Società Medico Chirurgica di Ferrara
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Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di FERRARA

Società Italiana Endocrinologia

Società Italiana Unitaria di Endocrinochirurgia

PERCORSO DIAGNOSTICO TERAPEUTICO DELLE LESIONI SURRENALICHE NELLA PROVINCIA DI FERRARA

Sabato 3 dicembre 2022
Aula Magna Nuovo Arcispedale S. Anna
Ferrara

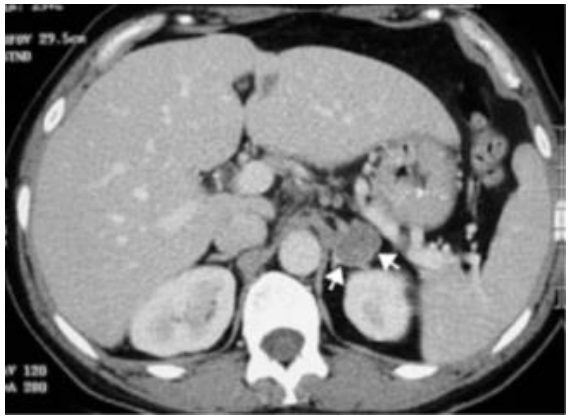
Definizione, eziologia ed epidemiologia

Marta Bondanelli

Università degli Studi di Ferrara

Adrenal Incidentaloma (AI)

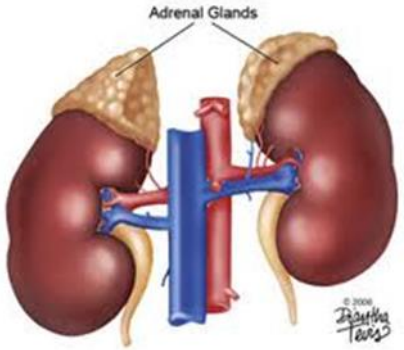
The term “incidentaloma” was coined in 1982 by Geelhoed and Druy
dilemma of early diagnosis of an asymptomatic adrenal mass



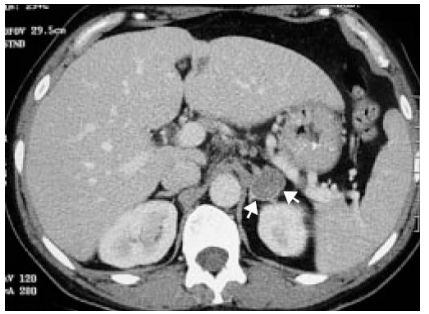
DEFINITION

A clinically unapparent adrenal mass
- greater than 1 cm in diameter -
detected during imaging performed for unrelated reasons

ESE/ ENSAT (2016) guidelines
exclude adrenal lesions discovered during
the screening of patients with hereditary syndromes
or extra-adrenal tumors



Adrenal Incidentaloma (AI)



A previously unsupected adrenal mass
discovered on an imaging study performed for an unrelated reason

Prevalence

Autopsy studies ⇨ ~ **3%** (ranging from 0.03 to 32%)
from 1 to **8.7 in series >1000 pts**

< 1 % < 30 yrs
4-7% > 50 yrs
~ 7 % elderly (> 70 yrs)

Radiological studies ⇨ ~ **2% (**ranging from 0.3 to 4.5%)

rare < 18 yrs
~ 3 % 50 yrs
7-10 % in the elderly

Sherlock M et al Endocrine Review 2020

Fassnacht M et al. Eur J Endocrinol 2016

Adrenal Incidentaloma (AI)

