FOLLOW UP DELL'INCIDENTALOMA SURRENALICO: QUANDO E COME TRATTARE

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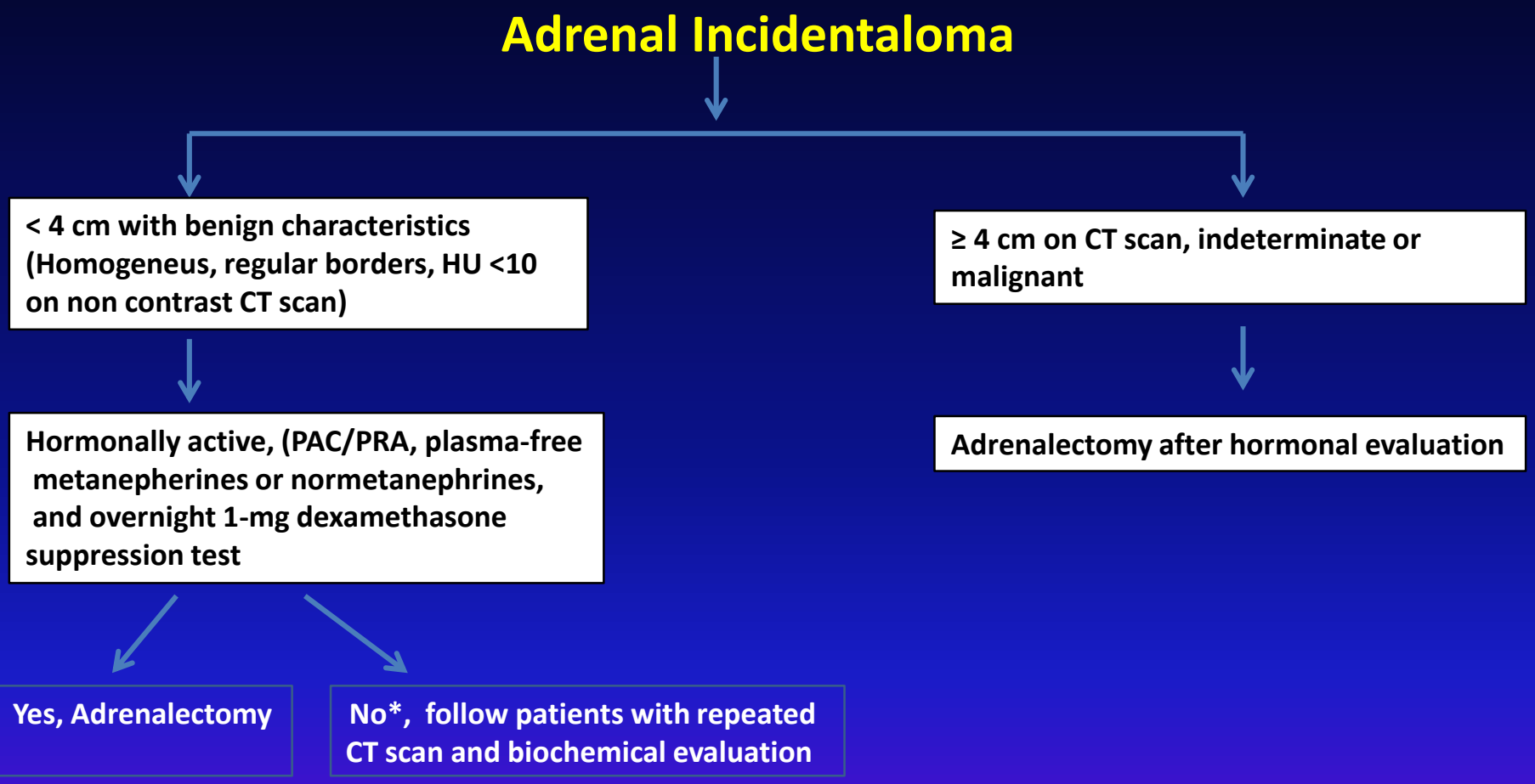
Algorithm for the evaluation and management of an adrenal incidentaloma



*Reimage in 3 to 6 months and annually for 1 to 2 years; repeat functional studies annually for 5 years. If mass grows more than 1 cm or becomes hormonally active, then adrenalectomy is recommended.

