Commentary on Adrenal wash-out CT: moderate diagnostic value in distinguishing benign from malignant masses

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Abstract
The increasing use of cross-sectional imaging, mainly CT, results in an accelerating number of incidental findings, for instance of adrenal tumours. Although most ‘adrenal incidentalomas’ are benign, it is important to identify the malignant and the hormone producing (functional) tumours. For a small fraction of adrenal incidentalomas, the diagnosis is apparent on imaging, but the large majority requires radiological characterisation. To this end, a previous joint European Society of Endocrinology and European Network for the Study of Adrenal Tumours publication in this journal, recommends CT measurements of the native (non-contrast) tumour attenuation $\leq 10$ Hounsfield units, consistent with a lipid-rich benign adrenocortical adenoma, and imaging at least 6 months apart, on which unchanged tumour size implies a benign tumour. Because of weak evidence, calculation of CT contrast medium washout was not recommended as a means for tumour characterisation, but this technique has nevertheless still been applied in several countries. The recent article by Schloetelburg et al. in this journal is important because, in the largest study to date, the authors confirm that calculation of CT contrast medium washout with established thresholds is insufficient to reliably characterise adrenal tumours. Their results are therefore expected to impact the management of these patients.

With the escalating radiological imaging in medicine, especially by CT, follows an increasing number of incidental imaging findings that need to be managed. So-called adrenal ‘incidentalomas’, defined as an adrenal tumour depicted on imaging performed for other reasons than adrenal disease, are found in approximately 5% of CT examinations, that is about every 20th scan that includes the adrenals in the field of view (1). CT of the abdomen always includes the adrenals and, in most protocols, CT of the thorax also includes the adrenals in the field of view. By way of illustration, according to the British National Health Service statistics, approximately 5 400 000 CT scans are performed each year and about 600 000 of those (12%) comprise CT examinations of the abdomen and thorax. This means that each year an adrenal incidentaloma is detected in about 30 000 examinations (5%). By applying the same percentages to the annual number of CT scans performed in the USA (80 000 000), adrenal incidentalomas are detected in roughly 500 000 examinations each year. This imposes a significant additional workload on healthcare because these adrenal incidentalomas need to be characterised as benign or malignant (radiology) and the patients require biochemical testing to establish whether the tumour is functioning or not, that is screening for mineralocorticoid, glucocorticoid, and catecholamine secretion (endocrinology, internal medicine). The vast majority of adrenal incidentalomas are benign. Also, in patients with
a cancer history diagnosis adrenal incidentalomas are benign in approximately three-quarters of the patients (2), although the finding of an adrenal tumour in a cancer patient is suspicious of an adrenal metastasis, and requires work-up accordingly.

There are some tumour diagnoses that are apparent on CT and MRI, for which the patient management of their adrenal incidentaloma therefore does not pose a problem, such as myelolipomas comprising varying proportions of myeloid tissue and macroscopic fat, which is easily identified on CT and MRI (3), and simple cysts, that are water-attenuating and without contrast enhancement, and adrenal hematomas, typically with characteristic imaging presentation on trauma-CT, but an adrenal bleed may also be unrelated to trauma. Further, large malignant tumours are easily recognised as such on CT and MRI because of their irregular-lobulated less well-defined margin, heterogeneous internal structure and contrast enhancement, consistent with tumour necrosis, and the patients have to be managed accordingly. However, adrenal incidentalomas with an apparent diagnosis, and those which clearly are malignant, and for which the subsequent patient management is clear, comprise a minor fraction and the vast majority of adrenal incidentalomas are morphologically uncharacteristic in their imaging appearance and require further characterisation.

Because older patients, in whom adrenal incidentalomas are most frequent, may have undergone previous imaging, a CT examination or MRI at least 6 months old, in which the tumour’s size and morphological appearance are similar, will suffice to establish that the incidentaloma is benign, and these patients need no imaging follow-up. In lack of previous radiology, CT measurements of the tumours’ attenuation on native (pre-contrast) examination applying ≤10 Hounsfield units (HU) as the upper limit (cut-off) is well established to diagnose lipid-rich adrenocortical adenomas, showing approximately 70% sensitivity and almost 100% specificity (4). Notably, because most CT examinations of the abdomen and thorax are performed during intravenous contrast enhancement, a native CT examination of the adrenals has to be scheduled. Thus, an additional CT examination is required in a large number of patients. To avoid unnecessary radiation exposure to young patients (<40 years), alternatively, an MRI of the adrenals with sequences of in-phase and out-of-phase may be scheduled, for follow-up. Except for size measurements and evaluation of tumour morphology, MRI of the adrenals with most protocols allows for detection of ‘chemical shift’, that is a decrease in the tumour signal in sequences out-of-phase in comparison with in-phase, which is consistent with intracellular fat in a benign adrenocortical adenoma (5), in which case no further imaging is needed.