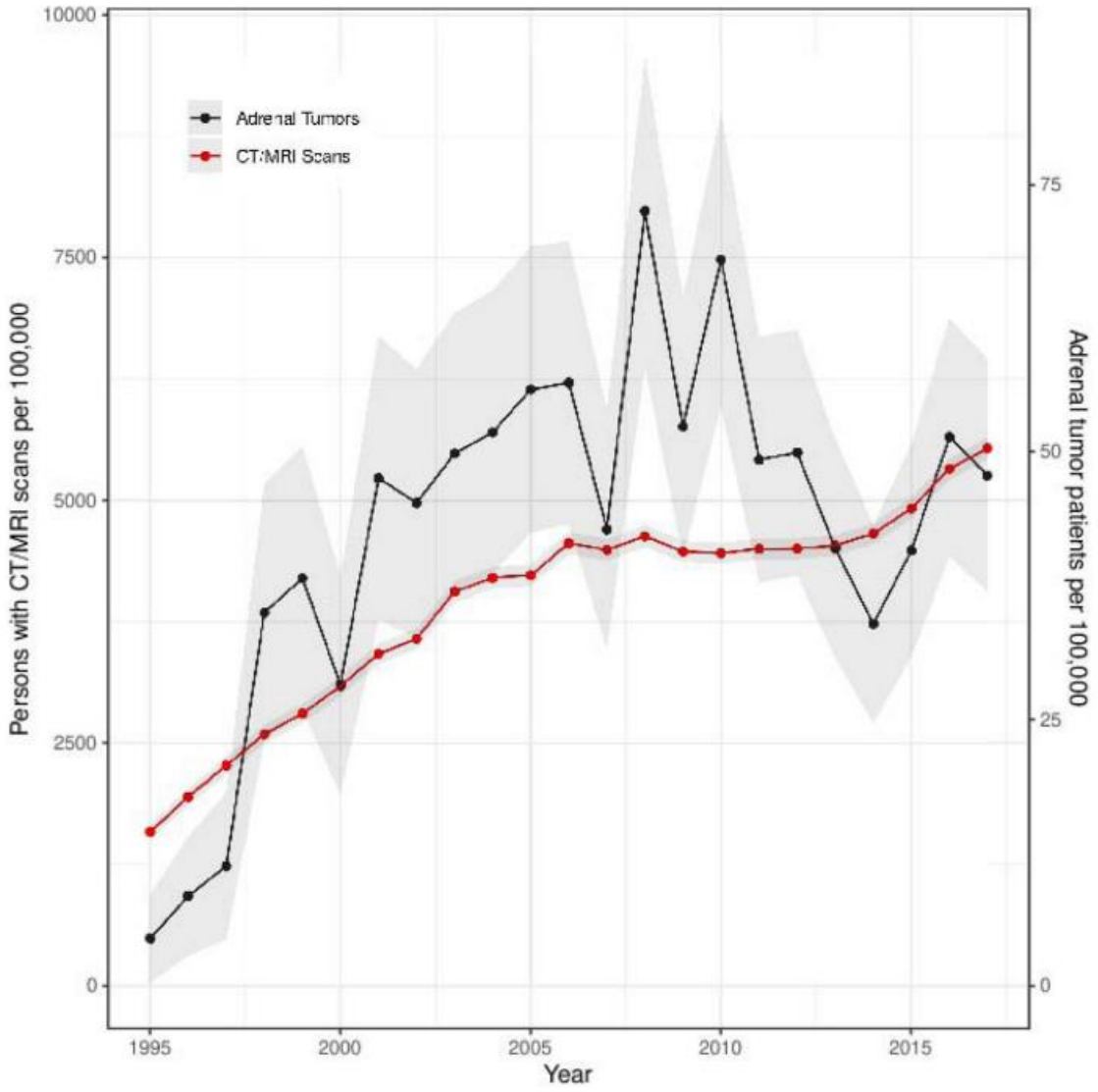
Standardized Incidence Rate of Adrenal Tumor Patients Diagnosed per 100,000 Person/years

A population-based retrospective cohort study of all patients diagnosed with adrenal masses from 01/01/1995 to 12/31/2017 living in Olmsted County, Minnesota, USA.
The population was 119,857 in 1995 and 160,089 in 2017 (average population 141,522, total of 375,969 unique persons during study period).

Adrenal Tumors and Abdominal CT and MRI Scan

Annual SIR of new patients diagnosed with adrenal tumors per 100,000 person-years and
annual SIR of persons undergoing CT or MRI of the abdomen in Olmsted County 1995–2017

Incidence of diagnosed adrenal tumors increased 10 times during the study period:
from 4·4 (95%CI 0·3–8·6)
to 47·8 (95%CI 36·9–58·7)
per 100,000 person-years



