

Incidentally detected adrenal lesions

Radiological aspects

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Cover illustration: A cute adrenal lesion found in the Adrenal Study

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*Vivas ut possis
quando nequis ut velis*

Till Ivar, Henry & Tess

ABSTRACT

Incidentally detected adrenal lesions (“adrenal incidentalomas”) have become a growing clinical problem due to increased and refined radiology methods. Autopsy studies show frequencies as high as 7-8% in the elderly. A large part of such lesions give no health problems but some can be related to hormone overproduction or malignant disease. Dedicated radiological imaging can often reveal whether the lesion is benign or malignant, based on e.g. its fat content and wash-out of contrast medium. Our first aim was to determine the frequency of adrenal lesions incidentally detected by radiological methods in a geographically defined region. Secondly, to characterize these lesions biochemically and radiologically in a 2-year follow-up study. Thirdly, the variability of adrenal lesion characterization was investigated. During 18 months all new cases of incidentally detected adrenal lesions were prospective reported from 19 radiology departments in Western Sweden. Included patients were examined with dedicated adrenal computed tomography (CT) and/or magnetic resonance imaging during 2 years follow-up. Biochemical and clinical examinations were performed at detection and after 2 years. To validate the frequency of submitted cases, a re-evaluation of 3.827 abdominal CT-examinations was performed. The characterization of adrenal lesions was validated by an interobserver analysis of 40 adrenal lesions and a phantom study of 8 different CT-machines. In total, 339 patients with adrenal lesions detected at CT were included. The re-evaluation showed that the CT frequency of adrenal lesions varied from 1.8 to 7.1% (mean 4.5%) between hospitals, while the initially reported mean frequency was 0.9%. Follow-up of patients with-out extra-adrenal malignant disease (n=226) revealed no primary adrenal malignancy. Fourteen patients (6.6%) were operated and benign hormone-producing tumours were verified in 3%. All were identified at first examination, and follow-up revealed no additional cases of hormone producing tumours. More than 80% of these patients had radiologically benign lesions. Benign adrenal lesions were found in 74% of patients with history of malignant disease, in 53% of those with concurrent malignancy and in 25% of those with metastatic disease. In patients with two or more adrenal CT-examinations performed over two years 20-25 % of adrenal lesions showed such variations in attenuation values that their classification as “benign” or “indeterminate” would change. Both interobserver analysis and phantom analysis showed some differences in attenuation measurements.

Adrenal lesions detected at radiological examinations are common and frequency figures approach those reported at autopsy. Dedicated imaging and biochemical testing is highly recommended early after detection and further follow-up is recommended for lesions that still are indeterminate after this process. Follow-up should preferably be done with the same CT equipment, including a calibration instrument and the same observer to minimize observer and inter-scanner variability.

Keywords: Incidental finding, Adrenal incidentaloma, Adrenal Gland Neoplasm, Computed Tomography, Magnetic Resonance Imaging, Follow-up Studies, Oncology, Observer Variation, Phantom Studies

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SAMMANFATTNING PÅ SVENSKA

Binjurarna är två små hormonproducerande organ som är lokaliserade strax ovanför och framför njurarna, en på varje sida. Hormonerna de producerar påverkar metabolismen och salt- och vatten balansen i kroppen. De tillverkar också hormoner vid stress.

Det är mycket vanligt med förändringar/tumörer i binjurarna, obduktionsstudier har visat att frekvensen ökar med åldern och upp till 7-8% av 70-åringar kan ha en binjurförändring. Det har blivit allt vanligare på senare år att man hittar en binjurförändring hos en patient som undersöks för andra än binjurerelaterade symptom, med hjälp av olika radiologiska metoder (datortomografi (DT), magnetkamera undersökning (MR) eller ultraljud). Dessa accidentellt hittade binjurförändringar har även kallats adrenala incidentalom i litteraturen. Att det blivit ett vanligare fynd nuförtiden beror delvis på att upplösningen i bilderna har blivit bättre och att användningen av dessa metoder har ökat kraftigt.

De flesta binjurförändringar ger inga hälsoproblem men en liten del kan vara förknippade med överproduktion av hormoner eller med malignitet. På senare tid har lätt grad av hormonöverproduktion så som subkliniskt Cushings syndrom och subklinisk aldosteronism uppmärksammas som potentiell orsak till symptom som exempelvis högt blodtryck, övervikt och diabetes. Att hitta hormonöverproducerande eller maligna (elakartade) binjurförändringar ger möjlighet till behandling. Nu för tiden kan man med hjälp av röntgen i form av DT eller med MR till stor del skilja maligna förändringar från de övriga. Man bedömer graden av fettinnehåll i binjurförändringen och finns det tillräcklig mängd fett är förändringen i princip aldrig en cancer.

Denna avhandling är ett samarbetsprojekt mellan radiologi (röntgen) och endokrinkirurgi/-medicin.

Vi studerade patienter med nyupptäckta binjurförändringar som rapporterats in från hela Västra Götaland och norra Halland under en 18-månaders period. Dessa patienter följdes upp under 2 år med upprepade röntgenundersökningar, främst datortomografi, med tanke på tillväxt och utseende av binjurförändringen. Läkarbesök med provtagning utfördes också för att hitta ofysiologiskt hormonproducerande tumörer.

Vi fann att frekvensen av fall med binjurförändringar påvisade med DT som rapporterades in från röntgenavdelningarna var relativt låg, från 0 till 2.4 %. En eftergranskning av ca 3800 DT-bukundersökningar ur samma material visade istället en medelfrekvens på 4.5%, med variation från 1.8 till 7.1% mellan de olika sjukhusen.

Uppföljningen av patienter med binjurförändring som inte hade några tecken på malignitet utanför binjurarna visade att av dessa patienter opererades 6.6% och totalt hade endast 3.1% hormonproducerande tumörer. Ingen primär binjurmalignitet hittades. Alla hormonproducerande binjurförändringar hittades vid första kontrollen och uppföljningen gav inga nya fall. Uppföljningen kan troligen minskas ner betydligt jämfört med tidigare riktlinjer. (De nationella riktlinjerna har redan nu förenklats).

Uppföljningen av patienter med annan malign sjukdom visade att mellan 25-74% av dessa patienter hade benigna (godartade) binjurförändringar, beroende på i vilket stadie av malign sjukdom patienterna var i.

