



ASSOCIAZIONE MEDICI
ENDOCRINOLOGI
PER LA QUALITÀ CLINICA



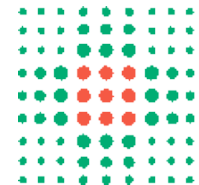
**1° CONVEGNO AME
EMILIA-ROMAGNA**

Bologna, 15 Maggio 2010

Incidentaloma surrenalico non secernente: quale follow up ?

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Il follow up degli incidentalomi surrenalici non secernenti ha lo scopo di verificare

- l'evoluzione a una forma ipersecernente
- la trasformazione maligna (di solito associata a un incremento dimensionale)

Piramide delle evidenze



Pubblicazioni primarie :

- studi osservazionali
- analisi rapporto costi/benefici

Pubblicazioni secondarie :

- revisioni narrative con “grading” delle evidenze
(UpToDate)

Consensus di esperti :

NIH state of science 2002

Statement AME 2008

- **NIH State-of-the-Science**

Statement on Management of the Clinically Inapparent Adrenal Mass (“Incidentaloma”) Volume 19, Number 2 February 4–6, 2002

The low prevalence of adrenal cortical carcinomas and the relatively low incidence of progression to hyperfunction call into question the advisability of the current practice of intense, longterm clinical follow-up of this common condition.

Data are insufficient to indicate the superiority of a surgical or nonsurgical approach to manage patients with subclinical hyperfunctioning adrenal cortical adenomas

Unfortunately, the lack of controlled studies makes formulating diagnostic and treatment strategies difficult. The paucity of evidence-based data highlights the need for well-designed prospective studies.



AME Position Statement

ADRENAL INCIDENTALOMAS



Torino 10-12 ottobre 2008

What is the risk of malignant transformation ?

- ✓ The risk of malignant transformation at long-term follow-up for untreated adrenal masses defined as benign at diagnosis is very low, and is estimated to be about 1:1000 incidentalomas.
- ✓ In 5-20% of cases mass size increases over time, however most growing adrenal masses are not malignant.
- ✓ Presence of endocrine abnormalities could be considered a risk factor for mass enlargement.

What is the risk of evolution toward overt hypersecretion?

- ✓ The occurrence of silent biochemical alterations during follow-up has been reported in a percentage ranging from 0 to 11% across different studies.
- ✓ The risk of progression from subclinical to overt Cushing's syndrome is minimal (< 1% of cases).
- ✓ The risk of developing hyperfunction is unlikely in lesion smaller than 3 cm and appears to plateau after 3-4 years.
- ✓ A spontaneous regression of the alterations of the HPA axis may be observed, suggesting that cortisol output may have a cyclical or intermittent pattern.

Evidenze in letteratura riguardanti le raccomandazioni cliniche correnti sul follow up relative a :

- utilizzo della diagnostica per immagini.
- studio della funzione ormonale
- utilità e superiorità in termini di rapporto costo-efficacia e di rischi/ benefici di un approccio rispetto a un altro

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- **Da UpToDate :**

Recommendation grades

- 1. Strong recommendation: Benefits clearly outweigh the risks and burdens (or vice versa) for most, if not all, patients
- 2. Weak recommendation: Benefits and risks closely balanced and/or uncertain

Evidence grades

- A. High-quality evidence: Consistent evidence from randomized trials, or overwhelming evidence of some other form
- B. Moderate-quality evidence: Evidence from randomized trials with important limitations, or very strong evidence of some other form
- C. Low-quality evidence: Evidence from observational studies, unsystematic clinical observations, or from randomized trials with serious flaws

- **Da UpToDate** (vers.17.3 liter .review:Oct '09)

Follow-up

- We suggest repeat imaging studies at 6, 12, and 24 months. The yield and cost effectiveness of such a strategy are not known ([Grade 2C](#)).
- We suggest removal of any tumor that enlarges by more than 1 cm in diameter during the follow-up period ([Grade 2C](#)).