Ebbehoj et al. Lancet Diabetes Endocrinol. 2021

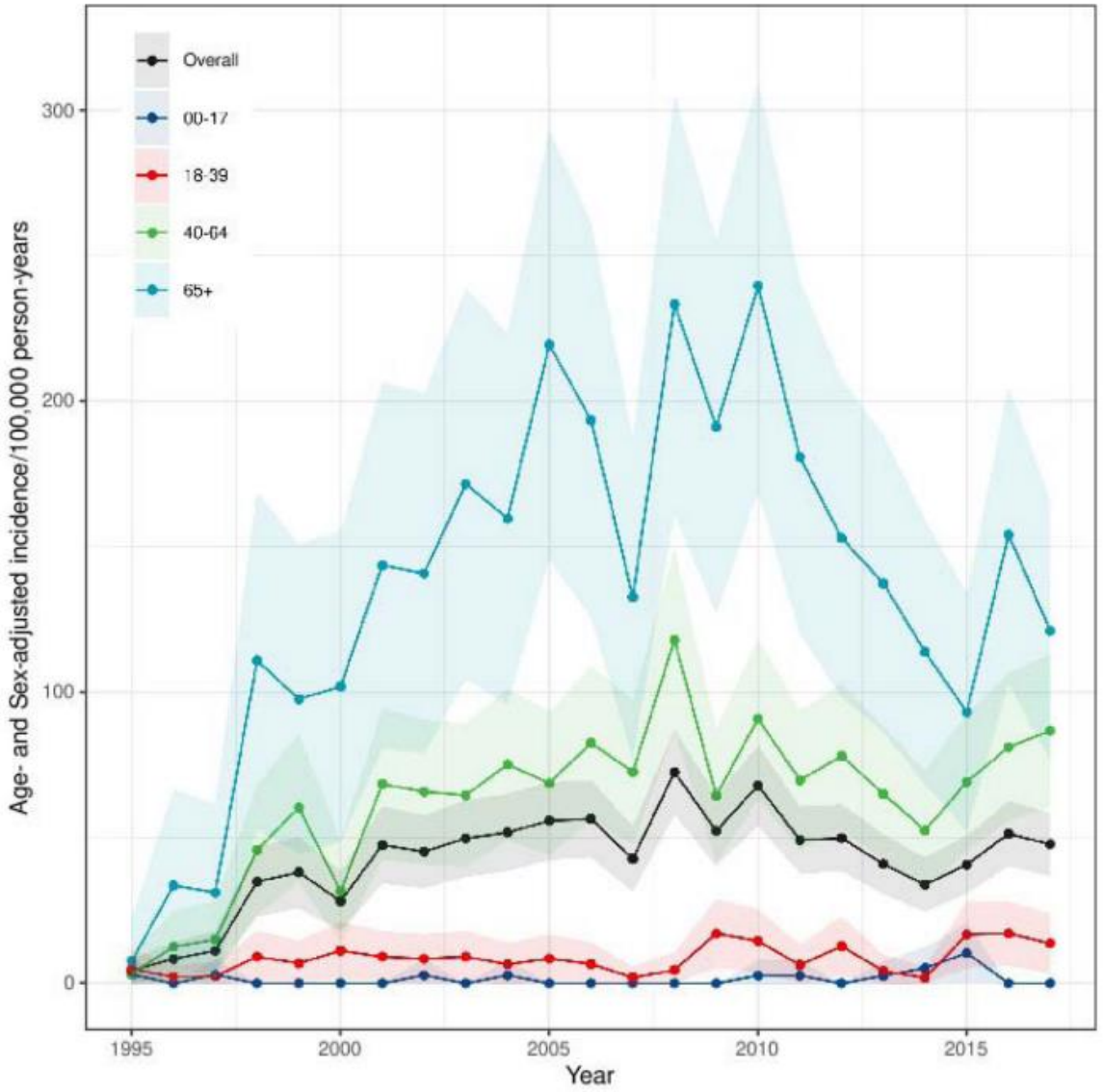
Adrenal Incidentaloma (AI)

Standardized Incidence Rate of Adrenal Tumor

Adrenal Tumors by Age and Sex

Incidence increased mostly in adults older than 40 years,
with relatively minor increases of SIR in younger adults and children