The finding that the ‘washout’ rate of iodine-based CT contrast media from the adrenal tumours could be applied as a means to characterize incidentalomas as benign was later incorporated into the radiological routine, especially valuable for incidentalomas with >10 HU native attenuation, and when a native examination was lacking. The contrast medium washout was calculated based on the tumour’s CT attenuation (HU) measured in the venous phase and in the delayed phase, typically 10–15 min after contrast medium injection start (relative washout) and, when available, also incorporating the native tumour attenuation into the equation (absolute washout). A relative washout >40% and an absolute washout >60% were found to indicate a benign tumour (6, 7).

However, because of the results of subsequent studies, showing benign washout characteristics for pheochromocytomas (8), and a meta-analysis reporting weak evidence for CT with contrast washout for incidentaloma characterisation (9), the accuracy of adrenal washout calculations was questioned. Based on the findings in this meta-analysis, the European Society of Endocrinology (ESE) and the European Network for the Study of Adrenal Tumours (ENSAT) published a joint guideline paper in this journal recommending that characterisation of adrenal incidentalomas should be based on native attenuation measurements and, when inconclusive, measurements of lesion size on examinations at least 6 months apart (10). Consequently, the radiological practice in several European countries changed, and CT with contrast medium washout calculations as a means to characterise adrenal incidentalomas was more or less abandoned, whereas other countries continued to apply this technique (11), and still are, as reflected in a recent review paper (12).

A recent paper from the Würzburg group by Schloetelburg et al. published in this journal (13) is therefore imperative, with high impact on the management of patients with adrenal incidentalomas, because it reports the diagnostic yield of relative and absolute washout in the largest study to date, assessing the technique in 216 patients with 252 adrenal incidentalomas, and with confirmation of the tumour diagnosis by histopathology and radiological and clinical long-term follow-up. Consistent with the results of the previous meta-analysis (9) the authors demonstrate failure of adrenal contrast medium washout calculations (relative washout >40%, absolute washout >60%) to characterise adrenal incidentalomas. Importantly, relative
and absolute washout calculations misclassified 35% and 36% of the adrenal tumours, respectively. The imaging characterisation of pheochromocytomas is generally not crucial, because they are usually diagnosed as such, based on biochemistry, and only a small fraction (approximately 10%) of pheochromocytomas are malignant. The authors included the pheochromocytomas in their analysis of potentially malignant adrenal tumours, and found that the absolute washout calculations indicated that 22% were benign, whereas conversely 36% of all benign lesions were indicated as malignant. In the latter situation, misdiagnosis of benign adrenal lesions as malignant can lead to unnecessary surgical resection and, except for the surgical risks and costs, also with undesirable consequences for the patient’s mental well-being. In the former situation, misdiagnosis will delay the resection of a malignant tumour, with the risk for a more complicated surgical procedure, or even the development of a non-curative situation.

Established prerequisites to use native CT attenuation measurements for tumour characterisation, are benign morphological imaging characteristics including harmonic rounded shape, homogenous internal structure and sharp borders, and this also applies to tumours suitable for calculations of contrast medium washout. Therefore, another important finding by the Würzburg group in their current paper is that homogeneity of adrenal tumours was not helpful as a means to identify benign lesions. Notably, the classical benign imaging features (homogenous internal structure, sharp delineation and harmonic rounded-oval form) were fulfilled in merely 63% of the adrenocortical adenomas. Conversely, 66% of the adrenocortical cancers and 68% of the metastases showed benign morphological features on imaging.

Except for the study by Schloetelburg et al., (13) there are two additional recent reports which also are likely to impact future guidelines, and therefore are appropriate to mention (14, 15). In these two studies, the authors have assessed an increased threshold, set to 20 HU, on native CT for adrenal tumour characterisation, the results of which however lie outside the scope of this commentary report.

To conclude, the results in the study by Schloetelburg et al. (13) have high impact on the management of patients with adrenal incidentalomas and support the previous ESE and ENSAT recommendations to base CT measurements for tumour characterisation on native CT and for tumours >10 HU on size and morphology comparison on imaging at least 6 months apart.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this commentary.

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