

Review

Imaging of Adrenal Masses with Emphasis on Adrenocortical Tumors

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Abstract

Because of the more widespread and frequent use of cross-sectional techniques, mainly computed tomography (CT), an increasing number of adrenal tumors are detected as incidental findings ("incidentalomas"). These incidentaloma patients are much more frequent than those undergoing imaging because of symptoms related to adrenal disease. CT and magnetic resonance imaging (MRI) are in most patients sufficient for characterization and follow-up of the incidentaloma. In a minor portion of patients, biochemical screening reveals a functional tumor and further diagnostic work-up and therapy need to be performed according to the type of hormonal overproduction. In oncological patients, especially when the morphological imaging criteria indicate an adrenal metastasis, biopsy of the lesion should be considered after pheochromocytoma is ruled out biochemically. In the minority of patients in whom CT and MRI fail to characterize the tumor and when time is of essence, functional imaging mainly by positron emission tomography (PET) is available using various tracers. The most used PET tracer, [¹⁸F]fluoro-deoxy-glucose (¹⁸FDG), is able to differentiate benign from malignant adrenal tumors in many patients. ¹¹C-metomidate (¹¹C-MTO) is a more specialized PET tracer that binds to the 11 β -beta-hydroxylase enzyme in the adrenal cortex and thus makes it possible to differ adrenal tumors (benign adrenocortical adenoma and adrenocortical cancer) from those of non-adrenocortical origin.

Key words: Adrenal, Incidentaloma, Adenoma, Adrenocortical cancer, Positron emission tomography, FDG, Metomidate, Computed tomography, Magnetic resonance imaging.

Introduction

Patients who present with clinical symptoms from adrenal disease are rare compared to those who are diagnosed with an adrenal tumor when they undergo radiological imaging, usually computed tomography (CT), for other reasons than suspicion of adrenal disease. These patients who are diagnosed with a so-called "incidentaloma" are increasing in parallel with the escalating use of cross sectional imaging by CT, magnetic resonance imaging (MRI) and ultrasonography (US). The work-up of the incidentaloma patient should aim at establishing whether the

incidentaloma is functioning, i.e. hormonally active or not, and if the lesion is benign or malignant.

The detection of an incidentaloma requires a clinical and biochemical work-up, usually performed by an endocrinologist, and the radiologist needs to characterize the adrenal mass as much as possible. The work-up must be governed by the situation for the individual patient. For example, it is of importance if the patient has a present or earlier cancer diagnosis. Generally, in cancer patients the incidentaloma is malignant in about 30%, and even 50%, in

occasional reports, whereas in non-cancer patients the incidentaloma rarely is malignant. Also, the size of the tumor must be considered in this respect since the risk of malignancy increases with the diameter of the lesion.

In patients with *functioning incidentalomas* the management needs to be adopted according to the symptoms and signs at presentation and the results of the biochemical and clinical work-up. Imaging usually comprises of CT or MRI to detect the adrenal tumor (for example adrenocortical cancer, pheochromocytoma, Conn adenoma) or to localize an extra-adrenal lesion (pheochromocytoma, paraganglioma).

The decision on a surgical versus a non-surgical management of patients with a *non-functioning incidentaloma* was previously governed primarily by the tumors size and all lesions larger than approximately 4 cm were removed because of the risk of a malignant tumor. Currently this decision is increasingly influenced by the imaging characterization of the incidentaloma. When an adrenal metastasis is suspected, core-needle biopsy or fine needle aspiration cytology may be more appropriate diagnostic procedure than further imaging, once pheochromocytoma has been ruled out biochemically.

This review examines the conventional and novel imaging techniques available for the evaluation of adrenal tumors, focusing on the diagnosis of adrenocortical lesions.

Radiological imaging

In the imaging evaluation, conventional morphological characteristics need firstly to be assessed to indicate whether the incidentaloma is benign or malignant. Radiographic features which likely support a benign tumor include rounded, well delineated tumor borders, clear separation of the tumor from surrounding structures, no evidence of tumor extension into adjacent organs and homogenous internal structure.

The existence of areas of *macroscopic fat*, typically measuring -100 Hounsfield units (HU) at CT, is characteristic of a myelolipoma comprising haematopoietic tissue and fat. The variation in this regard may be considerable and macroscopic fat may constitute almost the whole a myelolipoma or merely appear as minimal "islands" within the mass.

