ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:
‘‘ΕΛΑΧΙΣΤΑ ΕΠΕΜΒΑΤΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ,
ΡΟΜΠΟΤΙΚΗ ΧΕΙΡΟΥΡΓΙΚΗ ΚΑΙ ΤΗΛΕΧΕΙΡΟΥΡΓΙΚΗ’’

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ

Laparoscopic versus Open Adrenalectomy for localised/ locally advanced primary Adrenocortical Carcinoma (ENSAT I-III) in adults. Is the Margin-free (R0) resection the predominant key which designates the surgical technique? - A review of the literature

ΜΕΤΑΠΤΥΧΙΑΚΗ ΦΟΙΤΗΤΡΙΑ:
Μπαίλη Ευστρατία
Α.Μ.: 2014734

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ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ
ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ
ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ
Της Μεταπτυχιακής Φοιτήτριας Μπαίλη Ευστρατίας

Εξεταστική Επιτροπή

- Δημήτριος Δημητρούλης, Επικ. Καθηγητής Χειρουργικής **(Επιβλέπων)**
- Νικόλαος Νικητέας, Καθηγητής Χειρουργικής
- Ιωάννης Γκρινιάτσος, Αναπλ. Καθηγητής Χειρουργικής

Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της.....ης ..... 20.... για την αξιολόγηση και εξέταση της υποψηφίου κας **Μπαίλη Ευστρατίας**, συνεδρίασε σήμερα .../.../....

Η Επιτροπή διαπίστωσε ότι η Διπλωματική Εργασία της Κας **Μπαίλη Ευστρατίας** με τίτλο: **«Laparoscopic versus Open Adrenalectomy for localised/ locally advanced primary Adrenocortical Carcinoma (ENSAT I-III) in adults. Is the Margin-free (R0) resection the predominant key which designates the surgical technique? - A review of the literature»**, είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπ' όψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's Degree), στον παραπάνω Μεταπτυχιακό Φοιτητή.

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους ....., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους ....., και για τον βαθμό «ΚΑΛΩΣ» ψήφους ..... Κατά συνέπεια, απονέμεται ο βαθμός «.....».

Τα Μέλη της Εξεταστικής Επιτροπής

- Δημήτριος Δημητρούλης, **Επιβλέπων** (Υπογραφή) _____
- Νικόλαος Νικητέας, (Υπογραφή) _____
- Ιωάννης Γκρινιάτσος, (Υπογραφή) _____

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TABLE OF CONTENTS **Page**

1. Introduction 6

2. Aim of the study 11

3. Materials and methods 11

3.1 Literature search. 11

3.2 Method of review 11

3.3 Inclusion criteria. 12

3.4 Exclusion criteria. 12

3.5 Definitions and statistic measurements. 12

4. Results 13

4.1 Study Characteristics 13

4.2 Clinicopathological characteristics. 13

4.3 Operative outcomes. 14

4.4 Surgical and oncological outcomes. 14

5. Tables 15

5.1 Staging Systems for ACC (9) 15

5.2 The Weiss System [a] (10) 16

5.3 Characteristics of the included studies 17

5.4 Clinicopathological Characteristics of the included studies 18

5.5 *Perioperative outcomes of the included studies* 19

5.6 *Surgical + Oncological outcomes of the included studies* 20

6. Discussion 21

7. Conclusion 25

ABSTRACT 26

ΠΕΡΙΛΗΨΗ 27

REFERENCES 28

1. Introduction

Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy, with an annual incidence of approximately 1–2/ 1.000.000 people worldwide and account for 0.05–0.2 % of all malignancies. The age distribution is reported as bimodal with a first peak in childhood and a second higher peak in the 4^{th} and 5^{th} decade of life, with a slightly female predominance (1, 2).

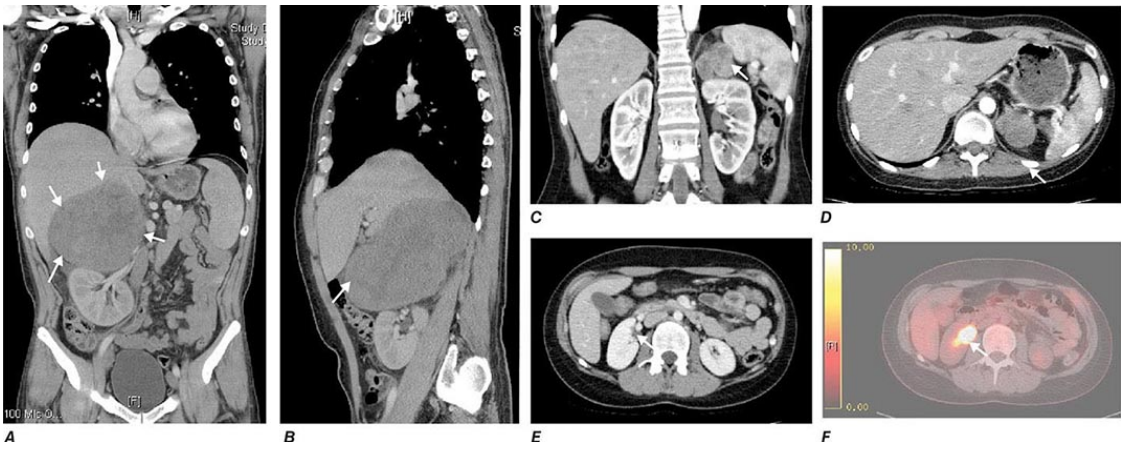
Although most ACCs are sporadic, there is an escalating evidence of an association with numerous hereditary syndromes, including Beckwith-Wideman syndrome, Multiple Endocrine Neoplasia type 1 , Li-Fraumeni, Congenital Adrenal Hyperplasia, Familial Adenomatous Polyposis, and Lynch syndrome (2-4).

