16° CONGRESSO NAZIONALE AME
Joint Meeting with AACE Italian Chapter

Endogenous Hypercotisolism
(Cushing from A to Z)

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Adrenal surgery: to whom, when, how

Roma, Ergife Palace Hotel
9-12 Novembre 2017

Prof. C.P. Lombardi
Chief Endocrine Surgery
C.I.C. – Policlinico "A. Gemelli"

Istituto di Semeiotica Chirurgica
Chairman: Prof. R. Bellantone
Università Cattolica del Sacro Cuore
Rome

Associazione Medici Endocrinologi

ITALIAN CHAPTER

to Whom?

Patients with hypercortisolism due to

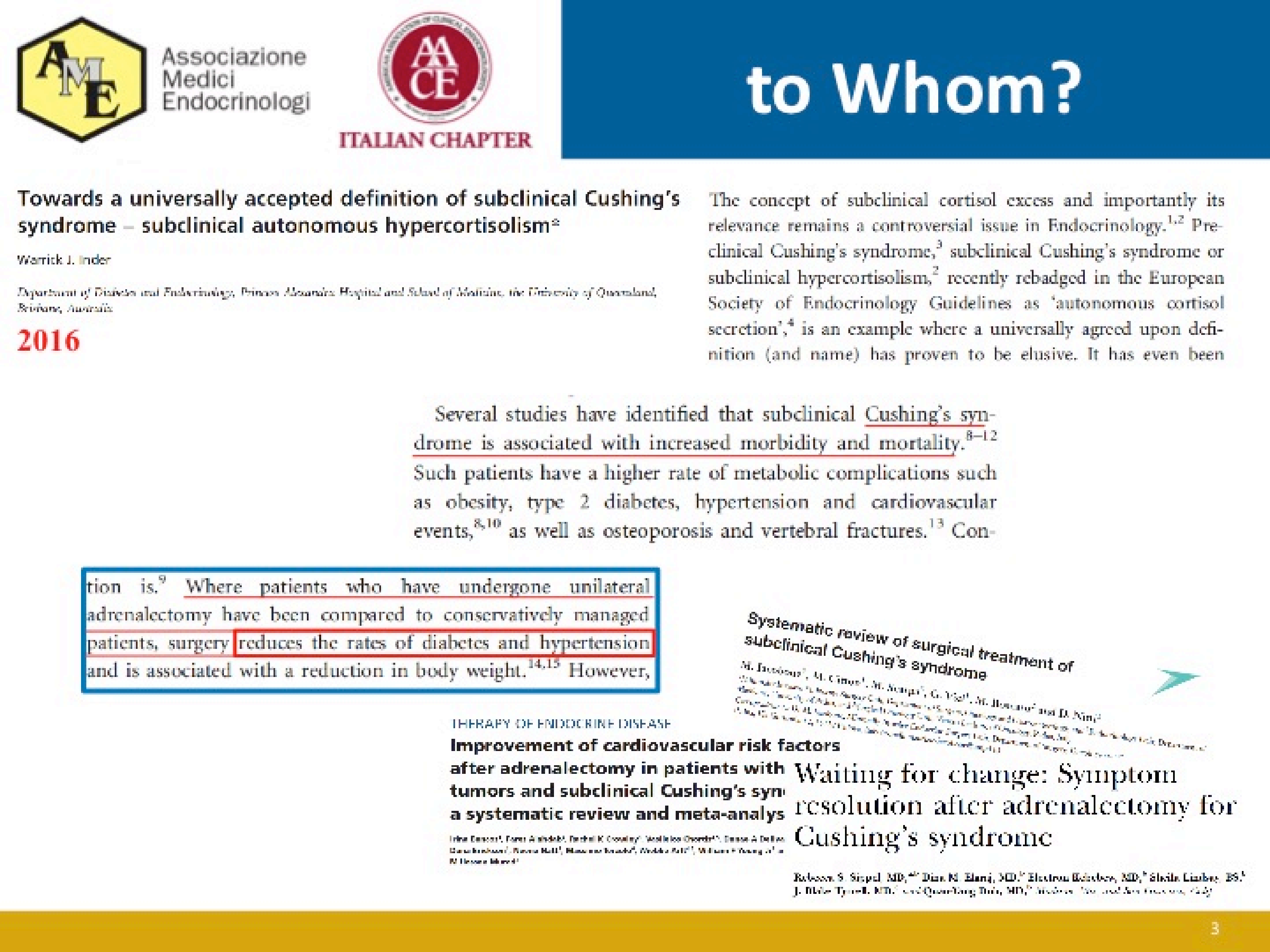
ACTH-independent cortisol hypersecretion

(ADRENAL CUSHING'S SYNDROME)

- OUVERT CUSHING'S SYNDROME
- SUBCLINIC CUSHING'S SYNDROME

ACTH-dependent cortisol hypersecretion

- CUSHING DISEASE
- ECTOPIC ACTH SECRETION



Associazione
Medici
Endocrinologi
AACE
ITALIAN CHAPTER
to Whom?
Towards a universally accepted definition of subclinical Cushing's syndrome – subclinical autonomous hypercortisolism
Warrick J. Inder
2016
The concept of subclinical cortisol excess and importantly its relevance remains a controversial issue in Endocrinology.[1,2] Pre-clinical Cushing's syndrome,[3] subclinical Cushing's syndrome or subclinical hypercortisolism,[2] recently rebadged in the European Society of Endocrinology Guidelines as 'autonomous cortisol secretion',[4] is an example where a universally agreed upon definition (and name) has proven to be elusive. It has even been
Several studies have identified that subclinical Cushing's syndrome is associated with increased morbidity and mortality.[8–12] Such patients have a higher rate of metabolic complications such as obesity, type 2 diabetes, hypertension and cardiovascular events,[8,10] as well as osteoporosis and vertebral fractures.[13] Con-
tion is.[9] Where patients who have undergone unilateral adrenalectomy have been compared to conservatively managed patients, surgery reduces the rates of diabetes and hypertension and is associated with a reduction in body weight.[14,15] However,
Systematic review of surgical treatment of subclinical Cushing's syndrome
THERAPY OF ENDOCRINE DISEASE
Improvement of cardiovascular risk factors after adrenalectomy in patients with tumors and subclinical Cushing's syn
a systematic review and meta-analys
Waiting for change: Symptom resolution after adrenalectomy for Cushing's syndrome
3

Associazione Medici Endocrinologi

ITALIAN CHAPTER

to Whom?