Il trattamento del paziente con incidentaloma surrenalico

- in età geriatrica va valutato in rapporto alle indagini sia di laboratorio che d'imaging più valide (RM, CT, PET con fluoro-desossi-glucosio) in modo da proporre la terapia chirurgica ai pazienti che rispondano in modo anomalo al test di soppressione con desametasone o abbiano valori anomali di cortisolo e ACTH.
- Potrà invece essere programmata una terapia conservativa se il paziente presenta solo un test di soppressione alterato o è asintomatico.

Trattamento dell'Incidentaloma Surrenalico

- Oggi la laparoscopia con accesso transperitoneale o retroperitoneoscopico, pur con un allungamento dei tempi operatori, è generalmente accettata quale metodica di scelta;
- Presenta poche controindicazioni che necessitano del convenzionale approccio aperto
  - un carcinoma che invade le strutture anatomiche circostanti
  - il feocromocitoma maligno
  - le neoplasie di diametro superiore a 10 cm
  - pazienti con patologie emocoagulative o con briglie aderenziali postoperatorie.
- Per lesioni fino a 4 cm di diametro la laparoscopia rappresenta il gold standard perché tecnica sicura, efficace e minimamente invasiva che permette scarso dolore postoperatorio, breve durata dell'allettamento e del ricovero postoperatorio, precoce ripresa dell'alimentazione, delle normali attività della vita sociale e di relazione.

Trattamento dell'incidentaloma surrenalico

An important issue in resection of functioning adrenal masses is **steroid suppletion peri- and postoperatively**, because of the risk of adrenal insufficiency, hemodynamic crisis and death. In most cases this can be tapered over time.

Pre-op Management Of Pheocromocytoma

- Early alpha blockade???
- Goal to control hypertension- phenoxybenzamine
- Do NOT use b-blocker before alpha
- IV hydration
- Prevent cardiac arrhythmias

Pheochromocytoma

Post-op

- hypotension (most common) secondary to hypovolemia

Surgical outcomes

-excision does NOT always lead to long-term cure

recurrence

5% benign
10% malignant

Subclinical Hypercortisolism

The classical triad commonly used to define SH is:

1. Alterations of the hypothalamus–pituitary–adrenal axis
2. Incidentally discovered adrenal masses
3. No signs and symptoms specific of overt Cushing's syndrome.

Di Dalmazi et. Al. Eur j Endocrinol 2015 Oct;173(4):M61-71.

Comorbidities in SCS

- SH has been associated with several metabolic and cardiovascular co-morbidities, even if there are contrasting results in the literature published up to now.
- The most common metabolic and cardiovascular correlates reported in patients with this condition are hypertension and impairment of glucose metabolism, mainly type 2 diabetes (T2D)

