# Caveats in imaging of adrenal masses-incidentalomas: Can we diagnose adrenocortical carcinoma by imaging modalities?

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## Introduction

Adrenocortical masses are common and are in general called "incidentalomas". Autopsy studies show that approximately 5%-15% of adults may have adrenal incidentalomas but very few of them, 0.06%, are adrenocortical carcinomas (ACC) [1].

We shall present recent applications of computed tomography (CT), magnetic resonance imaging (MRI) and nuclear medicine modalities in the diagnosis of ACC.

## The CT image

The cornerstone of imaging for diagnosis or for exclusion of ACC is thin-collimation computed tomography (TCCT) without contrast [2]. The CT scanner must be well calibrated in order to provide accurate Hounsfield Unit (HU) attenuation values. The accuracy of HU is checked during the common quality control procedures by imaging phantoms with reference materials.

Adrenal nodular lesions are detected in 5% of all adrenal imaging procedures. Nine percent to 13% of patients scanned for a known malignancy have an adrenal lesion, whereas in 26%-36% of such patients, these lesions represent metastases [3]. The size of adrenal lesions is taken into consideration to differentiate adenomas from other adrenal lesions. Adrenal lesions larger than 4cm carry a higher probability of malignancy [3, 4]. More in detail, lesions smaller than 4cm, between 4-6cm or larger than 6cm have 2%, 6% or 25% pre-test probability of being malignant, respectively [1, 5]. Although malignant lesions tend to have irregular borders, there is an overlap with benign lesions; thus an irregular border is not considered to be helpful [3].

When differentiating an adenoma versus a malignant mass, one should bear in mind that 70% of adenomas have high fat content and the rest have low fat content. Those having low fat content remain unenhanced, when measured with CT implementing a 10HU and upper attenuation threshold. Sensitivity and specificity of CT for detecting lipid-poor adenomas is 71% and 98%, respectively [6]. According to size, adrenal lesion density <10HU or >10HU changes considerably downwards or upwards the probability of non adenoma, including ACC (Fig. 1).

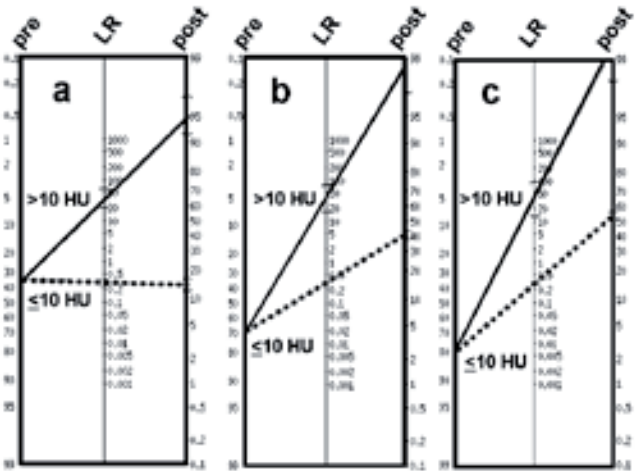


**Figure 1.** Fagan nomograms of pre-test and post-test probabilities and LRQ likelihood ratio, of non-adenomas evaluated by unenchanced CT according to lesion size (based on sensitivity/specificity data from [6]). a. An adrenal lesion smaller than 4cm carries a 35% chance of non-adenoma (including 2% possibility of ACC). With a CT attenuation value ≤10HU, the 35% pretest probability of being a non-adenoma, including ACC, becomes 15% post-test. Respectively, with a CT attenuation value >10HU, the 35% pretest probability of non-adenoma, including ACC, becomes 95% post-test. b. Adrenal lesions between 4cm and 6cm have a 70% probability of non-adenoma (including 6% probability of ACC). With a CT attenuation value ≤10HU the 70% pretest probability of non-adenoma, becomes 40% post-test, while with a CT attenuation value >10HU, the 70% pretest probability becomes 99% post-test. c. An adrenal lesion over 6cm carries a 80% probability of non-adenoma (including a 25% chance of being ACC) and a CT attenuation value ≤10HU moves the 80% pretest probability to 55% post-test whereas a CT attenuation value >10HU moves the post-test probability to 99%. Graphs drawn with Diagnostic test calculator by Professor A. Schwartz, University of Illinois College of Medicine, USA (http://araw.mede.uic.edu/cgi-bin/testcalc.pl)

Although adrenal disease pundits/experts are confident that the 10HU threshold is very useful (A. Hamrahian, Cleve-

land Clinic, USA, personal communication at ENDO 2012), it is known that the measured density of a material can diverge ±10HU from the nominal value and that the intraindividual variation in CT attenuation is reported to be as high as 12HU [1].