- ✓ **Subclinical Cushing's Syndrome** (SCS) is defined as a subtle autonomous cortisol hypersecretion without the typical signs and symptoms of hypercortisolism.
- ✓ **SCS** is reported in **5-48%** of patients with **incidentally discovered adrenal masses** and could be frequently encountered in the clinical practice, due to the increasing diagnosis of adrenal incidentaloma.
- ✓ **Controversies** in **SCS** :

DIAGNOSTIC CRITERIA

MANAGEMENT STRATEGY (observation Vs surgical treatment)

POSTOPERATIVE GLUCOCORTICOID REPLACEMENT THERAPY

Associazione Medici Endocrinologi

ITALIAN CHAPTER

to Whom?

DIAGNOSTIC CRITERIA

No clinical signs specific to Cushing´s syndrome

DST 1 mg >1µg/dL	+	DHEAS <30 µg/dL	or	ACTH <15 pg/mL	or	UFC 2xULN	or	AVS lateralization
DST 1 mg >1.8 µg/dL	+	LDDST >1.8 µg/dL	or	Midnight cortisol >7.5 µg/dL	or	ACTH <5 pg/mL	or	UFC >100 µg/day
DST 1 mg (no cut-off)	or	HDDST (no cut-off)	or	Low ACTH	or	High UFC	or	High serum cortisol
DST 1 mg >2.5 µg/dL	+	1 HPA axis alteration						
DST 1 mg >3 µg/dL	+	Low ACTH	or	Low DHEAS	or	No cortisol rhythm	or	Unilateral uptake adrenal scintigraphy
	or	HDDST >1 µg/dL						
	or	UFC >96 µg/day	or	ACTH <10 pg/mL	or	Midnight cortisol >5.4 µg/dL	*	
DST 1 mg >3.5 µg/dL								
DST 1 mg >4 µg/dL	+	Low ACTH	or	High UFC and/or 17OHC	or	No cortisol rhythm		
DST 1 mg >5 µg/dL	+	ACTH <10 pg/mL	+	UFC >76 µg/day				
	+	ACTH <9 pg/mL	or	UFC >120 µg/day	or	No cortisol rhythm		
	+	Impaired response to loperamide test 16 mg						
	or	ACTH <25 pg/mL	or	No cortisol rhythm	or	Unilateral uptake adrenal scintigraphy		
	+	HDDST >3 µg/dL	+	Normalization after adrenalectomy				
DST 3 mg >3 µg/dL	+	HDDST >3 µg/dL	+	UFC post-HDDST ≥ 50% baseline				
DST 4 mg >1.8 µg/dL	+	ACTH <10 pg/mL	or	UFC >100 µg/day	or	Cortisol 24.00/8.00 ratio >50%		

Di Dalmazi G, J Clin Endocrinol Metab 2014

Associazione Medici Endocrinologi

ITALIAN CHAPTER

to Whom?

MANAGEMENT STRATEGY

- ✓ Even if subclinical cortisol secretion can determine the metabolic and cardiovascular long-term consequences of Cushing's syndrome (CS), only a minority of patients with SCS will develop an overt CS

- ✓ Endoscopic adrenalectomy may have a beneficial effect on the long term metabolic consequences of subtle cortisol excess, with low morbidity rate

Surgical treatment

Medical treatment and observation

Associazione Medici Endocrinologi

ITALIAN CHAPTER

When?

Subclinical Cushing's syndrome: definition and management

M. Terzolo, A. Pia and G. Reimondo

Internal Medicine I, San Luigi Gonzaga Hospital, University of Turin, Orbassano, Italy

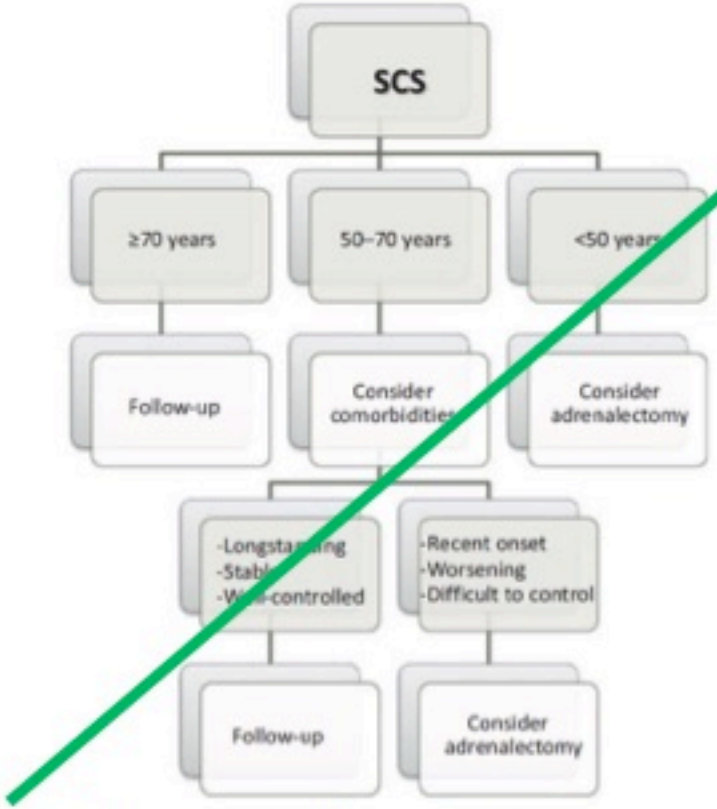


Fig. 2 Proposed management strategy of subclinical Cushing's syndrome.

2012

SPECIAL FEATURE
Clinical Practice Guideline

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, and Antoine Tabarin

When?