Inquadramento Clinico dell'Incidentaloma Surrenalico

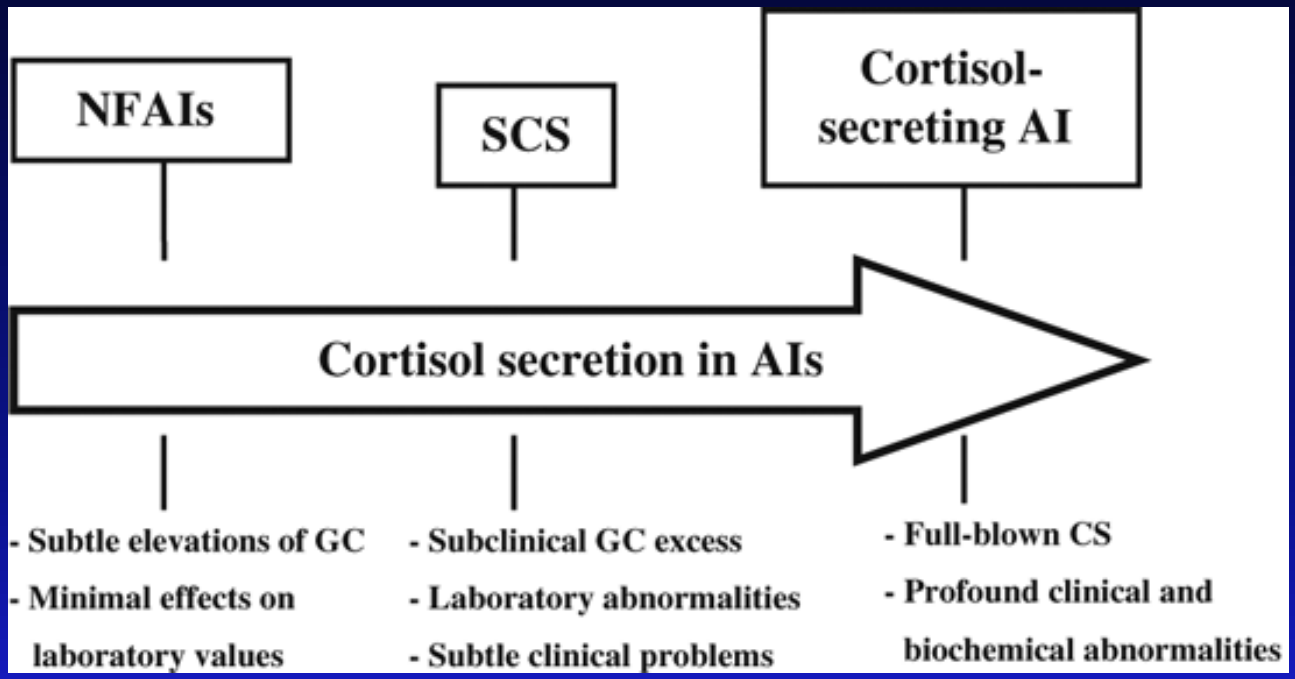
Clinical features in patients with NFAI

A growing body evidence supports the notion that also nonfunctioning adrenal incidentalomas (NFAI) are associated with **features of metabolic syndrome**

Authors (year of publication)	Number of patients examined	Type of AI based on endocrine activity	Cardiometabolic abnormalities associated with AIs
Ivović *et al.* (2006)	$n = 22$	NFAIs	Impaired insulin sensitivity
Zhang *et al.* (2006)	$n = 24$	NFAIs	Abdominal obesity, hypertension, dyslipidaemia, hyperglycaemia
Comlekci *et al.* (2009)	$n = 376$	NFAIs (predominantly)	Type 2 diabetes, hypertension, hyperlipidaemia
Yilmaz *et al.* (2009)	$n = 32$	NFAIs	Obesity, hypertension, impaired glucose tolerance
Wagnerova *et al.* (2009)	$n = 92$	NFAIs (predominantly)	Obesity, hypertension, diabetes
Yener *et al.* (2009)	$n = 49$	NFAIs	Increased carotid intima–media thickness
Yener *et al.* (2009)	$n = 45$	NFAIs	Increased D-dimer levels
Peppa *et al.* (2010)	$n = 29$	NFAIs	Impaired fasting and postabsorptive glucose, obesity, hypertension, dyslipidaemia, fatty liver disease, abnormal fat distribution

Peppa M et al. J Int Med 2010

Adrenal incidentalomas and cardiometabolic morbidity: an emerging association with serious clinical implications



Peppa M[1], Koliaki C, Raptis SA
Journal of Internal Medicine Volume 268, Issue 6, pages 555-566, 22 OCT 2010

