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Adrenal Incidentaloma: Clinical Assessment of 483 Patients between 2014-2018.

Degree Project in Medicine

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Abstract

Introduction: Adrenal incidentaloma (AI) is defined as a mass or lesion in the adrenal glands that is discovered incidentally by an imaging modality performed for reasons unrelated to the adrenals. Worldwide, AI is detected in up to 5% of patients who undergo an abdominal CT. In the West Gotaland County in Sweden, AI was found in 4.5% of all abdominal CT performed between 2002-2004. Once AI is detected, further investigations should be performed to see if the lesion is benign or malignant and if the lesion overproduces adrenal hormones.

Aim: The aim of this study was to see how common AI is in the modern era and to describe its characteristics as well as its management in the healthcare system.

Methods: A retrospective descriptive study was performed at Sahlgrenska University Hospital in Gothenburg. Clinical, radiological, biochemical and histopathological data of all AI referred to the departments of endocrinology and endocrine surgery, between the years 2014 to 2018, were reviewed.

Results: A total of 483 patients had an AI, 289 (60%) women and 194 (40%) men. The median age was 69 years (range 70; IQR 17). The AI was detected by a CT-scan in 456 (94%) and 340 (70%) were followed-up with additional imaging. Four hundred fifty-seven (95%) patients underwent biochemical screening. Benign and inactive lesions were detected in 431 (89%) cases. Malignant tumours were found in 14 (3%) patients; 8 (1.7%) adrenal metastases, 4 (0.8%) adrenocortical carcinoma and 2 (0.4%) primary adrenal leiomyosarcoma. Hormonally active tumours were found in 38 (8%) patients; 21 (4.3%) pheochromocytoma, 13 (2.7%) primary aldosteronism and 4 (0.8%) hypercortisolism. Adrenalectomy was performed in 54 (11%) cases.

Conclusion: The clinical, biochemical and radiological characteristics show that AIs are in most cases benign and inactive lesions, that do not require any medical or surgical treatment,

and excess follow-up should be avoided. However, a small but significant amount of the lesions are either hormone-producing or malignant tumours that need thorough management and treatment.

Keywords: Adrenal incidentaloma, pheochromocytoma, primary aldosteronism, Cushing's syndrome, adrenocortical carcinoma.

1. Introduction

1.1 Adrenal incidentaloma

Adrenal incidentaloma (AI) is defined as a mass or lesion in the adrenal glands that is discovered incidentally by an imaging modality performed for other unrelated reasons (1, 2). The use of medical imaging has remotely escalated as a result of advancement in technology, together with increasing availability and accessibility of these modalities. Imaging such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are being used daily in the diagnostic work-up of patients with various symptoms and diseases (3).

Worldwide, AI is detected in 0.4-5% of patients who undergo an abdominal CT (2). In the West Gotaland County in Sweden, AI was found at a mean frequency of 4.5% of all abdominal CT performed between 2002-2004 (4). Hence, AIs are common and although discovered by serendipity, have to be managed thoroughly. Once AI is detected, there are two main questions that need to be answered;

1) Is the lesion benign or malignant?

2) Does the lesion produce excessive amounts of adrenal hormones?

1.1.2 Epidemiology

AI is detected in 0.4 to 5% of cases, where patients undergo a CT-examination (5). A study that included 65 231 abdominal CT examinations, performed during a course of three years, found incidental adrenal lesions in 3307 cases which corresponds to 5% of the cases (6). A study from Western Sweden demonstrated that out of 34 044 abdominal CT scans that were performed during the period 2002 to 2004, at all radiological departments in Western Sweden,

AI was found at a frequency of 0.9% at the initial evaluation. However, a re-evaluation of the CT scans showed a mean frequency at 4.5%, ranging between 1.8 and 7.1 at the different hospitals (4, 7).

AI is more frequently detected in the right adrenal gland, in up to 60% of the cases (3). This could be due to the frequent use of ultrasound for the investigation of the liver and the biliary tract. Bilateral lesions are found in 10-15% of the cases (8, 9). AI is uncommon before the age of 40 and has a peak at 61-70 years (5, 7). A series of five autopsy studies showed that 6% of patients aged between 60 and 69 years had adrenal adenomas (5, 7).

1.1.3 Aetiology

AI is *not* a diagnosis. It is a lesion in the adrenal gland that needs to be further investigated in order to obtain a correct diagnosis. Over 80% of the cases are benign, inactive, non-functioning adrenal adenomas, myelolipomas or cysts that do not need any surgical or medical treatment and can be managed conservatively (5, 6, 10).

Some adrenal adenomas are hormonally active and overproduce hormones such as aldosterone and cortisol causing a primary aldosteronism and Cushing's syndrome, respectively. In some cases, pheochromocytoma is detected as an incidentaloma. Few cases of AI are malignant tumours. Lesions that appear malignant need to be further investigated to identify if it is a primary or a secondary adrenal tumour, i.e. metastasis. Primary adrenocortical carcinoma is very rare with an annual incidence of 1-2 per cases per million (1, 11). The most common malignant adrenal tumours are metastases from cancer in the lungs, kidneys and the gastrointestinal tract (4).

1.1.4 National guidelines

The first national guidelines for AI were established in the year 1996. In the guidelines, it was recommended that once AI was detected, a radiological follow-up should be performed at 6, 12 and 24 months after the initial imaging. If there was a sign of significant growth during this period, a surgical removal through an adrenalectomy was recommended. Furthermore, it was recommended that a thorough physical examination, routine blood tests and biochemical hormonal evaluation should be performed regularly during a course of two years (12). A summary of the old guidelines is presented in *panel 1*.

In a Swedish prospective study, 381 patients with AI identified between 1996 and 2001, were investigated and managed according to the first national guidelines. Eighty-five (22%) had undergone surgery, 10 (2.6%) had been diagnosed with a malignant adrenal tumour and 20 (5.2%) had a hormone-producing tumour (13). Two hundred twenty-nine patients were followed-up in the study, two per cent had a hypersecreting tumour at the last follow-up, that was not evident at the initial evaluation (14). No malignant tumours such as adrenocortical carcinoma were found, indicating that the risk for the incidentaloma to malignify over time is minimal.

Since the majority of AI are benign and non-functioning lesions, that do not require any medical or surgical treatment, it is important to limit the follow-up investigation. New and revised national guidelines were therefore introduced in 2017 (5). The imaging recommendations were also updated in the same year (15). The new guidelines are intended to avoid unnecessary CT-associated radiation and surgery in cases of benign disease. These new guidelines will probably change how patients with AI are treated and also lead to reduced costs within the healthcare system. A summary of the new guidelines is presented in *panel 2*. A summary of the imaging recommendations is presented in *table 1*.

NATIONAL GUIDELINES 1996

1) CLINICAL EXAMINATION

- MEDICAL AND FAMILY HISTORY
- BLOOD PRESSURE
- SIGNS OF MELANOMA
- BREAST EXAMINATION, MAMMOGRAPHY IF NECESSARY
- SIGNS THAT INDICATE INCREASED PRODUCTION OF CORTISOL, ALDOSTERONE, CATECHOLAMINES, ANDROGENS AND ESTRADIOL.

2) CHEST X-RAY SHOULD ALWAYS BE PERFORMED AT BASELINE.

3) ROUTINE BIOCHEMICAL LAB

- SR, HB, WBC, PLATELET COUNT, NA, K, CREATININE, AST, ALT, S-DHEAS/S-TESTOSTERONE.

4) URINE SAMPLES

- U-CATECHOLAMINES X 1 + CREATININE
- U-CORTISOL X 1 + CREATININE
- U- ALDOSTERONE X 1 + CREATININE.

PROCEED WITH SPECIFIC BIOCHEMICAL INVESTIGATION IF ABNORMAL URINE SAMPLES.

5) SURGERY IS RECOMMENDED IF:

- TUMOUR ≥3-4 CM AND/OR
- TUMOUR WITH ENDOCRINE ACTIVITY AND/OR
- GROWTH OF THE TUMOUR

6) FOLLOW UP

- IF THE INCIDENTALOMA IS <3-4 CM AND HAS NO CLINICAL OR BIOCHEMICAL SIGNS OF ACTIVITY THEN IT SHOULD BE FOLLOWED UP WITH A CT AFTER 3-6 MONTHS. IF THERE IS A GROWTH, THEN SURGERY IS RECOMMENDED.
- IF NO GROWTH, THEN FOLLOW UP WITH IMAGING, BIOCHEMICAL LAB AND CLINICAL EXAMINATION AFTER 1 AND 2 YEARS.
- IF NO CLINICAL SIGNS AFTER 2 YEARS, THEN NO FURTHER INVESTIGATION.

NATIONAL GUIDELINES 2017

1) CLINICAL EXAMINATION

- MEDICAL AND FAMILY HISTORY
- BLOOD PRESSURE
- SIGNS THAT INDICATE INCREASED PRODUCTION OF CORTISOL, ALDOSTERONE, CATECHOLAMINES, ANDROGENS AND ESTRADIOL.

2) ROUTINE BIOCHEMICAL LAB

- NA, K, CREATININE
- 1 MG DEXAMETHASONE SUPRESSION TEST
- P-METANEPHRINES OR U-METANEPHRINES
- P-ALDOSTERONE AND P-RENIN IF HYPERTENSION AND/OR HYPOKALEMIA

PROCEED WITH SPECIFIC BIOCHEMICAL INVESTIGATION IF ABNORMAL LAB RESULTS.

3) IMAGING

- LESIONS THAT HAVE A NATIVE ATTENUATION ≤10 HU OR HOMOGENOUS STRUCTURE < 4CM AND STATIONARY ≥6 MONTHS ARE CONSIDERED BENIGN AND NEED NO FURTHER IMAGING
- LESIONS WITH A NATIVE ATTENUATION >10 HU AND NO PREVIOUS IMAGING FOR COMPARISON SHOULD BE FOLLOWED UP WITH CT WITHOUT CONTRAST.

4) SURGERY IS RECOMMENDED IF:

- HORMONAL OVERPRODUCTION OR
- MALIGNANCY: NON-HOMOGENOUS STRUCTURE OR DIFFUSE DELIMITATION OR ≥4 CM OR SIGNIFICANT GROWTH (≥20% IN VOLUME AND ≥5MM)

5) FOLLOW UP

- IF ROUTINE LAB AND IMAGING IS NORMAL AT BASELINE THEN NO FURTHER FOLLOW UP IS RECOMMENDED.

Panel 1 and 2 demonstrate the old and new national guidelines (5, 12).

Table 1 is a summary of the national imaging recommendations for AI, which were updated 2017-09-13 (15).

