

Altogether
to Beat
Cushing's
Syndrome



Viaggio alla
(ri)scoperta
della **Sindrome
di Cushing**
Quarta Edizione

Napoli, 5-7 maggio 2015
Hotel S. Lucia



WEDNESDAY 6 MAY 2015 - ROOM CAPRI

- 09.00-10.00 **SESSION 4: A CHALLENGE IN THE MANAGEMENT OF CUSHING'S SYNDROME: SUBCLINICAL CUSHING'S SYNDROME**
Chairs: **Diego Ferone, Renato Pasquali**
- 09.00-9.15 THE WORK-UP OF ADRENAL INCIDENTALOMA
Maria Cristina De Martino
- 09.15-9.30 THE ENIGMA OF THE DIAGNOSIS OF SUBCLINICAL CUSHING'S SYNDROME
Massimo Mannelli
- 09.30-9.45 THE TREATMENT OF ADRENAL INCIDENTALOMA AND SUBCLINICAL CUSHING'S SYNDROME
Iacopo Chiodini
- 09.45-10.00 Discussion

THE WORK-UP OF ADRENAL INCIDENTALOMA

Maria Cristina De Martino

**Dipartimento di Medicina Clinica e Chirurgia,
Sezione di Endocrinologia
Università Federico II di Napoli**

Definition and epidemiology

Most experts agree on considering adrenal masses of 10 mm, or more, in size as incidentalomas;
asymptomatic; discovered on an imaging study performed for unrelated reason; excluding pts undergoing imaging procedures as part of staging and work-up for cancer.

✓ Prevalence in autopsy studies:

2% (range 1-8.7)

Increase with age

Is similar in ♂ and ♀

✓ Prevalence in radiological studies:

≈4% (up to 10-15% in elderly patients)