Because of the abundance of *cytoplasmic fat* in benign adrenocortical tumors, most of these lesions may be characterized as such by simple attenuation measurement of the tumor in non-contrast enhanced CT examination. The attenuation of the normal parenchymal organs measures approximately 30-70

HU and the presence of cytoplasmic fat decreases the attenuation of the tumor accordingly. This may be compared to the reduction of the hepatic attenuation at CT seen in patients with liver steatosis. Because the initial CT, at which the incidentaloma was diagnosed, usually was intravenously contrast-enhanced, the imaging work-up in the incidentaloma patient generally necessitates a new CT examination. This dedicated examination protocol of the adrenals generally comprise a pre-contrast CT, to allow for attenuation measurement, scanning in the venous contrast-enhancement phase (90-120 seconds after injection start) and a delayed examination at 10 or 15 minutes (depending on the local practice).

Incidentalomas which at CT appear morphologically benign and measure ≤ 10 HU in the pre-contrast CT examination can be diagnosed as a benign adrenocortical adenoma with 98-99% specificity (1-2). According to Swedish National guidelines benign adrenocortical adenomas measuring less than 3-4 cm in transaxial diameter generally require no further imaging or radiological follow-up but the routines in this respect varies in different countries. In order not to misdiagnose a simple cyst (attenuation approximately 0-15 HU) as a benign adrenocortical adenoma, it should, however, be confirmed that the lesion is contrast-enhancing. Similarly, there is generally no need for further imaging in larger lesions >4 cm that are apparently benign, for example a myelolipoma or a cyst. An example of a benign adrenocortical tumor characterized by attenuation measurements at CT is shown in Figure 1.

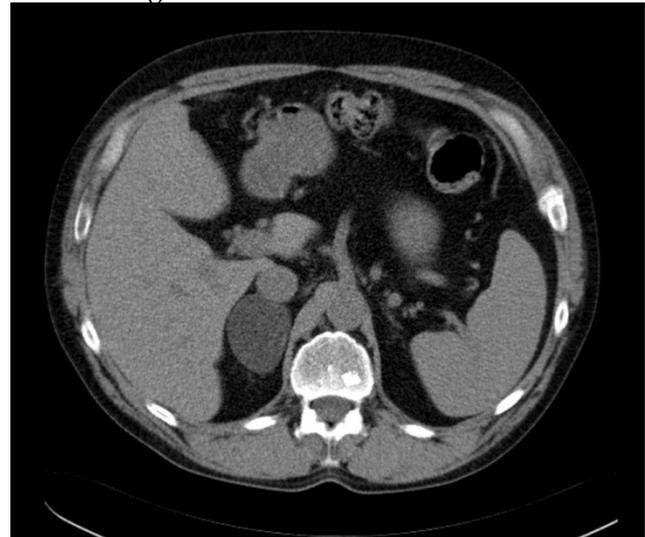


Figure 1: A transaxial CT image without contrast enhancement shows a 5 cm homogenous circumscribed well delineated tumor in the right adrenal. The attenuation in the tumor was measured by placing a circular region of interest (ROI) in three contiguous slices and resulted in a mean attenuation of minus 15 Hounsfield Units consistent with a benign adrenocortical adenoma.

Incidentalomas with a pre-contrast attenuation >10HU, may additionally be characterized depending on their degree of contrast-enhancement and wash-out. This is based on the characteristics of malignant as opposed to benign tumors. Malignant tumors are generally poorly vascularized and, compared to normal tissues, they have a larger interstitial space in which there is a high pressure impeding the contrast-enhancement and delaying the contrast medium wash-out. This is in distinction to the well vascularized benign lesions which like normal organs and tissues contrast-enhance rapidly and have a fast contrast medium wash-out. The degree of contrast-enhancement and wash-out is based on the attenuation measurements of the incidentaloma in the pre-contrast (unenhanced, U), contrast-enhanced (enhanced, E) and delayed (D) phases. The "absolute wash-out" can be calculated thus:

