Longevity and adrenal tumors

Dimitrios Linos, M.D., Ph.D.
Professor of Surgery
National & Kapodistrian University of Athens
Do the incidentally found adrenal tumors affect longevity?
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.
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%
- Aldosteronomia: 2%
- Carcinoma primary: 4%
- Carcinoma metastatic: 3%

The Goal of Evaluation

Rule out:

- Malignancy
- Function
R/O Malignancy
The 18 F-FDG-PET-scan is a useful tool confirming isolated metastases and selecting patients for adrenalectomy.
The regression line (y=0.85 + 1.09x) relating CT-estimated and histological tumor size was linear (r=0.90, P<.001).
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.
R/O Function
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

2016 ESE-ENSAT Guidelines

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. Forsham, MD

The suppressibility of morning plasma 17-hydroxycorticosteroid (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 (<3μg/dL or 80 nmol/L) excludes Cushing’s syndrome.
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
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 Giampaola, 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%)  
- Glymabetic 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).
Bone Mineral Density, Prevalence of Vertebral Fractures, and Bone Quality in Patients with Adrenal Incidentalomas with and without Subclinical Hypercortisolism: An Italian Multicenter Study

Iacopo Chiodini, Valentina Morelli, Benedetta Masserini, Antonio Stefano Salcuni, Cristina Eller-Vainicher, Raffaella Viti, Francesca Coletti, Giuseppe Guglielmi, Claudia Battista, Vincenzo Carnevale, Laura Iorio, Paolo Beck-Peccoz, Maura Arosio, Bruno Ambrosi, and Alfredo Scillitani

J Clin Endocrinol Metab, September 2009, 94(9):3207–3214

Multicenter, retrospective study 287 patients with AI (85 had SCS)

Patients with SCS had lower bone mineral density, increased spinal deformity index compared with both AI nonfunctioning and controls.
Hormonal activity of adrenal incidentalomas: results from a long-term follow-up study

E. Vassilatou*, A. Vryonidou†, S. Michalopoulou*, J. Manolist, J. Caratzast, C. Phenekos † and I. Tzavara*

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.
The authors suggest that the retroperitoneoscopic approach should become the method of choice in minimally invasive adrenal surgery.
170 pts with clinical (n=99) and subclinical (n=71) Cushing’s syndrome.

There were no mortalities or major complications reported.
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?
Adrenaloma: A Call for More Aggressive Management

Dimitrios A. Linos, M.D., Nikolaos Stylopoulos, Sotirios A. Raptis, M.D.

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 morbidity minimal. The mean operating time was 137 minutes (60–240 minutes). The posterior approach had the shortest operating times and the laparoscopic approach the shortest hospital stay and 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 for patients with adrenalomas because: (1) even small tumors may be malignant or potentially lethal (e.g., pheochromocytomas), (2) tumors that appear to be nonfunctioning may in reality be secreting, and (3) other nonfunctioning tumors may, with time (and clinical 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.
Thank you!