What is new in Adrenal Incidentaloma?

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What is an adrenal incidentaloma?
An adrenal incidentaloma is defined as an adrenal tumor initially diagnosed by imaging studies (CT, Ultrasound, MRI) for a clinical condition unrelated to adrenal disease.
The term *incidentaloma* was first coined by Dr. Glenn Geelhoed in 1982 at the meeting of the American Association of Endocrine Surgeons.
Adrenaloma: a better term than incidentaloma

Clinically Inapparent Adrenal Mass

How frequent?
The overall frequency of adrenal adenomas in 87,065 autopsies in 25 studies was 5.9%.

Young WF, Endocrinol Metab Clin North Am, 2000;29(1)159-185
At Mayo Clinic, in a 5-year period 61,054 patients underwent CT scanning.

In 2,066 (3.4%) patients, an adrenal abnormality was found.

Among these, 259 patients (12.5%) had an incidentaloma.
In the era of widespread use of high-resolution ultrasonography, new generation CT scans and MRI, we can anticipate a 5% incidence of incidentalomas.
What is the Pathology?
380 patients (Single Institution)

- Non functioning adenoma: 63%
- Subclinical cushing adenoma: 15%
- Pheochromocytoma: 7%
- Myelolipoma: 6%
- Aldosteronoma: 2%
- Carcinoma primary: 4%
- Carcinoma metastatic: 3%

3088 compiled patients with Incidentaloma

- Non Functioning adenoma 74%
- Subclinical Cushing 7%
- Pheochromocytoma 4.7%
- Aldosteronoma 1.2%
- Primary Adrenocortical Carcinoma 4.8%
- Metastatic adrenal carcinoma 2.3%

European Society of Endocrinology Clinical Practice Guidelines:

- Management of patients with adrenal incidentalomas should involve a multidisciplinary team including endocrinologists, radiologists, surgeons and pathologists.
- Imaging characteristics (specifically density on a non-contrast CT scan) is more important than the size of adrenal incidentalomas in determining risk of malignancy and indication for surgery.
- Autonomous cortisol secretion is a disease on a continuum that is best assessed by a 1 mg dexamethasone suppression test. Surgical indication depends on the presence of comorbidities and severity of autonomous cortisol secretion.
- Laparoscopic adrenalectomy is the usual recommended approach when surgery is indicated. Open adrenalectomy is indicated for large or locally invasive tumours.
- Small, non-secreting, benign-appearing adrenal tumours require no long-term follow-up.

Rule out:

- Function
- Malignancy
Although by definition incidentalomas are not “obviously” functioning tumors clinically apparent as Cushing’s disease, Primary Aldosteronism, Pheochromocytoma, or sex steroid producing tumors, they should be evaluated for potential “subclinical” function.
1,096 patients with adrenal incidentaloma:

- 9.2% had subclinical Cushing’s syndrome
- 4.2% had pheochromocytoma
- 1.6% had clinically unsuspected aldosteronomas

Mantero F, Horm Res, 1997;47:284-289
Subclinical Cushing’s Syndrome

An ill defined condition of altered phypothalamic-pituitary-adrenal axis secretion in patients who do not have the classical signs and symptoms of clinically apparent Cushing’s syndrome.

Chiodini et al, J Clin Endocrinol Metab, 2010;95:2736-45
Subclinical hypercortisolism: a state, a syndrome, or a disease?

Adrenal Mild Hypercortisolism

Mild hypercortisolism as a disease continuum

Autonomous cortisol secretion (>138nmol/Lt)

Possible autonomous cortisol secretion (>50nmol/Lt)
30% of patients with AI have mild increase in cortisol secretion.

Patients with SCS comprise between 0.2% to 2% in the general population.

Screening for SCS

1mg dexamethasone suppression test with the traditional threshold of 5μg/dl or 138nmol/L to define adequate suppression.