ENDOCRINE SOCIETY

1

2

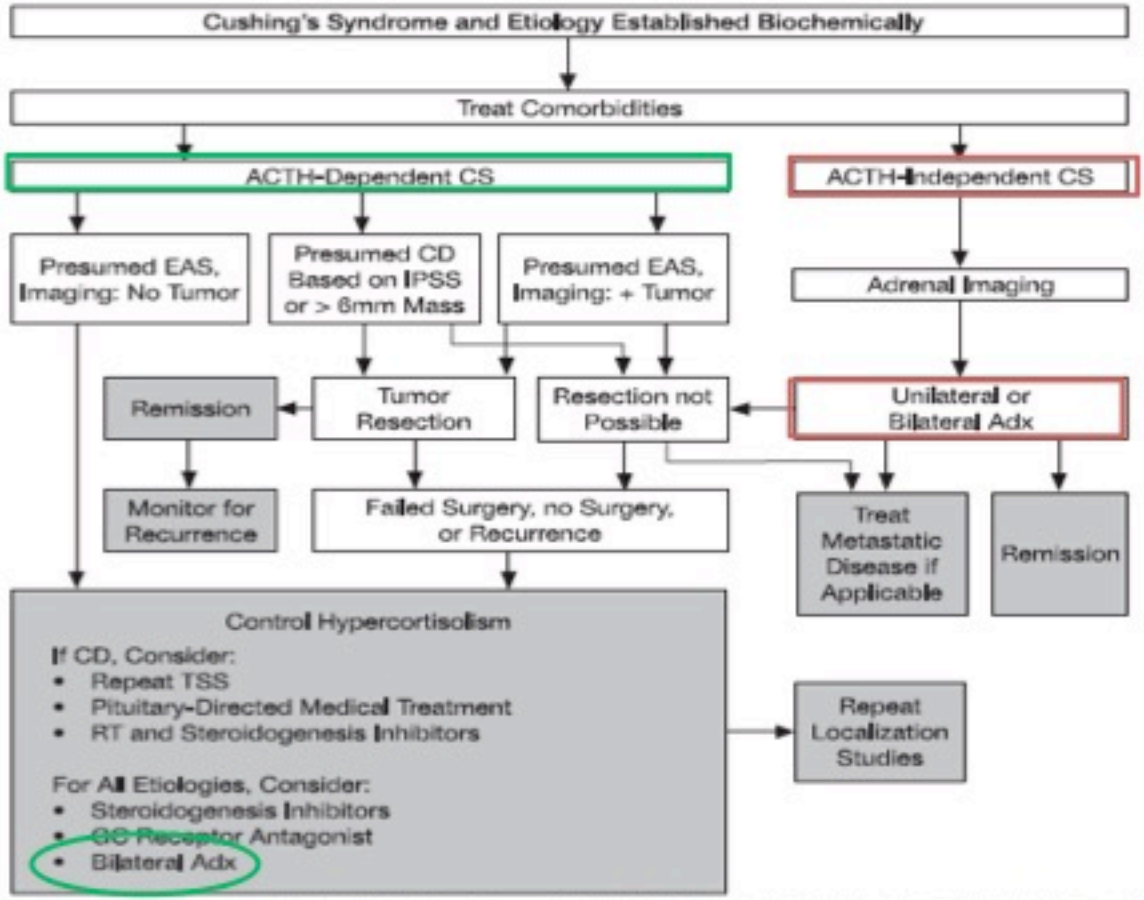


Figure 1. An algorithm for the treatment of CS. Derived from Nieman LK, Biller BM, Finding, JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:1526–1540. (17)

JCEM 2015; 100(8):2807-31

Associazione Medici Endocrinologi

ITALIAN CHAPTER

When?

Ultima spiaggia?

Associazione Medici Endocrinologi

ITALIAN CHAPTER

When?

Therapeutic options in patients with Cushing's disease after failure of transsphenoidal surgery

Second/third TSS	Radiation therapy	Medical therapy	Bilateral adrenalectomy
• Pro: – Persistent remission (success rate 37–70%) • Con: – Hypopituitarism in 5–50% – Adrenal insufficiency	• Pro: – 40–60% success rate • Con: – Delayed effect – Hypopituitarism (21–57%) – Cranial nerve palsy (5%) – Adrenal insufficiency	• Pro: – 25–90% success rate – Bridging therapy • Con: – Life-long therapy – Class-depending side effects – Adrenal insufficiency	• Pro: – Nearly 100% success rate – Immediate control of steroid excess • Con: – Life-long adrenal insufficiency – Risk of adrenal crisis – Nelson's tumour

Success:

Timing Related

A critical reappraisal of bilateral adrenalectomy for ACTH-dependent Cushing's syndrome
Martin Reincke et al, EJE 2015, 173, M23-M32

Associazione Medici Endocrinologi

ITALIAN CHAPTER

How?

ENDOSCOPIC ADRENALECTOMY

NEJM

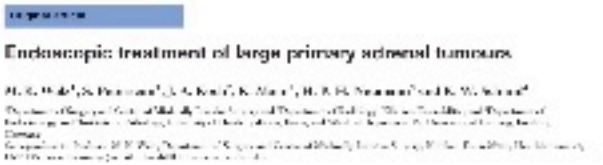
Laparoscopic adrenalectomy for Cushing syndrome and pheochromocytoma

"Gold standard"

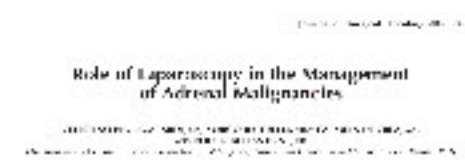
- benign adrenal lesions (hypersecretory and no)
- small / medium sized ...

... also proposed in the case of large lesions (potentially malignant)

Henry JF, *Best Practice & Research* 2001
Gumbs AA, *Best Practice & Research* 2006
Brunt LM, *Surg Endosc* 2006


Endoscopic treatment of large primary adrenal tumours


Long-term Outcome following Laparoscopic Adrenalectomy for Large Solid Adrenal Cortex Tumors


Role of Laparoscopy in the Management of Adrenal Malignancies

Associazione Medici Endocrinologi

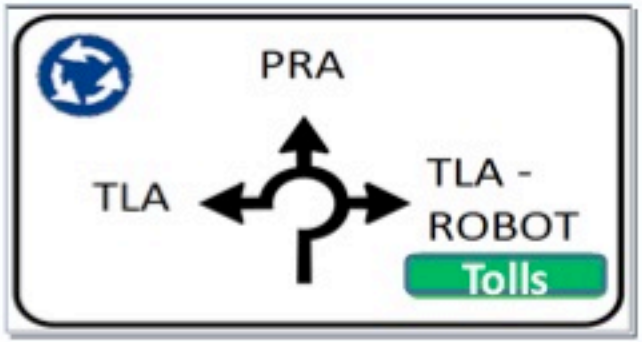
ITALIAN CHAPTER

How?

ENDOSCOPIC ADRENALECTOMY: techniques

Similar to conventional surgery, several approaches have been described also for the endoscopic adrenalectomy

Henry JF. Best Practice & Research 2001



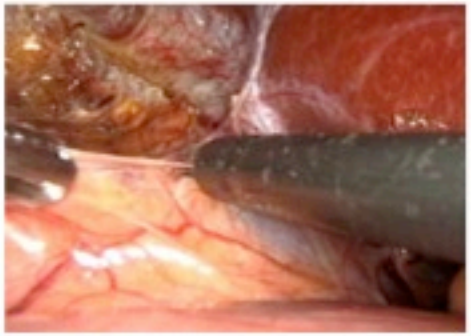
Associazione Medici Endocrinologi

ITALIAN CHAPTER

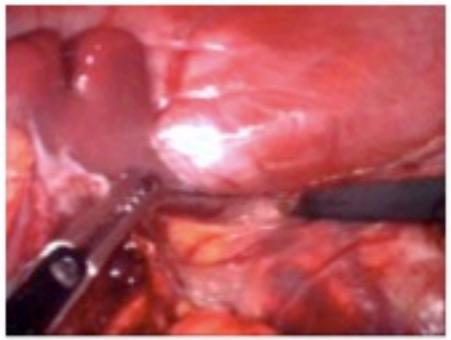
How?