Whether sporadic or familial, there are 3 main clinical manifestations in which ACC presents to patients. For 40% to 60% of patients, the major presenting complaints are symptoms and signs of excess hormone secretion, as a functional endocrinopathy. Another 30% with nonspecific symptoms related to local tumor growth and involvement of the surrounding viscera, such as abdominal or flank pain, sentiment of abdominal fullness, or early satiety. Roughly 20% to 30% of ACCs are incidentally diagnosed as a nonfunctional adrenal mass by imaging procedures for unrelated medical issues, with tumor size at presentation (mean diameter at diagnosis > 10 cm) to be the most important indicator of malignancy (2, 5). Most ACCs are diagnosed at an advanced stage, although this is predicted to alter in the near future due to the persistently increasing use of abdominal imaging procedures.

At the time of diagnosis, the initial evaluation should include a thorough physical examination and patient history with particular respect to symptoms and signs of hormone overactivity and essentially a focus on family history in order to identify potential hereditary contributions. Patients should undergo a complete biochemical and hormonal workup not only to rule out the presence of cortical hyperfunctionality in the form of subclinical Cushing syndrome, hyperaldosteronism, or hyperandrogenism, but also to exclude evidence of catecholamine excess, which may suggest the presence of a pheochromocytoma or extra-adrenal paraganglioma (4, 6-8).

Imaging evaluation is required for all suspected ACCs and considered to be crucial not only for the diagnosis but also for the staging of a potential ACC. It should, at the minimum, include a computed tomography scan (CT) or magnetic resonance imaging (MRI) of the abdomen- pelvis and a CT of the chest. Both MRI and CT are equivalent modalities in their capacity to identify ACCs, with MRI having a sensitivity of 81% - 89% and a specificity of 92% - 99% at distinguishing benign versus malignant adrenal masses and to may be better suited for the detection of intra- caval tumor thrombus and defining the extent of loco- regional disease. Other imaging methods should be guided by clinical suspicion, such as bone scan for skeletal metastasis, fluorodeoxyglucose positron emission tomography (FDG- PET) to provide a more complete clinical staging of an known ACC, or even Metomidate-Based Imaging with either 11C for PET-based techniques or with 123I for single-photon emission CT (SPECT)- based techniques (1, 2, 6) (**Figure 1**).

Figure 1: *Imaging in adrenocortical carcinoma. MRI scan with (*A*) frontal and (*B*) lateral views of a right adrenocortical carcinoma that was detected incidentally. CT scan with (*C*) coronal and (*D*) transverse views depicting a right-sided adrenocortical carcinoma. Note the irregular border and inhomogeneous structure. CT scan (*E*) and PET CT (*F*) visualizing a peritoneal metastasis of an adrenocortical carcinoma in close proximity to the right kidney (*arrow*). (published 06/04/2015 on clinicalgate.com/autoimmune polyendocrine syndromes)*



In 2004, the World Health Organization (WHO) and Union for International Cancer Control (UICC) introduced the first Tumour, Node and Metastasis (TNM) staging system for ACC based on the traditional McFarlane classification, modified by Sullivan (**Table 4.1**). This classification system has been recently challenged due to

failure in discrimination between the prognoses in Stages II and III, and the newly introduced European Network for the Study of Adrenal Tumors (ENSAT) system became widely adopted by the ACC community due to the better reflection of ENSAT stage to patients' outcome (**Table 5.1**). The ENSAT staging system defines 4 stages: Stage I (≤5 cm) and stage II (>5 cm) tumors are confined to the adrenal gland. Stage III tumors extend into surrounding tissue (eg, paraadrenal adipose tissue or adjacent organs) or involve loco-regional lymph nodes. Stage IV is reserved for patients with distant metastasis, as lung (40%–80%), liver (40%–90%), and bone (5%–20%)(9).

The histopathologic diagnosis of ACC still remains to be the gold standard, although it has been based on the subjective recognition at light microscopy of nine morphological parameters that comprise the Weiss criteria (**Table 5.2**), with a diagnosis of malignancy to be achieved if at least three parameters are identified (10). Due to the fact that this diagnostic performance is high, but does not reach a sensitivity and specificity of 100%, scientists have inserted additional specific and possibly less subjective markers of malignancy, such as reticulin silver-based histochemical staining, SF-1 immunohistochemistry and Ki-67 proliferation index with promising initial results at increasing reliability in the diagnostic procedure (8).

Although prognosis is certainly dependent on an accurate diagnosis, whether based on pathologic criteria, or on preoperative clinical, biochemical and imaging characteristics, survival of patients with ACC is mainly associated with both intraoperative findings concerning tumor stage and surgical R0 resection technique with the single most important prognostic factor to be the margin status (11-14). When surgical excision is deemed complete, the 5-year survival is reported to be 32–58%, but when incomplete, the median survival is expected to be less than 1 year (range, 2–16 months). Unfortunately, even after an apparent complete resection, local or distant relapse occurs in nearly 80% of patients.

This introduces and establishes the complete surgical excision with microscopically negative margins as the standard of care for localised/ locally advanced disease (ENSAT I-III), leading to both an abatement of symptoms for patients with functional ACCs, as well as an increased disease-free and overall survival (13, 15). Routine

regional lymphadenectomy should be considered for all patients with ACC. In addition to surgical therapy, adjuvant treatment consisted of chemotherapeutic regimens with cytotoxic agents such as single mitotane or in combinations with streptozocin, etoposide/ doxorubicin/ cisplatin in adjustment with/ without radiotherapy in patients with R1–R2 resections, stage III disease and IV metastatic disease, should also be considered since many patients will suffer from tumor recurrence even after seemingly complete removal of ACC (16, 17) (**Figure 2**).