Lesions which present with an unenhanced CT >10HU require further evaluation in order to be better characterized [3]. The delayed (after 5-15min) post-contrast adrenal density of the lesion is a key parameter that should not be (although in fact is) omitted: ACC in general remain unenhanced in CT>10HU with an absolute washout of less than 50%-60% and a relative washout of 40%, respectively.

Magnetic resonance imaging (MRI) may prove helpful, particularly in delineating ACC tumor vascular extension, but offers no particular advantages over CT and raises the cost of examination [7]. Approximately one third of adrenal lesions cannot initially be categorized with CT/MRI.

## Nuclear medicine techniques

Scintigraphy with adrenal-cortex specific iodine-131 6-beta-iodomethyl-19-norcholesterol ($^{131}$I-NP-59) is useful but onerous and its supply is limited. The medulla-specific iodine-123 meta-iodo-benzyl-guanidine ($^{123}$I-MIBG) is useful for patients with biochemically-proven pheochromocytoma and not for suspected ACC [8]. Positron emission tomography (PET) with fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG) is non-specific for the adrenal cortex but its wide availability has yielded extensive and useful information on the evaluation of adrenal and extra-adrenal lesions. $^{18}$F-FDG shows high uptake in malignant tumors (Warburg effect) [9]. Adrenal $^{18}$F-FDG uptake is considered to be indicative of malignancy when intensity is higher than hepatic uptake [3, 10]. Malignant lesions present with a mean standardized uptake value (SUV), of adrenal to hepatic activity ratio of 4 (1.53-17.08), while benign lesions show a mean value of 0.66 (0.22-0.94) [3, 11]. It has to be noted though that $^{18}$F-FDG PET cannot differentiate among malignant lesions [3, 10]. Although adrenolytic mitotane treatment has no influence on $^{18}$F-FDG uptake in tumors [3], high SUV post-adrenalectomy with mitotane treatment in the contralateral gland has been observed [12, 13]. $^{18}$F-FDG PET has 97% sensitivity and 91% specificity in evaluating adrenal lesions [14] and, based on these characteristics, this modality can change to a great degree the probability of an adrenal mass being a non-adenoma according to lesion size (Fig. 2) [15].

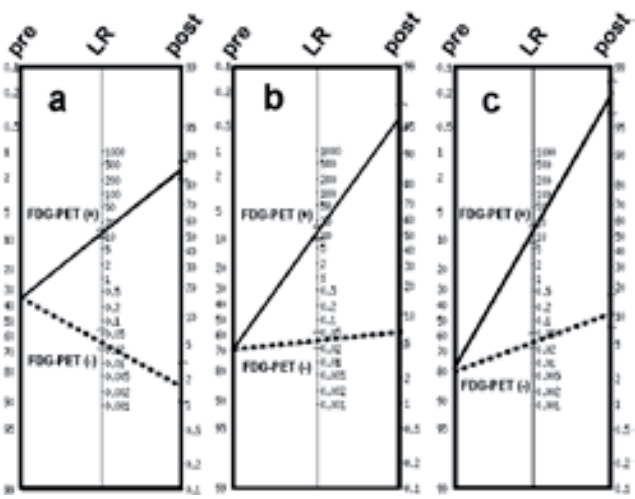


**Figure 2.** Fagan nomograms of pre-test and post-test probabilities and LR: likelihood ratio of non-adenomas evaluated by $^{18}$F-FDG PET according to lesion size (based on sensitivity/specificity data from [14]. a. An adrenal lesion < 4cm carries a 35% possibility of non-adenoma, including a 2% possibility of ACC. A negative $^{18}$F-FDG PET reduces this pretest to 1.5% post-test whereas a positive $^{18}$F-FDG PET raises it to 85% post-test. b. For adrenal lesions measuring 4cm-6cm, which carry a 70% pre-test probability of non-adenoma (including 6% probability of ACC), a negative $^{18}$F-FDG PET lowers the probability of non adenoma to 8% post-test, while a positive $^{18}$F-FDG PET raises the probability to 97% post-test. c. For lesions larger than 6cm, the 80% pre-test probability (including 25% probability of ACC) becomes 11% in case of a negative $^{18}$F-FDG PET and 98% post-test in case of a positive $^{18}$F-FDG PET.