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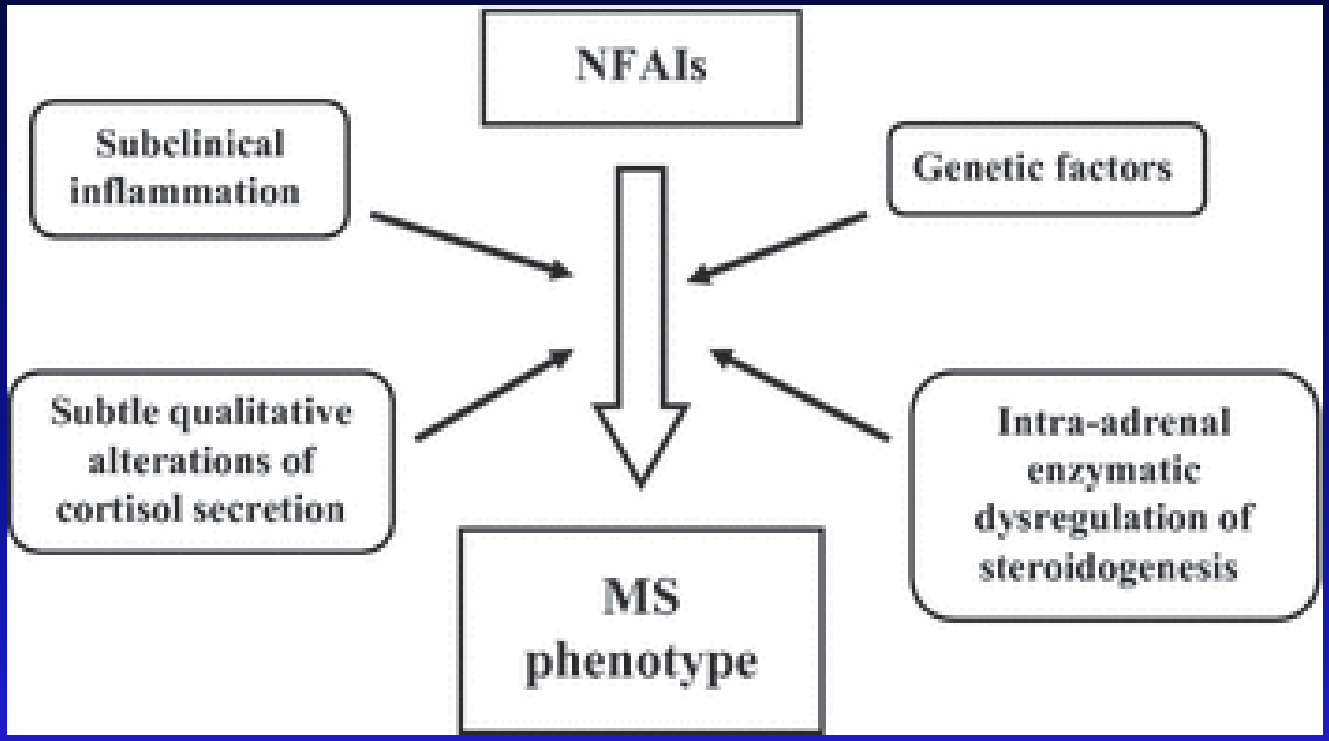

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Inquadramento Clinico dell'Incidentaloma Surrenalico

Impact of surgical intervention on cardiometabolic outcome

Removal of adrenal mass in patients with SCS

is associated with

SIGNIFICANT **IMPROVEMENT**
in
ALL (or some=BP)
Features of Metabolic Syndrome

Erbil et al. 2006 (n 11, follow-up 1 yr)
Toniato et al. 2009 (n 23, mean follow-up 7.7 yr)
Mauclère-Denost et al. 2009 (n 8, mean follow-up 12 mo)
Guerrieri et al. 2010 (n 19, mean follow-up 4 yr)
Chiodini et al. 2010 (n 25, follow-up 18-48 mo)

No effect on cardiometabolic outcome

- *only a minority of operated patients had SCS*

Sereg et al. 2009 [n 47 (5 SCS) mean follow-up: 9.1 yr (5-16)]

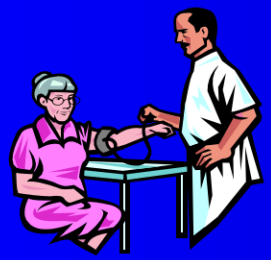
Inquadramento Clinico dell'Incidentaloma Surrenalico

Impact of surgical intervention on cardiometabolic outcome

Conservative approach

Not operated patients with SCS

experienced



worsening
of
- blood pressure
- body weight
- glucose and cholesterol levels

Guerrieri et al. 2010
Chiodini et al. 2010

Natural history of AI

Follow-up of adrenal incidentaloma thought to be benignant and non-functioning after the initial diagnostic work-up

11 studies (>20 pts/study) including 1410 patients, with mean follow-up of 3.2 yr (range 1-7, median 2.1)

	mean	range	median
Increased in size (%)	**14.7**	**0-41.5**	**14.1**
Decreased in size (%)	**7.0**	**0-44**	**0**
Became malignant (%)	**0.2**	**0-1.6**	**0**
Developed ACC (%)	**0**	**0**	**0**
Developed metastases (%)	**0.1**	**0**	**0**
Became functional (%)	**0.9**	**0-8**	**0**
Developed overt CS (%)	**0.3**	**0-2.7**	**0**
Developed SCS (%)	**0.3**	**0-4**	**0**
Developed pheochromocytoma (%)	**0.2**	**0-1.3**	**0**
Developed aldosteronoma (%)	**0**	**0**	**0**