More frequent in ♀ than ♂

Malignancy is more frequent in pts <20yrs

Frequency of the different types of adrenal incidentaloma

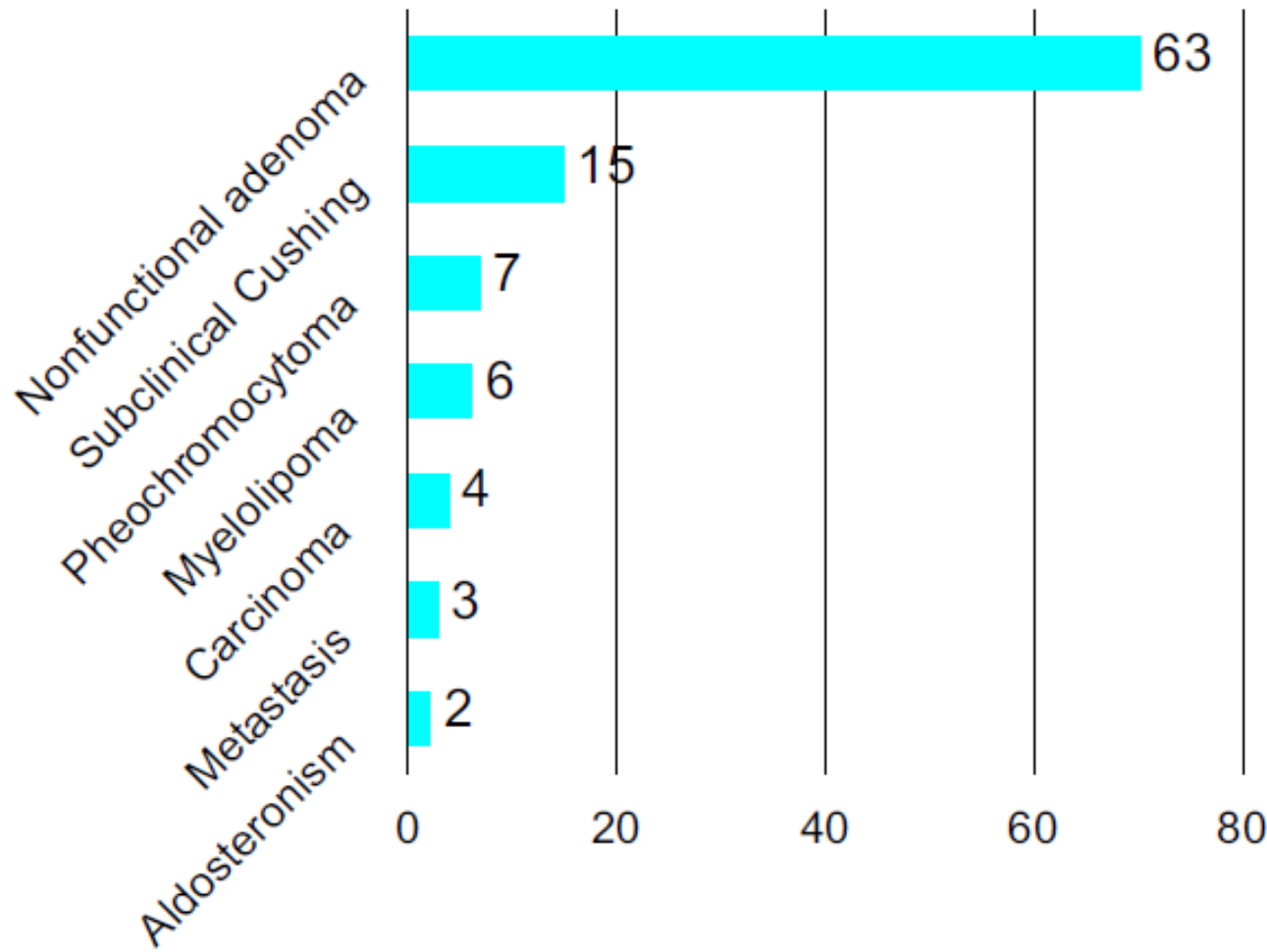


Fig. 1. Frequency of the common causes of adrenal incidentaloma (data are based on the authors' patient population; N = 380).

Frequency of the different types of adrenal incidentaloma

Table 2 Frequency of the different types of adrenal incidentaloma.

Type	Average (%)	Range
Clinical studies*		
Adenoma	80	33–96
Non-functioning	75	71–84
Cortisol secreting	12	1.0–29
Aldosterone secreting	2.5	1.6–3.3
Pheochromocytoma	7.0	1.5–14
Carcinoma	8.0	1.2–11
Metastasis	5.0	0–18
Surgical studies**		
Adenoma	55	49–69
Non-functioning	69	52–75
Cortisol secreting	10	1.0–15
Aldosterone secreting	6.0	2.0–7.0
Pheochromocytoma	10	11–23
Carcinoma	11	1.2–12
Myelolipoma	8.0	7.0–15
Cyst	5.0	4.0–22
Ganglioneuroma	4.0	0–8.0
Metastasis	7.0	0–21

*Data from references (6, 8, 9). **Data from references (4, 6, 8, 9, 14–17).

Frequency of the different types of adrenal incidentaloma

Table 2 Postoperative diagnosis for 282 laparoscopic adrenalectomies performed for incidentaloma with specimen dimensions

	lesions < 4 cm	lesions 4–6 cm	lesions > 6 cm
Non functioning adenoma	63(56.2)	28(35.8)	10(25)
Cortisol secreting adenoma	20(17.8)	15(19.2)	4(10)
Aldosterone secreting adenoma	8(7.1)	7(8.9)	3(7.5)
Pheochromocytoma	11(9.8)	10(12.8)	3(7.5)
Adrenocortical cancer	-----	1(1.2)	10 (25)
Myelolipoma	8(7.1)	13(16.6)	5(12.5)
Ganglioneuroma	2(1.7)	1(1.2)	1(2.5)
Hematoma	-----	-----	1(2.5)
Cyst	-----	3(3.8)	3(7.5)
Total	112(48.6)	78(33.9)	40(17.3)

Group A, 230/282 patients studied according to guidelines.
Dimensions, n. (%) of adrenalectomies.