- **Da UpToDate (vers.18.1 liter .review: Febr. '10)**

Follow-up

- We suggest a repeat imaging study at six to 12 months after initial discovery ([Grade 2C](#)). Whether an additional imaging procedure is obtained at 24 months and the type of image obtained (eg, CT, MRI, or ultrasound) should be guided by clinical judgment and imaging phenotype. The yield and cost effectiveness of such a strategy are not known.
- We suggest removal of any tumor that enlarges by more than 1 cm in diameter during the follow-up period ([Grade 2C](#)).

- Da “UpToDate :

Follow-up (vers.17-3 - 18.1)

- We recommend repeat imaging at three months in cases where the imaging phenotype is suspicious; the rationale is that many malignant lesions will grow in this interval, leading to earlier intervention ([Grade 1C](#)).



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IMAGING ASSESSMENT

- **We recommend against US as the unique imaging technique to characterize an adrenal incidentaloma ⊕ ⊕**
US may be useful in the follow-up of masses > 3 cm to reduce radiation exposure and costs.
- **We recommend unenhanced CT as the initial imaging procedure. ⊕ ⊕**
- **We suggest to consider an attenuation value of 10 HU to differentiate adenomas from non-adenomas. ⊕**
- **We suggest delayed contrast-enhanced CT studies when baseline density is > 10 HU. ⊕**
Assessment of contrast wash-out is able to identify lipid-poor adenomas from nonadenomas.

In sintesi, vengono suggerite :

scelta della diagnostica che fornisce lo stesso grado di informazione con minori effetti collaterali e costi (es. ecografia rispetto a TC senza mdc, TC senza mdc rispetto a mdc , RMN)

frequenza ravvicinata se rimangono incertezze ,
più dilazionata se caratteristiche benigne e definite della formazione (mediamente 6 – 12 mesi)

utilizzo della diagnostica per immagini

studio della funzione ormonale

utilità e superiorità in termini di rapporto
costo-efficacia e rischi/ benefici di un
approccio rispetto a un altro

Da “UpTodate :

Follow-up (vers.17-3 e18.1)

We suggest that hormonal testing be repeated annually for at least four years in cases where initial evaluation is negative, although the yield and cost effectiveness of such testing is also unknown. ([Grade 2C](#)).

However, autonomous function (glucocorticoid and catecholamine) not present at baseline may be detected at follow-up testing.



AME Position Statement

ADRENAL INCIDENTALOMAS



Torino 10-12 ottobre 2008

What is the diagnostic accuracy of the various biochemical tests used to detect functional autonomy of adrenal incidentalomas?

- ✓ There is no direct head-to-head comparison of the diagnostic accuracy of different DSTs, or different thresholds, to establish a gold standard for screening SCS. Moreover, there is insufficient data linking patient's outcome to the appointed diagnosis.
- ✓ It seems biologically plausible to consider that cortisol levels after DST lower than 1.8 $\mu\text{g/dl}$ clearly exclude autonomous cortisol secretion, whereas cortisol levels higher than 5 $\mu\text{g/dl}$ likely indicate SCS if no interfering conditions are present. Cortisol values after DST between 1.8 $\mu\text{g/dl}$ and 5 $\mu\text{g/dl}$ are indeterminate.

What is the diagnostic accuracy of the various biochemical tests used to detect functional autonomy of adrenal incidentalomas?

- ✓ Evaluation of 24h UFC excretion, midnight serum cortisol, plasma ACTH, or repeat DST after 3-6 months to confirm unsuppressibility (use of the standard 2-day low-dose DST or high-dose DST may be advocated in this context) are all plausible alternatives.
- ✓ Evaluation of UFC and ACTH are associated with technical problems and the high dose DST suppression tests have not been extensively employed for screening purpose.
- ✓ The 2 mg DST (LDDST) may be considered as a confirmatory procedure, but it is more difficult to perform in clinical practice.
- ✓ At present, the late night salivary cortisol cannot be included in the screening procedures for SCS until more data will become available.

What are the morbidity and the mortality of subclinical Cushing's syndrome (SCS)?

- ✓ The long-term complications, if any, of SCS remain virtually unknown.
- ✓ An increased frequency of hypertension, central obesity, impaired glucose tolerance, diabetes, hyperlipemia and osteoporosis has been described in patients with SCS, but there are no longitudinal studies addressing the progression over time of metabolic derangements that could be attributable to SCS
- ✓ There is little evidence of a relatively high mortality rate due to cardiovascular disease in these patients, but the issue of patient outcome remains unanswered by published studies.