National imaging recommendations for management of AI (2017)	
Lesion characteristics	**Recommendation**
<1cm lesion or at discovery been stationary in size ≥6 months compared to prior imaging.	No follow-up imaging!
1-4 cm and ≤10 HU (with or without contrast)	Lipid-rich adenoma. No follow-up imaging!
1-4 cm and >10 HU without contrast	Follow-up is recommended. CT without contrast 6 months after discovery.
1-4 cm and >10 HU in contrast phase	Follow-up is recommended. CT without contrast within 1 month or after 6 months. If ≤10 HU, no further imaging is required. If >10 HU, follow-up with CT without contrast 6 months post discovery. MRI is recommended in case of pregnancy and adults <40 years.
1-4 cm and discovered at ultra-sound or MRI	Follow-up is recommended. CT without contrast within 1 month. If ≤10 HU, no further imaging is required. If >10 HU, follow-up with CT without contrast 6 months post discovery.
Adrenal cyst or myelolipoma	No follow-up imaging!
Lesions with unusual characteristics, attenuation, size and form.	To multidisciplinary team conference for further management and investigation.

1.2 The adrenal glands

The adrenal glands are retroperitoneal organs located above the kidneys and have a primary function to secrete hormones to the body. Anatomically, each gland is approximately 50 mm and weighs 5 grams (16). The right adrenal gland has a pyramidal shape, whilst the left adrenal gland has a crescent shape and is usually larger (16).

The adrenal gland is morphologically divided into two main parts; the outer cortex and the inner medulla. The adrenal cortex is furthermore divided into three different layers; zona glomerulosa, zona fasciculata and zona reticularis. These different zones are responsible for the production of the mineralocorticoid aldosterone, the glucocorticoid cortisol and androgens such as DHEA and androstenedione. The centre of the adrenal gland is composed of the adrenal medulla where the catecholamines noradrenaline and adrenaline are produced (16).

All of these hormones play a vital role in the human body, maintaining metabolic balance and homeostasis. An overproduction and hypersecretion of any of these hormones leads to disruption of the homeostasis and cause various symptoms. Thus, it is important to perform a clinical and biochemical examination to investigate whether a patient with AI has any signs of hormonal overproduction.

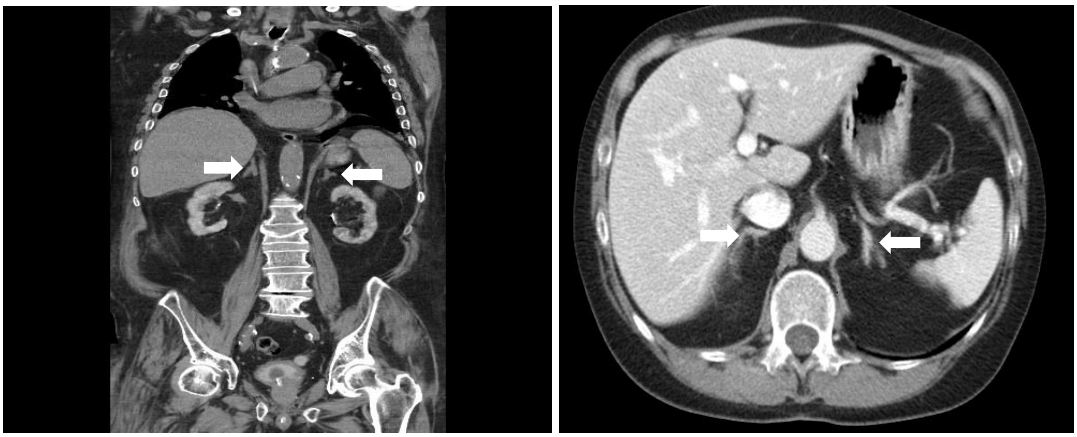

Figure 1 and 2. A CT-abdomen showing normal adrenal glands.

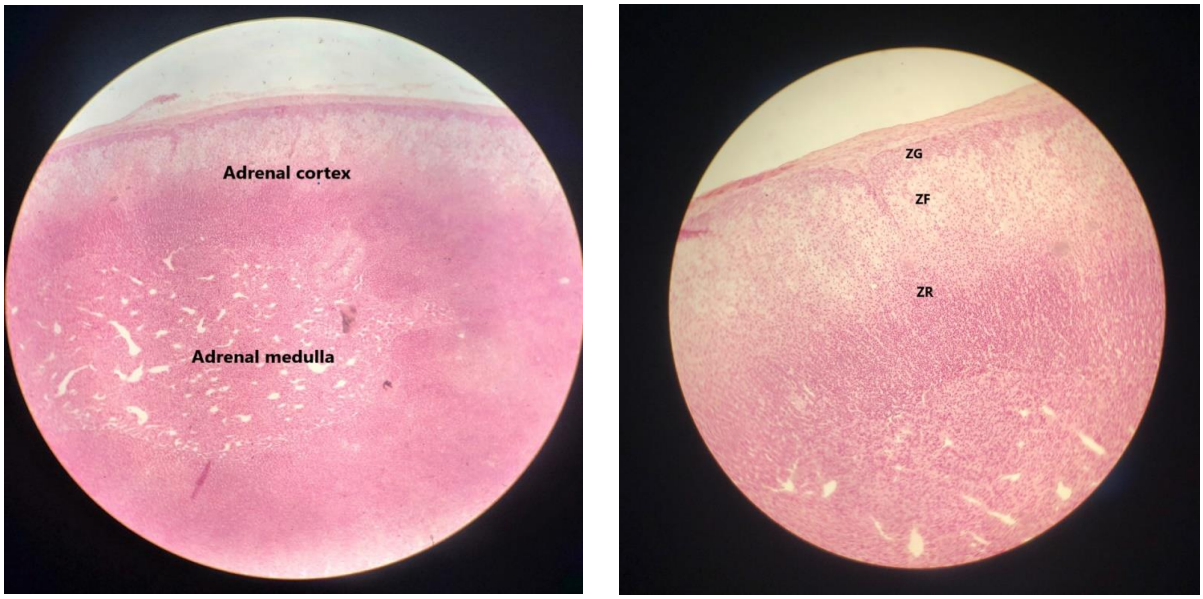

Figure 3a and 3b. Histologic sample of normal adrenal gland tissue under light microscope, illustrating the adrenal cortex and medulla. The adrenal cortex; zona glomerulosa (ZG), zona fasciculata (ZF) and zona reticularis (ZR).

1.3 Primary aldosteronism

Aldosterone is a hormone that plays a key role in maintaining ion balance as it stimulates the reabsorption of sodium (Na^+) and excretion of potassium (K^+) in the kidneys. Primary aldosteronism (PA) is a condition where one or both of the adrenal glands produce excess amounts of aldosterone that leads to higher circulating blood volume, hypertension and often hypokalaemia, and symptoms such as muscle weakness and arrhythmia (17). Reportedly, 35% of PA cases are due to an adrenal adenoma, whilst 65% are caused by bilateral adrenal hyperplasia (1). PA is treated either medically with mineralocorticoid receptor antagonists or surgically with adrenalectomy. Patients with AI should undergo a clinical examination and if there is a presence of hypertension, with or without hypokalaemia, then a screening with plasma aldosterone and renin levels should be measured, a high (≥60) aldosterone-renin-ratio (ARR) indicates PA. The diagnosis is then confirmed through a saline suppression test and the

aetiology is confirmed through an adrenal vein catheterization (17). Up to 3.3 % of AI cases produce excessive amounts of aldosterone (2).

1.4 Cushing's syndrome

Cortisol is a vital hormone that affects all the cells in the body. It stimulates gluconeogenesis, has a catabolic effect on bones, muscles, and skin, and causes water retention due to sodium reabsorption (18). Cushing's syndrome (CS) is a condition caused by chronic overproduction of cortisol in the adrenal gland. The characteristic clinical symptoms are abdominal fat accumulation, moon face, acne, hypertension, osteoporosis, muscle atrophy and fatigue (19). The most common cause of adrenal CS is a benign adrenal adenoma. Other and rarer causes are cortisol-producing adrenocortical carcinoma and bilateral hyperplasia. Patients with AI and a mild biochemical hypercortisolism, without overt clinical symptoms of CS, have a condition called subclinical CS, found in 1 to 29% of all AI cases (2).

The national guidelines for AI recommend clinical examination and biochemical investigation with 1 mg overnight Dexamethasone suppression test (DST) and measurement of S-cortisol to discover hypercortisolism, where a level >50 nmol/L is considered elevated (5). Clinical and biochemical follow-up is recommended for subclinical CS.

1.5 Pheochromocytoma

Pheochromocytoma is a rare adrenal tumour that produces catecholamines, i.e. noradrenaline and adrenaline, in excessive amounts. Pheochromocytomas originate from the adrenal medulla. Extra-adrenal catecholamine-producing tumours are seen in up to 10% of the cases and are called paraganglioma (3). The clinical symptoms of catecholamine-producing tumours are sudden attacks of a headache, palpitations and high blood pressure. The symptoms typically last between 10 to 30 minutes and are periodic. Although pheochromocytoma is rare

with an annual incidence of 2-8 cases per one million inhabitants, it is now more frequently discovered in connection with work-up of AI. A biochemical screening with plasma free metanephrine and plasma free normetanephrine is recommended, where a level ≥0.5 and ≥1.1 respectively, is considered elevated (5). Pheochromocytoma is found in 1.5% to 14% of cases of AI (2). The treatment is adrenalectomy.

The clinical symptoms of Pheochromocytoma:

Pressure (hypertension)

Pain (headache)

Palpitation

Perspiration

Pallor

Paroxysm

Panel 3. The clinical symptoms of Pheochromocytoma (1)

1.6 Adrenocortical carcinoma

Adrenocortical carcinoma (ACC) is a malignant tumour, originated in the adrenal cortex. It has an annual incidence of 1-2 cases per million citizens (1). ACC is typically very large at diagnosis, often ranging between 5 to 20 cm. ACC has a high mortality rate, with a 5-year prognosis ranging between 12 and 64% (11). The clinical symptoms are diffuse such as fatigue, weight loss, fever and abdominal pain. The tumour is hormonally active in 50% of the cases, where overproduction of cortisol or androgens, are most commonly encountered. ACC requires prompt diagnosis and management by a multidisciplinary team. The treatment is adrenalectomy, combined with oncologic treatment (1).

1.7 Adrenal metastases

Metastases in the adrenal glands are common and can be uni- or bilateral. In a study that included 1000 post-mortem cases of cancer, metastases to the adrenal gland(s) were present in 27% of the cases which was the seventh most common metastasis location. The study included 169 cases of breast cancers and 160 cases of lung cancers. Of these, 54% (n=90) and 36% (n=57) had adrenal metastases, respectively. Other malignancies such as colon cancer (14%), renal carcinoma (24%) and ovarian cancer (17%) also had a high prevalence of metastases to the adrenal glands (20).