American Association of Clinical Endocrinologists
American Association of Endocrine Surgeons
A Rapid Screening Test for Cushing's Syndrome

Fotios Ch. Pavlatos, MD, Renata P. Smilo, MD, and Peter H. Forsbäck, MD

The suppressibility of morning plasma 17-hydroxy-corticosteroid (17-OHCS) levels by 1 mg dexamethasone given by mouth at 11 PM the preceding night was used as a screening test for Cushing's syndrome. Plasma 17-OHCS in 16 normal subjects, 20 with simple obesity and 10 with diseases other than Cushing's syndrome were suppressed to levels below 5 μg/100 ml. In contrast, in 17 patients with Cushing's syndrome, the lowest observed value was 13 μg/100 ml and no false-negative results were obtained. Two obese, hirsute women proved to be partial responders only, as their plasma levels were not suppressed below 10.5 μg/100 ml. Mild abnormalities of adrenal cortical secretory activity may be present in such cases. Therefore, a single morning 17-OHCS value of less than 5 μg/100 ml plasma should exclude Cushing's syndrome.

carefully timed 24-hour urine collections and the cooperation of the patient in taking dexamethasone four times a day for two to four days.

We investigated a very simple and rapid screening method, first suggested by Nugent et al,14 which obviates some of the difficulties mentioned above. Normal and obese subjects, patients with Cushing's syndrome, and patients with other disorders were studied. The test requires only a single measurement of 17-OHCS in a morning specimen of plasma after the subject has been given 1 mg dexamethasone by mouth at 11 PM the preceding night.

Method

Plasma 17-OHCS.—Blood was drawn into hepar-
A 2- or 3-mg dose is better than the usual 1-mg dose to reduce false-positive results.

A suppressed serum cortisol (<3 μg/dL or 80 nmol/L) excludes Cushing’s syndrome.
Adrenal scintigraphy with \(^{131}\text{I-6\textbeta-iodomethylnorcholesterol (NP 59)}\) can reveal a “functioning” but not “hypersecretory” tumor when there is an uptake of the nucleotide in the tumor site and no-uptake in the contralateral suppressed gland.

Barzon L, J Clin Endocrinol Metab, 1998;83(1):55-62
Patients with AI and SCS have:

- Increased Mortality
- Associated Comorbidities
Cortisol as a Marker for Increased Mortality in Patients with Incidental Adrenocortical Adenomas

Miguel Debono, Mike Bradburn, Matthew Bull, Barney Harrison, Richard J. Ross, and John Newell-Price

J Clin Endocrinol Metab, December 2014, 99(12):4462–4470
Presented between January 2005 and July 2013 - Incidentaloma protocol (n=272)

Excluded
- 6 Phaeochromocytoma
- 2 Hyeraldosteronism
- 7 Intra-adrenal malignancy (4 metastasis & 3 ACC)
- 6 Surgery for size increase or >4cm
- 6 Surgery for metabolic deterioration
  - 3 Developed Cushing’s
  - 3 Worsening CV risk factors

Benign, adrenocortical adenoma (n=245)

"Primary Analysis"
Benign, adrenocortical adenoma with no size increase
Survival Rate and Cause-specific mortality Analysis
(n = 206)

- 21 lost to follow up or follow up scan to be arranged
- 18 on steroids (oral, inhaled, topical, parenteral)

"Sub-Analysis"
Benign, adrenocortical adenoma with no size increase
(n = 190)

16 patients with extra-adrenal malignancy
Patients with AI and post dexamethasone serum cortisol $>1.8\mu g/dl$ have increased mortality, mainly related to cardiovascular disease and infection.
Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing’s syndrome: a 15-year retrospective study

Guido Di Dalmazi, Valentina Vicennati, Silvia Garelli, Elena Casadio, Eleonora Rinaldi, Emanuela Giampalma, Cristina Mosconi, Rita Golferi, Alexandre Paccapelo, Uberto Pagotto, Renato Pasquali

Patients with adrenal incidentaloma and mild hypercortisolism have an increased risk of cardiovascular events and mortality.
ASSOCIATED COMORBIDITIES

- Metabolic Syndrome
- Cardiovascular Disease
- Osteoporosis
Subclinical Cushing’s Syndrome in Patients with Adrenal Incidentaloma: Clinical and Biochemical Features

R. ROSSI, L. TAUCHMANOVA, A. LUCIANO, M. DI MARTINO, C. BATTISTA, L. DEL VISCOVO, V. NUZZO, AND G. LOMBARDI

50 pts with Al (12/50 had SCS):

- 92% hypertension
- 50% obesity
- 42% type 2 diabetes mellitus
- 50% abnormal serum lipid concentrations
The clinical and hormonal features improved in all patients treated by adrenalectomy but were unchanged in all those who did not undergo surgery (follow up 9-73 months).