$$(E-D) / (E-U)$$

Depending on whether the investigators, in the various published studies, have performed the delayed scanning at 10 or 15 minutes they apply different threshold values for the resulting quotient to which the result in the individual patient can be compared and these "cut-off" values also vary depending on the local expertise. In the daily clinical setting, an "absolute wash-out" based on a 15 minutes delayed examination < 0,6 indicates that the adrenal tumor may be malignant and > 0,6 that the lesion is probably benign (3-6). The sensitivity to differentiate malignant from benign incidentalomas ranges in these studies ranges 79-89% and the specificity 87-96%. Also, a "relative washout" can be applied when there is no pre-contrast examination and is calculated as: $(E-D) / E$. At a threshold value of 0,4 the sensitivity in these studies ranges 82-96% and the specificity 92-100%. When using a 0,5 threshold value the sensitivity ranges 87-97% and the specificity 98-100% for differentiating the benign from the malignant adrenal tumors.

When interpreting the results of the these contrast medium wash-out calculations it is important to realise that the attenuation measurements may vary depending on technical parameters such as partial volume effects, especially if the incidentaloma is small and thin sections have not been reconstructed. Also, there are operator dependent factors to consider, mainly how the regions of interest (ROIs) for attenuation measurements are drawn and positioned. Moreover, factors related to maintenance such as calibration of the CT scanner, is of importance to acquire reliable attenuation measurements.

The impact of the "absolute wash-out" result on

the patient management varies between centres. In some departments, a quotient > 0,6 in previously uncharacterized incidentaloma with a pre-contrast attenuation >10HU may be taken as evidence that the lesion is benign and that further imaging is unnecessary. In other centers, the result is interpreted differently. Thus, to confirm or rule out the malignant nature of incidentalomas with a pre-contrast attenuation >10HU, radiological follow-up may be performed to measure any size change of the lesion and the result of the "absolute wash-out" may in some departments merely indicate whether this should be done at 3 or 6 months after the time point when the incidentaloma was first detected.

When time is of essence, MRI can be tried in order to visualize microscopic fat in at least some of the incidentalomas with a pre-contrast attenuation >10HU at CT. MRI of the adrenals is performed including signal sequences "in phase" and "out of phase" (7-8). In a benign adrenocortical adenoma, the protons in the mixture of microscopic fat and water within the cytoplasm will add to the signal intensity (in phase) in the image and will also counteract and decrease the signal (out of phase) in the image. Other tumors do not demonstrate, however, this so-called "chemical shift" phenomenon; some benign adrenocortical adenomas with a low concentration of fat - the so called "lipid-poor adenomas" - will escape characterization. As an alternative, especially in the young patients in whom one needs to consider the radiation dose, MRI is advantageous for follow-up of the tumor size when at the same time "in- and out of phase imaging" may be included in order to characterize the lesion if possible. A limitation in this respect are small tumors for which CT is generally preferred because of the better spatial resolution.

Nuclear Medicine Imaging

The imaging work-up and follow-up is for most incidentalomas adequately managed by CT and MRI. For a minority of these tumors further characterization is, however, advantageous and for these patients there are several molecular imaging techniques available.

¹³¹I-norcholesterol (NP-59) scintigraphy

¹³¹I-norcholesterol (NP-59) is no longer available in most European countries since the production of the tracer has been terminated. It was previously primarily used for scintigraphy including single photon emission computed tomography (SPECT) for preoperatively localization of aldosterone secreting adrenocortical tumors (Conn adenomas) in primary hyperaldosteronism (9).

Currently, hypertensive patients with a biochemical diagnosis of primary hyperaldosteronism instead undergo lateralisation of the Conn adenoma by selective venous sampling and subsequent hormonal analysis. A finding of an adrenal tumor at morphological imaging does not alone suffice for preoperative localization because in occasional patients this adenoma is non-secreting and a very small Conn adenoma is instead harbored in the contralateral adrenal.

Positron emission tomography of adrenal tumors

Positron emission tomography (PET) using [^{18}F]fluoro-deoxy-glucose (^{18}FDG) has developed as a powerful molecular imaging technique, mainly in oncological patients, and is today regularly combined with CT (PET/CT) to also acquire a morphological reference to the functional image findings and vice versa. The use of ^{18}FDG for oncological PET/CT is based on its accumulation to a higher extent in malignant compared to benign tumors and most normal tissues, except the brain. There is also a high accumulation of ^{18}FDG in kidney since it is excreted into the urine and high radioactivity concentrations are found in the urinary collective system and bladder. ^{18}FDG -PET/CT is mainly used in oncology for tumor characterization, staging, detection of current disease and therapy monitoring and is well established in lung cancer, lymphoma, colorectal cancer and melanoma.