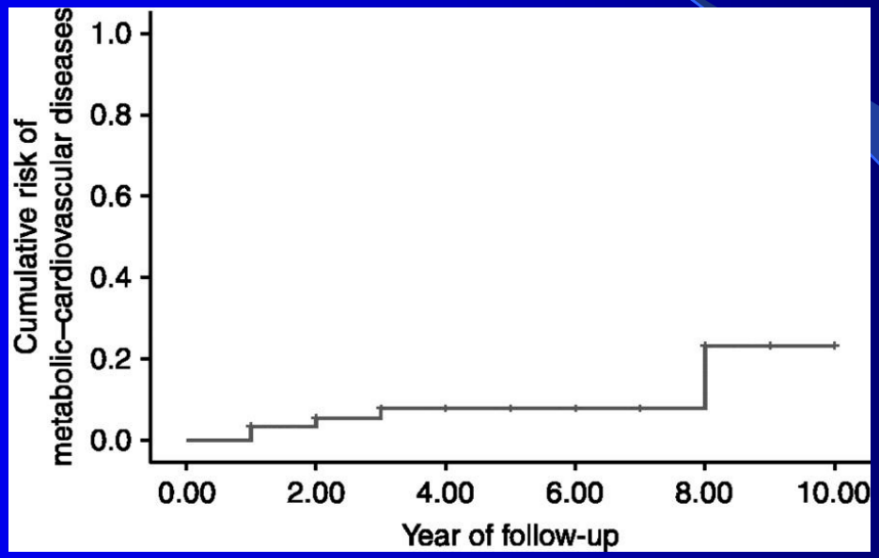
Adapted from Cawood TJ et al Eur J Endocrinol 2009

Inquadramento Clinico dell'Incidentaloma Surrenalico

Natural history of AI

Estimated cumulative risk of developing metabolic-cardiovascular disease overtime in patients with adrenal incidentalomas (n=118)

102 NFAI - 16 SCS



The cumulative risk of developing metabolic-cardiovascular abnormalities was globally low (22%), but progressive up to 8 years

New diseases were recorded only in the group of NFAI
(3 dyslipidemia, 4 impaired fasting glucose/impaired glucose tolerance, 3 diabetes mellitus)

None of NF patients developed subclinical or overt endocrine disease
None of SCS patients shifted to overt Cushing's syndrome

Giordano R et al. Eur J Endocrinol 2010;162:779

EFE 2012

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
Arnaldi, 2012	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

Arnaldi G & Boscaro M . Best Pract Clin Endocrinol Metab 2012

Radiation Dose Assessment
American College of Radiologist

- Many of the diagnostic imaging examinations in the ACR guidelines involve exposure of patients to ionizing radiation from radioactive materials or x-rays
- Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure

Table 1. Relative radiation level designations along with common example examinations for each classification

Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range	Example Examinations
O	0	0 mSv	Ultrasound; MRI
☢	<0.1 mSv	<0.03 mSv	Chest radiographs; Hand radiographs
☢☢	0.1-1 mSv	0.03-0.3 mSv	Pelvis radiographs; Mammography
☢☢☢	1-10 mSv	0.3-3 mSv	Abdomen CT, Nuclear medicine bone scan
☢☢☢☢	10-30 mSv	3-10 mSv	Abdomen CT without and with contrast; Whole body PET
☢☢☢☢☢	30-100 mSv	10-30 mSv	CTA chest abdomen and pelvis with contrast; Transjugular intrahepatic portosystemic shunt placement

*The RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, the region of the body exposed to ionizing radiation, the imaging guidance that is used, etc.). The RRLs for these examinations are designated as "Varies."

American College of Radiologists
Appropriateness Criteria Incidentally Discovered Adrenal Mass

Variant 1: No history of malignancy; mass 1 to 4 cm in diameter. Initial evaluation.