Clinical recommendation based on epidemiology of AIs

- ✓ Considering the possibility of primary adrenal malignancies and metastases from extra-adrenal tumors in all patients with AIs.
- ✓ Excluding adrenal metastases in oncological patients with AIs.
- ✓ Excluding primary adrenal malignancies in all pediatric patients with AIs.

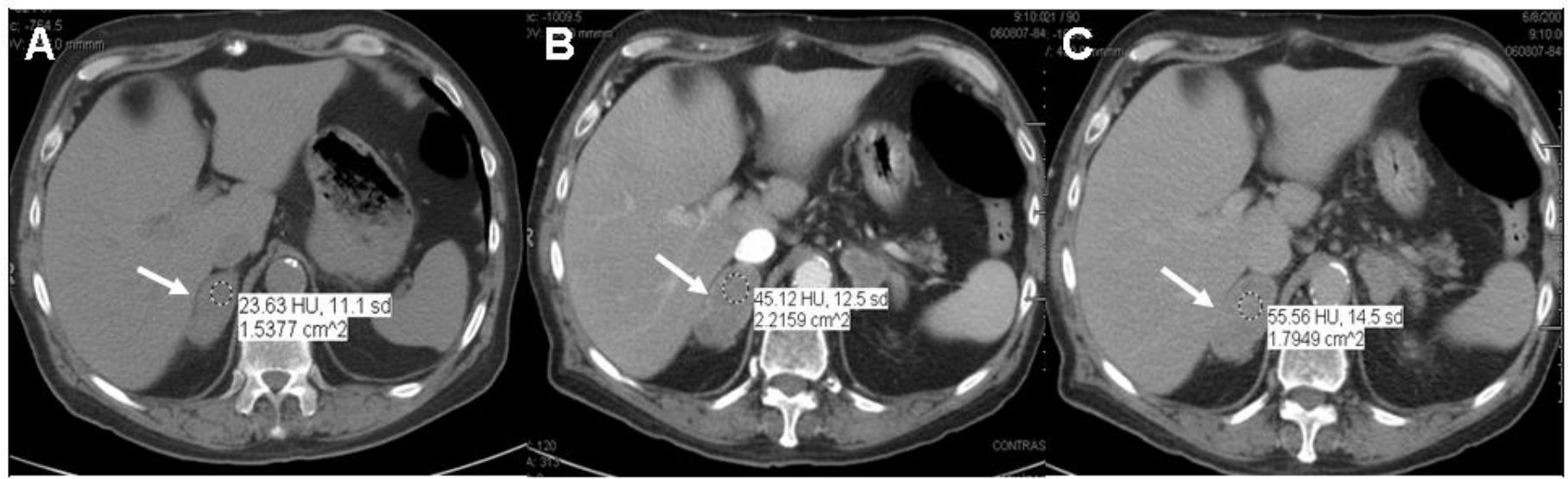
Radiological assessment (1)

- ✓ Ultrasonography:
 - Potential role in evaluating mass size and growth
 - No role in dd adenomas vs ACC
 - Several limitations
- ✓ Noncontrast CT scan:
 - dd adenomas vs ACC (size <4cm; homogeneous; regular borders; densitometry <10HU)
 - Limitation 10-40% lipid poor adenomas
- ✓ Enhanced CT scan:
 - dd lipid poor adenomas vs ACC (adenomas wash-out >50% after 10-15 min)