Det påvisades en variation i den radiologiska karaktäriseringen av binjurförändringarna vid uppföljningen. Flera påverkande faktorer verkar spela in såsom bedömare, utrustning (typ av DT-apparat), och hur DT-apparaten används. Om uppföljning behövs vid oklara binjurförändringar rekommenderas att samma bedömare och samma apparat används varje gång i kombination med ett kalibreringsinstrument för att undvika större variationer i den radiologiska karaktäristiken.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Hammarstedt L, Muth A, Wängberg B, Björnelid L, Sigurjónsdóttir H.A, Götherström G, Almqvist E, Widell H, Carlsson S, Ander S and Hellström M.
Adrenal lesion frequency: A prospective, cross-sectional CT study in a defined region, including systematic re-evaluation.
Acta Radiol 2010;51:1149-1156
- II. Muth A, Hammarstedt L, Hellström M, Sigurjónsdóttir H.A, Almqvist E and Wängberg B.
Cohort study of patients with adrenal lesions discovered incidentally.
Br J Surg 2011; 98:1383-1391
- III. Hammarstedt L, Muth A, Sigurjónsdóttir H.A, Almqvist E, Wängberg B and Hellström M.
Adrenal lesions in patients with extra-adrenal malignancy – benign or malignant?
Acta Oncol 2011 Aug 31. (e-publication ahead of print)
- IV. Hammarstedt L, Thilander-Klang A, Muth A, Wängberg B, Odén A and Hellström M.
Adrenal lesions – variability in radiological characterization
Manuscript

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ABBREVIATIONS

1-mg DST	1-mg overnight dexamethasone suppression test
¹¹ C-MTO	¹¹ Carbon-metomidate
ADC	apparent diffusion coefficient
AI	adrenal incidentaloma
APW	absolute percentage wash-out
CT	computed tomography
DWI	diffusion-weighted imaging
FDG	flourodeoxyglucose
HU	Hounsfield units
mA	milliAmpere
kV	kilovolt
MDCT	multi-detector row computed tomography
MRI	magnetic resonance imaging
NIH	National Institute of Health (United States)
PET	positron emission tomography
ROI	region of interest
RPW	relative percentage wash-out
SDCT	single detector computed tomography
SPECT	single-photon emission computed tomography
SI	signal intensity index

1 INTRODUCTION

This thesis is part of a joint project between the departments of radiology and surgery. The focus in this thesis will be on the radiological aspects of incidentally discovered adrenal lesions. The biochemical and clinical aspects have been reported in the published thesis by Andreas Muth (1).

1.1 Adrenal Gland

1.1.1 Localization and function

The adrenal glands are located in the retroperitoneal space, superior and slightly ventromedial to the kidneys. Each gland has a body with medial and lateral limbs. The shape can be linear, triangular, often as a V or inverted Y. Figure 1 shows examples of normal adrenal glands at computed tomography (CT).

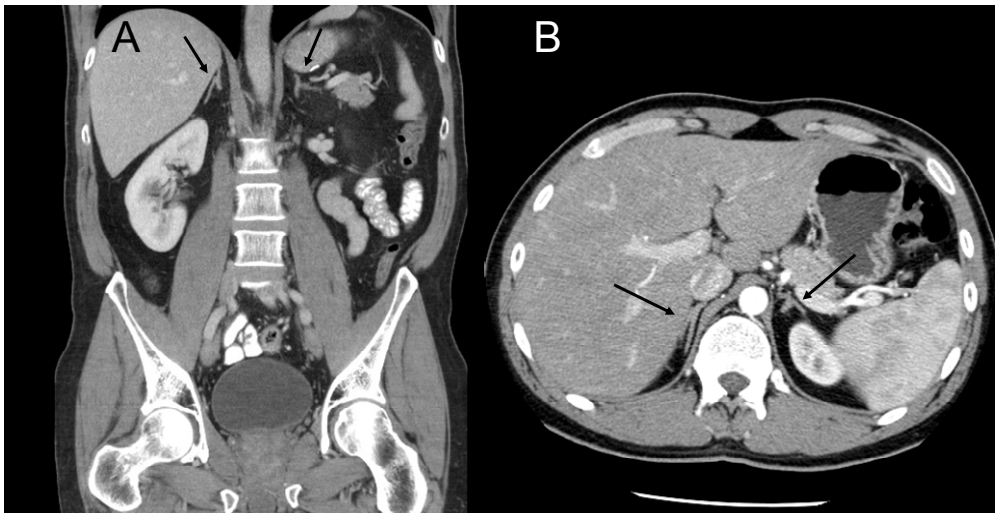


Figure 1. CT images of normal adrenal glands. A) Coronal/frontal view. B) Axial view.

The adrenal gland is composed of two separate embryological, functional and morphological units: the cortex and the medulla. Microscopically, the normal adrenal cortex shows three zones: the *zona glomerulosa*, which produces mineralocorticoids (principally aldosterone); the *zona fascicularis* and *zona reticularis*, which produce glucocorticoids (corticosteroids), androgens and estrogens. The adrenal medulla secretes adrenaline and noradrenaline. Most of the cortical tissue is located in the limbs, while the medullary tissue is located in the body of the gland (2). Normal cortical cells contain lipid, and cells with abundant lipid appear “clear” on routine histology, and those with less lipid appear as “compact” cells.

The size of the adrenal glands at axial CT was assessed by Vincent et al in 1994 (3). The mean body width (measured at the junction of the adrenal limbs and the body, perpendicular to the long axis of the body) was 0.61 (range 0.3-1.2) cm in the right and 0.79 (range 0.4-1.2) cm in the left adrenal. The authors also measured normal limb width in each adrenal gland showing a maximum width on both sides of 0.5 cm in the axial plane.

1.1.2 Lesions in the adrenals

Due to the increased use and improved technical quality of radiological imaging, incidentally detected adrenal lesions have become an important clinical issue. In the literature the term “adrenal incidentaloma” has often been used for this kind of lesions. For further discussion regarding this term see thesis by A. Muth (1).

In autopsy studies the smallest adrenal lesion classified as adenoma was 2-3 mm in diameter (4-6) and size limits are somewhat difficult to apply since the normal adrenal gland can provide a large variety in shape. Autopsy studies have also shown that the prevalence of adrenal mass lesions varies

depending on the age of the population – adrenal lesions are more common in the elderly. In patients over 60 years, adrenal lesions have been found in 8-12 % (4-6).