Transperitoneal Lateral Adrenalectomy

The TL approach, the most widespread, is access to a "conventional operating field" ...



... it allows proper exposure of the adrenal region, facilitated by displacement due to the force of gravity of the structures adjacent to the adrenal gland ...



The liver and the spleen-pancreatic block

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Robot-assisted adrenalectomy

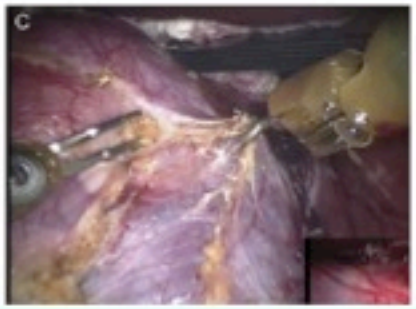
UNIVERSITÀ CATTOLICA del Sacro Cuore

U.O.C. Chirurgia Endocrina e Metabolica
Policlinico "A. Gemelli" - Roma

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Robot-assisted adrenalectomy



The Benefits of Robotic Approach:

- vision 3-D,

- best surgeon comfort,

- greater manuality (fine, unnatural movements such as 360 degree instrument rotations that theoretically can improve the peri- and postoperative outcome of surrenectomy).

Disadvantages:

High Costs (2.3 times higher than TLA)

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Robot-assisted RIGHT adrenalectomy

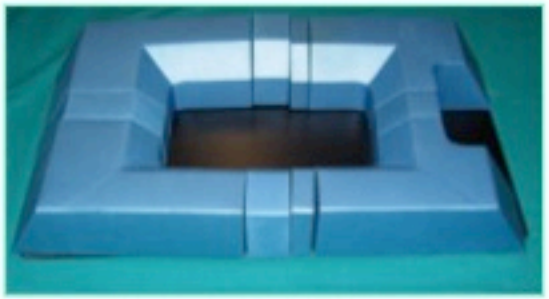
Associazione Medici Endocrinologi

ITALIAN CHAPTER

How?

POSTERIOR RETROPERITONEOSCOPIC ADRENALECTOMY

… the Posterior Retroperitoneoscopic Adrenalectomy (PRA) has been adopted by more than 20% of Centers.



Endoscopic adrenalectomy: Is there an optimal operative approach? Results of a single-center case-control study

Celestino Pio Lombardi, MD,* Marco Raffaelli, MD,* Carmela De Crea, MD,* Liliana Sollazzi, MD,† Valter Perilli, MD,† Maria Teresa Carnassa, MD,† and Rocco Bellantone, MD,* *Rome, Italy*

Walz M. Surgery 2006
Gumbs AA, Gagner M.. Best Practice & Research 2006

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Posterior Retroperitoneoscopic Adrenalectomy

Although PRA has been proposed also for large adrenal tumors...

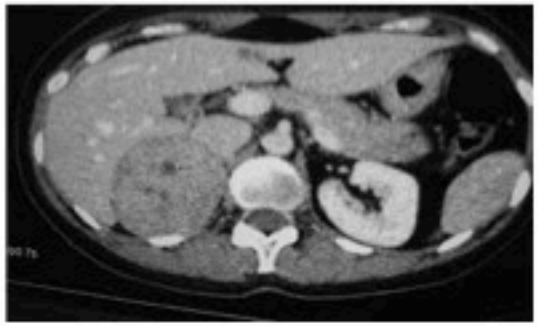
Original article

Endoscopic treatment of large primary adrenal tumours

M. K. Walz[1], S. Petersenn[3], J. A. Koch[2], K. Mann[5], H. P. H. Neumann[5] and K. W. Schmid[4]

[1]Department of Surgery and Centre of Minimally Invasive Surgery and [2]Department of Radiology, Kliniken Essen-Mitte, and [3]Department of Endocrinology and [4]Institute of Pathology, University of Duisburg-Essen, Essen, and [5]Medical Department IV, University of Freiburg, Freiburg, Germany

Correspondence to: Professor M. K. Walz, Department of Surgery and Centre of Minimally Invasive Surgery, Kliniken Essen-Mitte, Henricistrasse 92, D-45136 Essen, Germany (e-mail: mkwalz@kliniken-essen-mitte.de)



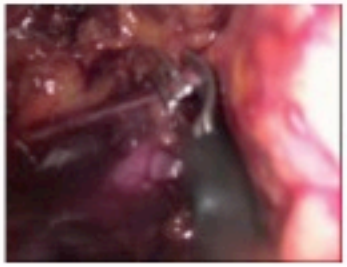
Large tumor size is indicated as the main limitation of PRA, mainly because of the small working space.

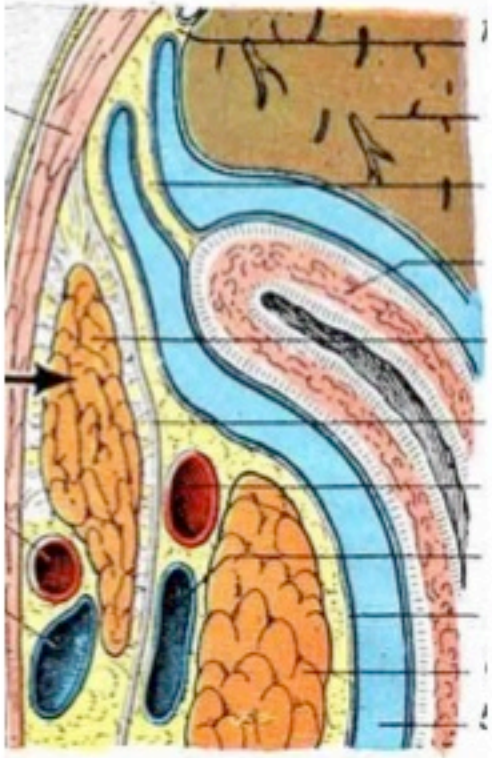
Associazione Medici Endocrinologi

ITALIAN CHAPTER

Posterior Retroperitoneoscopic Adrenalectomy





Advantages:

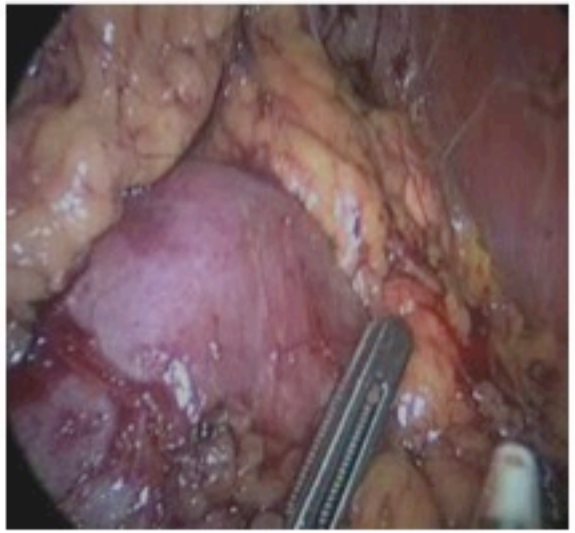
- Direct access to adrenal gland
- Excellent control of adrenal vein
- Extraperitoneal approach
- The best approach in case of previous surgery
- Bilateral adrenalectomy

Walz M, Surgery 2006
Lombardi CP, Surgery 2008
Perrier ND, Ann Surg 2008
Lombardi CP, Surgery 2011
Lee CR, Ann Surg Oncol 2013
Raffaelli M, World J Surg 2014

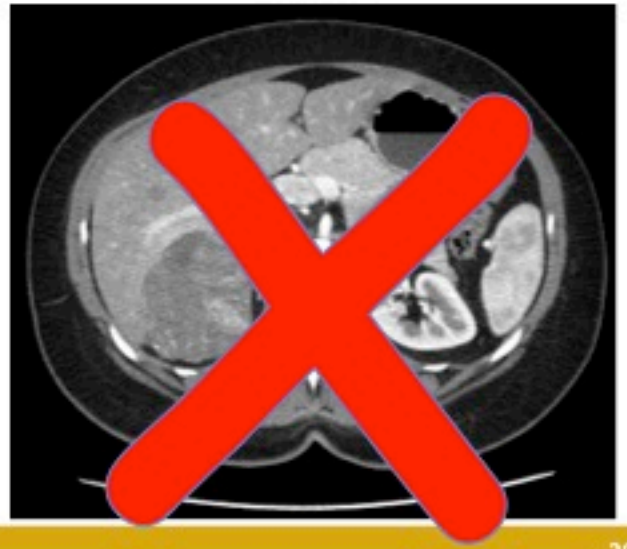
Posterior Retroperitoneoscopic Adrenalectomy

Disadvantages:

... lack of anatomical landmarks ?!?



- Limited exposure
- Contraindicated in case of >6-7 cm lesions

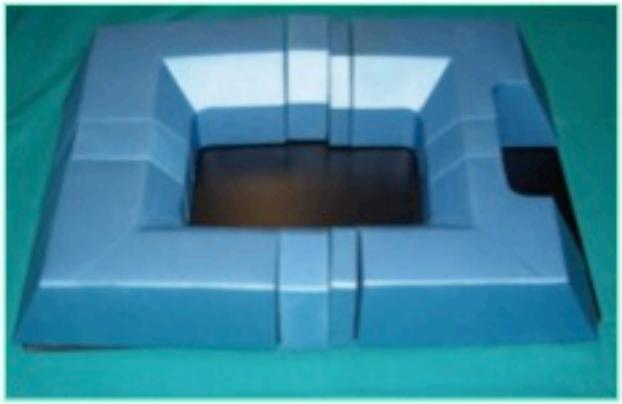


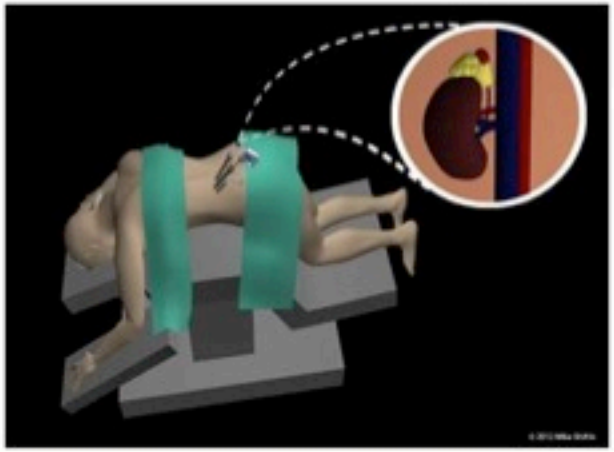
Associazione Medici Endocrinologi

ITALIAN CHAPTER

Posterior Retroperitoneoscopic Adrenalectomy

The patient is placed in prone position



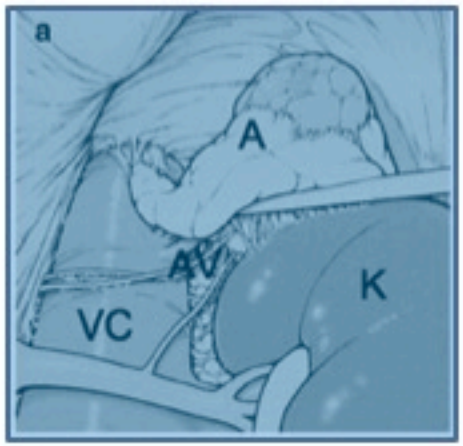


Walz et al

Associazione Medici Endocrinologi

ITALIAN CHAPTER

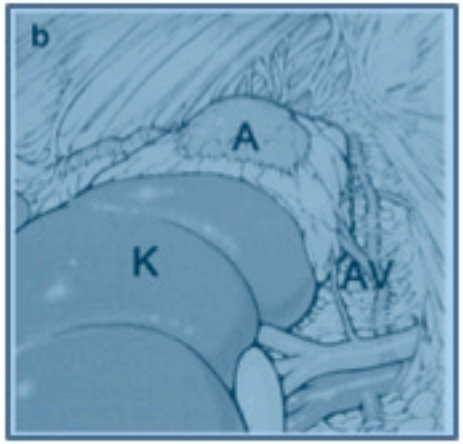
Posterior Retroperitoneoscopic RIGHT Adrenalectomy