2. Aim

The aim of this study was to compile and evaluate the clinical data of all AI referred between the years 2014 to 2018 to the departments of Endocrinology and Endocrine surgery at the Sahlgrenska University Hospital in Gothenburg. The most recent study on AI in Western Sweden was executed over ten years ago. A lot has changed since then in the management of AI. Therefore, the focus of this study was to see how common AI is in the modern era and to describe its clinical characteristics and management.

2.1 Specific research questions

1. How many AI cases were managed at Sahlgrenska University Hospital in Gothenburg during the period of 2014-2018?
2. How many of the lesions were benign and how many were malignant? How many of the malignant lesions were primary (ACC) and secondary (metastases), respectively?
3. How many of the lesions were hormonally active?
4. How many patients were followed up radiologically?
5. How many patients were followed up biochemically?
6. How many patients with AI underwent surgery?

3. Methods

3.1 Study design

This was a retrospective descriptive study performed at the department of Endocrinology and Endocrine surgery at Sahlgrenska University Hospital in Gothenburg.

3.2 Study population and data collection

The study included all patients from the three hospitals of the University Hospital in Gothenburg (Sahlgrenska, Mölndal and Östra), registered with one of the following ICD-codes between 2014-01-01 until 2018-05-31;

a) D350: Benign neoplasm of adrenal gland
b) D44.1: Neoplasm of uncertain behaviour of adrenal gland
c) C74: Malignant neoplasm of adrenal gland

In total, 822 patients with adrenal lesions were identified. To be eligible for the analysis the patients had to be referred to the department of endocrinology, or endocrine surgery, between 2014-01-01 until 2018-05-31. The medical files for each patient were reviewed in the journal system Melior to verify the correct diagnosis. A database was created in Excel that included all 822 patients where information on age, gender, date of the referral, imaging results, clinical symptoms, medical history, biochemical measurements, treatment and follow up procedures were registered. The specific variables are presented in *table 3*.

Excluded from the analysis were patients with a) incorrect diagnosis (n=19), b) paraganglioma (n=4), c) MEN 2 syndrome (n=5), d) neuroblastoma (n=4), e) referral due to a primary suspicion of an adrenal disease (n=103), f) referral due to a primary suspicion of a malignant adrenal tumour, ACC (n=20) or adrenal metastasis (n=29) and g) original referral before 2014-01-01 (n=155). In total, 483 patients were included in the statistical analysis.

Table 2 presents the number of patients at baseline and their preliminary diagnosis.

Preliminary diagnosis	Number of patients
Adrenal incidentaloma	638
Adrenocortical carcinoma	20
Adrenal metastasis	29
Adrenal disease	103
Paraganglioma	4
Neuroblastoma	4
MEN2-syndrome	5
Incorrect diagnosis -Benign neoplasm of pituitary gland -Neoplasm in the kidney -Pancreatic NET tumour -Malignant neoplasm of thyroid gland -Sarcoma -Pancreatic cyst	19 12 3 1 1 1 1

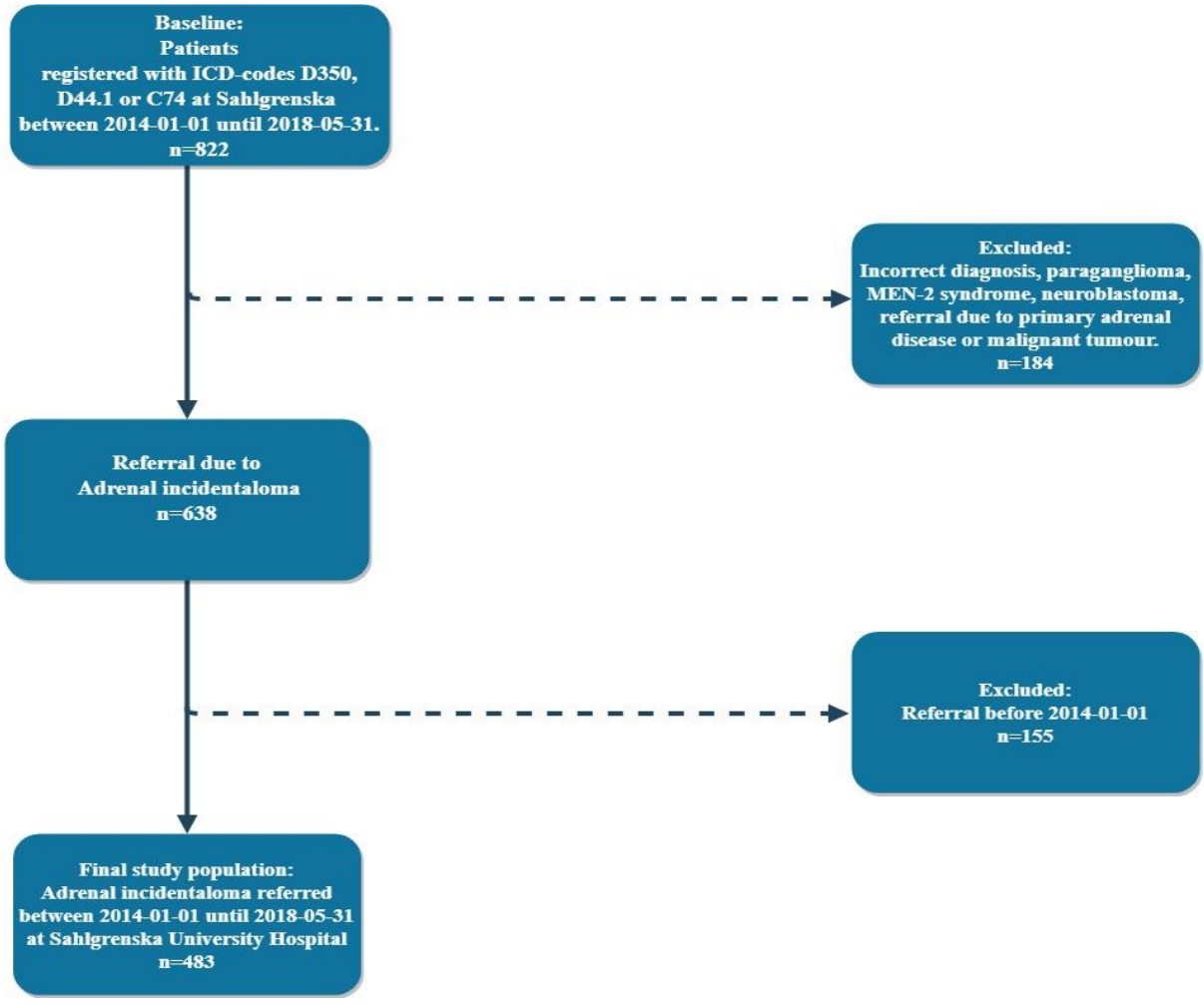

Figure 4. A schematic model of the study population.

Table 3 demonstrates the specific variables that were included in the Excel database.

Variables		
Clinical variables	**Radiological variables**	**Biochemical variables**
Age and gender (female/male)	Date of the initial imaging	Biochemical screening (yes/no)
Preliminary diagnosis	Imaging indication	S-cortisol post 1 mg DST
Clinical visit (yes/no) and the date	Type of imaging	P-aldosterone and P-renin
Measurements: height (cm), weight (kg) and blood pressure (mmHg).	Preliminary classification of the lesion	Aldosterone-renin-ratio (ARR)
History of malignancy (yes/no)	Size of the lesion (mm)	P-free metanephrine and P-free normetanephrine
Surgical treatment (yes/no)	Native attenuation (HU)	Additional cortisol tests (yes/no)
Final diagnosis and the responsible unit.	Follow-up imaging (yes/no)	Additional aldosterone tests (yes/no)
Deceased (yes/no)	Number of follow-up imaging procedures.	Additional catecholamine tests (yes/no)

3.3 Statistical methods

Data from the excel file was exported to and analysed in the statistical programme IBM Statistics SPSS version 25. Normally distributed continuous variables are presented as mean, ± standard deviation (SD) and non-normally variables as median (range; interquartile range). Categorical variables are presented as n (%). Pearson's chi-square was used to analyse the difference between categorical variables. For comparisons between normally distributed and non-normally distributed continuous variables, independent sample T-test and the Mann-Whitney U-test were used, respectively. The value of significance was set at 0.05.

4. Ethical considerations

The study was conducted according to the Helsinki code of declaration and was approved by the regional ethical review board in Gothenburg (DNR 814-18). Patient anonymity was preserved during the entire study.

5. Results

5.1 Overview of the results

Four hundred eighty-three patients had a preliminary diagnosis of AI. The median age was 69 years (range 70; IQR 17). Out of the 483 patients, 289 (60%) were female and 194 (40%) were male (P<0.001). The median age was 69 years for both women (range 70; IQR 19) and men, (range 55; IQR 16), (P=0.63). A total of 111 (23%) patients had a history of malignancy, 72 (65%) women and 39 (35%) men, (P=0.2).

The incidentaloma was detected by a CT-scan in 456 (94.4%) patients, MRI in 13 (2.7%), ultrasound in 13 (2.7%) and by a PET-scan in one (0.2%) patient. The most frequent indications for imaging were suspicion of malignancy (n=141), abdominal pain (n=109) and symptoms from the urinary tract (n=62). The indications for imaging are presented in *table 4.* A total of 340 (70%) patients were followed-up with additional imaging procedures. The number of additional imaging varied between one and eight, (*table 5).* Two hundred thirty-two lesions were found in the right adrenal gland and 338 in the left gland. Data on native attenuation was available in 393 patients. A total of 414 lesions were preliminarily classified as a benign lesion, of which one had a final diagnosis of a metastasis. Seventy-four lesions were preliminarily classified as a suspicious malignant tumour, of which 41 had a final diagnosis of a benign inactive adenoma. The final diagnoses are presented in *table 6*.

A total of 412 (85%) patients had a clinical visit, either with a nurse or a physician. Data on blood pressure was found in 290 (70%) patients. The mean systolic and diastolic blood pressure were 137±19 mmHg and 80±10 mmHg, respectively.

Four hundred fifty-seven (95%) patients underwent some form of a biochemical screening. Of these, 157 had a S-cortisol (post-DST) >50, 42 had ARR ≥60, 36 had p-free metanephrine ≥0.5 and 89 had p-free normetanephrine ≥1.1. One hundred ninety-five (41%) patients were followed-up with additional tests for evaluation of hypercortisolism, 137 (28%) for evaluation of primary aldosteronism and 190 (39%) for evaluation of pheochromocytoma *(figure 7).* Of 483 patients, 54 (11%) required surgical treatment with adrenalectomy.