Figure 2:

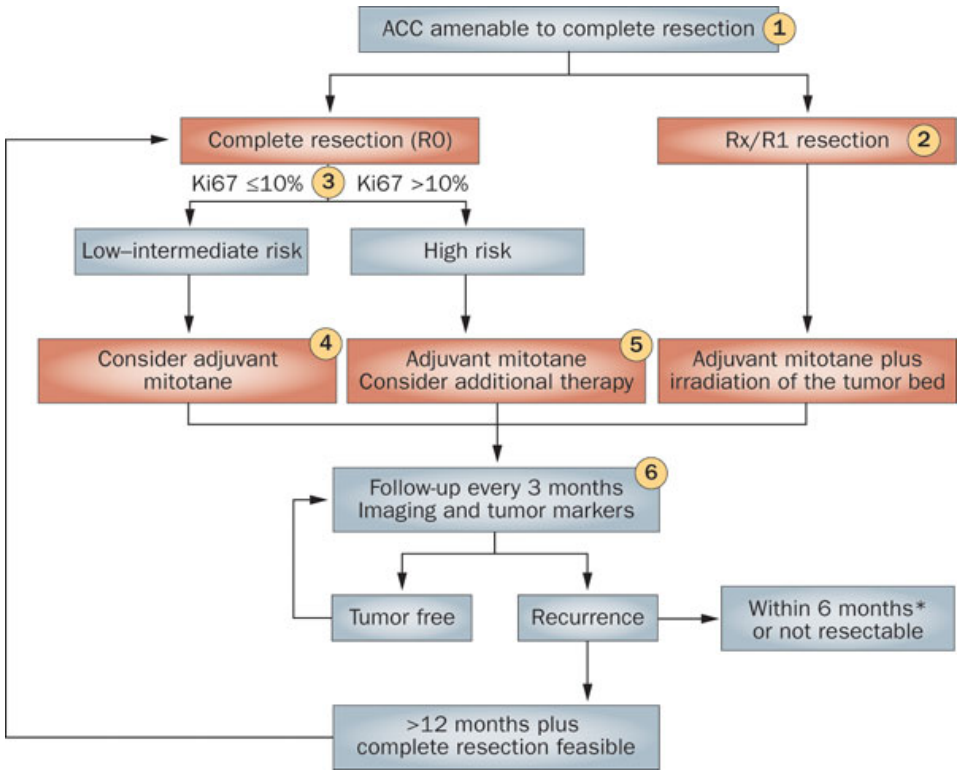


Figure 2: *Treatment of ACC amenable to complete resection. (1) ACCs amenable to complete resection include all patients with stage I and II tumors, most patients with stage III tumors and selected patients with stage IV tumors. (2) In patients with R2 resection, consider re-surgery by an expert surgeon (3) If Ki67 staining is not available, a high proliferative index (>5 mitoses per 50 high-power fields) may be used for risk stratification. Patients with stage IV or recurrence are judged high-risk patients independent of Ki67 index. (4) The following factors are suggestive of a low risk of recurrence: tumor size < 8 cm, no microscopic evidence of invasion of blood vessels or tumor capsule. If all these factors are fulfilled, observational follow-up may be justified. (5) Parameters favoring additional radiotherapy of the tumor bed: microscopic tumor invasion of blood vessels and capsule and a Ki67 index ≥20%. A tumor thrombus in the vena cava favors additional streptozotocin therapy. (6) After 2 years, the time intervals are gradually extended (18).*

There is a consensus among the scientific community that in localised/ locally advanced primary adrenocortical carcinoma (ENSAT I-III) in adults, only radical adrenal surgery provides a chance for a long-term cure (12). However, there is an ongoing debate throughout the past three decades on which is the best surgical approach which should be recommended to the patients related. While evidence of invasive-metastatic disease (ENSAT IV) before surgery undoubtedly requires open adrenalectomy (OA), some surgeons with the constantly improved technological advances in the field and the rising technical experience with benign disease, have successfully expanded the indications for laparoscopic adrenalectomy to large, nonfunctioning tumors with the potential for malignancy and to metastatic lesions, whereas others state that this approach is absolutely contraindicated.

The aim of this study was to review the current literature on the role of laparoscopic adrenalectomy versus open technique in the surgical management of primary adrenocortical carcinoma (ENSAT I-III) in adults.

2. Aim of the study

The aim of this study was to review the current literature on open versus laparoscopic adrenalectomy in the treatment of localized/ locally advanced primary adrenocortical carcinoma (ENSAT I-III) in adults and demonstrate that R0 Resection via its undeniable impact on Recurrence Rate (RR), Disease Free Survival (DFS) and Overall Survival (OS), is the actual predominant key factor which designates the selection of the appropriate surgical technique (11) .

3. Materials and Methods

3.1 Literature search.

A PubMed, Embase, Cochrane Library and Google Scholar database search was performed on literature published from January 1999 to February 2017. Only articles published in English and studies with comparative analysis between open and laparoscopic approach were included in this study. The following key terms were used to perform the research: "adrenocortical cancer", "laparoscopy" or laparoscopic", "open", "laparoscopic versus open", "adrenalectomy", "R0 resection", "margin status" and "oncological outcome".

3.2 Method of review.

The initial search for adrenocortical carcinoma yielded 3173 records, whose titles were screened. After initial screening and removal of duplicates based on title and abstract, 149 articles were considered and reviewed focused on surgical approach selected. At the end of the process, 19 studies were reviewed in full text and 13 confirmed to meet eligibility criteria. In those who had overlapping data, only the study with the most recent information was included in the analysis. An overview of the studies, all published between 1999 and 2017, is provided in **Table 5.3**. Even though the quality of studies was high (despite all being retrospective case control studies), they were - in the majority- with a low level of evidence.

The following parameters were extracted from each study to analyze: study features (first author, year of publication, study design, study period, country, number of patients included), surgical and pathological parameters (patients age, tumor size, ENSAT stage, type of surgical approach, period of follow-up), surgical outcomes

(operative time, estimated blood loss, length of hospital stay, conversion rate to laparotomy, R0 resection, surgical margins status) and oncological outcomes (rate of recurrence**,** disease free survival and overall survival rates).