1.1.3 Biochemical characterization of adrenal lesions

A thorough evaluation of the patient history and a physical examination combined with biochemical screening is important after the detection of adrenal lesions. The rationale behind this is to identify hypersecretory lesions that often require surgical treatment. The most common types of hormone-producing lesions are adrenocortical cortisol-producing tumours (Cushing's syndrome or subclinical hypercortisolism), adrenocortical aldosterone producing tumours (primary aldosteronism), and pheochromocytomas (catecholamine-secreting tumours originating from the adrenal medulla). The frequency of hypersecreting lesions among incidentally detected adrenal lesions has varied from 5 to 15 % in clinical studies (7-9). The details regarding biochemical and clinical tests are not further evaluated in this thesis but can be studied in the thesis by A. Muth (1).

1.1.4 Benign adrenal lesions

The most common lesion in the adrenal is a benign adenoma without evidence of hormone production. The precise frequency of the different adrenal lesions is unclear, as results in reported series vary.

Hematoma and cysts are usually non-neoplastic but may be related to an underlying tumour; e.g. adrenocortical carcinoma, pheochromocytoma or adrenal metastases. The majority of pheochromocytomas are benign but may give serious hormonal symptoms. Other benign lesions include myelolipomas, hemangiomas, lipomas and granulomatous lesions (10, 11).

1.1.5 Malignant adrenal lesions

Adrenocortical carcinoma and malignant pheochromocytoma are the most common primary adrenal malignancies but the most common malignancy in the adrenals is a metastasis from an extra-adrenal primary tumour. Abrams et al (12) found that adrenals were the seventh most common metastasis site, approximately 27% of post-mortem examinations in patients with a malignant neoplasm of epithelial origin showed adrenal metastases. Rich sinusoidal blood supply may be one of the explanations (13). The etiology of metastatic tumours of the adrenal gland is most often lung, stomach/oesophagus, colorectal, breast and pancreatic carcinoma followed by lymphoma (12, 14, 15).

1.2 Adrenal characterization in radiology

Adrenal lesions can be detected by different radiology techniques including ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). Further evaluation of the detected lesion can be performed by dedicated CT, MRI, positron emission tomography (PET) or other scintigraphic methods and by fine needle aspiration or biopsy. The most commonly used method for the evaluation/characterization of adrenal lesions is CT because of its widespread availability, capability, high speed and low cost. The other methods are often used as a complement and will be described in more detail below.

The important radiological question is whether the detected adrenal lesion is benign or malignant, which is the focus of this thesis. However, differentiation between various benign lesions can also be done, using e.g. CT and MRI. Examples of different adrenal lesions found in our studies (Paper I-III) at CT and MRI are shown in Figure 2-4.



Figure 2. CT images of right sided benign adenomas.

1.2.1 Lipid content in adrenal adenomas compared to other lesions

The adrenal cortex and many benign adrenocortical tumours contain cells with abundant intracytoplasmic fat (composed mainly of cholesterol, fatty acids, and neutral fat) whereas malignant adrenal lesions do not. Korobkin et al (16) compared the percentage of lipid-rich cortical cells in histological sections from resected adrenal adenomas with unenhanced CT and chemical shift MRI. The proportion of lipid-rich clear cells and lipid-poor compact cells were assessed in the resected adenomas. If fat is present in sufficient concentration the unenhanced CT attenuation value, measured by Hounsfield Units (HU), will be low and a relative change in signal intensity on chemical shift MRI will be visible.

Boland et al (17) made an analysis of pooled data from ten CT studies in an attempt to identify the optimal threshold of CT attenuation value to differentiate benign from non-benign lesions. They pointed out that the results were based on different CT scanners and different CT scanning

protocols. The thresholds chosen depend on e.g. the patient population and the cost-benefit approach to patient care. With a threshold of 10 HU the sensitivity and specificity in this study was 71 % and 98%, respectively. After the publication of this study, the threshold of 10 HU has been used in clinical practice worldwide. The authors also pointed out that to be sure that a lesion is benign (100% specificity), one should use a threshold value of 2 HU on unenhanced CT. However, this is at the cost of a very low sensitivity (47%).



Figure 3. A) Right-sided lipid-rich adenoma at MRI, in-phase image compared to B) same adenoma on out-of phase image where the lesion becomes darker than on in-phase image. C) Left-sided cystic adrenal lesions with calcified margin at CT and D) on MRI.

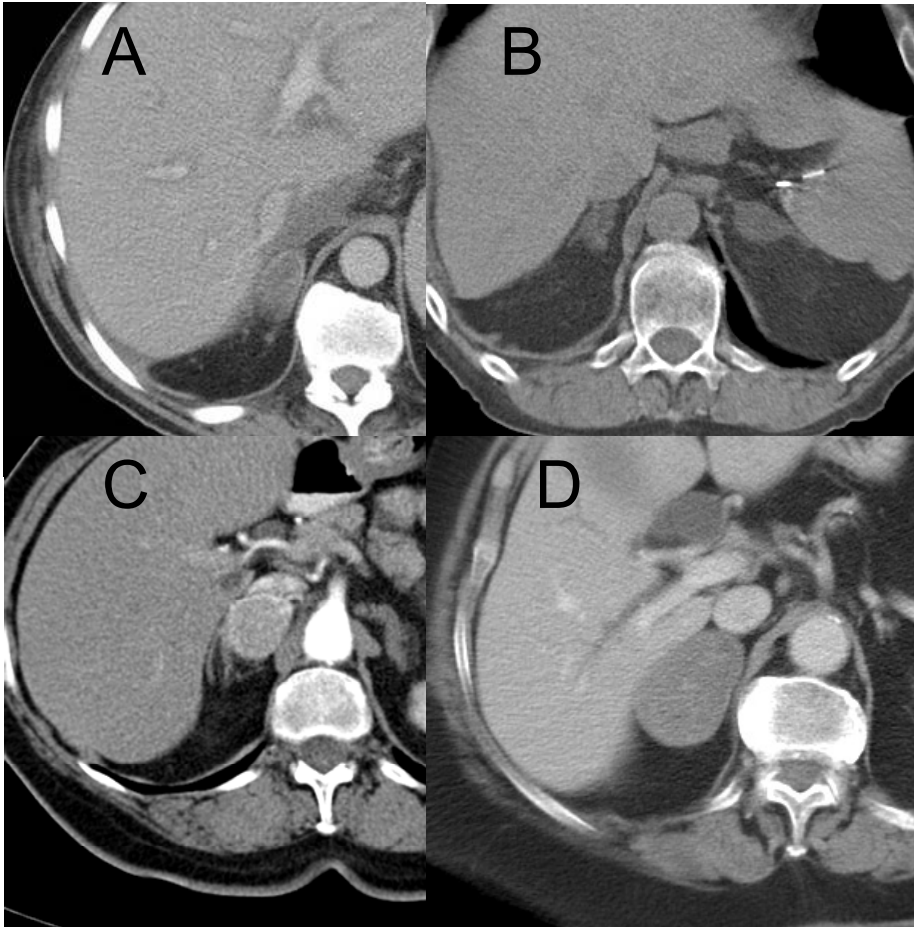


Figure 4. CT-images of adrenal lesions. A) Right-sided adrenal haemorrhage. B) Bilateral hyperplasia. C) Right-sided pheochromocytoma. D) Right-sided metastasis of lungcancer.

