with LT and AT approaches. Early control of the adrenal vein with minimal gland manipulation and less surgical dissection are the major advantages of the submesocolic approach. Although no statistically significant differences were observed, the postoperative results are similar to those reported in the literature with the other two approaches, which confirms that ATS proves to be equally safe and effective as compared to LT and AT, and that it is a viable

option in experienced hands. Prospective, randomized studies are required to identify the best laparoscopic approach for left LA.

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Disclosures

Dr. Andrea Balla, Dr. Silvia Quaresima, Dr. Livia Palmieri, Dr. Monica Ortenzi, Dr. Emilia Sbardella, Dr. Giulia Puliani, Prof. Andrea M. Isidori, Prof. Mario Guerrieri and Prof. Alessandro M. Paganini have no conflicts of interest or financial ties to disclose.

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Figure 1. The posterior peritoneum is opened between the first jejunal loop and the arch of the inferior mesenteric vein or immediately lateral to this vessel, based on its distance from the first jejunal loop.

Figure 2. The left renal vein is readily identified and it is followed medially up to its junction with the inferior adrenal vein, that it is closed with clips and divided.

Figure 3. The adrenal residual cavity.

Figure 4. Distribution of BMI, lesion size, operative time and hospital stay based on the type of approach.

	Group A n = 13	Group B n = 55	Group C n = 96	p value
Conn's syndrome, n (%)	7 (53.8)	32 (58.2)	60 (62.5)	Group A vs B: 1.0000 Group A vs C: 0.5580 Group B vs C: 0.6080
Cushing's syndrome, n (%)	6 (46.2)	23 (41.8)	36 (37.5)	
Sex ratio (M:F)	3:10	27:28	44:52	Group A vs B: 0.1237 Group A vs C: 0.1452 Group B vs C: 0.7367
Mean age ± SD, years (range)	48.54 ± 13.13 (27 - 67)	50.48 ± 15.33 (26 - 82)	52.20 ± 13.46 (17 - 81)	Group A vs B: 0.6800 Group A vs C: 0.3601 Group B vs C: 0.5022
BMI ± SD, kg/m² (range)	29.36 ± 6.71 (17 - 38)	28.7 ± 4.3 (21 - 39)	27.09 ± 5.4 (20 - 45)	Group A vs B: 0.6878 Group A vs C: 0.2731 Group B vs C: 0.1971
Previous abdominal surgery, n (%)	6 (46.15)	10 (18.81)	16 (16.66)	Group A vs B: 0.0630 Group A vs C: 0.0229 Group B vs C: 0.8256

Table 1. Patients' characteristics. BMI: Body Mass Index. Group A: lateral transperitoneal approach. Group B: anterior transperitoneal approach. Group C: anterior transperitoneal submesocolic approach. Vs: versus. Statistically significant differences in bold italic.

	Group A n = 13	Group B n = 55	Group C n = 96	p value
Mean lesion size ± SD, cm (range)	3.4 ± 1.8 (1.5 - 7)	3.7 ± 2.3 (1 - 10)	3.6 ± 2 (1 - 10)	Group A vs B: 0.7006 Group A vs C: 0.8182 Group B vs C: 0.7249
Mean operative time ± SD, min (range)	117.6 ± 33.7 (90 - 180)	107.6 ± 40.3 (35 - 180)	96.2 ± 47.5 (40 - 250)	Group A vs B: 0.4090 Group A vs C: 0.1188 Group B vs C: 0.1366
Conversion rate, n (%)	0 (0)	0 (0)	4 (4.1)	Group A vs B: 1.0000 Group A vs C: 1.0000 Group B vs C: 0.2970
Complications, n (%, Clavien's classification, class)	0 (0)	2 (3.6, II, III-b)	5 (5.2, 1 I, 3 II, 1 III-b)	Group A vs B: 1.0000 Group A vs C: 1.0000 Group B vs C: 1.0000
Blood transfusions in patients, n (%)	0 (0)	0 (0)	2 (2)	Group A vs B: 1.0000 Group A vs C: 1.0000 Group B vs C: 0.5338
Associated procedures, n (%)	0 (0)	1 (1.8)	4 (4.1)	Group A vs B: 1.0000 Group A vs C: 1.0000 Group B vs C: 0.6532
Mean hospital stay ± SD, days (range)	2.6 ± 2.5 (1 - 9)	2.8 ± 2.5 (1 - 12)	2.6 ± 3.6 (1 - 30)	Group A vs B: 0.8482 Group A vs C: 0.9904 Group B vs C: 0.7961

Table 2. Results. Group A: lateral transperitoneal approach. Group B: anterior transperitoneal approach. Group C: anterior transperitoneal submesocolic approach. Vs: versus.

	Tumor Size (cm)			p value
	0 – 3	3 – 6	6 – 10	
Group A, mean operative time ± SD, min (range), number of patients	126.1 ± 37.7 (80 - 180) 9	95 ± 7 (90 - 100) 2	102.5 ± 10.6 (95 - 110) 2	Group 0-3 vs 3-6: 0.2932 Group 0-3 vs 6-10: 0.4201 Group 3-6 vs 6-10: 0.4929
Group B, mean operative time ± SD, min (range), number of patients	108 ± 45.4 (35 - 180) 31	108.5 ± 38.8 (65 - 180) 17	103.5 ± 17.1 (85 - 130) 7	Group 0-3 vs 3-6: 0.9718 Group 0-3 vs 6-10: 0.7999 Group 3-6 vs 6-10: 0.7508
Group C, mean operative time ± SD, min (range), number of patients	91.7 ± 48.8 (40 - 250) 47	99.6 ± 46.8 (40 - 240) 40	104.4 ± 50.7 (60 - 210) 9	Group 0-3 vs 3-6: 0.4443 Group 0-3 vs 6-10: 0.4754 Group 3-6 vs 6-10: 0.7848
p value	Group A vs B: 0.2847 Group A vs C: 0.0482 Group B vs C: 0.1385	Group A vs B: 0.6378 Group A vs C: 0.8911 Group B vs C: 0.4943	Group A vs B: 0.9368 Group A vs C: 0.9598 Group B vs C: 0.9660	

Table 3. Mean operative time based on tumor size and type of approach. A: lateral transperitoneal approach. B: anterior transperitoneal approach. C: anterior transperitoneal submesocolic approach. Vs: versus. Statistically significant differences in bold.

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