3.3 Inclusion criteria.

For inclusion in the review, a study had to fulfil the following criteria: (a) Original studies comparing Open Adrenalectomy (OA) to Laparoscopic Adrenalectomy (LA) for ACC and with at least 5 cases per each surgical approach included, (b) report on at least one of the outcome measures mentioned above, (c) if multiple studies were reported by the same institution with overlapping data, the most recent publication was included in the analyses, (d) All titles were screened for manuscripts written in the English language, and (e) the surgical procedures were only performed on adult patients (>16 years).

3.4 Exclusion criteria.

Articles were excluded if: (a) they were abstracts, letters or expert opinions, (b) they reported on adrenalectomy for benign lesions, for metastatic adrenocortical carcinoma (ENSAT IV) or for recurrence , (c) there was overlap between authors or centres in the published literature, (d) there were case reports or less than 5 cases per each surgical approach was included.

3.5 Definitions and statistic measurements.

The surgical approach was based on surgeon preference and expertise, and the referral pattern was the same for patients treated with either methodology. The open procedure was in most of the cases conducted via anterior subcostal or midline approach, though, in few cases was held via posterior or flank approach. Laparoscopic procedure was conducted either via transperitoneal (lateral-anterior) or via retroperitoneal approach (lateral-posterior).

Complete (R0) surgical resection was the primary end point of this review, along with it’s association with the Recurrence Rate (RR), Disease Free Survival (DFS) and Overall Survival (OS) and was defined as no evidence of macro- or microscopic residual disease on the basis of surgical reports, histopathologic analysis, and pre- and postoperative imaging. Recurrence was defined a) as local, when involving the

operative site or regional lymph nodes, b) as peritoneal, when there was evidence of abdominal carcinomatosis or c) as distant. Disease recurrence was diagnosed on the basis of clinical, laboratory, and radiologic evidence without histological confirmation of the recurrence to be required.

Disease-free survival was defined as the period from surgery date and first time of recurrence or the date of last follow-up without recurrence. The overall survival was defined as the period between operation date and the death of the patient or the date of the last follow-up if the patient is still alive. In the majority of studies, the Kaplan-Meier method was used to analyse the overall and disease-free survival during long-term follow-up. Results were described using mean (±standard deviation) or median (range).

4. Results

4.1 Study Characteristics.

At the end of the search process, 13 studies were reviewed in full text and confirmed to meet eligibility criteria, an overview of which is provided in **Table 5.3**. A total of 1171 patients underwent adrenal surgery with diagnosis of primary adrenocortical carcinoma, 910 (77%) underwent open adrenalectomy and 261 (23%) laparoscopic adrenalectomy. Four of the studies were conducted in the USA, one both in Israel and Canada, three in France, three in Italy, one in Germany and one in Norway. Time of population's study period outspreads from 1985 till 2013 and the year of publication ranges from 2005 till 2016 **(Table 5.3)**.

4.2 Clinicopathological characteristics.

The general characteristics of the surgical groups are described in **Table 5.4**. The mean age of patients at surgery was 46.9 years for the open approach group and 49.4 years for the laparoscopic group. Tumor stage was classified via ENSAT (2008) classification system **(Table 5. 1)** with histological confirmation of surgical specimen in combination with pre-operative biochemical work-up along with imaging and patients of all stages (I-IV) included in the various studies. Median tumor size was 10.78 cm for OA group and 6.75 cm for LA group.

4.3 Operative outcomes.

The mean operative time was provided by five of the studies (< 50%). It ranged between 129 and 272.5 min for the open approach and between 133 and 297.5 min for laparoscopic approach. One of the studies showed a significantly longer operative time both in the OA and LA group (19). The estimated blood loss (EBL) was reported in only four studies and ranged from 550 to 1700 ml in the OA group and from 200 to 1500 ml in the LA group. The conversion rate was documented in nine studies with mean conversion rate to be calculated at 11%. The length of hospital stay was reported in six studies, with mean hospital stay to be 8.25 days in OA group and 4.7 days in the LA group (**Table 5.5).**

4.4 Surgical and oncological outcomes.

Data related to surgical and oncological outcomes are reported to **Table 5.6.** The margin status leading to complete R0 surgical resection or not, was not provided by only two of the thirteen reviewed studies (20, 21). In a total of 910 patients on whose open adrenalectomy was conducted for ACC, 896 had reported data concerning resection status and 649 of them were offered a complete (R0) resection: (72%). In a total of 261 patients on whose laparoscopic adrenalectomy was conducted for ACC, 251 had reported data concerning resection status and 182 of them were offered a complete (R0) resection: (72%). The overall recurrence rate was provided in 11 studies with range from 24 to 100% for OA group and a range from 22 to 100% for the LA group. The disease free survival rates were reported in 11 trials and ranged from 8.1 to 48.5 months in the open group and from 6.1 to 61.17 months in the laparoscopic group. The overall survival rates were documented in 9 trials and ranged from 36.5 to 103.1 months in the open group and from 27.5 to 108 months in the laparoscopic group.

5. Tables

Table 5. 1- Staging Systems for ACC (9)

STAGE	UICC/ WHO (2004)	ENSAT (2008)
Stage I	T1, N0, M0	T1, N0, M0
Stage II	T2, N0, M0	T2, N0, M0
Stage III	T1–2, N1, M0	T1–2, N1, M0
	T3, N0, M0	T3–4, N0, M0
Stage IV	T1–4, N0–1, M1	T1–4, N0–1, M1
	T3–4, N1, M0	
	T4, N0, M0	

Abbreviations:

UICC: International Union Against Cancer, WHO: World Health Organization.

Tumors are classified as follows: T1: <5-cm tumor, T2: >5-cm tumor, T3: tumor infiltration into surrounding tissue, T4: tumor invasion into adjacent organs, N0: no positive lymph nodes; N1: positive lymph node(s), M0: no distant metastases, M1: presence of distant metastasis.