1.2.2 CT contrast wash-out in adrenal lesions

Results from the late nineties showed that in late contrast phase, after 10 to 30 minutes, the attenuation in an adrenal adenoma was significantly lower than in other solid lesions (16, 18-22). Adenomas, both lipid-rich and lipid-poor, “wash-out” the contrast material faster than other lesions. The explanation for this is unknown but different angioarchitecture with “relative preservation of cellular membrane integrity and less expansion of the effective

extracellular space due to tumour infiltration in adrenal adenomas” is a possibility (19).

Using attenuation values from unenhanced, enhanced and late enhanced contrast phases a calculation of absolute (APW) or relative (RPW) percentage wash-out can be done using these formulas:

$$APW = \frac{\textit{Attenuation value}_{enhanced} - \textit{Attenuation value}_{delayed enhanced}}{\textit{Attenuation value}_{enhanced} - \textit{Attenuation value}_{unenhanced}} \times 100$$

$$RPW = \frac{\textit{Attenuation value}_{enhanced} - \textit{Attenuation value}_{delayed enhanced}}{\textit{Attenuation value}_{enhanced}} \times 100$$

In some studies (18, 19), calculation of RPW appears favourable for the diagnosis of adenoma, as compared to APW. Thus, the sensitivity and specificity are slightly higher for RPW than APW, but the RPW still tends to overestimate the true wash-out for adenomas and underestimate the wash-out of nonadenomas (18). Korobkin et al (18) recommended the use of 15-min delay enhanced scan but others have suggested 10-min delay (19, 22, 23). Szolar et al (19) recommended a 30 minute delayed scan if the lesion had low absolute and relative percentage wash-out calculated from 10 min delayed images. Other studies also evaluated 30 min delay, demonstrating sensitivity and specificity as high as 97% and 100%, respectively, for finding lipid-rich adenomas (18, 24). In clinical practice, however, a shorter delay is preferred for logistical reasons. The 10 min delay has lately been questioned because of the reduced sensitivity in calculating the APW and RPW compared to 15-min delay (25).

1.2.3 MRI of adrenal lesions

MRI has the advantage of not involving exposure to ionizing radiation. The images produced by MRI reflect the proton density and the chemical milieu of the tissue being imaged (26). On conventional T1-weighted and T2-weighted images without fat suppression, the adrenal glands have homogeneous, low signal intensity, in contrast to the surrounding high-signal intensity fat, and are isodense or hypointense relative to liver.

In 1992, Mitchell et al (27) reported that chemical shift MRI technique could be used to identify lipid-rich adenomas. The difference in resonance frequency between protons in water and in triglyceride molecules reflects the fat content (26). On out-of-phase gradient-echo imaging, there is a signal loss at the periphery of the gland as a result of fat-water phase cancellation at the interface with adjacent fat, leading to a chemical shift artefact. This artefact appears as a black-and-white band, see figure 3B. Lipid-poor adrenal lesions, which have a low lipid-to-water proton ratio, demonstrate signal intensity that is unchanged on out-of phase images compared with in-phase images. Lesions with either fat or water components, but not both, in the same image voxel will not display signal cancellation. The adrenal signal intensity index can be calculated to objectify the signal loss (28) but the evaluation of chemical shift change visually has been reported to be as effective as quantitative methods (29).

To differentiate non-adenomas from adenomas, also gadolinium-enhanced MR imaging has been tested. Studies show that contributing information can be archived from MR contrast enhancement with wash-in and wash-out calculations (30, 31) but this is not yet in common practical use and further studies may be needed.

Recent focus has been on diffusion-weighted MR imaging (DWI). DWI has been shown to be helpful in the characterization of tumours on the basis of diffusion effects using apparent diffusion coefficient (ADC) measurements, used to assess the mobility of water molecules (32). In theory, malignant tumours have lower ADC values compared with benign lesions, but in a recent study using ADC values, Miller et al (33) were unable to distinguish benign from malignant adrenal lesion.

1.2.4 Nuclear imaging of adrenal lesions

Adrenal gland scintigraphy uses radiopharmaceuticals with specific imaging characteristics for the adrenal cortex and medulla. These radiopharmaceuticals mimic substrates or native hormones and enter metabolic or adrenal hormone synthesis pathways and provide information regarding target tissue function. The integration of anatomical imaging with functional imaging is important for defining the adrenal function and in diagnosing and staging of malignant lesions. The combination of anatomical and functional imaging has been enhanced with PET-CT and single-photon emission computed tomography (SPECT). Functional imaging of hypercortisolism, primary aldosteronism, hyperandrogenism (virilisation), adrenomedullary tumours (pheochromocytomas and paragangliomas) is possible when evaluating patients with these diseases. Sometimes these methods also facilitate diagnostic localization, e.g. of paragangliomas (extraadrenal lesions producing nor-adrenaline).

In patients with malignant disease, integrated PET-CT can be cost effective for the evaluation of the detected adrenal lesion. Some studies have shown accuracy of PET-CT comparable to that of dedicated CT (34, 35) while others show slightly higher sensitivity and specificity with dedicated CT (36). Fluorodeoxyglucose (FDG) PET-CT is

interpreted as positive for malignancy if the FDG uptake in an adrenal lesion is greater than or equal to that of the liver. However, FDG uptake is not tumour specific. It can also be seen in conditions with inflammation and posttraumatic repair, but with the combination of FDG PET and CT most of the false-positive findings can be identified. Still, false-positive cases of adrenal lesions have been reported in 5-6 % at (FDG) PET-CT (35). False-negative cases have also been reported due to hemorrhage, necrosis and lesion size (≤ 10 mm) (34, 37, 38) and metastatic lesions from pulmonary adenocarcinoma can show little FDG uptake (38).