Interestingly, all 13 patients who had resection of truly nonfunctioning adenomas because of large size had improved clinically to such an extent that antihypertensive and antidiabetic therapy was reduced or discontinued.
41 pts with AI (12 SCS) and compared them with 41 controls.

Patients with these tumors (subclinically functioning or nonfunctioning) display some features of the **metabolic syndrome** such as impaired glucose tolerance, increased blood pressure and high triglyceride levels.

180 patients with AI:
Surgery in: 25pts with SH  
30pts without SH  
No surgery in: 16pts with SH  
37pts without SH

Patients with SH treated with surgery had improvement in weight (32%), blood pressure (56%) and glucose levels (48%).

Patients with SH non-treated BP, Glucose and LDL levels worsened more frequently than the ones treated surgically.
Adrenalectomy may improve cardiovascular and metabolic impairment and ameliorate quality of life in patients with adrenal incidentalomas and subclinical Cushing’s syndrome.

Maurizio Iacobone, MD, Marilisa Citton, MD, Giovanni Viel, MD, Riccardo Boetto, MD, Italo Bonadio, MD, Isabella Mondi, MD, Saveria Tropea, MD, Donato Nitti, MD, and Gennaro Favia, MD, Padua, Italy.
20 pts operated

The operated pts had:
- Normalization of laboratory corticosteroid parameter
- Decrease in BP (53%)
- Glymetabolic control improved (50%)
- BMI decreased
- Improvement of SF-36 evaluation

15 pts non operated

The Non-operated pts had:
- No improvement
- Worsening
60 pts with AI but no Diabetes, Hypertension, Hyperlipidemia
32 healthy controls with normal adrenal imaging

- Ultrasonographic measurement of carotid intima-media thickness (IMT) and flow-mediated dilatation (FMD)
26 pts had Cortisol Secreting AI
34 pts had Non Functioning AI

Patients with cortisol secreting adrenal incidentaloma without hypertension, diabetes, dyslipidemia exhibit adverse metabolic and CVR factors
Even patients with nonfunctioning AI also had less flow-mediated vasodilation compared with controls.
Bone Loss Rate in Adrenal Incidentalomas: A Longitudinal Study

IACOPO CHIODINI*, MASSIMO TRLONTANO*, VINCENZO CARNEVALE, GIUSEPPE GUGLIELMI, MARIO CAMMISA, VINCENZO TRISCHITTA, AND A. SCILLITANI

24 women with AI divided into two groups on the basis of the median value of urinary cortisol excretion.

The group with higher cortisol values (subclinical Cushing levels) had more lumbar trabecular bone loss than those with low cortisol secretion (not hypersecreting tumors).
Multicenter, retrospective study 287 patients with Al (85 had SCS)

Patients with SCS had lower bone mineral density, increased spinal deformity index compared with both Al nonfunctioning and controls.
Bilateral Adrenal Incidentalomas
Nine hospitals in S. Sweden

223 pts with AI

- Unilateral 180  76 (42%) had SH
- Bilateral  43   30 (70%) had SH

Subclinical hypercortisolism is more common in bilateral AIs
Bilateral adrenal incidentalomas differ from unilateral adrenal incidentalomas in subclinical cortisol hypersecretion but not in potential clinical implications

Evangeline Vassilatou, Andromachi Vryonidou¹, Dimitrios Ioannidis², Stavroula A Paschou¹, Maria Panagou² and Ioanna Tzavara²

BAI patients present more often with SCS when compared with UAI patients.