^{18}FDG -PET for characterization of adrenal tumors

^{18}FDG -PET and ^{18}FDG -PET/CT have also been used for adrenal imaging in several studies to differentiate benign from malignant tumors (10-24). For patients in whom the incidentaloma comprises a metastasis ^{18}FDG -PET/CT may be useful, to detect other metastases and to find the primary tumor when this has not previously been diagnosed. Also in adrenocortical cancer, ^{18}FDG -PET/CT can be used for staging of the disease.

In the image reading, evaluation of the ^{18}FDG uptake in various organs and tissues is generally assessed visually. To facilitate the PET image evaluation, measurements of the ^{18}FDG uptake in tumors and normal organs are regularly performed and often the liver is used as a normal tissue reference. The rationale for calculating the tumor-to-liver ratio is that malignant lesions generally exhibit a higher ^{18}FDG uptake than that of the liver.

Many previously published studies that have applied ^{18}FDG -PET and ^{18}FDG -PET/CT to differ be-

nign from malignant adrenal tumors have been included in a recent systematic review and meta-analysis (24). This comprises 21 studies published 1995-2009 including 1391 lesions (824 benign and 567 malignant) in 1217 patients. The mean sensitivity to differentiate a malignant from a benign adrenal lesion was (95% Confidence Interval, CI) 0,97 (0,93-0,98) and the specificity was 0,91 (0,87-0,94). The results were similar when ^{18}FDG -PET and ^{18}FDG -PET/CT was used. The various image evaluation techniques that had been applied to differentiate benign from malignant adrenal lesions such as visual analysis, measurements of tumor uptake of ^{18}FDG or tumor-to-normal tissue uptake ratios were equally efficient.

One large ^{18}FDG -PET study published after this meta-analysis that is worthy of mentioning aimed at differentiating benign from malignant adrenal tumors in 81 cancer patients by using the adrenal tumor-to-liver ratio. A cut-off value of 1,8 for the adrenal tumor-to-liver ratio corresponded to 87% sensitivity and 91% specificity whereas a cut-off value of 1,68 corresponded to 90% sensitivity and 91% specificity (2). However, the inherent problem in using uptake ratios, such as the adrenal tumor-to-liver ratio, is that the specificity in this assessment is impaired by the fact that some benign adrenal lesions also demonstrate a moderate to high ^{18}FDG uptake, such as benign and malignant pheochromocytomas that generally have a moderate to high ^{18}FDG uptake (25-26).

^{18}FDG -PET imaging of adrenocortical cancer

A French study on ^{18}FDG -PET/CT imaging of adrenocortical cancer (ACC) included 28 patients (27). The results of ^{18}FDG -PET/CT were correlated to those at CT that was performed separately. The reason for this was that the CT examination performed in conjunction with PET was used merely for attenuation correction and anatomical correlation of the PET findings and had been carried out without intravenous contrast-enhancement using reduced radiation dose. For ^{18}FDG -PET/CT the lesion based sensitivity and specificity was 90% and 93%, respectively, and the corresponding figures for CT was 88% and 82%. Interestingly, 12% of the lesions were diagnosed only by ^{18}FDG -PET/CT and 10% only by CT. In the patient-based analysis, the methods were concordant in 25 patients and showed 95% sensitivity for both ^{18}FDG -PET/CT and CT and 83% and 100% specificity, respectively. Thus, in only three patients the methods were discordant. ^{18}FDG -PET/CT was false positive in one patient that was true negative by CT, depicted recurrent tumor in one patient that was missed by CT and missed a liver lesion that was diagnosed by CT. In

a smaller study twelve patients underwent ^{18}F FDG-PET to assess recurrent or metastatic adrenocortical cancer the sensitivity was 83% (28). In two of the patients, small lung metastases and a liver metastasis, respectively, escaped detection.