^{11}C -metomidate (^{11}C -MTO) is another tracer that can be used for PET evaluation of adrenocortical lesions. Studies show that adrenocortical adenoma and adrenocortical carcinoma can be distinguished from non-cortical lesions (39-42). MTO-PET shows no uptake in metastases or necrotic areas. Another limitation is that uptake is shown both in adrenocortical adenoma and adrenocortical cancer (40) but with extra-adrenal uptake of the metomidate tracer, metastatic disease can be suspected. MTO-PET has also been shown to be able to detect and localize small (< 1 cm) adenomas in patients with primary aldosteronism (43). This could be an alternative for the cumbersome adrenal venous sampling that is the current practice.

1.2.5 Fine needle aspiration/biopsy of adrenal lesions

Percutaneous needle biopsy has a very limited role in the characterization of adrenal lesions and has successively declined in importance as CT wash-out calculations and other methods have been introduced. Biopsy is most useful for patients with known extra-adrenal malignancy with a suspected metastatic adrenal lesion, but these can usually be diagnosed by dedicated adrenal CT, MRI or integrated PET-CT. One important limitation of fine needle aspiration/

biopsy is that it cannot reliably differentiate benign cortical tissue from malignant cortical tissue (44, 45). Fine needle aspiration/biopsy should only be performed if clinical and imaging examinations are inconclusive and if the result of the aspiration/biopsy can be expected to change patient care.

1.3 Computed tomography (CT) technique

1.3.1 CT development

The word tomography derives from the Greek word “tomos” meaning “slice” or “section” and “graphia” meaning “describing”. Computed tomography is made possible by digital computation of differences in x-ray absorption in different tissues. CT can deliver a very precise anatomical map of the body and reveal pathological findings, providing an undisputable help in detection of disease.

In the early CT era, single axial slice imaging was used, usually with 10 mm slice collimations. In the late 80’s the spiral technique evolved that permitted a continuous instead of single slice scanning so that a volume could be calculated and continuous or overlapping images could be reconstructed. This technique used 1.2-5 mm collimation and reconstruction to 3-8 mm slices. In the mid 90’s multidetector-row CT (MDCT) was introduced that made the imaging procedure much faster and allowed slice collimation as small as 0.6 mm. Still, the preferred reconstructed images are usually 2-5 mm. These developments have reduced motion artefacts, partial volume effects, and improved image resolution (46), and allows anatomically accurate multiplanar reconstructions in e.g. coronal and sagittal planes, with increased diagnostic capabilities.

The CT attenuation measured in HU is used to characterize different tissues in the body and thus is also used in the characterization of adrenal lesions. However, it has been

shown that caution is necessary when using absolute HU values as threshold for diagnosis. Several studies indicate size and attenuation variations due to CT equipment, scanning protocol, examination technique, patient size and other factors (47-49).

2 AIM

The general aim of this thesis was to study incidentally detected adrenal lesions, identified at clinically indicated radiological examinations in a defined geographical region.

More specific aims were:

- To investigate the frequency of adrenal lesions incidentally detected at radiological examinations during an 18 month observation period in a defined geographical region (Paper I).
- To further investigate radiological and biochemical characteristics of the detected adrenal lesions by a 2-year follow-up program in patients with and without extra-adrenal malignant disease (Paper II-III).
- To investigate the variability of adrenal lesion characterization over time and factors that may contribute to this variability at computed tomography (Paper IV).

3 METHODOLOGICAL CONSIDERATIONS

Detailed description of materials and methods are given in each paper (I-IV), and only those of particular importance are described below.

A flow-chart describing the adrenal study population in all papers (I-IV) is shown in Figure 5.

3.1 Study region

The studies were performed in the Västra Götaland region including the Northern part of Halland (the region of Western Sweden). Nineteen radiological departments were included (10 local hospitals, 6 county hospitals and one university hospital (main study centre)). Seventeen departments had CT-equipment, 10 had MRI-equipment and all departments had ultrasound service.

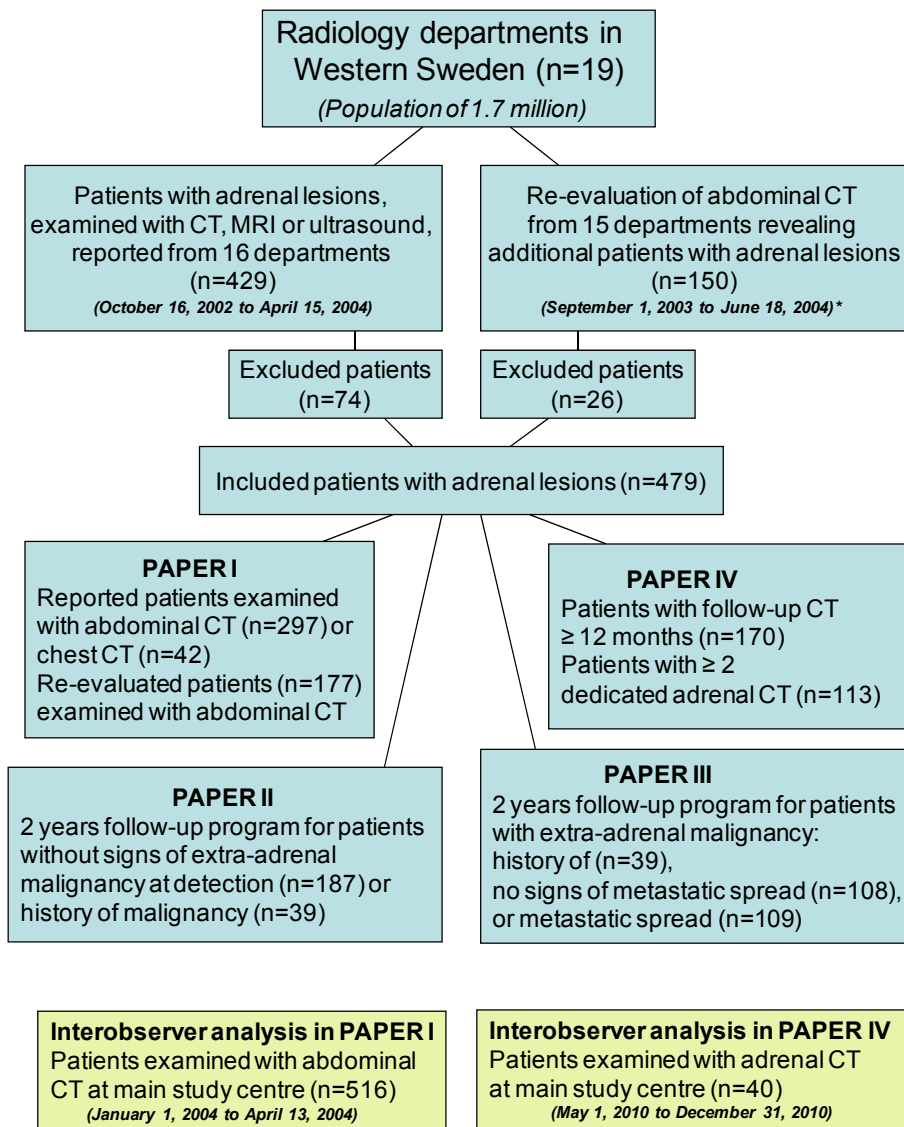


Figure 5. Summarised flow-chart over patient materials in Paper I-IV. There are overlaps in the patient groups in the different papers. * different time periods in different hospitals.