However comorbidities were of similar frequency in both groups.
Non Functioning AI are not necessarily evolving to functional, but
An increased prevalence of CV and Metabolic Risk Factors has been described in pts with NFAI

Due to:
A mild cortisol excess that cannot be detected with the available diagnostic test
Periodic secretion
Risk Factors and Long-Term Follow-Up of Adrenal Incidentalomas

LUISA BARZON, CARLA SCARONI, NICOLETTA SONINO, FRANCESCO FALLO, AGOSTINO PAOLETTA, AND MARCO BOSCARO

75 patients (median follow up 4 years)

The estimated cumulative risks for mass enlargement and hyperfunction were 18% and 9.5% respectively after 5 years, and 22.8% and 9.5% after 10 years.
The natural history of incidentally discovered adrenocortical adenomas: A retrospective evaluation

E. Grossrubatscher*, F. Vignati*, M. Possa**, and P. Loli*

53 patients with incidentalomas followed for 6-78 months.

22 lesions (41.5%) increased in size and 6 lesions (11.3%) decreased in size or disappeared.
77 patients with adrenal incidentaloma followed for a medium follow-up of 60 months using annual hormonal and CT evaluation.

A proportion of the non functioning incidentalomas developed overt hyperfunction.

Increase in size was not uncommon.
“Subclinical pheochromocytoma”

The totally asymptomatic incidentaloma that histologically proves to be a pheochromocytoma.

Measurement of catecholamines and their metabolites (metanephrines) in plasma and/or urine.
There is no indication for routine use of $^{131}$I-meta-iodobenzylguanidine (I-MIBG) scintigraphy in the evaluation of an incidentaloma unless catecholamine and urinary metabolites are elevated.
Prophylactic measures should always be taken (e.g., arterial line, immediate access to intravenous nipride) during surgery.
More than 40% of patients with primary aldosteronism are normokalemic.

The previously recommended measurement of potassium as the only test to rule out primary aldosteronism in the case of incidentaloma should be abandoned.
In a normotensive patient with a serum potassium level greater than 3.9 nmol/L, no further hormonal evaluation is necessary.

A detailed time-consuming evaluation is necessary, especially in all hypertensive patients, to rule out primary aldosteronism which may be the cause of hypertension in up to 15% of these patients.

The screening for subclinical primary aldosteronism should include, in addition to serum potassium, the upright aldosterone level to plasma renin activity (PRA) ratio.
Patients with two or more samples positive aldosterone/PRA ratio (>40) should undergo the fluorocortisone suppression test (0.4 mg every day for 4 days).

The acute saline suppression test (2L of 0.9% NaCl solution infused intravenously in 4 hours) to confirm the diagnosis.
Bilateral adrenal venous sampling with measurements of aldosterone and cortisol levels is the necessary next step to lateralize, determine the subtype of primary aldosteronism in order to identify the patient who will be cured through surgery.
Risk for Cancer

Adrenal Incidentaloma:

- Primary carcinoma 5%
- Metastatic carcinoma 3%
In addition to assessing distant metastasis and tumor size, imaging studies may suggest malignancy.
CT

A poorly delineated ragged tumor with stippled calcifications and with areas of necrosis.
CT

Attention value
≤10 Hounsfield units probably a benign tumor

>10 Hounsfield units ...... suspicious
MRI

Heterogeneously increased, early T2-weighted signal, weak and late enhancement after gadolinium injection or an intravascular signal identical to the tumor signal.
The 18 F-FDG-PET-scan is a useful tool confirming isolated metastases and selecting patients for adrenalectomy.
Fine-Needle Aspiration

- Fine-needle aspiration (FNA) biopsy of an incidentaloma has a limited role.

- FNA cannot differentiate cortical adenoma from carcinoma because it cannot detect invasion of the tumor into the capsule.
Although most clinically treated adrenal malignancies are discovered when they are larger than 6 cm in diameter, several reports have described very large tumors that never metastasized and small adrenal tumors that proved malignant.

