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Metomidate-Based Imaging of Adrenal Masses

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Abstract Due to broader use of conventional imaging techniques, adrenal tumors are detected with increasing frequency comprising a wide variety of different tumor entities. Despite improved conventional imaging techniques, a significant number of adrenal lesions remain that cannot be easily determined. A particular diagnostic challenge are lesions in patients with known extra-adrenal malignancy because these patients frequently harbor adrenal metastases. Furthermore, adrenal masses with low fat content and no detectable hormone excess are difficult to diagnose properly. Fine needle biopsy is invasive, often unsuccessful, and puts patients at risk, e. g., in cases of pheochromocytoma or adrenal cancer. Noninvasive characterization using radiotracers has therefore been established in recent years. ^{18}F-FDG PET helps to differentiate benign from malignant lesions. However, it does not distinguish between adrenocortical or nonadrenocortical lesions (e.g., metastases or adrenocortical carcinoma). More recently, enzyme inhibitors have been developed as tracers for adrenal imaging. Metomidate is most widely used. It binds with high specificity and affinity to CYP11B enzymes of the adrenal cortex. As these enzymes are exclusively expressed in adrenocortical cells, uptake of labeled metomidate tracers has been shown to be highly specific for adrenocortical neoplasia. ^{11}C-metomidate PET and ^{123}I-iodometomidate SPECT imaging has been introduced into clinical use. Both tracers not only distinguish between adrenocortical and nonadrenocortical lesions but are also able to visualize metastases of adrenocortical carcinoma. The very specific uptake has recently led to first application of ^{131}I-iodometomidate for radiotherapy in ACC. In conclusion, metomidate-based imaging is an important complementary tool to diagnose adrenal lesions that cannot be determined by other methods.

Keywords Adrenal tumors · Adrenal imaging · 11C-metomidate PET · Metomidate SPECT

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Introduction

The most frequent adrenal imaging problem is the incidentally detected adrenal mass found while reading an imaging study, usually computed tomography (CT), that has been performed for other reasons than adrenal disease. The incidence of these masses, the so-called adrenal incidentalomas, increases with age, and tumors are found in approximately 5% of CT examinations of the abdomen and thorax that include the adrenals in the field of view. These tumors are almost always benign when there is no cancer history and, conversely, malignant in up to about half of cancer patients [1, 13]. The radiologist needs to characterize the incidentaloma and define whether it is benign or malignant, and the clinician is required to perform a biochemical testing to diagnose any adrenal hormonal overproduction and to finally decide on the therapeutic consequences.

Radiological characterization of an adrenal mass relies on determining the delineation of the mass and to assess its internal structure. A benign adrenal lesion typically is small has a rounded oval shape, well-defined peripheral margins,

and homogenous internal structure as opposed to malignant masses which often are larger and may be heterogeneous, lobulated, diffusely delineated, and sometimes invading adjacent organs and tissues. An area of macroscopic fat is typical of a benign myelolipoma and may be restricted to a very small region or can constitute almost the whole tumor. Attenuation measurement in the nonenhanced CT examination by placing a region of interest (ROI) in the fatty part of the myelolipoma will typically show −100 Hounsfield Units (HU).

Compared to the normal adrenal, the cytoplasmatic fat in a benign adrenocortical adenoma will decrease its attenuation and if the lesion measures ≤10 HU, it can be considered to be a benign adrenocortical adenoma with 71% sensitivity and 98% specificity [6]. A recent study confirms this almost maximum specificity and reports 65% sensitivity and 99% specificity [33]. The sensitivity to detect fat is comparably high by magnetic resonance imaging (MRI) using in- and out-of-phase sequences, and incidentalomas may therefore be characterized as benign adrenocortical adenomas also by this method [26, 27]. However, with the use of a CT examination protocol to calculate the contrast medium washout after 10–15 min as readout, the diagnostic accuracy seems to further improve [9, 10, 22, 25, 34, 35].

Despite improved conventional imaging techniques, there are still a significant number of adrenal lesions that cannot be easily determined. A particular diagnostic challenge is the evaluation of lesions in patients with known extra-adrenal malignancy, because these patients frequently harbor adrenal metastases. Furthermore, adrenal masses with low fat content and no detectable hormone excess are difficult to diagnose properly. Fine needle biopsy is invasive, often unsuccessful, and puts patients at risk, e. g., in cases of pheochromocytoma or adrenal cancer. Thus, there is a need for additional diagnostic tools helping to differentiate between lesions of adrenocortical and nonadrenocortical origin.