^{11}C -metomidate-PET for characterization of adrenal tumors

Etomidate (ETO) has been used as an anesthetic agent in veterinary medicine. Metomidate (MTO) is the methyl-ester of etomidate and both are inhibitors of the CYP11B enzymes 11 β -hydroxylase (CYP11B1, P45011 β) and aldosterone synthase (CYP11B2, P450aldo) that are involved in the cortisol and aldosterone synthesis, respectively. Based on the high affinity to these enzymes and the consequently specific adrenocortical binding properties, ETO and MTO have been labeled with ^{11}C and ^{18}F and used as PET tracers for adrenal imaging. In the first report on ^{11}C -MTO and ^{11}C -ETO their binding capacity was investigated by frozen section autoradiography using adrenal cortical tissue from different species. The binding of both ^{11}C -MTO and ^{11}C -ETO was high and specific and was confirmed in vivo by PET imaging in monkeys. In the first clinical study (29) ^{11}C -MTO was chosen as the tracer because of the better radiochemical characteristics. In this study, 15 patients with various adrenal masses underwent ^{11}C -MTO-PET. All tumors of adrenocortical origin (6 adenomas, 1 hyperplasia, 2 adrenocortical cancers) showed a high ^{11}C -MTO uptake and were unequivocally distinguished from the non-cortical lesions (1 myelolipoma, 1 pheochromocytoma, 1 metastasis, 1 mesenchymal tumor and 2 cysts) that were devoid of tracer uptake. ^{11}C -MTO uptake was found in the normal adrenals and in the stomach high radioactivity concentration appeared in the gastric juice into which the tracer and/or its metabolites are transported.

Interestingly, also for ^{18}F FDG a large variation in tracer uptake in adrenocortical cancer has been reported in a prospective study of 77 patients with adrenal incidentalomas that included 22 subjects with adrenocortical cancer (30) and in two studies PET using ^{11}C -MTO and ^{18}F FDG have been compared in the same patients (31-32). In 19 patients with various types of adrenal lesions (10 benign cortical adenomas, 2 pheochromocytomas, 1 adrenocortical cancer, 3 malignant non-cortical tumors, 1 lipoma, 1 cyst, 1 normal adrenal) ^{11}C -MTO accumulated in all tumors of adrenocortical origin and ^{18}F FDG-PET detected 2/3 malignant tumors whereas the benign lesions were difficult to visualize or not seen at all (31). In 16 patients with a mixture of adrenal tumors (1 adrenal metastasis, 1 adrenocortical cancer, 1 malignant

phaeochromocytoma, 10 adenomas, 1 hyperplasia, 2 benign pheochromocytomas) ^{11}C -MTO-PET differed the adrenocortical tumors from those of non-adrenocortical origin and ^{18}F FDG-PET differentiated the malignant from the benign tumors (32).

The largest study to date on ^{11}C -MTO-PET comprised 73 patients with 75 adrenal tumors (26 adenomas, 13 adrenocortical cancers, 8 hyperplasia, 6 pheochromocytoma, 3 metastases, 19 tumors of non-adrenal origin) in a wide size range of 1-20cm (33). By applying a strict correlation of the PET findings with the histopathological diagnosis, 89% sensitivity and 96% specificity was determined in distinguishing adrenocortical from the non-adrenocortical lesions. Three tumors that all had a diameter $\leq 1\text{cm}$, were missed and led to the lower sensitivity in this study than in previous reports. Measurements of ^{11}C -MTO adrenal tumor uptake were correlated to the histopathological findings. The PET measurements could, however, not distinguish the benign from the malignant adrenocortical tumors but with a tumor-to-normal (contralateral)-adrenal ratio $>1,4$ there was a 99,5% risk of an adrenocortical tumor (adenoma or cancer).

The role of ^{11}C -MTO-PET in comparison with CT and MRI was tested in the clinical setting for the imaging work-up of 44 adrenal incidentalomas in 38 patients (34). Morphological imaging proved sufficient for all but a few patients in whom CT and MRI failed to characterize the tumor but where ^{11}C -MTO-PET added information by defining the adrenocortical or non-adrenocortical origin of the lesion.