1st



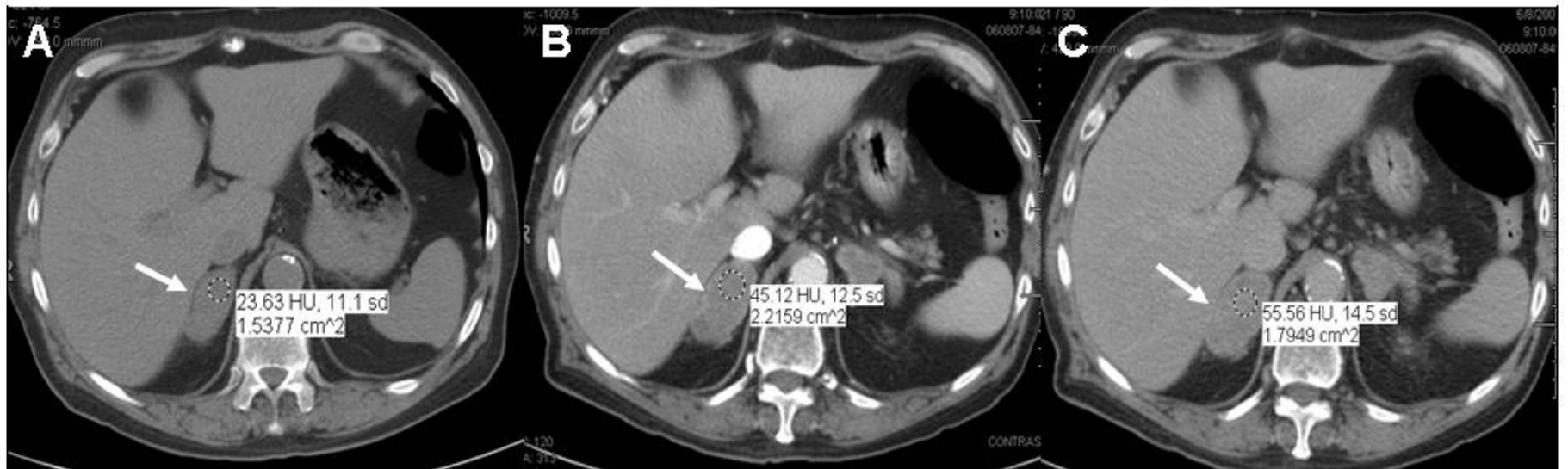
2nd



lipid poor adenoma



metastasis



Radiological assessment (2)

✓ MRI:

dd adenomas vs ACC (chemical shift)

Limitations: lipid poor adenomas; costs

✓ Scintigraphy (norcholesterol):

Dd functioning vs non functioning

dd adenomas vs ACC

Limitations: high radiation; low specificity

✓ PET and particularly PET/CT:

dd adenomas vs ACC

✓ FNAB :

selected patients with a suspicious of adrenal metastasis from non adrenal tumors.

Hormonal evaluation

- ✓ Screening of pheo:
 - In all patients with AI
 - Urinary fractionated metanephrines or plasma free methanephrines



*Terzolo M. et al for AME; EJE 2011;
Arnaldi G. et al Best Pract Res Clin Endocrinol Metab 2012;
Zeiger MA. Et al AACE/AAES Guidelines; Endocr Pract 2009*

Hormonal evaluation

- ✓ Screening of pheo:
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- ✓ Screening of primary aldosteronism:
 - Patients with AI and hypertension/hypokalemia
 - Aldosterone (ng/dl)/renin ratio (PRA ng/ml) >30-50

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- ✓ Screening of overt/subclinical CS:
 - In all patients with AI
 - DST 1 mg or more?
 - Which cut-off? -> Prof Mannelli

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 - DST 1 mg or more?
 - Which cut-off?

Hyperandrogenism?



Follow-up

Table 2

"Summary of management strategy for patients with adrenal incidentaloma".