Table 5.2- The Weiss System [a] (10)

HISTOLOGICAL CRITERIA	WEIGHT OF CRITERIA	
	0	1
Nuclear grade[b]	1 and 2	3 and 4
Mitoses	≤5 for 50 fields ×400	≥6 for 50 fields ×400
Atypical mitoses	No	Yes
Clear cells	>25%	≤25%
Diffuse architecture	≤33% surface	>33% surface
Confluent necrosis	No	Yes
Venous invasion	No	Yes
Sinusoidal invasion	No	Yes
Capsular infiltration	No	Yes

Abbreviations:

a. The presence of three or more criteria highly correlates with malignancy.

b. According to Fuhrman criteria: grade 1 (round nuclei, homogenous, small size, no nucleoli), grade 2 (nuclei slightly irregular, more voluminous, conspicuous nucleoli at ×400), grade 3 (irregular nuclei, voluminous nucleoli at ×100), grade 4 (idem grade 3 with monstrous cells with very irregular nuclei) (22).

Table 5.3- Characteristics of the included studies

Study (Ref.)	Study design	Country	Year of publication	Study Period	Number of patients with ACC	Surgical Approach (OA:LA) (n-%)
Brix et al. (23)	Retrospective case control	Germany	2010	1996–2009	152	117(77%): 35(23%)
Cooper et al. (24)	Retrospective case control	Texas, USA	2013	1993-2012	302	256(85%): 46(15%)
Donatini et al. (25)	Retrospective case control	France	2013	1985–2011	34	21(61%): 13(39%)
Fossa et al. (26)	Retrospective case control	Norway	2013	1998-2011	32	15(47%): 17(53%)
Gonzalez et al. (27)	Retrospective case control	Texas, USA	2005	1991-2004	139	133(95%): 6(5%)
Kirshtein et al. (20)	Retrospective case control	Israel-Canada	2008	1995-2005	12	7(58%): 5(42%)
Leboulleux et al. (28)	Retrospective case control	France	2010	2003-2009	64	58(90%): 6(10%)
Lodin et al. (21)	Retrospective case control	Italy	2007	1997-2005	12	7(58%):5(42%)
Lombardi et al. (29)	Retrospective case control	Italy	2012	2003-2010	156	126(80%): 30(20%)
Miller et al. (30)	Retrospective case control	Michigan, USA	2012	2005-2011	156	110(70%): 46(30%)
Mir et al. (19)	Retrospective case control	Cleveland, USA	2012	1993–2011	44	26(59%):18(41%)
Porpiglia et al. (31)	Retrospective case control	Italy	2010	2002-2008	43	25(58%):18(42%)
Vanbrugghe et al. (32)	Retrospective case control	France	2016	2002-2013	25	9(36%):16(64%)
Total=13					**1171**	**910(77%: 261(23%)**

Abbreviations: (OA): open adrenalectomy, (LA): laparoscopic adrenalectomy

Table 5.4- Clinicopathological Characteristics of the included studies

Study (Ref.)	Mean Age (OA:LA) (years)	Tumor stage (ENSAT)	Tumor size median (OA:LA) (cm)	Follow up (OA:LA) – median (months)
Brix et al. (23)	52.3:50.7	I–III	8:6.2	32:64
Cooper et al. (24)	46.5: 45.8	I-IV	12:8	35,5:29.2
Donatini et al. (25)	44:46	I-II	6.8:5.5	57:80
Fossa et al. (26)	52:45	I–III	13:8	60:60
Gonzalez et al. (27)	46	I-IV	13:6	28:21
Kirshtein et al. (20)	40:56	I-IV	8:4	NR
Leboulleux et al. (28)	54	I-IV	14:7.0	35
Lodin et al. (21)	47.7:47.4	I-IV	8.7:5.8	NR
Lombardi et al. (29)	46.6:52.2	I-II	9.04:7.73	40:50
Miller et al. (30)	47:50	I-III	12.0:7.4	29.5:19
Mir et al (19)	48:53	I–IV	13:7	31:18
Porpiglia et al. (31)	41.3:47	I-II	10.5:9.0	38:30
Vanbrugghe et al. (32)	44.31:48.9	I-III	11.6:6.2	52.9:36.4

Abbreviations: (NR): Not Reported

Table 5.5- Perioperative outcomes of the included studies

Study (Ref.)	Operative time (OA:LA) (min)	Estimated Blood Loss (OA:LA) (ml)	Conversion Rate (%)	Length of Hospital Stay (OA:LA) (days)
Brix et al. (23)	NR	NR	34%	NR
Cooper et al. (24)	NR	NR	NR	NR
Donatini et al. (25)	NR	NR	0%	9:7
Fossa et al. (26)	230:150	1700:400	11%	13:6
Gonzalez et al. (27)	NR	NR	16%	NR
Kirshtein et al. (20)	170:153	550:200	7%	7:2
Leboulleux et al. (28)	NR	NR	NR	NR
Lodin et al. (21)	161:133	1500:900	4%	5.2:4
Lombardi et al. (29)	129:135	NR	0%	9.3:5.3
Miller et al. (30)	NR	NR	NR	NR
Mir et al (19)	272.5: 297.5	1100:1500	27%	6:4
Porpiglia et al. (31)	NR	NR	NR	NR
Vanbrugghe et al. (32)	NR	NR	0%	NR