Nuclear Medicine Imaging of the Adrenals

^{131}I-Norcholesterol Scintigraphy

Several years ago, ^{131}I-norcholesterol (NP-59) was the only radiotracer that was available for adrenal imaging. However, it is no longer available for adrenal scintigraphy in most European countries since the production of the tracer has been terminated. This tracer was previously used for scintigraphy including single-photon emission computed tomography (SPECT) mainly to preoperatively localize aldosterone-secreting adrenocortical tumors (Conn adenomas) in primary aldosteronism (PA). Drawbacks of the technique were the limited spatial resolution of SPECT, making small tumors difficult to visualize, and the high radiation dose to the patient (30 mSv or even higher).

^{18}F-FDG PET

The spatial resolution and image contrast of positron emission tomography (PET) is generally much better than that of SPECT. The most common PET tracer is ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) which is extensively used for oncological imaging because it is taken up in malignant tumors to a higher extent than in most normal organs and tissues. Although unspecific, ^{18}F-FDG has in several studies been used also for adrenal imaging to differ benign from malignant tumors [3, 5, 7, 8, 11, 17, 21, 24, 28–30, 37–39]. A recent systematic review and meta-analyses comprises 21 studies including 1391 lesions (824 benign and 567 malignant) in 1,217 patients and showed mean (95% CI) 0.97 (0.93–0.98) sensitivity and 0.91 (0.87–0.94) specificity [4].

Metomidate-Based Imaging

Background

Metomidate (MTO) is the methyl ester of etomidate (ETO) that has been used for decades as an anesthetic agent in veterinary medicine [12, 14]. Etomidate and metomidate are both inhibitors of the two CYP11B enzymes 11β-hydroxylase (CYP11B1, P45011β) and aldosterone synthase (CYP11B2, P450aldo) that are involved in the cortisol and aldosterone synthesis, respectively. Because of their specific adrenocortical binding properties, MTO and ETO have been labeled with ^{11}C and ^{18}F as PET tracers [2, 32] and metomidate has been labeled with ^{123}I for scintigraphy [16] and ^{131}I for the purpose of therapy.

^{11}C-Metomidate PET

The first report on ^{11}C-metomidate and ^{11}C-etomidate was published in 1998 [2]. In this paper the binding capacity of ^{11}C-metomidate and ^{11}C-etomidate was investigated by frozen section autoradiography, and the binding of the tracers to adrenal cortical tissue from different species was shown to be high and specific. In vivo PET imaging of the adrenals in monkeys was successful and because of the better radiochemical characteristics of ^{11}C-metomidate (shorter synthesis time and higher yield and specific radioactivity), ^{11}C-metomidate was chosen as the candidate for clinical PET imaging. In the first clinical study [2], 15 patients with unilateral adrenal masses underwent ^{11}C-metomidate PET and those of adrenocortical origin (six adenomas, one hyperplasia, twp adrenocortical cancers) were all easily identified with a high tracer uptake whereas

the noncortical lesions (one myelolipoma, one pheochromocytoma, one metastasis, one mesenchymal tumor, and two cysts) displayed virtually no uptake. The normal adrenals showed a high uptake, and the liver uptake was intermediate. High radioactivity concentrations also appeared in gastric juice into which the tracer and/or its metabolites were transported. The traditional method according to Patlak to calculate the transport rate constant of the flux of tracer from plasma or blood into various tissues was nonlinear and very varying between patients. This indicated that ^{11}C-metomidate was rapidly metabolized and another modified method had to be applied whereby the spleen was used as a reference tissue in the Patlak analysis. A study focused on ^{11}C-metomidate PET of adrenocortical cancer was published in 2003 [23] and in which 13 examinations were performed in 11 patients. PET visualized all viable tumors with a high tracer uptake and diagnosed two lesions that were missed by CT. However, three completely necrotic adrenocortical cancer lesions were false negative at ^{11}C-metomidate PET. On the other hand, ^{11}C-metomidate PET correctly characterized a lymph node as nonmetastatic that by CT was diagnosed as an adrenocortical cancer lesion. A large variation in the ^{11}C-metomidate uptake was found in the various adrenocortical cancers (peak SUV 5–32). Treatment with adrenal steroid inhibitors and chemotherapy was found to decrease the tumor uptake (Fig. 1).