Experts opinion	Endocrine tests	Tests and frequency	Duration	Imaging	Frequency
NIH Consensus statement 2002 ⁴	1 mg DST, plasma free metanephrines, K and PRA/aldo in hypertensive patients	Annual	4 years	Monitor mass <4 cm. In addition to size use additional criteria in 4–6 cm mass	Two CTs, at least 6 months apart, no data to support continued imaging if size remain stable
Young, 2007 ¹³	1 mg DST, urinary metanephrines and catecholamines, K and PRA/aldo in hypertensive patients	Annual	4 years	Monitor mass <4 cm	CT at 6, 12 and 24 months
French Society of Endocrinology Consensus, 2008 ⁶²	1 mg DST, glycemia, plasma and urinary metanephrines, K and PRA/aldo in hypertensive patients	1 mg DST, plasma and urinary metanephrine at 6 months then 1 mg DST at 2 and 5 years	5 years	Monitor mass <4 cm	CT at 6 months and then at 2 and 5 years
AACE/AAES Medical Guidelines, 2009 ²³	1 mg DST, plasma and urinary metanephrines/catecholamines and PRA/aldo in hypertensive patients	Annual	5 years	Monitor mass <4 cm	Imaging reevaluation at 3–6 months and then annually for 1–2 years.
Nieman, 2010 ²⁷	1 mg DST or late-night cortisol test, plasma and urinary metanephrines/catecholamines and PRA/aldo in hypertensive patients	Annual No repeat screening for aldosteronism if previously excluded	4 years if mass <3 cm, nonfunctional and benign at imaging 1–2 years (or more)	Monitor mass <4 cm, in addition to size use additional criteria	Imaging reevaluation at 1–2 years (or more) and for intermediate mass at 3–12 months.
AME Position ³	1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldo in hypertensive and/or hypokalemic patients	To be judged on individual basis after clinical monitoring	To be judged on individual basis after clinical monitoring	Monitor 2–4 cm mass; in addition to size use additional criteria	CT or MRI at 3–6 months. No further imaging if mass is <2 cm with clear benign features. If mass >2 cm judge on individual basis
Authors	1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldo in hypertensive patients	Annual No repeat screening for aldosteronism if previously excluded	5 years	Monitor mass <4 cm; in addition to size use additional criteria	CT or MRI at 6 months (before if suspect mass) then after 3 and 5 years

Screening for complication

- ✓ In which patients?
- ✓ How often?
- ✓ How?



Grazie



Long-Term Follow-Up in Adrenal Incidentalomas: An Italian Multicenter Study

J Clin Endocrinol Metab, March 2014, 99(3):827–834

Valentina Morelli, Giuseppe Reimondo, Roberta Giordano, Silvia Della Casa, Caterina Policola, Serena Palmieri, Antonio S. Salcuni, Alessia Dolci, Marco Mendola, Maura Arosio, Bruno Ambrosi, Alfredo Scillitani, Ezio Ghigo, Paolo Beck-Peccoz, Massimo Terzolo, and Iacopo Chiodini

European Journal of Endocrinology (2012) 166 669–677

ISSN 0804-4643

CLINICAL STUDY

Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major metabolic and cardiovascular outcomes: a large cross-sectional study

Guido Di Dalmazi, Valentina Vicennati, Eleonora Rinaldi, Antonio Maria Morselli-Labate, Emanuela Giampalma¹, Cristina Mosconi¹, Uberto Pagotto and Renato Pasquali

Endocrinology Unit, Department of Clinical Medicine, S. Orsola-Malpighi Hospital, Alma Mater Studiorum, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy and ¹Division of Radiology, S. Orsola-Malpighi Hospital, 40138 Bologna, Italy

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- ✓ Subclinical hypercortisolism is associated with the risk of incident CVEs.
- ✓ a long-term biochemical follow-up is also required because of the risk of subclinical hypercortisolism development.

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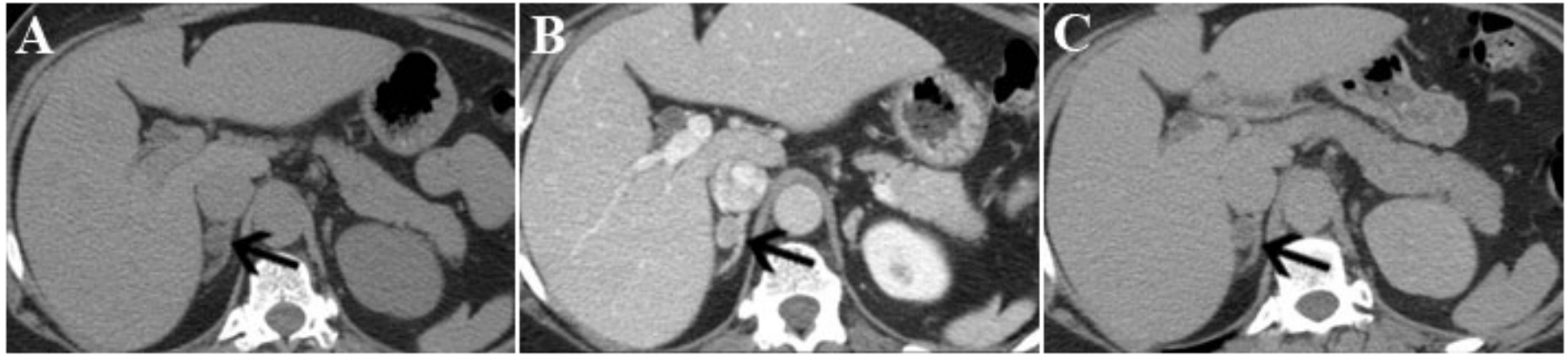