Abbreviations: (NR): Not Reported

Table 5.6- Surgical + Oncological outcomes of the included studies

Study (Ref.)	R0 Resection (OA: LA) (n-%)	Overall Recurrence Rate (OA: LA) (n-%)	Local Recurrence Rate (OA: LA) (n-%)	Disease free survival (OA: LA)- median (months-%)	Overall survival (OA: LA)- median (months-%)
Brix et al. (23)	64:24 (55:69%)	81:27 (69:77%)	(38:50%)	21.5-24.2	NR
Cooper et al. (24)	134:25 (52:71%)	*** 87.3:58.7:76 .1%	***NR	***9.5:19.5: 10.9	***46:109.8 : 53.5
Donatini et al. (25)	21:13 (100:100%)	5:4 (24:31%)	2:1 (9:7%)	47:46	(81:85%)
Fossa et al. (26)	12:12 (80:70%)	15:12 (100:70%)	1:1 (6:5%)	8.1:15.2	36.5:103.6
Gonzalez et al. (27)	133:6 (100:100%)	115:6 (86:100%)	51:3 (38:50%)	13:NR	43:NR
Kirshtein et al. (20)	NR	NR	NR	NR	(5%)
Leboulleux et al. (28)	37:5 (63:83%)	*(27:67%)	(72:34%)	*20	(38:5%)
Lodin et al. (21)	NR	NR	NR	up to 58	NR
Lombardi et al. (29)	126:30 (100:100%)	48:8 (38:26%)	14:4 (11:13%)	48:72(38.3: 58.2%)	60:108 (48: 67%)
Miller et al. (30)	72:26 (65:56%)	(40:85.7%)	NR	Stage II=30.5:11.7 Stage III=13.1:6.1	Stage II= 103.1: 50.9 Stage III: 43.7:27.5
Mir et al (19)	16:11 (61:61%)	** (27:22%)	12:10 (46:55%)	13.8;9.7 (60:39%)	**(54:58%)
Porpiglia et al. (31)	25:18 (100:100%)	16:9 (64:50%)	6:6 (24:33%)	18:23	NR
Vanbrugghe et al. (32)	9:12 (100:75%)	4:6 (44.4:37.5%)	0:2 (0:12.5%)	40.45:61.17 (55.6:62.5%)	70.1:67.3

Abbreviations: (NR): Not Reported , * Peritoneal Carcinomatosis, **Adjustment for stage resulted in statistically significant differences *** 3 groups OA index: OA outside: LA

6. Discussion

Adrenal surgery has a long history, with the first adrenalectomy to be described in 1889 by Thonton and successfully carried out by Mayo and Roux for pheochromocytoma in 1927. For decades, multiple changes to adrenal surgery were developed, to lead to the first laparoscopic adrenalectomy described by Gagner in 1992 (33), the introduction of which revolutionised the principles of adrenal surgery.

Laparoscopic adrenalectomy (LA) has become the gold standard of care for the management of benign adrenal tumors since then (34). A number of studies have demonstrated its advantages over laparotomy, which include reduced blood loss, decreased perioperative complications and postoperative pain, shorter recovery time and hospital stay, improved cosmesis and more efficient use of health care expenditure (6, 20, 26, 35) .

LA is an established procedure and can be performed using a transperitoneal (anterior/lateral) or retroperitoneal (lateral/ dorsal) approach (36). While each approach has its relative advantages and potential limitations, comparative studies showed no significant discrepancies in outcome (37-39). The recent wide adoption of the robotic surgical system, especially among urologists, has found its way into adrenal surgery, along with single-port surgery as the latest addition to the minimal invasive techniques, as progress is being made in skills, instruments and technology (40, 41).

The basic principle of LA is to perform gentle and elegant dissection of the surrounding tissues away from the adrenal mass, to avoid tumour rupture or excessive release of catecholamines during aggressive manipulation (42). Another principle of this procedure is the early control of the main adrenal vein to avoid an intraoperative hypertensive crisis secondary to catecholamine release. A complete laparoscopic resection (R0) and the use of an entrapment sac for specimen extraction, as well as wound protection have further made the laparoscopic approach a reliable technique for malignant tumors (28, 43).

Nevertheless, the laparoscopic approach has not come up with a widespread embracement from the scientific community for the management of large, nonfunctioning tumors with the high potential for malignancy and to metastatic lesions (24, 44).

Several studies have shown the feasibility, the safety and the potential benefits of laparoscopic surgery in the treatment of adrenocortical cancer provided that the surgeon has adequate experience and a low threshold for conversion when the local conditions compel it (23, 25, 26, 29).

However, some results are conflicting (24, 28, 30, 44).

Therefore, we reviewed the current literature with the aim of summarizing the role of laparoscopic radical adrenalectomy in adrenocortical cancer.

Our review consists of 13 non-randomized controlled studies and analyses their results on open versus laparoscopic surgery in primary adrenocortical carcinoma (ENSAT I-III) in adults.

The mean age of patients at surgery was 46.9 years for the open approach group and 49.4 years for the laparoscopic group and the median tumor size was 10.78 cm for OA group and 6.75 cm for LA group.

The median operational time was shorter in laparoscopic adrenalectomy, in comparison with the open method, as well as the estimated blood loss which was also found to be lower in the laparoscopic group in most comparative studies. The outcome of lower operational time can be probably explained by the less incisional surface as well as the smaller tumor size in the laparoscopic approach. The reasons for the reduced blood loss in the laparoscopic group include less traumatic surface, better view of the target area and more precise and delicate dissection with the laparoscopic instruments (45). Nevertheless, less than 50% of the studies provided reported data for these two variables, thus we may have a significant bias in the above observations.

Furthermore, the duration of hospital stay as an additional important outcome variable, affecting patient satisfaction and cost analysis, is reported in 50% of the studies and was also shorter with laparoscopic approach compared to standard open technique.

Our primary key point in the present review was to reveal the trials' results regarding R0 surgical resection and compare these results with the overall recurrence rates (RR), the disease free survival (DFS) and the overall survival (OS) rates. In an amount of 896 patients on whose open adrenalectomy was conducted for ACC with reported data concerning resection status, a total of 649 were offered a complete (R0) resection (72%). In an amount of 251 patients on whose laparoscopic adrenalectomy was conducted for ACC with reported data concerning resection status, a total of 182 were offered a complete (R0) resection, (72%). Hence, the present review strongly identifies that there is no significant difference between OA and LA approach concerning the achievement of R0 resection throughout the literature.

Analyzing overall recurrence rates, disease free survival and overall survival rates, there is an unambiguous affect of the R0 resection and margin status on these variables **(Table 5.6)**. Series with high grade of achievement of R0 resection are considerably accompanied by lower RR and simultaneously higher DFS and OS rates (25, 29, 31, 32) and vice versa (23). Studies with similar results regarding R0 resection between the two groups, demonstrate also similar results regarding RR, DFS and OS (19, 25, 29, 31, 32). These observations can most likely lead to the result that since R0 resection is achieved, there is no major difference between the OA and LA approach as regard the beneficial outcomes of the methods (RR, DFS and OS) offered to the ACC patients' population.