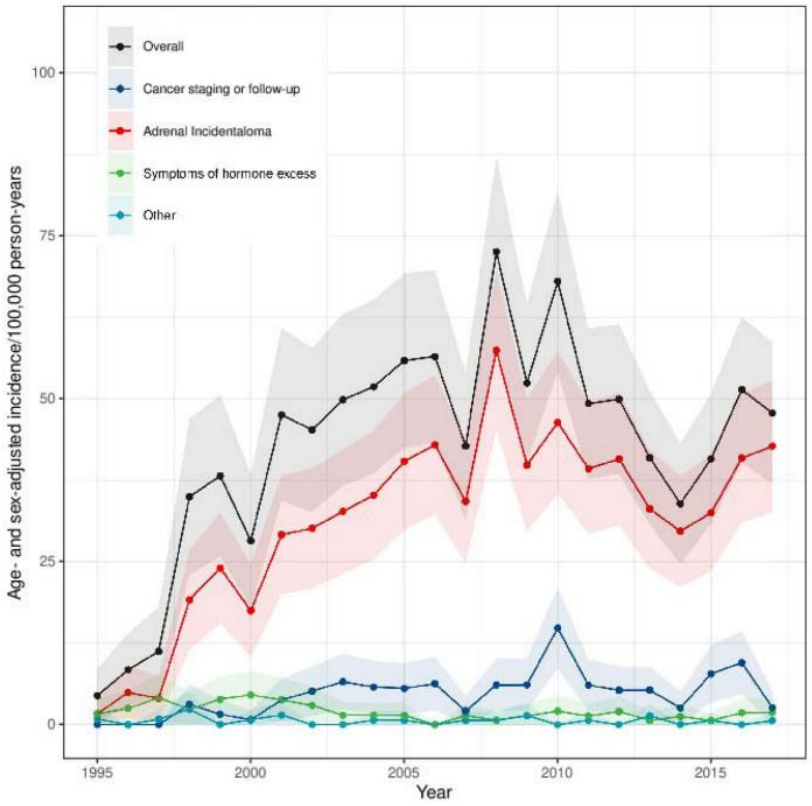
No sex differences in SIRs were observed



Ebbehoj et al. Lancet Diabetes Endocrinol. 2021

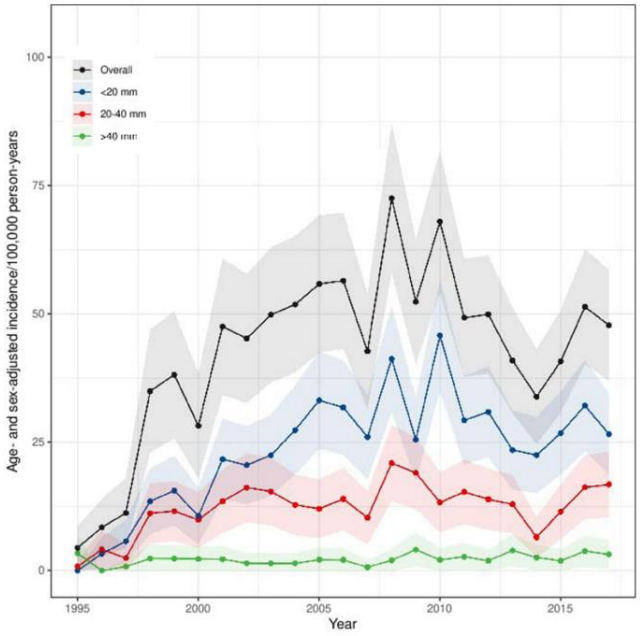
Standardized Incidence Rate of Adrenal Tumor

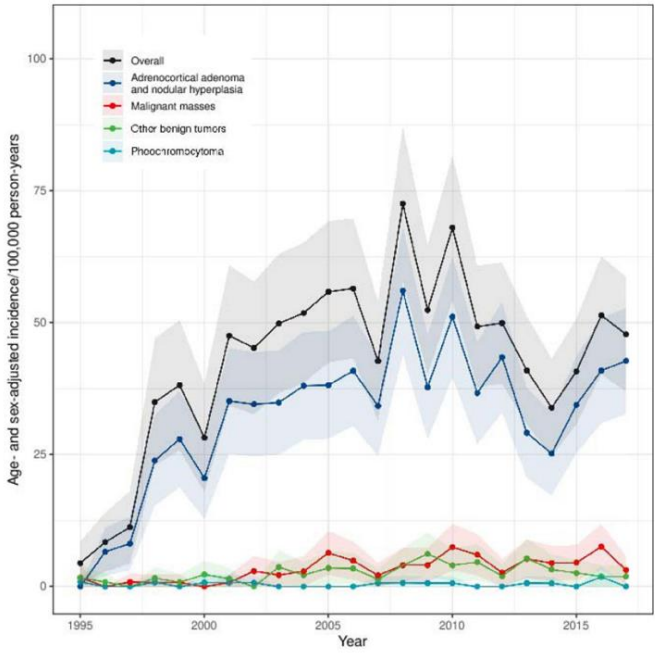
Adrenal Tumors by Mode of Discovery



Ebbehoj et al. Lancet Diabetes Endocrinol. 2021

Adrenal Tumors by Size and Tumor Type





The increase in incidence of adrenal tumors was mainly observed among **incidentally discovered tumors, smaller tumors,** and **benign adenomas without overt hormone excess**

Prevalence of adrenal tumors

- Highest among patients > 65 years (1,900 per 100,000 inhabitants, 95%CI 1,727–2,086)
- Lowest among children (13 per 100,000 inhabitants, 95%CI 4–30),
  (1% of all adrenal tumors diagnosed in patients <18 years)