Associazione Medici Endocrinologi

ITALIAN CHAPTER

Posterior Retroperitoneoscopic LEFT Adrenalectomy



Associazione Medici Endocrinologi

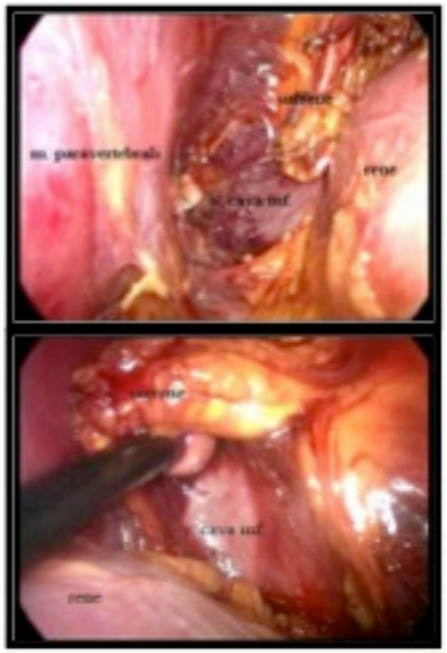
ITALIAN CHAPTER

Posterior retroperitoneoscopic adrenalectomy

"Tricks and Traps"

A carbon dioxide pneumoretroperitoneum is established at 20-25 mmHg

- High pressures facilitate the opening of the retroperitoneal space
- Better control of small bleeding



- Complete mobilization of the upper renal pole greatly facilitates retroperitoneoscopic dissection of the adrenal gland;
- Careful dissection clearly identifies the main vessels.

Systematic review and meta-analysis of retroperitoneoscopic *versus* laparoscopic adrenalectomy

V. A. Constantinides, I. Christakis, P. Touska and F. F. Palaz: *British Journal of Surgery* 2012; **99**: 1639–1648

22 Published Articles **1257 TLA** **Vs** **238 PostRA** **471 LatRA**

	No. of studies	No. of patients	Odds ratio or SMD	*P*	Heterogeneity χ^2	Heterogeneity *P*
Operative parameters						
Duration of operation (min)	7	444	−0·23 (−1·43, 0·98)*	0·711	176·67	< 0·001
Operative blood loss (ml)	4	271	−0·33 (−1·40, 0·74)*	0·552	41·35	< 0·001
Intraoperative bleeding	4	301	0·83 (0·17, 4·14)	0·825	3·11	0·373
Postoperative parameters						
Time to oral intake (days)	2	66	0·07 (−0·42, 0·56)*	0·789	1·38	0·242
Time to full ambulation (days)	2	66	0·07 (−0·41, 0·56)*	0·761	1·35	0·251
Length of hospital stay (days)	5	269	−1·45 (−2·76, −0·14)*	0·034	85·11	< 0·001
Overall complications	3	138	1·58 (0·40, 6·23)	0·510	1·49	0·478
Pneumothorax/haemothorax	2	62	0·60 (0·07, 5·22)	0·643	0·30	0·589
Neuralgia	3	272	4·88 (0·80, 29·76)	0·091	0·27	0·875
Death	2	196	0·27 (0·03, 2·48)	0·226	0·30	0·587

There were no differences in duration of operation, blood loss, time to ambulation and oral intake, or complication rates between techniques

*"**PostRA/LatRA** overall has **equivalent** outcomes to **TLA**…*

*…but may be associated with a **shorter hospital stay**"*

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Simultaneous bilateral posterior retroperitoneoscopic adrenalectomy

…The posterior approach exposes both the adrenal glands at the same time

Bilateral Adrenalectomy

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Bilateral Adrenalectomy

Author (year)	Diagnosis (n)	Approach	Operative time (min)	Conversion	Blood loss (ml)	Hospital stay (days)	Postoperative morbidity & mortality (n)
Fernandez-Cruz et al. [3]	CS (4) Pheo (1)	Transperitoneal	285	None	475	6	None
Chapuis et al. [15]	CS (10)	Transperitoneal	295	None	NA	6	Subphrenic abscess (1)
Acosta et al. [2]	CS (17)	Transperitoneal	360	1	NA	6	Hypoglycemia (1) Back pain (1) Death from gastrointestinal bleed (1)
Shichman et al. [16]	CS (5)	Transperitoneal	403	None	190	3.8	None
Bonjer et al. [17]	CS (13) Pheo (3)	Retroperitoneal	214	1	121	5	Hematoma (1), UTI (1), Death from sepsis (1)
Lezoche et al. [18]	CS (5) Pheo (1)	Transperitoneal	220	1	NA	NA	Death from colon injury (1)
Vella et al. [19]	CS (19)	Transperitoneal	252	3	NA	2.7	DVT (1)
Hasan et al. [20]	CS (3) Pheo (3) Metastases (1)	Transperitoneal	308	None	138	5.1	None
Hawn et al. [21]	CS (18)	Transperitoneal	296	None	218	3	Hemorrhage (1) Pancreatitis (1)
Porpiglia et al. [1]	CS (13)	Transperitoneal	234	2	340	5.7	Wound infection (1)
Jager et al. [22]	CS (16) Pheo (2)	Transperitoneal (16) Retroperitoneal (2)	289	None	125	7	Death from pulmonary embolus (1)
Mikhail et al. [23]	CS (5)	Transperitoneal	295	None	200	7	DVT (2) Wound infection (1)
Current series 2007	CS (25) Pheo (5)	Transperitoneal	290	None	81	3.5	UTI (2) Addisonian crisis (1) Pneumonia (1) Wound infection (1)
Total				4.7%	Mean 236	Mean 5.5	

Mean operative time **288**

13% Complications

2.4% Mortality

CS, Cushing's syndrome; Pheo, pheochromocytoma; NA, not available; UTI, urinary tract infection; DVT, de
insipidus

Takata MC, Kebebew E, Clark OH, Duh QY. ***Surg Endosc 2008***

Associazione Medici Endocrinologi

ITALIAN CHAPTER

Bilateral Adrenalectomy

"Even if TLA has been successfully performed also in the case of bilateral adrenalectomy, it is associated with significantly longer operative time when compared with *conventional technique*, because of the need to repositioning the patients".