Some of the studies nevertheless, hand over equivocal results (28, 30) with higher RR and lower DFS and OS for the LA group, even though the R0 resection status is presented to be high or equal with the OA group. This may be associated with the low median period of follow- up in these two studies or with the inclusion of larger and probably of higher malignant potential of tumors resulting to worse overall morbidity and mortality after all.

It has been advocated in the literature that the pneumoperitoneum may favour the transit of malignant cells intraperitoneally and free intraabdominal cancer cell implantation at the wound site or in the abdominal cavity. Aerosolization of tumor cells is deemed thus to be possible but supposes previous tumor impairment during the dissection (28, 46). As regards our observations concerning local/ peritoneal recurrence, six out of thirteen studies identify higher rates of recurrence for the laparoscopic group with a tendency to decrease it's occurrence in the more recent studies (23, 27, 30-32, 47). This possibly implies that the continuously increasing knowledge on this issue plus the progressively improvement on surgical skills and learning curves can confine this phenomenon, even though it does not seem to affect substantially the overall RR, DFS and OS rates throughout the literature.

The overall analysis of the RR, DFS and OS in the present review displayed no major differences between the OA and LA group, with RR ranges from 24-100% for OA group and 22-100% for the LA group, with DFS ranges from 8.1-48.5 months in the open group and from 6.1-61.17 months in the laparoscopic group and OS ranges from 36.5-103.1 months in the open group and from 27.5-108 months in the laparoscopic group- results which may suggest the safety and additionally the efficacy of an laparoscopic versus an open technique (25, 26, 32).

The present study has several limitations:

a. It was not a meta-analysis in order to come to more accurate conclusions.
b. All the included trials were observational of relatively low total number of patients and their results cannot be generalized to the extent that those of randomized controlled trials can.
c. There was heterogeneity between the two groups because it was impossible to match patient characteristics in all studies.
d. There were few studies with partially reported data regarding oncological outcomes.
e. Finally, between individual studies, the follow-up time varied significantly.

7. Conclusion

Adrenocortical carcinoma (ACC) is a highly malignant tumor of the adrenal cortex with multi-variety in its behaviour and pattern of recurrence. The complete surgical excision with microscopically negative margins constitutes the gold standard of care and the only chance for cure, for localised/ locally advanced disease, leading to an increased disease-free and overall survival period (48, 49).

The aim of this study was to review the current literature on open versus laparoscopic approach in the treatment of localised/ locally advanced primary adrenocortical carcinoma (ENSAT I-III) in adults and demonstrate that R0 Resection via its undeniable impact on Recurrence Rate (RR), Disease Free Survival (DFS) and Overall Survival (OS), is the actual predominant key factor which designates the selection of the appropriate surgical technique and not the surgical technique itself (42, 50, 51).

Thirteen study trials have been selected after thorough investigation of the literature. There are no randomised studies comparing open adrenalectomy versus laparoscopic adrenalectomy for ACC. There is a strong evidence of peri- and post-operative advantage for the patients undergoing laparoscopic adrenalectomy compared to open adrenalectomy (52). Results from comparison of oncological outcomes in ACC between open and laparoscopic approaches are controversial: increased risk of local recurrence and peritoneal carcinomatosis by the laparoscopic route, but no major differences between the two approaches in variables of rate of overall recurrence, disease free survival and overall survival (53). R0 resection was achieved in 72% in both laparoscopic and open groups. In all the studies which provided high quality resection status via the laparoscopic approach, they managed to offer equally high quality of long term oncological outcomes in comparison with the open approach. In more recent studies (29, 31, 32), there is also a hint that laparoscopic approach can be even more beneficial than the open one, result which may reflect the significant technical improvement of the laparoscopic surgical teams during the last years and the increasing number of laparoscopic operations conducted (54).

In conclusion, the extent of surgery with adequate tumor resection is the predominant endpoint, rather than the surgical approach itself (laparoscopic or open). The data

presented supports our hypothesis that the most important component of the surgical approach to ACC is to ensure adequate resection margins. This goal can be achieved by both laparoscopic and open surgical methods with a multidisciplinary team to build up an individual treatment strategy for each patient (55, 56). Open surgery remains the standard approach for patients with a metastatic ACC (ENSAT IV). Despite the fact that laparoscopic adrenalectomy for ACC is a technically demanding procedure, the results of this study suggest that it can be a feasible and secure alternative to the classic open approach for primary ACC (ENSAT I-III) tumours in the hands of an experienced surgeon (performing >10 LAs/year), held in a referral specialised centre with sufficient experience in such cases (23, 48, 55, 57, 58). Tribute to general surgical oncological principles, such as the avoidance of tumour capsule rupture, as well as wound protection during specimen extraction are mandatory (46, 48, 59). Multicentre randomized controlled trials with long follow- up time periods exploring its long-term oncological outcomes are required to determine the benefits of the laparoscopic over the open approach in adrenocortical carcinoma

Conflicts of Interest:

All Authors declare that they have no competing interests in regard to this study.