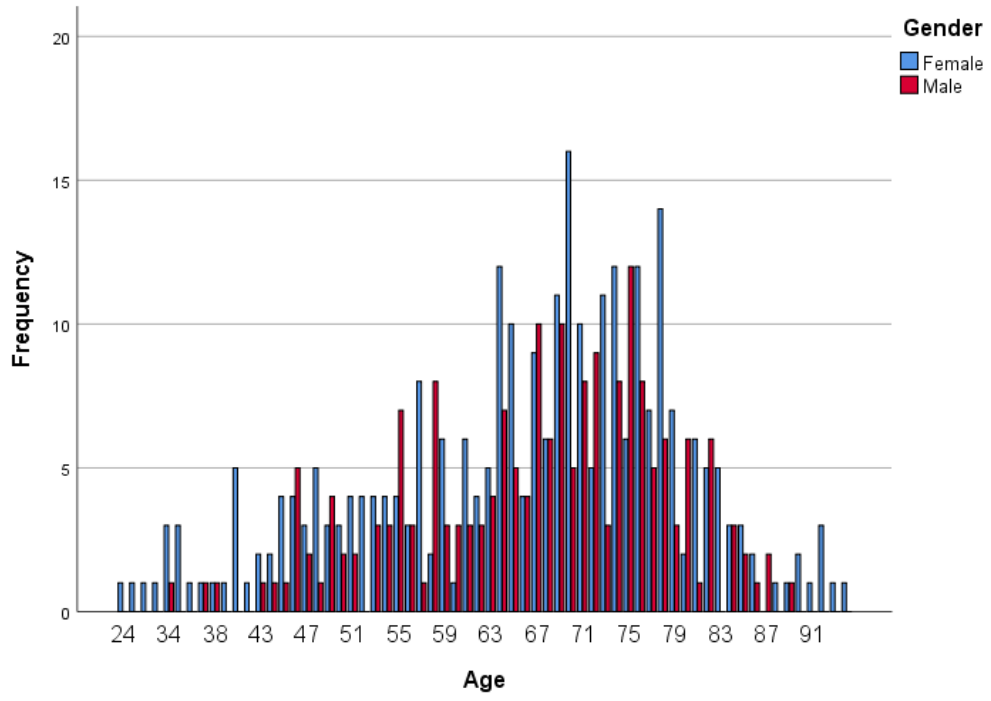

Figure 5. The age distribution amongst the study population.

Table 4. Indications for imaging in the study's cohort.

Imaging indication	N (%)
Suspected malignancy	141 (29.2%)
Abdominal pain	109 (22.6%)
Symptoms from the urinary tract	62 (12.8%)
Reason not stated or found	30 (6.2%)
Pulmonary embolism	28 (5.8%)
Symptoms from the biliary tract and/or the pancreas	23 (4.8%)
Trauma	21 (4.3%)
Aortic dissection and other cardiovascular reasons	18 (3.7%)
Lung disease	16 (3.3%)
Abnormal biochemical tests	12 (2.5%)
Participation in a clinical trial (SCAPIS)	9 (1.9%)
Other specified indication	14 (2.9%)

Table 5. The number of additional imaging procedures for the entire AI study population.

Number of additional imaging	N (%)
0	143 (29.6%)
1	203 (42.0%)
2	89 (18.4%)
3	33 (6.8%)
4	11 (2.3%)
5	3 (0.6%)
8	1 (0.2%)

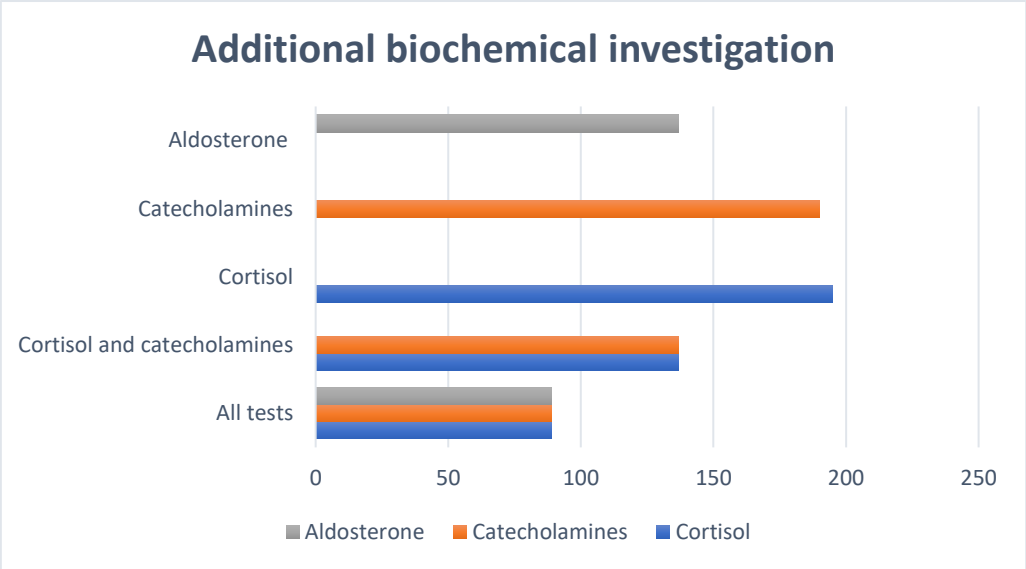

Figure 6. Additional biochemical investigation for the entire AI study population.

Table 6. A table summarizing the final diagnoses for the AI study population.

Final diagnosis	**N (%)**
Benign inactive adenoma	353 (73.1%)
Bilateral benign inactive adenomas	69 (14.3%)
Pheochromocytoma	21 (4.3%)
Primary aldosteronism	13 (2.7%)
Adrenal metastases	8 (1.7%)
Adrenal gland cyst	5 (1.0%)
Cushing's syndrome and Subclinical Cushing's syndrome	4 (0.8%)
Adrenocortical carcinoma	4 (0.8%)
Primary adrenal leiomyosarcoma	2 (0.4%)
Enlarged normal adrenal gland	2 (0.4%)
Normal adrenal gland without adenoma	1 (0.2%)
Ganglioneuroma	1 (0.2%)

5.2 Benign inactive adenoma

Three hundred fifty-three patients (73%) had a final diagnosis of a benign inactive adenoma; 215 (61%) women and 138 (39%) men. The median age was 70 years (range 65; IQR 17).

A total of 367 lesions were found, 130 in the right gland and 237 in the left. Two hundred sixty-five were preliminarily classified as a benign adenoma, 36 as a suspicious malignant tumour, 40 as a lesion of uncertain behaviour and 26 as an enlarged normal gland. Data on size was available in 343 lesions; 284 were <40 mm (range 5-38) and 59 were ≥40 mm (range 40-140). The median size of the lesions was 20 mm (range 135; IQR 17). Data on native attenuation was available in 252 (69%) lesions; 174 (69%) had attenuation ≤10 HU and 78 (31%) had attenuation >10 HU (up to 69 HU).

A biochemical screening was performed in 333 (94%) cases. Two hundred sixty (74%) patients were screened with S-cortisol (post-DST), of which 105 (40%) had a value >50 (range 51-440). Two hundred thirty-two (66%) patients were screened with p-aldosterone and p-renin, of which 28 (12%) had an ARR ≥60 (range 60-138). Three hundred nineteen (90%) were screened with p-free metanephrine, 18 (5%) had a level ≥0.5 (range 0.5-1.6). Three hundred twenty-one (91%) were screened with p-free normetanephrine, of whom 54 (15%) had a level ≥1.1 (range 1.1-3.2). One hundred twenty-three (35%) patients were followed-up for evaluation of hypercortisolism, 85 (24%) for evaluation of primary aldosteronism and 118 (33%) for evaluation of pheochromocytoma.

Adrenalectomy was performed in 10 (3%) patients. Histopathological evaluation confirmed a benign cortical adenoma in four cases, benign cystic masses in two cases, benign haemangioma and haemorrhage in two cases, myelolipoma in one case and one case was defined as a normal benign adrenal gland without any adenoma or hyperplasia.

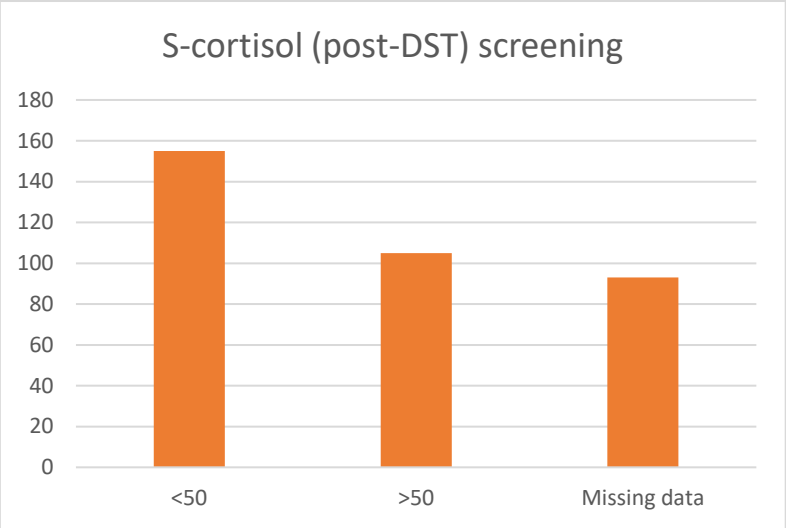

Figure 7. The distribution of S-cortisol (post 1 mg DST) in patients who had a final diagnosis of benign inactive adenoma.

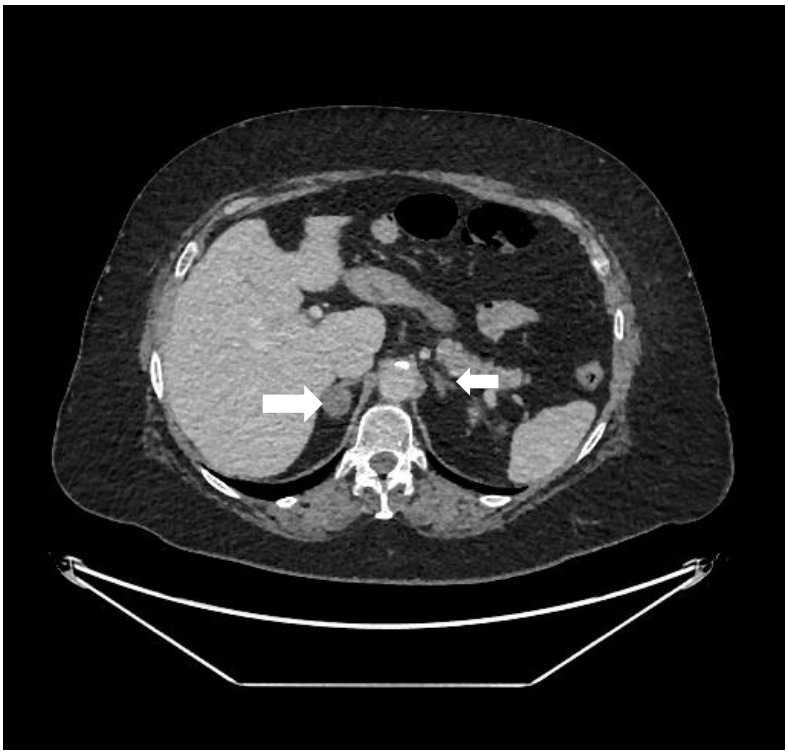

Figure 8. Benign inactive adenoma. A 49-year-old patient, with a history of thyroiditis, was investigated with a CT-chest with contrast due to symptoms from the respiratory tract. An incidentaloma was discovered in the right adrenal gland. An additional CT-abdomen showed a 20 mm lesion in the right adrenal gland with a native attenuation of 0 HU. The biochemical screening was normal; S-cortisol 38, ARR 7.7, p-free metanephrine 0.1 and p-free normetanephrine 0.4. No further radiological or biochemical follow-up was required.