3.2 Frequency/incidence analysis

Autopsy studies have shown that the incidence of adrenal lesions could reach as high as 8 % in elderly populations (>70 years old) (4, 5). A prospective autopsy study by Hedeland et al (6) showed an even higher incidence (12.8%)

in people aged 60 to 69 years. Clinical studies from Italy and Sweden (8, 9, 50) demonstrated high frequency of serious adrenal findings, 22-38% of incidentally detected adrenal lesions were operated and 5-15% were hormonally active. In the region of Western Sweden the population is 1.7 million inhabitants and approximately 280 000 people are over 65 years old. If calculating with an incidence of 7 % there would be a least 19 600 people with adrenal lesions in our elderly population and, based on the above figures from the literature, 4300 (22%) of them would potentially need an operation. If one instead calculates with the whole adult population of Western Sweden (1.3 million) using the lower overall incidence figures (1.45%) reported by Russi et al (51), about 18850 people would have an adrenal lesion and 4147 of them would be candidates for surgery. In our region approximately 22 patients are operated with adrenalectomy per year, (mean figure from 2002-2005) due to adrenal disease/tumour. The figures do not match. The National Institutes of Health (NIH) consensus on management of the clinically inapparent adrenal mass from 2002 (52) called for prospective studies regarding adrenal lesion prevalence and natural history. To try to determine the frequency of incidentally detected adrenal lesions in our defined geographical region we chose to make a prospective study, reporting cases from the source of diagnosis, i.e. the radiological departments. In order to validate the frequency of reported cases, also a re-evaluation was performed on random samples of cases from departments performing abdominal CT examinations (15 of 16 departments).

It is difficult to study the true frequency of a disease in a population. With this study design we hoped to minimize possible patient selection bias. We chose to study CT examinations as it is the most prevalent abdominal examination demonstrating the adrenals, and as it allowed

reliable collection of statistical figures regarding the total number of CT examinations performed in the region.

3.3 Radiological examinations

Radiological detection examinations comprised routinely performed CT, MRI and ultrasound examination, designed for the specific clinical situation. Follow-up examinations were, on the other hand, performed according to a predesigned dedicated adrenal CT and/or MRI-protocol. All images were digital and all cases were sent to the main study centre for validation and were stored in a common digital archive. All lesion measurements and calculations could therefore be performed in the same way in papers I-IV using one digital workstation (Centricity RA600; GE Healthcare, Chalfont St. Giles, UK).

3.3.1 Dedicated adrenal imaging

At the time of planning our study several studies had shown comforting sensitivity and specificity using 10 minute delayed wash-out imaging (19, 22, 24). It also seemed easier to implement the study protocol in our region with this shorter delay and therefore all dedicated follow-up adrenal imaging with CT was performed with 10 instead of 15 minutes delay. Recent studies have subsequently shown that a longer delay (15 minutes) is preferable, with higher sensitivity and specificity (25). In questionable cases one should consider even longer delay (30 minutes), as suggested by Szolar et al (19). The dedicated imaging protocol used in the study is described in detail in paper II.

In paper IV the interobserver analysis was based on dedicated adrenal imaging with 15 minutes delay wash-out since the adrenal imaging protocol in the main study centre was modified after the completion of the follow-up study (paper II and III) in 2007.

3.4 Interobserver analysis (Paper I and IV)

In paper I, the re-evaluation frequency figures were validated by an interobserver analysis with two observers. To understand some of the underlying factors contributing to variability in adrenal measurements, a larger interobserver analysis including 5 observers with varying experience was conducted (Paper IV). A large part of the latter statistical analysis was performed by professor Anders Odén, Department of Mathematical Sciences.

3.5 Phantom analysis (Paper IV)

A limitation in the adrenal lesion study was the variety of CT-scanners used in the study region and also that patients sometimes were examined at a different hospital during follow-up. Thus, in paper IV the variability of repeated measurement within a scanner, and between different scanners were analysed in a phantom study.

3.6 Ethics

The adrenal lesion study was approved by the local Regional Ethical Review Board in Gothenburg (s202-02). Participating patients received oral and written information about the study and gave their consent to participate.

4 RESULTS AND DISCUSSION

4.1 Adrenal lesion frequency

Paper I firstly describes the frequency of adrenal lesions incidentally detected at CT and subsequently reported to the study centre directly from the local radiologists, and secondly the frequency of adrenal lesions identified in a re-evaluation of a large sample (nearly 4000 abdominal CT examinations) from the same population.

All radiology departments with CT equipment (n=17) in the Västra Götaland region and the northern part of the county of Halland participated in this study and results were reported from 16 of 17 departments. The frequency of incidentally detected adrenal lesions in patients without clinically evident malignant disease reported from the radiology departments was 0.5%. This is comparable to other CT studies reporting frequencies from 0.01 to 0.42 % in similar groups of patients (7, 53, 54). Our frequency figures are based on reported cases divided by the number of examinations done in the region during the study period (n=34 044). The number of examinations is not identical to the number of patients examined during this period because some patients were examined more than once. As patients with adrenal lesions were only included once in the statistics we can assume that our frequency figures somewhat underestimate the true frequency.

The overall reported frequency (including patients with a history of malignancy or present malignant disease) in our study varied between the radiology departments, ranging from 0-2.4 % (mean 0.9 %). No single explanation for this variation could be found. In some departments a low reporting frequency could possibly be explained by the use of large CT slice thickness (10 mm), which may have

hampered detection of small adrenal lesions, but other departments used the same slice thickness and reported more lesions. Some small radiology units had low reporting frequency but others had not. The combination of thin slice technique at CT and small size of the department (all reports by the same dedicated radiologist) gained the highest reporting frequency in this study. The re-evaluation performed by one independent radiologist (LH), showed considerably higher frequency figures that varied from 1.8 % to 7.1% (mean 4.6%) between departments. For some units the frequency was rather low even in the re-evaluation, despite the use of thin CT slice technique. The involved radiology departments represented different levels of patient care, and it seems plausible that differences in patient populations regarding age, sex, indications for CT examinations and disease panorama were responsible for parts of the variation in frequency.