Median age of diagnosis: 62 years

Minor sex differences (F 55%; M 45%)

Size and lateralization

- Mean diameter: 30 mm (8* - 230 mm)

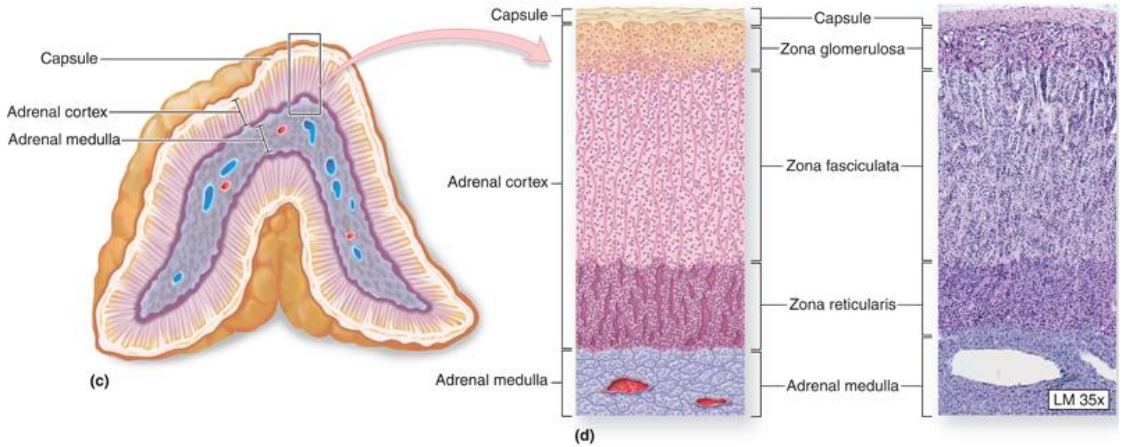
- Righ= Left
- Bilateral

*the 8-mm lesions reflect the results of older studies before adopting 1 cm as the threshold for the definition of an AI

Ebbehoj et al. Lancet Diabetes Endocrinol. 2021

Adrenal Incidentaloma (AI)

ETIOLOGY



Five categories:

(1) Adrenal adenomas and nodular hyperplasia
(2) Other benign lesions (myelolipomas, cysts, hematomas, other)
(3) Adrenocortical carcinomas (ACC)
(4) Other malignant tumors (metastases, sarcomas, lymphoma)
(5) Pheochromocytomas

Frequency of different type of Adrenal Incidentaloma

Tumor entity	Median (%)	Range (%)
Series including all patients with an adrenal mass*		
Adenoma	80	33–96
Nonfunctioning	75	71–84
Autonomously cortisol-secreting	12	1.0–29
Aldosterone-secreting	2.5	1.6–3.3
Pheochromocytoma	7.0	1.5–14
Adrenocortical carcinoma	8.0	1.2–11
Metastasis	5.0	0–18
Surgical series**		
Adenoma	55	49–69
Nonfunctioning	69	52–75
Cortisol-secreting	10	1.0–15
Aldosterone-secreting	6.0	2.0–7.0
Pheochromocytoma	10	11–23
Adrenocortical 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

Fassnacht M et al. Eur J Endocrinol 2016

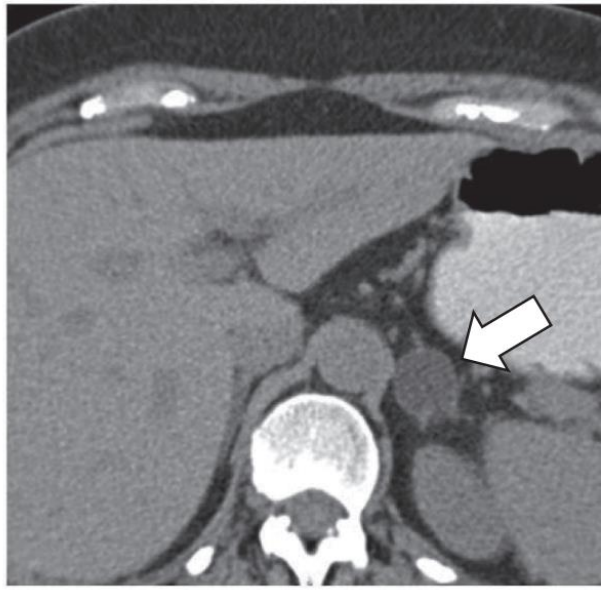
Adrenal Incidentaloma (AI)

Adrenal Adenoma

the majority of incidentally discovered adrenal tumors
in both the population setting (88%)
as well as in the endocrine clinic (81%-88%)

Median tumor size: 1.5 -2.5 cm
<4 cm in 95- 98%of cases
Bilateral in 15-20% of patients.