Other research groups later published their results [31, 40] on ^{11}C-metomidate PET in comparison with FDG PET. The Finnish group examined 21 patients in whom the ^{11}C-metomidate uptake was ranked in various types of adrenal lesions that was highest in the adrenocortical cancers, followed by the functioning adenomas and nonfunctional adenomas, and was lowest in the noncortical tumors. FDG PET detected two out of the three malignant adrenal lesions, and the nonmalignant adrenal lesions were either difficult to visualize or not seen at all. The Austrian study comprised 16 patients all undergoing ^{11}C-metomidate PET and FDG PET (1 adrenal metastasis, 1 adrenocortical cancer, 1 malignant pheochromocytoma, 10 adenomas, 1 hyperplasia, 2 benign pheochromocytomas), and nine of the adrenocortical tumors were functioning. As in the previous studies, ^{11}C-metomidate PET differed the adrenocortical tumors from those of nonadrenocortical origin (SUV 19 and

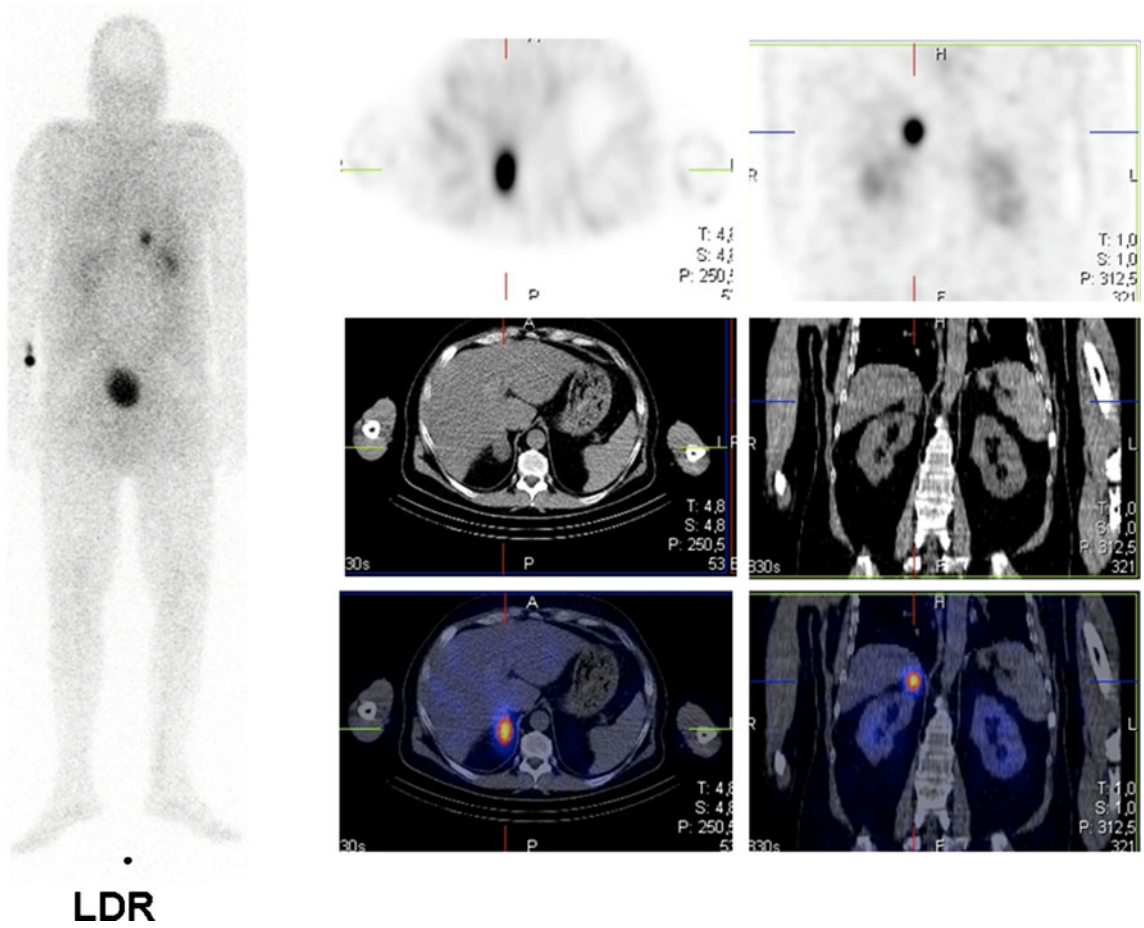

Fig. 1 ^{123}I-iodometomidate imaging in a patient with a 2-cm Cushing adenoma on the right side. Planar images (*left panel*) and SPECT/CT

1.9 respectively, $p<0.01$). FDG PET differentiated the malignant from the benign tumors. An interesting finding was that the ^{11}C-metomidate uptake in the contralateral normal adrenal was not suppressed in patients with Conn tumors whereas this was the case in those with Cushing's syndrome.