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen without contrast	8	Presumes that a noncontrast CT has not already been performed and that there are no suspicious imaging features. Should be evaluated by radiologist to determine if contrast administration is needed.	☢☢☢
CT abdomen without and with contrast	8	Indicated if noncontrast CT is not diagnostic or if there are concerning imaging features of malignancy. Delayed imaging obtained to calculate washout.	☢☢☢☢
MRI abdomen without contrast	8	May be helpful when nonenhanced CT is equivocal or if there are suspicious imaging features. Appropriate for patient with iodinated contrast allergy.	O
MIBG	2	Only for suspicion of pheochromocytoma.	☢☢☢
MRI abdomen without and with contrast	2		O
US adrenal gland	1		O
Biopsy adrenal gland	1		Varies
CT abdomen with contrast	1		☢☢☢
X-ray abdomen	1		☢☢
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	☢☢☢☢
FDG-PET/CT skull base to mid-thigh	1		☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

National Guideline Clearinghouse. Revised 2012

American College of Radiologists
Appropriateness Criteria Incidentally Discovered Adrenal Mass

Variant 2: No history of malignancy; mass 1 to 4 cm in diameter. Follow-up evaluation for indeterminate lesion on initial evaluation.

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen without contrast	8	Alternative to MRI without contrast to assess for size change in 12 months.	☢☢☢
MRI abdomen without contrast	8	Alternative to CT without contrast to assess for size change in 12 months.	O
MRI abdomen without and with contrast	1		O
CT abdomen with contrast	1	Contrast unnecessary to assess for size change.	☢☢☢
CT abdomen without and with contrast	1		☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

National Guideline Clearinghouse. Revised 2012

American College of Radiologists
Appropriateness Criteria Incidentally Discovered Adrenal Mass

Variant 3: No history of malignancy; mass >4 cm in diameter. (If not typical for adenoma, myelolipoma, hemorrhage, or simple cyst, consider resection.)

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen with contrast	8	As part of preoperative staging. Alternative to MRI.	☢☢☢
MRI abdomen without and with contrast	8	As part of preoperative staging. Alternative to CT. See statement regarding contrast in text under "Anticipated Exceptions."	O
FDG-PET/CT skull base to mid-thigh	5	As part of preoperative staging.	☢☢☢☢
MIBG	2	Only for suspicion of pheochromocytoma.	☢☢☢
CT abdomen without and with contrast	2		☢☢☢☢
MRI abdomen without contrast	1		O
US adrenal gland	1		O
CT abdomen without contrast	1		☢☢☢
X-ray abdomen	1		☢☢
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	☢☢☢☢
Biopsy adrenal gland	1		Varies
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

National Guideline Clearinghouse. Revised 2012

American College of Radiologists
Appropriateness Criteria Incidentally Discovered Adrenal Mass

Variant 4: History of malignancy; mass <4 cm in diameter. Initial evaluation.

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen without contrast	8	Should be evaluated by radiologist to determine if contrast administration is needed.	☢☢☢
CT abdomen without and with contrast	8	Indicated if noncontrast CT is indeterminate (attenuation >10 HU) or lesion does not lose signal on out-of-phase images. Delayed imaging obtained to calculate washout.	☢☢☢☢
MRI abdomen without contrast	8	Alternative to CT without contrast.	O
FDG-PET/CT skull base to mid-thigh	8	Alternative to CT and MRI.	☢☢☢☢
Biopsy adrenal gland	5	A biopsy should only be performed for mass with suspicious imaging characteristics that cannot be characterized as benign and if pheochromocytoma is excluded. CT or US guidance could be used.	Varies
MIBG	2	Only for suspicion of pheochromocytoma.	☢☢☢
MRI abdomen without and with contrast	1		O
US adrenal gland	1		O
CT abdomen with contrast	1		☢☢☢
X-ray abdomen	1		☢☢
Iodocholesterol scan	1	This agent may be used to detect functionally active adenomas.	☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

National Guideline Clearinghouse. Revised 2012

American College of Radiologists
Appropriateness Criteria Incidentally Discovered Adrenal Mass

Variant 5: History of malignancy; mass >4 cm in diameter.

Radiologic Procedure	Rating	Comments	RRL*
Biopsy adrenal gland	8		Varies
FDG-PET/CT skull base to mid-thigh	8	Alternative to biopsy to diagnose metastasis.	☢☢☢☢
MRI abdomen without and with contrast	1		O
MRI abdomen without contrast	1		O
US adrenal gland	1		O
CT abdomen with contrast	1		☢☢☢
CT abdomen without contrast	1		☢☢☢
MIBG	1		☢☢☢
X-ray abdomen	1		☢☢
CT abdomen without and with contrast	1		☢☢☢☢
Iodocholesterol scan	1		☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

National Guideline Clearinghouse. Revised 2012