Non functioning:	40-50%
Cortisol secretion:	35-50% (MACSs)
	1-3% CS
Aldosterone excess	3-10%
Androgen excess	<0.1%



A. Adrenocortical adenoma

Imaging (unenhanced TC)
- lipid rich (HU <10) 60%
- HU: 10- 19 25%
- HU >20 15%

Adenomas with overt hormone excess are often diagnosed only after incidental discovery with adrenal mass, rather than upon presentation with features of Cushing's Syndrome or Aldosteronism

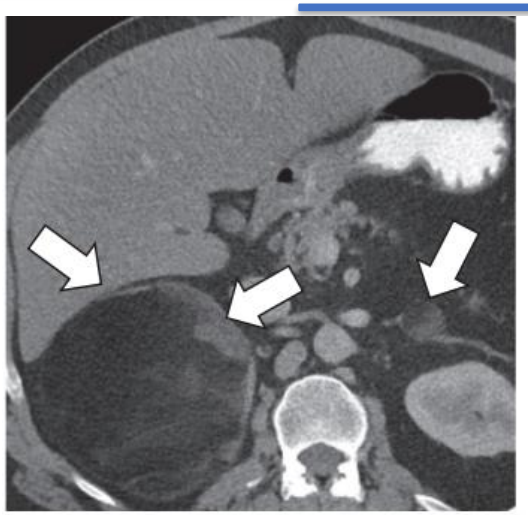
Bancos I & Prete A J Clin Endocrinol 2021

Myelolipoma and Other Benign Adrenal Masses

Myelolipoma: 3.3- 6.2% of patients with AI

Median size: 2 -2.5 cm (0.5 - >15 cm)
< 4 cm in 60% of cases

Bilateral: 5% of all patients
20% of patients with large tumors >6 cm.



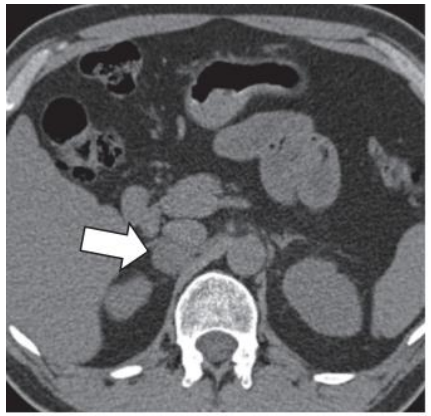
G. Myelolipoma

Benign Non-Cortical Adrenal Masses

1-3%

ganglioneuromas, cysts, hemangiomas, lymphangiomas, schwannomas

Variable imaging
diagnosis is frequently made on histology after adrenalectomy for a suspicious mass



H. Ganglioneuroma

Benign Adrenal Masses are Incidentally Discovered in 90% of cases

Malignant tumors

Adrenocortical Carcinoma (ACC)

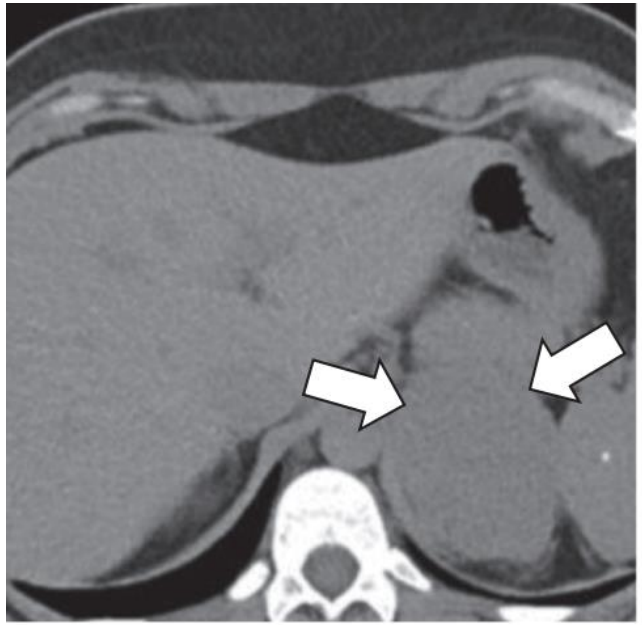
0.3% of all adrenal tumors
3.6% of malignant adrenal tumors in a population setting

