Comment on "A Modern Assessment of Cancer Risk in Adrenal Incidentalomas

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Letter to the Editor

Comment on "A Modern Assessment of Cancer Risk in Adrenal Incidentalomas: Analysis of 2219 Patients" by Kahramangil B et al.

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Dear Editor,

We have read with great interest the paper 'A Modern Assessment of Cancer Risk in Adrenal Incidentalomas – Analysis of 2219 Patients' by Kahramangil *et al* [1]. The diagnostic work-up of incidentally discovered adrenal masses remains challenging, in particular with regard to the critically important differentiation of adrenocortical carcinoma (ACC) from benign adrenal lesions. This study on a large retrospective cohort of adrenal incidentalomas (AI) is a welcome contribution to the literature. We recently published a prospective, multi-center study validating a new biochemical diagnostic test for adrenal tumors, urine steroid metabolomics, in a similarly sized cohort of 2017 patients with newly discovered adrenal masses including 98 ACC (Evaluation of URINE steroid metabolomics in the differential diagnosis of AdrenoCortical Tumors, EURINE-ACT) [2]. Notably, 84% of the tumors in our cohort were incidental findings (AI); patients with biochemical evidence of pheochromocytoma or recent extra-adrenal malignancy were excluded.

Our prospective study[2] and the retrospective study by Kahramangil *et al.* [1] concur on two important points of direct relevance to clinical practice. First, both studies report that ACCs are extremely rare in lesions measuring <4 cm (post-test probability of ACC 0.1% in Kahramangil et al. [1], 0.13% in the EURINE-ACT cohort). Second, both studies provide evidence that an unenhanced CT tumor attenuation value of >20 Hounsfield Units (HU) is a more specific diagnostic cut-off than the hitherto applied threshold of 10 HU. In the prospective EURINE-ACT study, we found a specificity of 64% (95%CI 61.4%-66.4%) for >10HU, which increased to 80% (95%CI 77.9%-82.0%) when applying >20HU, with similar sensitivities (100% and 99%, respectively). Kahramangil et al. [1] reported a similar specificity for >20HU (76.8%; sensitivity 94.1%, no 95%Cis reported).

However, we would like to voice important concerns about the implementation of the management algorithm proposed by Kahramangil *et al.* [1] into clinical practice. Their algorithm suggests that all adrenal masses with a size >4.6cm or with an attenuation >20HU on non-contrast CT should be surgically excised. Although these criteria indeed minimize the risk of missing an ACC, this comes at the very substantial cost of frequent unnecessary adrenalectomies in a much larger number of patients with benign adrenal tumors, with all attendant risks and costs[3,4]. This is due to the poor positive predictive value (PPV) of tumor size and tumor attenuation, as a result of the low overall ACC prevalence in patients with AI[1,2]. By our calculations, in the Kahramangil *et al.* cohort (1.7% overall rate of ACC), a tumor size >4.6 cm would correctly detect 35 out of 38 ACCs. However, this would also yield 231 false positive results, corresponding to patients who would end up undergoing adrenalectomy for non-ACC tumors. This is equivalent to 6.6 unnecessary adrenalectomies for each surgically removed ACC, excepting the rare cases of hormonally active adrenal tumors. Similarly, when applying a tumor attenuation of >20HU, only 6.3% of those lesions were actually confirmed as ACC by histopathology; the disproportionally high false-positive rate of 93.7% will result in 14.7 unnecessary adrenalectomies per excised ACC.

We also urge caution regarding their proposed algorithm from a methodological point of view. Kharangil et al. performed univariable logistic regression to identify risk factors, followed by multivariable logistic regression to present a prognostic model. However, the

proposed cut-points were derived from their retrospective dataset only, without any further internal or external validation. It is also problematic to use unadjusted models to select variables for adjusted models and the authors did not report confidence intervals in the main manuscript.

In our recently published prospective test validation study[2], we propose a management algorithm for patients with a newly diagnosed adrenal mass, based on a 'triple test', taking a stepwise approach, with sequential application of size criteria (diameter>4 cm), imaging characteristics (non-contrast attenuation > 20 HU) and urine steroid metabolomics (USM) [2]. USM is a new diagnostic biomarker test that combines mass spectrometry-based steroid metabolite profiling with steroid data analysis by a machine learning-based algorithm. [2,5,6]. This strategy provided a positive predictive value of 76·4% and a negative predictive value of 99·7% for ACC diagnosis [2]. This triple test approach has the great advantage of drastically curtailing the number of unnecessary adrenalectomies, while remaining highly sensitive to the detection of ACCs. In addition, it dramatically decreases the numbers of additional imaging procedures, which all have lower specificity than USM, as nicely demonstrated by Kahramangil et al. [1] for the widely used CT contrast wash-out studies, which they found to falsely predict malignancy in 91% of patients.

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