5.3 Bilateral benign inactive adenomas

Sixty-nine (14%) out of 483 patients had bilateral benign inactive adenomas, 42 (61%) women and 27 (39%) men. The median age was 70 years (range 46; IQR 16).

The right adrenal gland was preliminarily radiologically defined as a benign adenoma in 65 cases, as a suspicious malignant tumour in two cases and as a lesion of uncertain behaviour in two cases. The size of the lesion was stated in 66 patients: 61 had <40 mm (range 5-37mm) and five had ≥40 mm (range 42-187). The median size was 16 mm (range 182; IQR 11). The native attenuation was stated in 54 (78%) cases, nine (17%) patients had an attenuation >10HU (up to 30 HU).

The left adrenal gland was preliminarily radiologically classified as a benign adenoma in 64 cases, as a suspicious malignant tumour in three cases and two cases were defined as a lesion of uncertain behaviour. The size of the lesion was stated in 65 patients; 57 had <40 mm (range 8-38) and eight patients had ≥40 mm (range 40-70). The median size was 20 mm (range 62; IQR 15). The attenuation was stated in 55 (80%) cases, nine (16%) patients had a native attenuation >10HU (up to 45 HU).

A biochemical screening was performed in 65 (94%) cases. Fifty-three (77%) had a screening with S-cortisol (post-DST), of which 35 (66%) had a value >50 (range 51-563). Thirty-nine (57%) were screened with p-aldosterone and p-renin, 3 (8%) had an ARR ≥60 (range 82-139). Sixty-one (88%) patients were screened with p-free metanephrine and p-free normetanephrine, two (3%) had a p-free metanephrine level ≥0.5 (range 0.5-0.6) and 13 (21%) had a p-free normetanephrine level ≥1.1 (range 1.1-3.2). Thirty-eight (55%) patients were followed-up with additional tests for evaluation of hypercortisolism, 23 (33%) for evaluation of primary aldosteronism and 35 (51%) for evaluation of pheochromocytoma. None of the patients required surgical treatment.

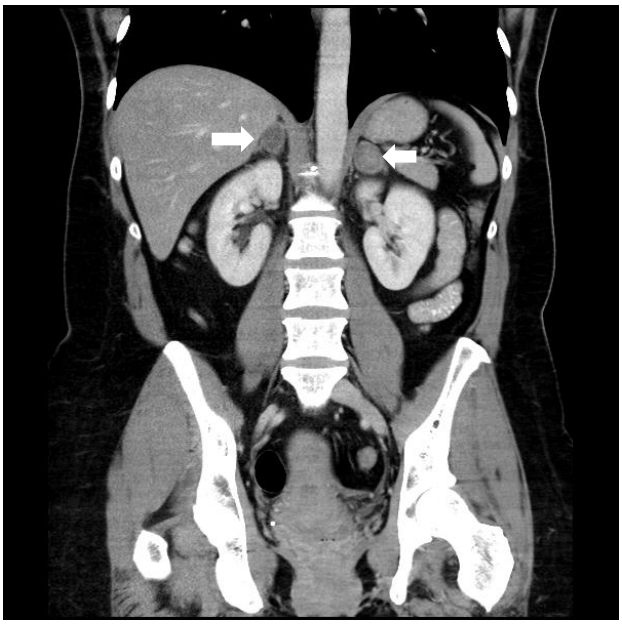

Figure 9. Bilateral benign inactive adenomas. A 47-year-old patient, with a history of diverticulosis, was investigated with a CT-abdomen with contrast due to abdominal pain which showed bilateral incidentalomas. Additional CT-abdomen with and without contrast showed a 30 mm lesion in the right gland and 35 mm in the left gland. Both lesions had a native attenuation <10 HU. The patient had no clinical symptoms that indicated an adrenal disease. The biochemical screening showed a slight elevated S-cortisol (post-DST) at 85, additional hypercortisolism investigation was considered normal.

5.4 Pheochromocytoma

Twenty-one (4.3%) patients were found to have pheochromocytoma, nine (43%) women and twelve (57%) men. The median age was 67 years (range 44; IQR 19).

The lesions were preliminarily defined as a malignant tumour in 18 patients, as a benign adenoma in three and one patient had an enlarged normal gland simultaneously. Eight patients had a lesion size <40 mm (range 19-30) and 14 had ≥40 mm (range 40-150). The median size was 41 mm (range 131; IQR 33). Data on attenuation was stated in 13 (62%) cases, 12 (92%) had a native attenuation >10 HU (up to 40 HU).

A biochemical screening was performed in all 21 patients. Eleven (52%) patients were screened with S-cortisol (post-DST), 6 (55%) had a value >50 (range 59-160). Fourteen (67%) were screened with p-aldosterone and p-renin, one (7%) patient had an ARR≥60. Twenty (95%) were screened with p-free metanephrine, 16 (76%) had a level ≥0.5 (range 0.5-30). Twenty (95%) were screened with p-free normetanephrine, 19 (95%) had a level ≥1.1 (range 1.1-18). Nine (43%) patients had additional tests for evaluation of hypercortisolism, eight (38%) for evaluation of primary aldosteronism and twenty (95%) for evaluation of pheochromocytoma. Eighteen (86%) were investigated with an adrenal gland scintigraphy. Twenty (95%) patients received surgical treatment with an adrenalectomy and the diagnosis pheochromocytoma was histopathologically confirmed for all cases.

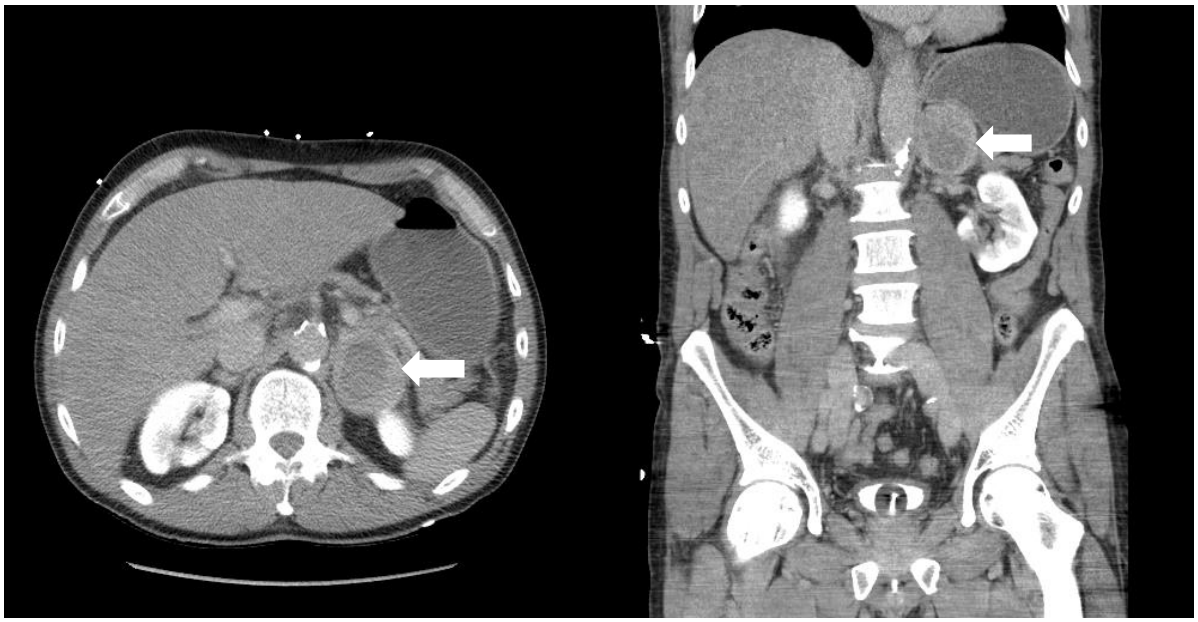

Figure 10. Pheochromocytoma. A 63-year-old patient, with a history of hypertension and heart failure, was investigated with a CT-chest and CT-abdomen due to suspected embolism. A 55 mm lesion was found in the left adrenal gland with attenuation of 100 HU with contrast. The biochemical screening showed elevated levels of p-free metanephrines and further investigation was performed with a scintigraphy of the adrenal medulla. The patient was treated with Alpha-receptor blocker which improved the cardiological symptoms. An adrenalectomy was performed shortly after, the histopathology confirmed a pheochromocytoma. Post-surgery, the heart failure had considerably improved and p-free metanephrines were normalised.

5.5 Cushing's syndrome and Subclinical Cushing's syndrome

Four (0.8%) patients had a final diagnosis of CS (n=2) and subclinical CS (n=2), two (50%) women and two (50%) men. The median age was 52 years (range 22; IQR 20). The lesions were defined as a benign adenoma in one case, as a suspicious malignant tumour in one case, as a lesion with uncertain behaviour in two cases and one patient had also had an enlarged normal adrenal gland simultaneously. The median size was 32 mm (range 33; IQR 19). Attenuation was stated in all four cases, three (75%) were >10 HU (up to 30 HU).

All four patients had a biochemical screening, S-cortisol (post-DST) was >50 in all (range 140-840). The rest of the screening tests were normal. Additional cortisol and aldosterone tests were performed in all four (100%) patients and additional catecholamine tests in three (75%) patients. All four patients underwent surgical treatment through an adrenalectomy.