ABSTRACT

Background: The aim of this study was to review the current literature on the role of laparoscopic adrenalectomy in the treatment of primary adrenocortical carcinoma (ENSAT I-III) in adults. Materials and Methods: Non-randomized control trials published between January 1999 to February 2017 were identified by searching the Pubmed, EMBASE, Cochrane Library and Google Scholar databases. Primary and secondary endpoints included surgical and pathological parameters (patients age, tumor size, ENSAT stage, type of surgical approach, period of follow-up), surgical outcomes (operative time, estimated blood loss, length of hospital stay, conversion rate to laparotomy, R0 resection, surgical margin's status) and oncological outcomes (rate of recurrence, disease free survival and overall survival rates)were analysed. Results: A total of 13 studies with a total number of 1171 patients were included in the review. Compared with open approach, laparoscopic adrenalectomy demonstrated lower tumor size, shorter operative time, lower intraoperative blood loss, shorter postoperative hospital stay and higher local recurrence rates. No significant differences were observed between groups treated with an open or laparoscopic approach for the following criteria: R0 surgical resection status, tumor overall recurrence, postoperative disease free survival and overall survival rates. Conclusion: R0 Resection Status via its undeniable impact on Recurrence Rate (RR), Disease Free Survival (DFS) and Overall Survival (OS), is the actual predominant

key factor which designates the selection of the appropriate surgical technique in the treatment of primary adrenocortical carcinoma (ENSAT I-III) in adults. Although a technically demanding procedure, laparoscopic adrenalectomy appears to be secure and feasible in the management of adrenocortical cancer in the hands of an experienced surgeon (performing >10 LAs/year), held in a referral specialised centre with sufficient experience in such cases, under the auspices of a multidisciplinary team, with respect to general surgical oncological principles.. Multicentre randomized controlled trials exploring its long-term oncological outcomes are required to determine the benefits of this procedure over the open approach.

Key Words: "adrenocortical cancer", "laparoscopy" or laparoscopic", "open", "laparoscopic versus open", "adrenalectomy", "R0 resection", "margin status" and "oncological outcome".

ΠΕΡΙΛΗΨΗ

Σκοπός της εργασίας ήταν η μελέτη και ανασκόπηση της βιβλιογραφίας ως προς τη θέση της λαπαροσκοπικής επινεφριδεκτομής στην αντιμετώπιση του πρωτοπαθούς τοπικού/ τοπικά προχωρημένου αδενοκαρκινώματος των επινεφριδίων (ENSAT I-III) στους ενήλικες. Μη τυχαιοποιημένες μελέτες που δημοσιεύτηκαν από τον Ιανουάριο του 1999 έως τον Φεβρουάριο του 2017 αναγνωρίστηκαν μέσω αναζήτησης στις βάσεις δεδομένων Pubmed, EMBASE, Cochrane Library και Google Scholar. Οι πρωταρχικές και οι δευτερεύουσες παράμετροι περιέλαβαν: χειρουργικές και παθολογικές μεταβλητές (ηλικία ασθενών, μέγεθος όγκου, στάδιο ENSAT, είδος χειρουργικής προσέγγισης, περίοδος παρακολούθησης), περιεγχειρητικά αποτελέσματα (χειρουργικός χρόνος, εκτιμώμενη απώλεια αίματος, διάρκεια νοσηλείας, ποσοστό μετατροπής σε ανοικτή μέθοδο , εκτομή R0, μικροσκοπικά όρια εκτομής χειρουργικού παρασκευάσματος) και ογκολογικά αποτελέσματα (ποσοστό συνολικής υποτροπής, ποσοστό υγιούς επιβίωσης/ ελεύθερης νόσου και συνολικό ποσοστό επιβίωσης), τα οποία αναλύθηκαν διεξοδικά στην παρούσα εργασία. Συνολικά 13 μελέτες με συνολικό αριθμό 1171 ασθενών περιλήφθηκαν στην ανασκόπηση. Σε σύγκριση με την ανοιχτή προσπέλαση, η λαπαροσκοπική επινεφριδεκτομή ανέδειξε επιλογή ασθενών με μικρότερο μέγεθος όγκου, παρουσίασε βραχύτερο χειρουργικό χρόνο με μικρότερη διεγχειρητική απώλεια αίματος και βραχύτερη μετεγχειρητική νοσηλεία, αλλά και υψηλότερα ποσοστά τοπικής υποτροπής. Δεν παρατηρήθηκαν σημαντικές διαφορές μεταξύ των ομάδων στις οποίες διενεργήθηκε ανοικτή ή λαπαροσκοπική μέθοδος για τις ακόλουθες μεταβλητές: R0 εκτομή με αρνητικά μικροσκοπικά χειρουργικά όρια, συνολική υποτροπή, συνολική ελεύθερης νόσου επιβίωση και ολική επιβίωση. Συμπερασματικά, αναδεικνύεται μέσω της παρούσας μελέτης, ότι η R0 εκτομή με αρνητικά μικροσκοπικά όρια εκτομής στο χειρουργικό παρασκεύασμα, μέσω του αδιαμφισβήτητου αντίκτυπού της στις μεταβλητές της συχνότητας υποτροπής (RR), της ελεύθερης νόσου επιβίωσης (DFS) και της ολικής επιβίωσης (OS), αποτελεί τον κυρίαρχο βασικό παράγοντα- κλειδί που υποδεικνύει την επιλογή της κατάλληλης χειρουργικής τεχνικής στη θεραπεία του πρωτοπαθούς αδενοκαρκίνωματος των επινεφριδίων (ENSAT I-III) σε ενήλικες. Αν και είναι τεχνικά απαιτητική, η λαπαροσκοπική επινεφριδεκτομή φαίνεται να είναι ασφαλής και εφικτή μέθοδος στα

χέρια ενός έμπειρου χειρουργού (που εκτελεί> 10/ έτος), που διεξάγεται σε ειδικό κέντρο παραπομπής με επαρκή εμπειρία σε τέτοιες περιπτώσεις, υπό την αιγίδα μιας διεπιστημονικής ομάδας και πάντα με σεβασμό στις γενικές χειρουργικές ογκολογικές αρχές. Διεξαγωγή πολυκεντρικών τυχαιοποιημένων μελετών ελέγχου με σκοπό τη διερεύνηση των μακροχρόνια ογκολογικών αποτελεσμάτων των δύο τεχνικών, απαιτείται για να προσδιοριστούν τα πιθανά οφέλη της λαπαροσκοπικής σε σχέση με την ανοιχτή προσέγγιση στην χειρουργική αντιμετώπιση του αδενοκαρκινώματος των επινεφριδίων των ενηλίκων.

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