5% of patients seen by endocrinologist

Median size: 10 cm
<4 cm in 1- 2% of cases

Bilateral < 0.1 %

ACC is discovered incidentally in 42 - 44% of cases



B. Adrenocortical carcinoma

Imaging (unenhanced TC) :
•Heterogeneous tumors
•HU > 20 (median 35 HU)
•HU 10-20 only 1%

Primary ACC
Rare
Incidence: 1-2 per million per year

Peak incidence: before the age of 5 and between the ages of 40 and 60 years of age

Sporadic in most cases

May occurs in genetic syndromes
- Li–Fraumeni syndrome (TP53 gene)
- Multiple Endocrine Neoplasia type I (MEN1 gene)
- Beckwith–Weidemann syndrome (abnormalities in 11p15I gene
- Familial adenomatous polyposis (FAP gene), neurofibromatosis type 1 (NF1 gene), and Carney complex (PRKAR1A gene)

Functional in 40-60% of cases
- Cushing's Syndrome 45%
- Glucocorticoids and androgens 25%
- Androgen-secretion 10%

Other malignant tumors (metastases, sarcomas, lymphoma)

Adrenal metastases

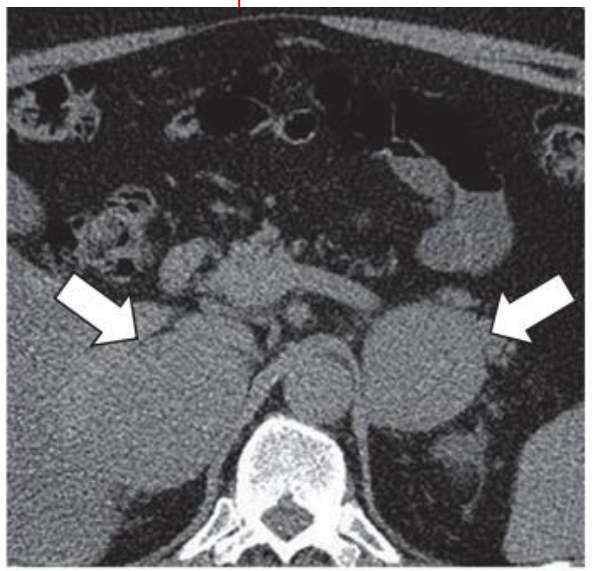
- lung, breast, ovarian, kidney and GI cancer, melanoma -

The most common etiology of a malignant adrenal mass,
- 7.5% of all adrenal tumors
- 86% of all malignant adrenal tumors in a population based study

Uncommon in the endocrine clinic: 1-3%
(only 25% of patients with adrenal metastasis undergo endocrine work up)

Median mass size: 3 cm (0.5 - 20 cm)
< 4 cm in 60% of cases

Bilateral adrenal metastases are common
24% at initial diagnosis
43% during follow-up



D. Bilateral metastases

Imaging (unenhanced TC) :
HU > 20 96-98%

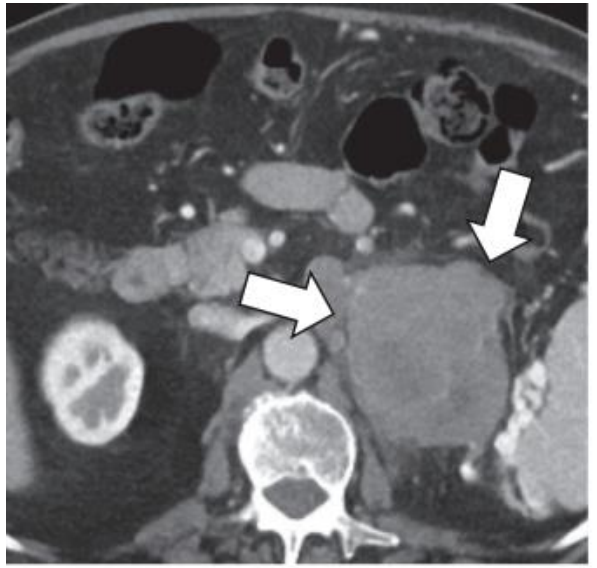
Preclinical or symptomatic primary adrenal insufficiency in 12% of patients

Other malignant tumors

Adrenal lymphoma

Adrenal gland involvement in up to 25% of patients with non-Hodgkin lymphoma usually as part of disseminated disease.