The role of ^{11}C -MTO-PET in patients with primary hyperaldosteronism was investigated in two studies (35-36). Nine patients with small Conn adenomas (average 1,7 cm; range 1-2,5 cm) were examined and then re-examined after three days of per oral dexametasone medication. For matters of comparison, two patients with non-functioning adrenocortical adenomas were included into the study. The tumor visibility was similar in both examinations and, although the tumor-to-normal-adrenal ratios were lower in the post-treatment examinations, this difference was not statistically significant. It was hypothesized that corticoid treatment decreases ACTH secretion and thereby the 11beta-hydroxylase concentrations in normal adrenal parenchyma but not in Conn adenomas. The expected increase of the tumor-no-normal tissue contrast should thereby facilitate detection of small Conn adenomas. This hypothesis could, however, not be verified (35). In a further attempt to improve the image contrast, principal compartment analysis (PCA) was applied to ^{11}C -MTO-PET from

seven patients who were examined according to the same protocol before and after dexametasone treatment (36). By PCA it was possible to isolate separate image volumes, representing the early, intermediate and late pharmacokinetic phases of ^{11}C -metomidate in these dynamic examinations performed 0-45 minutes after tracer injection. The Conn adenomas were best depicted in the PCA component that represented the intermediate ^{11}C -MTO pharmacokinetics. In this component the image noise decreased and the tissue contrast improved. No firm conclusions could be drawn regarding the effect of dexametasone treatment on the ^{11}C -MTO uptake in Conn adenomas and normal adrenals.

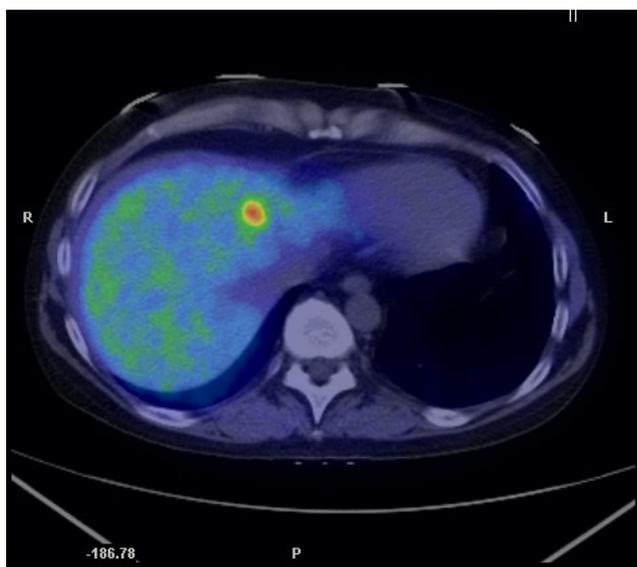


Figure 2: A transaxial PET/CT fusion image with ^{11}C -metomidate in a patient with recurrent disease from a previously resected adrenocortical cancer. A high focal tracer uptake is seen in a liver metastasis.

^{11}C -metomidate-PET in adrenocortical cancer

In a study concentrated exclusively on adrenocortical carcinoma patients 13 ^{11}C -MTO examinations were performed in 11 subjects and correlated to CT, findings at surgery, autopsy and histopathological together with clinical follow-up (37). ^{11}C -MTO-PET visualized all viable tumors with high tracer uptake, and revealed two more lesions compared to CT. Three necrotic tumors, detected by CT were detected as false negative observations by ^{11}C -MTO-PET, as confirmed at surgery and histopathological examination. A true negative observation was obtained at PET in the case of a suspected liver metastasis at CT. The ^{11}C -MTO uptake was higher in tumors than in normal adrenal

and liver. ^{11}C -MTO-PET performed in connection with medication that could potentially affect the tracer uptake, such as adrenal steroid inhibitors (metapyrone, ketoconazole) and chemotherapy (streptozocin, p'-DDD, 5-FU), resulted in lower uptake in viable tumors and in normal tissues, for example liver and normal adrenal, compared to examinations executed when the patients were without such treatment. An example of metastatic adrenocortical cancer diagnosed by ^{11}C -MTO-PET/CT is illustrated in Figure 2.

Conclusion

In most patients, CT and MRI are sufficient for characterization and follow-up of adrenal tumors. Functional imaging by PET with ^{18}F FDG-PET and ^{11}C -MTO may be used as problem solving tools when CT and MRI fail. In centers where this technique is available, ^{11}C -MTO-PET/CT is currently, used also preoperatively in patients with suspected adrenocortical cancer and for follow-up and detection of recurrent disease.

Competing Interests

The author has declared that no competing interest exists.

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