In the national Swedish multicentre study by Bülow et al (9) 381 patients with adrenal lesions were reported during 5½ years inclusion time (January 1996 to July 2001). This corresponds to approximately 69 new cases/year in a population of 8.5 million. In our study from a smaller part of Sweden (population of 1.7 million), 151 cases without clinically evident malignancy were reported during 1½ year, corresponding to 101 new cases/year. Our re-evaluation gave fivefold higher figures showing that by focusing on a limited anatomical area at CT (just looking for adrenal lesions), in a non-stressful situation frequency figures will be higher than in a busy clinical situation. Our findings illustrate a potential weakness of multicenter studies that rely on diagnosing and reporting lesions from a large number of participating departments and individuals, in a clinical setting. Participation in a multicentre study is a demanding and time consuming task both for the study centre and the participating units. This must be considered, not only in the initial phase, when exchange and assimilation of study concept, protocols and other information occurs, but also later when continuous reporting of study cases needs to be incorporated into the clinical situation. It is therefore not

surprising that frequency figures tend to get higher when a single, dedicated reader performs the analysis. In order to optimize compliance, it is essential to appoint local contact persons at each site in multicentre settings. Our findings also emphasize the importance of validation of data from multicentre studies.

4.2 Follow-up data on adrenal lesions

Results of the 2-year follow-up programme are presented in Table 1.

Table 1. Summary of the 2-year follow-up programme.

Group	Clinical outcome	N	Radiological outcome		
			Benign	Stationary	Indeterminate
No history or present signs of extra-adrenal malignancy n=187	Adrenalectomy	14	7	0	7
	Complete follow-up with no evidence of hormone production	100	97	3	0
	Normal initial biochemistry, deceased or discontinued follow-up	32	25	3	4
	Regression of lesion	10	7	0	3
	Isolated biochemical abnormalities, not operated	4	3	0	1
	Dead before biochemical follow-up	27	10	2	15
<i>Subtotal</i>		187	149	8	30
History of extra-adrenal malignancy n=39	Adrenalectomy	1	0	0	1
	Complete follow-up with no evidence of hormone production	26	23	3	0
	Normal initial biochemistry, deceased or discontinued follow-up	4	4	0	0
	Isolated biochemical abnormalities, not operated	1	0	0	1
	Dead before biochemical follow-up	7	2	1	4
<i>Subtotal</i>		39	29	4	6
Concurrent extra-adrenal malignancy n=217	Adrenalectomy	7	0	0	7
	Complete follow-up with no evidence of hormone production	31	29	1	1
	Normal initial biochemistry, deceased or discontinued follow-up	42	21	0	21
	Isolated biochemical abnormalities, not operated	1	1	0	0
	Dead before follow-up	136	33	5	98
<i>Subtotal</i>		217	84	6	127
Total		443	262	18	163

4.2.1 Clinical outcome in paper II and III

The NIH-consensus from 2000 (52) recommended a follow-up scheme for incidentally detected adrenal lesions. The major concern was the reported high rate of hormonal hyper-functioning and/or malignant lesions. A review of studies published from 1980 to 2008 by Cawood et al (55) showed that if only studies with “true adrenal incidentalomas” (without extra-adrenal malignancy, without adrenal complaints and often with a size limit of > 1 cm) were included, the prevalence figures of malignant and hyper-functional adrenal lesions were considerably lower. Our follow-up study reported in Paper II confirms this. In our study 187 patients without extra-adrenal malignancy and without symptoms related to the adrenals were included for follow-up. One of them had a lesion < 1 cm (8 mm) which leaves 186 patients in our study with “true adrenal incidentaloma” as defined by Cawood. A total of 7.5 % (14/186 patients) were operated and no primary adrenal malignancy was found. Seven of the 186 patients (3.8 %) had signs of hormone over-production. Follow-up revealed no additional hormonally hyper-functioning and/or malignant cases. This is comparable with studies by for example Reincke et al (56) and Tsvetov et al (57) that found no primary adrenal carcinomas but hormonal over-production in 14.7% and 11.9% cases, respectively, in patients with “true adrenal incidentaloma”. Other clinical studies have shown a rate of 1.2 to 4.7 % adrenal carcinomas and hyper-functioning lesions in 4.1 to 14.9 % of the cases (7, 8, 58, 59). A special aspect is the role of subclinical hypercortisolism in patients with adrenal lesions. A limitation of our study is that detailed work-up for revealing such cases was not included and the rate of subclinical hypercortisolism in our study may be underestimated. However, the issue is complicated by the lack of consensus regarding the definition and diagnostic criteria of this condition (1).

In the group of 39 patients with a history of previous extra-adrenal malignancy one patient underwent adrenalectomy (2.6%), revealing a metastasis from a previously resected renal cell carcinoma. One patient had elevated chromogranin A possibly indicative of a pheochromocytoma but declined further examinations and no other cases of hormone over-production were revealed.

Patients with signs of ongoing extra-adrenal malignancy are presented in paper III. Six of 217 patients were operated (2.8%) and no primary adrenal malignant or hyper-functional hormonal disease was found among these. Seventy-six patients were tested biochemically and only one patient had signs of subtle cortisol overproduction but was not further evaluated due to advanced tumour disease.

Results from patients with history of or ongoing malignancy show that biochemical evaluation reveals very few cases with treatable adrenal disease and no patients had signs of primary adrenal malignancy. Radiological staging remains important in patients with apparently isolated adrenal metastases to identify patients with potentially resectable disease, as surgery may be associated with prolonged survival (60).

As all cases of hormonal over-production were identified already at first biochemical evaluation, our study results do not support hormonal follow-up unless future studies prove the usefulness of follow-up of subclinical hypercortisolism.

4.2.2 Radiological outcome/characterization in paper II and III

As pointed out in the introduction, characterization of adrenal lesions has evolved dramatically from the time when the radiologist almost only described the size of the lesion. First, the ability of unenhanced CT attenuation measurements and MRI chemical shift imaging to show high lipid content of adrenal lesions, allowed differentiation between benign adenoma and non-adenoma. Secondly, the use of contrast media wash-out characteristics at CT improves the distinction of benign from non-benign lesions.