A strict correlation of the histopathological diagnosis and findings at ^{11}C-metomidate PET was performed in 73 patients with 75 adrenal tumors (26 adenomas, 13 adrenocortical cancers, 8 hyperplasia, 6 pheochromocytoma, 3 metastases, and 19 tumors of nonadrenal origin) that also included small adrenal tumors (1–20 cm) [19]. Thereby the sensitivity to distinguish the adrenocortical from the non-adrenocortical lesions, as compared to previous studies, decreased to 89% due to false-negative observations in three tumors that all had a diameter ≤1 cm. The specificity was 96% because of a false-positive finding in the lower abdomen in one patient. PET measurements of the tracer uptake could not distinguish benign from malignant adrenocortical tumors. Uptake measurements, however, showed that, in the individual patient, an adrenal peak SUV >24.3 equals a 95% risk of an adrenocortical tumor (adenoma or adrenocortical cancer), and with a tumor-to-normal (contralateral) adrenal ratio >1.4, there was a 99.5% risk of an adrenocortical tumor. In contrast to the findings by Zetting et al., the ^{11}C-metomidate uptake in the contralateral adrenal was similar in patients with functioning and nonfunctioning adenomas.

A recent paper investigated the role of ^{11}C-metomidate PET in the clinical setting for characterization of 44 adrenal incidentalomas in 38 patients [18] in comparison with CT and MRI. It was found that morphological imaging is sufficient in the vast majority of patients and that ^{11}C-metomidate PET is best used as a problem-solving tool in the few cases in whom CT and MRI fail to characterize the tumor.

Further work has been concentrated on the use of ^{11}C-metomidate PET in PA. In two studies [20, 36] ^{11}C-metomidate PET was performed before and after 3 days of premedication with peroral dexamethasone with the aim of visualizing small Conn adenomas. The hypothesis was that corticoid treatment decreases ACTH secretion and thereby the 11beta-hydroxylase concentrations in normal adrenal parenchyma but not in Conn adenomas and thereby increasing the tumor-to-normal tissue contrast. There were nine patients with Conn adenomas and for matters of comparison two patients with nonfunctioning tumors. The tumors were small (average 1.7 cm; range 1–2.5 cm) but were visualized by ^{11}C-metomidate PET in all examinations and with similar visibility in examinations performed before and after corticoid pretreatment. The tumor-to-normal adrenal ratios were higher in the posttreatment examinations, but this difference was not shown to be statistically significant.

The pre- and posttreatment ^{11}C-metomidate PET performed in part of the same patient cohort, constituting