- utilizzo della diagnostica per immagini
- studio della funzione ormonale
- utilità e superiorità in termini di rapporto costo-efficacia e di rischi/ benefici di un approccio rispetto a un altro

Perché un approccio e non un altro ?

Criteri di scelta:

- Prevenzione di morbidità e/o mortalità
- Precocità diagnostica di patologia clinicamente rilevante
- Riduzione di rischi o effetti collaterali
- Riduzione dei costi

MISURE DI ESITO :

- Clinico(mortalità, eventi morbosi, parametri di laboratorio)
- Economico (direttamente correlato alla clinica, come ospedalizzazione, terapia farmacologica, visite mediche; indirettamente correlato come perdita di giorni lavorativi; intangibile come “ stress, ansia, dolore “)
- Umanistico (qualità di vita, cenestesi, presenza di sintomi, soddisfazione del paziente)

Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink?

- [Cawood TJ](#), [Hunt PJ](#), [O'Shea D](#), [Cole D](#), [Soule S](#).
- Department of Endocrinology, Christchurch Hospital, Private Bag 4710, Christchurch, New Zealand. tom.cawood@cdhb.govt.nz
- Eur J Endocrinol. 2009 Oct;161(4):513-27. Epub 2009 May 13.

The most complete analysis of this issue :

- a review of all 828 published articles on adrenal incidentalomas from 1980 to 2008 . Only 20 of the 828 articles were selected as having met the strict criteria for a "true" adrenal incidentaloma; of these, only 9 had adequate data on both diagnosis and follow-up.
- Patients who were suspected as having cancer were excluded. 1800 patients in these 9 series,

OBJECTIVE: To assess the performance of current clinical recommendations for the evaluation of an adrenal incidentaloma.

RESULTS: The prevalence of functional and malignant lesions presenting as adrenal incidentaloma was similar to that quoted in most reviews, other than a lower incidence of adrenal carcinoma (1.9 vs 4.7%) and metastases (0.7 vs 2.3%); pheochromocytoma 3.1 %, primary aldosteronism 0.6 %

- The development of functionality or malignancy during follow-up was rare (<1% becoming functional and 0.2% becoming malignant).
- During follow-up, false-positive rates of the recommended investigations are typically 50 times greater than true positive rates.
- The average recommended computed tomography (CT) scan follow-up exposes each patient to 23 mSv of ionising radiation, equating to a 1 in 430 to 2170 chance of causing fatal cancer.

CONCLUSION: Current recommendations for evaluation of adrenal incidentaloma are likely to result in significant costs, both financial and emotional, due to high false-positive rates.

- The dose of radiation involved in currently recommended CT scan follow-up confers a risk of fatal cancer that is similar to the risk of the adrenal becoming malignant. This argues for a review of current guidelines.

CONCLUSIONI :

- Falso positivo 50 volte > vero positivo
- Esposizione a radiazioni ionizzanti
- Alto costo
- Ansia per sospetta neoplasia non confermata



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HOW TO FOLLOW-UP?

We suggest to consider adrenalectomy in patients with nonfunctioning tumors showing clinical worsening despite optimal medical treatment and progression of hormonal status (catecholamine, mineralocorticoid secretion). ⊕

STOP TO FOLLOW UP ?

- **NIH State-of-the-Science**

**Statement on Management of the Clinically
Inapparent Adrenal Mass (“Incidentaloma”)**

.....

- In patients with tumors that remain stable on two imaging studies carried out at least 6 months apart and do not exhibit hormonal hypersecretion over 4 years, further follow up may not be warranted.....

HOW TO FOLLOW-UP?