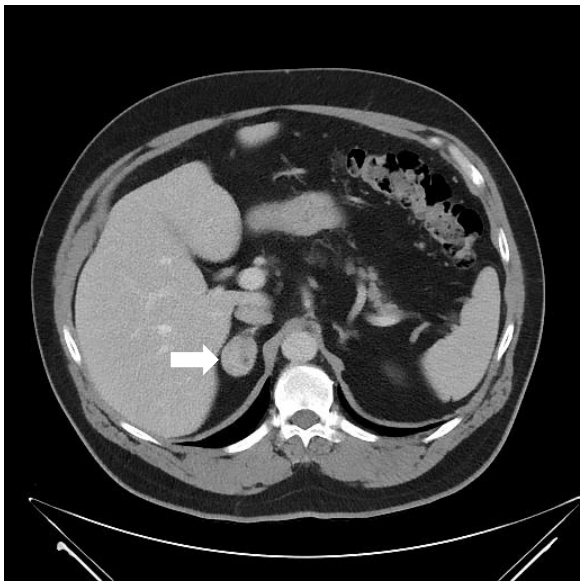

Figure 11. Cushing's syndrome. A 45-year-old patient with obesity, BMI 40, and a history of hypertension was investigated with a CT-abdomen due to symptoms from the biliary tract. A 35 mm lesion with native attenuation of 15 HU was found in the right adrenal gland. Large portions of the lesion indicated macroscopic fat and one portion showed signs of post-haemorrhage. Biochemical screening showed a S-cortisol (post-DST) of 420 nmol/L. Additional urinary free cortisol and serum cortisol at midnight indicated Cushing's syndrome. The patient was treated surgically with an adrenalectomy, histopathology confirmed a benign adenoma.

5.6 Primary aldosteronism

Thirteen (2.7%) patients had a final diagnosis of primary aldosteronism, of which five (38%) were women and eight (62%) men. The median age was 63 years (range 29; IQR 8). The lesions were preliminarily radiologically defined as a benign adenoma in all 13 patients and two patients had an enlarged adrenal gland simultaneously. The size of the lesions was stated in 13 cases, all had a size <40 mm (range 7-38). The median size was 16 mm (range 31; IQR 10). Data on native attenuation was stated in 10 (77%) cases; three (30%) had >10 HU (up to 17 HU).

A biochemical screening was performed in all thirteen (100%) patients. Seven (54%) patients had a S-cortisol (post-DST) screening, of which two (29%) had a value >50 (range 52-54). Twelve (92%) patients were screened with p-aldosterone and p-renin, ten (77%) had an ARR≥60 (range 75-664). All thirteen (100%) were screened with p-free metanephrines, one (8%) patient had p-free normetanephrine level ≥1.1, the rest were normal. Twelve (92%) patients were followed-up with additional tests for evaluation of hypercortisolism, six (46%) for evaluation of pheochromocytoma and all thirteen (100%) for evaluation of primary aldosteronism. Twelve (92%) patients were investigated with saline suppression test and adrenal vein catheterization. Nine (70%) patients were treated surgically through an adrenalectomy, histopathology showed benign lesions in all cases.

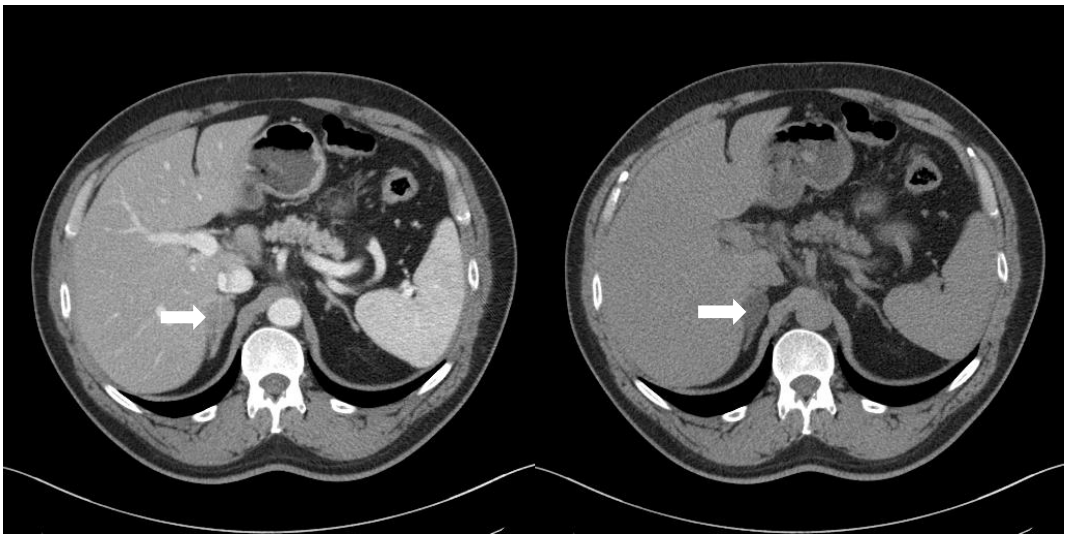

Figure 12. Primary aldosteronism. A 48-year-old patient was investigated with a CT-abdomen due to abdominal pain which showed a 18 mm lesion in the right adrenal gland with a native attenuation of -7HU. The left adrenal gland was enlarged, 7 mm, with native attenuation of -3 HU. Biochemical screening showed elevated ARR at 94, serum potassium of 4.5 mmol/L. The blood pressure was 130/80. The patient had developed hypertension (155/88) at follow-up 24 months later, repeated ARR was 109. A saline suppression test and adrenal vein catheterization confirmed a primary aldosteronism, with a right sided dominance. The patient was treated surgically with an adrenalectomy and histopathology confirmed a benign cortical adenoma.

5.7 Adrenocortical carcinoma

Four (0.8%) patients had a final diagnosis of ACC, three (75%) women and one (25%) man. The median age was 48 years (range 35; IQR 30). Three lesions were found in the right adrenal gland and one in the left gland, all four were defined as a suspicious malignant tumour and had a size ≥40 mm (range 68-220). The median size was 123 mm (range 152; IQR 115). Data on native attenuation was missing in all four cases. A biochemical screening was performed in all four (100%) patients, one patient had elevated S-cortisol (post-DST) level at 628.

All four (100%) patients had an adrenalectomy and were alive at the end of the study, two were diagnosed in 2016 and two in 2017. The diagnosis was confirmed with histopathology. Three (75%) patients had disseminated ACC, with metastases to the lungs (n=2), the liver (n=2) and the bones (n=1).

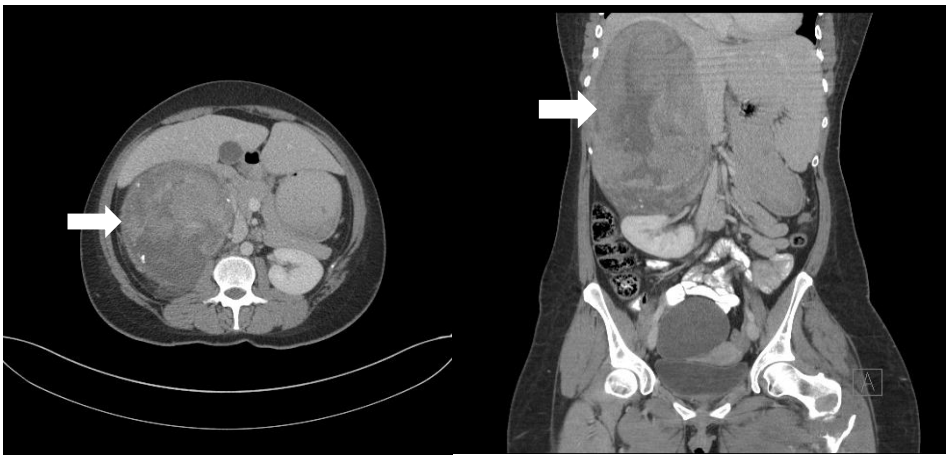

Figure 13. ACC. A 33-year-old patient was investigated with a CT-abdomen due to suspected cystic lesions in the lower abdomen, where a massive 220 mm right-sided lesion was found. The patient underwent surgery and histopathology confirmed adrenocortical carcinoma. The patient had metastases to the liver, lungs and bones.

5.8 Adrenal metastases

Eight (1.7%) patients had a final diagnosis of adrenal metastasis, six (75%) women and two (25%) men. Six (75%) of the patients had a prior history of malignancy. The median age was 76 years (range 28; IQR 13). The lesions were radiologically defined as a suspicious malignant tumour in seven cases and as a benign adenoma in one. The size of the lesions ranged between 10-70 mm. The median size was 35 mm (range 60; IQR 45). Data on native attenuation was stated in four (50%) cases; 3 (75%) had >10 HU (up to 77 HU). None of the patients underwent surgical treatment.

The primary tumours were breast cancer (n=2), uterus cancer (n=2), lung cancer (n=1), renal cancer (n=1), melanoma (n=1) and rectal cancer (n=1). Seven of the patients had deceased at the end of the study. The time from diagnosis to death varied between 2 and 24 months (2, 4, 6, 7, 8, 8 and 24 months).

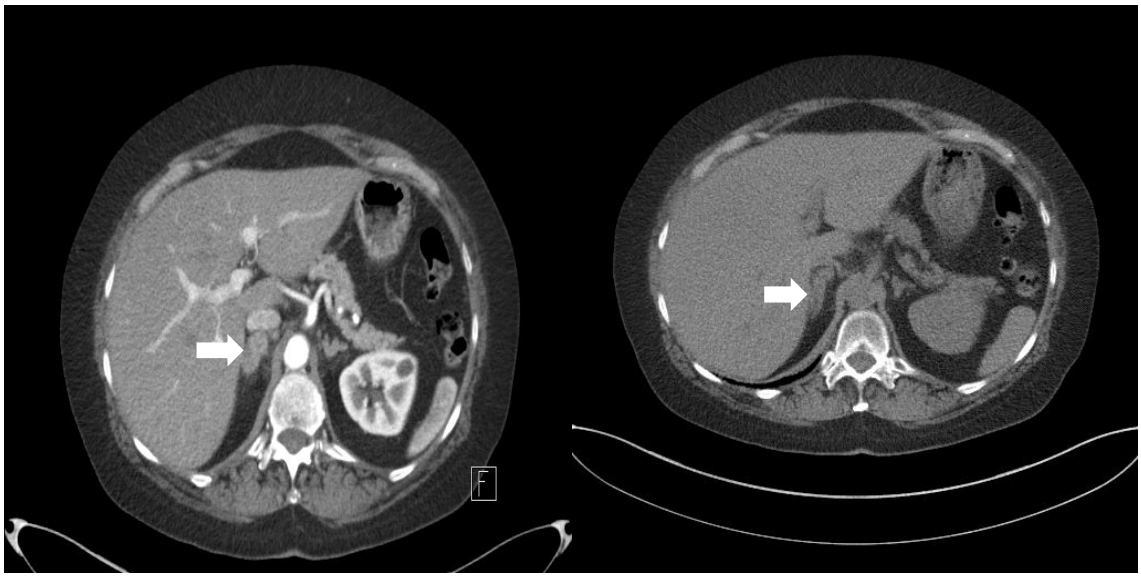

Figure 14. Adrenal metastasis. A 64-year-old patient, diagnosed and operated for breast cancer 7 years earlier, was investigated with a CT due to suspected kidney stone. A 25 mm lesion was found in the right adrenal gland, with native attenuation of 30 HU. Biochemical screening was normal. Subsequent PET-scan showed metastases in the thorax, abdomen and the right adrenal gland.