Primary adrenal lymphoma is rare



F. Lymphoma

Pheochromocytoma

- 1.1% (population setting)
- 4 - 8.5% (endocrine setting)

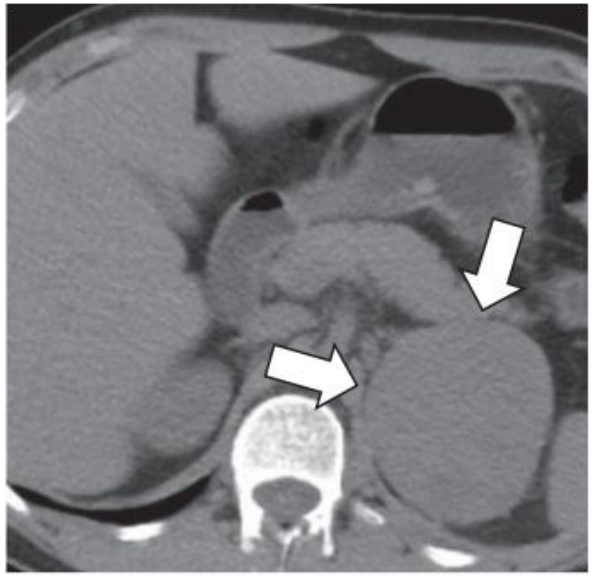
Median size: 4 - 5 cm
< 4 cm in 45% of cases *

Bilateral: 4% to 10% of cases *

**Diagnosis of pheochromocytoma*

•symptoms of catecholamine excess	27%
•**incidentally discovered**	**61%**
•genetic case detection testing	12%

**smaller and often bilateral in genetic forms*



C. Pheochromocytoma

Imaging (unenhanced TC) :
HU > 20 ⇒ 92%
HU: 10 -20 ⇒ 8%

4% of pheochromocytomas may be biochemically silent

Genetic disorders associated with pheochromocytomas

	gene
•Multiple endocrine neoplasia type 2	**RET**
•Von Hippel–Lindau disease	**VHL**
•Paraganglioma syndrome type 1	**SDHD**
•Paraganglioma syndrome type 4	**SDHB**
•Paraganglioma syndrome type 2	SDHAF1
•Paraganglioma syndrome type 3	SDHC
•Paraganglial tumors	TMEM127
•Paraganglial tumors	MAX
•Paraganglial tumors	SDHA

Genetic disorders associated with both pheochromocytomas and adrenocortical tumors

•Neurofibromatosis type 1	**NF1**

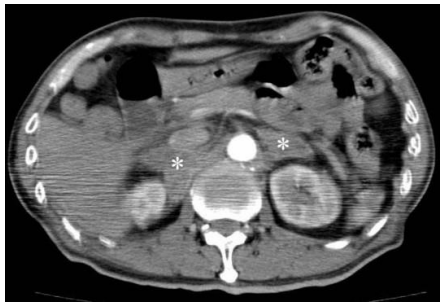
Bilateral adrenal masses (up to 15-20% of AI)

The most likely diagnoses are

- Metastatic diseases
- Bilateral cortical adenomas
- Primary bilateral macronodular adrenal hyperplasia (PBMAH)
- Congenital adrenal hyperplasia (CAH)
- Pheochromocytoma
- Infiltrative diseases
- Infection (tubercolosis, fungal), hemorrhage

In oncological patients

40–75% of adrenal incidentalomas are metastases



bilateral adrenal enlargement consistent with lung cancer metastases

Unknown primary cancer may present as

- Bilateral adrenal masses in 5.8% of cases
- Monolateral adrenal mass in 0.2%

Genetic disorders associated with adrenocortical adenomas only

PBMAH from ARMC5 mutations — ARMC5 (autosomal dominant)

Partial glucocorticoid resistance associated with bilateral adrenal hyperplasia
Heterozygous mutations of NR3C1, encoding for the glucocorticoid receptor

Genetic disorders associated with both adrenocortical adenomas and carcinomas

Multiple endocrine neoplasia syndrome type 1 — MEN1 (autosomal dominant)

Familial adenomatous polyposis — APC (autosomal dominant)

Adrenal Incidentaloma (AI)

The finding of an adrenal mass is frequent
especially after the age of 50 yrs

Only 3.3% of all adrenal incidentalomas are malignant,
compared with

43% of adrenal tumors discovered on cancer staging imaging in those with history of extra-adrenal malignancy

Of all patients discovered with an adrenal mass,
only **3%** are diagnosed based on symptoms of overt hormone excess

GRAZIE A TUTTI
PER
L’ATTENZIONE