*In conclusion,* unenhanced CT as a first imaging modality can characterize a substantial number of adrenal lesions and exclude ACC, while post-contrast CT and $^{18}$F-FDG PET can better diagnose or be of further assistance in the diagnosis of ACC. Years after first being introduced, it remains to be seen whether more detailed CT reports (vis-à-vis attenuation values) can be delivered by examining radiologists and whether $^{18}$F-FDG PET can be more widely used.

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*The authors declare that they have no conflicts of interest.*

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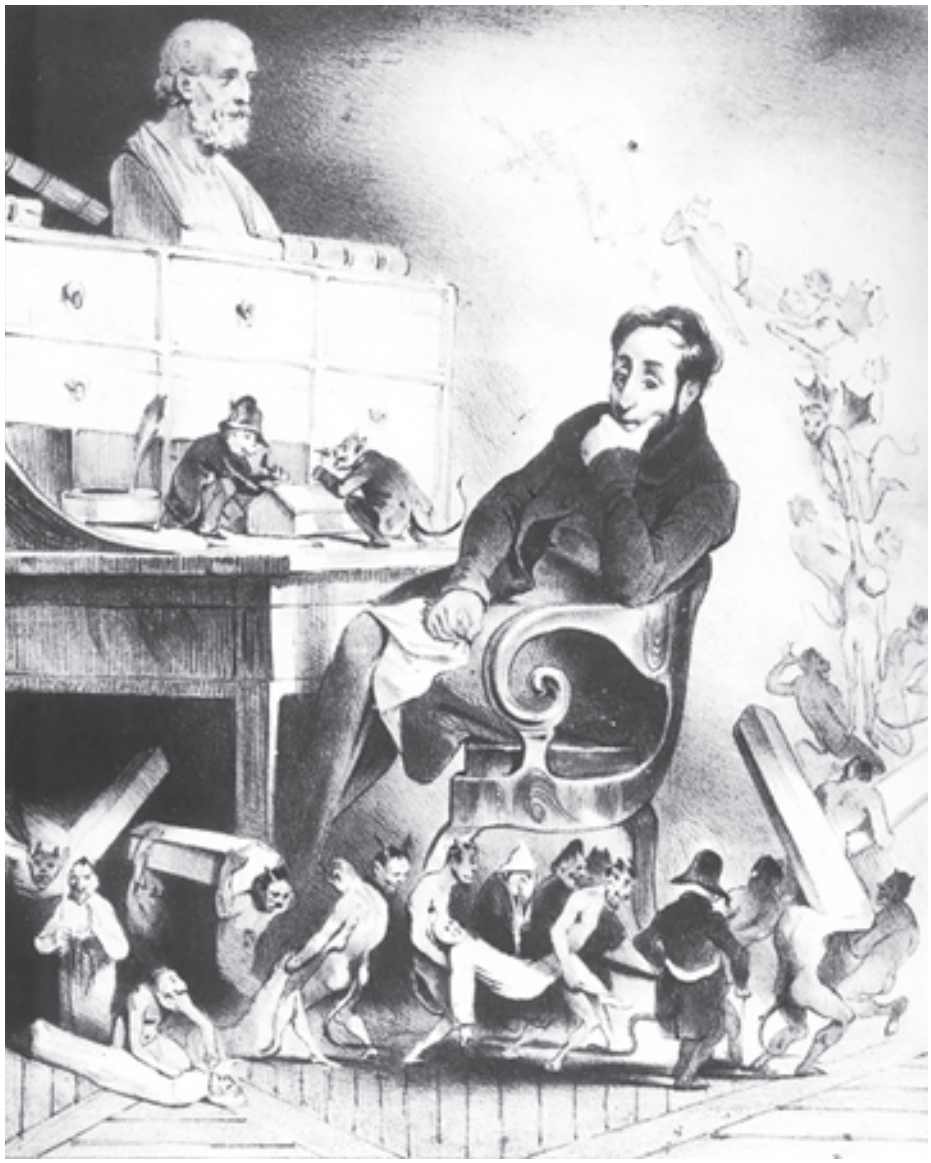

*Honore Daumier (France)-1833: Le médecin*