Gagner M, Best Practice & Research 2006

	TLA	Open
		
[illegible]	[illegible]	[illegible]
Porpiglia et al. (2004)	234'	181'

Associazione Medici Endocrinologi

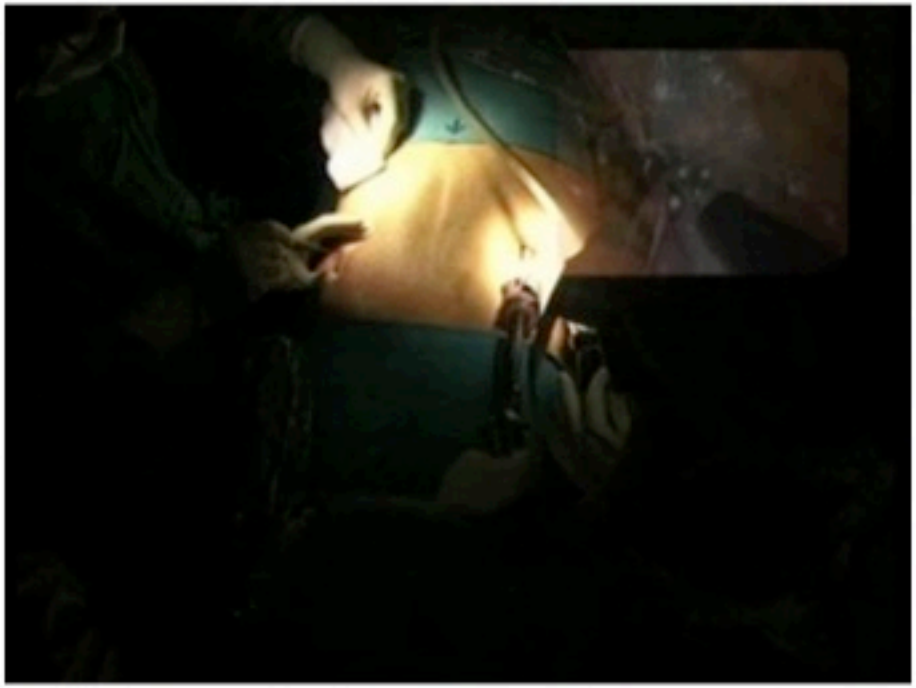
ITALIAN CHAPTER

Bilateral Adrenalectomy

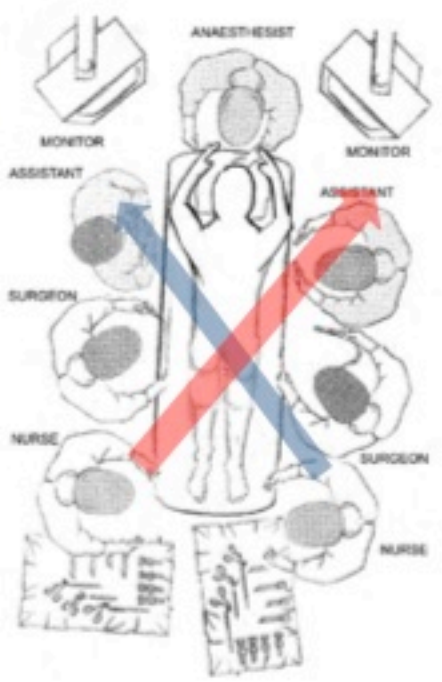
ACTH-dependent Cushing syndrome: The potential benefits of simultaneous bilateral posterior retroperitoneoscopic adrenalectomy.
Lombardi CP, Raffaelli M, De Crea C, Bellantone R, Fusco A, Bianchi A, Pontecorvi A, De Marinis

Synchronous Bilateral Adrenalectomy for Cushing's Syndrome: Laparoscopic Versus Posterior Retroperitoneoscopic Versus Robotic Approach
Raffaelli M, Brunaud L, De Crea C, Hoche G, Oragano L, Bresler L, Bellantone R, Lombardi CP

2007 ⟹ **2014**



LEFT ADRENALECTOMY Equipe



RIGTH ADRENALECTOMY Equipe

Synchronous Bilateral Adrenalectomy for Cushing's Syndrome: Laparoscopic Versus Posterior Retroperitoneoscopic Versus Robotic Approach

Marco Raffaelli · Laurent Brunaud · Carmela De Crea · Guillaume Hoche · Luigi Oragano · Laurent Bresler · Rocco Bellantone · Celestino P. Lombardi

World Journal of Surgery 2014

Operative time was significantly shorter in the PR-BilA group, because it eliminates the need to repositioning the patient. The number of drains and the length of hospital stay were reduced after RA-BilA, but this was likely related to different management protocols in different settings.

Variables	RA-BilA	PR-BilA	TL-BilA	*P* value
Patients	13	11	5	
Age (years)[a]	42.8 ± 13.6 (18–63)	41.2 ± 13.1 (18–62)	46.8 ± 19.9 (15–67)	0.777
Gender (male/female)	2/11	2/9	2/3	
Preoperative diagnosis				0.591
Cushing's disease	7 (43.7 %)[b]	8 (72.7 %)[c]	2 (40.0 %)[d]	
Ectopic ACTH secretion	4 (25 %)[b]	3 (27.3 %)[c]	2 (40.0 %)[d]	
ACTH-independent Cushing	2 (12.5 %)[b]	0 (0.0 %)[c]	1 (20.0 %)[d]	
Previous abdominal surgery	3 (25.0 %)[b]	3 (27.2 %)[c]	2 (40.0 %)[d]	0.772
BMI (kg/m^2)[a]	30.2 ± 6.5 (18.5–46.0)	27.9 ± 4.6 (22.5–36.7)	31.9 ± 4.8 (25.4–36.6)	0.379
ASA score				
I/II/III/IV/V	0/10/3/0/0	0/8/3/0/0	0/4/1/0/0	0.945
Operative time (min)[a]	221.5 ± 42.2 (155–285)	157.4 ± 54.6 (85–240)	256.0 ± 43.4 (210–300)	<0.001
Conversion to open approach	0	0[e]	0	NS
Blood transfusion	0	1 (9.1 %)[c]	1 (20.0 %)[d]	0.304
Drain yes/no	4/9	11/0	5/0	<0.001
Intraoperative complications	3 (18.7 %)[b]	1 (9.1 %)[c]	0	0.378
Postoperative complications	2 (12.5 %)[b]	3 (27.2 %)[c]	0	0.397
Clavien–Dindo classification	IIIa, IV	I, II, II		
Time to first flatus (days)[a]	1.8 ± 0.6 (1–3)	1.6 ± 0.5 (1–2)	2.3 ± 1.2 (1–3)	0.195
Hospital stay (days)[a]	4.4 ± 1.7 (2–8)[f]	10.8 ± 3.7 (5–18)[f]	12.0 ± 5.7 (8–22)[f]	<0.001[f]
Follow-up (months)[a]	18.8 ± 16.4 (2–48)	33.5 ± 22.4 (8–72)	46.8 ± 43.6 (2–98)	0.094
Disease-related death	0 (0 %)[b]	0 (0 %)[c]	0 (0 %)[d]	NS
Death for unrelated causes	0 (0 %)[b]	1 (9.1 %)[c]	1 (20.0 %)[d]	0.304