- > 6cm
- > 4cm Indication for surgery
- > 3cm
The size of an incidentaloma as reported on a CT scan is usually less than the size reported on the histology report.
The regression line \( y = 0.85 + 1.09x \) relating CT-estimated and histological tumor size was linear \( (r=0.90, \ P<.001) \).
Correlation between Radiologic and Pathologic Dimensions of Adrenal Masses

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Abstract. The size of adrenal tumors has been shown to be a good predictor of malignancy. There is still some controversy about the concordance between radiologic and real pathologic measurements. The aim of this study is to determine the correlation between direct and corrected radiologic computed tomography scan dimensions and the measurements of the resected specimen. A total of 41 adrenal tumors were included. Direct and corrected measurements of the largest diameters were compared with the pathologic dimensions. The Linos formula was used to determine the proper management of adrenal incidentalomas in individual patients.

The Linos formula turned out to be significantly more accurate than direct radiologic measurements when means of the groups were compared, whereas when individual correlations were determined the two were similar. The Linos formula and radiologic measurements can be used to determine the proper management of adrenal incidentalomas in individual patients.
Currently, the only accepted criteria to determine whether an incidentaloma is benign or malignant are metastasis (synchronous or metachronous) and local invasion into adjacent structures.

The mapping and identification of genes responsible for hereditary syndromes (e.g. multiple endocrine neoplasia type 1, Li-Fraumeni) have increased our understanding of adrenocortical tumorigenesis.
What is the best surgical approach in the management of adrenal incidentalomas?

- Laparoscopic adrenalectomy
- Posterior retroperitoneoscopic adrenalectomy
Open adrenalectomy should be reserved for very large adrenal carcinomas invading the surrounding tissue.
Suspicious AI for malignancy

43 patients with Stage I and II ACC (25 patients open adrenalectomy and 18 laparoscopic).

Recurrence rate, median recurrence free survival, overall survival did not differ between the two groups.
The German ACC Registry published their results on 152 patients with Stage I and II tumors less than 10 cm in diameter. 35 had undergone laparoscopic and 117 open adrenalectomy.

Disease-specified survival as well as recurrence free survival, frequency of tumor capsule violation and postoperative peritoneal carcinomatosis were not different between the two groups.
156 patients with stage I and II adrenocortical carcinoma. (30 laparoscopic and 126 open adrenalectomy).

No significant differences were found between the two groups in terms of 5 year disease free survival and 5 year overall survival rates.
The most important factor for the success of any adrenalectomy, especially for tumors suspicious for carcinoma is the experience of the surgeon on how to approach the adrenal tumors. This is true for either open or laparoscopic adrenalectomy.
Impact of posterior retroperitoneoscopic adrenalectomy in a tertiary care center: a paradigm shift

Andreas Kiriakopoulos · Konstantinos P. Economopoulos · Efthimios Poulos · Dimitrios Linos

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Abstract

Background Posterior retroperitoneoscopic adrenalectomy has substituted its anterior laparoscopic counterpart as the treatment of choice in the management of adrenal tumors at the authors’ institution. The authors present their comparative results between these operative techniques, demonstrating the reasons for this change.

Methods From May 2008 to September 2010, 30 patients underwent posterior retroperitoneoscopic adrenalectomy. Operative time, complications, hospital stay, postoperative pain, and cost were compared with those of 30 selected laparoscopic control subjects treated from 2005 to 2010. Statistical analysis was based on Chi-square, the Mann–Whitney U test, the independent-samples t-test, and the Wilcoxon matched pairs test, as appropriate.

Results The median tumor size was 3.8 cm (range, 1.5–8.0 cm) in the retroperitoneoscopic group and 4.9 cm (range, 2.4–8.0 cm) in the laparoscopic group. The median operative time was similar between the two groups (90.0 min; range, 60–165 min vs. 77.5 min; range, 55–120 min; \( P = 0.138 \)). It was, however, significantly reduced after the 20th case (97.5 min; range, 80–165 min vs. 70 min; range, 60–110 min; \( P < 0.001 \)) in the retroperitoneoscopic group. The median visual analog pain scores were significantly lower in the retroperitoneoscopic group on both the first and the third postoperative days, respectively (1; range, 0–1 vs. 4; range, 3–6; \( P < 0.001 \) and 0; range, 0–1 vs. 3; median postoperative hospital stay in the retroperitoneoscopic group was 4 days; range, 3–6 days; anterior approach was significantly faster (median hospital stay in this group was 3 days; range, 2–7 days), and vastly superior cost–benefit ratios. Postoperative pain was significantly lower in the former group, and the authors suggest that the retroperitoneoscopic approach should become the method of choice in minimally invasive adrenal surgery.