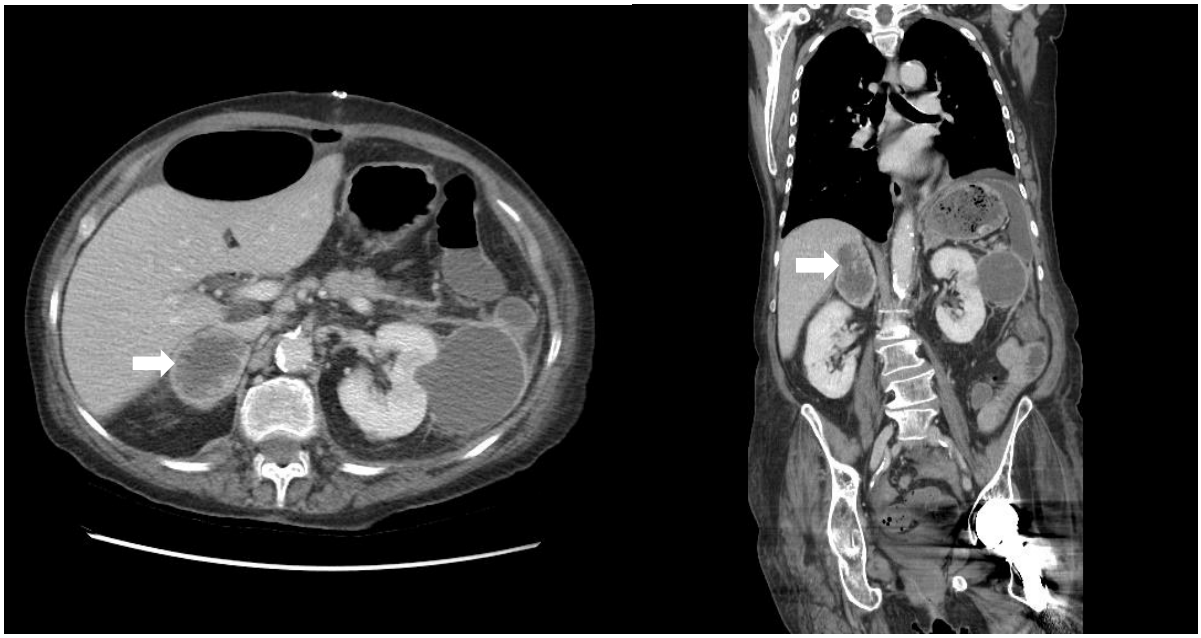

Figure 15. Adrenal metastasis. A 55-year-old patient without any prior history of malignancy, was investigated with a CT-abdomen due to abdominal pain. A 70 mm lesion was found in the right adrenal gland as well as a suspected lesion in the gallbladder and several lesions in the left lung. Biochemical screening was normal. An ultrasound guided biopsy from the right adrenal gland confirmed metastasis, originating from a malignant melanoma.

5.9 Primary adrenal leiomyosarcoma

Two (0.4%) of the AI cases had a primary adrenal leiomyosarcoma. Both were male, aged 68 and 75. None of the patients had a history of malignancy or an immunodeficiency. One lesion was found in the right gland which was radiologically defined as a suspicious malignant tumour, the size was 70 mm and native attenuation data was missing. The second lesion was found in the left gland which was radiologically classified as a suspicious malignant tumour, the size was 100 mm and attenuation data was missing. Both patients had normal biochemical screening. Both patients had an adrenalectomy and the diagnosis was confirmed with histopathology and immunohistochemistry. Both patients had a disseminated malignancy, one had metastases to the liver, lungs, sternum, gluteal muscle and the mesentery 24 months after diagnosis, the other patient had metastases in the thorax and femur within a month after diagnosis. Both patients were alive at the end of the study.

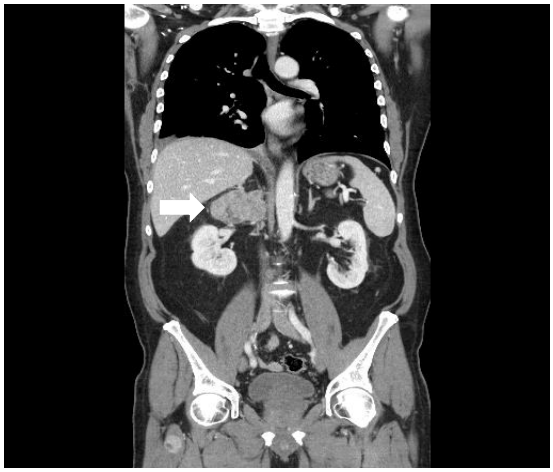

Figure 16. A 67-year-old patient was investigated with a CT due to symptoms from the urinary tract. A 70 mm lesion was found on the right side. Further follow-up with a PET scan and an endoscopic ultrasound guided fine needle aspiration (EUS) showed inconclusive results but a suspected malignancy. The patient underwent an adrenalectomy, histopathology and immunohistochemistry confirmed a primary adrenal leiomyosarcoma, Trojani grade 2.

Table 7. A summary of the characteristics and management of the adrenal lesions.

	N (%)	Female % /Male %	Median age	Gland size <40/≥40 mm	Native attenuation ≤10/>10HU	Adrenalectomy n (%)
Benign inactive adenoma	353 (73.1)	61/39	70	284/59	174/78	10 (2.8)
Bilateral benign inactive adenomas	69 (14.3)	61/39	70	118/13	91/18	0 (0)
Pheochromocytoma	21 (4.3)	43/57	67	8/14	1/12	20 (95)
Cushing's syndrome and Subclinical CS	4 (0.8)	50/50	52	3/1	1/3	4 (100)
Primary aldosteronism	13 (2.7)	39/61	63	13/0	7/3	9 (69)
Adrenocortical carcinoma	4 (0.8)	75/25	48	0/4	Missing data	4 (100)
Adrenal metastasis	8 (1.7)	75/25	76	5/3	1/3	0 (0)
Primary adrenal leiomyosarcoma	2 (0.4)	0/100	72	0/2	Missing data	2 (100)

6. Discussion

The key findings of this study are;

a) 483 cases of AI were managed at Sahlgrenska University Hospital in Gothenburg during the period of 2014-2018.
b) Out of 483 lesions, 431 (89%) were benign inactive lesions and 14 (3%) were malignant tumours. The malignant lesions were adrenal metastases (n=8), ACC (n=4), and primary adrenal leiomyosarcoma (n=2).
c) 38 (8%) patients had hormonally active lesions; 21 pheochromocytoma, 13 primary aldosteronism and 4 Cushing's syndrome and Subclinical CS.
d) 340 (70%) patients were followed-up with additional imaging procedure.
e) 457 (95%) patients underwent a biochemical screening.
f) 54 (11%) patients had surgical treatment with adrenalectomy.

6.1 Demographics

In autopsy studies, adrenal lesions are most frequently found in the sixth and seventh decade, in up to 6% of patients (5, 21). Our results are in agreement with these studies and also with two previous Swedish AI studies, where the median age was 64 and 65 years, respectively (13, 22), as well as with a European study where the mean age was 63 years (10). The average life expectancy has increased with time in Sweden, which can explain the slightly higher median age in our study compared to the prior Swedish studies (23). Age is most probably the explanatory factor behind the high occurrence of suspected malignancy (29.2%) as an indication for imaging. Age by itself is a risk factor for developing a malignancy, it is common to have it as a primary or differential diagnosis during an investigation, hence it was highly prevalent as an imaging indication.

The predominance of women with AI in our study is also in agreement with previous studies (13, 22, 24). However, autopsy studies have not shown a significant difference in prevalence of adrenal lesions between men and women (21). The slightly higher prevalence of AI in women in this study, and previous studies could be due to that conditions such as gallstones are more prevalent in women (25), gallstone and cholecystitis are common during pregnancy as well (26), which then leads to diagnostic investigation with ultrasound or abdominal CT. Other gynaecological conditions such as endometriosis, cervicitis and salpingitis typically present with abdominal pain, which in turn leads to seeking medical help and investigation with imaging due to abdominal pain.

6.2 Imaging indications and characteristics

The most frequent indication for imaging was suspected malignancy. However, one must bear in mind that other indications such as symptoms from the biliary tract and/or the pancreas as well as symptoms from the urinary tract frequently presents with abdominal pain. Thus, the most common indication for imaging was presumably abdominal pain and not suspected malignancy.

Seventy-four (15%) patients had a lesion that was preliminarily classified as a suspicious malignant tumour on the imaging procedure, of which 31 (42%) had either pheochromocytoma or a malignant tumour. The rest were benign lesions, meaning that 58% were initially wrongly classified. One reason behind this could be that lesions such as adrenal cysts, haemangioma, adrenal gland haemorrhage and large lesions could look suspicious. The specificity was higher for those who had a preliminary classification of a benign lesion, a total of 414 lesions were classified as a benign adenoma, of which only one (0.2%) had a final clinical diagnosis of a metastasis, although it was a 10 mm lesion with attenuation ≤10 HU. The patient had a disseminated malignancy and the diagnosis of adrenal metastasis was not confirmed with a biopsy.

6.3 Bilateral incidentalomas

Bilateral benign inactive adenomas were frequent in our study, which is in agreement with previous international studies (9, 10, 24, 27). A cohort study from Western Sweden that included 226 AI patients, found bilateral lesions in 22.6% of the cases (28). Another AI study from Southern Sweden, that included 228 patients with AI, found bilateral adenomas in 18.9%. An interesting finding in that study was that 70% of those with bilateral adenomas had an inadequate response after 1 mg DST and 42% fulfilled the criteria of subclinical Cushing's syndrome (22). Our study found similar results where 51% had a S-cortisol (post-DST) value >50 nmol/L, which is inadequate suppression. Further research and investigation should be performed to see if there is a correlation between bilateral adenomas and subclinical CS.

6.4 Functional tumours

According to European guidelines, previous studies have shown an occurrence of pheochromocytoma in 1.5-14% of patients with AI, primary aldosteronism in 1.6-3.3% and hypercortisolism in 1.0-29% (2). A study from Southern Sweden found pheochromocytoma in two (0.9%) cases and primary aldosteronism in one (0.4%) case (22). Another study from Sweden which included 381 patients with AI found pheochromocytoma in 14 (3.7%) cases, overt Cushing's syndrome in four (1%) cases and primary aldosteronism in two (0.5%) cases (13). Cushing's syndrome is a rare disease, with an incidence of 3-4 per million per year, however, the low frequency of it in our study could be due to the fact that CS has distinct and characteristic clinical symptoms and signs. Thus, it is more likely that CS is detected through a primary suspicion of an adrenal disease rather than an incidentaloma.