In our adrenal lesion study, lesions were divided into three subgroups using radiological characteristics; benign, stationary indeterminate or indeterminate, se Paper II and III. The follow-up study showed benign lesions in 79.7% (149/187) of patients without extra-adrenal malignancy and in 74.4% (29/39) of patients with a history of malignancy. There was incomplete radiological follow-up in 15.5% (29/187) and 15.4% (6/39) of cases, respectively. Among patients with concurrent extra-adrenal malignancy 38.7 % (84/217) had benign lesions and data was incomplete in 50.7 % (110/217). In other studies 70-94% benign adrenal lesions have been demonstrated in non-oncologic populations (10, 61, 62) and benign lesions occur frequently also in populations with malignancy. In a study by Oliver et al (63) 32% metastatic adrenal lesions were found in patients with non small-cell bronchogenic carcinoma and in a study by Lenert et al (64) 42 % of patients with different kinds of extra-adrenal cancer had metastatic adrenal lesions. Our figures are comparable with these.

A limitation in our studies (Paper II and III) was the use of 10 minutes (instead of 15 minutes) wash-out series in the dedicated adrenal study protocol. The use of this shorter delay and the incompleteness of dedicated radiological

follow-up examinations have probably increased the proportion of cases with indeterminate lesions. Dedicated adrenal examination, including thin sections, non-enhanced and 15 minutes post contrast series, with attenuation measurements and wash-out calculation is highly recommended in all patients with adrenal lesions.

4.3 Variation of adrenal characterization

In our study of patients with adrenal lesions there were signs of variations in the characterization of the lesions during follow-up. In interobserver studies both high and low concordance between observers has been demonstrated regarding size and attenuation measurements (65-70). Our interobserver analysis showed an overall good agreement between the five observers regarding size measurements, there was a 50 % chance that the observers would differ less than 2.5 mm. When measuring attenuation, maximum difference between observers ranged from 0 to 20 HU (mean 4.6 HU) on unenhanced series. Nevertheless, with characterization based on established threshold values (benign lesion if $HU \leq 10$ and/or relative (15 minutes) wash-out > 40 %) the interobserver analysis showed agreement in the classification (benign or indeterminate) in 37 of the 40 lesions (92%).

Other studies have shown that absolute attenuation values measured in Hounsfield units (HU) can vary between different scanners and scanner protocol (47-49, 71, 72). Our results from the phantom study showed a mean intrascanner difference of 2.7 (range 1.8 to 5.1) HU for tap water. Intrascanner attenuation differences for acrylic and polypropylene test tubes showed similar range, from 1.0 to 5.7 HU and 1.0 to 3.7 HU, respectively. The interscanner differences between mean values of tap water were both higher and lower than the intrascanner differences with a

range of 0.3 to 8 HU. The data obtained from the interobserver and phantom analyses show that some of the variance of adrenal attenuation can be caused by the scanner and/or observer.

To reduce adrenal attenuation variability when radiological follow-up is needed we recommend the use of the same CT-scanner, identical CT protocol and the same observer. The use of a calibration instrument each time attenuation values are measured on CT is likely to further improve the reproducibility.

When applying established diagnostic criteria for benign versus indeterminate lesions, 50 of 113 patients (56/136 lesions) examined with dedicated adrenal CT could be reclassified, as benign or indeterminate, during follow-up. This means that almost 50% of our studied lesions could have changed classification if the attenuation value would have been the only classification tool. We have to bear in mind that all these lesions showed size stability for at least 6 months and this alone is used in several studies as proof of benign etiology. Absolute CT numbers are only a part of the evaluation of the adrenals and this emphasizes the importance of utilizing all available information in the images. In a study by Gufler et al (73) four radiological features (contour, internal structure, size and attenuation value) of adrenal lesions at unenhanced CT images were used to create a total score. Applying this scoring system with combined parameters yielded a sensitivity of 100% and specificity of 96.8% for differentiation between adenomas and metastases. The validity of such a scoring system for adrenal lesions, with information from both unenhanced and enhanced images, remains to be evaluated. Further studies of routine methods are needed for improved identification of indeterminate lesions in need of further investigations.

5 CONCLUDING REMARKS

Adrenal lesions are common findings in patients subjected to radiological examinations. Reported frequencies of adrenal lesions incidentally detected by CT in our study showed figures comparable to other CT-studies, but a re-evaluation of a random sample from the same study population showed considerably higher figures, closer to those from autopsy studies. The re-evaluation demonstrates that underreporting of cases in multicentre settings and probably also in routine clinical settings may be common.

We found that at detection only a small percentage of our adrenal study patients had hypersecretory lesions and no one had a primary adrenal malignancy. Of the patients without any history of malignancy 80% (149/187) had radiologically benign lesions. In the groups of patients with history of or present malignancy and an adrenal lesion, radiologically benign lesions were common. No additional cases of hyperfunctioning and/or malignant lesions were found at follow-up. Radiological follow-up of adrenal lesions still has a place for indeterminate lesions but our study does not support the need for follow-up of lesions that can be radiologically characterized early in the process. Guidelines for management of incidentally detected adrenal lesions can probably be simplified both biochemically and radiologically.

We also found that there is variability in attenuation values over time in adrenal lesions, (otherwise stable ≥ 6 months), to some extent due to the usage of different CT scanners and observers. A recommendation is therefore, if follow-up of an adrenal lesions is needed, to mimic the previous examination using the same observer, CT protocol and CT equipment (preferably together with a calibration instrument).

6 FUTURE PERSPECTIVES

The combination of a lower threshold value (2 HU) at unenhanced CT and a 15-30 minute delayed imaging may improve the sensitivity and specificity for diagnosing adrenal lesions in patients with or without history of malignant disease. As referred to earlier, Boland et al (17) showed that the unenhanced threshold value of 2 HU gave 100% specificity but lowered the sensitivity compared to 10 HU threshold. If one takes into account the aspect of variation of attenuation values in each lesion, noticed in our study, a lowered absolute threshold may be supported. When combining this unenhanced threshold value with measurements of late CT wash-out test (> 15 minutes) the sensitivity will rise. Further studies in this area are warranted.

Although we obtained assuring data on the benign course of most lesions over time, the long-term consequences of incidentally detected adrenal lesions is less well known. We are currently performing a long-term (>10 years) follow-up study of patients with adrenal lesions using the study population from the previous, national study, by Bulow et al (9, 74). This will provide unique, long-term radiological and biochemical information on the natural course of incidentally discovered adrenal lesions.

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