Associazione Medici Endocrinologi

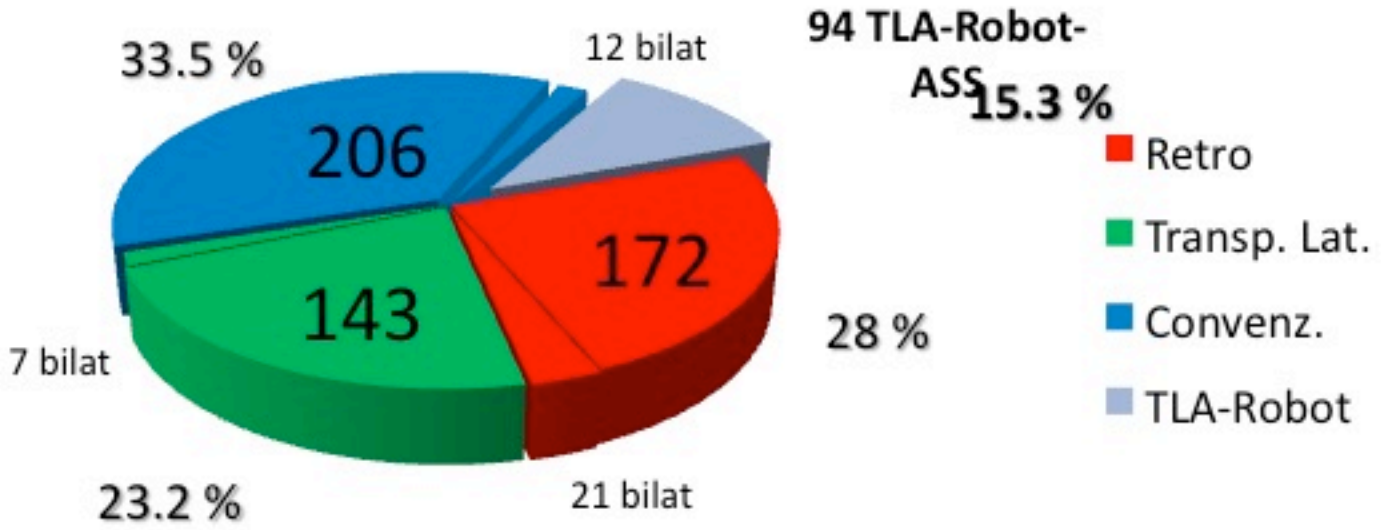
ITALIAN CHAPTER

615 ADRENALECTOMIES

U.O.C. Chirurgia Generale ed Endocrina

Policlinico "A. Gemelli" – Roma

July 1997- October 2017



Associazione Medici Endocrinologi

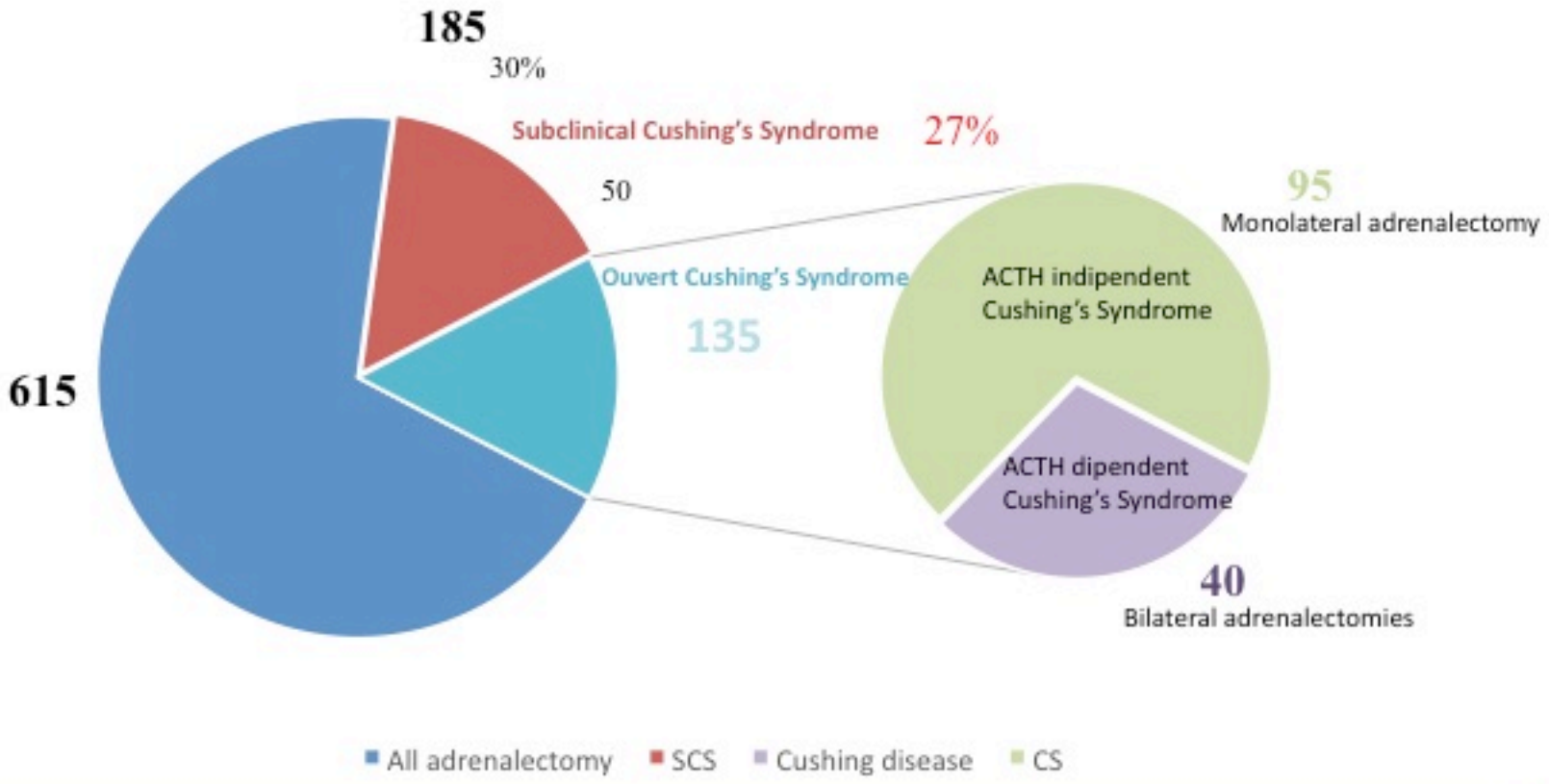
ITALIAN CHAPTER

615 ADRENALECTOMIES

U.O.C. Chirurgia Generale ed Endocrina

Policlinico "A. Gemelli" – Roma

July 1997- October 2017



Associazione Medici Endocrinologi

ITALIAN CHAPTER

Thanks for your attention!