This study had a higher occurrence of pheochromocytoma compared to previous Swedish studies (13, 22). This could be due to new screening methods. Previous studies have analysed metanephrines or catecholamines in urine which has a 87-90% sensitivity whilst this study

included plasma-free metanephrines which has a 98% sensitivity (29). Pheochromocytoma is today more frequently detected through investigation of AI since it is a disease with diffuse symptoms that are not always recognized by the patient or the physician. Our results show that pheochromocytoma is often large (≥40 mm) and have a high native attenuation (>10HU) compared to other benign hormone-producing lesions *(table 7).*

6.5 Malignant adrenal tumours

ACC was found in 2.6% in a previous Swedish study and in 0.6% in a European study (10, 13). In our study, patients with ACC were younger and had larger lesions compared to patients with benign inactive adenomas *(table 7).*

Metastases to the adrenal glands are common (20). Adrenal metastases were found in 0.4% in two previous Swedish studies, no cases of ACC were reported (22, 28). Our study had a higher frequency of metastases compared to these studies. This could be due to the fact that 23% of the study population had a history of malignancy. Patients who have a history of extra-adrenal malignancy are generally not included in the AI diagnosis. We chose to include these patients since they reflect a real-life setting and a more general representation of the population. Also, previous studies have shown that benign adrenal lesions are common in patients with extra-adrenal malignancy. A study in Western Sweden showed that 74% of the adrenal lesions that were detected in patients with a history of extra-adrenal malignancy were benign adenomas (30).

6.6 Primary adrenal leiomyosarcoma

Two (0.4%) cases of primary adrenal leiomyosarcoma (PAL) were found in this study which was highly unexpected. PAL is a very rare malignant tumour that origins from the smooth muscle of the central adrenal artery and its branches. It is the aetiology behind 0.1-0.2% of all intra-abdominal soft tissue malignancies (31). It was first reported by Choi and Liu year 1981

(32) and roughly 30-40 cases of PAL have been reported since then and, to our best knowledge, none from Sweden. Previous case reports (*summarized in table 8*) have shown that the characteristic symptom of PAL is abdominal pain. The lesion is often ≥40 mm. There are no specific tumour markers, biochemical tests or imaging characteristics that can distinguish a PAL from other malignancies (31, 33-37). Histopathology and immunohistochemistry are required for the correct diagnosis. The treatment is surgery and adjuvant therapy is required in most cases.

PAL in our study occurred in two elderly patients with no history of malignancy. The lesions were larger than 60 mm and both patients had advanced metastatic disease. Since much is not known about this diagnosis, further follow-up and research is required.

Table 8. A summary of the reported cases of primary adrenal leiomyosarcoma.

Author	**Year of publication**	**Gender**	**Age**	**Lesion size (mm)**	**Metastasis**	**Follow-up (months)**
Mencoboni et al.	2008	Female	75	50	No	12
Deshmukh et al.	2013	Female	60	52	No	21
Wei et al.	2014	Female	57	77	No	29
Zhou et al.	2015	Female	49	60	No	6
Nagaraj et al.	2015	Male	61	160	Missing data	Missing data
Onishi et al.	2016	Male	34	52	Lymph node	10

6.7 National guidelines

Seventy per cent of the patients were followed-up with additional imaging in our study, the reason for this high prevalence could be due to the old national guidelines *(panel 1)* and also due to lack of information on native attenuation on the primary imaging. Also, a large number of patients had additional biochemical investigation. One hundred ninety-five patients (40%) were further investigated with additional cortisol tests while 157 patients had a S-cortisol (post-DST) above the reference value >50 nmol/L. One hundred ninety patients (39%) underwent additional catecholamine tests, however 125 had a value of p-free metanephrines above the reference level (≥0.5 and ≥1.1 respectively). One hundred thirty-seven patients (28%) had additional aldosterone tests, 42 had an ARR≥ 60. These results indicate that excess investigations were performed.

The previous national guidelines recommended surgical adrenalectomy in the case of a lesion size ≥3cm, even if the lesion was benign and inactive (12). This led to numerous surgical procedures that could have been avoided. For instance, a Swedish study that was performed between 1996-2001 found a total of 381 AI cases, of whom 85 (22%) were operated. However only 30 (35%) lesions were hormone-producing or malignant lesions, the rest (65%) were benign inactive lesions. Compared to this previous study, our study had a lower occurrence of surgical treatment (11% versus 22%) and also had fewer benign lesions that were operated (28% versus 65%). Thus, we concluded that the new national guidelines have helped to reduce the number of unnecessary surgeries in patients with benign inactive adrenal tumours.

6.8 Information to the patient

Receiving an unexpected diagnosis of a lesion in the adrenal gland can be a turmoil for the patient. It is unforeseen, and one might worry that it is a malignant lesion. A Swedish follow-up study, which was performed to evaluate the impact of an AI diagnosis, found that 77% of the patients felt worried upon receiving an AI diagnosis (7). It is important that AI is carefully managed within the healthcare system. The patients should receive proper information regarding what AI is, that the radiological evaluation and biochemical screening is performed to rule out hormonal overproduction. It is important that the patients get reassurance that benign inactive lesions are not dangerous and do not require any medical or surgical treatment.

6.9 Limitations and weaknesses

The limitations of this study need to be discussed. As with many retrospective studies, we had a substantial amount of data that was missing and variables that should have been investigated but were not. For example, data was missing for important variables such as height, weight, native attenuation which affected the results and also led to that some variables could not be included in the final analysis. The database did not include any clinical information concerning history of hypertension and presence of anti-hypertensive medication, these are variables that should have been investigated. Although we had data on measured blood pressure, we could therefore not draw any conclusions if the adrenal lesion had any correlation to it or if it was due to other confounding factors.

Our results show that the AIs were detected by a CT-scan in 94% of the cases. However, it would have been useful to further categorize into abdominal CT, CT-colon, CT-thorax or CT-kidneys. We should have included whether the original CT was performed with contrast, to better understand the reason behind an additional follow-up imaging procedure. It would also

have been valuable information if the type of additional imaging was specified, to estimate exposure to radiation. An important weakness in this study is that it is not specified whether the additional biochemical tests were due to the old national recommendations or a suspicion of a primary adrenal disease. If we had specified the reason, then we could have analysed the amount of excess investigation that could have been avoided. We should also have further specified whether the clinical visit was with a nurse or a physician, as the waiting time between referral date and date of the clinical visit could vary.

Our results showed that majority of the lesions were benign inactive tumours. However, we should have categorized the AIs further into benign inactive adenoma, myelolipoma and haemangioma, to describe the outcomes and composition of AIs in a better way.

An interesting finding in this study was that 157 (33%) patients had a S-cortisol (post-DST) >50, yet only four patients had a final diagnosis of hypercortisolism and required surgical treatment. Prior studies have shown that subclinical CS can be found in up to 29% of the AI cases (2, 22, 38). There is no consensus on the diagnostic criteria for subclinical CS, hence it was not diagnostically classified and therefore the low prevalence in our study. Further research is required for these patients, to obtain better knowledge regarding subclinical CS so that there are set diagnostic criteria in the future and national guidelines for optimal management of this diagnosis.

7. Conclusion

AI is a common phenomenon in the daily clinical life today due to the increasing use of imaging procedures. The clinical, biochemical and radiological characteristics of AI in this study show that AIs are in the vast majority benign and inactive lesions. These findings illustrate the importance of a thorough and balanced information to the patients, to avoid futile concern regarding their diagnosis. It is also essential to avoid unnecessary radiological and biochemical follow-up as well as surgery in benign cases that do not need any medical or surgical treatment.

A small, yet a significant proportion of the AIs are either hormone-producing or malignant tumours that need proper management and treatment, which shows the importance of the initial AI investigation.

Populärvetenskaplig sammanfattning

Accidentellt upptäckta binjuretumörer: Klinisk sammanställning av 483 patienter mellan 2014–2018.

Ett adrenalt incidentalom (AI) är en tumör i binjuren som upptäcks accidentellt vid en radiologisk utredning som är utförd på grund av en annan anledning än en misstanke om en binjuresjukdom. Tidigare studier har visat en förekomst av AI hos 0,4–5% av alla som genomgår en datortomografiundersökning av buken, vilket gör att AI är väldigt vanligt förekommande inom sjukvården. Trots att AI upptäcks slumpmässigt, så måste det handläggas på ett noggrant sätt.

Under en AI utredning så måste man ta reda på om tumören är godartad eller elakartad och ifall tumören överproducerar binjurehormoner som då kan orsaka en primär binjuresjukdom så som feokromocytom, primär aldosteronism och Cushing's syndrom. Elakartade fynd måste utredas vidare för att se om det är en primär cancer (binjurebarkscancer) eller sekundär (binjuremetastas). En hormonell utredning utförs för att se om fyndet överproducerar binjurehormoner som då kan orsaka diverse symptom så som hjärtklappningar, huvudvärk, svettningar, högt blodtryck, förhöjt blodsocker, benskörhet och övervikt.

Syftet med denna studie var att sammanställa och beskriva den kliniska data och egenskaper av AI samt dess utfall. Därav utfördes en retrospektiv beskrivande studie inom Sahlgrenska Universitetssjukhuset i Göteborg. Man granskade patienternas journaler som hade remitterats till endokrinologen mellan 2014-01-01 tills 2018-05-31 och analyserade relevant klinisk information så som röntgenfynd, blodprovsresultat och allmän handläggning.

I studien fann man totalt 483 patienter med ett AI, varav 289 (60%) var kvinnor och 194 (40%) män. Medianåldern var 69 år. Tumören upptäcktes via datortomografi hos 456 (94%) och 340 (70%) följdes upp med ytterligare radiologisk undersökning. 457 (95%) patienter

hade genomgått någon form av en hormonell screening. Av de 483 fallen, hittade man godartade inaktiva fynd hos 431 (89%). Godartade hormonöverproducerande tumörer hittades hos 38 (8%). Elakartade tumörer hittades hos 14 (3%). 54 (11%) patienter genomgick kirurgisk borttagande av binjuren genom adrenalektomi.

De kliniska, radiologiska och biokemiska egenskaperna av denna studie visar att AI utgörs av godartade inaktiva förändringar i majoriteten av fallen, som inte kräver någon medicinsk eller kirurgisk behandling och därav borde överflödig uppföljning undvikas i dessa fall. En signifikant andel av tumörerna är maligna eller hormonöverproducerande som orsakar en primär binjuresjukdom, dessa kräver noggrann handläggning med utförlig behandling samt uppföljning.

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