Figure 3. Axial images from an adrenal mass protocol CT scan performed to characterize an incidentally discovered right adrenal mass in a 48 year old woman. **(A)** The attenuation of the adrenal mass (arrow) in the unenhanced scan was 15 HU, which is indeterminate and could indicate a lipid-poor adenoma or a malignant lesion. **(B)** In the dynamic contrast-enhanced scan the mass (arrow) had an attenuation of 80 HU and **(C)** in the delayed washout scan, performed 10 minutes later, the mass (arrow) had an attenuation of 30 HU. The absolute adrenal washout rate was calculated to be 71.7% and the rel

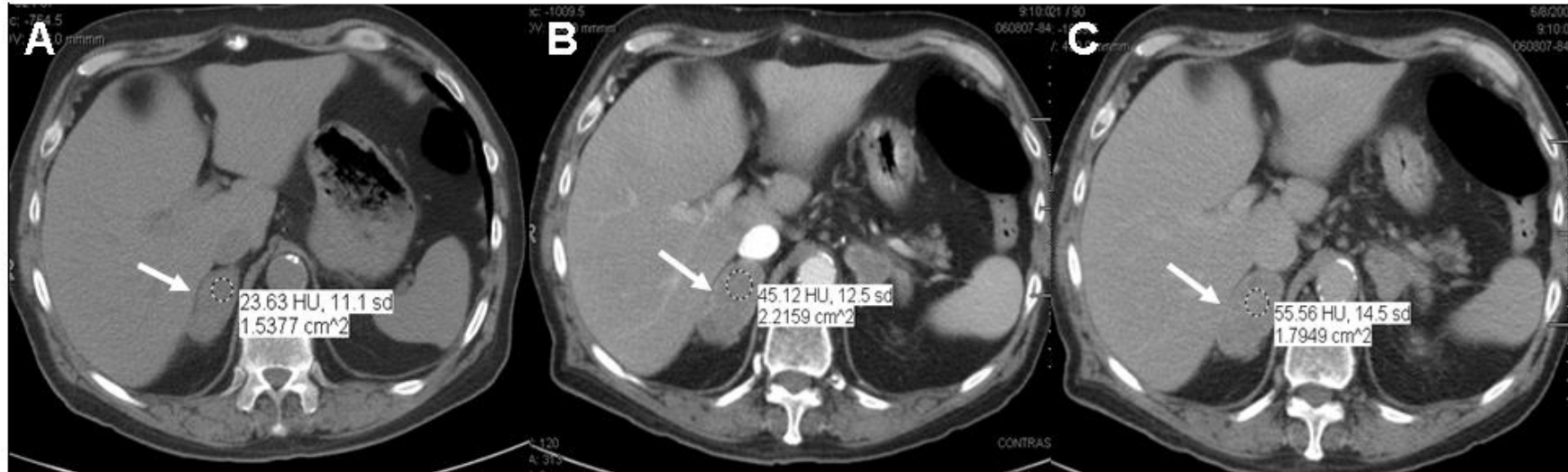


Figure 2. Abdominal CT of bilateral adrenal masses (arrow) shows persistent enhancement of the right adrenal gland after intravenous contrast at 1.5 (panel B) and 5 min (panel C) after contrast injection in a pattern compatible with metastases to the adrenals.