Keywords Adrenal tumors · Laparoscopic adrenalectomy · Retroperitoneoscopic adrenalectomy · Retroperitoneum
170 pts with clinical \( (n=99) \) and subclinical \( (n=71) \) Cushing’s syndrome.

There were no mortalities or major complications reported.
Retroperitoneoscopic Adrenalectomy in Conn’s Syndrome Caused by Adrenal Adenomas or Nodular Hyperplasia

Martin K. Walz · Roland Gwosdz · Stephanie L. Levin · Piero F. Alesina · Anna-Carinna Suttorp · Klaus A. Metz · Frank A. Wenger · Stephan Petersenn · Klaus Mann · Kurt W. Schmid

183 pts with Conn’s syndrome

The retroperitoneoscopic approach provided a time efficient and safe surgical approach.
PRA resulted in decreased operative times, blood loss and postoperative length of stay compared with LA.
L Adrenal Incidentaloma causing Subclinical Cushing's Syndrome in a 50 y.o. WF
56 y.o. WF with a 4.5cm Adrenal Incidentaloma with mild hypercortisolemia
Most endocrinologists treat this

**Adrenal Incidentaloma Discovered Serendipitously**

Conservatively.........
But ..... 

- The Increased Mortality of pts with AI
- The Associated Comorbidities (Metabolic Sx, CVR Factor, Osteoporosis) frequently followed by significant improvement after surgery
- The safety of endoscopic adrenalectomy
Should we change our current management?
Surgical management:

- Evidence for a subclinically functioning tumor (mild hypercortisolism)
- Associated comorbidities (hypertension, obesity, diabetes, osteoporosis, etc)
- Size >4cm
- Age
- Radiological suspicion (CT>10HU)
Conservative management:

- No clinical or laboratory evidence for subclinical function of the tumor.
- No associated comorbidities potentially related to the incidentaloma.
- No suspicion of adrenal carcinoma.
Adrenaloma: A Call for More Aggressive Management

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Abstract. We review our experience from the surgical management of 57 patients (24 males, 33 females) with a mean age of 48.5 years who underwent adrenalectomy because of the computed tomography (CT) finding of a “nonfunctioning” adrenal tumor (adrenaloma). We found that CT consistently underestimated the real histologic size of the adrenal tumor ($p = 0.001$). Of the 57 resected tumors, 23 were cortical adenomas, 7 myelolipomas, 8 adrenal cysts, 11 nodular hyperplasias, 2 primary adenocarcinomas, 2 metastatic carcinomas, and 4 pheochromocytomas. The mean diameter was 5.89 cm and the mean weight 114.07 g. The mean diameter of the resected primary adenocarcinomas was 3.0 cm, respectively. The operative mortality was zero and the overall morbidity minimal. The mean operating time was 137 minutes (60–240 minutes). The posterior approach had the shortest hospital stay and the laparoscopic approach the shortest hospital stay and the postoperative need for narcotics. During the 6.2 years follow-up period, five patients with preoperative hypertension remained hypertensive, and both patients with the resected primary adenocarcinomas were alive without recurrence. We suggest a more liberal surgical approach to patients with adrenalomas because: (1) even small tumors are malignant or potentially lethal (e.g., pheochromocytomas) and (2) other nonfunctioning tumors may, with this (and notice), function. The low risk of adrenalectomy especially via the laparoscopic approach can provide an early definitive diagnosis and treatment, avoiding the cost of repeated CT scans and other studies as suggested by the currently prevailing conservative management of these tumors.

The low risk of adrenalectomy especially via the laparoscopic approach can provide an early definitive diagnosis and treatment
Thank you!