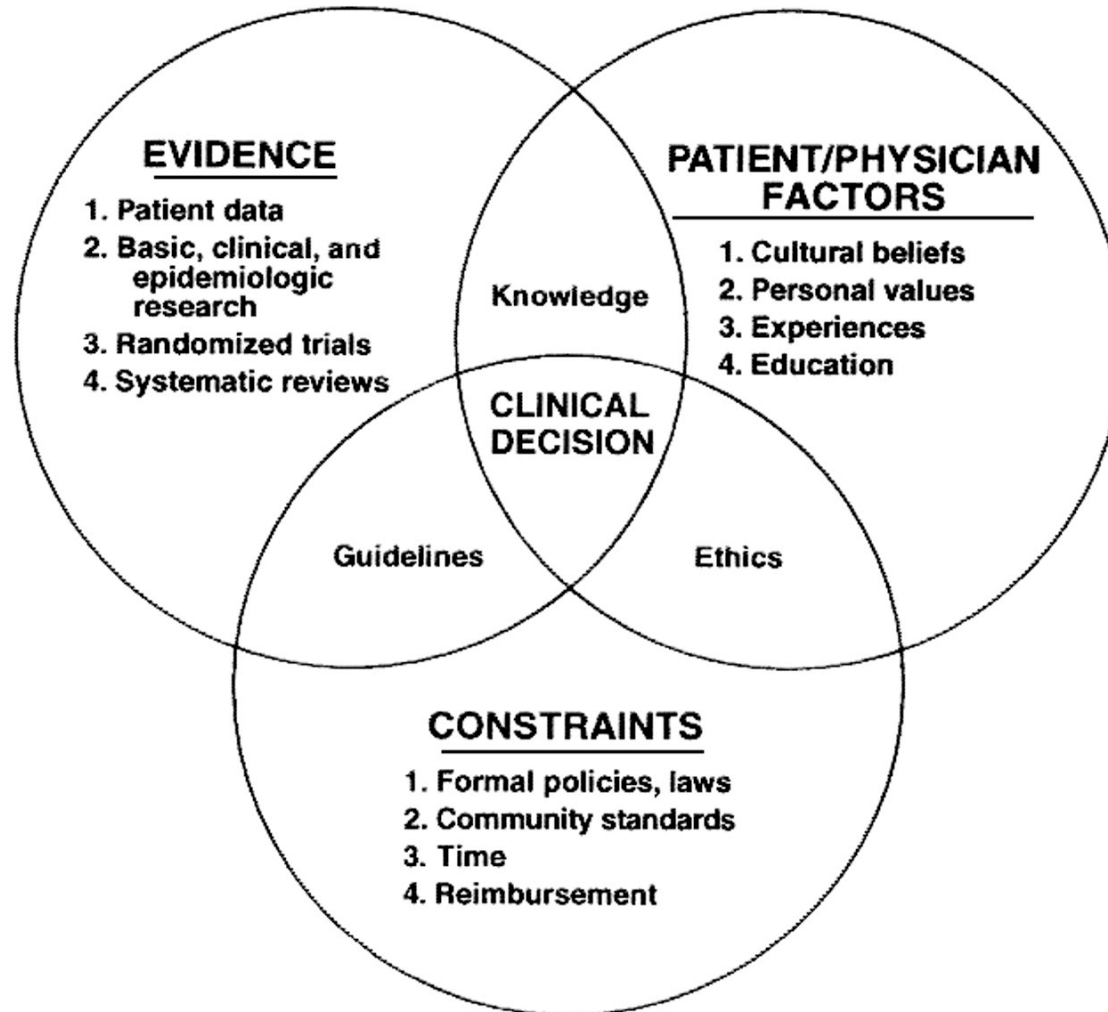
.....We suggest to discontinue active follow up if no change in the functional state or adrenal imaging occurs after 5 years, unless for younger patients. ⊕

- Da “UpToDate :

Follow-up

We suggest less frequent imaging follow-up in patients who have no history of malignancy and who have small (less than 2 cm), uniform, hypodense, cortical nodules (ie, benign imaging phenotype) ([Grade 2C](#)).

Factors that enter into clinical decisions



Mulrow, C. D. et. al. Ann Intern Med 1997;126:389-391

Farabegoli AME Maggio 2010

Annals of Internal Medicine

Conclusioni :

Elementi guida per il follow-up

- Mancanza di evidenze comparative sugli esiti dei vari approcci
- Necessità di bilanciare rischio di mancata diagnosi di neoplasia con aumentata esposizione a radiazioni ionizzanti
- Scelte individualizzate per singolo paziente