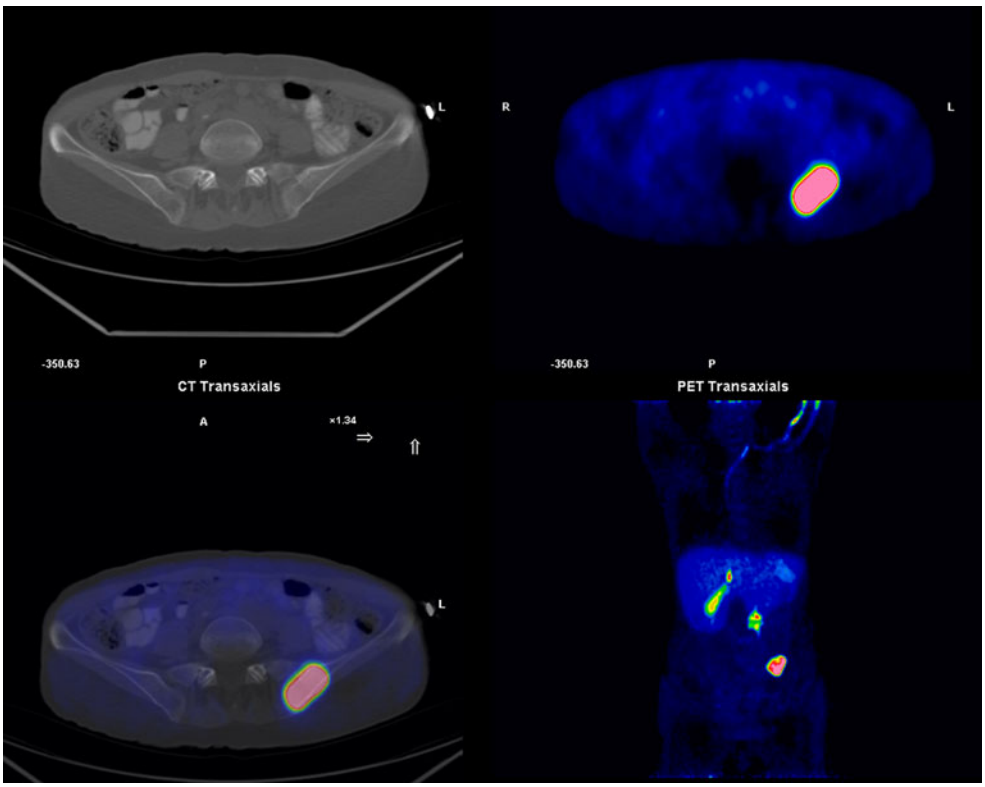

Fig. 2 ^{11}C-metomidate PET/CT of a patient operated on with adrenalectomy on the right side because of adrenocortical cancer. Examination performed as follow-up shows unexpected bone metastasis

seven subjects with Conn tumors, was analyzed by principal compartment analysis (PCA) [36]. By applying PCA on these dynamic examinations (acquisition 0–45 min after tracer injection), separate image volumes were isolated, representing the early, intermediate, and late pharmacokinetic phases of ^{11}C-metomidate. The tumors were best delineated in the PCA component representing the intermediate pharmacokinetics with a decreased image noise and improved tissue contrast. This PCA component allowed a more precise delineation of the Conn adenomas. However, only when applying these ROIs to create time–activity curves (TACs), the mean SUVs for the TACs of the Conn tumors and the normal (contralateral) adrenals were shown to significantly decrease by the corticoid pretreatment. The main conclusion of the study was that PCA allows better tissue delineation that might further improve the precision of PET measurements.

^{123}I-Metomidate SPECT

[^{123}I]-Iodometomidate ([^{123}I]IMTO) has been recently developed as a SPECT tracer [16], bearing the advantage of a broader availability compared to PET (Fig. 2). Binding properties to the target enzymes are comparable to metomidate and etomidate in vitro, indicating that radioiodination did not alter pharmacological properties. Preclinical and clinical evaluation demonstrated high and specific uptake of [^{123}I]IMTO in normal adrenals as well as in adrenocortical tumors and also in distant metastases of ACC with relatively low uptake in the liver compared to ^{11}C-metomidate. The effective dose in humans was only 3–4 mSv, which is by far lower than the dose reached by norcholesterol scintigraphy. Good visualization of tumor manifestations in humans can be observed 4-6 h after [^{123}I]IMTO with best target to background ratios after 24 h. Background activity was very low. Like [^{11}C]MTO PET, [^{123}I]IMTO SPECT is unlikely to differentiate benign from malignant adrenocortical lesions. SPECT imaging has lower resolution which might be relevant when assessing very small adrenal lesions, however it also bears the potential of broader availability due to the longer half-life of ^{123}I-iodine.

^{131}I-Metomidate-Based Therapy

As some adrenocortical cancer lesions exhibit very high uptake of [^{123}I]IMTO, the potential for treatment of patients with [^{131}I]IMTO has been recently evaluated in 11 patients with advanced ACC [15]. Patients received up to 20 GBq [^{131}I]IMTO. Of note, in 6 of 11 treated patients with stage IV ACC, stable disease or even partial response could be achieved for many months with ongoing disease stabilization in several patients for more than 2 years so far. Main side effects were transient thrombocytopenia and leukopenia that occurred in all patients. The tracer is rapidly metabolized within few minutes mainly by hepatic esterases. Elimination of [^{131}I]IMTO from the whole body showed a half-life of 20 h. In all patients treatment was very well tolerated.

Conclusions

The growing detection of adrenal incidentalomas representing a wide range of both benign and malignant lesions requires new diagnostic approaches that enable noninvasive characterization of the lesions for further decision on the therapeutical consequences. Molecular imaging of metabolic function and tissue-specific protein expression by using ^{18}F-FDG PET and metomidate-based nuclear imaging as complementary tools are highly promising new approaches for the distinction between tumor lesions that need to be surgically removed and those who will not require surgery or even long-term assessment. Furthermore, the high specificity of metomidate uptake in adrenocortical tissue not only makes it to a suitable diagnostic tool but also opens up a new treatment option for ACC by using [^{131}I]IMTO for radiotherapy.

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Conflict of Interest The authors declare that there is no conflict of interest.

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